Technical report on neonatal and paediatric patient blood management

Volume 1 – Review of the evidence

August 2015

Note

This volume presents the main body of evidence found by a systematic literature review on neonatal and paediatric patient blood management. Volume 2 presents the related appendixes (Appendix A to Appendix F). These two volumes cover all research questions developed for this topic.

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Abbreviations and acronyms

|  |  |
| --- | --- |
| APTT | activated partial thromboplastin time |
| AHD | alloimmune haemolytic disease |
| ALI | acute lung injury |
| AML | acute myeloid leukaemia |
| ANH | acute normovolemic haemodilution |
| ASBT | Australasian Society of Blood Transfusion |
| BPD | bronchopulmonary dysplasia |
| CBP | critical bleeding protocol |
| CHD | congenital heart disease |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| COWA | controlled oral word association |
| CPB | cardiopulmonary bypass |
| CRG | Consumer/Clinical Reference Group |
| DAR | darbepoetin alfa |
| DCC | delayed cord clamping |
| DVT | deep vein thrombosis |
| EACA | epsilon-aminocaproic acid |
| ECC | early cord clamping |
| ECMO | extracorporeal membrane oxygenation |
| ECLS | extracorporeal life support |
| EHEC | enterohaemorrhagic *Escherichia coli* |
| ELBW | extremely low birth weight |
| ENT | ear, nose and throat |
| ES | evidence statement |
| ESA | erythropoiesis stimulating agent |
| ESRD | end-stage renal disease |
| EWG | Expert Working Group |
| FDA | Food and Drug Administration |
| FFP | fresh frozen plasma |
| GCS | Glasgow Coma Scale |
| Hb | haemoglobin |
| HDFN | haemolytic disease of the fetus and newborn |
| HTA | health technology assessment |
| HUS | haemolytic uremic syndrome |
| ICC | immediate cord clamping |
| ICU | intensive care unit |
| IM | intramuscular |
| INR | international normalisation ratio |
| IQR | interquartile range |
| IR | interventional radiology |
| ISS | injury severity score |
| ITT | intent-to-treat |
| IUT | intrauterine transfusion |
| IV | intravenous |
| IVH | intraventricular haemorrhage |
| IVIg | intravenous immunoglobulin |
| LBW | low birth weight |
| MD | mean difference |
| MDI | mental developmental index |
| MODS | multiple organ dysfunction syndrome |
| NBA | National Blood Authority |
| NEC | necrotising enterocolitis |
| NHMRC | National Health and Medical Research Council |
| NICE | National Institute for Health and Clinical Excellence (UK) |
| NICU | neonatal intensive care unit |
| NNNI | Northern Neonatal Nursing Initiative |
| NNTH | number needed to treat to harm |
| NR | not reported |
| OR | odds ratio |
| PCV | packed cell volume |
| PDI | psychomotor development index |
| PBM | patient blood management |
| PDA | patent ductus arteriosus |
| PELD | paediatric end-stage liver disease |
| PELOD | paediatric logistic organ dysfunction |
| PHD | preoperative haemodilution |
| PICO | population, intervention, comparator, outcome |
| PICU | paediatric intensive care unit |
| PIM | paediatric index of mortality |
| POC | point of care |
| POC | point of care |
| PP | practice point |
| PPT | prophylactic platelet transfusion |
| PRISM | paediatric risk of mortality |
| PROM | prolonged rupture of membrane |
| PT | prothrombin time |
| PVL | periventricular leukomalacia |
| QoL | quality of life |
| R | recommendation |
| RBC | red blood cell |
| RCT | randomised controlled trial |
| RDI | recommended daily intake |
| rFVIIa | recombinant activated factor VII |
| RhHDFN | Rh haemolytic disease of the fetus and newborn |
| rHuEPO | recombinant human epoetin |
| RNI | recommended nutrient intake |
| ROP | retinopathy of prematurity |
| RR | relative risk |
| SAE | serious adverse event |
| SD | standard deviation |
| SE | standard error |
| SMD | standardised mean difference |
| SNAP | score for neonatal acute physiology |
| TACO | transfusion-related circulatory overload |
| TANEC | transfusion-associated necrotising enterocolitis |
| TCD | transcranial Doppler |
| TGA | Therapeutic Goods Administration |
| TISS | therapeutic Intervention Scoring System |
| TPN | total parenteral nutrition |
| TPT | therapeutic platelet transfusion |
| TRALI | transfusion-related acute lung injury |
| TTP | thrombocytopenic purpura |
| TXA | tranexamic acid |
| UAC | umbilical arterial catheter |
| VLBW | very low birth weight |
| WHO | World Health Organization |
| WMD | weighted mean difference |

# Introduction

This document presents the methods and results relating to the findings from a systematic literature review on paediatric patient blood management. It is the first volume of a technical report produced as part of the development process for the *Patient blood management guidelines: Module 6 – Neonatal and paediatrics*; the sixth and final in a series of six modules that focus on evidence-based patient blood management and will replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*.1 The six modules of the guidelines are being developed in three phases, as shown in **Table 2.1.1**.

Table 2.1.1 Phases of development of guideline modules

|  |  |
| --- | --- |
| Phase | Modules |
| I | Critical bleeding/massive transfusion |
|  | Perioperative |
| II | Medical |
|  | Critical care |
| III | Obstetrics and Maternity |
|  | Paediatric/neonatal |

This volume covers all the research questions. Volume 2 of the technical report presents the related appendixes.

The document *Patient blood management guidelines:* Module 6 – Neonatal and paediatrics gives information on:

* governance arrangements for the guidelines
* committee memberships and affiliations
* the background research team.

# Methods

## Research question development

An Expert Working Group (EWG) met for the first time in July 2008. At this meeting members were provided with a comprehensive analysis of existing guidelines relevant to the clinical areas of focus. An independent systematic review expert provided a detailed presentation on framing clinical questions for systematic review. EWG members self-nominated to participate in relevant areas of clinical focus for each module. This action formed the basis for the establishment of a Consumer/Clinical Reference Group (CRG) for each module.

Following the July 2008 meeting, members of each CRG generated questions to be considered for inclusion in their respective guidelines. Before the next meeting, CRG members discussed first-draft questions, and acknowledged that question content would mean that there was a need to consider expanding the CRG memberships to ensure relevant clinical and consumer representation. CRG members agreed that it would be appropriate to circulate draft questions to relevant clinical colleges and societies for input and feedback at an early stage, and before inclusion in a statement of requirement for a systematic reviewer.

The EWG met in September 2008 to further develop and prioritise the proposed questions. During the development of research questions, it became apparent that several questions would be relevant for systematic review for all modules (Phases I to III). These became known as generic questions; six such questions were ultimately developed.

Another two workshop meetings were held in November 2008. All EWG members attended these meetings, where questions were further prioritised, combined and refined. In January 2009, a meeting of the CRG Chairs finalised questions that were subsequently provided to systematic reviewers.

This process resulted in *generic foreground questions* (i.e. relevant to all six modules in the series) and *specific foreground questions* (i.e. specific to each module) for systematic review, and questions for background research. The background questions were to be addressed through general research undertaken by registrars supervised by CRG members. Background questions were designed to provide general information for the guidelines and to assist in providing generalised clinical practice tips, in the form of expert opinion points. The questions were intended to capture information that was considered to fall outside the scope of the foreground questions addressed by the systematic literature review. Foreground and background questions were further refined through consultation among the systematic reviewers and technical writer, the CRG, the National Blood Authority (NBA) and the independent systematic review expert.

Research questions were developed for all but the critical care module. The requirement for this module was only identified after the initial systematic review for Phase I had commenced.

The intervention questions were intended to determine the effects on patient outcomes of various strategies that can be used in patient blood management. The aetiology question was designed to determine whether the risk factor anaemia causes adverse outcomes. The prognostic question was concerned with clinical information that predicts outcomes.

### Foreground research questions

Research questions to be investigated in the neonatal and paediatrics module were reviewed or developed by the CRG at an initial face-to-face workshop held on 18–19 February 2013. Generic research questions and a specific research question were developed and refined at the workshop, and were then further refined via email correspondence and during teleconferences held between February and 7 June 2013. A second face-to-face workshop was held on 18–19 November 2013 to further clarify the research questions and help refine the systematic literature search strategies.

There are four foreground research questions for this module. Questions 1–3 are generic questions (relevant to all six modules of these guidelines), whereas Question 4 is specific to this module:

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

When describing the patient population of interest through the module and technical reports, the term ‘neonate’ was used to reflect the evidence when referring to the newborn; it specifically refers to a defined period of time up to 28 days following birth. The term ‘preterm’ was used to describe patients born before 37 weeks gestational age. The specific gestational age of the preterms was reported where available. In some cases, the evidence refers to both preterm and term infants. This population is discussed according to birth weight. The term ‘infants’ was used to refer to those aged between 1 and 24 months, ‘children’ were those aged between 2 and 12 years, and ‘adolescents’ were those aged between 13 and 18 years. The term ‘paediatric’ was used to encompass all infants, children and adolescents.

Two questions were excluded from the Phase II and Phase III modules because they were not interventional questions; hence, clinical recommendations could not easily be made. The first was an aetiological question (Is anaemia an independent risk factor for adverse outcomes?) and the other was a prognostic question (At what international normalised ratio (INR) (or prothrombin time [PT]/partial thromboplastin time [APTT]) for FFP, fibrinogen level for cryoprecipitate, platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?).

One further question (What is the effect of rFVIIa [prophylaxis or treatment] on morbidity, mortality and transfusion rate?) was not covered in the Phase II modules because it had already been covered in Phase I. This question was excluded as a separate question from the Phase III modules, but rFVIIa was included as an intervention within the specific question (i.e. Question 4).

Details of research question criteria are presented in **Appendix 1** of this volume.

### Background research questions

The background research questions developed for paediatric/neonatal patient blood management were:

* *Background Question 1* – For paediatric, neonatal or fetal patients, does selection of specific blood products, when compared with routine blood products improve outcomes?
* *Background Question 2* – In fetuses at risk for thrombocytopenia 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* – Do non-pharmacologic strategies for minimisation of blood loss from sampling reduce the need for red cell transfusion?
* *Background Question 4* – In perioperative neonatal and paediatric patients needing cardiac surgery, do strategies to minimise blood loss reduce the need for transfusion?
* *Background Question 5* – What recommendations should be made for the detection, diagnosis and management of iron deficiency anaemia in neonates and children?

### Aboriginal and Torres Strait Islander populations

Prevalence of anaemia in Aboriginal and Torres Strait Islander populations is known to be higher than in the general Australian population.2-6 The electronic search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, in accordance with NHMRC guideline development requirements, 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.

## Literature searches

NHMRC standards and procedures require that clinical practice guidelines be based on systematic identification and synthesis of the best available scientific evidence.7 Systematic reviews were conducted for all generic and specific research questions, using a stepped process in which the highest level body of evidence was assessed before lower levels of evidence were considered. If there was sufficient Level I evidence to address all primary outcomes of a research question (as specified in the population, intervention, comparator, outcome [PICO] criteria), Level II and III evidence was not assessed. However, the literature search was updated to identify any Level II studies published since the search date of the key Level I evidence. If no relevant Level I evidence was available for a particular research question, a literature search was conducted to identify Level II studies, and if no studies were identified, the process was repeated for lower level evidence (if specified in the PICO criteria). For primary outcomes not addressed in higher level evidence, a search of lower level evidence was conducted for those particular outcomes only.

Three main strategies were used to identify all potentially relevant literature: electronic database searching, manual searching, and literature recommended by expert members of the CRG.

### Electronic databases

The systematic reviewers carried out searches using the following primary databases:

* EMBASE and Medline via the EMBASE.com interface
* Cochrane Library Database: a database of systematic reviews, other reviews, clinical trials, methods studies, technology assessments, economic evaluations and Cochrane Groups.

Search strategies for all primary databases were developed in consultation with a specialist search strategist. All strategies were based on the PICO criteria developed for the research questions (**Appendix 1** in this volume). Full details of all search strategies for the primary databases (including search dates) are presented in **Appendix A** (Volume 2).

Additional secondary databases searched included:

* Health Technology Assessment (HTA) agency websites (e.g. NICE in the UK, CADTH in Canada)
* Guideline websites and databases (e.g. Guidelines International Network, National Guidelines Clearing House)
* Clinical trial registries (e.g. Current Controlled Trials MetaRegister)
* PreMedline (Medline in process, accessed via the PubMed interface and limited to 12 months prior to the search date).

Each secondary database was searched by a single reviewer using simple search strategies (based on those developed for the primary databases) and articles that met the inclusion criteria identified. Searches of the secondary databases occurred on 13-14 June 2013, and again on 2–3 September (Question 2), 22–23 October (Question 1 and Question 3) and 4–5 November (Question 4).

To maintain the rigor of the systematic review process, studies published after the literature search date were not eligible for inclusion in the technical report. However, pivotal new evidence could be discussed in the guideline document and could be used to develop consensus-based ’expert opinion’. Literature search start dates were defined by the CRG for each question (see **Appendix 1** in this volume). Studies were excluded for each question if they were published prior to 1995 (except primary studies if they were included as part of a systematic review). The rationale from the CRG was that papers published prior to 1995 were unlikely to reflect the current context of care, due to advances in neonatal and paediatric care.

### Manual searching of reference lists

Members of the systematic review/technical writing group manually hand-searched reference lists included in relevant articles identified by the systematic literature search. This strategy identified some additional articles that were not found in electronic database searches. Additional articles found by manual searching are indicated in the literature search results presented in **Appendix C** (Volume 2).

### Expert sources

Articles recommended by CRG members were considered for inclusion, provided the articles met the criteria for inclusion.

### Background question research

Research for background questions was undertaken by registrars under the supervision of CRG members. These questions were not researched by applying systematic review processes. Registrars were advised to use sources ranging from medical textbooks, grey literature, published scientific and review articles (identified through PubMed, EMBASE or Cochrane databases), series yearbooks and other relevant medical literature. Because the intention was to identify relevant information that could inform best practice, background research was not limited to evidence or general information only applicable to Australia and New Zealand.

### Issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities

The focus of the systematic review was on physiological parameters surrounding the decision to transfuse. As such, there were no distinct physiological issues relevant to Aboriginal and Torres Strait Islander peoples, and culturally and linguistically diverse communities.

The greater prevalence of certain conditions (e.g. anaemia and chronic kidney disease) in some Indigenous Australian communities has a socioeconomic, not physiological, basis. No literature pertaining to Australia’s Aboriginal and Torres Strait Islander peoples was identified in the literature searches for any research question.

### Cost effectiveness

A specific literature search for economic evidence was not conducted. Any economic evidence identified in the literature that met the PICO criteria was not considered.

## Inclusion and exclusion criteria

Inclusion criteria were determined from the PICO criteria that formed the basis of the systematically reviewed research questions (**Appendix 4.1** in this volume). Studies reporting at least one of the primary outcomes were eligible for inclusion if they also satisfied the correct intervention and comparator criteria. Studies that did not meet one or more of these criteria were excluded.

Additional reasons for excluding studies were:

* non-human studies
* non-English language studies
* non-systematic reviews, editorials, opinion pieces and letters
* case series, pre–post or post studies
* research or systematic review protocols not defined.

Titles and abstracts of every record retrieved by searching the primary and secondary databases were reviewed, and full articles were retrieved for further assessment where the articles were considered to meet the inclusion criteria. Articles that could not be included or excluded on the basis of information in the title or abstract were retrieved as full text before a final decision was made on inclusion or exclusion.

One reviewer from the evidence review team screened the titles and abstracts (where available) for all citations retrieved by the literature search. A second reviewer then performed quality checks on a random subset of excluded citations. All citations listed for inclusion for full text review were independently assessed by a second reviewer. Any disagreements were resolved by a third reviewer.

Articles reporting on the basis of the following study designs were considered for inclusion when PICO criteria were met:

* systematic reviews of randomised controlled trials (RCTs) and/or cohort studies
* RCTs or pseudo-RCTs
* cohort studies
* case–control studies

Studies that initially met inclusion criteria but were later excluded are documented, with reasons for their exclusion, in **Appendix B** (Volume 2). Examples of reasons for exclusion in this circumstance include different systematic reviews reporting the same primary studies (in which case, the highest quality systematic review reporting the best available data was used), and inadequate data reporting.

## Classification and assessment of evidence

Studies identified for inclusion from the literature search were classified according to the NHMRC levels of evidence hierarchy (**Table 2.4.1**). To ensure that modules were based on the best available evidence, studies of higher levels of evidence (Levels I or II) were included in preference to those presenting lower levels of evidence (Levels III or IV). This was to minimise the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Studies identified from the systematic literature review were assessed according to NHMRC dimensions of evidence (**Table 2.4.2**).8 There are three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain was derived directly from the literature identified for a particular intervention, aetiology or prognostic study. The other two domains were determined in consultation with the CRG as part of the study assessment process during the review of the evidence considered for module development. An aspect of the strength of the evidence domain is the level of evidence of the study, which was determined as described above using the NHMRC levels of evidence hierarchy outlined in **Table 2.4.1**.

Table 2.4.1 NHMRC evidence hierarchy: designations of levels of evidence according to type of research question

|  |  |  |  |
| --- | --- | --- | --- |
| Level | Interventiona | Prognosis | Aetiologyb |
| Ic | A systematic review of Level II studies | A systematic review of Level II studies | A systematic review of Level II studies |
| II | A randomised controlled trial | A prospective cohort studyd | A prospective cohort study |
| III–1 | A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) | All or nonee | All or nonee |
| III–2 | A comparative study with concurrent controls:   * non-randomised, experimental trialf * cohort study * case–control study * interrupted time series with a control group | Analysis of prognostic factors among persons in a single arm of a randomised controlled trial | A retrospective cohort study |
| III–3 | A comparative study without concurrent controls:   * historical control study * two or more single-arm studiesg * interrupted time series without a parallel control group | A retrospective cohort study | A case–control study |
| IV | Case series with either post-test or pre-test/post-test outcomes | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series |

Source: NHMRC (2009)8  
 **a** Definitions of these study designs are provided on pages 7–8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000)9**b** If it is possible and ethical to determine a causal relationship using experimental evidence, then the ‘intervention’ hierarchy of evidence should be used. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g. groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the ‘aetiology’ hierarchy of evidence should be utilised.  
**c** A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.  
**d** At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.  
**e** All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.  
**f** This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C).  
**g** Comparing single-arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Table 2.4.2 NHMRC dimensions of evidence

| Dimension | Definition |
| --- | --- |
| Strength of evidence | |
| Level | Each included study is assessed according to its place in the research hierarchy. This illustrates the potential of each included study to adequately answer a particular research question and indicates the degree to which design has minimised the impact of bias on the results |
| Quality | Included studies are critically appraised for methodological quality. Each study is assessed according to the potential that bias, confounding and/or chance has influenced the results |
| Statistical precision | Primary outcomes of included studies are assessed to establish whether the effect is real, rather than due to chance. Using a level of significance such as a *P-*value and/or confidence interval, the precision of the estimate of the effect is evaluated. This considers the degree of certainty regarding the existence of a true effect |
| Size of effect | The clinical importance of the findings of each study is assessed. This concept refers to the measure of effect or point estimate reported in the results of each study (e.g. mean difference, relative risk). For meta-analysis pooled measures of effect are assessed. Size of effect refers to the distance of the point estimate from its null value and also the values included in the corresponding 95% confidence interval. Size of effect indicates the clinical impact a particular factor or intervention will have on a patient and is considered in the context of patient relevant clinical differences |
| Relevance of evidence | The translation of research evidence to clinical practice is addressed by this dimension. It is regarded as potentially the most subjective of the evidence assessments. There are two questions concerning the appropriateness of outcomes and relevance of study questions:  Are the outcomes measured in the study relevant to patients?  How closely do the elements of the study research question match with those of the clinical question being considered? |

Source: NHMRC (2009)8

### Quality appraisal

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

### Data extraction

Data and information were extracted into evidence summary tables according to the inclusion criteria. Evidence summary tables were based on NHMRC requirements for externally developed guidelines.10 All articles retrieved for full text review were initially screened, critically appraised, and data extracted by one evidence reviewer. A second reviewer independently checked and reviewed all articles, data extractions, and quality assessments. Any disagreements were resolved by a third reviewer.

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

## Assessment of the body of evidence and formulation of recommendations

The body of evidence for each module recommendation was graded in accordance with the NHMRC framework for developing evidence-based recommendations.8 Assessment of the body of evidence considers the dimensions of evidence of studies relevant to that recommendation (**Table 2.4.2**). A modified NHMRC evidence statement form was used with each clinical research question considered in the development of the guidelines (see **Appendix 4.3** of this volume). That is, a separate form was used for consolidation of the evidence (evidence statement form) and the development of recommendations (recommendation form). The decision to separate out the two components of the NHMRC evidence statement form was due to the inevitability of several evidence statement forms leading to only one recommendation. Also, the current NHMRC evidence statement form does not provide a space to capture the actual wording of evidence statements.

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

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

Completed evidence statement forms and recommendation forms for each research question are presented in **Appendix D** (Volume 2).

### Use of the modified NHMRC evidence statement form

The modified NHMRC evidence statement form was applied in five steps.

#### Step 1 Rating each of the five components

To inform grading of recommendations, the body of evidence underpinning each evidence statement was assessed. Five key components were rated (**Table 2.5.1**). The first two components – evidence base and consistency – were derived directly from the literature identified for each research question. During review of identified evidence, CRG guidance was also required to assess the clinical impact, generalisability and applicability of included studies.

For each evidence statement, the five components presented in **Table 2.5.1** were rated according to the matrix shown in **Table 2.5.2**. This grading system was designed to accommodate variation in the body of evidence. For example, a large number of studies with minimal bias may be included, but have limited applicability to the Australian health-care context. Alternatively, a body of evidence may consist of a small number of trials with a moderate risk of bias, but have a significant clinical impact and high applicability to the Australian health-care context. Rating results were entered into the modified NHMRC evidence statement form, together with any additional explanatory information relevant to each component. The results section for each research question includes the body-of-evidence matrix-rating assessment for each evidence statement.

Table 2.5.1 Components of the evidence statement

| Component | | Definition |
| --- | --- | --- |
| Evidence base | |  |
|  | Quantity | Reflects the number of studies included as the evidence base. Also takes into account the number of patients in relation to frequency of the outcomes measured (i.e. study statistical power). Meta-analysis can be used to combine results of studies to increase the power and statistical precision of effect estimates. |
|  | Level | Reflects the best study type for the specific type of research question (intervention, prognosis). Level I evidence would be the best evidence to answer each question. |
|  | Quality | Reflects how well studies were designed and conducted in order to eliminate bias. |
| Consistency | | Assesses whether findings are consistent across included studies, including a range of study populations and study designs. Meta-analysis of randomised studies should present statistical analysis of heterogeneity that demonstrates little statistical difference between studies. Presentation of an I2 statistic illustrates the extent of heterogeneity between studies. Clinical heterogeneity between studies should also be explored. |
| Clinical impact | | Measures the potential benefit from application of the guidelines to a population. Several factors need to be considered when estimating clinical impact, including relevance of the evidence to the clinical question; statistical precision and size of the effect; relevance of the effect to patients compared with other management options or none. Other relevant factors are the duration of therapy required to achieve the effect, and the balance of risks and benefits (taking into account the size of the patient population). |
| Generalisability | | Addresses how well the subjects and settings of included studies match those of the recommendation. Population issues that could affect recommendations include sex, age, ethnicity, and baseline risk or level of care (e.g. community or hospital setting). This is an important consideration when evidence comes from randomised controlled trials, where setting and entry requirements are generally narrow and therefore may not be representative of all patients to whom the recommendation may be applied in practice. In this circumstance broader-based population studies may be useful for confirming evidence from randomised controlled trials. |
| Applicability | | Addresses whether the evidence base is relevant to the Australian health-care setting in general or to more local settings for specific recommendations (e.g. rural areas or cities). Factors that will affect the applicability of study findings include organisational factors (e.g. availability of trained staff, specialised equipment and resources) and cultural factors (e.g. attitudes to health issues, including those that may affect compliance with guidelines recommendations). |

Source: NHMRC (2009)8

Table 2.5.2 Body-of-evidence matrix

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

Source: NHMRC (2009)8

A rating of ‘NA’ was attributed for consistency when only one study was included.

#### Step 2 Preparation of an evidence statement matrix

An evidence statement matrix was completed to summarise the synthesis of the evidence relating to the evidence statement or statements for each research question. This summary presented ratings for the five components of the body-of-evidence matrix assessed for each evidence statement. Multiple statements were required where the evidence differed in population subgroups, or where differences in an intervention (e.g. dose/mode of administration) could lead to different results. Other relevant issues and dissenting opinions were recorded if required.

In practice, Steps 1 and 2 to complete the modified NHMRC evidence statement forms were conducted concurrently for each evidence statement.

#### Step 3 Formulation of a recommendation based on the body of evidence

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

#### Step 4 Determination of the grade for the recommendation

The overall grade for each recommendation was determined from a summary of the rating for each component of the body of evidence. Definitions of the NHMRC grades of recommendations are presented in **Table 2.5.3**. In accordance with the NHMRC framework, recommendations were not graded A or B unless the evidence base and consistency of evidence were both rated A or B (unless only one study was included, and consistency was rated ‘NA’ – in this situation the quality, size and strength of the evidence base was relied upon to grade the recommendation). The grading of recommendations was determined in conjunction with the CRG.

Developed recommendations were entered into the recommendation forms, and the corresponding evidence statement forms were noted, along with the overall grade determined in this step (**Appendix D**, Volume 2).

Table 2.5.3 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)8

#### Step 5 Implementation of guidelines recommendations

The NHMRC framework directs that guidelines implementation should be considered at the same time as recommendations are formulated. The recommendation form contains questions related to the implementation of each module (**Appendix 4.3** in this volume). These are:

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

This section of the recommendation form was completed in consultation with the CRG when each recommendation was formulated and graded. Implementation issues are recorded in the recommendation forms presented in **Appendix D** (Volume 2).

### Practice points

Practice points were developed by the CRG through a facilitated group discussion and consensus process (**Appendix 4.4** in this volume) in the following circumstances:

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

The preferred term for this type of recommendation is a ‘consensus-based recommendation’.11 However, to be consistent with the first four modules of the patient blood management guidelines and to avoid confusion, the term ‘practice point’ will continue to be used for the final two modules. The new terminology will be adopted across all six modules at the first review.

Recommendations, practice points and expert opinion points were formulated, discussed, and agreed by the CRG at face-to-face meetings. No major debate or dissenting viewpoints about the evidence occurred.

## Limitations of the review methodology

This review used a structured approach to reviewing the literature. However, as with all study types can be subject bias. Reporting biases are a particular problem related to systematic reviews and include publication bias (small, negative trials tend not to be published), time-lag bias (delayed publication of negative findings), multiple publication bias (positive results published and counted multiple times), language bias (significant results tend to be published in English language journals) and outcome reporting bias (selective reporting of favourable outcomes).

Some of these biases are potentially present in these reviews. For example, only data published in peer-reviewed journals were included. Unpublished material was not included as such material typically has insufficient information upon which to base quality assessment, and it has not been subject to the peer-review process. In addition, the search was limited to English language publications only, so language bias is also a potential problem. Outcome reporting bias and inclusion criteria bias are unlikely as the methodology used in the review and the scope of the review was defined in advance.

## Protocol deviation

It was not intended that individual evidence statement forms would be prepared for any of the secondary outcomes identified in this review. This is because the secondary outcomes were only extracted from studies that reported one or more primary outcomes, and therefore had not undergone a strict systematic review process. However, in question 1, evidence statements for each severe morbidity outcome were completed as it was realised during the review process that in order to assess full text papers for the primary outcomes (composite of severe morbidity and mortality) we had inadvertently also systematically screened for each severe morbidity outcome. It was therefore deemed appropriate to consider the evidence for each severe morbidity outcome in the same manner as other primary outcomes considered for this review.

# Findings of systematic review

This chapter provides the findings of the systematic review, based on the four questions listed in Chapter 2.

## Question 1

Question 1 (Interventional)

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

RBC, red blood cell

|  |  |
| --- | --- |
| Recommendations –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. |
| 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 ultrasonography12 *and* MRI.13 b See PP11 for methods of assessment. |
| Practice points –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*.14 |
| 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  a See Appendix F (*RBC transfusions in preterm infants*) and Appendix J (*Transfusion volume calculation for neonates, infants and small children*) |
| 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*.14 |
| 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*14 |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.a  a See Appendix F (*RBC transfusions in preterm infants*) and 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.a This reassessment will also guide the decision on whether to retest the Hb level.  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*15 |
| 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. |
| PP11 | Children and adolescents with SCD should be assessed for stroke risk using both TCD ultrasonography12 and MRI.13 |
| 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; Hct, haematocrit; MRI, magnetic resonance imaging; PP, practice point; R, recommendation; RBC, red blood cell; SCD, sickle cell diseaseTCD, transcranial Doppler  Note: 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 yet available. We await publication of the full trial results before a reassessment of current recommendations (R2 and R4) and practice points (PP11) are made. | |

|  |
| --- |
| Evidence gaps and areas for future research |
| There is a need for further research on:   * the effect on RBC transfusion on morbidity (including BPD) and mortality in preterm infants * in other paediatric patients who are chronically transfused (e.g. acquired or inherited bone marrow failure or anaemia syndromes), evidence to guide particular Hb thresholds * the use of restrictive transfusions strategies in the following populations: critically ill neonates, surgical patients, cardiac surgical patients and oncology patients * alloimmunisation in regularly transfused patients * in paediatric patients with sickle cell disease, optimal strategies for identifying patients at high risk of silent and asymptomatic stroke. |

### Background

Neonatal and paediatric patients are transfused with RBCs to treat symptoms of acute blood loss or anaemia, to reduce morbidity and mortality and improve quality of life. The systematic review aimed to establish whether receiving a RBC transfusion affects clinically important patient outcomes. It examined the effect of RBC transfusions in a general population of neonatal and paediatric patients, and in subsets of patients in whom a different management strategy might be appropriate.

Six different populations were considered for this question: (1) preterm infants (<37 weeks gestational age); (2) infants (aged 0–23 months); (3) Children and adolescents (aged between 2 and 18 years); (4) medical neonatal and paediatric patients; (5) neonatal and paediatric patients requiring surgery; and (6) critically ill neonatal and paediatric patients.

### Methods

Two comparisons were assessed for this review: (1) RBC transfusion compared with no transfusion (or alternative RBC transfusion dose); and (2) restrictive transfusion compared with liberal transfusion (based on different transfusion triggers) (see **Section 4.1**).

Because this is an intervention question, the levels of evidence are as follows:

* Level I – a systematic review of two or more Level II studies
* Level II – an RCT
* Level III–1 – a pseudo-RCT
* Level III–2 – a comparative study with concurrent controls (including non-randomised, experimental trials, cohort studies, case–control studies and interrupted time series with a control group)
* Level III–3 – a comparative study without concurrent controls (including historical control studies, two or more single-arm studies, and interrupted time series without a parallel control group)
* Level IV – case series with either post-test, or pre-test and post-test outcomes.

For the purposes of this review, a systematic review of Level III–2 or Level III–3 evidence was classified as Level III evidence.

For this question, the evidence was limited to studies published after 1995. Articles published before 1995 that had been included in a Level I study were included. A search of lower level evidence was only conducted for primary outcomes not addressed in higher level evidence (see **Section 2.3**). Secondary outcomes were extracted from studies that reported one or more primary outcomes.

For the first comparison (RBC transfusion compared with no transfusion), we considered Level III–2 evidence or higher. Only Level III–2 studies that included at least 100 subjects and were adjusted for potential confounding variables were considered. Although the results of these adjusted Level III studies can indicate whether or not RBC transfusions are an independent risk factor for specific outcomes, they do not prove that RBC transfusions *cause* these outcomes. This is because proof of causation can only be determined using an RCT. For the second comparison (restrictive transfusion compared with liberal transfusion), Level I and Level II evidence were considered.

Overall, nine Level I studies that included seven Level II studies relevant to our research question, four additional Level II studies, 20 Level III–2 studies, and two systematic reviews of Level III studies were identified in the systematic review and hand-searching process that evaluated the use of RBC transfusions in neonatal and/or paediatric patients, and reported outcomes relevant to our research questions (see **Appendix C, Volume 2**).

There was no literature specifically pertaining to Australia’s Aboriginal and Torres Strait Islander peoples relevant to this research question.

### Preterm and low birth weight infants

| Evidence statements – preterm and low birth weight infants (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √ | √√√ | √ |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 | √√ | √ |
|  | 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 | √ | √√√ | √ |
|  | 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 | √√ | √√ |
|  | 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 | √√ | √ |
|  | 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 | √√ | √√ |
|  | 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 | √√ | √√ |
|  | 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 | √ | √√ | √√ |
|  | 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; NEC, necrotising enterocolitis; RBC, red blood cell; ROP, retinopathy of prematurity  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendations – 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*.14 |
| 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  a See Appendix F (*RBC transfusions in preterm infants*) and 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

In infants born before term, the physiological decline in circulating RBCs is more pronounced than in term infants. Contributing factors include inadequate erythropoiesis, rapid growth and phlebotomy blood losses that may occur within the first few weeks of life. This anaemia of prematurity can be treated with RBC transfusions, which raise haemoglobin levels and help to increase red cell volume. However, concerns have been raised about the use of RBC transfusions in preterm infants, because of a potential association with a number of developmentally specific adverse events such as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and intraventricular haemorrhage (IVH). There is considerable variability in practice, due to uncertainty regarding the indications for RBC transfusion and appropriate haemoglobin thresholds for transfusion.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

The literature search did not identify any Level I studies of Level II evidence that examined the effect of RBC transfusion compared with no transfusion in preterm infants (<37 weeks gestational age) that reported primary outcomes relevant to our research question.

###### Level II evidence

The literature search did not identify any Level II studies that examined the effect of RBC transfusion compared with no transfusion in preterm infants (<37 weeks gestational age) that reported primary outcomes relevant to our research question.

###### Level III evidence

Two systematic reviews of Level III studies (Mohamed 2012, Kirpalani 2012) and 14 Level III–2 studies (AlFaleh 2014, Baer 2011, Demirel 2012, Dos Santos 2011, Elabaid 2013, Feghhi 2012, Fortes Filho 2013, Hakeem 2012, Kabatas 2013, Li 2013, Navaei 2010, Stritzke 2013, Wan-Huen 2013, Weintraub 2011) were identified from the systematic review and hand-searching process that examined the effect of RBC transfusion compared with no transfusion in preterm or very low birth weight (VLBW) infants (see **Appendix C, Volume 2**). The main characteristics of these studies are summarised in **Table 3.1.1**.

Mohamed (2012) was a good-quality systematic review of 11 retrospective case–control studies and one cohort study that examined the association between RBC transfusion and necrotising enterocolitis in 4857 preterm infants. The included studies were assessed by Mohamed (2012) to be of moderate risk of bias (scoring 6–8 out of 10 on the Newcastle-Ottawa scale), with the main causes of bias being the selection of control subjects and the lack of adjustment for confounders.

Kirpalani (2012) was a poor-quality systematic review of 10 Level III studies that assessed RBC transfusion as a risk factor for NEC in 22,722 neonates. The included studies were assessed to be of moderate risk of bias, with the main cause of bias being the inability to confirm that the outcome was absent at the start of the study. The main characteristics of the Level III studies included in these two reviews are summarised in **Table 3.1.2**.

Of the 13 additional Level III studies identified in this review, five (AlFaleh 2014, Demirel 2012, Elabaid 2013, Stritzke 2013, Wan-Huen 2013)also examined the association between RBC transfusion and NEC in preterm infants, and were published subsequent to the systematic reviews by Mohamed (2012) and Kirpalani (2012). The newly identified studies were either retrospective case–control studies (AlFaleh 2014, Stritzke 2013, Wan-Huen 2013) or cohort studies (Demirel 2012, Elabaid 2013), and were conducted in a variety of settings, including single neonatal intensive care units (NICU) in Saudi Arabia (AlFaleh 2014), Turkey (Demirel 2012), and the United States (Elabaid 2013, Wan-Huen 2013), and multiple NICUs in Canada (Stritzke 2013)

Baer (2011) was a retrospective case–control study of 155 VLBW (<1500 g) neonates admitted to three perinatal centres in the USA. Cases were matched 1:2 to controls with similar gestational age (± 2 weeks) and birth weight (± 200 g). Various risk factors, including RBC transfusion within 72 hours of birth, were assessed for development of severe IVH (grade 3–4).

Dos Santos (2011) was a retrospective cohort study of 1077 VLBW preterm infants aged 23 to 37 weeks gestation, who were admitted to eight centres in Brazil. Mortality was compared in patients who received a RBC transfusion before the 28th day of life with patients who did not receive a transfusion.

Navaei (2010) was a retrospective cohort study that investigated factors associated with survival among 194 preterm infants with VLBW admitted to two NICUs in Iran over a period of 15 months. Survival was defined as the discharge of live infants within 75 days.

The remaining six Level III studies (Feghhi 2012, Fortes Filho 2013, Hakeem, 2012, Kabatas 2013, Li 2013, Weintraub 2011) included in this systematic review reported on various risk factors (including RBC blood transfusion) associated with the development of ROP in preterm and/or low birth weight infants. There were three prospective cohort studies conducted in single NICUs in Southern Brazil (Fortes Filho 2013), Egypt (Hakeem 2012), and Turkey (Kabatas 2013). One (Feghhi 2012) was a cross-sectional case–control study of low birth weight infants admitted to multiple NICUs in Iran. One (Li 2013) was a retrospective cohort study conducted in a single hospital in Taiwan and one (Weintraub 2011) was a retrospective case–control study assumed to be conducted in Israel (study location not reported).

Table 3.1.1 Characteristics and quality of Level III evidence identified in this review – RBC transfusion versus no transfusion in preterm infants

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Systematic reviews of observational studies | | | | |
| Mohamed (2012)16 | Systematic review of observational studies  *Good* | Preterm infants or neonates  12 studies, N>2000 | RBC transfusion versus no transfusion | NEC |
| Kirpalani (2012)17 | Systematic review of observational studies  *Poor* | Neonates who developed NEC  10 studies, N=22,722 | RBC transfusion versus no transfusion | NEC |
| Level III–2 studies | | | | |
| AlFaleh (2014)18 | Retrospective case–control  *Fair* | Preterm infants (≤32 weeks gestation) with VLBW (<1500 g)  N=152 | RBC transfusion (n=110) versus no transfusion (n=42) | NEC |
| Baer (2011)19 | Retrospective case–control  *Fair* | VLBW neonates who developed severe IVH matched 1:2 for gestational age and birth weight with no IVH  N=101 (cases, n=54; controls, n=101) | RBC transfusion (n=118) versus no transfusion (n=37) | IVH (grade 3 or 4) |
| Demirel (2012)20 | Retrospective cohort  *Fair* | Preterm infants (mean gestational age 29 ± 3.1 weeks) admitted to NICU with VLBW (mean 1157 ± 237 g)  N=647 | RBC transfusion (n=296) versus no transfusion (n=351)  \*irradiated, leukoreduced | NEC |
| Dos Santos (2011)21 | Retrospective cohort  *Fair* | Preterm infants with VLBW  N=1077 | RBC transfusion (n=574) versus no transfusion (n=503) | Mortality |
| Elabaid (2013)22 | Retrospective cohort  *Fair* | Preterm infants admitted to NICU with VLBW (≤1500 g)  N=3060 | RBC transfusion (n=1842) no transfusion (n=1218)  \*irradiated, leukoreduced | NEC (≥stage 2) |
| Feghhi (2012)23 | Cross-sectional case–control  *Fair* | Preterm infants (≤32 weeks gestational age) and/or LBW infants  N=576 | RBC transfusion (n=40) versus no transfusion (n=536) | ROP |
| Fortes Filho (2013)24 | Prospective cohort  *Fair* | Preterm infants with ELBW  N=157 | RBC transfusion (n=124) versus no transfusion (n=33) | ROP (≥stage 3) |
| Hakeem (2012)25 | Prospective cohort  *Fair* | Preterm infants (≤32 weeks gestational age) with VLBW;  Infants (>32 weeks gestational age or >1500 g birth weight) exposed to oxygen therapy for >7 days;  Preterm infants (32–34 weeks gestational age) who had had a course of instability e.g. sepsis, ventilation  N=172 | >1 RBC transfusion (n=23) versus 1 RBC transfusion (n=25) versus no transfusion (n=124) | ROP (stage 1–3) |
| Kabatas (2013)26 | Prospective case–control  *Poor* | Preterm infants (<32 weeks gestational age) with VLBW, or preterm infants (32–37 weeks gestational age) with anaemia, apnoea, RDS, PDA, ICH, NEC, CLD perinatal asphyxia or sepsis requiring prolonged mechanical ventilation  N=113 | RBC transfusion (n=87) versus no transfusion (n=26) | ROP |
| Li (2013)27 | Retrospective cohort  *Fair* | Preterm (<32 weeks gestational age) or VLBW infants  N=503 | RBC transfusion (n=228) versus no transfusion (n=275) | ROP |
| Navaei (2010)28 | Retrospective cohort  *Fair* | Preterm infants (≤30 weeks gestational age) with VLBW (≤1500 g)  N=194 | RBC transfusion (n=84) versus no transfusion (n=110) | Mortality |
| Stritzke (2013)29 | Retrospective case–control  *Fair* | Preterm infants admitted to NICU with NEC stage ≥2 matched 1:3 to preterm infants admitted to NICU without NEC  N=3708 (cases, n=927; controls, n=2781) | RBC transfusion (n=357) versus no transfusion (n=3351) | NEC |
| Wan-Huen (2013)30 | Retrospective case–control  *Fair* | Preterm infants admitted to NICU with NEC stage ≥2 matched 1:2 to preterm infants admitted to NICU without NEC  N=146 (cases, n=49; controls, n=97) with 3652 48-hr epochs | RBC transfusion (n=557) versus no transfusion (n=3095) | NEC |
| Weintraub (2011)31 | Retrospective case–control  *Poor* | Preterm infants (<32 weeks gestational age) with VLBW and ROP (≥stage 3) matched 1:2 to preterm infants (<32 weeks gestational age) with VLBW, without ROP  N=165 (cases, n=55; controls, n=110) | RBC transfusion (n=135) versus no transfusion (n=30) | ROP (≥stage 3) |

CLD, chronic lung disease; ELBW, extremely low birth weight; ICH, intracranial haemorrhage; IVH, intraventricular haemorrhage; LBW, low birth weight; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; RBC, red blood cell; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; VLBW, very low birth weight

Table 3.1.2 Characteristics and quality of Level III evidence identified by included systematic reviews – RBC transfusion versus no transfusion in preterm infants

| Study | Study type *Study quality* | Population  N | Comparison |
| --- | --- | --- | --- |
| Level III studies identified and assessed by (1) Mohamed (2012)16 and/or (2) Kirpalani (2012) | | | |
| Blau (2011)a 32 | (1) Case–control  *8/10*  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | Preterm (<32 weeks gestational age) or VLBW infants (<1500 g)  N=36 | Cases (n=9): TANEC ≥stage 2  Control 1 (n=15): NEC ≥stage 2 not associated with transfusion  Control 2 (n=12): NEC ≥stage 2 and never transfused |
| Christensen (2010)b 33 | (1) Case–control  *8/10*  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | Preterm infants (<32 weeks gestational age) with VLBW (<1500 g)  N=112 | Cases (n=40): TANEC ≥stage 3 (surgical)  Control (n=72): surgical NEC ≥stage 3 not associated with transfusion  \*Kirpalani (2012) sought additional data on total cohort |
| El-Dib  (2011)a 34 | (1) Case–control  *8/10*  (2) Case–control  *High risk of bias in 1 out of 5 measures* | Preterm (<32 weeks gestational age) infants with VLBW (<1500 g)  N=625 | Cases (n=14): TANEC ≥stage 2  Control (n=611): NEC ≥stage 2 not associated with transfusion |
| Harsono (2011)c 35 | (1) Retrospective cohort  *6/10*  (2) Not included | Infants with ELBW (<1000 g)  N=43 | Cases (n=26): TANEC after 28 days of age  Control (n=17): neonates (less than 28 days of age) with NEC not associated with transfusion |
| Holder (2009)36 | (1) Case–control  *8/10*  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | Preterm infants (<37 weeks gestation) with VLBW (<1500 g)  N=4833 | Cases (n=7): TANEC ≥stage 2  Control (n=30): NEC not associated with transfusion |
| Josephson (2010)37 | (1) Case–control  *8/10*  (2) Case–control  *High risk of bias in 0 out of 5 measures* | Preterm infants (≤34 weeks gestation) admitted to NICU  N=184 | Cases (n=18): TANEC ≥stage 2  Control (n=75): NEC not associated with transfusion |
| Mally (2006)a 38 | (1) Case–control  *8/10*  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | Preterm infants (<32 weeks gestation) with VLBW (<1500 g)  N=908 | Cases (n=6): TANEC ≥stage 2  Control (n=11): NEC ≥stage 2 not associated with transfusion |
| McGrady (1987)e 39 | (1) Not included  (2) Case–control  *High risk of bias in 1 out of 5 measures* | NR |  |
| Paul (2011)40 | (1) Case–control  *8/10*  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | Preterm infants (<32 weeks gestation) with VLBW (<1500 g)  N=2311 | Cases (n=33): NEC ≥stage 2 within 48 hours or transfusion  Control 1 (n=59): NEC >48 hours after transfusion  Control 2 (n=30): NEC with no exposure |
| Perciaccante (2008)b 41 | (1) Case–control  *6/10*  (2) Not included | NR | Cases (n=7, n=0): TANEC  Control (n=11, n=11): NEC not associated with transfusion  Epoch 1 N=18  Epoch 2 N=11 |
| Singh (2011)42 | (1) Case–control  *8/10*  (2) Case–control  *High risk of bias in 0 out of 5 measures* | NR  N=67 | Cases (n=44): TANEC ≥stage 2  Control (n=23): matched control |
| Stritzke  (2011)c 43 | (1) Case–control  *6/10*  (2) Not included | VLBW (<1500 g) infants  N=3708  Nested study N=927 | Cases (n=927): NEC ≥stage 2  Control (n=2781): no NEC  Nested study  Cases (n=144): TANEC ≥stage 2  Control (n=783): NEC not associated with transfusion |
| Wan-Huen (2011)c 44 | (1) Case–control  *6/10*  (2) Not included | Preterm (<32 weeks gestational age) infants with ELBW (<1000 g)  N=49 | Cases (n=17): TANEC ≥stage 2  Control (n=32): NEC not associated with transfusion |
| Valieva (2009)a 45 | (1) Not included  (2) Retrospective cohort  *High risk of bias in 3 out of 8 measures* | NR |  |

ELBW, extremely low birth weight; NR, not reported; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; TANEC, transfusion-associated necrotising enterocolitis; VLBW, very low birth weight

**a.** Study not included. Data not sufficiently reported to compare infants that received a transfusion with those who did not.

**b.** Study does not meet our inclusion criteria. Level III–3.

**c.** Study does not meet our inclusion criteria. Conference abstract.

**d.** Study not included. Total cohort numbers not provided. Sample size <100.

**e.** Study does not meet our inclusion criteria. Published prior to 1995.

##### Results

###### Mortality

Two Level III–2 studies (dos Santos 2011, Navaei 2010) of fair-quality were identified that assessed the association between RBC transfusion and mortality among preterm infants with VLBW[[1]](#footnote-1). A summary of the results from these studies is provided in **Table 3.1.3.**

Dos Santos (2011) was a retrospective cohort study of 1077 preterm infants aged 23 to 37 weeks gestation. The authors reported in-hospital mortality in 197 infants who received RBC transfusion (34.3%) compared with 102 infants who did not receive a transfusion (20.3%). Patients in the transfused group were sicker than those who were not transfused. The data were assessed using a multivariate Cox regression, which adjusted for variables independently associated with higher mortality rates in a univariate analyses. These variables included gestational age, Apgar score, Score for Neonatal Acute Physiology–Perinatal Extension (SNAPPE II), respiratory distress syndrome, IVH, necrotising enterocolitis, and early- or late-onset sepsis. The authors concluded that the relative risk of in-hospital mortality remained significantly increased among infants who received at least one RBC transfusion before the 28th day of life (RR 1.49; 95% CI 1.17, 1.78) compared with those who did not received a transfusion.

The study by dos Santos (2011) also assessed mortality after 28 days of life in the 839 infants who survived beyond the neonatal period. After adjusting for potential confounders, the authors found that the relative risk of death 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 (RR 1.89; 95% CI 1.19, 2.69).

While an association between RBC transfusion and hospital mortality rates was evident, causality has not been established. Several others factors assessed by dos Santos (2011) also remained significantly associated with mortality.

Navaei (2010) reported mortality among 194 preterm infants with VLBW admitted to two NICUs in Iran over a period of 15 months. The study reported that RBC transfusion were required in 43.3% of infants, with no significant difference observed among those who received a transfusion (63.1%) compared with those not transfused (65.5%) (complete data NR).

The study by Boo (1997) assessed risk factors associated with mortality in 868 VLBW infants admitted to NICUs in Malaysia. Subjects were enrolled during a 6 month period between January and June 1993. Using a stepwise logistic regression, the use of blood transfusion was found to be associated with a significant lower risk of mortality (OR 0.4; 95% CI 0.2, 0.7; *P =*0.0021), however due to advances in neonatal care this data was judged to be of historical interest only.

Table 3.1.3 Preterm infants: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III Evidence | | | | | | | | | |
| Dos Santos 201121  Level III–2  *Fair* | Retrospective cohort study  N=1077 | Preterm infants (23.0–36.9 weeks gestation) with VLBW (<1500 g) | 8 centres, Brazil | RBC transfusion before the 28th day of life versus no transfusion | In-hospital mortality | 197/574 (34.3%) | 102/503 (20.3%) | RR 1.46 [1.20, 1.53]c | *Favours no transfusion*  *P <*0.001 |
| Multivariate Cox proportional hazards regression model adjusted for independent variables associated with higher mortality rates, including: gestational age, 1- and 5-minute Apgar scores, SNAPPE II score, RDS, IVH, early- and late-onset clinical sepsis, and NEC. | | RR 1.49 [1.17, 1.78] | *Favours no transfusion*  *P =*0.001 |
| Mortality after 28 days of life  N=839 | NR | NR | RR 4.17 [1.83, 6.91]c | *Favours no transfusion*  *P =*NR |
| Multivariate Cox proportional hazards regression model adjusted for independent variables associated with higher mortality rates, including: gestational age, small for gestational age, 1- and 5-minute Apgar scores, SNAPPE II score, RDS, IVH, early- and late-onset clinical sepsis, and NEC. | | NR | *No significant difference*d  *P =*NR |
| >2 RBC transfusions during hospital stay versus one or two RBC transfusions | In-hospital mortality | NR | NR | RR 0.96 [0.88, 1.03]c | *Favours no transfusion*  *P =*NR |
| Multivariate Cox proportional hazards regression model adjusted for independent variables associated with higher mortality rates, including: gestational age, 1- and 5-minute Apgar scores, SNAPPE II score, RDS, IVH, early- and late-onset clinical sepsis, and NEC. | | NR | *No significant difference*d  *P =*NR |
| Mortality after 28 days of life  N=839 | NR | NR | RR 2.63 [1.91, 3.30]c | *Favours no transfusion*  *P =*0.010 |
| Multivariate Cox proportional hazards regression model adjusted for independent variables associated with higher mortality rates, including gestational age, small for gestational age, 1- and 5-minute Apgar scores, SNAPPE II score, RDS, IVH, early- and late-onset clinical sepsis, and NEC. | | RR 1.89 [1.19, 2.69] |
| Navaei 201028  Level III-2 | Retrospective cohort study  N=194 | Preterm infants (≤30 weeks gestation) with VLBW (≤1500 g) | 2 NICUs, Iran | RBC transfusion vs no transfusion | In-hospital mortality | 63.1% | 65.5% | NR | *No significant difference*  *P >*0.05 |

CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NR, not reported; RBC, red blood cell; RDS, respiratory distress syndrome; RR, risk ratio; SNAPPE, score for neonatal acute physiology perinatal extension; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Univariate analysis entered as single variable in proportional hazards Cox regression.

**d.** Onlyvariables associated with mortality (in-hospital or after 28 days of life) were reported. An absence of reported data was assumed to infer no significant association.

###### Composite of mortality and severe morbidity

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in preterm infants that reported on a composite of mortality and severe morbidity outcomes (e.g. BPD, ROP or brain injury on ultrasound).

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

Bronchopulmonary dysplasia

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in preterm infants that reported on the outcomes of bronchopulmonary dysplasia[[3]](#footnote-3).

Necrotising enterocolitis

The systematic review and hand-searching process identified two systematic reviews of Level III studies (Mohamed 2012, Kirpalani 2012) and five additional Level III studies (AlFaleh 2014, Demirel 2012, Elabaid 2013, Stritzke 2013, Wan-Huen 2013) that provided evidence for the association between RBC transfusion and NEC in preterm infants. **Table 3.1.4** summarises the results from these studies.

The five additional Level III studies (AlFaleh 2014, Demirel 2012, Elabaid 2013, Stritzke 2013, Wan-Huen 2013) were published subsequent to the literature searches conducted by Mohamed (2012) and Kirpalani (2012). The studies by Elabaid (2013), Stritzke (2013) and Wan-Huen (2013) were published reports of the preliminary data identified and included in the meta-analysis of Mohamed (2012).

Mohamed (2012) assessed the association between RBC transfusions and NEC in VLBW infants by comparing those who had transfusion-associated NEC (defined as within 48-hours of transfusion) with those who had NEC not associated with transfusion. Five trials (Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Wan-Huen 2011) involving 916 infants were identified that reported unadjusted estimates for the association between NEC and exposure to transfusion in the previous 48 hours. A meta-analysis of these five trials suggested a significant association between RBC transfusion and NEC (OR 3.91; 95% CI 2.97, 5.14) but there was substantial heterogeneity (I2=58%) for this outcome. Four of the identified studies (Harsono 2011, Paul 2011, Stritzke 2011, Wan-Huen 2011) reported estimates adjusted for potential confounders. A meta-analysis of these four studies, which involved 3863 infants, found a similar (albeit lower) association between NEC and exposure to RBC transfusions (OR 2.01; 95% CI 1.61, 2.50). Heterogeneity was substantial (I2=91%).

To explore the statistical heterogeneity, Mohamed (2012) removed Harsono (2011) from the analysis because the study reported conflicting results in favour of RBC transfusions. Removal of this outlier improved the homogeneity of the studies, but no further explanation for the divergent results was discerned. Analysis using a random-effects model indicated that the association between RBC transfusion and NEC was not statistically significant (OR 1.51; 95% CI 0.62, 3.68).

Kirpalani (2012) performed a meta-analysis of six cohort studies involving 22,155 infants and compared the incidence of NEC among those that received a transfusion with those that developed NEC but had not received a transfusion. The study reported a significant association between RBC transfusion and NEC (OR 7.48; 95% CI 5.87, 9.53). Heterogeneity was substantial (I2= 98%). These data included two studies in which the total cohort numbers were unknown (i.e. NEC events were reported but the total number of patients in each treatment arm was not, leading to an overestimation of the incidence of NEC). Removal of these two studies from the meta-analysis revealed that the association between RBC transfusion and NEC was not significant when analysed using a random-effects model (RR 4.55; 95% CI 0.78, 26.45; *P =*0.09). The association remained significant when assessed using a fixed-effects model (RR 6.80; 95% CI 5.51, 8.41; *P <*0.00001). Heterogeneity was substantial (I2= 97%).

Kirpalani (2012) also reported a meta-analysis of four case–control studies involving 567 infants that revealed similar results. That is, a significant association between RBC transfusions and NEC was reported using a fixed-effects model (OR 2.19; 95% CI 1.52, 3.17; *P <*0.001), but the association was not significant when assessed using a random-effects model (RR 1.66; 95% CI 0.75, 3.64; *P =*0.21). Heterogeneity was substantial (I2=94%). Again, outcome data were incomplete for one of the case–control studies.

Cohort studies

The study by Demirel (2012) reported no significant between-group differences in the incidence of NEC when comparing infants who received a RBC transfusion with those who did not (RR 1.09; 95% CI 0.75, 1.58). The authors explored clinical characteristics of those who developed NEC and found no statistically significant difference between groups for a variety of measures, including gestational age, delivery route, Apgar scores, ROP and type of nutrition.

Elabaid (2013) evaluated development of NEC within 48 hours of exposure to RBC transfusion among 3060 infants with VLBW (≤1500 g); this publication was assumed to be an updated report encompassing infants included in the study by Harsono (2011). There was no significant difference between groups for the incidence of NEC in a univariate analysis (RR 1.32; 95% CI 0.97, 1.80). When assessed according to birth weight or severity of illness, exposure to RBC transfusions was protective in infants with ELBW (≤1000 g), those who stayed longer on a ventilator, and those who required a longer umbilical arterial catheter insertion period. These data were adjusted for gender, race and small for gestational age. Elabaid (2013) also examined the association between RBC transfusion and the development of NEC after the 28th day of life, and again reported that exposure to RBC transfusions was protective in infants with ELBW (≤1000 g). There was no statistically significant association between late-onset NEC and RBC transfusions in infants weighing 1001 to >1250g and the data were not estimable for infants weighing between 1250 and ≤1500 g. This was a multivariate analysis that adjusted for gender, race and small for gestational age.

The meta-analysis of cohort studies conducted by Kirpalani (2012) was updated with the unadjusted data reported by Demirel (2012) and Elabaid (2013) (see **Figure 3.1.1**). Studies that did not meet our inclusion criteria (total N<100, incomplete data) were not included in the analysis. The pooled data showed that an increased risk of development of NEC within 48 hours of exposure to RBC transfusion is not statistically significant (RR 1.55; 95% CI 0.94, 2.54).

Case–control studies

AlFaleh (2014) investigated the association between RBC transfusion and the development of NEC in VLBW preterm infants, and reported that infants (<32 weeks gestational age) who had received RBC transfusion were significantly less likely to develop NEC within 48 hours of exposure (OR 0.39; 95% CI 0.18, 0.84).

The case–control study by Stritzke (2013) evaluated the association between RBC transfusions and the development of NEC within 48 hours of exposure in 3708 preterm infants admitted to NICUs in the Canadian Neonatal Network. After adjusting for birth weight, outborn status, 5-minute Apgar score, SNAP II score and prenatal steroid use, Stritzke (2013) reported that RBC transfusions in the previous 2 days remained significantly associated with the development of NEC (OR 2.44; 95% CI 1.87, 3.18).

The case–control study by Wan-Huen (2013) assessed the association between RBC transfusion and the development of NEC in 146 preterm infants admitted to the NICU. Each 48-hour period during weeks 1–9 of an infant’s life was assessed, corresponding to 29 epochs for each infant and a total of 3652 epochs. After adjusting for gestational age, enteral feeding status by prior epoch, within-subject chronological age and indicators of disease severity, Wan-Huen (2013) confirmed the association between RBC transfusion and NEC (OR 2.97; 95% CI 1.46, 6.05).

The meta-analysis of case–control studies conducted by Kirpalani (2012) was updated with the unadjusted data reported by AlFaleh (2104), Stritzke (2013) and Wan-Huen (2013) (see **Figure 3.1.2**). Studies that did not meet our inclusion criteria (total N<100, incomplete data) were not included in the analysis. The pooled data showed that an increased risk of development of NEC within 48 hours of exposure to RBC transfusion was not statistically significant (RR 1.43; 95% CI 0.88, 2.34).

Table 3.1.4 Preterm infants: Results for RBC transfusion versus no transfusion (or alternate dose) – Severe morbidity (NEC)

| Study  Level of evidencea  *Quality* | No. of trials /  sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  N/N (%) | No transfusion  N/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | |
| Mohamed 201216  Level I/III  *Good* | 5 trials (Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Wan-Huen 2011)33-34; 40; 42  N=916 | Preterm infants | NR | RBC transfusion versus no transfusion | NEC  \*studies that did not adjust for confounders | NR | NR | OR 3.91 [2.97, 5.14] | *Favours no transfusion*  *P <*0.00001  I2 = 58% |
| 4 trials (Harsono 2011, Paul 2011, Stritzke 2011, Wan-Huen 2011)35; 40; 43-44  N=3863 | NEC  \*studies that adjusted for potential confounders | NR | NR | OR 2.01 [1.61, 2.50] | *Favours no transfusion*  *P <*0.0001c  I2 = 91% |
| 3 trials (Paul 2011, Stritzke 2011, Wan-Huen 2011)40; 43-44  N=NR | To explore the statistical heterogeneity, Mohamed (2012) removed Harsono (2011) from the analysis as the study reported conflicting results in favour of RBC transfusions. | | OR 2.48 [1.97, 3.12] | *Favours no transfusion*  *P =*NR  I2 = 0% |
| Kirpalani 201217  Level I/III  *Poor* | 6 cohort studies (Blau 2011, Christensen 2009, Holder 2009, Mally 2006, Paul 2011, Valieva 2009)32-33; 36; 38; 40; 45  N=22,155 | Neonates | NR | RBC transfusion versus no transfusion | NEC | 150/2940 (5.1%) | 182/19215 (9.47%) | OR 7.48 [5.87, 9.53] | *Favours no transfusion*  *P <*0.00001  I2 = 98% |
| 4 cohort studies (Christensen 2009, Holder 2009, Paul 2011, Valieva 2009)33; 36; 40; 45  N=22,155 | 135/2940 (4.6%) | 144/19215 (0.7%) | RR 4.55 [0.78, 26.45]d | *No significant difference*  *P =*0.09e  I2=97% |
| 4 case–control studies (El-Dib 2011, Josephson 2010, McGrady 1987, Singh 2011)34; 37; 39; 42  N=567 | 129/186 (69.4%) | 129/381 (33.9%) | OR 2.19 [1.52, 3.17] | *Favours no transfusion*  *P <*0.0001  I2 = 92% |
| 3 case–control studies (El-Dib 2011, Josephson 2010, Singh 2011)34; 37; 42  N=567 | 105/186 (56.5%)d | 124/381 (32.5%)d | RR 1.66 [0.75, 3.64]d | *No significant difference*  *P =*0.21f  I2= 94% |
| *Additional Level III–2 cohort studies* | | | | | | | | | |
| AlFaleh 201418  Level III–2  *Fair* | Retrospective case–control  N=152 | Preterm infants (≤32 weeks gestation) with VLBW (<1500 g) | Single NICU, Saudi Arabia | RBC transfusion versus no transfusion | NEC (stage 2–3) within 48 hours of exposure | 23/110 (20.9) | 17/42 (40.5) | OR 0.39 [0.18, 0.84] | *Favours RBC transfusion*  *P =*0.02 |
| Demirel 201220  Level III–2  *Fair* | Retrospective cohort study  N=647 | Preterm infants with VLBW (<1500 g) | Single NICU, Turkey | RBC transfusion versus no transfusion | NEC | 46/296 (15.5%) | 50/351 (14.2%) | RR 1.09 [0.75, 1.58]d | *No significant difference*  *P =*0.64d |
| NEC <48 hours of RBC transfusion versus NEC no exposure | 15/265 (5.7%) | 50/351 (14.2%) | RR 0.40 [0.23, 0.69]d | *Favours RBC transfusion*  *P =*0.001 |
| NEC >48 hours of RBC transfusion versus NEC no exposure | 31/281 (11.0%) | 50/351 (14.2%) | RR 0.77 [0.51, 1.18]d | *No significant difference*  *P =*0.23 |
| NEC <48 hours of RBC transfusion versus NEC no exposure and >48 hours of exposure | 15/265 (5.7%) | 81/632 (12.82%) | RR 0.44 [0.26, 0.75] | *Favours RBC transfusion*  *P =*0.003 |
| Elabaid 201322  Level III–2  *Fair* | Retrospective cohort study  N=3060 | Preterm infants with VLBW (≤1500 g) or ELBW (≤1000 g) | Single NICU, USA | RBC transfusion versus no transfusion | NEC within 48 hours of exposure | 116/1842 (6.3%) | 58/1218 (4.8%) | RR 1.32 [0.97, 1.80]d | *No significant difference*  *P =*0.07 |
| Subgroup analysis: birth weight g  Multivariate analysis adjusted for gender, race and small for gestational age | | |  |
| ELBW (≤750 g)  N=662 | 39/619 | 13/43 | RR 0.14 [0.07, 0.30] | *Favours RBC transfusion*  *P <*0.01 |
| ELBW (751–1000 g)  N=747 | 37/633 | 14/114 | RR 0.46 [0.24, 0.89] | *Favours RBC transfusion*  *P =*0.021 |
| VLBW (1001–1250 g)  N=810 | 31/413 | 15/397 | RR 1.83 [0.95, 3.5] | *No significant difference*  *P =*0.071 |
| VLBW (>1250, ≤1500 g)  N=828 | 9/170 | 16/658 | RR 1.78 [0.77, 4.19] | *No significant difference*  *P =*0.17 |
|  | Subgroup analysis: number of ventilator days g  Multivariate analysis adjusted for gender, race and small for gestational age | | |  |
| 0  N=839 | 3/NR | 5/NR | RR 3.5 [0.82, 15.15] | *No significant difference*  *P =*0.09 |
| 1–2  N=797 | 17/NR | 14/NR | RR 1.04 [0.50,2.14] | *No significant difference*  *P =*0.92 |
| 3–13  N=650 | 49/NR | 23/NR | RR 0.29 [0.7, 0.51] | *Favours RBC transfusion*  *P <*0.01 |
| >13  N=761 | 47/NR | 16/NR | RR 0.11 [0.06, 0.23] | *Favours RBC transfusion*  *P <*0.01 |
|  | Subgroup analysis: UAC insertion day periods g  Multivariate analysis adjusted for gender, race and small for gestational age | | |  |
| 0  N=1352 | 28/NR | 24/NR | RR 2.11 [1.2, 3.69] | *Favours no transfusion*  *P <*0.01 |
| 1–2  N=184 | 8/NR | 4/NR | RR 1.44 [0.41, 5.12] | *No significant difference*  *P =*0.31 |
| 3–7  N=707 | 37/NR | 16/NR | RR 0.81 [0.44, 1.49] | *No significant difference*  *P =*0.49 |
| >7  N=804 | 43/NR | 14/NR | RR 0.2 [0.1, 0.39] | *Favours RBC transfusion*  *P <*0.01 |
| Late-onset NEC after day 28 | Subgroup analysis: birth weight g  multivariate analyses adjusted for gender, race and small for gestational age | | |  |
| ELBW (≤750 g)  N=629 | 10/NR | 9/NR | RR 0.057 [0.021, 0.15] | *Favours RBC transfusion*  *P <*0.01 |
| ELBW (751–1000 g)  N=711 | 8/NR | 7/NR | RR 0.17 [0.058, 0.49] | *Favours RBC transfusion*  *P <*0.01 |
| VLBW (1001–1250 g)  N=771 | 6/NR | 1/NR | RR 4.32 [0.49, 37] | *No significant difference*  *P =*0.19 |
| VLBW (>1250, ≤1500 g)  N=810 | 0/NR | 1/NR | Not estimable | NA |
| Stritzke 201329  Level III–2  *Fair* | Retrospective case–control study  N=3708 | Preterm infants admitted to NICU | 26 NICUs, Canada | RBC transfusion versus no transfusion | NEC (stage 2 or 3) within 48 hours of exposure | 144/357 (40.3%) | 783/3351 (23.4%) | RR 1.73 [1.50, 1.99]d | *Favours no transfusion*  *P <*0.00001d |
| Multiple logistic regression adjusted for birth weight, outborn status, 5-minute Apgar score, SNAP II score, and prenatal steroid use. | | OR 2.44 [1.87, 3.18] | *Favours no transfusion*  *P <*0.01 |
| Wan-Huen 201330  Level III–2  *Fair* | Retrospective case–control study (N=3,652) | Preterm infants admitted to NICU | Single NICU, USA | RBC transfusion versus no transfusion | NEC (stage 2 or 3) within 48 hours of exposure | 17/557 (3.1%) | 32/3095 (1.0%) | OR 3.01 [1.67, 5.47] | *Favours no transfusion*  *P <*0.001 |
| Data adjusted for “missing epochs” (infants who died, were transferred or discharged before study end). | | OR 2.70 [1.51, 4.85] | *Favours no transfusion*  *P <*0.001 |
| Multivariate logistic regression adjusted for gestational age, enteral feeding status by prior epoch, within-subject chronological age, and indicators of disease severity (symptomatic PDA, sepsis, urinary tract infection or phlebitis, pressor use, mechanical ventilation, exposure to inspired oxygen >40%). | | OR 2.97 [1.46, 6.05] | *Favours no transfusion*  *P <*0.003 |
| *Included in meta-analysis reported by Kirpalani (2012)* | | | | | | | | | |
| Paul 201140  Level III–2  *Poor* | Retrospective cohort study  N=2311 | Preterm infants with VLBW (<1500 g) | Single NICU, USA | RBC transfusion versus no transfusion  \*RBC transfusions after NEC diagnosis were excluded | NEC | 92/1148 (8.0%) | 30/1162 (2.6%) | OR 2.9 [1.9–4.4]  RR 3.10 [2.07, 4.65]d | *Favours no transfusion*  *P =*NR  *P <*0.00001d |
| Multivariable model adjusted for gestational age, gender, antenatal steroids, maternal preeclampsia, antenatal magnesium sulphate, antenatal indomethacin, and SNAP. | | OR 2.3 [1.2, 4.2] | *Favours no transfusion*  *P =*NR |
| Multivariable model adjusted for gestational age, gender, antenatal steroids, maternal preeclampsia, antenatal magnesium sulphate, antenatal indomethacin, SNAP, ventilator days, surfactant, postnatal steroids, PDA, and sepsis. | | OR 2.1 [1.1, 4.3] | *Favours no transfusion*  *P =*NR |
|  | *Subgroup analysis: timing of RBC transfusion* | | |  |
| NEC within 48 hours of exposure | 33/1089 (3.0%) | 30/1162 (2.58%) | RR 1.17 [0.72, 1.91]d | *No significant difference*  *P =*0.52d |
| NEC >48 hours of exposure | 59/1115 (5.3%) | 30/1162 (2.58%) | RR 2.05 [1.33, 3.16]d | *Favours no transfusion*  *P =*0.001 |
| NEC <48 hours of exposure versus NEC >48 hours of exposure or not exposed | 33/1089 (3.0%) | 89/1221 (7.3%) | RR 0.42 [0.28, 0.61]d | *Favours RBC transfusion*  *P <*0.0001d |
| Singh 201142  Level III–2  *Fair* | Retrospective case–control study  N=333 | Preterm infants (≤32 weeks gestational age) | Two NICUs, USA | RBC transfusion versus no transfusion | NEC ≥stage 2a within 24 hours of exposure | 36/51 (70.6%) | 75/282 (26.6%) | RR 2.65 [2.04, 3.45]d | *Favours no transfusion*  *P <*0.00001d |
| Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 7.60 [2.19, 26.42] | *Favours no transfusion*  *P =*0.001 |
|  | Subgroup analysis: age at onset of NEC | | |  |
| Early NEC (within 21 days of life) | Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 15.49 [2.20, 109.08] | *Favours no transfusion*  *P =*0.006 |
| Late NEC (after 21 days of life) | OR 2.05 [0.20, 21.29] | *No significant difference*  *P = 0.55* |
| NEC ≥stage 2a within 48 hours of exposure | 44/67 (65.7%) | 67/266 (25.2%) | RR 2.61 [1.99, 3.42]d | *Favours no transfusion*  *P <*0.00001d |
| Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 5.55 [1.98, 15.59] | *Favours no transfusion*  *P =*0.001 |
|  | Subgroup analysis: age at onset of NEC | | |  |
| Early NEC (within 21 days of life) | Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 10.22 [1.83, 57.15] | *Favours no transfusion*  *P =*0.008 |
| Late NEC (after 21 days of life) | OR 6.39 [1.00, 40.83] | *Favours no transfusion*  *P =*0.05 |
| NEC ≥stage 2a within 96 hours of exposure | 49/95 (51.6%) | 62/238 (26.1%) | RR 1.98 [1.48, 2.64]d | *Favours no transfusion*  *P <*0.00001d |
| Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 2.13 [0.95, 4.80] | *No significant difference*  *P =*0.07 |
|  | Subgroup analysis: age at onset of NEC | | |  |
| Early NEC (within 21 days of life) | Multivariate logistic regression adjusted for propensity score, PROM, AEDF, hypotension, breast milk feeding, additives, iron supplementation, PDA, central line and antacid. | | OR 3.03 [0.94, 9.80] | *No significant difference*  *P =*0.06 |
| Late NEC (after 21 days of life) | OR 1.11 [0.24, 5.11] | *No significant difference*  *P =*0.89 |

AEDF, abnormal end-diastolic placental flow; CI, confidence interval; ELBW, extremely low birth weight; NA, not applicable; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; PROM, prolonged rupture of membrane; RBC, red blood cell; RR, risk ratio; SNAP, score for neonatal acute physiology; UAC, umbilical arterial catheter; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.**The result was not significant when assessed using a random-effects model (OR 1.51; 95% CI 0.62, 3.68, *P =*0.36).

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** The result was significant when assessed using a fixed-effects model (RR 6.80; 95% CI 5.51, 8.41; *P <*0.00001).

**f.** The result was significant when assessed using a fixed-effects model (RR 1.53; 95 CI 1.28, 1.83; *P <*0.00001).

**g.** Data were missing for 20 patients due to incomplete data.

Figure 3.1.1 Pooled data from cohort studies assessing the association between RBC transfusions and NEC in preterm and/or low birth weight infants



Figure 3.1.2 Pooled data from case–control studies assessing the association between RBC transfusions and NEC in preterm and/or low birth weight infants



Retinopathy of prematurity

The systematic review and hand-searching process identified six Level III studies (Feghhi 2012, Fortes Filho 2013, Hakeem 2012, Kabatas 2013, Li 2013, Weintraub 2011) that examined the association between RBC transfusion and ROP in preterm infants[[4]](#footnote-4). The results of these studies are summarised in **Table 3.1.5**.

Feghhi (2012) reported 183 incidences of ROP (all stages) among 576 preterm (<32 weeks gestation) or LBW (<2000 g) infants. A univariate analysis suggested a significant association between RBC transfusion and the development of ROP (RR 2.32; 95% CI 1.80, 2.99). However, after adjusting for gestational age, birth weight, gender, single/twin birth, glaucoma, cataract, strabismus, sepsis, duration of oxygen therapy, jaundice and phototherapy in a multiple logistic regression, Feghhi (2012) reported that the association between ROP and RBC transfusion was no longer significant (OR 0.43; 95% CI 0.89, 1.61).

Fortes Filho (2013) examined the incidence and risk factors associated with the development of severe ROP (≥stage 3) among ELBW (<1000 g) and reported 19 cases of severe ROP among 124 (15.3%) infants who received a RBC transfusion, compared with one (3.0%) case of severe ROP among those who did not receive a transfusion. This difference was not statistically significant (RR 5.06; 95% CI 0.70, 36.40), and remained nonsignificant when assessed in a multivariate logistic regression (data not reported). The authors noted that 15 of the 20 infants with severe ROP were administered rHuEPO to minimise the need for RBC transfusions, and that NICU practices changed significantly over the 10 years of patient enrolment.

Hakeem (2012) reported a significant association between ROP and frequency of RBC transfusions among 172 preterm infants (<32 weeks gestational age or 32–34 weeks gestation with a course of instability) when assessed in a univariate analysis (*P =*0.03); and found that the association remained significant when analysed in a multivariate logistic regression that adjusted for gestational age, sepsis and oxygen therapy (OR 2.48; 95% CI 1.82, 5.22). It is not clear whether the univariate and multivariate analyses are referring to infants who developed ROP and received one RBC transfusion (3 out of 25 infants) or those who received more than one RBC transfusion (9 out of 23 infants) when compared with those who developed ROP but were not transfused (21 out of 124 infants) (RR 0.71; 95% CI 0.23, 2.20 and RR 2.31; 95% CI 1.22, 4.39, respectively).

Kabatas (2013) examined the risk factors that affect the progression of ROP, and reported 49 incidences of ROP among preterm infants who received a RBC transfusion (56.3%) compared with four incidences of ROP among the 26 infants who were not transfused (15.4%). ROP requiring laser photocoagulation occurred in 18 infants. The number of transfusions and the need for transfusion in the first 10 days of life were significantly associated with the development of ROP (RR 3.66; 95% CI 1.46, 9.19 and RR 2.16; 95% CI 1.52, 3.09, respectively) but not ROP requiring laser photocoagulation. The need for transfusion in the first 10 days of life remained significantly associated with the development of ROP when adjusted for gestational age, respiratory distress syndrome, patent ductus arteriosis, sepsis, use of caffeine, duration of total parenteral nutrition and oxygen exposure (OR 1.9; 95% CI 1.1, 3.3).

The study by Li (2013) identified RBC transfusions as a risk factor for the development of ROP. Some 110 preterm (<32 weeks gestation) or VLBW infants who received a RBC transfusion (48.2%) developed ROP, compared with 80 incidences of ROP among those who did not receive a transfusion (29.1%) (RR 1.66; 95% CI 1.32, 2.08). When the data were adjusted for potential confounders, including respiratory distress syndrome, chronic lung disease, patent ductus arteriosis, surfactant use, indomethacin use, sepsis, upper gastrointestinal bleeding and NEC, the association between ROP and transfusion was no longer observed.

The study by Weintraub (2011) identified 55 incidences of severe ROP (≥stage 3) among consecutive preterm infants that were matched 1:2 to a control group of consecutive preterm infants without ROP. A statistically significant association between RBC transfusions and ROP (≥stage 3) was reported (RR 12.00; 95% CI 1.73, 83.34). This result remained statistically significant in a multiple logistic regression model that adjusted for potential confounders, including gestational age, gender and sepsis (OR 14.16; 95% CI 1.57, 127.7).

Table 3.1.5 Preterm infants: Results for RBC transfusion versus no transfusion (or alternate dose) – Severe morbidity (ROP)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | |
| Feghhi 201223  Level III–2  *Fair* | Cross-sectional case–control study  N=576 | Preterm infants (≤32 weeks gestation) or infants with LBW (<2000 g) | Multiple NICUs, Iran | RBC transfusion versus no transfusion | ROP (all stages) | 27/40 (67.5%) | 156/536 (29.1%) | RR 2.32 [1.80, 2.99]c | *Favours no transfusion*  *P <*0.00001c |
| Multiple logistic regression analysis adjusted for gestational age, birth weight, gender, single/twin birth, glaucoma, cataract, strabismus, sepsis, duration of oxygen therapy, jaundice, and phototherapy. | | OR 0.43 [0.89, 1.61] | *No significant difference*  *P =*NR |
| Fortes Filho 201324  Level III–2  *Fair* | Prospective cohort study  N=157 | Preterm infants with ELBW (<1000 g) | Single NICU, Brazil | RBC transfusion versus no transfusion | ROP (≥stage 3) in either eye | 19/124 (15.3%) | 1/33 (3.0%) | RR 5.06 [0.70, 36.40]c | *No significant difference*  *P =*0.11c |
| Hakeem 201225  Level III–2  *Fair* | Prospective cohort study  N=172 | Preterm infants (≤32 weeks gestation) with VLBW (<1500 g), preterm infants (32–34 weeks gestation with a course of instability), and infants exposed to oxygen therapy for >7 days | Single NICU, Egypt | One or more RBC transfusion versus no transfusion | ROP (stages 1–3) | 12/48 (25%) | 21/124 (16.9%) | RR 1.48 [0.79, 2.76]c | *No significant difference*  *P =*0.22c |
|  | *Subgroup analysis: number of RBC transfusions* | | |  |
| One RBC transfusion versus no transfusion | 3/25 (12%) | 21/124 (16.9%) | RR 0.71 [0.23, 2.20]c | *No significant difference*  *P =*0.55c |
| More than one RBC transfusion versus no transfusion | 9/23 (39.1%) | 21/124 (16.9%) | RR 2.31 [1.22, 4.39]c | *Favours no transfusion*  *P =*0.01 |
| Logistic regression adjusted for gestational age, sepsis and oxygen therapyd | | OR 2.483 [1.182, 5.222] | *Favours no transfusion*  *P =*0.016 |
| Kabatas 201326  Level III–2  *Poor* | Prospective case–control study  N=113 | Preterm infants (<32 weeks gestation) with VLBW (<1500 g), or preterm infants (32–37 weeks gestation) with anaemia, apnoea, RDS, PDA, ICH, NEC, CLD, perinatal asphyxia or sepsis requiring prolonged mechanical ventilation | Single NICU, Turkey | RBC transfusion versus no transfusion | ROP (all stages) | 49/87 (56.3%) | 4/26 (15.4%) | RR 3.66 [1.46, 9.19]c | *Favours no transfusion*  *P =*0.006c |
| ROP requiring laser photocoagulation | 18/87 (20.7%) | 4/26 (15.4%) | RR 1.34 [0.50, 3.62]c | *No significant difference*  *P =*0.56c |
| RBC transfusion in first 10 days of life versus no transfusion in first 10 days of life | ROP (all stages) | 25/33 (75.8%) | 28/80 (35.0%) | RR 2.16 [1.52, 3.09]c | *Favours no transfusion*  *P <*0.0001c |
| Multivariate logistic regression analysis adjusted for gestational age, RDS, PDA, sepsis, use of caffeine, duration of TPN, and total oxygen exposure. | | OR 1.9 [1.1, 3.3] | *Favours no transfusion*  *P =*0.01 |
| ROP requiring laser photocoagulation | 6/33 (18.2%) | 28/80 (35.0%) | RR 1.18 [0.37, 3.76]c | *No significant difference*  *P =*0.78c |
| Li 201327  Level III–2  *Fair* | Retrospective cohort study  N=503 | Preterm infants (<32 weeks gestation) and/or infants with VLBW (<1500 g) | Single hospital, Taiwan | RBC transfusion versus no transfusion | ROP (all stages) | 110/228 (48.2%) | 80/275 (29.1%) | RR 1.66 [1.32, 2.08] c | *Favours no transfusion*  *P <*0.0001 c |
| Stepwise multivariable logistic regression adjusted for RDS, chronic lung disease, PDA, surfactant use, indomethacin use, sepsis, upper GI bleeding and NEC. | | NR | *No significant difference*  *P >*0.05 |
| Weintraub 201131  Level III–2  *Poor* | Retrospective case–control  N=165 | Preterm infants (<32 weeks gestation) with VLBW (<1500 g) | NR | Blood transfusion versus no transfusion | ROP (≥stage 3) | 54/135 (40.0%) | 1/30 (3.3%) | RR 12.00 [1.73, 83.34]c | *Favours no transfusion*  *P =*0.01c |
| Logistic regression adjusted for gestational age, gender and sepsis.e | | OR 14.159 [1.570, 127.7] | *Favours no transfusion*  *P =*0.018 |

CI, confidence interval; CLD, chronic lung disease; ELBW, extremely low birth weight; GI, gastrointestinal; ICH, intracranial haemorrhage; LBW, low birth weight; NEC, necrotising enterocolitis; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RBC, red blood cell; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; RR, risk ratio; TPN, total parenteral nutrition; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Hakeem 2012 compared data for (1) One RBC transfusion to (2) >1 RBC transfusion to (3) no transfusion. It is not clear from the study whether the adjusted data refers to group 1, group 2 or both.

**e.** Not clear if other potential confounders were included in the model.

Brain injury on ultrasound

The systematic review and hand-searching process identified one Level III study (Baer 2011) that examined the association between RBC transfusion and severe IVH in preterm infants. The results of these studies are summarised in **Table 3.1.6**.

The study by Baer (2011) included 54 neonates who developed severe (grade 3–4) IVH (evidenced by a normal head ultrasound prior to the development of IVH) matched with 101 controls who did have IVH. All control infants had one or more head ultrasounds showing no haemorrhage during the first week of life and at approximately 1 month. 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 at 1 month. This effect remained statistically significant in a stepwise logistic regression analysis that adjusted for FFP and platelet use within the first 48 hours of life, vasopressor use in the first 72 hours of life, number of days on ampicillin, and nucleated RBC count (RR 2.02; 95% CI 1.54, 3.33).

Baer (2011) reported the results of a sensitivity analysis and stated that there remained “*a high likelihood that RBC transfusion, independent of Hb level or other factors, increases the risk of developing a severe IVH”*.

Table 3.1.6 Preterm infants: Results for RBC transfusion versus no transfusion (or alternate dose) – Severe morbidity (brain injury on ultrasound)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | |
| Baer 201119  Level III–2  *Fair* | Retrospective case–control  N=155 | VLBW (<1500 g) neonates admitted to NICU | Three large perinatal centres, USA | | One or more RBC transfusions versus no transfusion | Severe IVH (grade 3 or 4) at one month | 52/118 (44.1%) | 2/37 (5.4%) | RR 8.15 [2.09, 31.86]c | *Favours no transfusion*  *P =*0.003c |
| Multiple logistic regression adjusted for potential risk factors, including FFP and platelet use within the first 48 hours of life, vasopressor use in the first 72 hours, number of days on ampicillin, and nucleated RBC count. | | RR 2.02 [1.54, 3.33] | *Favours no transfusion*  *P =*NR |

CI, confidence interval; FFP, fresh frozen plasma; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; RBC, red blood cell; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Neurodevelopmental disability

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in preterm infants and reported on neurodevelopmental disability.

Transfusion-related serious adverse events

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in preterm infants and reported on transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified four Level I studies (Ibrahim 2014, Venkatesh 2012, Whyte 2011, Bassler 2008) that examined the effect of a restrictive RBC transfusion protocol compared with a liberal RBC transfusion protocol in preterm or VLBW infants (see **Appendix C, Volume 2**). The main characteristics of these reviews are summarised in **Table 3.1.7**.

The good-quality reviews by Ibrahim (2014), Venkatesh (2012), Whyte (2011) and Bassler (2008) examined the effects of different transfusion thresholds on clinically important outcomes in VLBW (<1500 g) infants, and each reported slightly different data for various outcomes. Venkatesh (2012) also included studies that enrolled term or preterm neonates of <28 days postnatal corrected age; and Bassler (2008) included studies that enrolled preterm (<37 weeks gestational age) or LBW (<2500 g) infants.

All four systematic reviews (Ibrahim 2014, Venkatesh 2012, Whyte 2011, Bassler 2008) included data from three RCTs (Bell 2005, Chen 2009, Kirpalani 2006) involving 590 VLBW infants in their analyses that met our inclusion criteria. Both Venkatesh (2012) and Whyte (2011) also provided additional data for neurodevelopmental outcomes that were reported in the long-term follow-up reports by McCoy (2011)[[5]](#footnote-5) or Whyte (2009)[[6]](#footnote-6).

Three RCTs (Brooks 1999, Connelly 1998, Ransome 1989) were excluded by Ibrahim (2014) because they did not meet their inclusion criteria – Brooks (1999) had enrolled infants on day 29 of life, Connelly (1998) was published in abstract form only, and Ransome (1989) had enrolled preterm infants (<34 weeks gestational age) that were clinically well (average 39 days old at enrolment) but was not limited by birth weight. The RCTs by Brooks (1999) and Ransome (1989)[[7]](#footnote-7) were included in the reviews by Venkatesh (2012) and Bassler (2008), and unpublished data from the study by Connelly (1998) was included in the analysis by Whyte (2011).

The review by Venkatesh (2012) included one additional RCT (Mukhopadhyay 2004) that was published in abstract form only, and two other RCTs (Meyer 1993, Ross 1989) reported by Bassler (2008) did not report outcomes of interest for our review.

The review by Whyte (2011) also included one additional RCT (Blank 1984) that examined a restrictive transfusion strategy that involved transfusion based on clinical signs of anaemia compared with transfusions given at a Hb threshold of 100 g/L (regardless of clinical signs). Because the criteria for transfusion in this RCT were different to other studies, data from this study were reported separately.

Table 3.1.7 Characteristics and quality of Level I evidence - restrictive RBC transfusion versus liberal RBC transfusion

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Ibrahim (2014)46 | Systematic review  *Good* | Infants with VLBW (<1500 g)  3 RCTs, N=590 | Restrictive RBC transfusion (n=292) versus liberal RBC transfusion (n=298) | Mortality  Severe morbidity (brain injury, BPD, NEC, ROP ≥stage 3) |
| Venkatesh (2012)47 | Systematic review  *Good* | Neonates (term or preterm) <28 days corrected postnatal age  6 RCTs, N=694 | Restrictive RBC transfusion (n=343) versus liberal RBC transfusion (n=351) | Mortality  Severe morbidity (chronic lung disease)  Neurodevelopmental disability |
| Whyte (2011)48 | Systematic review  *Good* | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestational age) admitted to NICU at less than one week of age  5 RCTs, N=670 | Restrictive RBC transfusion (n=335) versus liberal RBC transfusion (n=335) | Mortality  Composite of mortality and severe morbidity  Severe morbidity (brain injury, BPD, NEC, ROP)  Neurodevelopmental disability |
| Bassler (2008)49 | Systematic review  *Good* | Preterm (<37 weeks gestational age) or LBW (<2500 g) infants  7 RCTs, N=712 | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality  Composite of mortality and severe morbidity,  Severe morbidity (brain injury, PVL, IVH, BPD, NEC, ROP) |

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; LBW, low birth weight; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; VLBW, very low birth weight

The main characteristics of the seven Level II studies (Bell 2005, Blank 1984, Brooks 1999, Chen 2009, Connelly 1998, Kirpalani 2006, Mukhopadhyay 2004) and the two long-term follow-up studies (McCoy 2011, Whyte 2009) identified in the included Level I studies are presented in **Table 3.1.8**.

Data from these included RCTs was sought if additional information about the study was deemed necessary (e.g. study design). It was noted that the RCTs described by Connelly (1998) and Mukhopadhyay (2004) were published in abstract form only; therefore the data from these should be interpreted with caution. Further, the study by McCoy (2011) was not considered when developing evidence statements because of poor follow-up rates. This was deemed to contribute a clear high risk of bias and therefore was not suitable for inclusion.

Bell (2005) was a fair-quality RCT that enrolled 103 preterm infants with VLBW (500–1300 g) admitted to a single hospital in the USA. Restrictive and liberal transfusion thresholds varied according to the infant’s respiratory status. Infants enrolled in this RCT were contacted 8–15 years later, as described by McCoy (2011), to assess neurodevelopmental outcomes including cognitive, language, visual spatial/motor and memory measures. Fifty-six of the original participants were available for the long-term follow-up study.

The RCT by Blank (1984) was a single centre study conducted in the USA involving 56 infants who weighed <1500 g at birth. The restrictive transfusion protocol required clinical signs of anaemia prior to transfusion that included tachycardia (>170 beats per minute) for 4 days, no weight gain for 7 days, or clinical notable apnoea. Infants in the liberal transfusion group received RBCs when Hb levels fell below 100 g/L. The study was published before 1985 and it is likely that clinical practice has significantly changed since that time.

Brooks (1999) was a poor-quality RCT involving 50 infants with VLBW (≤1250 g) admitted to a single NICU in the USA, which aimed to compare the effect of restrictive and liberal RBC transfusion strategies on ROP and other severe morbidities. Transfusions guidelines were applied during days 29–71 of life, with the goal being to maintain haematocrit between 20 and 30% in the restrictive group and ≥40% in the liberal group. There was significant attrition bias, with more than 30% of enrolled patients lost to follow-up, and the methods for randomisation and allocation concealment were not reported.

Chen (2009) was a poor-quality RCT that assessed 36 preterm infants with VLBW (<1500 g) admitted to a single NICU in Taiwan. The study aimed to compare the effect of restrictive and liberal RBC transfusion strategies on mortality and severe morbidities. Restrictive and liberal transfusion thresholds varied according to the infant’s respiratory status. Quality was poor owing to lack of allocation concealment and blinding, and unclear reporting of the method of randomisation.

Kirpalani (2006) was a good-quality multicentre RCT involving 451 ELBW infants (<1000 g) less than 31 weeks gestational age and less than 48 hours old. Infants were enrolled from 10 NICUs across Australia, Canada and the USA. Restrictive and liberal transfusion thresholds varied according to the infant’s respiratory status. Follow-up data from this RCT conducted at 18–21 months was reported by Whyte (2009), and included 431 infants of the original cohort.

###### Level II evidence

There were no additional Level II studies identified in out literature search that examined the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in preterm infants (see **Appendix C, Volume 2**).

Table 3.1.8 Characteristics and quality of Level II evidence – restrictive RBC transfusion versus liberal RBC transfusion

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Included and assessed by Ibrahim (2014) | | | | |
| Bell (2005)50 | RCT  *Fair* | Preterm infants with VLBW (500–1300 g)  N=103 | Restrictive RBC transfusion (n=50) versus liberal RBC transfusion (n=53) | Mortality  Severe morbidity (BPD, ROP, PVL, IVH)  Transfusion reaction |
| Chen (2009)51 | RCT  *Poor* | Preterm infants with VLBW (<1500 g)  N=36 | Restrictive RBC transfusion (n=19) versus liberal RBC transfusion (n=17) | Mortality  Severe morbidity (BPD, ROP, NEC, IVH) |
| Kirpalani (2006)52  \*also known as PINT 2006 | RCT  *Good* | Preterm infants (<31 weeks gestational age) with ELBW (<1000 g) and <48 hours old  N=451 | Restrictive RBC transfusion (n=223) versus liberal RBC transfusion (n=228) | Mortality  Composite of mortality and severe morbidity  Severe morbidity (BPD, ROP, NEC, brain injury) |
| Included and assessed by Venkatesh (2012) | | | | |
| Brooks (1999)53 | RCT  *Fair* | VLBW infants (≤1250 g)  N=50 | Restrictive RBC transfusion (n=24) versus liberal RBC transfusion (n=26) | Mortality  Severe morbidity (BPD, ROP, NEC) |
| Mukhopadhyay (2004)54  \*abstract only | RCT  *Unclear risk of bias* | Preterm infants with LBW (1000–1800 g)  N=38 | Restrictive RBC transfusion (n=20) versus liberal RBC transfusion (n=18) | Mortality |
| Included and assessed by Whyte (2011) | | | | |
| Blank (1984)55 | RCT  *Unclear or high risk of bias* | Infants (<1500 g)  N=56 | Restrictive RBC transfusion (n=30) versus liberal RBC transfusion (n=26) | Mortality |
| Connelly (1998)a 56  \*abstract only | RCT  *High risk of bias* | Infants (<1500 g) up to 72 hours of age  N=24 | Restrictive RBC transfusion versus liberal RBC transfusion  Hb thresholds postnatal week one: 110 g/L versus 130 g/L.  Hb thresholds postnatal week two: 90 g/L versus 100 g/L except those requiring >40% oxygen maintained week one thresholds | Mortality  Composite of mortality and severe morbidity  Severe morbidity (ROP, BPD, brain injury) |
| Follow-up reports identified by Venkatesh (2012) and Whyte (2011) | | | | |
| McCoy (2011)57  \*follow-up of Bell (2005) | RCT  *Poor* | Preterm infants with VLBW (500–1300 g)  ~13 years post-transfusion  N=56 | Restrictive RBC transfusion (n=33) versus liberal RBC transfusion (n=23) | Neurodevelopmental outcomes |
| Whyte (2009)58  \*18–21 month follow-up PINT 2006 | RCT  *Fair* | Preterm infants (<31 weeks gestational age) with ELBW (<1000 g) and <48 hours old  N=421 | Restrictive RBC transfusion (n=156) versus liberal RBC transfusion (n=165) | Mortality  Composite of mortality and severe morbidity  Neurodevelopmental disability |

BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; IVH, intraventricular haemorrhage; LBW, low birth weight; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; VLBW, very low birth weight

**a.** The result from this study should be interpreted with caution. Connelly (1998) was a poor-quality trial with approximately 25% non-compliance by the attending physician, likely due to the non-blinded nature of the study.

##### Results

###### Mortality

Seven Level II studies (Bell 2005, Blank 1984, Brooks 1999, Chen 2009, Connelly 1998, Kirpalani 2006, Mukhopadhyay 2004) and one follow-up study (Whyte 2009) compared restrictive and liberal RBC transfusion strategies, and provided evidence for mortality among preterm infants. One study was assessed to be of good-quality (Kirpalani 2006), two were rated as fair-quality (Bell 2005, Whyte 2009), and the remaining four were of poor-quality (Brooks 1999, Chen 2009) or had been assessed by others to have a high risk of bias (Blank 1984, Connelly 1998). The results of these studies are summarised in **Table 3.1.9**.

All studies reported no significant difference between a restrictive RBC transfusion strategy and a liberal RBC transfusion strategy on the outcome of mortality (see **Figure 3.1.3**).

Ibrahim (2014) conducted a meta-analysis of three RCTs (Bell 2005, Chen 2009, Kirpalani 2006) involving 590 infants with VLBW (<1500 g), and found no statistically significant difference between groups comparing a restrictive or liberal transfusion strategy (RR 1.23; 95% CI 0.86, 1.76) for the outcome of mortality. Similar results were reported by Venkatesh (2012) and Whyte (2011) in pooled analyses that included infants enrolled after 28 days of life (RR 1.22; 95% CI 0.84, 1.75) or unpublished trial data (RR 1.23; 95% CI 0.86, 1.76), respectively.

The review by Venkatesh (2012) also reported data from one RCT (Mukhopadhyay 2004) that was published in abstract form only. Mukhopadhyay (2004) reported no significant difference between a restrictive and liberal transfusion strategy on the rate of mortality among term or preterm neonates (RR 3.5; 95% CI 0.62, 1.18), but the data were incomplete and therefore could not be included in the pooled analysis.

The review by Whyte (2011) reported data from a small RCT described by Blank (1984) that was reported separately, because the restrictive and liberal transfusion strategies were not comparable with the other included studies. There were no deaths before hospital discharge recorded in either group, but the study was small and underpowered.

Whyte (2011) also reported the 18–21 month follow-up results of infants enrolled in the PINT 2006 study (described by Whyte 2009), and found no significant difference in the rate of mortality between infants enrolled in the restrictive transfusion group and those in the liberal RBC transfusion group (RR 1.09; 95% CI 0.76, 1.56). Similar results were reported in the report by Whyte (2009) that included 10 additional patients for whom the outcome of mortality was available and had been adjusted for birth weight and centre (OR 1.8; 95% CI 0.72, 1.93).

Table 3.1.9 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I Evidence | | | | | | | | | |
| Ibrahim 201446  Level I  *Good* | 3 trials (Bell 2005, Chen 2009, Kirpalani 2006)50-52  N=590 | Infants with VLBW (<1500 g) | Multicentre x1, Aus, USA, Canada  Single centre x2, USA, Taiwan | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality | 53/292 (18.2%) | 44/298 (14.8%) | RR 1.23 [0.86, 1.76] | *No significant difference*  *P =*0.26  I2= 0% |
| Venkatesh 201247  Level I  *Good* | 4 trialsc (Bell 2005, Brooks 1999, Chen 2009, Kirpalani 2006)50-53  N=636 | Term or preterm neonates <28 days corrected postnatal age | Multicentre x1, Aus, USA, Canada  Single centre x3, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality | 51/313 (16.3%) | 43/323 (13.3%) | RR 1.22 [0.84, 1.75] | *No significant difference*  *P =*0.30  I2= 0% |
| Whyte 201148  Level I  *Good* | 4 trialsd (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)50-52; 56  N=614 | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestational age), admitted to NICU at <1 week of age | Multicentre x1, Aus, USA, Canada  Single centre x3, USA, Canada, Taiwan | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality prior to first hospital discharge | 53/305 (17.4%)) | 44/309 (14.2%) | RR 1.23 [0.86, 1.76] | *No significant difference*  *P =*0.26  I2= 0% |
| Level II Evidence | | | | | | | | | |
| Venkatesh 201247  Level I/II  *Good* | 1 trial (Mukhopadhyay 200454)  N=38  \*abstract only | Term or preterm neonates <28 days corrected age | NR | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality | NR/20 | NR/18 | RR 3.5 [0.62, 1.18] | *No significant difference*  *P =*NR |
| Whyte 201148  Level I/II  *Good* | 1 trial (Blank 1984)  N=56 | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestational age), admitted to NICU at <1 week of age | Single centre, USA | Restrictive RBC transfusion (for clinical signs only) versus transfusion at Hb threshold | Mortality prior to hospital discharge | 0/30 (0%) | 0/26 (0%) | RR 0.0 [0.0, 0.0] | *No significant difference*  *P =*NA |
| Whyte 2011e 48  Level I/II  *Fair* | 1 trial (Whyte 2009)58  N=421  \*follow-up of Kirpalani 2006 | Preterm infants (<31 weeks gestation) with ELBW (<1000 g) | 10 NICUs, Australia, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality 18–21 months post-transfusion | 48/208 (23.1%) | 45/213 (21.1%) | RR 1.09 [0.76, 1.56] | *No significant difference*  *P =*0.63 |

CI, confidence interval; ELBW, extremely low birth weight; Hb, haemoglobin; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

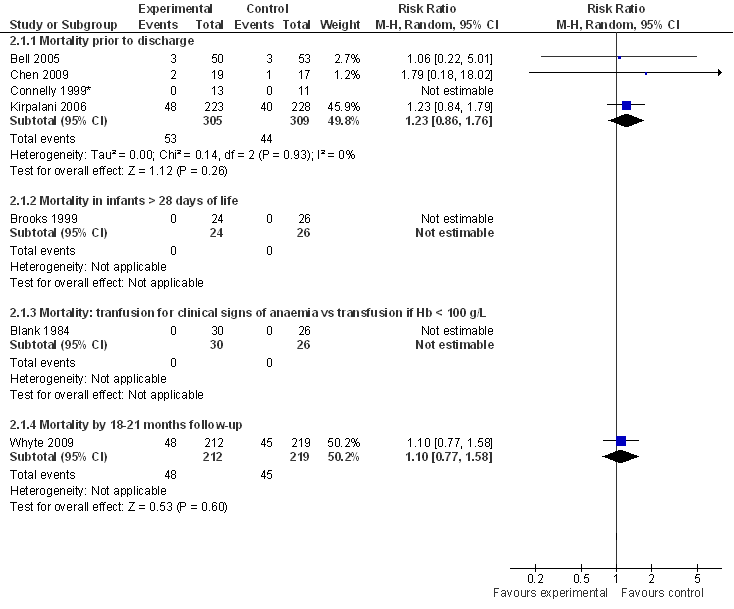
**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one RCT (Brooks, 1999) that enrolled infants >28 days of life.

**d.** Analysis includes unpublished data from one RCT (Connelly 1998) (published in abstract form only).

**e.** Published data reported by Whyte (2009) included all patients (N=431) for which the primary outcome was available and had been adjusted for birth weight and centre (48/212 (22.6%) versus 45/219 (20.6%); OR 1.18; 95% CI 0.72, 1.93; *P =*0.52).

Figure 3.1.3 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – mortality



###### Composite of mortality and severe morbidity

The systematic review and hand-searching process identified four Level II studies (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006), including one follow-up report (Whyte 2009) comparing restrictive and liberal transfusion strategies among preterm infants that provided evidence for a composite of mortality and severe morbidity. The results of these studies are summarised in **Table 3.1.10** and **Figure 3.1.4**.

The review by Whyte (2011) assessed the effect of different transfusion strategies on a composite of mortality and severe morbidity before first hospital discharge, and reported a meta-analysis of three trials (Chen 2009, Connelly 1998, Kirpalani 2006) involving 511 preterm infants. In the restrictive transfusion group, 180 infants died or had severe morbidity (70.6%) at discharge compared with 167 infants in the liberal transfusion group (65.2%). This difference was not statistically significant (RR 1.07; 95% CI 0.96, 1.20).

Whyte (2011) also reported a meta-analysis of four trials (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006) involving 614 preterm infants that provided data on a composite of mortality and severe brain injury before first hospital discharge. No statistically significant difference between restrictive and liberal transfusion strategies was reported (RR 1.12; 95% CI 0.81, 1.55).

The PINT 2006 study was reported by Whyte (2011) to assess a composite of mortality and cognitive delay defined as Mental Developmental Index (MDI) <70 (>2 SDs below age norm) at 18–21 months post-transfusion. No significant difference was found between infants randomised to a restrictive RBC transfusion strategy at birth, and those randomised to a liberal RBC transfusion strategy; however, the point estimate leaned in favour of liberal transfusion (RR 1.17; 95% CI 0.94, 1.47). In a post-hoc analysis, which assessed a composite of mortality and cognitive delay defined as MDI <85 (>1 SD below age norm), statistical significance was reached (RR 1.21; 95% CI 1.01, 1.44).

Table 3.1.10 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Composite of mortality and severe morbidity (BPD, ROP, NEC, brainy injury)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | | Setting  Location | | Intervention versus comparator | | | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I Evidence | | | | | | | | | | | | | |
| Whyte 201148  Level I  *Good* | 3 trialsc (Kirpalani 2006, Chen 2009, Connelly 1998)51-52; 56  N=511 | | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestational age), admitted to NICU at <1 week of age | | Multicentre x1, Aus, USA, Canada  Single centre x2, Canada, Taiwan | | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality or severe morbidity (BPD, ROP, NEC, brain injury) by first hospital discharge | | 180/255 (70.6%) | 167/256 (65.2%) | RR 1.07 [0.96, 1.20] | *No significant difference*  *P =*0.22  I2= 0% |
| 4 trialsc (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1998)50-52; 56  N=614 | | Multicentre x1, Aus, USA, Canada  Single centre x3, USA, Canada, Taiwan | | Mortality or severe brain injury by first hospital discharge | | 87/305 (28.5%) | 79/309 (25.6%) | RR 1.12 [0.81, 1.55] | *No significant difference*  *P =*0.48  I2= 6% |
| Level II Evidence | | | | | | | | | | | | | |
| Whyte 201148  Level I/II  Good | 1 trial (Whyte 2009)58  N=421 | | Preterm infants (<31 weeks gestation) with ELBW (<1000 g) at 18–21 months follow-up | | 10 NICUs, Aus, USA, Canada | | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality or severe morbidity 18–21 months post-transfusion with MDI <70 (>2 SDs below age norm) | | 94/208 (45.2%) | 82/213 (38.5%) | RR 1.17 [0.94, 1.47] | *No significant difference*  *P =*0.16 |
|  | | Post-hoc analysis | | |  |
| Mortality or severe morbidity 18–21 months post-transfusion with MDI <85 (>1 SD below age norm) | | 125/208 (60.1%) | 106/213 (49.8%) | RR 1.21 [1.01, 1.44] | *Favours liberal RBC transfusion*  *P =*0.034 |

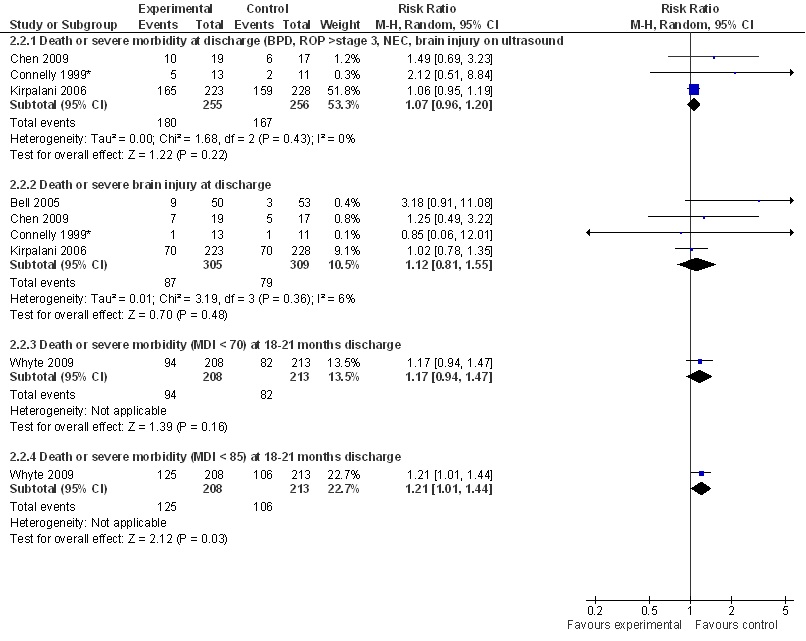
BPD, bronchopulmonary dysplasia; CI, confidence interval; ELBW, extremely low birth weight; MDI, Mental Developmental Index; NEC, necrotising enterocolitis, NICU, neonatal intensive care unit; RBC, red blood cell; ROP, retinopathy of prematurity; RR, risk ratio; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes unpublished data from one RCT (Connelly 1998) (published in abstract form only).

Figure 3.1.4 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – composite of mortality and severe morbidity (BPD, ROP, NEC, brain injury)



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

Five Level II studies (Bell 2005, Brooks 1999, Chen 2009, Connelly 1998, Kirpalani 2006) were identified that compared restrictive and liberal transfusion strategies among preterm infants and that provided evidence for the individual severe morbidity outcomes of ROP, BPD and NEC. Four of these studies (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006) also provided evidence for the outcome of brain injury, IVH or PVL. One study (Kirpalani 2006) was assessed to be of good-quality, two (Bell 2005, Brooks 1999) were of fair-quality and one (Chen 2009) was of poor-quality. One RCT (Connelly 1998) had an assumed high risk of bias because the data were not published and the study quality could not be assessed.

Bronchopulmonary dysplasia

The systematic review by Ibrahim (2014) included pooled results of three RCTS (Bell 2005, Chen 2009, Kirpalani 2006) involving 491 preterm infants with VLBW (<1500 g) that assessed oxygen dependence at 36 weeks gestation. There was no significant difference between restrictive and liberal transfusion strategies for this outcome, which was present in 50.2% and 49.6% of infants respectively (RR 1.03; 95% CI 0.86, 1.22). Similar results were observed in pooled analyses reported by Venkatesh (2012) and Whyte (2011), which included infants enrolled after 28 days of life (RR 0.99; 95% CI 0.84, 1.15) or had included unpublished trial data (RR 1.03; 95% CI 0.87, 1.21).

The review by Whyte (2011) also included a meta-analysis of four trials (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006) involving 544 preterm infants that reported oxygen dependence at 28 days. Again, there was no significant difference between restrictive and liberal RBC transfusion strategies for this outcome (RR 0.99; 95% CI 0.92, 1.06). The results of these studies are summarised in **Table 3.1.11** and pooled results of all included Level II studies are shown in **Figure 3.1.5**.

Figure 3.1.5 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – severe morbidity (BPD)

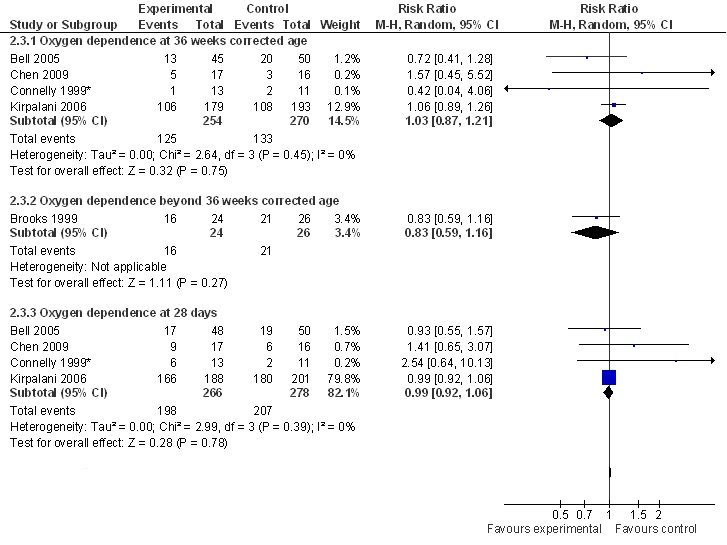


Table 3.1.11 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion –Severe morbidity (BPD)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level I Evidence | | | | | | | | | | | | |
| Ibrahim 201446  Level I  *Good* | 3 trials (Bell 2005, Chen 2009, Kirpalani 2006)50-52  N=491 | Infants with VLBW (<1500 g) | Multicentre x1, Aus, Canada, USA  Single centre x2, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | BPD | 119/237 (50.2%) | | 126/254 (49.6%) | | RR 1.03 [0.86, 1.22] | | *No significant difference*  *P =*0.77  I2= 0% |
| Venkatesh 201247  Level I  *Good* | 4 trialsc (Bell 2005, Brooks 1999, Chen 2009, Kirpalani 2006)50-53  N=544 | Term or preterm neonates <28 days corrected age | Multicentre x1, Aus, Canada, USA  Single centre x3, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Chronic lung disease | 135/263 (51.3%) | | 147/281 (52.3%) | | RR 0.99 [0.84, 1.15] | | *No significant difference*  *P =*0.82  I2= NR |
| Whyte 201148  Level I  *Good* | 4 trialsd (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)50-52; 56  N=544 | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestation), admitted to NICU at <1 week of age | Multicentre x1, Aus, Canada, USA  Single centre x3, Canada, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | BPD (oxygen requirement at 28 days)e | 198/266 (74.4%) | | 207/278 (74.5%) | | RR 0.99 [0.92, 1.06] | | *No significant difference*  *P =*0.78  I2= 0% |
| BPD (oxygen requirement at 36 weeks postmenstrual age) | 125/254 (49.2%) | | 133/270 (49.3%) | | RR 1.03 [0.87, 1.21] | | *No significant difference*  *P =*0.75  I2= 0% |

BPD, bronchopulmonary dysplasia; CI, confidence interval; NICU, neonatal intensive care unit; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one RCT (Brooks, 1999) that administered transfusions between 28–72 days of life.

**d.** Analysis includes unpublished data from one RCT (Connelly 1998) (published in abstract form only).

**e.** Includes additional data retrieved from PINT 2006 study (Kirpalani 2006).

Necrotising enterocolitis

The systematic review by Ibrahim (2014) reported a meta-analysis of three RCTs (Bell 2005, Chen 2009, Kirpalani 2006) involving 590 preterm infants that assessed the effect of restrictive and liberal transfusion strategies on the development of NEC. Twenty-one infants in the restrictive transfusion group (7.2%) and 13 infants in the liberal transfusion group (4.4%) developed NEC. This result was not statistically significant (RR 1.62; 95% CI 0.83, 3.13).

The systematic review by Bassler (2008) reported data from one additional RCT (Brooks 1999) that assessed the development of NEC among VLBW infants enrolled at 29 days of life; this additional RCT was not included in the review by Ibrahim (2014). No statistically significant difference in the rate of NEC comparing restrictive and liberal transfusion strategies was found (RR 0.93; 95% CI 0.36, 2.37).

The results from these studies are summarised in **Table 3.1.12**,and pooled results of all included Level II studies are shown in **Figure 3.1.6.**

Figure 3.1.6 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – Severe morbidity (NEC)



Table 3.1.12 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (NEC)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level I Evidence | | | | | | | | | | | | |
| Ibrahim 201446  Level I  *Good* | 3 trials (Bell 2005, Chen 2009, Kirpalani 2006)50-52  N=590 | Infants with VLBW (<1500 g) | Multicentre x1, Aus, Canada, USA  Single centre x2, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | NEC | 21/292 (7.2%) | | 13/298 (4.4%) | | RR 1.62 [0.83, 3.13] | | *No significant difference*  *P =*0.16  I2= 0% |
| Level II Evidence | | | | | | | | | | | | |
| Bassler 200849  Level I/II  *Good* | 1 trial (Brooks 1999)53  N=501 | Preterm infants (<37 weeks gestation) with VLBW (<1250 g) | Single NICU x 1, USA | Restrictive RBC transfusion versus liberal RBC transfusion between 28–72 days of life | NEC | 6/24 (25%) | | 7/26 (27%) | | RR 0.93 [0.36, 2.37]c | | *No significant difference*  *P =*0.88c  I2= NA |

CI, confidence interval; NA, not applicable; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; RBC, red blood cell; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Retinopathy of prematurity

The systematic review by Ibrahim (2014) reported pooled results of three RCTS (Bell 2005, Chen 2009, Kirpalani 2006) that assessed severe ROP (≥stage 3) among 496 preterm infants with VLBW (<1500 g). Thirty-five infants developed severe ROP in the restrictive transfusion group (14.5%) compared with 37 infants in the liberal transfusion group (14.5%). This result was not statistically significant (RR 1.04; 95% CI 0.68, 1.58).

Whyte (2011) conducted a meta-analysis of four trials (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006) involving 517 VLBW preterm infants to assess ROP among survivors, and found no statistically significant difference on the rate of ROP (all severities) (RR 0.98; 95% CI 0.84, 1.14), ROP stage 1 or 2 (RR 0.96; 95% CI 0.78, 1.18), or ROP stage >3 (RR 1.04; 95% CI 0.68, 1.58) (See **Figure 3.1.7** and **Figure 3.1.8**).

The systematic review by Bassler (2008) reported data from one additional RCT (Brooks 1999) that assessed the development of ROP among VLBW (<1250 g) infants enrolled at 29 days of life; this additional RCT was not included in the reviews by Ibrahim (2014) or Whyte (2011). Upon further investigation, the RCT by Brooks (1999) assessed ROP in infants stratified by birth weight. In all three birth weight categories (≤750 g, 751–1000 g, 1001–1250 g) there was no significant difference between restrictive RBC transfusion and liberal RBC transfusion strategies on the rate of ROP reported (see **Table 3.1.13**). These findings were also reflected in the overall result (RR 1.14; 95% CI 0.85, 1.53).

The results from these studies are summarised in **Table 3.13**, and pooled results of all included Level II studies are shown in **Figure 3.1.7** and **Figure 3.1.8**.

Figure 3.1.7 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – severe morbidity (ROP – all cases)



Figure 3.1.8 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – severe morbidity (ROP – by stage)



Table 3.1.13 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (ROP)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level I Evidence | | | | | | | | | | | | |
| Ibrahim 201446  Level I  *Good* | 3 trials (Bell 2005, Chen 2009, Kirpalani 2006)50-52  N=496 | Infants with VLBW (<1500 g) | Multicentre x1, Aus, Canada, USA  Single centre x2, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | ROP ≥grade 3 | 35/241 (14.5%) | | 37/255 (14.5%) | | RR 1.04 [0.68, 1.58] | | *No significant difference*  *P =*0.87  I2= 0% |
| Whyte 201148  Level I  *Good* | 4 trialsc (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)50-52; 56  N=517 | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestation), admitted to NICU at <1 week of age | Multicentre x1, Aus, Canada, USA  Single centre x3, Canada, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | ROP among survivors (all cases), | 134/252 (53.2%) | | 146/265 (55.1%) | | RR 0.98 [0.84, 1.14] | | *No significant difference*  *P =*0.81  I2= 0% |
| ROP among survivors (grade 1 or 2) | 99/252 (39.3%) | | 109/265 (41.1%) | | RR 0.96 [0.78, 1.18] | | *No significant difference*  *P =*0.67  I2= 0% |
| ROP among survivors (≥grade 3) | 35/252 (13.9%) | | 37/265 (14.0%) | | RR 1.04 [0.68, 1.58] | | *No significant difference*  *P =*0.87  I2= 0% |
| Level II Evidence | | | | | | | | | | | | |
| Bassler 200849  Level I/II  *Good* | 1 trial (Brooks 1999)53  N=50 | Preterm infants (<37 weeks gestation) with LBW (<2500 g) | Single centre x 1, USA | Restrictive RBC transfusion versus liberal RBC transfusion | ROP (all cases) | 20/24 (83%) | | 19/26 (73%) | | RR 1.14 [0.85, 1.53]f | | *No significant difference*  *P =*0.87f  I2= NA |
| Brooks 199953  Level II  *Fair* | N=50 | VLBW preterm infants <1250 g | Single NICU, USA | Restrictive RBC transfusion versus liberal RBC transfusion  \*administered between 28–72 days of life | ROP (all cases) | Stratified by birth weight e | | | | | |  |
| ≤750 g | 6/6 (100%) | | 3/5 (60.0%) | | RR 1.59 [0.79, 3.23]d | | *No significant difference*  *P =*0.20d |
| 751–1000 g | 9/11 (81.8%) | | 10/13 (76.9%) | | RR 1.06 [0.71, 1.60]d | | *No significant difference*  *P =*0.77d |
| 1001–1250 g | 4/7 (57.1%) | | 6/8 (75.0%) | | RR 0.76 [0.36, 1.62]d | | *No significant difference*  *P =*0.48d |

CI, confidence interval; LBW, low birth weight; NA, not applicable; NICU, neonatal intensive care unit; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c** Analysis includes unpublished data from one RCT (Connelly 1998) (published in abstract form only).

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** Missing data on 1 patient. Brooks (1999) reports a total of 20 cases of ROP in the restrictive transfusion group, but when stratified by weight the total number adds 19.

Brain injury on ultrasound

The systematic review by Ibrahim (2014) reported a meta-analysis of three RCTs (Bell 2005, Chen 2009, Kirpalani 2006) involving 491 preterm infants that compared the effect of restrictive and liberal transfusion strategies on brain injury at ultrasound (composite of IVH and/or PVL). The number of study participants who were diagnosed with IVH and/or PVL in each treatment group was specifically retrieved by Ibrahim (2014) from the study authors as the published reports did not provide complete data. In the restrictive transfusion group, 118 infants (49.6%) developed brain injury, compared with 105 infants in the liberal transfusion group (41.5%). This analysis resulted in a borderline statistically significant effect (*P =*0.05) favouring the liberal transfusion group (RR 1.21 95% CI 1.00, 1.46).

Whyte (2011) conducted a meta-analysis of four trials (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006) that included unpublished data and compared the effect of restrictive and liberal transfusion strategies on brain injury at ultrasound (IVH grades 3–4, hydrocephalus, cortical atrophy or periventricular leukomalacia) in 517 preterm infants. No statistically significant difference between treatment groups (RR 1.07; 95% CI 0.50, 2.27) was reported. The data included in the pooled analyses did not completely match those reported in the Level II studies. Bell (2005) is the composite of IVH grade 4 and PVL among survivors, and Chen (2009) is IVH all grades.

The results from these studies are summarised in **Table 3.1.14,** and pooled results as reported by the Level I studies are shown in **Figure 3.1.9**.

Figure 3.1.9 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – severe morbidity (brain injury on ultrasound)

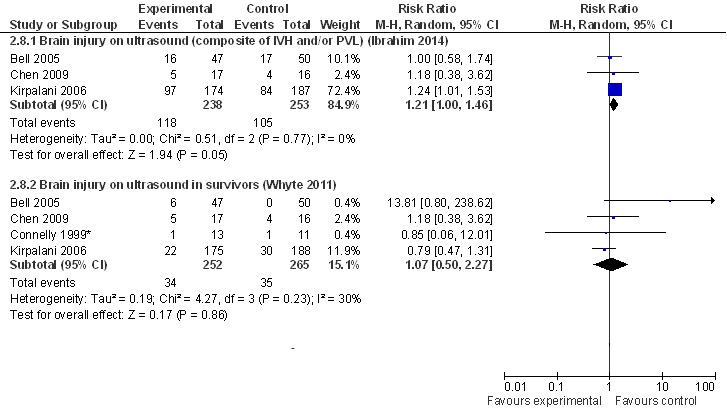


Table 3.1.14 Preterm infants: results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (brain injury on ultrasound)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I Evidence | | | | | | | | | |
| Ibrahim 201446  Level I  *Good* | 3 trials (Bell 2005, Chen 2009, Kirpalani 2006)50-52  N=491 | Infants with VLBW (<1500 g) | Multicentre x1, Aus, Canada, USA  Single centre x2, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Brain injury on ultrasound (composite of IVH and/or PVL) | 118/238 (49.6%) | 105/253 (41.5%) | RR 1.21 [1.00, 1.46] | *Favours liberal RBC transfusion*  *P =*0.05  I2= 0% |
| Whyte 201148  Level I  *Good* | 4 trialsc (Bell 2005, Chen 2009, Connelly 1998; Kirpalani 2006)50-52; 56  N=517 | Infants with VLBW (≤1500 g) or preterm infants (<32 weeks gestation), admitted to NICU at <1 week of age | Multicentre x1, Aus, Canada, USA  Single centre x3, Canada, Taiwan, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Brain injury on ultrasound among survivors (IVH grades 3 or 4, hydrocephalus, cortical atrophy, or PVL) | 34/252 (13.5%) | 35/265 (13.2%) | RR 1.07 [0.50, 2.27] | *No significant difference*  *P =*0.86  I2= 30% |
| Level II Evidence | | | | | | | | | |
| Bell 200550  Level II  *Fair* | N=100 | Preterm infants with VLBW (500–1300 g) | Single NICU, USA | Restrictive RBC transfusion versus liberal RBC transfusion. | IVH (any grade) | 14/49 (28.6%) | 17/51 (33.3%) | RR 0.86 [0.48, 1.54]d | *No significant difference*  *P =*0.669 |
| IVH (grade 3 or 4) | 5/49 (10.2%) | 8/51 (15.7%) | RR 0.65 [0.23, 1.85]d | *No significant difference*  *P =*0.555 |
| IVH (grade 4) | 4/49 (8.2%) | 0/51 (0%) | RR 9.36 [0.52, 169.40]d | *No significant difference*  *P =*0.054 |
| PVL | 4/49 (8.2%) | 0/51 (0%) | RR 9.36 [0.52, 169.40]d | *No significant difference*  *P =*0.115 |
| IVH (grade 4) or PVL | 6/49 (12.2%) | 0/51 (0%) | RR | *Favours liberal RBC transfusion*  *P =*0.012 |
| Chen 200951  Level II  *Poor* | N=33 | Preterm infants with VLBW (≤1500 g) | Single NICU, Taiwan | Restrictive RBC transfusion versus liberal RBC transfusion | IVH (all cases) | 5/17 (29.4%) | 4/16 (25.0%) | RR 1.18 [0.38, 3.62] | *No significant difference*  *P =*0.776 |
| IVH (grade 3 or 4) | 1/17 (5.9%) | 2/16 (12.5%) | RR 0.47 [0.05, 4.70] | *No significant difference*  *P =*0.509 |

CI, confidence interval; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c** Analysis includes unpublished data from one RCT (Connelly 1998) (published in abstract form only).

Neurodevelopmental disability

Two Level II studies (Whyte 2009, McCoy 2011) comparing restrictive and liberal transfusion strategies provided evidence for neurodevelopmental disability in preterm infants. Whyte (2009) was a planned, fair-quality follow-up report of the infants enrolled in the PINT 2006 (Kirpalani 2006) study conducted 18–21 months post-transfusion. McCoy (2011) was a poor-quality study of infants enrolled in the Bell (2005) cohort, conducted and planned 8–15 years post-transfusion. The study by McCoy (2011) was not considered when developing evidence statements and recommendations because there was a clear high risk of attrition bias, but the data are presented here for completeness. The results of these studies are summarised in **Table 3.1.15**.

Whyte (2011) reported results from the PINT 2006 study (Whyte 2009) that assessed cognitive delay,[[9]](#footnote-9) cerebral palsy, severe visual and hearing impairment, and any neurosensory impairment at 18–21 months post-transfusion. All outcomes were adjusted for birth weight and cognitive delay, and neurosensory impairments were also adjusted for study sites. There was no statistically significant difference between restrictive and liberal RBC transfusion strategies for any outcome reported; however, cognitive delay approached statistical significance in favour of liberal transfusion when adjusted for birth weight and study site (OR 1.74; 95% CI 0.98, 3.11). In a post-hoc analysis using an amended definition for cognitive delay[[10]](#footnote-10) (also adjusted for birth weight and centre), Whyte (2009) reported a statistically significant effect in favour of liberal transfusion (OR 1.81; 95% CI 1.12, 2.93).

McCoy (2011) assessed a variety of cognitive, language, visual spatial/motor and memory measures in 56 preterm infants at 8–15 years post-transfusion. Forty-seven infants were lost to follow-up. There was no significant difference between restrictive and liberal transfusion strategies for the cognitive measures of General Ability Index, Verbal Comprehension Index and Perceptual Reasoning Index. However, a significant effect in favour of restrictive transfusion was reported for the Wide Range Achievement Test (WRAT-III) (which included reading ability). Here, the mean WRAT-III score in the restrictive transfusion group was 93.94 ± 15.0 compared with 105.83 ± 10.2 in the liberal transfusion group.

There was no significant difference between restrictive and liberal transfusion strategies for the language, visual spatial/motor and memory measures of rapid automatized naming, Judgment of Line Orientation, Grooved Pegboard, Bender visual-motor gestalt test, and verbal memory scores. However, a significant effect in favour of restrictive transfusions was reported for controlled oral word association (COWA) with a mean score of –1.30 ± 1.24 reported in the restrictive transfusion group compared with a mean score of –0.31 ± 1.10 in the liberal transfusion group. A similar result was seen for visual memory score, with those in the restrictive transfusion group performing significantly better than those in the liberal transfusion group (mean score of –3.05 ± 1.75 compared with –1.95 ± 1.38, respectively).

Table 3.1.15 Preterm infants: results for restrictive RBC transfusion versus liberal RBC transfusion – Neurodevelopmental disability

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Whyte 201148  Level I/II  *Good* | 1 trial (Whyte 2009)58  N=321 | Preterm infants (<31 weeks gestation) with ELBW (<1000 g), <48 hours old at 18–21 months post-transfusion | 10 NICUs, Aus, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Cognitive delay:18–21 months post-transfusion | | | |  |
| MDI <70 (>2 SDs below age norm) | 38/156 (24.4%) | 29/165 (17.6%) | RR 1.39 [0.90, 2.13] | *No significant difference*  *P =*0.14 |
| Adjusted for birth weight and study site c | | OR 1.74 [0.98, 3.11] | *No significant difference*  *P =*0.06 |
|  | *Post-hoc analysis* | | |  |
| MDI <85 (>1 SD below age norm) | 70/156 (44.9%) | 56/165 (33.9%) | RR 1.32 [1.00, 1.74] | *Favours liberal RBC transfusion*  *P =*0.05 |
| Adjusted for birth weight and study site c | | OR 1.81 [1.12, 2.93] | *Favours liberal RBC transfusion*  *P =*0.016 |
| Cerebral palsy and neurosensory impairments: 18–21 months post-transfusion | | | |  |
| Cerebral palsy | 11/163 (6.8%) | 9/172 (5.2%) | RR 1.29 [0.55, 3.03] | *No significant difference*  *P =*0.56 |
| Adjusted for birth weight c | | OR 1.32 [0.53, 3.27] | *No significant difference*  *P =*0.55 |
| Severe visual impairment | 2/161 (1.2%) | 1/173 (0.6%) | RR 2.15 [0.20, 23.47] | *No significant difference*  *P =*0.53 |
| Adjusted for birth weight c | | OR 2.16 [0.19, 24.09] | *No significant difference*  *P =*0.53 |
| Severe hearing impairment | 4/161 (2.5%) | 3/173 (1.7%) | RR 1.43 [0.33, 6.30] | *No significant difference*  *P =*0.63 |
| Adjusted for birth weight c | | OR 1.45 [0.32, 6.58] | *No significant difference*  *P =*0.63 |
| McCoy  2011d 57  Level II  *Poor* | N=56 | Preterm infants with VLBW (500–1300 g) at ~13 years post-transfusion | USA | Restrictive RBC transfusion versus liberal RBC transfusion | Cognitive measures: ~13 years post-transfusion | | | |  |
| GAI | 93.21 ± 20.7 (n=33) | 103.61 ± 15.7 (n=23) | 0.267 [NR] | *No significant difference*  *P =*0.047e |
| VCI | 93.85 ± 26.0 (n=33) | 104.78 ± 15.7 (n=23) | 0.238 [NR] | *No significant difference*  *P =*0.078e |
| PRI | 91.67 ± 18.1 (n=33) | 99.70 ± 15.5 (n=23) | 0.229 [NR] | *No significant difference*  *P =*0.089e |
| WRAT-III (reading ability) | 93.94 ± 15.0 | 105.83 ± 10.2 (23) | 0.410 [NR] | *Favours restrictive RBC transfusion*  *P =*0.002e |
| Language, visual spatial/motor and memory measures: ~13 years post-transfusion | | | |  |
| COWA | –1.30 ± 1.24 (n=33) | –0.31 ± 1.10 (n=23) | 0.386 [NR] | *Favours restrictive RBC transfusion*  *P =*0.003f |
| RAN | 0.08 ± 1.70 (n=33) | 0.59 ± 1.02 (n=23) | 0.189 [NR] | *No significant difference*  *P =*0.167f |
| JOL (visual spatial reasoning) | –1.06 ± 1.54 (n=33) | –0.81 ± 1.23 (n=23) | 0.091 [NR] | *No significant difference*  *P =*0.593g |
| GPB (fine motor coordination) | –0.75 ± 2.00 (n=33) | –0.24 ± 0.97 (n=23) | 0.152 [NR] | *No significant difference*  *P =*0.152g |
| Bender-II (visual-motor integration) | 0.12 ± 1.19 (n=33) | 0.75 ± 0.90 (n=23) | 0.279 [NR] | *No significant difference*  *P =*0.037g |
| Visual memory | –3.05 ± 1.75 (n=33) | –1.95 ± 1.38 (n=23) | 0.324 [NR] | *Favours restrictive RBC transfusion*  *P =*0.015f |
| Verbal memory | –1.41 ± 1.42 (n=33) | –0.92 ± 0.96 (n=23) | 0.192 [NR] | *No significant difference*  *P =*0.157f |

CI, confidence interval; COWA, controlled oral word association; ELBW, extremely low birth weight; GAI, General Ability Index; GPB, grooved pegboard; JOL, Benton Judgment of Line Orientation Test; MDI, Mental Development Index; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PRI, Perceptual Reasoning Index; RAN, rapid automatized naming; RBC, red blood cell; RR, risk ratio; SD, standard deviation; VCI, Verbal Comprehension Index; VLBW, very low birth weight; WRAT-III, Wide Range Achievement Test

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Published data reported by Whyte (2009).

**d.** McCoy (2011) not considered when developing evidence statements due to attrition bias.

**e.** Effect sizes (r) were calculated by r=√[t2/(t2+df )]. P <0.01 was considered statistically significant.

**f.** Effect sizes (r) were calculated by r=√[t2/(t2+df )]. P <0.025 was considered statistically significant.

**g.** Effect sizes (r) were calculated by r=√[t2/(t2+df )]. P <0.017 was considered statistically significant.

Transfusion-related serious adverse events

One Level II study (Bell 2005) comparing restrictive and liberal transfusion strategies in preterm infants provided evidence for transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions). The results of these studies are summarised in **Table 3.1.16**.

The fair-quality study by Bell (2005) assessed transfusion reactions; however, no infants in either group experienced any event. The study was small and was not sufficiently powered to detect such reactions.

Table 3.1.16 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Transfusion-related serious adverse events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Bell 200550  Level II  *Fair* | N=100 | Preterm infants with VLBW (500–1300 g) | Single NICU, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Transfusion reaction | 0/49 (0%) | 0/51 (0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit; RBC, red blood cell; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

### Infants, children and adolescents

| Evidence statements – infants, children and adolescents (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In infants, children and adolescents, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Recommendations – 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 and PP3 for guidance for preterm neonates. |
| Practice points – infants, children and adolescents (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*.14 |
| 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*.14 |
| 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*14 |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.a  a See Appendix F (*RBC transfusions in preterm infants*) and 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.a This reassessment will also guide the decision on whether to retest the Hb level.  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*15 |
| 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. |
| CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; Hct, haematocrit; PP, practice point; R, recommendation; RBC, red blood cell | |

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of RBC transfusions in a general medical population of infants, children or adolescents at risk of anaemia.

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

There were no Level I or Level II studies identified in the systematic review and hand-searching process that compared the safety and effectiveness of restrictive and liberal RBC transfusion strategies in a general medical population of infants, children or adolescents at risk of anaemia.

### Neonatal and paediatric patients with sickle cell disease

| Evidence statements – sickle cell disease (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In neonates and infants with sickle cell disease, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | In children and adolescents with sickle cell disease, 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 | √√ | √√ |
|  | In neonates and infants with sickle cell disease, the effect of RBC transfusion compared with no transfusion on stroke occurrence is unknown. | NA | NA | NA | NA | NA |
|  | 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.) | √√ | √√√ | √√√ | √√√ | √√ |
|  | In neonatal and paediatric patients with sickle cell disease, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | In neonatal and paediatric patients with sickle cell disease, 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  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |
| **a** assessed by transcranial Doppler ultrasonography12 or magnetic resonance imaging13 for evidence of previous stroke-like lesions. | | | | | | |

|  |  |
| --- | --- |
| Recommendations – sickle cell disease (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 ultrasonography12 *and* MRI.13 b See PP11 for methods of assessment. |
| Practice points – sickle cell disease (RBC transfusion) | |
| PP11 | Children and adolescents with SCD should be assessed for stroke risk using both TCD ultrasonography12 and MRI.13 |
| MRI, magnetic resonance imaging; PP, practice point; R, recommendation; RBC, red blood cell; SCD, sickle cell disease; TCD, transcranial Doppler  Note: 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 yet available. We await publication of the full trial results before changes to current recommendations (R1 and R4) and practice points (PP11) are made. | |

##### Background

People with sickle cell disease have increased blood viscosity and abnormal interactions between the sickled RBCs and other blood components (e.g. leukocytes, platelets and clotting factor); this results in haemolytic anaemia, tissue and organ damage, and vaso-occlusive events that may include painful crises caused by local infarcts or ischaemia. Ultimately, people with sickle cell disease are at increased risk for stroke and acute chest syndrome, and have a lower life expectancy than the general population. In people with sickle cell disease, RBC transfusions help to dilute the volume of circulating sickle cells, and are used to reduce the risk of anaemia and incidence of vaso-occlusive events. There are inherent risks associated with regular RBC transfusion, including iron overload.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified two Level I studies (Cherry 2012; Wang 2013) that examined the effect of RBC transfusion in paediatric patients with sickle cell disease (see **Appendix C, Volume 2**). The main characteristics of these studies are summarised in **Table 3.1.17**.

The good-quality systematic reviews by Cherry (2012) and Wang (2013) identified the same two Level II studies (Adams 1998, Adams 2005) that examined the association between RBC transfusion and stroke in 209 children aged <16 years with sickle cell disease. Cherry (2012) also reported transfusion-related SAEs, whereas Wang (2013) included data on mortality from these trials.

Table 3.1.17 Characteristics and quality of Level I evidence – RBC transfusion versus no transfusion (or alternate dose) in paediatric patients with sickle cell disease

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Cherry (2012)59 | Health Technology Assessment report *Good* | Children (<16 years) with sickle cell disease and a high risk of stroke  2 RCTs, N=209 | RBC transfusion (n=101) versus no transfusion (n=108) | Stroke  Transfusion-related SAEs |
| Wang (2013)60 | Systematic review  *Good* | Persons with sickle cell disease, with or without a history of prior stroke or transient ischaemic attack  2 RCTs, N=209 | RBC transfusion (n=101) versus no transfusion (n=108) | Mortality  Stroke |

RBC, red blood cell; RCT, randomised controlled trial; SAEs, serious adverse events

###### Level II evidence

The systematic review and hand-searching process identified two additional Level II studies (Debaun 2014, Pegelow 2001) that examined the effect of RBC transfusions in paediatric patients with sickle cell disease (see **Appendix C, Volume 2**). The main characteristics of all Level II studies (including those identified by the Level I studies) are summarised in **Table 3.1.18**.

Adams (1998) (also known as the Stroke Prevention Trial in Sickle Cell Anaemia [STOP]), was a good-quality RCT conducted in the USA that examined the use of chronic RBC transfusion in paediatric patients with sickle cell disease. Children aged 2–16 years with sickle cell anaemia or sickle beta thalassemia, and at high risk of stroke based on transcranial Doppler (TCD) screening, were eligible to receive either RBC transfusion or standard care (no transfusion).

The STOP 2 trial reported by Adams (2005) was a good-quality trial conducted in the USA and Canada that aimed to compare stroke risk in chronically transfused children. Patients with sickle cell anaemia or sickle beta thalassemia and at high risk of stroke either continued RBC transfusions or had their RBC transfusion regimen halted. A proportion of patients had participated in the original STOP trial. Both STOP and STOP 2 were finished early by the Data Safety and Monitoring Board due to the high rate of stroke in control groups.

Debaun (2014) was a fair-quality multicentre trial conducted in Canada, France, the United Kingdom and the USA. The authors compared the effect of regular RBC transfusions with standard care (no treatment for silent infarcts) among paediatric patients with sickle cell anaemia. Eligible participants aged 5–15 years had a confirmed diagnosis of sickle cell anaemia or sickle beta thalassemia and at least one infarct-like lesion on an MRI scan.

The poor-quality study by Pegelow (2001) reported data from the STOP cohort collected at 36 months follow-up. The authors assessed the incidence of stroke and new or worse silent lesions.

###### Level III evidence

There were no Level III studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusion compared with no transfusion (or alternate dose) in neonatal and/or paediatric patients with sickle cell disease.

Table 3.1.18 Characteristics and quality of Level II evidence - RBC transfusion versus no transfusion (or alternate dose) in paediatric patients with sickle cell disease

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Adams (1998)12  STOP | RCT  *Good* | Paediatric patients (2–16 years) with sickle cell anaemia or sickle beta thalassemia and a high risk of stroke  N=130 | RBC transfusion (n=63) versus no transfusion (n=67) | Mortality  Stroke  Transfusion-related SAEs |
| Adams (2005)61  STOP II | RCT  *Good* | Paediatric patients (2–16 years) with sickle cell anaemia or sickle beta thalassemia and a high risk of stroke who had been receiving chronic RBC transfusions  N=79 | Continued RBC transfusion (n=38) versus halted RBC transfusion (n=41) | Mortality  Stroke  Transfusion-related SAEs |
| Debaun (2014)13 | RCT  *Fair* | Paediatric patients (5–15 years) with sickle cell anaemia  N=196 | Regular blood transfusion (n=99) versus standard care (observation group) (n=97) | Mortality  Stroke  Transfusion-related SAEs |
| Pegelow (2001)62  \*follow-up of STOP | RCT  *Poor* | Paediatric patients (2 to 16 years) with sickle cell anaemia or sickle beta thalassemia and a high risk of stroke  N=124 | Chronic RBC transfusion (n=55) versus no transfusion (n=69) | Stroke |

RBC, red blood cell; RCT, randomised controlled trial; SAEs, serious adverse events

##### Results

###### Mortality

Three Level II studies (Adams 1998, Adams 2005, Debaun 2014) examined the effect of RBC transfusions in paediatric patients with sickle cell disease and provided evidence for mortality. The STOP (Adams 1998) and STOP II (Adam 2005) trials were assessed to be of good-quality and Debaun (2014) was assessed as fair-quality. The results of these studies are summarised in **Table 3.1.19**.

All studies found no significant difference in mortality comparing RBC transfusions with no transfusion in paediatric patients with sickle cell disease, but the studies were not sufficiently powered to detect a significant difference in this outcome.

The RCT by Adams (1998) reported no deaths in either the RBC transfusion or the no transfusion group. Adams (2005) reported one patient death in the continued transfusion group (2.6%) compared with no deaths in the halted transfusion group (0%). This result was not statistically significant. Debaun (2014) reported no deaths in either the regular transfusion group or the standard care group.

Table 3.1.19 Paediatric patients with sickle cell disease: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Wang 201360  Level I/II  *Good* | 1 trial (Adams 1998)12  N=130 | Children (2–16 years) with HbSS or sickle beta thalassemia and a high risk of stroke | Multicentre, USA | RBC transfusion versus standard care | Mortality | 0/63 (0%) | 0/67 (0%) | Not estimable | *P =*NA |
| 1 trial (Adams 2005)61  N=79 | Children (2–16 years) with sickle cell disease and a high risk of stroke based on TCD screening | Multicentre, Canada, USA | Continued RBC transfusion versus halted RBC transfusion | Mortality | 1/38 (2.6%) | 0/41 (0%) | OR 3.32 [0.13, 84.01] | *No significant difference*  *P =*0.47 |
| Debaun 201413  Level II  *Fair* | N=196 | Children (5–15 years) with sickle cell anaemia | Multicentre, Canada, France, UK and USA | Regular RBC transfusion versus standard care | Mortality | 0/99 (0%) | 0/97 (0%) | Not estimable | *P =*NA |

CI, confidence interval; HbSS, sickle cell anaemia; NA, not applicable; OR, odds ratio; RBC, red blood cell; TCD, transcranial Doppler

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Stroke

There were two Level I studies (Cherry 2012, Wang 2013) that reported data from two Level II studies (Adams 1998, Adams 2005), and two additional Level II studies (Debaun 2014, Pegelow 2001) that examined the effect of RBC transfusions in paediatric patients with sickle cell disease and provided evidence for stroke. Two of the studies were assessed to be of good-quality (Adams 1998, Adams 2005), one as fair-quality (Debaun 2014) and one as poor-quality (Pegelow 2001). The results of these studies are summarised in **Table 3.1.20**.

The RCT by Adams (1998) was reported in the systematic review by Wang (2013) to show a statistically significant effect in favour of RBC transfusion for reducing the risk of stroke among paediatric patients with sickle cell disease (RR 0.10; 95% CI 0.01, 0.73). One patient in the transfusion group experienced stroke (1.6%) compared with 11 patients in the no transfusion group (16.4%). In a subgroup analysis reported by Adams (1998), patients who received RBC transfusions were significantly less likely to experience a cerebral infarct than those in the no transfusion group (RR 0.11; 95% CI 0.01, 0.81], but there were no statistically significant between-group differences in the rate of intracerebral hematoma (RR 0.35; 95% CI 0.01, 8.54).

The 36-month follow-up study (Pegelow 2001) of the cohort enrolled in the STOP trial found that long-term transfusion therapy continued to reduce the risk of stroke among paediatric patients with sickle cell disease compared with those in the no transfusion group (RR 0.10; 95% CI 0.01, 0.72). The authors also reported a subgroup analysis of patients with normal MRI at baseline, and of patients with silent infarcts at baseline. Among the patients with normal MRI at baseline, there was no significant difference in the incidence of stroke comparing long-term transfusion therapy with no transfusion (RR 0.27; 95% CI 0.03, 2.31). Among patients with silent infarcts at baseline, there was a trend towards more stroke events in the no transfusion group (RR 0.08; 95% CI 0.01, 1.35), but this did not reach statistical significance.

In the study by Adams (2005), none of the patients (0%) in the continued transfusion group experienced stroke compared with two patients (4.9%) in the halted transfusion group. This difference was not statistically significant (RR 0.22; 95% CI 0.01, 4.35). However, when analysed using TCD, a statistically significant effect favouring continued transfusions was reported for reversion to abnormal TCD (RR 0.04; 95% CI 0.00, 0.60) and when analysed as a composite outcome with stroke (RR 0.03; 95% CI 0.00, 0.53).

The study by Debaun (2014) reported six patients (6.1%) in the transfusion group experiencing a recurrence of infarct or haemorrhage[[11]](#footnote-11) compared with 14 patients (14.4%) in the standard care group. The incidence rate of infarct recurrence was reported to favour RBC transfusions (2/100 person-years at risk versus 4.8/100 person-years at risk), with the number needed to treat for 3 years to prevent one infarct calculated to be 13. None of the patients (0%) in the transfusion group experienced a transient ischaemic attack[[12]](#footnote-12) compared with three patients (3.1%) in the standard care group. Adding these TIA events to the infarct recurrence, the incidence rate for all neurologic events was reported to be 2/100 person-years at risk compared with 5.6/100 person-years at risk.

Table 3.1.20 Paediatric patients with sickle cell disease: RBC transfusion versus no transfusion (or alternate dose) – Stroke

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Wang 201360  Level I/II  *Good* | 1 trial (Adams 1998)12  N=130 | Children (2–16 years) with sickle cell anaemia or sickle beta thalassemia and a high risk of stroke | Multicentre, USA | RBC transfusion versus standard care | Stroke | 1/63 (1.6%) | 11/67 (16.4%) | OR 0.08 [0.01, 0.66]  RR 0.10 [0.01, 0.73]c | *Favours RBC transfusion*  *P =*0.02 |
| Adams 199861  Level II  *Good* | N=130 | Cerebral infarction | 1/63 (1.6%) | 10/67 (14.9%) | RR 0.11 [ 0.01, 0.81]c | *Favours RBC transfusion* d  *P =*0.03c |
| Intracerebral haematoma | 0/63 (0%) | 1/67 (1.5%) | RR 0.35 [0.01, 8.54]c | *No significant difference*  *P =*0.52 |
| Pegelow 200162  Level II  *Poor*  \*follow-up of Adams 1998 | N=124 | Children (2–16 years) with HbSS or Sβ0 thalassemia and elevated TCD velocity | Multicentre, USA | Long-term transfusion therapy versus standard care | Stroke at 36 months (all patients) | 1/55 (1.8%) | 13/69 (18.8%) | RR 0.10 [0.01, 0.72]c | *Favours RBC transfusion*  *P =*0.02c |
| Stroke at 36 months (subjects with normal MRI at baseline) | 1/37 (2.7%) | 4/40 (10.0%) | RR 0.27 [0.03, 2.31]c | *No significant difference*  *P =*0.23c |
| Stroke at 36 months (subjects with silent infarcts at baseline) | 0/18 (0%) | 9/29 (31.0%) | RR: 0.08 [0.01, 1.35]c | *No significant difference*  *P =*0.08c |
| Cherry 201259  Level I/II  *Good* | 1 trial (Adams 2005)61  N=79 | Children (2–16 years with sickle cell disease and a high risk of stroke based on TCD screening | Multicentre, USA and Canada | Continued RBC transfusion versus halted RBC transfusion | Stroke | 0/38 (0%) | 2/41 (4.9%) | RR 0.22 [0.01, 4.35]c | *No significant difference*  *P =*0.32c  *P =*0.31e |
| Reversion to abnormal TCD | 0/38 (0%) | 14/41 (34.1%) | RR 0.04 [0.00, 0.60]c | *Favours continued RBC transfusion*  *P =*0.02c  *P =*0.01e |
| Stroke or reversion to abnormal TCD | 0/38 (0%) | 16/41 (39.0%) | RR 0.03 [0.00, 0.53]c | *Favours continued RBC transfusion*  *P =*0.02c  *P <*0.001e |
| Debaun 201413  Level II  *Fair* | N=196 | Children (5–15 years) with sickle cell anaemia | Multicentre, Canada, France, UK, USA | Regular RBC transfusion versus standard care | Recurrence of infarct or haemorrhages | 6/99 (6.1%)  2.0/100 person-years at risk | 14/97 (14.4%)  4.8/100 person-years at risk | RR 0.42 [0.17, 1.05]c  IRR 0.41 [0.12, 0.99] | *Favours RBC transfusions*  *P =*0.04f |
| TIA | 0/99 (0%) | 3/97 (3.1%) | RR 0.14 [0.01, 2.67]c | *No significant difference*  *P =*0.19c |
| Incidence rate of all neurologic events (including TIA) | 2.0/100 person-years at risk | 5.6/100 person-years at risk | RR 0.36 [0.10, 0.83] | *Favours RBC transfusions*  *P =*0.02 |

CI, confidence interval; HbSS, sickle cell anaemia; IRR, incidence rate ratio; MRI, magnetic resonance imaging; OR, odds ratio; RBC, red blood cell; RR, risk ratio; Sβ0, sickle beta zero; TCD, transcranial Doppler; TIA, transient ischaemic attack

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Reported by Adams (1998) as a 91% lower risk reduction in transfusion group (*P =*0.002).

**e.** *P-*value reported by study authors.

**f.** When calculated in RevMan 5.1.2 the effect is borderline significant (*P =*0.06).

###### Secondary outcomes[[13]](#footnote-13)

Transfusion-related serious adverse events

One Level I study (Cherry 2012) included data from two Level II studies (Adams 1998, Adams 2005) and one additional Level II study (Debaun 2014) assessing the effect of RBC transfusions provided evidence for transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) among paediatric patients with sickle cell disease. Both STOP trials (Adams 1998, Adams 2005) were assessed to be of good-quality, and Debaun (2014) was rated as fair-quality. The results of these studies are summarised in the **Table 3.1.21**.

In the study by Adams (1998), there were 10 patients (15.9%) who were reported to experience alloimmunisations to RBCs, and 12 patients (19%) who experienced a transfusion reaction. No patients developed hepatitis C.

Adams (2005) reported one patient (2.6%) who experienced alloimmunisation to RBCs, seven patients (18.4%) who experienced a transfusion reaction, and one patient (2.6%) who experienced a serious transfusion reaction.

In the study by Debaun (2014), there were 15 patients (16.7%) in the transfusion group who experienced a transfusion reaction, compared with one patient (0.95%) in the standard care group. There were 25 transfusion reactions in total, of which 13 were allergic (52.0%) and 8 (32.0%) were febrile non-haemolytic.

Functional/performance measures

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in neonatal and paediatric patients with sickle cell disease that reported functional and performance measures.

Table 3.1.21 Paediatric patients with sickle cell disease: RBC transfusion versus no transfusion (or alternate dose) – Transfusion-related serious adverse events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Cherry 201259  Level I  *Good* | 1 trial (Adams 1998)12  N=130 | Children (2–16 years) with HbSS or sickle beta thalassemia and a high risk of stroke | Multicentre, USA | RBC transfusion versus standard care. | Alloimmunisations to RBC | 10/63 (15.9%) | NR | Not estimable | NA |
| Transfusion reaction | 12/63 (19.0%) | NR | Not estimable | NA |
| Hepatitis C | 0/63 (0%) | NR | Not estimable | NA |
| 1 trial (Adams 2005)61  N=79 | Children (2–16 years) with sickle cell disease and a high risk of stroke based on TCD screening | Multicentre, Canada, USA | Continued RBC transfusion versus halted RBC transfusion. | Alloimmunisations to RBC | 1/38 (2.6%) | NR | Not estimable | NA |
| Transfusion reaction | 7/38 (18.4%) | NR | Not estimable | NA |
| Serious transfusion reaction | 1/38 (2.6%) | NR | Not estimable | NA |
| Debaun 201413  Level II  *Fair* | N=196 | Children (5–15 years) with sickle cell anaemia | Multicentre, Canada, France, UK, USA | Regular RBC transfusion versus standard care | Transfusion reaction | 15/90 (16.7%)c | 1/106 (0.95%) | RR 17.67 [2.38, 131.15] | *Favours no transfusion*  *P =*0.005 |
| Transfusion reaction (allergic) | 13/25 (52.0%) | NR | Not estimable | NR |
| Transfusion reaction (febrile non-haemolytic) | 8/25 (32.0%) | NR | Not estimable | NR |

CI, confidence interval; HbSS, sickle cell anaemia; NA, not applicable; NR, not reported; RBC, red blood cell; RR, risk ratio; TCD, transcranial Doppler

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** 9 participants had 1 reaction, 6 had 2 reactions and 1 had 4 reactions.

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

There were no Level I or Level II studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in neonatal and/or paediatric patients with sickle cell disease.

### Neonatal and paediatric patients with cancer

| Evidence statements – anaemia associated with cancer (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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*.14 |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.a  a See Appendix F (*RBC transfusions in preterm infants*) and 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.a This reassessment will also guide the decision on whether to retest the Hb level.  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*15 |
| 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. |
| CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell; | |

##### Background

People with cancer will frequently develop anaemia as a result of bone marrow infiltration by malignancy, bone marrow failure 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. RBC transfusion can rapidly correct anaemia and the associated symptoms; however, the effect may be temporary and can place patients are risk of unwanted transfusion reactions, iron overload and alloimmunisation.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusion compared with no transfusion in neonatal and/or paediatric patients with anaemia associated with cancer.

###### Level II evidence

There were no Level II studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusion compared with no transfusion in neonatal and/or paediatric patients with anaemia associated with cancer.

###### Level III evidence

There were no Level III-2 studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusion compared with no transfusion in neonatal patients with anaemia associated with cancer.

The systematic review and hand-searching process identified one Level III-2 study (Jaime-Perez 2011) that examined the effect of RBC transfusions in paediatric patients with anaemia associated with cancer (see **Appendix C, Volume 2**). The main characteristics of this study are summarised in **Table 3.1.22**.

Jaime-Perez (2011) was a poor-quality retrospective longitudinal study conducted at a single hospital in Mexico. The authors compared transfusion of more than five units of leukoreduced RBC with between one and five units of leukoreduced RBCs or no transfusion, and assessed overall survival at 60 months in 108 children aged <15 years with acute lymphoblastic leukaemia.

Table 3.1.22 Characteristics and quality of Level III evidence – RBC transfusion versus no transfusion in paediatric patients with cancer

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Jaime-Perez (2011)63 | Retrospective longitudinal  *Poor* | Children (aged <15 years) diagnosed with acute lymphoblastic leukaemia  N=108 | Transfusion of >5 units leukoreduceda RBC (n=24) versus 1–5 units leukoreduced RBC (n=72) versus no transfusion (n=12) | Mortality |

RBC, red blood cells

**a.** Leukoreduced RBCs are not available in Australia (product was leukoreduced but not leukodepleted or irradiated).

##### Results

###### Mortality

There was one Level III study of poor-quality (Jaime-Perez 2011) that assessed the association between RBC transfusions and mortality in paediatric patients with cancer. The results of this study are summarised in **Table 3.1.23**.

The study by Jaime-Perez (2011) assessed mortality in 108 children aged <15 years with acute lymphoblastic leukaemia, and reported transfusion of more than five units of RBC to be a significant predictor of mortality (HR 4.453; 95% CI 1.64, 12.09). This was determined in a multivariate Cox regression analysis adjusted for T-cell immunophenotype, leukocytosis, ‘high risk’ patients, extramedullary disease, age, and number and type of blood products transfused. The study was not sufficiently powered to detect a significant difference for this outcome.

Table 3.1.23 Neonatal and paediatric patients with cancer: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | | No transfusion (or alternate dose)  n/N (%) | | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | | |
| Jaime-Perez 201163  Level III–2  *Poor* | Retrospective longitudinal  N=108 | Children (<15 years) with acute lymphoblastic leukaemia | Single hospital, Mexico | Transfusion of >5 units RBC versus 1–5 units RBC versus no transfusion c | Overall survival at 60 months | >5 units  NR (29%) | 1–5 units  NR (78%)0 units | | 0 units  NR (100%) | NR | *Favours transfusion of less than 5 units RBC*  *P =*0.001 |
| Mortality | NR | NR | | NR | HR 4.453 [1.64, 12.09] | *Favours transfusion of less than 5 units RBC*  *P =*0.003 |
| Multivariate Cox regression analysis adjusted for T-cell immunophenotype, leukocytosis ≥50,000, high risk group, presence of extramedullary disease, age <2 or >10 years, and number and type of blood products transfused. | | | | |

CI, confidence interval; Hct, haematocrit; HR, hazard ratio; NR, not reported; RBC, packed red blood cell; RBC, red blood cell

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Leukoreduced RBCs are not available in Australia.

###### Secondary outcomes[[14]](#footnote-14)

Transfusion-related serious adverse events

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in paediatric or neonatal patients with cancer that reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

Functional/performance status

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in paediatric patients with cancer that reported on functional/performance measures.

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

There were no Level I or Level II studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in neonatal and/or paediatric patients with anaemia associated with cancer.

### Neonatal and paediatric patients with severe anaemia associated with malaria

| Evidence statements – severe anaemia associated with malaria (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal patients with severe anaemia associated with malaria, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | In paediatric patients with severe anaemia associated with malaria, the effect of RBC transfusion compared with no transfusion on mortality is uncertain.  (See evidence matrix D1.M in Volume 2 of the technical report.) | √√ | √√√ | NA | √ | X |
|  | In paediatric patients with severe anaemia associated with malaria, the effect of low-dose RBC transfusion compared with high-dose RBC transfusion on mortality is uncertain.  (See evidence matrix D1.M in Volume 2 of the technical report.) | √√ | NA | NA | √ | X |
|  | In neonatal and paediatric patients with severe anaemia associated with malaria, 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 | | | | | | |

Recommendations and practice points concerning the use of RBC transfusion in children with malaria were not made because they were judged by the CRG to be outside the scope of the guidelines.

Neonatal and paediatric patients with malaria are therefore not discussed in the Module 6 Guidelines.

The evidence identified during the systematic review and hand-searching process is presented here for completeness.

##### Background

Malaria can lead to the development of severe anaemia as a result of the red cell rupture and destruction that occurs during the lifecycle of the parasite, and because of the decreased red cell production that may occur in the acute phase of infection. RBC transfusions are used to prevent death in very ill patients, and shorten recovery from anaemia in more stable patients, but can also result in circulatory overload, transfusion reactions and infections.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study (Meremikwu 2010) that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in neonatal and paediatric patients with severe anaemia (defined as Hct <20%) associated with malaria (see **Appendix C, Volume 2**). The main characteristics of this study are summarised in **Table 3.1.24**.

Meremikwu (2010) was a good-quality systematic review that identified two Level II studies (Bojang 1997, Holzer 1993) that examined the effect of RBC transfusions on the outcome of mortality in 230 children residing in the Gambia and Tanzania with severe haemolytic anaemia (Hct <20%) and confirmed malaria. Both studies (Bojang 1997, Holzer 1993) excluded children with PCV <12%, haemorrhage or features of congestive cardiac failure (i.e. very severe cases). Holzer (1993) also excluded patients with temperature >38 °C and Bojang (1997) excluded those with sickle cell disease or severe malnutrition. The studies were rated as having overall unclear risk of bias due to concerns about allocation concealment and high attrition bias.

Table 3.1.24 Characteristics and quality of Level I evidence – RBC transfusion versus no transfusion (or alternate dose) in paediatric patients with malaria

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Meremikwu (2010)64 | Systematic review  *Good* | Children with severe anaemia (Hct <20 %) and malaria parasitaemia  N=230 | RBC transfusion (n=118) versus no transfusion (n=112) | Mortality |

Hct, haematocrit; RBC, red blood cell

###### Level II evidence

The systematic review and hand-searching process identified one additional Level II study (Olupot-Olupot 2014) that examined the effect of RBC transfusion compared with no transfusion (or alternate dose) in neonatal and paediatric patients with severe anaemia associated with malaria (see **Appendix C, Volume 2)**. The main characteristics of this study are summarised in **Table 3.1.25**.

The good-quality study by Olupot-Olupot (2014) was conducted in two centres in Uganda; it compared transfusion of a standard volume (20 mL/kg) of whole blood with an increased transfusion volume (30 mL/kg) in paediatric patients aged >60 days and <12 years with severe anaemia (defined as a haemoglobin level <6 g/dL). Participants could also receive packed RBCs as an alternative to whole blood transfusion, but this only occurred once during the trial period, with all other transfusions administered as whole blood. The applicability of this trial to the Australian context is therefore limited. Malaria was present in 59% of patients (slide positive and/or malaria rapid diagnostic test), 20% of patients had sickle cell anaemia (HbSS), 5% of patients were homozygous for α-thalassaemia, and 12% of patients had glucose-6-phosphate dehydrogenase deficiency.

Table 3.1.25 Characteristics and quality of Level II evidence – RBC transfusion versus no transfusion (or alternate dose) in paediatric patients with malaria

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Included and assessed by Meremikwu (2010) | | | | |
| Bojang (1997)65 | RCT  *Unclear risk of bias* | Paediatric patients aged 9 months to 9 years with malaria and severe anaemia (PCV 12–15%)  N=114 | RBC transfusion versus no transfusion (with oral iron)  \*all participant received chloroquine (25 mg/kg) plus sulphadoxine-pyrimethamine | Mortality |
| Holzer (1993)66 | RCT  *Unclear risk of bias* | Paediatric patients aged 2 months to 6 years with malaria and severe anaemia (PCV 12–17%)  N=116 | RBC transfusion versus no transfusion  \*all participant received chloroquine (25 mg/kg) plus mebendazole | Mortality |
| Additional Level II studies identified in this review | | | | |
| Olupot-Olupot (2014)67 | RCT  *Good* | Paediatric patients aged >60 days and <12 years with severe anaemia (Hb <6 g/dL)a  N=160 | Whole blood (20 mL/kg) or RBC (10 mL/kg) transfusion (n=78) versus whole blood (30 mL/kg) or RBC (15 mL/kg) transfusion (n=82) | Mortality  Transfusion-related SAEs |

Hb, haemoglobin; PCV, packed cell volume; RBC, red blood cell; RCT, randomised controlled trial; SAEs, serious adverse events

**a.** Only 59% of patients had malaria; those with malignancy, surgery, acute trauma, or acute severe malnutrition were excluded from the study.

###### Level III evidence

There were no Level III studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusions compared with no transfusion (or alternate dose) in neonatal and/or paediatric patients with severe anaemia associated with malaria.

##### Results

###### Mortality

There were two Level II studies (Bojang 1997, Holzer 1993) included in one Level I study (Meremikwu 2010) and an additional Level II study (Olupot-Olupot 2014) that assessed the effect of RBC transfusion in paediatric patients with severe anaemia that provided evidence for mortality. One study (Olupot-Olupot 2014) was assessed to be of good-quality, and two studies (Bojang 1997, Holzer 1993) were rated as poor-quality. The results of these studies are summarised in **Table 3.1.26**.

The systematic review by Meremikwu (2010) reported pooled results from two Level II studies (Bojang 1997, Holzer 1993) that included 230 children with malaria and severe haemolytic anaemia (Hct <20%). There was one death (0.8%) in the RBC transfusion group compared with three deaths (2.7%) in the no transfusion group, representing no statistically significant difference between treatment groups on the rate of mortality (RR 0.41; 95% CI 0.06, 2.70).

The RCT by Olupot-Olupot (2014) assessed the effect on mortality of two different doses of whole blood cell transfusions in paediatric patients with severe anaemia. Four patients (4.9%) died before 48 hours in the group receiving 20 mL/kg whole blood cells compared with no deaths in the group administered 30 mL/kg whole blood cells (RR 8.57; 95% CI 0.47, 156.54). There were six deaths (7.3%) before 28 days post-admission in the lower volume group compared with one death (1.3%) in the higher volume group (RR 0.18; 95% CI 0.02, 1.42). Neither outcome reached statistical significance.

Table 3.1.26 Paediatric patients with malaria: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion (or alternate dose)  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Meremikwu 200064  Level I  *Good* | 2 trials (Bojang 1997, Holzer 1993)65-66  N=230 | Children with severe anaemia (Hct <20 %) and confirmed malaria parasitaemia | Gambia and Tanzania | Blood transfusion versus no transfusion (conservative management) | Mortality | 1/118 (0.8%) | 3/112 (2.7%) | RR 0.41 [0.06, 2.70] | *No significant difference*  *P =*0.35  I2= 0% |
| Level II evidence | | | | | | | | | |
| Olupot-Olupot 201467  Level II  *Good* | N=160 | Children (>60 days and <12 years) with severe anaemia | Two centres, Uganda | Whole blood (20 mL/kg) or RBC (10 mL/kg) transfusion versus whole blood (30 mL/kg) or RBCs (15 mL/kg) transfusion | Died before 48 hours | 4/82 (4.9%) | 0/78 (0%) | RR 8.57 [0.47, 156.54]c | *No significant difference*  *P =*0.15c  *P =*0.12d |
| Died before 28 days post-admission | 6/82 (7.3%) | 1/78 (1.3%) | RR 0.18 [0.02, 1.42] | *No significant difference*  *P =*0.12 |

CI, confidence interval; Hct, haematocrit; RBC, packed red blood cell; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value reported by study authors using Fisher’s Exact test

###### Secondary outcomes[[15]](#footnote-15)

Transfusion-related serious adverse events

There was one Level II study of good-quality (Olupot-Olupot 2014) that provided evidence for transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) among paediatric patients with severe anaemia. The results of this study are summarised in **Table 3.1.27**.

The RCT by Olupot-Olupot (2014) reported no allergic reactions (0.0%) in the group receiving 20 mL/kg whole blood cells compared with one allergic reaction (1.3%) in the group administered 30 mL/kg whole blood cells. Three of the six fatal events that occurred in-hospital among infants in the low-volume group were judged to be possibly related to transfusion, but none were due to volume overload, pulmonary oedema, heart failure or TRALI.

Functional/performance status

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in neonatal and paediatric patients with severe anaemia associated with malaria and reported functional and performance measures.

Table 3.1.27 Paediatric patients with malaria: Results for RBC transfusion versus no transfusion (or alternate dose) – Transfusion-related serious adverse events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion (or alternate dose)  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Olupot-Olupot 201467  Level II  *Good* | N=160 | Children (>60 days and <12 years) with severe anaemia | Two centres, Uganda | Whole blood (20 mL/kg) or RBC (10 mL/kg) transfusion versus whole blood (30 mL/kg) or RBCs (15 mL/kg) transfusion | Allergic reaction/transfusion reaction | 0/82 (0%) | 1/78 (1.3%) | NR | NR |
| Fatal adverse event possibly related to transfusion | 3/82 | 0/78 | NR | NR |

CI, confidence interval; NR, not reported; RBC, red blood cell

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

There were no Level I or Level II studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in neonatal and/or paediatric patients with severe anaemia associated with malaria.

### Neonatal and paediatric patients requiring surgery

| Evidence statements – surgical (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal patients undergoing surgery, the effect of RBC transfusion compared with no transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 | √√ | √ |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 | √√√ | √√ |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Recommendations – 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*.14 |
| 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*.14 |
| PP8 | In paediatric patients less than 20 kg, calculate transfusion volume (mL) based on weight and desired Hb increment.a  a See Appendix F (*RBC transfusions in preterm infants*) and 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.a This reassessment will also guide the decision on whether to retest the Hb level.  a See PP2 in *Patient Blood Management Guidelines: Module 2 – Perioperative*15 |
| 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

Neonatal and paediatric patients undergoing major surgery are at risk of perioperative blood loss that can be treated with RBC transfusions to improve tissue oxygenation, and to treat hypovolaemia and anaemia. Cardiac surgery in particular often leads to RBC transfusion because of the disparity between the priming volumes of the cardiopulmonary bypass circuits and the patient’s circulating blood volume. Patients undergoing cardiothoracic surgery for congenital cardiac disease may be hypoxic and polycythaemic and have altered coagulation profiles. Their surgeries are complex, necessitating long cardiopulmonary bypass times, extended periods of hypothermia and circulatory arrest. Other surgical procedures associated with significant blood loss in the paediatric setting that may necessitate RBC transfusion include liver transplantation, and surgery for scoliosis or craniosynostosis. RBC transfusions may also be administered during the postoperative period, but the optimal haemoglobin threshold for transfusion is unknown. Transfusions are also associated with infection, transfusion reactions, excessive intravascular volume and immunosuppressive effects in this population.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in neonatal and/or paediatric patients requiring surgery.

###### Level II evidence

There were no Level II studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in neonatal and/or paediatric patients requiring surgery.

###### Level III evidence

The systematic review and hand-searching process identified three Level III–2 studies (Kneyber 2013, Nacoti 2012, Redlin 2013) that examined the effect of RBC transfusion compared with no transfusion (or alternate dose) in neonatal and/or paediatric patients requiring surgery (see **Appendix C, Volume 2**). The main characteristics of these studies are summarised in **Table 3.1.28**.

Kneyber (2013)68 was a good-quality retrospective cohort study of 335 children aged from birth to 18 years who were admitted and transfused within 48 hours of paediatric ICU (PICU) admission after cardiac surgery. The study was conducted in the Netherlands and examined the association between RBC transfusion and mortality.

Nacoti (2012)69 was a fair-quality retrospective cohort study of 243 paediatric liver transplant patients aged <18 years. The study was conducted at a single hospital in Italy and assessed the association between the use of RBC and survival at 12 months.

Redlin (2013)70 was a fair-quality, three-armed retrospective cohort study of 288 paediatric cardiac surgery patients weighing less than 16 kg conducted in Germany. The authors examined the effect of intraoperative RBC transfusion compared with postoperative RBC transfusion compared with no transfusion on in-hospital mortality.

Table 3.1.28 Characteristics and quality of Level III evidence – RBC transfusion versus no transfusion (or alternate dose) in paediatric patients requiring surgery

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Kneyber (2013)71 | Retrospective cohort  *Good* | Children aged 0 to 18 years admitted to PICU after cardiac surgery  N=335 | RBC transfusion within 48 hours of admission (n=86) versus no RBC transfusion within 48 hour (n=249)a | Mortality |
| Nacoti (2012)69 | Retrospective cohort  *Fair* | Paediatric patients aged <18 years requiring liver transplant  N=243 | Perioperative transfusion of ≥3 units RBC (n=39) versus 2 units RBC (n=75) versus ≤1 unit RBC (n=129) | Mortality |
| Redlin (2013)70 | Retrospective cohort  *Fair* | Paediatric patients requiring cardiac surgery weighing less than 16 kg  N=288 | Intraoperative RBC transfusion (n=149) versus postoperative RBC transfusion (n=68) versus no transfusion (n=71) | Mortality |

PICU, paediatric intensive care unit; RBC, red blood cell

**a.**There were 25 patients in the ‘no transfusion’ group who received a RBC transfusion 48 hours after admission.

##### Results

###### Mortality

There were three Level III studies (Kneyber 2013, Nacoti 2012, Redlin 2013) included in the systematic review that provided evidence for mortality among neonatal and/or paediatric patients requiring surgery. The results of these studies are summarised in **Table 3.1.29**.

Kneyber (2013) assessed in PICU mortality in 335 children post-surgery in the Netherlands, and found no statistically significant difference between transfusion of RBC within 48 hours of admission or no RBC transfusion (RR 5.79; 95% CI 0.53, 63.06). Two children (2.3%) in the transfusion group died compared with one patient (0.4%) in the control group. In a subgroup analysis, no patient with normal physiology died post-surgery. The authors noted that transfused patients were significantly younger (p <0.001), weighed less (p <0.001) and had a higher PRISM II score (p <0.001) than non-transfused patients.

Nacoti (2012) assessed mortality in paediatric liver transplant patients. In a propensity score adjusted analyses, transfusion of three or more RBC units was significantly associated with mortality at 12 months (HR 3.010; 95% CI 1.009, 8.979) but transfusion of two RBC units was not (HR 2.170; 95% CI 0.747, 6.301).

Redlin (2013) assessed in-hospital mortality in 288 paediatric patients weighing <16 kg requiring cardiac surgery. Nine patients (6.0%) in the intraoperative transfusion group died compared with one patient (1.5%) in the postoperative transfusion group and no patients (0%) in the no transfusion group. The authors noted that although a significant difference was observed, the mortality rate was too low for detailed statistical analysis.

Table 3.1.29 Neonatal and/or paediatric patients requiring surgery: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | | Outcome | Results | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | | | No transfusion (or alternate dose)  n/N (%) | | | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | | | | | |
| Kneyber 201371  Level III–2  *Good* | Retrospective cohort  N=335 | Children (0–18 years) admitted to PICU post-surgery | Single tertiary PICU, The Netherlands | RBC transfusion within 48 hours of admission (leukocyte depleted) versus no transfusion within 48 hours | | In PICU mortality (all patients) | 2/86 (2.3%) | | | 1/249 (0.4%) | | | RR 5.79 [0.53, 63.06]c | *No significant difference*  *P =*0.15c  *P =*0.163d |
|  | *Subgroup analysis: patients with normal physiology post-surgery.* | | | | | | |  |
| In PICU mortality | 0/66 (0%) | | | 0/205 (0%) | | | Not estimable | NA |
| Nacoti 201269  Level III–2  *Fair* | Retrospective cohort  N=243 | Children (<18 years) requiring liver transplant | Single hospital, Italy | | Transfusion of ≥3 units RBC versus 2 units RBC versus ≤1 unit RBC | Survival at 12 months | ≥3 units  NR (69.9%) | | 2 units  NR (89.1%) | | | ≤1 unit  NR (94.3%) | NR | *Significant difference*  *P <*0.001 |
| Propensity score adjusted analysis for transfusion of 2 units RBC. | | | | | | HR 2.170 [0.747, 6.301] | *No significant difference*  *P =*0.154 |
| Propensity score adjusted analysis for transfusion of ≥3 units RBC. | | | | | | HR 3.010 [1.009, 8.979] | *Favours <3 units RBC transfusion*  *P =*0.048 |
| Redlin 201370  Level III–2  *Fair* | Retrospective cohort  N=288 | Children weighing <16 kg requiring cardiac surgery | Germany | | Intraoperative RBC transfusion versus postoperative RBC transfusion versus no transfusion | In-hospital mortality | Intraoperative transfusion 9/149 (6.0%) | Postop transfusion 1/68 (1.5%) | | | No transfusion 0/71 (0%) | | NR | *Significant difference*  *P =*0.04 |
| In-hospital mortality was too low for detailed statistical analysis; a chi-square test was used to generate the *P-*value. | | | | | | |

CI, confidence interval; HR, hazard ratio; NA, not applicable; NR, not reported; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value reported by study authors.

###### New or progressive multiple organ dysfunctions

There were no studies identified in the systematic review and hand-searching process that assessed the effect of RBC transfusion compared with no transfusion in neonatal and/or paediatric patients requiring surgery that reported on new or progressive multiple organ dysfunctions (MODs).

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

###### Level I evidence

One Level I study (Wilkinson 2014) identified in the systematic review and hand-searching process examined the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in neonatal and/or paediatric patientsundergoing surgery (see **Appendix C, Volume 2**). The main characteristics of this study are summarised in **Table 3.1.30.**

Wilkinson (2014) was a good-quality systematic review that identified two Level II studies (Cholette 2011, Willems 2010) that compared restrictive and liberal RBC transfusion strategies in 185 paediatric or neonatal patients aged 0–16 years undergoing cardiac surgery for congenital heart disease. The authors assessed all-cause mortality at 30 days and 2 years post-surgery; and included data on adverse events from these trials.

Table 3.1.30 Characteristics and quality of Level I evidence - restrictive RBC transfusion versus liberal RBC transfusion in neonatal and/or paediatric patients requiring surgery

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Wilkinson (2014)72 | Systematic review  *Good* | Paediatric or neonatal patients aged 0 to 16 years undergoing cardiac surgery for congenital heart disease  2 RCTs, N=185 | Restrictive RBC transfusion (n=93 ) versus liberal RBC transfusion (n=92) | Mortality |

RBC, red blood cell; RCT, randomised controlled trial

###### Level II evidence

The literature search identified one additional Level II study (Rouette 2010) that examined the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in neonatal and/or paediatric patients undergoing surgery (see **Appendix C, Volume 2**). The main characteristics of all Level II studies (including those identified by the Level I study) are summarised in **Table 3.1.31.**

The poor-quality RCT by Cholette (2011) assessed the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in 60 children (mean age 30 months) scheduled for elective partial or total cavopulmonary connection at a single centre in the USA. The authors reported data on mortality before discharge and was rated as poor-quality because the method for randomisation was not reported and allocation concealment was unclear. Also, the liberal transfusion threshold used in the study (13 g/dL) was much higher than that recommended in current Australian practice.

The good-quality studies by Rouette (2010) and Willems (2010) reported data from two separate subgroups of patients enrolled in the TRIPICU study (Lacroix 2007), a multicentre RCT of 637 critically ill paediatric patients aged 3 days to 14 years. Subjects were randomised to either a restrictive or liberal RBC transfusion group and were located in Belgium, Canada, the UK or the USA (see **Section 3.1.9.2** for further details of this trial). A significant proportion of patients in the restrictive transfusion group did not receive a transfusion, and the studies by Rouette 2010 and Willems 2010 were not sufficiently powered to demonstrate statistical significance.

Rouette (2010) included 124 postoperative general surgery paediatric patients, and Willems (2010) included 125 patients paediatric patients aged 28 days to 14 years post-cardiac surgery or catheterisation. The authors assessed overall 28-day mortality, in PICU mortality, new or progressive MODs, and other markers of organ system dysfunction.

The systematic review and hand-searching process identified one additional RCT (Robitaille 2013) that met our inclusion criteria but that RCT was stopped after only six patients had been recruited; therefore, it did not provide any suitable data for inclusion. The authors intended to examine the effect of a restrictive transfusion strategy (maintain Hb ≥70 g/L) compared with a liberal transfusion strategy (maintain Hb ≥120 g/L) on granulocyte recovery in children aged 1–18 years who were undergoing an allogeneic bone marrow transplant. Mortality was a secondary outcome. The first three patients allocated to the liberal transfusion arm developed vaso-occlusive disease, and the trial was stopped by the Data Safety and Monitoring Board.

Table 3.1.31 Characteristics and quality of Level II evidence - restrictive RBC transfusion versus liberal RBC transfusion in neonatal and/or paediatric patients requiring surgery

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Cholette (2011)73 | RCT  *Poor* | Paediatric patients (mean age ~30 months) scheduled for elective partial or total cavopulmonary connection (BDG or Fontan procedures)  N=60 | Restrictive RBC transfusion (Hb <9.0g/dL plus clinical symptoms of anaemia) (n=30) versus liberal RBC transfusion (Hb <13.0 g/dL with or without clinical symptoms) (n=30) | Mortality |
| Rouette (2010)74  \*subgroup of patients from the TRIPICU study | RCT  *Good* | Postoperative general surgery patients aged 3 days to 14 years admitted to PICU  N=124 | Restrictive RBC transfusion (threshold 70 g/L) (n=60) versus liberal RBC transfusion (threshold 95 g/L). (n=64)  \*all RBC were pre-storage leukocyte reduced allogeneic | Mortality  New or progressive MODs |
| Willems (2010)75  \*subgroup of patients from the TRIPICU study | RCT  *Good* | Paediatric patients aged 28 days to 14 years post-cardiac surgery or catheterisation  N=125 | Restrictive RBC transfusion (threshold 70 g/L) (n=63) versus liberal RBC transfusion (threshold 95 g/L). (n=62)  \*all RBC were pre-storage leukocyte reduced allogeneic | Mortality  New or progressive MODs  Transfusion-related SAEs |

BDG, Bidirectional Glenn; Hb, haemoglobin; MODs, multiple organ dysfunction; PICU, paediatric intensive care unit; RBC, red blood cells; RCT, randomised controlled trial; SAEs, serious adverse events; TRIPICU, transfusion requirements in the paediatric intensive care unit

##### Results

###### Mortality

There were two Level II studies (Cholette 2011, Willems 2010) identified in one Level I study (Wilkinson 2014) and one additional Level II study (Rouette 2010) comparing restrictive and liberal transfusion strategies in neonatal and/or paediatric patients requiring surgery that provided evidence for mortality. Two studies (Rouette 2010, Willems 2010) were assessed to be of good-quality and one study (Cholette 2011) was rated as poor-quality. The results of these studies are summarised in **Table 3.1.32**.

None of the studies reported a statistically significant difference between restrictive and liberal transfusion strategies on the rate of mortality among paediatric patients requiring surgery.

Cholette (2011) assessed mortality before discharge in 60 children scheduled for cardiac surgery and reported no deaths (0%) in the restrictive transfusion group compared with one death (3.3%) in the liberal transfusion group (RR 0.33; 95% CI 0.01, 7.87).

Rouette (2010) assessed overall mortality in 124 paediatric patients 28 days post-general surgery. There was one patient death in each of the restrictive (1.7%) and liberal (1.6%) transfusion groups (RR 1.07; 95% CI 0.07, 16.67). The death in the restrictive transfusion group occurred in PICU, and the death in the liberal transfusion group occurred in the 28 days post-PICU discharge.

Willems (2010) assessed all-cause mortality in 125 paediatric patients 28 days post-cardiac surgery. Two patients from each of the restrictive (3.2%) and liberal (3.2%) transfusion groups died (RR 0.98; 95% CI 014, 6.77). The authors also reported in PICU mortality, with two deaths (3.2%) occurring in the restrictive transfusion group compared with no deaths (0%) in the liberal transfusion group.

Table 3.1.32 Neonatal and/or paediatric patients requiring surgery: Results for restrictive RBC transfusion versus liberal RBC transfusion – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Wilkinson 201472  Level I/II  *Good* | 1 trial (Cholette 2011)73  N=60 | Children (mean age ~30 months) scheduled for elective partial or total cavopulmonary connection | Single centre, USA | Restrictive RBC transfusion versus liberal RBC transfusion | All-cause mortality before discharge | 0/30 (0%) | 1/30 (3.3%)  \*due to staphylococcal sepsis on day 39 | RR 0.33 [0.01, 7.87] | *No significant difference*  *P =*0.50  I2= NA |
| 1 trial (Willems 2010)75  N=125 | Children (aged 28 days to 14 years) post-cardiac surgery or catheterisation | Multicentre, Belgium, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | All-cause mortality 28 days post-surgery | 2/63 (3.2%) | 2/62 (3.2%) | RR 0.98 [0.14, 6.77] | *No significant difference*  *P =*0.99  I2= NA |
| Rouette 201074  Level II  *Good*  \*subgroup of patients from the TRIPICU study | N=124 | Children (aged 3 days to 14 years) post-general surgery | Multicentre, Belgium, Canada, UK, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Overall 28 day mortality | 1/60 (1.7%) | 1/64 (1.6%) | RR 1.07 [0.07, 16.67] | *No significant difference*  *P =*0.96 |
| Mortality in PICU | 1/60 (1.7%) | 0/64 (0%) | RR 3.20 [0.13, 76.98] | *No significant difference*  *P =*0.47 |
| Mortality 28 days post-PICU | 0/60 (0%) | 1/64 (1.6%) | RR 0.36 [0.01, 8.55] | *No significant difference*  *P =*0.52 |
| Willems 201075  Level II  *Good*  \*subgroup of patients from the TRIPICU study | N=125 | Children (aged 28 days to 14 years) post-cardiac surgery or catheterisation d | Multicentre, Belgium, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | All-cause mortality in PICU | 2/63 (3.2%) | 0/62 (0%) | RR 4.92 [0.24, 100.49] | *No significant difference*  *P =*0.30 |

CI, confidence interval; NA, not applicable; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio; TRIPICU, transfusion requirements in the paediatric intensive care unit

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### New or progressive MODs

The systematic review and hand-searching process identified two Level II studies (Willems 2010, Rouette 2010) that provided evidence for new or progressive MODs among neonatal and/or paediatric patients requiring surgery. Both studies were assessed to be of good-quality. The results of these studies are summarised in **Table 3.1.33**.

Rouette (2010) reported that five (8.3%) patients in the restrictive transfusion group experienced new or progressive MODs compared with six patients (9.4%) in the liberal transfusion group. This result was not statistically significant (ARR 1; 95% CI –9, 11). In a subgroup analysis based on patient age, the authors found no significant difference in new or progressive MODs in neonates (patients aged ≤28 days), those aged between 29 and 364 days, or those aged ≥1 year. Rouette (2010) also assessed the highest number or organ dysfunctions, highest daily PELOD score, change in PELOD score and average daily PELOD score during PICU stay. No significant difference between restrictive transfusion and liberal transfusion was found for any of these outcomes (see **Table 3.1.33**).

In the study by Willems (2010), there were eight patients (12.7%) in the restrictive transfusion group who experienced new or progressive MODs compared with four patients (6.5%) in the liberal transfusion group. This result was not statistically significant (ARR 6.2; 95% CI –7.6, 10.4). In a subgroup analysis based on patient age, the authors found no significant difference in new or progressive MODs in neonates (patients aged ≤28 days) or infants aged 29–364 days. In patients aged ≥1 year, Willems (2010) reported a trend towards new or progressive MODs favouring liberal RBC transfusion but the sample size was too small to permit any conclusions (ARR 13.3; 95% CI 1.2, 25.5). The authors also assessed highest number of organ dysfunctions, highest daily PELOD score, change in PELOD score and average daily PELOD score during PICU stay. No significant difference between restrictive transfusion and liberal transfusion was found for any of these outcomes (see **Table 3.1.33**).

Table 3.1.33 Neonatal and/or paediatric patients requiring surgery: Results for restrictive RBC transfusion versus liberal RBC transfusion – New or progressive MODs

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%)  Mean ± SD (n) | Liberal RBC transfusion  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level II evidence | | | | | | | | | | | |
| Rouette 201074  Level II  *Good*  \*subgroup of patients from the TRIPICU study | N=124 | Children (aged 3 days to 14 years) post-general surgery | Multicentre, Belgium, Canada, UK, USA | Restrictive RBC transfusion versus liberal RBC transfusion | New or progressive MODs (total) | 5/60 (8.3%) | 6/64 (9.4%) | | ARR 1 [–9, 11] | | *No significant difference*  *P =*0.83 |
|  | *Subgroup analysis: patient age* | | | | |  |
| age ≤28 days | 1/2 (50.0%) | 0/0 (0%) | | Not estimable | | NA |
| age 29–364 days | 1/12 (8.3%) | 1/14 (7.1%) | | RR 1.17 [0.08, 16.72]c | | *No significant difference*  *P =*0.91c |
| age ≥1 year | 3/46 (6.5%) | 5/50 (10.0%) | | RR 0.65 [0.17, 2.58]c | | *No significant difference*  *P =*0.54c |
| Highest number of organ dysfunctions | 1.3 ± 1.2 (60) | 1.3 ± 1.0 (64) | | MD 0.0 [–0.4, 0.4] | | *No significant difference*  *P =*NR |
| Average daily PELOD score during PICU stay | 4.0 ± 7.1 (60) | 3.5 ± 3.8 (64) | | MD –0.5 [–2.5, 1.5] | | *No significant difference*  *P =*NR |
| Average PELOD score on day 1 | 5.3 ± 6.3 (60) | 4.9 ± 5.4 (64) | | MD –0.4 [–2.5, 0.4] | | *No significant difference*  *P =*NR |
| Highest daily PELOD score after day 1 | 7.4 ± 9.6 (60) | 7.6 ± 8.8 (64) | | MD 0.3 [–3.0, 3.5] | | *No significant difference*  *P =*NR |
| Change in PELOD score | 2.1 ± 6.3 (60) | 2.8 ± 6.7 (64) | | MD 0.6 [–1.7, 2.9] | | *No significant difference*  *P =*NR |
| Willems 201075  Level II  *Good*  \*subgroup of patients from the TRIPICU study | N=125 | Children (aged 28 days to 14 years) post-cardiac surgery or catheterisation c | Multicentre, Belgium, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | New or progressive MODs (total) | 8/63 (12.7%) | 4/62 (6.5%) | | ARR 6.2 [–7.6, 10.4] | | *No significant difference*  *P =*0.36 |
|  | *Subgroup analysis: patient age* | | | | |  |
| age ≤28 days | 0/0 (0%) | 0/1 (0%) | | ARR 0.0 [0.0, 0.0] | | *No significant difference*  *P =*NR |
| age 29–364 days | 4/33 (12.1%) | 4/36 (11.1%) | | ARR 1.0 [–14.1, 16.2] | | *No significant difference*  *P =*NR |
| age ≥1 year | 4/30 (13.3%) | 0/25 (0%) | | ARR 13.3 [1.2, 25.5] | | *Favours liberal RBC transfusion* d  *P =*NR |
| Highest number of organ dysfunctions | 1.4 ± 1.2 (63) | 1.34 ± 0.96 (62) | | MD 0.09 [–0.29, 0.47] | | *No significant difference*  *P =*NR |
| Average daily PELOD score during PICU stay | 6.6 ± 9.4 (63) | 5.8 ± 6.4 (62) | | MD 0.78 [–2.06, 3.62] | | *No significant difference*  *P =*NR |
| Average daily PELOD score after day 1 | 3.9 ± 4.7 (63) | 3.3 ± 4.3 (62) | | MD 0.58 [–1.02, 2.17] | | *No significant difference*  *P =*NR |
| Highest daily PELOD score after day 1 | 7.0 ± 10.6 (63) | 6.7 ± 7.3 (62) | | MD 0.27 [–2.96, 3.51] | | *No significant difference*  *P =*NR |
| Change in PELOD score from day 1 | 2.9 ± 9.9 (63) | 3.1 ± 6.5 (62) | | MD –0.18 [–3.13, 2.78] | | *No significant difference*  *P =*NR |

ARR, absolute risk reduction; CI, confidence interval; MD, mean difference; MODs, multiple organ dysfunctions; NA, not applicable; NR, not reported; PELOD, paediatric logistic organ dysfunction; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio; SD, standard deviation; TRIPICU, transfusion requirements in the paediatric intensive care unit

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** The authors noted that although there was a trend towards more organ dysfunction in patients older than 365 days in the restrictive group, the number of patients was too small to permit any conclusions.

###### Secondary outcomes[[16]](#footnote-16)

Transfusion-related serious adverse events

One Level II study (Willems 2010) provided evidence for transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) among paediatric patients requiring surgery. The results of this study are summarised in **Table 3.1.34**.

Willems (2010) reported no significant difference in the number of number of RBC transfusion reactions comparing restrictive and liberal transfusion strategies in paediatric patients requiring cardiac surgery (RD –1.61; 95% CI –4.75, 1.52). No patients in the restrictive group experienced a reaction to RBCs, compared with one patient (1.6%) in the liberal group, but the study was small and not powered to detect a significant difference for this outcome.

Table 3.1.34 Paediatric patients requiring surgery: Results for restrictive RBC transfusion versus liberal RBC transfusion – Transfusion-related serious adverse events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%)  Mean ± SD (n) | Liberal RBC transfusion  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level II evidence | | | | | | | | | | | |
| Willems 201075  Level II  *Good*  \*subgroup of patients from the TRIPICU study | N=125 | Children (aged 28 days to 14 years) post-cardiac surgery or catheterisation | Multicentre, Belgium, Canada, USA | Restrictive RBC transfusion versus liberal RBC transfusion | Reaction to RBC | 0/63 (0%) | 1/62 (1.6%) | | RD –1.61 [–4.75, 1.52] | | *No significant difference*  *P =*NR |

CI, confidence interval; NR, not reported; RBC, red blood cell; RD, risk difference; SD, standard deviation; TRIPICU, transfusion requirements in the paediatric intensive care unit

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

### Critically ill neonatal and paediatric patients

| Evidence statements – critically ill (RBC transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 | √√√ | √√ |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Recommendations – 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 points – critically ill (RBC transfusion) | |
| 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*) |
| 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*.14 |
| 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; Hct, haematocrit; PP, practice point; R, recommendation; RBC, red blood cell; | |

##### Background

Neonatal and paediatric patients are at risk of anaemia in the critical care setting due to factors including the underlying illness, small circulating blood volumes, proportionally higher phlebotomy losses from blood testing and discard volumes (central venous access and arterial lines), surgical or trauma related blood loss and malnutrition. The physiological anaemia of infancy may also contribute.

Critically ill neonates and children have higher rates of RBC transfusion. Such transfusion may be life-saving and should not be withheld in the actively bleeding or hemodynamically unstable patient. However, for patients with mild-moderate anaemia without haemodynamic compromise, the benefit of RBC transfusion is uncertain. All transfusions have potential risks such as transfusion reactions, volume overload, infections, and alloimmunisation.

* + - 1. RBC transfusion versus no transfusion (or alternate dose)

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in critically ill neonatal and/or paediatric patients.

###### Level II evidence

There were no Level II studies identified in the systematic review and hand-searching process that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in critically ill neonatal and/or paediatric patients.

###### Level III evidence

The literature search identified four Level III–2 studies (Acker 2014, Fremgen 2014, Hassan 2014, Kneyber 2007) that examined the effect of RBC transfusions compared with no transfusions (or alternate dose) in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**). The main characteristics of these studies are summarised in **Table 3.1.35.**

Acker (2014)76 was a fair-quality retrospective cohort study involving paediatric patients aged ≤18 years with traumatic brain injury. The study was conducted in two urban paediatric trauma centres in the USA, and assessed the association between transfusions (RBCs, FFP, platelets and cryoprecipitate) and patient outcomes affecting survival. Children were identified from the trauma registries and survival to hospital discharge was examined. To eliminate any confounding factors due to intraoperative blood loss, any children who underwent specified surgical procedures, including any orthopaedic procedure, were excluded. The authors concluded that patients who received blood transfusion have worse outcomes than non-transfused patients and suggested a transfusion trigger of Hb 8.0 g/dL in paediatric patients with TBI.

Fremgen (2014)77 was a poor-quality retrospective cohort study of infants and children aged 1 month to 17 years with blunt abdominal trauma resulting in liver laceration. It included patients with liver lacerations graded 3–6 by scans interpreted by paediatric radiologists (based on American Association for the Surgery of Trauma organ injury scaling). The study examined the clinical factors associated with need for ICU admission and reported the effect of RBC transfusion compared with no RBC transfusion on various clinical parameters (including mortality) in a paediatric trauma centre in the USA.

Hassan (2014)78 was a fair-quality retrospective cohort study involving paediatric trauma patients <18 years of age. It was conducted in a paediatric trauma centre in the USA, and compared the clinical course of patients who received RBC transfusions compared with non-transfused patients. The authors concluded that transfusion of RBCs and the use of older units of RBCs were associated with higher risk of adverse outcomes, independent of injury severity.

Kneyber (2007) was a good-quality retrospective cohort study of a heterogamous population of critically ill paediatric patients <18 years of age who were admitted to a single PICU in the Netherlands. The authors assessed whether RBC transfusions were independently associated with increased mortality, irrespective of pretransfusion Hb level and disease severity. After adjusting for a number of confounders, they concluded that RBC transfusions in critically ill children are independently associated with increased mortality, as well as prolonged duration of mechanical ventilation and PICU length of stay.

Table 3.1.35 Characteristics and quality of Level III evidence – RBC transfusion versus no transfusion (or alternate dose) in critically ill neonatal and/or paediatric patients

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Acker 201476 | Retrospective cohort  *Fair* | Patients aged 18 years and younger (mean 6.4 years) with traumatic brain injury  N=1607 | RBC transfusion (n=178) versus no RBC transfusion (n=1429) | Mortality |
| Fremgen 201477 | Retrospective cohort  *Poor* | Infants and children aged 1 month to 17 years with blunt abdominal trauma resulting in liver laceration  N=117 | RBC transfusion (n=74) versus no RBC transfusion (n=43) | Mortality |
| Hassan 201478 | Retrospective cohort  *Fair* | Paediatric trauma patients aged less than 18 years  N=363 | RBC transfusion (n=81) versus no RBC transfusion (n=282) | Mortality  Transfusion-related SAEs |
| Kneyber 200768 | Retrospective cohort  *Good* | Critically ill neonatal and paediatric patients aged 0 to 18 years admitted to PICU  N=295  \*combined medical and surgical PICO that includes all specialties except preterms and cardiothoracic | RBC transfusion (n=67) versus no RBC transfusion (n=228)  \*leukocyte depleted | Mortality |

PICU, paediatric intensive care unit; RBC, red blood cell; SAEs, serious adverse events

##### Results

###### New or progressive multiple organ dysfunction/failure

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of RBC transfusions compared with no RBC transfusions (or alternate dose) and reported the outcome of new or progressive multiple organ dysfunction or failure in critically ill neonatal and/or paediatric patients.

###### Mortality

Four Level III–2 studies (Acker 2014, Fremgen 2014, Hassan 2014, Kneyber 2007) assessed the association between RBC transfusions and mortality in critically ill neonatal and/or paediatric patients. The data were limited by the retrospective nature of the studies and, although an association between RBC transfusion and mortality may be inferred, causation was not established. Further, a meta-analysis of these studies was judged to be inappropriate due to inconsistency between the study populations and the presence of likely confounders. **Table 3.1.36** summarises the results of these studies.

Acker (2014) reported univariate and multivariate analyses for all patients who received any blood transfusion (RBCs, FFP, platelets and cryoprecipitate), with a significant association between no transfusions and survival observed (OR 2.414; 95% 1.163, 5.009; *P =*0.0180).[[17]](#footnote-17) The authors did not report the data for all patients who received RBCs, but stated that, on multivariate analysis, patients who received RBCs were more likely to die (p <0.05) than those who were not transfused, and that results were identical to those when comparing all blood products.

Ackers (2014) also explored the nadir haemoglobin below which this adverse effect was eliminated. Univariate analyses suggested a significant association between RBC transfusions and death among patients with nadir haemoglobin <10 g/dL (RR 3.26; 95% CI 1.70, 6.24; *P =*0.0004) and among patients with nadir haemoglobin <9 g/dL (RR 2.21; 95% CI 1.06, 4.62; *P =*0.03). However, there was no significant association with RBC transfusions and death among patients with a nadir haemoglobin <8 g/dL (RR 1.53; 95% CI 0.57, 4.12; *P =*0.40). Using logistic regression and adjusting for Glasgow Coma Scale (GCS) score, age, gender and injury severity score (ISS), the results showed no significant association between RBC transfusions and mortality for any level of haemoglobin assessed.

The study by Fremgen (2014) reported mortality among PICU patients with blunt abdominal trauma resulting in liver laceration. The authors reported five deaths in those that received RBC transfusions (11.6%), and no deaths in those that were never transfused. This difference bordered on statistical significance in favour of no transfusions (RR 18.75; 95% CI 1.06, 331.04; *P =*0.05). The data were not adjusted for any confounding variables and the confidence interval is wide; therefore, these results should be interpreted with caution.

The study by Hassan (2014) assessed the association between RBC transfusions and mortality among paediatric trauma patients. There were 17 deaths reported among patients who received RBC transfusions (21.0%) compared with five deaths in patients who were not transfused (1.8%). Using logistic regression and adjusting for ISS, Hassan (2014) reported a statistically significant increased chance of mortality among patients who were transfused compared with no RBC transfusion (OR 8.6; 95% CI 2.6, 28.6; *P <*0.001). A multivariate logistic regression was conducted in transfused patients to assess the impact of various risk factors on patient outcomes (including mortality). Only data for significant results were reported. The age of transfused RBCs was associated with increased odds of mortality (OR 1.1; 95% CI 1.01, 1.20), but not volume transfused or number of transfusions.

Kneyber (2007) assessed whether RBC transfusions were independently associated with increased mortality among 295 paediatric patients admitted to PICU. Eleven out of 67 patients (16.4%) who received a RBC transfusion died, compared with 6 out of 228 patients (2.6%) who did not receive a transfusion. In a logistic regression analysis that adjusted for Paediatric Index of Mortality (PIM) probability of death, mean Therapeutic Intervention Scoring System (TISS)-28 score during the first 48 hours of PICU admission, postoperative admission, presence of sepsis or malignancy, and pretransfusion Hb concentration, a significant association between RBC transfusion and mortality was reported (OR 9.95; 95% CI 1.28, 77.16; *P =*0.028). The authors also performed a number of bivariate analyses which separately adjusted for each of the above confounders. All showed a significant association between RBC transfusion and mortality (see **Table 3.1.36**). Kneyber (2007) also noted a significant association between mortality and the number of RBC transfusions (*P =*0.002) and that mortality rates were equally distributed among patients with Hb of <9 g/dL compared with ≥9 g/dL (2/36 vs 14/225, *P =*nonsignificant) but did not provide data comparing those who were transfused with those who were not.

Table 3.1.36 Critically ill neonatal and/or paediatric patients: Results for RBC transfusion versus no transfusion (or alternate dose) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | | No transfusion  n/N (%) | | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level III Evidence | | | | | | | | | | | |
| Acker 201476  Level III–2  *Fair* | Retrospective cohort study  N=845 | Patients aged 18 years and younger with traumatic brain injury | Two urban paediatric trauma centre, USA | RBC transfusion versus no RBC transfusion | Deaths up to hospital discharge | 53/363 | | 28/482 | | RR 2.51 [1.62, 3.89] c | *Favours no transfusion*  *P <*0.0001c |
|  | Subgroup analysis: nadir haemoglobin  Univariate analysis | | | | |  |
| Patients with nadir Hb <10 g/dL | 23/146 (15.8%) | | 13/269 (4.8%) | | RR 3.26 [1.70, 6.24]c | *Favours no transfusion*  *P =*0.0004 |
| Patients with nadir Hb <9 g/dL | 18/126 (14.3%) | | 10/155 (6.5%) | | RR 2.21 [1.06, 4.62]c | *Favours no transfusion*  *P =*0.03 |
| Patients with nadir Hb <8 g/dL | 12/91 (13.2%) | | 5/58 (8.6%) | | RR 1.53 [0.57, 4.12]c | *No significant difference*  *P =*0.40 |
| Survived to hospital discharge | Subgroup analysis: nadir haemoglobin  Multivariate analysis using logistic regression adjusted for GCS score, age category, gender (male), and ISS | | | | |  |
| Patients with nadir Hb <10 g/dL | 123/146 (84.2%) | | 256/269 (95.2%) | | OR 1.377 [0.622, 3.050] | *No significant difference*  *P =*0.4307 |
| Patients with nadir Hb <9 g/dL | 108/126 (85.7%) | | 145/155 (93.5%) | | OR 1.240 [0.506, 3.039] | *No significant difference*  *P =*0.6378 |
| Patients with nadir Hb <8 g/dL | 79/91 (86.8%) | | 53/58 (91.4%) | | OR 1.072 [0.324, 3.544] | *No significant difference*  *P =*0.9098 |
| Fremgen 201477  Level III–2  *Poor* | Retrospective cohort study  N=117 | Infants and children aged 1 month to 17 years with blunt abdominal trauma resulting in liver laceration | Paediatric trauma centre, USA | RBC transfusion versus no RBC transfusion | Death (among ICU patients) | 5/43 (11.6%) | | 0/74 (0%) | | RR 18.75 [1.06, 331.04] | *No significant difference*  *P =*0.05 |
| Hassan 201478  Level III–2  *Fair* | Retrospective cohort study  N=363 | Paediatric trauma patients aged less than 18 years | Level I paediatric trauma centre, USA | RBC transfusion versus no RBC transfusion | Mortality | 17/81 (21.0%) | | 5/282 (1.8%) | | RR 11.84 [4.51, 31.10] | *Favours no transfusion*  *P <*0.001 |
| Logistic regression adjusted for JSS only | | | | OR 8.6 [2.6, 28.6] |
| RBC transfusion versus alternate dose  1 versus 2 versus >3 RBC transfusions | Mortality | 13/56 (23.2%) | 3/16 (18.8%) | | 1/9 (11.1%) | NR | *No significant difference*  *P =*0.84 |
| Kneyber 200768  Level III-2  *Good* | Retrospective cohort study  N=295 | Critically ill neonatal and paediatric patients | Single PICU, The Netherlands | RBC transfusion versus no RBC transfusion | Mortality | 11/67 (16.4%) | | 6/228 (2.6%) | | RR 6.24 [2.40, 16.24]c | *Favours no transfusion*  *P <*0.001 |
| Logistic regression adjusted for PIM probability of death, mean TISS-28 score during the first 48 hours of PICU admission, postoperative admission, presence of sepsis and/or malignancy, and pretransfusion haemoglobin concentration | | | | OR 9.951 [1.283, 77.157] | *Favours no transfusion*  *P =*0.028 |
| Bivariate analysis adjusted for PIM probablay of death | | | | OR 5.730 [1.89, 17.31] | *Favours no transfusion*  *P =*0.002 |
| Bivariate analysis adjusted for TISS-28 during first 48h of PICU stay) | | | | OR 4.699 [1.14, 19.30] | *Favours no transfusion*  *P =*0.032 |
| Bivariate analysis adjusted for sepsis and/or malignancy | | | | OR 7.157 [2.49, 20.60] | *Favours no transfusion*  *P <*0.001 |
| Bivariate analysis adjusted for postoperative admission | | | | OR 7.065 [2.50, 20.00] | *Favours no transfusion*  *P <*0.001 |
| Bivariate analysis adjusted for pretransfusion Hb (N=261) | | | | OR 9.309 [2.37, 36.59] | *Favours no transfusion*  *P =*0.001 |
| RBC transfusion versus alternate dose | Mortality | Subgroup analysis: number of RBC transfusions | | | | |  |
| 1 RBC transfusion vs no RBC transfusion | 4/39 (10.26%) | | 6/228 (2.6%) | | RR 3.90 [1.15, 13.18]c | *Favours fewer RBC transfusions*  *P =*0.002 |
| 2 RBC transfusions vs no RBC transfusion | 0/12 (0%) | | 6/228 (2.6%) | | RR 1.36 [0.08, 22.77]c |
| 3 RBC transfusions vs no RBC transfusion | 1/5 (20%) | | 6/228 (2.6%) | | RR 7.60 [1.11, 51.98]c |
| 4 RBC transfusions vs no RBC transfusion | 1/4 (25%) | | 6/228 (2.6%) | | RR 9.50 [1.46, 61.76]c |
| > 4 RBC transfusions vs no RBC transfusion | 5/7 (71.4%) | | 6/228 (2.6%) | | RR 27.14 [10.84, 67.98]c |

CI, confidence interval; GCS, Glasgow Coma Scale; Hb, haemoglobin; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; PIM, Paediatric Index of Mortality; RBC, red blood cell; RR, risk ratio; TISS, Therapeutic Intervention Scoring System

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2

###### Secondary outcomes[[18]](#footnote-18)

Transfusion-related serious adverse events (TACO, TRALI, other[[19]](#footnote-19))

One Level III–2 study (Hassan 2014) reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in critically ill neonatal and paediatric patients. **Table 3.1.37** summarises the results from this study.

Hassan (2014) reported transfusion reactions among trauma patients admitted to intensive care, with no patients experiencing TRALI or haemolysis. Nine patients developed febrile reactions (11.11%) after transfusion, with three transfusions being discontinued.

Table 3.1.37 Critically ill neonatal and paediatric patients: Results for RBC transfusion versus no transfusion (or alternate dose) – Transfusion-related serious adverse events

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | | Patient population | | Setting  Location | | Intervention versus comparator | | | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| RBC transfusion  n/N (%) | No transfusion  n/N (%) | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level III evidence | | | | | | | | | | | | | | | | |
| Hassan 201478  Level III–2  *Fair* | | Retrospective cohort study  N=363 | | Paediatric trauma patients aged less than 18 years | | Paediatric trauma centre, USA | | RBC transfusion versus no RBC transfusion | TRALI | | 0/81 (0%) | 0/282 (0%) | | NA | | Not estimable |
| Transfusion-related febrile reactions | | 9/81 (11.11%) | 0/282 (0%) | | OR 74.03 [4.26,1286.95]c | | *Favours no RBC transfusion*  *P =* 0.003 |
| Haemolysisd | | 0/81 (0%) | 0/282 (0%) | | NA | | Not estimable |

CI, confidence interval; NA, not applicable; OR, odds ratio; RBC, red blood cell; TRALI, transfusion-related acute lung injury

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c**. Calculated post-hoc using RevMan 5.1.2.

**d.** Not specified if this was transfusion-related.

* + - 1. Restrictive RBC transfusion versus liberal RBC transfusion

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified two Level I studies (Carson 2012, Desjardins 2012) that examined the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in critically ill neonatal and paediatric patients (see **Appendix C, Volume 2**). The main characteristics of these reviews are summarised in **Table 3.1.38.**

Carson (2012) was a good-quality systematic review that examined the evidence regarding the effect of transfusion thresholds on clinical outcomes in surgical and medical patients of any age (excluding neonates). Nineteen RCTs were identified, of which one (Lacroix 2007) was in a paediatric population. The authors examined the effect of a restrictive RBC transfusion strategy compared to a liberal RBC transfusion strategy on a variety of outcomes, including 30-day mortality, mortality in ICU and transfusion-related SAEs.

Desjardins (2012) was a good-quality systematic review of Level II and Level III studies that evaluated the effect of transfusion thresholds in neurocritically ill patients admitted to ICU. Six RCTs were identified, of which one was in a paediatric population (Lacroix 2007). A subgroup of 66 patients from the TRIPICU study (Lacroix 2007) who were neurocritically ill was examined. The effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy was assessed on a variety of outcomes, including mortality and new or progressive MODs.

Table 3.1.38 Characteristics and quality of Level I evidence – restrictive RBC transfusion versus liberal RBC transfusion

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Carson (2012)79 | Systematic review  *Good* | Surgical or medical patients (adults and/or children)  19 RCTs, N=6264  *Paediatric patients*  1 RCT, N=637 | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality  Transfusion-related SAEs |
| Desjardins (2012)80 | Systematic review  *Good* | Adult and paediatric neurocritically ill patients admitted to ICU  6 studies, N=537  *Paediatric patients*  1 RCT, N=637  Subgroup, N=66 | Restrictive RBC transfusion versus liberal RBC transfusion | Mortality,  New or progressive MODs |

ICU, intensive care unit; MODs, multiple organ dysfunctions; RBC, red blood cell; RCT, randomised controlled trial; SAEs, serious adverse events

###### Level II evidence

There were no additional Level II studies identified from the systematic review and hand-searching process that examined the effect of a restrictive RBC transfusion strategy compared with a liberal RBC transfusion strategy in critically ill neonatal and paediatric patients. However, the Level II study by Lacroix (2007) that was identified by the Level I studies (Carson 2012, Desjardins 2012) was retrieved to obtain additional study details. The main characteristics of this RCT are summarised in **Table 3.1.39**.

Lacroix (2007), also known as the TRIPICU study, was a good-quality multicentre RCT of 637 critically ill paediatric patients aged 3 days to 14 years, admitted to PICU with haemoglobin levels ≤9.5 g/dL. Nineteen PICUs in four countries participated (10 in Canada, and three each in Belgium, the USA and the UK). Patients were randomised to either a restrictive RBC transfusion strategy (7 g/dL) or a liberal (9.5 g/dL) RBC transfusion strategy. The study provided evidence for mortality, new or progressive MODs, and transfusion-related SAEs.

Table 3.1.39 Characteristics and quality of Level II evidence – restrictive RBC transfusion versus liberal RBC transfusion

| Study ID | Study type  Study quality | Population  N | Comparison (n) | Outcomes |
| --- | --- | --- | --- | --- |
| Lacroix (2007)81  TRIPICU study | RCT  *Good* | Stable, critically ill children aged 3 days to 14 years (mean age 38 months) with anaemia (Hb ≤9.5 g/dL)  N=637 | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | Mortality  New or progressive MODSa  Transfusion-related serious adverse events |

Hb, haemoglobin; MODS, multiple organ dysfunction syndrome; RBC, red blood cell; RCT, randomised controlled trial; TRIPICU, transfusion requirements in the paediatric intensive care unit

**a.** Defined as concurrent dysfunction of two or more organ systems, or had progression as evidenced by the worsening of one or more organ dysfunctions.

##### Results

###### New or progressive MODs

One Level I study (Desjardins 2012) identified in the systematic review and hand-searching process, and one good-quality RCT (Lacroix 2007) comparing restrictive and liberal transfusion strategies, provided evidence for new or progressive MODs in critically ill neonatal and paediatric patients. **Table 3.1.40** summarises the results of these studies.

Lacroix (2007) assessed new or progressive MODs in 637 stable, critically ill children aged 3 days to 14 years. Thirty-eight patients in the restrictive transfusion group (11.9%) developed new or progressive MODs compared with 39 patients in the liberal transfusion group (12.3%). This result was not statistically significant (RR 0.97; 95% CI 0.63, 1.47). The effect remained nonsignificant when assessed by age and severity of illness. The authors also assessed the severity of organ dysfunction by assessing the number of dysfunctional organs, change in PELOD score, and average daily PELOD score. No significant differences were reported for any outcome when comparing restrictive and liberal RBC transfusion strategies.

Desjardins (2012) reported on a subgroup of patients enrolled in the RCT by Lacroix (2007) who were neurocritically ill (n=66). Five (16.6%) patients in the restrictive group developed new or progressive MODs compared with three (8.3%) patients in the liberal transfusion group. This result did not achieve statistical significance (RR 2.00; 95% CI 0.52, 7.69).

Table 3.1.40 Critically ill neonatal and paediatric patients: Results for restrictive RBC transfusion versus liberal RBC transfusion – New or progressive MODs

| Study  Level of evidencea  Quality | | No. of trials / sample size included in analysis | | Patient population | | Setting  Location | | Intervention versus comparator | | Outcome | | Results | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb | |
| Level II evidence | | | | | | | | | | | | | | | | | | |
| Lacroix 200781  Level II  *Good* | N=637 | | Stable, critically ill children aged 3 days to 14 years (mean 38 months) with Hb levels <9.5 g/dL | | 19 PICUs, 3x Belgium, 10x Canada, 3x UK, 3x US | | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | | New or progressive MODs | | 38/320 (11.9%) | | | 39/317 (12.3%) | | ARR 0.4% [–4.6, 5.5]c  RR 0.97 [0.63, 1.47]d | | *No significant difference*  *P =*NI  *P =*0.87d |
|  | | *Subgroup analysis: age* | | | | | | |  |
| ≤28 days | | 1/11 (9%) | | | 0 | | ARR –9.1% [–26.1, 7.9] | | *No significant difference*  *P =*1.00 |
| 29–364 days | | 14/143 (10%) | | | 20/142 (14%) | | ARR 4.3% [–3.2, 11.8] | | *No significant difference*  *P =*0.28 |
| >364 days | | 23/166 (14%) | | | 19/167 (11%) | | ARR –2.5% [–9.6, 4.7] | | *No significant difference*  *P =*0.51 |
|  | | *Subgroup analysis: severity of illness (PRISM score)* | | | | | | |  |
| 0 | | 3/64 (5%) | | | 4/64 (6%) | | ARR 1.5 [–6.3, 9.4] | | *No significant difference*  *P =*1.00 |
| 1–4 | | 13/128 (10%) | | | 11/111 (10%) | | ARR –0.3 [–7.9, 7.4] | | *No significant difference*  *P =*0.94 |
| 5–7 | | 6/54 (11%) | | | 6/67 (9%) | | ARR –2.2 [–13.0, 8.7] | | *No significant difference*  *P =*0.69 |
| ≥8 | | 16/74 (22%) | | | 18/75 (24%) | | ARR 2.4 [–11.1, 15.9] | | *No significant difference*  *P =*0.73 |
| Number of dysfunctional organs | | 1.6 ± 1.4 (320) | | | 1.5 ± 1.2 (317) | | MD –0.1 [–0.26, 0.13] | | *No significant difference*  *P =*0.87 |
| Change in PELOD score | | 3.8 ± 10.9 (320) | | | 3.8 ± 9.9 (317) | | MD –0.1 [–1.7, 1.5] | | *No significant difference*  *P =*0.97 |
| Average daily PELOD score | | 5.0 ± 6.1 (320) | | | 4.2 ± 5.1 (317) | | MD –0.8 [–1.7, 0.1] | | *No significant difference*  *P =*0.13 |
| Desjardins 201280  Level I/II  *Good* | 1 trial (Lacroix 2007)81  N=66 | | Subgroup of neurocritically ill patients | | 19 PICUs, 3x Belgium, 10x Canada, 3x UK, 3x US | | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | | New or progressive MODs | | 5/30 (16.6%) | | | 3/36 (8.3%) | | RR 2.00 [0.52, 7.69]d | | *No significant difference*  *P =*0.45 |

ARR, absolute risk reduction; CI, confidence interval; Hb, haemoglobin; MD, difference in means; MODs, multiple organ dysfunctions, NI, non-inferiority; PELOD, paediatric logistic organ dysfunction; PICU, paediatric intensive care unit; PRISM, paediatric risk of mortality; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** The authors also reported per protocol analysis, excluding 11 patients who did not meet the 80% adherence criteria. New or progressive MODs occurred in 37/319 (11.6%) in the restrictive transfusion group compared with 38/307 (12.4%) in the liberal transfusion group (ARR 0.8%; 95% CI –4.3, 5.9)

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** Change in PELOD score calculated as difference between in the daily PELOD score at study entry and the worst PELOD score thereafter.

###### Mortality

The two Level I studies (Carson 2012, Desjardins 2012) identified in the systematic review and hand-searching process reported data from one good-quality RCT (Lacroix, 2007) comparing restrictive and liberal transfusion strategies that provided evidence for mortality in critically ill neonatal and paediatric patients. **Table 3.1.41** summarises the results of these studies.

Lacroix (2007) assessed 28-day mortality and in PICU mortality in 637 stable, critically ill children aged 3 days to 14 years. Fourteen patients each from the restrictive (4.4%) and liberal (4.4%) transfusion groups died within 28 days. Eleven patients in the restrictive transfusion group died in PICU (3.4%) compared with eight patients in the liberal transfusion group (2.5%). Neither of these results were statistically significant (RR 0.99; 95% CI 0.48, 2.04 and RR 1.36; 95% CI 0.56, 3.34; respectively).

Desjardins (2012) reported on a subgroup of patients from the RCT by Lacroix (2007) who were neurocritically ill (n=66). Two patients died in the restrictive transfusion group (6.7%) compared with one patient in the liberal transfusion group (2.8%). Again, this result was not statistically significant (OR 2.50; 95% CI 0.22, 29.01). However, the authors noted that the low mortality rate in this population does not provide sufficient power to detect meaningful differences in death rates.

Table 3.1.41 Critically ill neonatal and paediatric patients: Results for restrictive RBC transfusion versus liberal RBC transfusion – Mortality

| Study  Level of evidencea  Quality | | No. of trials / sample size included in analysis | | Patient population | | Setting  Location | | Intervention versus comparator | | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | | | | | |
| Carson 201279  Level I/II  *Good* | 1 trial (Lacroix 2007)81  N=637 | | Stable, critically ill children aged 3 days to 14 years (mean 38 months) with Hb levels <9.5 g/dL | | 19 PICUs, 3x Belgium, 10x Canada, 3x UK, 3x US | | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | | 28-day mortality | | 14/320 (4.4%) | 14/317 (4.4%) | RR 0.99 [0.48, 2.04] | *No significant difference*  *P =*0.98 |
| Mortality in PICU | | 11/320 (3.4%) | 8/317 (2.5%) | RR 1.36 [0.56, 3.34] | *No significant difference*  *P =*0.50 |
| Desjardins 201280  Level I/II  *Good* | 1 trial (Lacroix 2007)81  N=66 | | Subgroup of neurocritically ill patients | | 19 PICUs, 3x Belgium, 10x Canada, 3x UK, 3x US | | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | | 28-day mortality | | 2/30 (6.7%) | 1/36 (2.8%) | OR 2.50 [0.22, 29.01] | *No significant difference*  *P =*0.46 |

CI, confidence interval; Hb, haemoglobin; OR, odds ratio; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Secondary outcomes[[20]](#footnote-20)

Transfusion-related serious adverse events

One Level II study (Lacroix 2007) comparing restrictive and liberal transfusion strategies provided evidence for transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions) in critically ill neonatal and paediatric patients. **Table 3.1.42** summarises the results of this study.

Lacroix (2007) assessed transfusion-related reactions in 637 stable, critically ill children aged 3 days to 14 years and reported no significant between-group differences with respect to red cell transfusion reactions (ARR 1.0; 95% CI –0.9, 2.8). Three patients in the restrictive transfusion group experienced a transfusion reaction (0.9%) compared with six patients in the liberal transfusion group (1.9%).

Table 3.1.42 Critically ill neonatal and paediatric patients: Results for restrictive RBC transfusion versus liberal RBC transfusion – Transfusion-related serious adverse events

| Study  Level of evidencea  Quality | | No. of trials / sample size included in analysis | | Patient population | | Setting  Location | | Intervention versus comparator | | Outcome | | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Restrictive RBC transfusion  n/N (%) | | Liberal RBC transfusion  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | | | | | | | |
| Lacroix 200781  Level II  *Good* | N=637 | | Stable, critically ill children aged 3 days to 14 years (mean 38 months) with Hb levels <9.5 g/dL. | | 19 PICUs, 3x Belgium, 10x Canada, 3x UK, 3x US | | Restrictive RBC transfusion (7 g/dL) versus liberal RBC transfusion (9.5 g/dL) | | Transfusion reaction | | 3/320 (0.9%) | | 6/317 (1.9%) | | ARR 1.0 [–0.9, 2.8] | *No significant difference*  *P =*0.34 |

ARR, absolute risk reduction; CI, confidence interval; Hb, haemoglobin; PICU, paediatric intensive care unit; RBC, red blood cell

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

## Question 2

Question 2 (interventional)

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

RBC, red blood cell

|  |  |  |
| --- | --- | --- |
| Recommendation – erythropoiesis stimulating agents | | |
| R3  (Grade C) | | In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised. |
| Practice points –erythropoiesis stimulating agents | | |
| 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*14 |
| 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*14  b The KDIGO guidelines82 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 guidelines83 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*14 |
| 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*14 |
| PP21 | | Where ESAs are indicated for the treatment or prevention of anaemia in neonatal and paediatric patients, they should be combined with iron therapy. |
| 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. |
| 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*84 | |
| 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; R, recommendation; RBC, red blood cell; | | |

|  |  |
| --- | --- |
| Recommendation –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*15 |
| Practice point – 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. |
| 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)85 and Pottie *et al* (2011)86  b See Section 3.6 and Section 4.5 *Patient Blood Manaagement Guidelines: Module 6* |
| PP16 | Infants and children with iron deficiency should be treated with iron supplements and dietary modifications. |
| 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 Hb 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. |
| PP27 | Critically ill paediatric patients should receive iron supplementation as necessary to achieve the RNI. |
| AI, adequate intake; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell; RDI, recommended daily intake; RNI, recommended nutrient intake | |

|  |  |
| --- | --- |
| Recommendation –hydroxyurea | |
| R4  (Grade B) | In paediatric patients with SCD, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.a  a Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke (see R2 and PP22) |
| Practice point –hydroxyurea | |
| PP22 | In paediatric patients over 9 months of age with sickle cell disease, hydroxyurea may be used to reduce vaso-occlusive pain crises and acute chest syndromes. |
| IDA, iron deficiency anaemia PP, practice point; R, recommendation; RBC, red blood cell; SCD, sickle cell disease; TCD, transcranial Doppler  Note: 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 yet available. We await publication of the full trial results before a reassessment of current recommendations (R2 and R4) and practice points (PP11) are made. | |

|  |
| --- |
| Evidence gaps and areas for future research |
| There is a need for further research on:   * use of ESAs in preterm infants, using contemporary transfusion thresholds and addressing potential adverse effects and long-term outcomes * optimal dosing and timing of starting iron supplementation in preterm infants * in infants with delayed onset of enteral feeding, the role of parenteral iron (could early intervention prevent the need for later iron supplementation or reduce the need for transfusion, and what are the long-term outcomes?) * dose, duration, mode of administration, and long-term effects of iron supplementation in infants and children at risk for anaemia * in the palliative care setting, whether ESAs improve quality of life in paediatric patients with cancer * the long-term safety of ESAs in children with CKD * effect of hydroxyurea on stroke prevention (clinical and sub-clinical) in paediatric patients with sickle cell disease.a |
| **a.** 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 transcranial Doppler 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 the current recommendations (R2 and R4) and practice points (PP11) are reassessed. |

### Background

People with anaemia have lower than normal levels of circulating RBCs; a situation that is often determined by measuring the concentration of haemoglobin (Hb) in the blood. Low Hb 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 systematic review examined the evidence for three interventions that aim to increase Hb concentration in neonatal and paediatric patients: (1) erythropoiesis stimulating agents (ESAs), (2) iron and (3) hydroxyurea (in sickle cell disease only) (see **Section 4.1**).

ESAs such as recombinant human epoetin (rHuEPO) alpha, epoetin beta, and darbepoetin alpha (DAR) promote erythropoiesis (i.e. RBC production). They are used to treat anaemia associated with a variety of conditions, including anaemia of prematurity and chronic kidney disease (CKD). ESAs can also be used to treat anaemia associated with cancer or cancer therapy, and to increase Hb levels before or after surgery.

Iron is an essential mineral that is required for many biological processes, including cellular growth and development, the production of Hb, and immune system regulation. Excess iron can be toxic to cells; therefore, iron is usually stored as ferritin (within cells) or as transferrin (within serum). Iron is usually absorbed through the gastrointestinal (GI) tract; however, when the diet is inadequate or iron stores are insufficient, supplementation with iron may be necessary to avoid the development of iron deficiency and iron deficiency anaemia.

Hydroxyurea acts by supressing bone marrow production, inhibiting DNA synthesis and repair; it also leads to production of fetal Hb. The elevated circulating fetal Hb helps to suppress the deformation of RBCs in sickle cell disease; also, lower levels of circulating leukocytes and reticulocytes may help to reduce vascular occlusion. However, hydroxyurea therapy can have adverse effects (e.g. neutropenia and thrombocytopenia), meaning that frequent monitoring of the therapy is required.

### Methods

The use of ESAs was compared with no ESAs or placebo. All modes of administration of ESA were eligible for inclusion, as were any active head-to-head comparisons with iron alone, or different combinations of ESAs plus iron. Studies were included if they reported the primary outcomes of transfusion volume or incidence, thromboembolic events or mortality. Also included were studies in preterm infants that reported the outcomes of ROP, bronchopulmonary dysplasia (BPD) and necrotising enterocolitis (NEC).

For iron, we examined the evidence for the use of oral or parenteral iron supplementation (or both) compared with no iron, and included any studies that compared modes of administration of iron. Studies that examined the role of micronutrients (and that included elemental iron) as a population health intervention in neonatal and paediatric patients were determined to be out of scope for this review; however, studies that combined iron with a second intervention were included provided that the control group also received the second intervention. For this intervention, studies were included if they reported the primary outcomes of transfusion volume or incidence, or mortality.

Included in the review were all studies in paediatric patients with sickle cell disease that examined the use of hydroxyurea compared to no hydroxyurea (or placebo), and reported transfusion incidence or incidence of stroke. Studies that compared hydroxyurea with other therapies were determined to be out of scope for this review.

For this question, the only evidence that was considered was Level II or higher, published after 1995(see **Section 3.1.2** for details on the levels of evidence for intervention studies). Articles published before 1995 that had been included in a Level I study were included in the review. A search of lower level evidence was only conducted for primary outcomes not addressed in higher level evidence (see **Section 2.3**). Secondary outcomes were only extracted from studies that reported one or more primary outcomes.

Overall, 15 Level I studies and 23 Level II studies were identified in the systematic review and hand-searching process that evaluated the use of ESAs, iron or hydroxyurea in neonatal and/or paediatric patients and reported primary outcomes relevant to our research question (see **Section 4.1**).

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

### Preterm and low birth weight infants

* + - 1. ESAs (with or without iron)

| Evidence statements – preterm and low birth weight infants (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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.) | √√√ | √ | √√ | √√ | √√√ |
|  | 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 | √√ | √√ | √ |
|  | 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.) | √√√ | √ | √√ | √√√ | √√√ |
|  | 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 |
|  | 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 | √√ | √√ |
|  | 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 | √√ | √√ |
|  | 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 | √√ | √√ |
|  | 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 (erythropoiesis stimulating agents) | |
| 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

Anaemia of prematurity goes beyond the normal physiologic decline in circulating RBCs that occurs in all infants during the first weeks of life. This rapid decline in Hb can be made worse by the need to frequently withdraw blood for monitoring of these critically ill infants. As a result, infants born before term often require RBC transfusions to treat anaemia. To minimise the need for RBC transfusions, ESAs have been used to prevent or treat anaemia of prematurity. However, early studies have shown that the administration of 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 often differences in the dosing, timing and route of administration of iron. Where information on these aspects was available, it has been noted.

##### Summary of evidence

###### Level I evidence

Six Level I studies were identified from the systematic review and hand-searching process that examined the use of ESAs in preterm infants (see **Appendix C, Volume 2**). The main characteristics of these reviews are summarised in **Table 3.2.1**.

Table 3.2.1 Characteristics and quality of Level I evidence – ESAs (with or without iron) in preterm infants

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Aher  (2014)87 | Level I  *Good* | Preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates between 8 and 28 days of age  30 RCTs, N=1591 | rHuEPO (± iron) versus placebo or no intervention (± iron)  \*Initiation of rHuEPO 8–28 days after birth | Transfusion incidence and volume  Mortality  ROP  BPD  NEC  Long-term outcomesa |
| Garcia  (2002)88 | Level I  *Poor* | Neonates with VLBW (1500 g) after the first week of life  8 RCTs, N=357 | rHuEPO (+ iron) v placebo/no treatment (+ iron)  \*Initiation of rHuEPO after the first week of life | Transfusion incidence and volume |
| Kotto-Kome (2004)89 | Level I  *Poor* | Neonates with VLBW (<1500 g) in the 1st week of life  12 RCTs, N=1090 | rHuEPO (+ iron) versus placebo or no treatment (+ iron)  \*Initiation of rHuEPO in the first week of life | Transfusion incidence and volume |
| Ohlsson (2014)90 | Level I  *Good* | Preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates <8 days of age  27 RCTs, N=2209 | rHuEPO or DAR (± iron) versus placebo or no treatment (± iron)  \*Initiation of ESAs <8 days after birth | Transfusion incidence and volume  Mortality  ROP  BPD  NEC  Long-term outcomesa |
| Vamvakas (2001)91 | Level I  *Fair* | Infants <4 months of age with anaemia of prematurity  21 RCTs, N=1319 | rHuEPO (± iron) versus no rHuEPO (± iron) | Transfusion incidence and volume |
| Xu (2014)92 | Level I  *Good* | Preterm neonates  14 studies, N=3484  \*Includes 6 RCTs and 8 cohort or case–control studies | rHuEPO or DAR (± iron) versus placebo or no treatment (± iron) | ROP |

BPD, bronchopulmonary dysplasia; DAR, darbepoetin alpha; LBW, low birth weight; NEC, necrotising enterocolitis; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; ROP, retinopathy of prematurity; VLBW, very low birth weight

**a.** Assessed at any age beyond 1 year of age by a validated cognitive, motor; language or behavioural, school, social interaction or adaptation test

Two (Aher 2014, Ohlsson 2014) of the six systematic reviews provided the most recent and comprehensive data that formed the basis of this review for the primary outcomes (transfusion volume and incidence, mortality, BPD and NEC) and the secondary outcome (functional and performance status). The good-quality Level I study by Xu (2014) reported a meta-analysis that included RCTs, cohort and case–control studies examining the effect of ESAs on one outcome –ROP. The remaining three Level I studies (Kotto-Kome 2004, Garcia 2002, Vamakas 2001) provided some additional data not included in the meta-analyses reported by Aher (2014) or Ohlsson (2014).

The good-quality reviews by Ohlsson (2014) and Aher (2014) both assessed the effectiveness and safety of ESA therapy to reduce the need for blood transfusions in preterm (<37 weeks gestational age) and/or low birth weight infants (<2500 g). Ohlsson (2014) included 27 RCTs enrolling 2209 infants that examined the early (within the first week of life) use of rHuEPO or DAR, whereas Aher (2014) included 30 RCTs (31 comparisons) enrolling 1591 infants that examined the late (after the first week of life) administration of rHuEPO to treat anaemia of prematurity. The cut-off for early or late administration of ESAs is somewhat arbitrary, and was based on previously published meta-analyses (Garcia 2002, Kotto-Kome 2004).[[21]](#footnote-21) Some RCTs included in the Ohlsson (2014) review (early ESA therapy) were based on the mean age of infants at enrolment, and may therefore have included infants who were more than 7 days old when rHuEPO was administered. Similarly, some RCTs included in the Aher (2014) review (late ESA therapy) were based on the mean age of infants at enrolment, and may therefore have included infants who were aged less than 7 days or older than 28 days when rHuEPO was administered.

One RCT (Bierer 2009)94 was removed from the analysis reported by Aher (2014) because only some of the infants in the study met their eligibility criteria (about half of them were below the gestation and birth weight criteria). Bierer (2009) enrolled 20 neonates scheduled for major surgery (defined as surgery requiring at least 15 minutes of general anaesthesia or surgery where anticipated blood loss was 10 mL/kg or greater). Only 4 out of 20 neonates had necrotising enterocolitis (an acquired condition related to prematurity), whereas all others required surgery due to major congenital anomalies. All other RCTs included in the Aher (2014) review enrolled neonates who were ≤1750 g, and many of them specifically excluded neonates with major congenital anomalies likely to need surgery, as well as those with acquired or congenital infections. The RCT by Bierer (2009) is assessed in **Section 3.2.9**.

Of the 27 RCTs included in the review by Ohlsson (2014), 18 included compulsory iron therapy in both the intervention and control groups, five included compulsory iron therapy that differed between the intervention and control groups (delayed or different dose), two (Carnielli 1992, Carnielli 1998) did not administer iron to infants in the control arm, one did not mention the use iron in either group (Fauchere 2008), and one (He 2008) did not clarify whether iron was administered.

Of the 30 RCTs included in the review by Aher (2014), 23 included compulsory iron therapy in both the intervention and control groups, two included compulsory iron therapy that differed between the intervention and control groups (delayed or different dose) (Al-Kharfy 1996, Rocha 2001), and five did not administer iron to infants in the control arm (Atasay 2002, Javier Manchon 1997, Romagnoli 2000, Yamada 1999a, Yamada 1999b). The main characteristics of the RCTs included in these reviews are summarised in **Table 3.2.2.**

Table 3.2.2 Characteristics and quality of Level II evidence – ESAs (with or without iron) in preterm infants

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Studies identified and assessed by Ohlsson (2014) – early rHuEPO | | | | |
| Arif (2005)95 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW (<1500 g)  N=292 | rHuEPO (200 IU/kg, sc biw) for 6 weeks from the seventh day of life versus no rHuEPO  \*All infants received oral iron (3–5 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence  Mortality  ROP  NEC |
| Avent (2002)96 | Level II  *Low/unclear risk of bias* | Neonates (<7 days of life) with VLBW (900–1500 g), in room air or requiring 30% oxygen at study entry  N=93 | rHuEPO (400 IU/kg sc tiw) versus rHuEPO (250 IU/kg sc tiw) versus  no rHuEPO  \*All infants received oral elemental iron (6 mg/kg/day) increased to 8–10 mg/kg/day if the hypochromic cells became 20% or more  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality |
| Carnielli (1992)97 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age) with LBW (<1750 g) and age >2 days  N=22 | rHuEPO (400 IU, iv tiw then continued sc) + iron (20 mg/kg, iv qwk) from second day of life versus no rHuEPO or iron  \*Infants in control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence  Mortality |
| Carnielli (1998)98 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age) with LBW (<1750 g) and between the 2nd day to 8 weeks of life  N=63 | rHuEPO (400 IU/kg, iv or sc, tiw) + iron (20 mg/kg/wk, iv) versus rHuEPO (400 IU/kg, iv or sc, tiw) versus no rHuEPO  \*Infants in control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence  ROP  BPD |
| Chang (1998)99 | Level II  *Low/unclear risk of bias* | Preterm infants (≤35 weeks gestational age) with LBW (≤1800 g), age 1 day  N=45 | rHuEPO (150 IU/kg, sc tiw) for 6 weeks versus rHuEPO (250 IU/kg, sc tiw) for 6 weeks versus no rHuEPO  \*All infants received oral iron (20 mg) from day 7 after birth  \*It is not stated whether or not transfusion guidelines were in place | Transfusion incidence |
| Fauchere (2008)100 | Level II  *Low risk of bias* | Preterm infants (≥25 and <32 weeks gestational age)  N=45 | rHuEPO (3000 IU/kg, iv 3–6, 12–18 and 36–42 hours after birth) versus placebo (iv saline)  \*Use of iron not mentioned  \*Transfusion guidelines were not provided | Mortality  ROP  BPD  NEC |
| Haiden (2005)101 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age) and ELBW (<800 g)  N=40 | rHuEPO (300 IU/kg, iv qd or 700 IU/kg, iv tiw) + iron dextran (1.5 mg/kg/day, iv) or oral iron polymerase complex (9mg/kg/day) versus no rHuEPO  \*Infants in the control group received oral iron from day 15 of life or when infants tolerated 60 mL/kg of enteral feeding (whichever came first)  \*Transfusion guidelines were in place | Transfusion incidence  Mortality  ROP  NEC  BPD |
| He (2008)102  \*Abstract only | Level II  *Unclear risk of bias* | Preterm infants, 7 days old  N=44 | rHuEPO (250 IU/kg/day, iv tiw) for 4 weeks) versus control (not further specified)  \*Not clear if iron used  \*Not clear if transfusion guidelines were in place | Functional/ performance status |
| Lauterbach (1995)103 | Level II  *Unclear risk of bias* | Preterm infants (<35 weeks gestational age) with VLBW (≤1500 g)  N=19 | rHuEPO (100 IU/kg, iv biw), day 7–37 versus rHuEPO (400 IU/kg, iv biw), day 7–37 versus no rHuEPO  \*All infants received iron (10 mg/kg/wk, iv)  \*Transfusion guidelines were in place | Transfusion volume |
| Lima-Roogel (1998)104 | Level II  *Low/unclear risk of bias* | Preterm infants (<26 weeks gestational age) with VLBW (750–1500 g)  N=40 | rHuEPO (150 IU/kg/day) during the first 6 weeks of life versus placebo (not specified)  \*All infants received iron (4 mg/kg/day) | Transfusion incidence  NEC  BPD |
| Maier (1994)105 | Level II  *Low/unclear risk of bias* | Infants with VLBW (750–1499 g)  N=244 | rHuEPO (250 IU/kg, iv tiw) until day 40–42 versus no rHuEPO  \*All infants received oral iron (2 mg/kg/day) started on day 14  \*Transfusion guidelines were in place | Transfusion incidence  Mortality  ROP  NEC |
| Maier (2002)106 | Level II  *Low risk of bias* | Infants with ELBW  N=219 | rHuEPO (250 IU/kg, iv or sc tiw) from day 3 of life for 9 weeks versus rHuEPO (250 IU/kg, iv or sc tiw) from the 4th week of life for 6 weeks versus sham injections  \*All infants received enteral iron (3 mg/kg/day) on days 3–5 of life and increased to 6 mg/kg/day (days 12–14), then 9 mg/kg/day (days 24–26)  \*Transfusion guidelines were in place  \*Data from early rHuEPO versus sham included in the analysis | Transfusion incidence  Mortality  ROP  NEC  BPD  Growth |
| Meister (1997)107 | Level II  *Unclear risk of bias* | Preterm infants with VLBW (750–1499 g), aged 5–10 days including those on ventilation or continuous positive airway pressure  N=30 | rHuEPO (300 IU/kg, sc tiw) for 4 weeks versus no rHuEPO  \*All infants received oral iron (6 mg/kg/day) increased after two weeks to 8 mg/kg/day  \*Transfusion guidelines were in place | Transfusion volume |
| Meyer (2003)108 | Level II  *Low risk of bias* | Preterm infants (<33 weeks gestational age) with LBW (<1700 g)  N=43 | rHuEPO (400 IU/kg, sc tiw) until the age of 3 weeks then dose halved versus sham treatment (not specified)  \*All infants received elemental oral iron (2 mg/kg/day) from 2 weeks postnatal age  \*Transfusion guidelines were in place | Transfusion incidence |
| Obladen (1991)109 | Level II  *Low/unclear risk of bias* | Preterm infants (28–32 weeks gestational age)  N=93 | rHuEPO (30 IU/kg sc every 3rd day) from days 4–25 of life versus no rHuEPO  \*All infants received elemental iron (2 mg/kg/day) from day 14  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  ROP  NEC  BPD |
| Ohls (1995)110 | Level II  *Low/unclear risk of bias* | Infants (>27 weeks gestational age) with VLBW (750–1500 g), less than 48 hours of age  N=20 | rHuEPO (200 IU/kg/day, iv qd) for 14 days versus placebo (iv saline)  \*All infants received oral iron (2 mg/kg/day) when taking 70 mL/kg/day enterally, increased to 6 mg/kg/day when feeds reached >100 mL/kg/day  \*Transfusion guidelines were in place | Transfusion incidence and volume  NEC  BPD |
| Ohls (1997)111 | Level II  *Low risk of bias* | Infants with ELBW (≤750 g), 72 hours of age or younger  N=28 | rHuEPO (200 IU/kg/day, iv qd) for 14 days versus placebo (iv)  \*All infants received iron dextran (1 mg/kg/day) in TPN solution  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  ROP  BPD |
| Ohls (2001)112 (group a)  \*Long-term outcomes (18–22 months) for participants in this trial reported by Ohls (2004)113 | Level II  *Low risk of bias* | Preterm infants (<32 weeks gestational age) with ELBW (401–1000 g), 24–96 hours old at time of study entry and likely to survive >72 hours  N=172 | rHuEPO (400 IU/kg, iv or sc tiw) versus sham (iv or sc injections)  \*Infants in the intervention group received iron dextran (5 mg/kg, iv qwk)  \*Infants in the control group received iron dextran (1 mg/kg, iv qwk)  \*Once infants in both groups had an enteral intake of 60 mg/kg/day, they were given iron (3 mg/kg/day), gradually increased to 6 mg/kg/day depending on enteral intake  \*A strict transfusion protocol was in place | Transfusion incidence and volume  Mortality  ROP  NEC  BPD  Functional and performance status (MDI, PDI, any neurological impairment) |
| Ohls (2001)112  (group b) | Level II  *Low risk of bias* | Preterm infants (<32 weeks gestational age) with VLBW (1001–1250 g), 24–96 hours old at time of study entry and likely to survive >72 hours  N=118 | rHuEPO (400 IU/kg, iv or sc tiw) versus sham (iv or sc injections)  \*Infants in the intervention group received iron dextran (5 mg/kg, iv qwk)  \*Infants in the control group received iron dextran (1 mg/kg, iv qwk)  \*Once infants in both groups had an enteral intake of 60 mg/kg/day, they were given iron (3 mg/kg/day), gradually increased to 6 mg/kg/day depending on enteral intake.  \*A strict transfusion protocol was in place | Transfusion incidence and volume  Mortality  ROP  NEC  BPD |
| Ohls (2013)114 | Level II  *Low risk of bias* | Infants with ELBW to VLBW (500–1250 g), and less than 48 hours of age  N=102 | rHuEPO (400 IU/kg, sc tiw) versus DAR (10 µg/kg, sc qwk) + sham versus sham (sc, tiw)  \*All infants received iron dextran (3 mg/kg, qwk) added to parenteral nutrition until enteral feedings were ≥60 mL/kg/day, oral iron (3 mg/kg/day) was then started and increased to 6 mg/kg/day when feedings reached 120 mL/kg/day  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  ROP  NEC  BPD  Functional and performance status (Bayley Score) |
| Salvado (2000)115 | Level II  *Low risk of bias* | Infants with VLBW (<1500 g)  N=60 | rHuEPO (200 IU/kg sc tiw) for 4 weeks versus control (isotonic saline)  \*All infants received oral iron (3 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence |
| Soubasi (1993)116 | Level II  *Low/unclear risk of bias* | Infants with VLBW (<1500 g), age 1–7 days  N=44 | rHuEPO (150 IU/kg/dose, biw) for 4 weeks versus placebo  \*All infants received iron (3 mg/kg/day) from day 15 of life  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality |
| Soubasi (1995)117 | Level II  *Low/unclear risk of bias* | Preterm infants (≤31 weeks gestational age) with VLBW (≤1500 g), age 1–7 days  N=97 | rHuEPO (150 IU/kg, biw) for 6 weeks versus rHuEPO (250 IU/kg, tiw) versus no rHuEPO  \*All infants received oral elemental iron (3 mg/kg/day) from day 15 of life  \*Transfusion guidelines were in place | Transfusion incidence  Mortality |
| Soubasi (2000)118 | Level II  *Low/unclear risk of bias* | Preterm infants (<31 weeks gestational age) with VLBW (<1300 g), clinically stable at study entry  N=36 | rHuEPO (200 IU/kg, sc qad) versus no rHuEPO  \*Intervention group received oral iron (12 mg/kg/day)  \*Control group received oral iron (4 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence |
| Yasmeen (2012)119 | Level II  *Unclear risk of bias* | Preterm infants (<35 weeks postmenstrual age) with VLBW (<1500 g), less than 7 days of age  N=60 | rHuEPO (200 IU/kg, sc tiw) for 2 weeks starting on day 7 of life versus no rHuEPO (control not specified)  \*All infants received oral iron (6 mg/kg/day) from day 14 of life or as soon as enteral feeding was initiated, up to 12 weeks of age  \*Not clear if transfusion guidelines were in place | Mortality |
| Yeo (2001)120 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW and Hct 40–60% at birth  N=100 | rHuEPO (250 IU/kg, sc tiw) from day 5 to day 40 versus no rHuEPO  \*All infants received oral elemental iron (3 mg/kg/day) from day 10, increased to 6 mg/kg/day when full enteral feeds were tolerated  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  ROP  NEC  BPD |
| Identified by Ohlsson (2014) but not included in a meta-analysis (no usable data) | | | | |
| Khatami (2008)121 | Level II  *Poor* | Preterm infants (>28 and <34 weeks gestational age) with VLBW (>1000 g to <1750 g), 48–96 hours old at study entry and likely to survive >72 hours as per the attending neonatologist  N=40 | rHuEPO (500 IU/kg/day, sc biw) for 4 weeks or until discharge or transfer versus no rHuEPO  \*All infants received oral elemental iron (ferrous sulphate) at 3 mg/kg/day (control group from the 2nd week of age)  \*Transfusion guidelines in place | Transfusion incidence and volume  Laboratory measures (Hct) |
| Studies identified and assessed by Aher (2014) – late rHuEPO | | | | |
| Akisu (2001)122 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW (<1500 g), and 10 days old at study entry  N=40 | rHuEPO (250 IU, sc tiw) versus no rHuEPO  \*All infants received elemental iron (3 mg/kg/day)  \*Transfusion guidelines were not stated | Transfusion incidence |
| Al-Kharfy (1996)123 | Level II  *Low/unclear risk of bias* | Preterm infants with VLBW (<1250 g), postnatal age 10–17 days, Hct <45 % and a >75% probability of BPD  N=55 | rHuEPO (200 IU/kg sc tiw) for 6 weeks versus sham injections  \*Intervention group received oral iron (6 mg/kg/day)  \*Control group received oral iron (2 mg/kg/day)  \*Transfusions guidelines were in place | Transfusion incidence  Mortality  ROP  BPD |
| Atasay (2002)124 | Level II  *Unclear risk of bias* | Preterm infants (<32 weeks gestational age) with VLBW (<1500 g), aged 7–10 days at study entry  N=27 | rHuEPO (600 IU/kg/wk sc) for 7–8 weeks versus no rHuEPO  \*Intervention group received Oral iron (3 mg/kg/day)  \*Infants in control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence |
| Bader (1996)125 | Level II  *Low/unclear risk of bias* | Preterm infants (<34 weeks gestational age) with LBW (<1750 g), aged of 3–5 weeks at study entry (mean postnatal age 34 ± 14 days)  N=29 | rHuEPO (300 IU/kg sc tiw) for 4 weeks versus no rHuEPO  \*All infants received elemental iron (6 mg/kg/day) 2 weeks after study start  \*Transfusions guidelines were in place | Transfusion incidence |
| Bechensteen (1993)126 | Level II  *Low/unclear risk of bias* | Preterm infants with VLBW (900–1400 g), aged 3 weeks at study entry  N= 29 | rHuEPO (100 IU/kg, sc tiw) from 3–7 weeks versus no rHuEPO  \*All infants received oral iron (18 mg/day) regardless of weight, beginning at the start of the study, increased to 36 mg/day if serum concentration fell below 16 µmol/L  \*Transfusions guidelines were in place | Transfusion incidence  Mortality  Laboratory measures (change in Hb values) |
| Bierer (2009)94 | Level II  *Low risk of bias* | Infants with a disease requiring major surgerya  \*rHuEPO group mean birth weight (SEM) 2034 ± 308 g, aged 8 ± 2 days  \*Placebo group mean birth weight (SEM) 2400 ± 184 g, aged 7 ± 2 days  N=20 | rHuEPO (200 IU /kg/day, iv) or rHuEPO (400 IU/kg/day, sc tiw) for 2 weeks versus iv placebo (saline) or sc sham  \*All infants received oral iron supplementation (dose not specified) when enteral feeds reached 60 mL/kg/day  \*Transfusion guidelines were in place | Transfusion volume and incidence |
| Chen (1995)127 | Level II  *Low/unclear risk of bias* | Preterm infants (≤33 weeks gestational age) with LBW (≤1750 g), mean age at study entry >22 days  N=37 | rHuEPO (150 mg/kg, iv biw) versus RBC transfusion (10–15 mL/kg, during 2–4 hr period when Hb <10 g/dL and symptoms of anaemia or when Hb <8 g/dL regardless of symptoms) versus no treatment  \*All infants received oral elemental iron (3 mg/kg/day)  \*Transfusion guidelines were not in place (given based on frequent episodes of apnoea)  \*Only comparison of rHuEPO versus no rHuEPO (based on ITT) included here |  |
| Corona (1998)128 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW (<1500 g), mean age (days) at study entry in any group ≥9.5  N=60 | rHuEPO (150 IU/kg/wk, sc) versus rHuEPO (300 IU/kg/wk, sc) versus no rHuEPO  \*All infants received oral iron (4 mg/kg/day)  \*Transfusion guidelines were in place  \*Data from rHuEPO groups combined for analysis | Transfusion incidence and volume |
| Donato (1996)129 | Level II  *Low/unclear risk of bias* | Preterm infants (<34 weeks gestational age) with VLBW (<1500 g), aged 21–35 days of life at study entry  N=32 | rHuEPO (50 IU/kg, sc tiw) versus rHuEPO (100 IU/kg, sc tiw) versus rHuEPO (250 IU/kg, sc tiw) versus placebo (albumin, sc) for 8 consecutive weeks.  \*All infants received oral iron (6 mg/kg/day) starting day 15 and continuing through treatment period  \*Transfusions guidelines were in place  \*Data from rHuEPO groups combined for analysis | Transfusion incidence  Mortality |
| Emmerson (1993)130 | Level II  *Low/unclear risk of bias* | Preterm infants (27–33 weeks gestational age), postnatal age >7 days at study entry  N=24 | rHuEPO (50 IU/kg, sc biw) versus rHuEPO (100 IU/kg, sc biw) versus rHuEPO (150 IU/kg, sc biw) versus placebo (4% albumin) administered until discharge  \*All infants received iron (6.25 mg, ferrous glycine sulphate) from 4 weeks of age  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality |
| Giannakopoulou (1998)131 (group a) | Level II  *Low/unclear risk of bias* | Preterm infants with ELBW (<1000 g), postnatal age >20 days  N=32 | rHuEPO (300 IU/kg, sc tiw) from day 20 for 6–8 weeks versus no rHuEPO  \*All infants received oral elemental iron 10 mg/kg/day  \*Transfusions guidelines were in place | Mortality |
| Giannakopoulou (1998)131 (group b) | Level II  *Low/unclear risk of bias* | Preterm infants with VLBW (1000–1300 g), postnatal age >20 days  N=36 | rHuEPO (300 IU/kg, sc tiw) from day 20 for 6–8 weeks versus no rHuEPO  \*All infants received oral elemental iron 10mg/kg/day  \*Transfusions guidelines were in place | Mortality |
| Griffiths (1997)132 | Level II  *Low risk of bias* | Preterm infants (≤32 weeks gestational age) and/or VLBW (≤1500 g) requiring mechanical ventilation and/or supplemental oxygen from birth until day 7–14  N=43 | rHuEPO (240 IU/kg, sc biw) until aged 40 weeks postmenstrual age versus placebo (4% albumin)  \*All infants received oral iron (3.0 mL/kg/day) from 4 weeks after birth  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  BPD |
| Javier Manchon  (1997)133 | Level II  *Low/unclear risk of bias* | Preterm infants (<34 weeks gestational age) with Hb <10.5 g/dL at 28 days after birth  N=28 | rHuEPO (200 IU/kg, sc tiw) for 4 weeks versus no rHuEPO or iron  \*Intervention group received iron (ferrous sulphate, 4 mg/kg/day)  \*Infants in control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence |
| Kivivuori (1999)134 | Level II  *High/unclear risk of bias* | Infants with ELBW or VLBW (625–1470 g)  N=41 | rHuEPO (300 IU/kg, sc tiw) versus rHuEPO (300 IU/kg, sc tiw) versus no rHuEPO  \*Intervention group A received oral iron (6 mg/kg/day)  \*Intervention group B received im iron (12 mg/kg/week)  \*Control group received im iron (12 mg/kg/week)  \*Transfusion guidelines were in place (not described) | Transfusion incidence |
| Kumar (1998)135 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age) with VLBW (<1250 g and anaemia of prematurity, postnatal age (days) 40.3 ± 20.4 (rHuEPO group) or 36.5 ± 16.6 (placebo group)  N=30 | rHuEPO (300 IU/kg sc biw) for 6 weeks versus placebo (saline)  \*All infants received elemental iron (6 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence |
| Maier (2002)106 | Level II  *Low risk of bias* | Infants with ELBW  N=219 | rHuEPO (250 IU/kg, iv or sc tiw) from day 3 of life for 9 weeks versus rHuEPO (250 IU/kg, iv or sc tiw) from the 4th week of life for 6 weeks versus sham injections  \*All infants received enteral iron (3 mg/kg/day) on days 3–5 of life and increased to 6 mg/kg/day (days 12–14), then 9 mg/kg/day (days 24–26)  \*Transfusion guidelines were in place  \*Data from late rHuEPO versus sham included in the analysis | Transfusion incidence  Mortality  ROP  NEC  BPD  Growth |
| Meyer (1994)136 | Level II  *Low risk of bias* | Preterm infants (<32 weeks gestational age) with VLBW (<1500 g) and postnatal age 2–8 weeks  N=80 | rHuEPO (200 IU/kg, sc tiw) increased by 50 IU/kg/dose if Hct declined by 6% during any 2 week period but was withheld if the Hct >45% versus placebo (not described)  \*All infants received iron (3 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence  NEC |
| Pollak (2001)137 | Level II  *Low/unclear risk of bias* | Preterm infants (<31 weeks gestational age) with VLBW (<1300 g) aged >7 days  N=38 | rHuEPO (300 IU/kg/day, iv e3d) versus rHuEPO (300 IU/kg/day, iv e3d) + iron sucrose (2 mg/kg/day, iv) versus no rHuEPO  \*All infants received oral iron polymaltose complex (9 mg/kg/day) for 3 days before study start, continuing through the treatment period  \*Transfusion guidelines were in place | Mortality  ROP  BPD |
| Reiter (2005)138 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age and Hct ≤28%) or infant (<48 weeks conceptual age or 5 months chronological age) with a diagnosis of anaemia of prematurity  N=60 | rHuEPO (300 IU/kg, sc qd) for 10 days versus no rHuEPO  \*All infants received oral elemental iron (6 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence and volume |
| Romagnoli (2000)139 | Level II  *Low/unclear risk of bias* | Preterm infants (<30 weeks gestational age) or 31–34 weeks gestational age with respiratory distress syndrome and requiring mechanical ventilation, aged 7 days at study entry  N=230 | rHuEPO (300 IU/kg, sc tiw) from 2–7 weeks of life versus no rHuEPO  \*Intervention group received iron (1 mg/kg/day, iv) from 2–4 weeks of life then oral iron (12 mg/kg/day) until 7 weeks of life  \*Infants in the control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence  ROP  NEC  BPD |
| Samanci (1996)140 | Level II  *Low risk of bias* | Preterm infants (≤32 weeks gestational age) with VLBW (≤1250 g) and postnatal age 2–4 weeks at first dose  N=24 | rHuEPO (200 IU/kg, sc tiw) for 4 weeks versus placebo (not specified, sc)  \*All infants received oral elemental iron (3 mg/kg/day)  \*Transfusions guidelines were in place | Transfusion incidence  NEC |
| Shannon (1991)141 | Level II  *Low/unclear risk of bias* | Preterm infants aged 10–35 days stratified at study entry according to weight (before randomisation)  \*Group A (n=10), VLBW (901–1250 g)  \*Group B (n=10), ELBW (≤900 g)  N=20 | rHuEPO (100 IU/kg, iv biw) for 6 weeks versus placebo (not specified, iv)  \*All infants received oral elemental iron (3 mg/kg/day), continued at the discretion of the attending physician  \*Transfusions were administered at the discretion of the attending physician | Transfusion incidence  Mortality  NEC |
| Shannon (1992)142  \*Pilot study | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW (<1250 g) and postnatal age 8–28 days  N=8 | rHuEPO (100 IU/kg, sc 5 times per week) versus placebo (not specified)  \*All infants received oral iron (3 mg/kg/day) divided in 3 doses and given between feedings, increased to 6 mg/kg/day for infants tolerating full caloric feedings  \*Transfusion guidelines were in place | Transfusion incidence |
| Shannon (1995)143 | Level II  *Low risk of bias* | Preterm infants (<31 weeks gestational age) with VLBW (≤1250 g)  N=157 | rHuEPO (100 IU/kg, sc Monday through Friday) for 6 weeks or until discharge versus placebo (not specified, sc)  \*All infants received oral iron supplements to achieve 3 mg/kg/day elemental iron, increased to 6 mg/kg/day when the infant tolerated full caloric enteral feeds  \*Transfusion guidelines were in place | Transfusion incidence  Mortality  NEC  ROP |
| Whitehall (1999)144 | Level II  *Low risk of bias* | Preterm infants (≤32 weeks gestational age) with VLBW (>1000 g, n=22) or ELBW (≤1000 g, n=20), aged 14 days  N=42 | rHuEPO (400 IU/kg, sc qad) for 20 days (10 doses) versus no rHuEPO  \*All infants received oral iron (3 mg/kg/day), increased to 6 mg/kg/day as tolerated  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality |
| Yamada (1999a)145 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with VLBW (1000–1499 g) and postnatal age <40 days  N=55 | rHuEPO (200 IU/kg, sc biw) for 8 weeks versus no rHuEPO  \*Infants in the intervention group received oral iron (3 mg/kg/day)  \*Infants in the control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence and volume |
| Yamada (1999b)146 | Level II  *Low/unclear risk of bias* | Preterm infants (<33 weeks gestational age) with ELBW (500–999 g) and postnatal age <40 days  N=27 | rHuEPO (200 IU/kg, sc biw) for 8 weeks versus no rHuEPO  \*Infants in the intervention group received oral iron (3 mg/kg/day)  \*Infants in the control group did not receive iron  \*Transfusion guidelines were in place | Transfusion incidence and volume |
| Identified by Aher (2014) but not included in meta-analysis (no usable data) | | | | |
| Rocha (2001)147 | Level II  *Poor* | Preterm infants (≤33 weeks gestational age) with VLBW (≤1550 g), 10–35 days postnatal age  N=45 | rHuEPO (100 IU/kg, sc qd) versus rHuEPO (350 IU/kg, sc biw) versus no rHuEPO  \*Infants in the intervention groups received oral iron (3 mg/kg/day, ferrous sulphate) increased to 6 mg/kg/day in the second week of treatment  \*Infants in the control group received oral iron at around day 30 (usual care)  \*Transfusion guidelines were in place | Transfusion incidence and volume |
| Ronnestad (1995)148 | Level II  *Low/unclear risk of bias* | Preterm infants (<32 weeks gestational age) with VLBW (875–1650 g), able to tolerate enteral feeding and 14–22 days postnatal age | rHuEPO (150 IU/kg, sc tiw) for 6 weeks versus placebo (not further described)  \*All infants received iron (2–4 mg/kg/day, ferrous fumarase) at study entry  \*rHuEPO stopped if Hb >13.0 g/dL after 4 weeks of treatment | Transfusion incidence and volume |
| Juul (2003)149 | Level II  *Poor* | Preterm infants with VLBW (700–1500 g) receiving ≥30 mL/kg/day enteral feeding of human milk or infant formula and deemed non-infected by the attending neonatologist  N=32 | rHuEPO (500 IU/kg, oral bid) for 14 days versus placebo (D5W)  \*All infants received supplemental iron dextran (1 mg/kg/day) or oral iron (6 mg/kg/day) when enteral feeding reached 100 mL/kg/day  \*Transfusion guidelines were in place | Transfusion volume |

bid, twice daily; biw, twice weekly; BPD, bronchopulmonary dysplasia; D5W, dextrose 5 % in water; DAR, darbepoetin alpha; e3d, at 3-day intervals; ELBW, extremely low birth weight; Hb, haemoglobin; Hct, haematocrit; im, intramuscular; ITT, intent-to-treat; IU, international units; iv, intravenous; LBW, low birth weight; MDI, mental and development index; NEC, necrotising enterocolitis; PDI, psychomotor developmental index; qd, once daily; qad, every other day; qwk, once a week; rHuEPO, recombinant human epoetin; ROP, retinopathy of prematurity; sc, subcutaneous; SEM, standard error of mean; tiw, three times per week; TPN, total parenteral nutrition; VLBW, very low birth weight

**a.** Defined as surgery requiring at least 15-minutes of general anaesthesia or surgery where anticipated blood loss was 10 mL/kg or greater. Bierer (2009) was removed from the meta-analyses conducted by Aher (2014) and considered under **Section 3.2.9.**

The RCTs included in Ohlsson (2014) and Aher (2014) were conducted in a variety of countries and were of predominantly small sample size (8–292 infants enrolled). All but one study (Juul 2003) administered rHuEPO either subcutaneously or intravenously, or in a combination (i.e. intravenous followed by subcutaneous when intravenous access was no longer available). Guidelines for RBC transfusions were followed in 23 of the 27 RCTs included in Ohlsson (2014),[[22]](#footnote-22) and in 28 of the 30 RCTs included in Aher (2014),[[23]](#footnote-23) but the guidelines varied markedly between the studies (i.e. different haematocrit or Hb levels, with or without subjective measures). Only two RCTs (Arif 2005, Samanci 1996) stated that infants who had received prior RBC transfusions were ineligible for inclusion.

###### Level II evidence

The literature search and hand-searching process identified four additional Level II studies150-153 involving ESA therapy in preterm infants that were not identified or included in the Level I studies. The main characteristics of these RCTs are summarised in **Table 3.2.3**.

The RCT by El-Ganzoury (2014) was conducted in multiple NICUs at a single centre in Egypt, and was published subsequent to the literature searches of Ohlsson (2014) and Aher (2014). It examined the safety and effectiveness of enteral rHuEPO and/or granulocyte colony-stimulating factor (G-CSF) in preventing feeding intolerance among very low birth weight (VLBW) neonates, and was a four-armed trial that compared G-CSF alone, rHuEPO alone, or G-CSF plus rHuEPO to placebo. The use of iron was not mentioned.

The RCT by Ovali (1996) was a pilot study conducted in a single centre in Turkey. It examined the safety and effectiveness of ESA therapy in reducing the need for RBC transfusion in preterm infants with Rh haemolytic disease. All infants received iron therapy.

The RCTs by Jim (2000) and Kremenopoulos (1997) both examined the effectiveness and safety of ESA therapy to reduce the need for blood transfusions in preterm and/or low birth weight (LBW) infants. The Jim (2000) study was conducted at a single centre in Taiwan, and the Kremenopoulos (1997) study was conducted at a single centre in Greece.

The populations included in the RCTs by El-Ganzoury (2014) and Ovali (1996) did not meet the inclusion criteria of Ohlsson (2014) or Aher (2014). However, it is not clear why the RCTs by Jim (2000) or Kremenopoulos (1997) were not included in the Ohlsson (2014) or Aher (2014) reviews.

Table 3.2.3 Characteristics and quality of additional Level II evidence – ESAs (with or without iron) in preterm infants

| Study ID | Study type  *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Studies not identified in Level I studies | | | | |
| Anaemia of prematurity | | | | |
| Jim (2000)151 | Level II  *Poor* | Preterm infants (<33 weeks gestational age) with VLBW (<1500 g) and postnatal age >7 days  N=23 | rHuEPO (200 IU/kg, sc tiw)for 6 weeks versus placebo (saline)  \*All infants received oral iron supplements (3 mg/kg/day) from 21 days of age  \*Transfusion guidelines in place | Transfusion incidence and volume  Laboratory measures (Hb, Hct, serum ferritin) |
| Kremenopoulos (1997)152 | Level II  *Poor* | Preterm infants (≤31 weeks gestational age) with VLBW (≤1500 g)  Group A (rHuEPO 750), N=50  \*Administered early after birth for (3–7 days) for 6 weeks  Group B (rHuEPO 600), N=35  \*Administered when they were receiving full enteral feeding and after their problems had resolved (mean age 3.4 ± 2.3 weeks of life) until discharge | Group A  rHuEPO (250 IU/kg, sc tiw) versus no rHuEPO  \*All infants received oral iron supplements (3 mg/kg/day) from the 15th day of life  Group B  rHuEPO (200 IU/kg, sc tiw) versus no rHuEPO  \*All infants received oral iron supplements (3 mg/kg/day) from the 15th day of life | Transfusion incidence and volume  Laboratory measures (Hb, Hct, ferritin) |
| Feeding intolerance | | | | |
| El-Ganzoury (2014)150 | Level II  *Fair* | Preterm infants (≤33 weeks gestational age)  N=90 | rHuEPO (88 IU/kg, oral qd) versus G-CSF (4.5 µg/kg) versus rHuEPO + G-CSF versus placebo (1 mL distilled water)  \*rHuEPO administered orally as a single daily dose with the start of enteral feeding  \*use of iron not mentioned | NEC  Mortality  Laboratory measures (Hb) |
| Rh haemolytic disease of the fetus and newborn | | | | |
| Ovali (1996)153 | Level II  *Poor* | Preterm infants with Rh isoimmunisation diagnosed in utero  N=20 | rHuEPO (200 IU/kg, sc tiw)for 6 weeks versus placebo (saline)  \*rHuEPO started at 14 days  \*All infants received iron (3 mg/kg/day) (mode NR) | Transfusion  Laboratory measure (Hb) |

G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; Hct, haematocrit; IU, international units; NEC, necrotising enterocolitis; NR, not reported; qd, once daily; rHuEPO, recombinant human epoetin; sc, subcutaneous; tiw, three times per week; VLBW, very low birth weight

##### Results

###### Transfusion incidence and volume

One or more RBC transfusion

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the incidence of RBC transfusions in preterm infants administered ESAs compared with those given no ESA or placebo, stratified according to the age at which ESA treatment was initiated. One long-term follow-up study (Ohls 2004) and four additional RCTs (Kremenopoulos 1997, Ohls 1993, Ronnestad 1995, Rocha 2001) were identified that also reported on this outcome. **Table 3.2.4** summarises the results from these studies.

Early rHuEPO or DAR

Ohlsson (2014) identified 16 trials involving 1661 neonates comparing early rHuEPO with no rHuEPO or placebo, which reported the proportion of subjects who received one or more RBC transfusions. A meta-analysis of the data showed a statistically significantly lower risk of transfusion in infants who received early rHuEPO treatment (relative risk [RR] 0.79; 95% confidence interval [CI] 0.73, 0.85); however, there was substantial heterogeneity for this outcome (I2=54%). The same effect was observed when the analysis was restricted to NICUs using mostly satellite units of RBCs (4 trials; RR 0.89, 95% CI 0.80, 0.99), or when analysed according to rHuEPO and iron-dosing subgroups. High-dose rHuEPO and high or low-dose iron significantly reduced the proportion of infants who received a RBC transfusion (14 trials; RR 0.76, 95% CI 0.68, 0.86), but not low-dose rHuEPO with low-dose iron (2 trials; RR 0.80, 95% CI 0.60, 1.07).

Ohlsson (2014) also identified one RCT (Ohls 2013) that compared early DAR with sham injections and reported the proportion of subjects who received one or more RBC transfusions. Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 0.62; 95% CI 0.38, 1.02, *P =*0.058), although there was a trend towards fewer RBC transfusions in the DAR group.

One additional RCT was identified (Kremenopoulos 1997) that reported the proportion of infants who received one or more RBC transfusions and had received rHuEPO within the first week of life compared with no rHuEPO. Kremenopoulos (1997) found no significant difference between treatment groups (group A versus control) (RR 0.75; 95% CI 0.55, 1.03); however, the authors reported a secondary analysis that showed an effect favouring early rHuEPO in infants without complications (RR 0.27; 95% CI 0.07, 0.96) but not in infants with complications (e.g. sepsis and mechanical ventilation) (RR 1.00; 95% CI 0.88, 1.14).

One other study was identified (Ohls 2004) that reported long-term outcomes at 18–22 months follow-up of infants enrolled in the RCT reported by Ohls (2001, group a). Ohls (2004) noted that no infants in either treatment group received a transfusion after discharge.

Late rHuEPO

Aher (2014) identified 20 trials involving 1142 neonates comparing late rHuEPO with no rHuEPO or placebo that reported the proportion of infants administered late rHuEPO who received one or more RBC transfusions. A meta-analysis of the data showed a statistically significantly lower risk of transfusion in infants who received late rHuEPO treatment (RR 0.71; 95% CI 0.64, 0.79); however, there was substantial heterogeneity for this outcome (I2=68%). The same effect was observed when the analysis was restricted to high-quality RCTs (5 trials; RR 0.84, 95% CI 0.73, 0.96), or studies that reported strict RBC transfusion guidelines (15 trials; RR 0.76, 95% CI 0.68, 0.85), but not when it was restricted to those with less strict or no transfusion guidelines (3 trials; RR 0.25 95% CI, 0.08, 0.77). When analysed according to rHuEPO and iron-dosing subgroups, a significant reduction in the proportion of infants who received a RBC transfusion was reported, regardless of dosing combinations.

Two of the RCTs identified by Aher (2014) (Ronnestad 1995, Rocha 2001) were not included in their meta-analysis for this outcome. Ronnestad (1995) showed a significant effect favouring late rHuEPO for the number of infants who received one or more RBC transfusion (RR 0.13, 95% CI 0.2, 0.85) (reported by Vamvakas 2001). It is not clear why these figures were not included in the Aher (2014) meta-analysis. Rocha (2001) reported a significant difference favouring late rHuEPO administered daily or twice weekly compared to no rHuEPO for the number of infants who received ‘excessive’ RBC transfusions (defined as two or more RBC transfusion); however, the effect was nonsignificant when comparing rHuEPO (daily) with no rHuEPO (RR 0.17; 95% CI 0.02, 1.30), or when comparing rHuEPO (twice weekly) with no rHuEPO (RR 0.56; 95% CI 0.17, 1.88). These data were not included in the meta-analysis by Aher (2014), because infants who received one or more transfusions were not reported.

One additional RCT was identified (Kremenopoulos 1997) that reported the proportion of infants who received one or more RBC transfusions, and had rHuEPO administered after their problems had resolved. Kremenopoulos (1997) reported no significant difference between treatment groups comparing late rHuEPO (group B) with no rHuEPO (RR 0.23; 95% CI 0.09, 0.57).

The systematic review by Garcia (2002) identified one RCT (Ohls 1993) that examined the effectiveness of ESA treatment in VLBW infants with bronchopulmonary dysplasia (mean age 99 ± 12 days at study entry); this study was therefore not included in the meta-analyses by Aher (2014). The authors reported a significant reduction in the proportion of infants that received a RBC transfusion favouring rHuEPO treatment in these infants (RR 0.13; 95% CI 0.02, 0.84).

Early or late ESA therapy

A meta-analysis was conducted to update the Ohlsson (2014) and Aher (2014) reviews, and to evaluate the effectiveness of ESA therapy compared with no ESA therapy on the incidence of RBC transfusion in preterm infants, regardless of the age at which they received ESA therapy (see **Figure 3.2.1**). The analysis showed a significantly reduced risk of transfusion in preterm infants treated with ESAs compared with no ESAs or placebo (725/1556 versus 932/1422; RR 0.71; 95% CI 0.64, 0.80). Heterogeneity was substantial (I2=63%).

Table 3.2.4 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Transfusion incidence (one or more RBC transfusion)

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%)  Mean ± SD | Placebo ± iron  n/N (%)  Mean ± SD | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I  *Good* | 16 trials(Maier 2002, Meyer 2003, Ohls 1995, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Salvado 2000, Arif 2005, Avent 2000, Chang 1998, Haiden 2005, Maier 1994, Obladen 1991, Soubasi 1995, Soubasi 2000, Yeo 2001)95-96; 99; 101; 105-106; 108-110; 112; 114-115; 117-118; 120  N=1661 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Austria, Chile, China, Europe, Greece, NZ, Singapore South Africa, Turkey, USA | Early rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO <8 days after birth | One or more RBC transfusions | 437/862 (50.7%) | 545/799 (68.2%) | RR 0.79 [0.73, 0.85] | *Favours early rHuEPO + iron*  *P <*0.00001  Substantial heterogeneity  I2= 54% |
| 4 trials (Maier 2002, Ohls 2001a (group a) Ohls 2001 (group b), Ohls 2013)  N=501  Europe x1, USA x3 | *Subgroup analysis: NICUs using mostly satellite units of RBCs* | | | |
| 166/253 (65.6%) | 182/248 (73.4%) | RR 0.89 [0.80, 0.99] | Favours early rHuEPO + iron  P = 0.035  No significant heterogeneity  I2= 0% |
|  | Subgroup analysis: dosing | | | |
| High-dose rHuEPO (>500 IU/kg/week) + high or low-dose iron | 14 trials (Maier 2002, Meyer 2003, Ohls 1995, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Salvado 2000, Avent 2000, Chang 1998, Haiden 2005, Maier 1994, Soubasi 1995, Soubasi 2000, Yeo 2001)  N=1228 | 335/629 (55.8%) | 417/599 (69.9%) | RR 0.79 [0.73, 0.85] | Favours early rHuEPO + iron  P < 0.00001  Substantial heterogeneity  I2= 81% |
| High-dose rHuEPO (>500 IU/kg/week) + high-dose iron (>5 mg/kg/day) or given intravenously | 11 trials (Avent 2002, Chang 1998, Haiden 2005, Maier 2002, Meyer 2003, Ohls 1995, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Soubasi 2000, Yeo 2001)  N=863 | 252/452 (55.8%) | 287/411 (69.8%) | RR 0.84 [0.77, 0.92] | Favours early rHuEPO + iron  P = 0.00014  Moderate heterogeneity  I2 = 32% |
| High-dose rHuEPO (>500 IU/kg/week) + low-dose iron (≤5 mg/kg/day) | 3 trials (Maier 1994, Salvado 2000, Soubasi 1995)  N=365  Europe, Chile, Greece | 83/177 (46.9%) | 130/188 (69.1%) | RR 0.66 [0.55, 0.80] | Favours early rHuEPO + iron  P < 0.00001  Substantial heterogeneity  I2 = 5% |
| Low-dose rHuEPO (≤500 IU/kg/week) + high or low-dose iron | 4 trials (Arif 2005, Chang 1998, Obladen 1991, Soubasi 1995)  N=484  Turkey, China, Europe, Greece | 102/233 (43.8%) | 144/251 (57.4%) | RR 0.77 [0.65, 0.91] | Favours early rHuEPO + iron  P = 0.0026  No significant heterogeneity  I2 = 0% |
| Low-dose rHuEPO (≤500 IU/kg/week) + high-dose iron (>5 mg/kg/day) or given intravenously | 2 trials (Arif 2005, Chang 1998)  N=322  Turkey, China | 67/157 (42.7%) | 94/165 (57.0%) | RR 0.75 [0.61, 0.93] | Favours early rHuEPO + iron  P = 0.0091  No significant heterogeneity  I2 = 0.0% |
| Low-dose rHuEPO (≤500 IU/kg/week) + low-dose iron (≤5 mg/kg/day) | 2 trials (Obladen 1991, Soubasi 1995)  N=162  Europe, Greece | 35/76 (46.1%) | 50/86 (58.1%) | RR 0.80 [0.60, 1.07] | No significant difference  P = 0.13  Substantial heterogeneity  I2 = 70% |
| Aher 201487  Level I  *Good* | 20 trialsc (Akisu 2001, Atasay 2002, Bader 1996, Bechensteen 1993, Corona 1998, Donato 1996, Emmerson 1993, Javier Manchon 1997, Kivivuori 1999, Kumar 1998, Maier 2002, Meyer 1994, Reiter 2005, Romagnoli 2000, Samanci 1996, Shannon 1991, Shannon 1992, Shannon 1995, Yamada 1999a, Yamada 1999b)106; 122; 124-126; 128-130; 133-136; 138-143; 145-146  N=1142 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged between 8 and 28 days of age | Argentina, Australia, Austria, Brazil, Canada, Europe, Finland, Greece, Israel, Italy, Japan, Norway, South , Africa, Spain, Taiwan, Turkey, UK, USA | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | One or more RBC transfusions | 254/605 (42.0%) | 322/537 (60.0%) | RR 0.71 [0.64, 0.79] | *Favours late rHuEPO + iron*  *P <*0.00001  Substantial heterogeneity  I2 = 68% |
|  | Secondary analysis: study quality | | | |
| 5 trials of high-quality  N=357 | 116/182 | 133/175 | RR 0.84 [0.73, 0.96] | Favours late rHuEPO + iron  P < 0.0095  Substantial heterogeneity  I2 = 58% |
| 15 trials of uncertain quality  N=785 | 138/423 | 189/362 | RR 0.63 [0.54, 0.73] | Favours late rHuEPO + iron  *P <*0.00001  Substantial heterogeneity  I2 = 71% |
|  | Secondary analysis: use of RBC transfusion protocol | | | |
| 15 trials with strict RBC guidelines  N=963 | 232/513 | 275/450 | RR 0.76 [0.68, 0.85] | Favours late rHuEPO + iron  P < 0.00001  Substantial heterogeneity  I2 = 64% |
| 3 trials with no/less strict RBC guidelines  N=97 | 3/49 | 13/48 | RR 0.25 [0.08, 0.77] | No significant difference  P = 0.016  No significant heterogeneity  I2 = 0% |
|  | Subgroup analysis: dosing | | | |
| High-dose rHuEPO (>500 IU/kg/week) + high or low-dose iron | 14 trialsc (Bader 1996, Donato 1996, Kivivuori 1999, Kumar 1998, Maier 2002, Reiter 2005, Akisu 2001, Atasay 2002, Javier Manchon 1997, Meyer 1994, Romagnoli 2000, Samani 1996, Shannon 1992, Shannon 1995)  N=912 | 202/465 (43.4%) | 259/447 (57.9%) | RR 0.76 [0.68, 0.86] | Favours late rHuEPO + iron  *P <*0.00001  Substantial heterogeneity  I2 = 66% |
| High-dose rHuEPO (>500 IU/kg/week) + high-dose iron (>5 mg/kg/day) or given intravenously | 6 trials (Bader 1996, Donato 1996, Kivivuori 1999, Kumar 1998, Maier 2002, Reiter 2005)  N=318 | 72/168 (42.9%) | 91/150 (60.7%) | RR 0.74 [0.62, 0.88] | Favours late rHuEPO + iron  P = 0.00075  Substantial heterogeneity  I2 = 79% |
| High-dose rHuEPO (>500 IU/kg/week) + low-dose iron (≤5 mg/kg/day) | 8 trialsc (Akisu 2001, Atasay 2002, Javier Manchon 1997, Meyer 1994, Romagnoli 2000, Samani 1996, Shannon 1992, Shannon 1995)  N=594 | 130/297 (43.8%) | 168/297 (56.6%) | RR 0.78 [0.67, 0.91] | Favours late rHuEPO + iron  P = 0.0013  Substantial heterogeneity  I2 = 58% |
| Low-dose rHuEPO (≤500 IU/kg/week) + high or low-dose iron | 7 trialsc (Bechensteen 1993, Donato 1996, Emmerson 1993, Corona 1998, Shannon 1991, Yamada 1999a, Yamada 1999b)  N=239 | 52/140 (37.1%) | 70/99 (70.7%) | RR 0.53 [0.42, 0.67] | Favours late rHuEPO + iron  P < 0.00001  Substantial heterogeneity  I2 = 59% |
| Low-dose rHuEPO (≤500 IU/kg/week) + high-dose iron (>5 mg/kg/day) or given intravenously | 3 trials (Bechensteen 1993, Donato 1996, Emmerson 1993)  N=77 | 15/45 (33.3%) | 18/32 (56.3%) | RR 0.50 [0.31, 0.79] | Favours late rHuEPO + iron  P = 0.0028  No significant heterogeneity  I2 = 0% |
| Low-dose rHuEPO (≤500 IU/kg/week) + low-dose iron (≤5 mg/kg/day) | 4 trialsc (Corona 1998, Shannon 1991, Yamada 1999a, Yamada 1999b)  N=162 | 37/95 (38.9%) | 52/67 (77.6%) | RR 0.54 [0.41, 0.71] | Favours late rHuEPO + iron  P < 0.00001  Substantial heterogeneity  I2 = 76% |
| Level II evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trial (Ohls 2013)114  N=66 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | USA | Early DAR + iron versus placebo + iron | One or more RBC transfusions | 13/33 (39.4%) | 21/33 (63.6%) | RR 0.62 [0.38, 1.02] | *No significant difference*  *P =*0.058 |
| Kremenopoulos 1997152  Level II  *Poor* | N=85 | Preterm infants (≤31 weeks gestation) with VLBW (≤1500 g) | Greece | rHuEPO + oral iron versus oral iron  \*Group A (rHuEPO750) initiation of rHuEPO 3–7 days after birth  \*Group B (rHuEPO600) initiation of rHuEPO >3 weeks after birth | Transfusion incidence  \*Group A |  |  |  |  |
| 16/24 (66.67%) | 23/26 (88.46%) | RR 0.75 [0.55, 1.03]d | *No significant difference*  *P =*0.08d |
| \*Group B | 4/20 (20%) | 13/15 (87%) | RR 0.23 [0.09, 0.57]d | *Favours late rHuEPO + iron*  *P =*0.001d |
|  | Secondary analysis (Group A only): complications (mechanical ventilation, sepsis) | | |  |
| Infants without complications | 2/10 (20%) | 9/12 (75%) | RR 0.27 [0.07, 0.96]d | Favours early rHuEPO + iron  *P =*0.04 |
| Infants with complicationse | 14/14 (100%) | 14/14 (100%) | RR 1.00 [0.88, 1.14]d | No significant difference  *P =*1.00d |
| Ohls 2004f113  Level II  Fair | N=102 | Preterm infants with ELBW (<1000 g)  \*18–22 months follow-up | Multicentre, USA | Early rHuEPO + iron versus iron | Number of infants transfused between discharge and follow-up (18–22 months) | 0/51 (0%) | 0/51 (0%) | Not estimable | Not applicable |
| Vamvakas 2001g91  Level I/II  Fair | 1 trial (Ronnestad 1995)148  N=24 | Preterm infants, aged less than 4 months | Norway | Late rHuEPO + oral iron versus oral iron  \*Initiation of rHuEPO 10 to 20 days after birth | Transfusion incidence | 1/12 (8.3%) | 8/12 (66.6%) | OR 0.05 [0.004, 0.49]  RR 0.13 [0.02, 0.85]d | *Favours late rHuEPO + iron*  *P <*0.05  *P =*0.03d |
| Rocha 2001h147  Level II  *Poor* | N=45 | Preterm infants (≤33 weeks gestation) with VLBW (≤1550 g) | Brazil | Late rHuEPO + iron versus iron  Group 1 (daily rHuEPO)  Group 2 (twice weekly rHuEPO) | Two or more RBC transfusions |  |  |  | *Favours late rHuEPO + iron*  *P =*0.043i |
| \*Group 1  \*Group 2 | 1/15 (6.7%)  3/14 (21.4%) | 5/13 (38.5%) | NR |
| Bronchopulmonary dysplasia | | | | | | | | | |
| Garcia 2002j88  Level I/II  Poor | 1 trial (Ohls 1993)154  N=15 | VLBW (<1500 g) infants aged 99±12 days with bronchopulmonary dysplasia | USA | rHuEPO + iron versus iron only | Number of patients receiving RBC transfusion | 1/10 (10%) | 4/5 (80%) | RR 0.13 [0.02, 0.84]d | *Favours rHuEPO + iron*  *P =*0.03d |

CI, confidence interval; DAR, darbepoetin alpha; ELBW, extremely low birth weight; ESA, erythropoiesis stimulating agent; IU, international units; LBW, low birth weight; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes five trials (Atasay 2002, Javier Manchon 1997, Romagnoli 2000, Yamada 1999a, Yamada 1999b) that compare rHuEPO + iron with no rHuEPO (no iron in control group).

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** Authors reported in text that after rHuEPO was discontinued, the rHuEPO group received significantly fewer transfusions than the control group (*P <*0.05)

**f.** Long-term outcomes for participants enrolled in the NICHD Neonatal Research Network Trial reported by Ohls et al (2001, group a).

**g.** Vamvakas et al (2001) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher et al (2014) or Ohlsson et al (2014) are presented here.

**h.** Rocha (2001) compared rHuEPO + iron with no rHuEPO (infants in control group received iron later than intervention group)

**i.** *P-*value reported by trial authors (includes both groups). Nonsignificant when comparing rHuEPO (daily) with no rHuEPO (RR 0.17; 95% CI 0.02, 1.30; *P =*0.09) or when comparing rHuEPO (twice weekly) with no rHuEPO (RR 0.56; 95% CI 0.17, 1.88; *P =*0.35).

**j.** Garcia et al (2002) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher 2014 are presented here.

Figure 3.2.1 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – One or more RBC transfusion



Mean number of RBC transfusions per infant

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the mean number of RBC transfusions per infant in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. There were 11 RCTs (Carnielli 1998, Avent 2002, Haiden 2005, Khatami 2008, Kremenopoulos 1997, Ohls 1993, Ovali 1996, Griffiths 1997, Giannakopoulou 1998, Rocha 2001, Jim 2000) identified that also reported on this outcome but did not provide sufficient or suitable data for inclusion in a meta-analysis. **Table 3.2.5** summarises the results from these studies.

Early rHuEPO or DAR

Ohlsson (2014) identified 13 trials involving 951 neonates comparing early rHuEPO with no rHuEPO or placebo that reported the mean number of RBC transfusions per infant. A meta-analysis of the data showed a statistically significant reduction in the mean number of RBC transfusions per infant favouring rHuEPO treatment (mean difference [MD] –0.27; 95% CI –0.42, –0.12). However, heterogeneity was substantial (I2=64%).

Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with no DAR that reported the mean number of RBC transfusions per infant. Ohls (2013) found no significant difference comparing DAR with sham injections for the mean number of RBC transfusions per infant (MD –1.2; 95% CI –2.48, 0.08; *P =*0.067), although there was a trend towards fewer RBC transfusions in the DAR group.

Four RCTs (Carnielli 1998, Avent 2002, Haiden 2005, Khatami 2008) identified by Ohlsson (2014) reported the mean number of RBC transfusions per infant, but did not provide sufficient or suitable data for inclusion in their meta-analysis. Carnielli (1998) reported a significant effect favouring rHuEPO (with or without iron) compared with no rHuEPO for the mean number of RBC transfusions per infant (no SD’s provided). Avent (2002) reported a significant effect favouring rHuEPO for the median number of RBC transfusions per infant (mean not provided), and Haiden (2005) reported no significant difference between treatment groups (no SDs provided). Khatami (2008) reported a difference in the mean number of RBC transfusions per infant for early rHuEPO, but the significance of this effect was not reported and the data were insufficient to interpret further.

The RCT by Kremenopoulos (1997) also reported the mean number of RBC transfusions per infant in those that received rHuEPO within the first week of life (group A); however, the authors only reported data from a secondary analysis that showed a significant reduction in the mean number of RBC transfusions favouring early rHuEPO in infants without complications (MD –0.80, 95% CI –1.27, –0.33), not data from infants with complications (MD 0.10; 95% CI –1.72, 1.92). We are unable to unambiguously combine these data to determine the effectiveness of rHuEPO on the mean number of RBC transfusions in all infants that received rHuEPO within the first week of life.

Late rHuEPO

Aher (2014) identified 11 trials involving 817 neonates comparing late rHuEPO with no rHuEPO or placebo that reported the mean number of RBC transfusions per infant. A meta-analysis of the data showed a statistically significant reduction in the mean number of transfusion per infant who received late rHuEPO treatment (MD –0.22; 95% CI –0.38, –0.06); however, this difference was not significant when analysed using a random-effects model (MD –0.58; 95% CI –1.26, 0.10), and there was substantial heterogeneity for this outcome (I2=94%). Further investigation revealed that Aher (2014) included one RCT (Bierer 2009) that examined the effectiveness of ESA treatment in neonates requiring surgery. This removal of this trial from the meta-analysis resulted in a significant difference in the mean the number of transfusions using either a fixed-effects model (MD –0.27; 95% CI –0.42, –0.12) or a random-effects model (MD –0.77; 95% CI –1.00, –0.54) favouring late rHuEPO treatment. Heterogeneity was moderate (I2=27%)

One additional study was identified (Kremenopoulos 1997) that reported the mean number of transfusions administered to infants who received late rHuEPO. This RCT reported a statistically significantly reduction in the mean number of transfusion per infant comparing late rHuEPO (group B) with no rHuEPO (MD –1.40; 95% CI –2.17, –0.63).

Four RCTs (Griffiths 1997, Giannakopoulou 1998, Rocha 2001, Jim 2000) were identified that did not provide sufficient data for inclusion in any meta-analysis. Griffiths 1997 (identified by Aher 2014) reported a difference in median number of RBC transfusions per infant for late rHuEPO. Giannakopoulou (1998) (identified by Vamvakas 2001) reported a significant difference favouring late rHuEPO for the mean number of RBC transfusions per infant in VLBW infants (MD 5.5; standard error [SE] 0.7) and extremely LBW (ELBW) infants (MD 2.8; SE 0.7) (no standard deviation [SD] provided). Rocha (2001) reported no significant difference in the mean number of RBC transfusions per infant for late rHuEPO administered daily or twice weekly (MD 1.29 and 0.98, respectively; no SD provided). Jim (2000) reported a significant difference in the mean number of transfusions per infant favouring late rHuEPO, but did not provide sufficient data for inclusion in any meta-analysis (MD 0.5; no SD provided).

The systematic review by Garcia (2002) identified one RCT (Ohls 1993) that examined the effectiveness of ESA treatment in VLBW infants with bronchopulmonary dysplasia (mean age 99 ± 12 days at study entry); this study was therefore not included in the meta-analyses by Aher (2014). The authors reported a significant reduction in the mean number of RBC transfusions per infant (MD –1.70; 95% CI –2.18, –1.22) favouring rHuEPO treatment in these infants.

One additional RCT (Ovali 1996) was identified that examined the effectiveness of ESA treatment in preterm infants with Rh haemolytic disease of the fetus and newborn. The authors reported a significant difference in the mean number of RBC transfusions (MD 2.4) favouring ESA treatment (no SD provided).

Early or late ESA therapy

A meta-analysis was conducted to update the Ohlsson (2014) and Aher (2014) reviews with data from the RCT by Kremenopoulos (1997), and to evaluate the effectiveness of ESA therapy compared with no ESA therapy in reducing the incidence of RBC transfusions in preterm infants, regardless of the age at which infants received ESA therapy (see **Figure 3.2.2**). The analysis showed that the administration of ESAs significantly reduced the mean number of RBC transfusions (MD –0.76; 95% CI –0.99, –0.53); however, there was substantial heterogeneity for this outcome (I2=63%).

Table 3.2.5 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Transfusion incidence (mean/median number of transfusions)

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  Mean ± SD  Median (range) | Placebo ± iron  Mean ± SD  Median (range) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I  *Good* | 13 trialsc (Carnielli 1992, Maier 2002, Meyer 2003, Ohls 1995, Ohls 1997, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Salvado 2000, Soubasi 1993, Soubasi 1995, Soubasi 2000, Yeo 2001)97; 106; 108; 111-112; 114-118; 120  N=951 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Chile x1, Europe x1, Greece x3, Italy x1, New Zealand x1, Singapore x1, USA x5 | Early rHuEPO ± iron versus placebo / no intervention ± iron  \*Initiation of rHuEPO <8 days after birth | Mean number of RBC transfusions per infant | NR | NR | MD –0.27  [–0.42, –0.12] | *Favours early rHuEPO + iron*  *P =*0.00036  Substantial heterogeneity  I2 = 64% |
| Aher 201487  Level I  *Good* | 11 trialsd (Al-Kharfy 1996, Bierer 2009, Donato 1996, Kumar 1998, Maier 2002, Romagnoli 2000, Samanci 1996, Shannon 1995, Whitehall 1999, Yamada 1999a, Yamada 1999b)94; 106; 123; 129; 135; 139-140; 143-146  N=817 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | Argentina x1, Australia x1, Canada x1, Europe x1, Italy x1, Japan x2, Turkey x1, USA x3 | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | Mean number of RBC transfusions per infant | NR | NR | MD –0.22 [–0.38, –0.06]e | *Favours late rHuEPO + iron*  *P =*0.0075e  Substantial heterogeneity  I2 = 94% |
| Level II evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trialsc (Carnielli 1998)98  N=63 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Single centre, Italy | Early rHuEPO + iron versus no rHuEPO  \*Initiation of rHuEPO <8 days after birth | Mean number of RBC transfusions per infant  \*Group 1 (rHuEPO + iron) | 1.0 (95% CI 0.28, 1.18) | 2.9 (95% CI 1.84, 3.88) | MD 1.9 (NR) | *Favours rHuEPO + iron*  *P =*0.035 |
| \*Group 2 (rHuEPO alone) | 1.3 (95%CI 0.54, 2.06) | MD 1.6 (NR) | *Favours rHuEPO alone*  *P =*0.065 |
| 1 trial (Avent 2002)96  N=93 | Multicentre, South Africa | Early rHuEPO + iron versus no rHuEPO + iron  \*Initiation of rHuEPO <8 days after birth | Median number of RBC transfusions  \*Group 1 (high-dose rHuEPO)  \*Group 2 (low-dose rHuEPO) | 0 (0–2)  0 (0–1) | 0 (0–4) | NR | *Favours rHuEPO*  *P =*0.03 |
| 1 trial (Haiden 2005)101; 114  N=40 | Multiple NICUs, Austria | Early rHuEPO + iron versus no rHuEPO + iron  \*Initiation of rHuEPO <8 days after birth | Mean (range) number of RBC transfusions per infant | 2 (0–15) | 4.5 (0–12) | NR | *No significant difference*  *P =*NR |
| 1 trial (Ohls 2013)  N=66 | USA | Early DAR + iron versus placebo + iron  \*Initiation of DAR <8 days after birth | Mean number of RBC transfusions per infant | 1.2 ± 2.4 | 2.4 ± 2.9 | MD –1.2 [–2.48, 0.08] | *No significant difference*  *P =*0.067 |
| Khatami 2008121  Level II  *Poor* | N=40 | Preterm infants (28–34 weeks gestation) with VLBW (1000–1750 g) | Iran | Early rHuEPO + iron (n=20) versus iron (n=20)  \*Initiation of rHuEPO between 48 and 96 hours after birth | Mean number of RBC transfusions per patient | 2.20 ± NR | 8.20 ± NR | MD 6 [NR] | NR |
| Kremenopoulos 1997152  Level II  *Poor* | N=85 | Preterm infants (≤31 weeks gestation) with VLBW (≤1500 g) | Greece | rHuEPO + oral iron versus oral iron  \*Group A (EPO750) initiation of rHuEPO 3–7 days after birth  \*Group B (EPO600) initiation of rHuEPO >3 weeks after birth | Mean number of RBC transfusions per infant  \*Group A (n=50) | NR | NR | NR | *NR* |
| \*Group B (n=35) | 0.4 ± 0.9 | 1.8 ± 1.3 | MD –1.40 [–2.17, –0.63]f | *Favours late rHuEPO + iron*  *P =*0.0003f |
| Infants without complications | Secondary analysis (Group A only): complications (mechanical ventilation, sepsis) | | | |
| 0.2 ± 0.4 | 1 ± 0.7 | MD –0.80 [–1.27, –0.33]f | Favours early rHuEPO + iron  *P =*0.0008f |
| Infants with complicationsg | 5 ± 2.5 | 4.9 ± 2.4 | MD 0.10 [–1.72, 1.92]f | No significant difference  *P =*0.91f |
| Aher 201487  Level I/II  *Good* | 1 trial (Griffiths 1997)132  N=43 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | 4 x NICUs, England | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | Median number of blood transfusion per infant | NR | NR | Difference in medians  –2 [–4, 0] | NR |
| Vamvakas 2001h 91  Level I/II  Fair | 1 trial (Giannakopoulou 1998)131  N=68 | Preterm infants, aged less than 4 months | Switzerland | Late rHuEPO + oral iron versus oral iron  \*Initiation of rHuEPO 10 to 20 days after birth | Mean number of transfusions per infant | NR | NR | NR | NR |
| Infants 1000–1300g (N=36) | Subgroup analysis: weight | | | |
| NR | NR | MD 5.5 ± 0.7 (SE) | Favours late rHuEPO + iron  *P <*0.05 |
| Infants <1000g (N=32) | NR | NR | MD 2.8 ± 0.7 (SE) | Favours late rHuEPO + iron  *P <*0.05 |
| Rocha  2001i 147  Level II  *Poor* | N=45 | Preterm infants (≤33 weeks gestation) with VLBW (≤1550 g) | Brazil | Late rHuEPO + iron versus iron  Group 1 (daily rHuEPO)  Group 2 (twice weekly rHuEPO) | Mean number of transfusions per patient  \*Group 1  \*Group 2 | 0.33 ± NR  0.64 ± NR | 1.62 ± NR | MD 1.29 [NR]  MD 0.98 [NR] | *No significant difference*  *P =*0.091j |
| Jim 2000151  Level II  *Poor* | N=23 | Preterm infants (<33 weeks gestation) with VLBW (<1500 g) | Taiwan | Late rHuEPO + oral iron versus placebo + iron  \*Initiation of rHuEPO 7 days after birth | Mean number of transfusions per infant | 1.3 ± NR | 1.8 ± NR | MD 0.5 [NR] | *Favours late rHuEPO + iron*  *P <*0.05 |
| bronchopulmonary dysplasia | | | | | | | | | |
| Garcia 2002k 88  Level I/II  Poor | 1 trial (Ohls 1993)154  N=15 | VLBW (<1500 g) infants aged 99±12 days with bronchopulmonary dysplasia | USA | rHuEPO + iron versus iron only | Mean number of RBC transfusions per patient | 0.1 ± 0.31 | 1.8 ± 0.5 | MD –1.70 [–2.18, –1.22]f | *Favours rHuEPO + iron*  *P <*0.00001f |
| Rh haemolytic disease of the fetus and newborn | | | | | | | | | |
| Ovali 1996153  Level II  Fair | N=20 | Preterm infants with RhHDFN | Single NICU, Turkey | Late rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO ~2 weeks of age | Mean number of RBC transfusions per patient | 1.8 ± NR | 4.2 ± NR | 2.4 [NR] | *Favours rHuEPO + iron*  *P <*0.05 |

CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent, LBW, low birth weight; MD, mean difference; NICU, neonatal intensive care unit; NR, not reported; RBC, red blood cell; RhHDFN, Rh haemolytic disease of the fetus and newborn; rHuEPO, recombinant human epoetin; SD, standard deviation; SE, standard error; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one study (Carnielli 1992) that compared rHuEPO + iron to placebo (no iron in control group).

**d.** Analysis includes three studies (Romagnoli 2000, Yamada 1999a, Yamada 1999b) that compared rHuEPO + iron with no rHuEPO (no iron in control group). One study (Bierer 2009) enrolled infants requiring surgery and was subsequently removed from this analysis.

**e.** The effect was nonsignificant when using a random-effects model (MD –0.58; 95% CI –1.26, 0.10; *P =*0.10).

**f.** Calculated post-hoc using RevMan 5.1.2.

**g.** Authors reported in text that after rHuEPO was discontinued, the rHuEPO group received significantly fewer transfusions than the control group (*P <*0.05)

**h.** Vamvakas et al (2001) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher et al (2014) or Ohlsson et al (2014) are presented here.

**i.** Rocha (2001) compared rHuEPO + iron with no rHuEPO (infants in control group received iron later than intervention group)

**j.** *P-*value reported by trial authors (assumed to be across the three groups).

**k.** Garcia et al (2002) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher 2014 are presented here.

Figure 3.2.2 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – mean number of RBC transfusions per infant



Transfusion volume

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the volume of RBCs transfused in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. Twelve RCTs (Carnielli 1998, Lauterbach 1995, Maier 2002, Meister 1997, Corona 1998, Soubasi 1993, Giannakopoulou 1998, Khatami 2008, Rocha 2001, Juul 2003, Jim 2000, Griffiths 1997) were identified that also reported on this outcome, but did not provide sufficient or suitable data for inclusion in a meta-analysis. **Table 3.2.6** summarises the results from these studies.

Early rHuEPO or DAR

Ohlsson (2014) identified seven trials involving 581 neonates comparing early rHuEPO with no rHuEPO or placebo that reported the total volume of RBCs transfused per infant. A meta-analysis showed a statistically significant lower volume of RBCs (mL/kg) transfused in infants who received early rHuEPO treatment (fixed effect, MD –6.82; 95% CI –11.52, –2.11); however, there was substantial heterogeneity for this outcome (I2=63%). Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with sham injections that reported the total volume of RBCs transfused per infant (mL/kg). There was no significant difference between treatment groups for this outcome (MD –21.0; 95% CI –50.72, 8.72; *P =*0.17).

Five RCTs (Carnielli 1998, Lauterbach 1995, Maier 2002, Meister 1997, Khatami 2008) identified by Ohlsson (2014) and one RCT identified by Kotto-Kome (Sabousi 1993) reported the volume of blood transfused per infant but did not provide sufficient or suitable data for inclusion in any meta-analysis.

Carnielli (1998) reported a significant reduction in the mean volume of blood (mL/kg) transfused per infant when comparing rHuEPO plus iron to no rHuEPO or iron (MD 27.7; *P =*0.009), and comparing rHuEPO alone to no rHuEPO (MD 24.3; *P =*0.028) (no SDs provided). Lauterbach (1995) reported a significantly lower volume of blood (mL/kg) transfused between days 7 and 37 of life (MD 28.2, *P <*0.04) and between day 7 of life and discharge (MD 58.4, *P <*0.04) (no SDs provided). Maier (2002) reported a significant reduction in the mean volume of blood transfused per day (mL/kg/day) favouring rHuEPO (MD –0.40; 95% CI –0.76, –0.01). Meister (1997) reported a significant reduction in the median (interquartile range [IQR]) volume of blood transfused per infant per day (mL/kg/day) favouring rHuEPO (0.0 versus 0.86), and Khatami (2008) reported a significant reduction in the mean total volume (mL) of RBC transfused per infant (MD –5.54, 95% CI –8.17, –2.91) favouring early rHuEPO treatment.

Sabousi (1993) compared rHuEPO plus iron to no rHuEPO (with or without iron), and reported a significant reduction in the mean total volume of blood (mL) transfused per patient favouring rHuEPO in infants with ‘no complications’ (MD 20.9; *P =*0.0255) but not in infants ‘with complications’ (MD 1.4; *P =*0.0255) (no SDs provided).

Late rHuEPO

Aher (2014) identified five trials involving 197 neonates comparing late rHuEPO with no rHuEPO or placebo that reported the total volume of RBCs transfused per infant. A meta-analysis showed no difference in the volume of RBCs transfused in infants who received late rHuEPO treatment (MD –1.61; 95% CI –5.78, 2.57); however, there was substantial heterogeneity for this outcome (I2=92%). Further investigation revealed that Aher (2014) included one RCT (Bierer 2009) that examined the effectiveness of ESA treatment in infants requiring surgery. Removal of this trial from the meta-analysis resulted in a significant difference in the mean total volume (mL/kg) of RBCs transfused per infant using a fixed-effects model (MD –7.29; 95% CI –11.86, –2.72, *P =*0.002), favouring late rHuEPO treatment. The result remained nonsignificant when using a random-effects model (MD –12.84’ 95% CI –27.43, 1.74, *P =*0.08). Heterogeneity was substantial (I2=83%).

Three RCTs (Corona 1998, Giannakopoulou 1998, Griffiths 1997) identified by Aher (2014) also reported the total volume of RBCs transfused (mL/kg) per infant but did not provide sufficient data for inclusion in their meta-analysis. Corona (1998) reported a significant difference in the mean total volume (mL/kg) of RBCs transfused per infant (MD –12, *P <*0.01) favouring late rHuEPO treatment (no SDs provided). Giannakopoulou (1998) (reported by Vamvakas 2001) showed a significant difference in the mean total volume (mL/kg) of RBCs transfused per infant (MD –65.1 for VLBW infants and MD –42.6 for ELBW infant, *P <*0.05 for both groups) favouring late rHuEPO treatment (no SDs provided). Griffiths (1997) reported a difference in median volume transfused, but the significance of the effect was not reported.

Three RCTs (Rocha 2001, Juul 2003, Jim 2000) not included in any meta-analysis reported the total volume of RBCs transfused (mL). Rocha (2001) reported no significant difference between treatment groups comparing late rHuEPO (daily), late rHuEPO (twice weekly) and no rHuEPO (*P =*0.156 across the three groups) (no SDs provided). Juul (2003) found no significant reduction in the total volume of blood transfused during the study (MD 2.00; 95% CI –7.10, 11.10) or at follow-up (MD 3.00; 95% CI –14.01, 20.04). Jim (2000) reported a reduction in the total volume of RBC transfused (mL) per infant (MD 6.0, *P <*0.05) favouring late rHuEPO (no SDs provided).

Early or late ESA therapy

A meta-analysis was conducted to update the Ohlsson (2014) and Aher (2014) reviews, and to evaluate the effectiveness of ESA therapy compared with no ESA therapy in preterm neonates on the volume of RBCs transfused per infant, regardless of the age at which the neonates received ESA therapy (see **Figure 3.2.3**). The analysis showed that administration of ESAs significantly reduced the mean total volume (mL/kg) of RBCs transfused per infant (MD –11.45; 95% CI –18.29, –4.62). There was substantial heterogeneity (I2=68%) for this outcome.

Table 3.2.6 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Transfusion volume

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs + iron  Mean ± SD  Median (IQR) | Iron  Mean ± SD  Median (IQR) | Risk estimate (95% CI) | | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | | |
| Ohlsson 201490  Level I  Good | 7 trials (Obladen 1991, Ohls 1995, Ohls 1997, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Yeo 2001)109-112; 114; 120  N=581 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | USA x5, Europe x1, Singapore x1 | Early rHuEPO + iron versus placebo / no intervention + iron  \*Initiation of rHuEPO <8 days after birth | Total volume of blood transfused per infant (mL/kg) | NR | NR | MD –6.82  [–11.52, –2.11] | | Favours early rHuEPO + iron  *P =*0.0045  Substantial heterogeneity  I2 = 63% |
| Aher 201487  Level I  Good | 5 trialsc (Bierer 2009, Emmerson 1993, Reiter 2005, Whitehall 1999, Yamada 1999a)94; 130; 138; 144-145  N=197 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | Argentina, Australia, Austria, Brazil, Canada, Europe, Finland, Greece, Israel, Italy, Japan, Norway, South , Africa, Spain, Taiwan, Turkey, UK, USA | Late rHuEPO + iron versus placebo / no intervention ± iron  \*Initiation of rHuEPO 8 to 28 days after birth | Total volume of RBCs transfused per infant (mL/kg) | NR | NR | MD –1.61 [–5.78,2.57] | | No significant difference  *P =*0.45  Substantial heterogeneity  I2 = 92% |
| Level II evidence | | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 triald (Carnielli 1998)98  N=63 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Italy | Early rHuEPO + iron (n=22) versus placebo (n=21) | Mean volume of blood transfused per infant (mL/kg) | 16.7 [95% CI 4.9, 28.6] | 44.4 [95% CI 29.0, 59.7] | MD 27.7 [NR] | | *Favours early rHuEPO + iron*  *P =*0.009e |
| Early rHuEPO (n=20) versus placebo (n=21) | 20.1 [95% CI 6.2, 34.2] | MD 24.3 [NR] | | *Favours early rHuEPO*  *P =*0.028e |
| 1 trial (Lauterbach 1995)103  N=19 | Poland | Early rHuEPO + iron versus placebo / no intervention ± iron | Total volume of blood transfused per infant (mL/kg)  \*between 7 to 37 days of life | 18.6 ± NR | 46.8 ± NR | MD 28.2 [NR] | | *Favours early rHuEPO + iron*  *P <*0.04e,i |
| \*between 7 days of life and up to discharge | 35.8 ± NR | 94.2 ± NR | MD 58.4 [NR] | | *Favours early rHuEPO + iron*  *P <*0.04e |
| 1 trial (Maier 2002)106  N=145 |  | Europe | Early rHuEPO + iron versus placebo / no intervention + iron | Total volume of blood transfused per infant (mL/kg/day) | 0.7 ± 1.2 (n=74) | 1.1 ± 1.2 (n=71) | MD –0.40 [–0.76, –0.01]f | | *Favours early rHuEPO + iron*  *P =*0.04f |
| 1 trial (Meister 1997)107  N=30 | Preterm infants with VLBW aged 5–10 days, including those on ventilation or continuous positive airway pressure | Single hospital, Austria | Early rHuEPO + iron versus placebo / no intervention + iron  \*Initiation of rHuEPO on ~day 7 of life | Median volume of blood transfused per infant (mL/kg/day) | 0.0 (0.0, 0.47) | 0.86 (0.5, 1.1) | NR | | Favours early rHuEPO + iron  *P =*0.038e |
| 1 trial (Ohls 2013)114  N=66 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates | USA | DAR + iron versus placebo + iron | Total volume of blood transfused per infant (mL/kg) | 30 ± 58 | 51 ± 65 | MD –21.0 [–50.72, 8.72] | | *No significant difference*  *P =*0.17 |
| Aher 201487  Level I/II  *Good* | 1 trial (Corona 1998)128  N=60 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | Italy | Late rHuEPO ± iron versus placebo / no intervention ± iron  \*Initiation of rHuEPO 8 to 28 days after birth | Total volume of blood transfused per infant (mL/kg) | 20 ± NR | 32 ± NR | MD –12 [NR] | | *Favours early rHuEPO + iron*  *P <*0.01e |
| Kotto-Kome 200489  Level I/II  Poor | 1 trial (Soubasi 1993)116  N=42 | Preterm neonates with VLBW (<1500 g) | Greece | Early rHuEPO + iron versus placebo ± iron  \*Initiation of rHuEPO <8 days after birth | Total volume of blood transfused per patient (mL) | Subgroup analysis: complications | | | | |
| not complicated (N=16) | NR | NR | MD 20.9 ± 5.00 (SE) | | *Favours early rHuEPO + iron*  *P =*0.0255 |
| complicated (N=28) | NR | NR | MD 1.40 ± 15.11 (SE) | | *No significant difference*  *P =*0.2596 |
| Vamvakas 200191  Level I/II  Fair | 1 trial (Giannakopoulou 1998)131  N=68 | Preterm infants, aged less than 4 months | Switzerland | Late rHuEPO + iron versus placebo / no intervention + iron  \*Initiation of rHuEPO 10 to 20 days after birth | Volume of blood transfused (mL/kg)  \*Infants 1000–1300g (N=36)  \*Infants <1000g (N=32) | NR | NR | MD 65.1 ± 10.9 (SE) | | *Favours late rHuEPO + iron*  *P <*0.05 |
| NR | NR | MD 42.6 ± 7.9 (SE) | | *Favours late rHuEPO + iron*  *P <*0.05 |
| Khatami 2008121  Level II  *Poor* | N=40 | Preterm infants (28–34 weeks gestation) with LBW (1000–1750 g) | Iran | Early rHuEPO + iron (n=20) versus iron (n=20) | Volume of RBC transfused per patient (mL) | 4.02 ± 1.31 | 9.55 ± 5.85 | MD –5.54 [–8.17, –2.91]f | | *Favours early rHuEPO + iron*  *P =*0.05 |
| Rocha 2001g 147  Level II  *Poor* | N=45 | Preterm infants (≤33 weeks gestation) with VLBW (≤1550 g) | Brazil | Late rHuEPO + iron versus iron alone  \*Group 1 (daily rHuEPO)  \*Group 2 (twice weekly rHuEPO) | Volume (mL) |  |  |  | | *No significant difference*  *P =*0.156h |
| \*Group 1  \*Group 2 | 4.6 ± NR  9.6 ± NR | 17.6 ± NR | MD 13.0 [NR]  MD 8.0 [NR] | |
| Juul 2003149  Level II  Poor | N=32 | VLBW (700–1500 g) neonates | Single NICU, USA | Late rHuEPO + iron (n=15) versus placebo + iron (n=17)  \*Initiation of enteral rHuEPO 2 to 8 weeks after birth | Total volume of RBC transfusion during study (mL) | 9 ± 14 | 7 ± 12 | MD 2.00 [–7.10, 11.10]f | | *No significant difference*  *P =*0.67f |
|  | Subgroup analysis: weight | | |  | |
| \*Infants 750–1000g (N=11) | 9 ± 11 (n=NR) | 16 ± 15 (n=NR) | MD 7.0 [NR] | | NR |
| \*Infants 1001–1500g (N=21) | 9 ± 15 (n=NR) | 2 ± 6 (n=NR) | MD –7.0 [NR] | | NR |
| Total volume of RBC transfusion after study (mL) | 15 ± 25 | 12 ± 24 | MD 3.00 [–14.01, 20.04]f | | *No significant difference*  *P =*0.73f |
|  | Subgroup analysis: weight | | |  | |
| \*Infants 750–1000g (N=11) | 20 ± 33 (n=NR) | 22 ± 36 (n=NR) | MD 2.0 [NR] | | NR |
| \*Infants 1001–1500g (N=21) | 13 ± 21 | 6 ± 13 | MD –7.0 [NR] | | NR |
| Jim 2000151  Level II  *Poor* | N=23 | Preterm infants (<33 weeks gestation) with VLBW (<1500 g) | Taiwan | Late rHuEPO + oral iron versus placebo + iron | Volume of transfusions per infant (mL) | 23 ± NR | 29 ± NR | MD 6.0 [NR] | | *Favours rHuEPO + iron*  *P <*0.05 |
| Griffiths 1997132  Level II  *Good* | N=42 | Preterm (≤32 weeks gestation) and/or VLBW (≤1500 g) infants | 4x NICUs, England | Late rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO from 4 weeks after birth | Volume to weight ratio of blood transfused (mL/kg) | NR | NR | Difference in medians  –31 [–56, 4] | | NR |

CI, confidence interval; ESA, erythropoiesis stimulating agent; IQR, interquartile range; LBW, low birth weight; MD, mean difference; NICU, neonatal intensive care unit; NR, not reported; RBC, red blood cell; rHuEPO, recombinant human epoetin; SD, standard deviation; SE, standard error; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis included one study (Yamada 1999a) that compared rHuEPO + iron with no rHuEPO (no iron in control group). Analysis also included one study (Bierer 2009) that enrolled infants requiring surgery. Removal of this trial from the meta-analysis changed the statistical significance when using a fixed effect model (MD –7.29; 95% CI –11.86, –2.72, *P =*0.002) favouring late rHuEPO treatment; but not when using a random-effects model (MD –12.84; 95% CI –27.43, 1.74, *P =*0.08]. Heterogeneity was substantial (I2 = 83%).

**d.** Carnielli (1998) compared rHuEPO + iron to placebo (no iron in control group).

**e.** *P-*value according the trial authors.

**f.** Calculated post-hoc using RevMan 5.1.2.

**g.** Rocha (2001) compared rHuEPO + iron with no rHuEPO (infants in control group received iron later than intervention group).

**h.** *P-*value reported by trial authors (assumed to be across the three groups).

**i.** Reported by Kotto-Kome 2004 as nonsignificant (*P =*0.0592).

Figure 3.2.3 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – transfusion volume (mL/kg)



###### Thromboembolic events

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of ESA treatment (with or without iron supplementation) in preterm or LBW infants that reported on the outcome of thromboembolic events.

###### Retinopathy of prematurity

The systematic reviews by Xu (2014), Ohlsson (2014) and Aher (2014) assessed the rate of ROP (all stages or stages not reported) and the rate of severe ROP (≥ stage 3) in preterm infants administered ESAs compared with no ESA or placebo. **Table 3.2.7** summarises the results from these studies.

Our search identified no additional Level II studies that reported on this outcome.

ROP all stages or not reported

Xu (2014) included five RCTs and six cohort or case–control studies involving 2355 neonates that reported the effect of ESA treatment compared with no ESA treatment or placebo on ROP, regardless of the age at which the neonates received ESA therapy. The analyses by Xu (2014) included one RCT (Shannon 1995) that reported threshold ROP, which was considered ROP (≥ stage 3) in the analyses by Ohlsson (2014) and Aher (2014). The authors also included a three-arm RCT (Ohls 2013) that contributed two datasets: rHuEPO versus no rHuEPO and DAR versus no DAR (also considered separately by Ohlsson 2014). A meta-analysis of the data showed no significant difference between treatment groups for this outcome (odds ratio [OR] 1.59; 95% CI 0.90, 2.81); however, heterogeneity was substantial (I2=82.9%). A sensitivity analysis restricted to RCTs found no significant difference between treatment groups for rate of ROP (OR 1.11; 95% CI 0.61, 2.01); however, heterogeneity was substantial (I2=55.4%). A nonsignificant effect was also reported when analysed according to rHuEPO dose or timing of administration subgroups (see **Table 3.2.7**).

Ohlsson (2014) and Aher (2014) assessed the rate of ROP (all stages, or stages not reported) in preterm infants administered ESAs according to the timing of treatment. Ohlsson (2014) included data from eight RCTs involving 982 neonates, and found no significant difference in the incidence of ROP (RR 0.99; 95% CI 0.81, 1.21) in preterm infants administered rHuEPO within the first week of life. There was no heterogeneity for this outcome (I2=0%). Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with sham injections that reported the proportion of subjects who had ROP (all stages). Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 0.94; 95% CI 0.50, 1.75).

Aher (2014) included data from three RCTs involving 404 neonates, and found no significant difference on the incidence of ROP (RR 1.27; 95% CI 0.88, 1.64) in preterm infants administered rHuEPO between days 8 and 28 of life; however, heterogeneity was substantial (I2=83%).

A meta-analysis was conducted to update the Ohlsson (2014) and Aher (2014) reviews with data from the review by Xu (2014), and to evaluate the effect of ESA therapy compared with no ESA therapy on the incidence of ROP (all stages or stage NR) in preterm neonates, regardless of the age at which the neonates received ESA therapy. The analysis showed a nonsignificant increased risk of ROP (all stages or stage NR) (639/1537 versus 533/1489; RR 1.22; 95% CI 0.90, 1.65) in preterm infants administered ESAs (see **Figure 3.2.4**). There was substantial heterogeneity (I2=91%) for this outcome. A sensitivity analysis restricted to RCTs found no significant difference between treatment groups for rate of ROP (all stages, or stage not reported) (227/746 versus 205/702; RR 1.06; 95% CI 0.87, 1.27; *P =*0.57) in preterm infants administered ESAs (see **Figure 3.2.5**). There was no significant heterogeneity for this outcome (I2=24%).

Severe ROP (stage 3–4)

The review by Xu (2014) also reported on the rate of severe ROP (stage 3–4) in preterm infants that were administered ESAs; it included four RCTs and five cohort or case–control studies involving 2497 neonates for this outcome. A meta-analysis of the data showed no significant difference between treatment groups for the rate of severe ROP (stage 3–4) (OR 1.20; 95% CI 0.76, 1.90); however, heterogeneity was substantial (I2=63.8%). A sensitivity analysis restricted to RCTs also found no significant difference between treatment groups for this outcome (OR 1.35; 95% CI 0.76, 2.40), with no significant heterogeneity (I2=18.3%). A nonsignificant effect was also observed for the outcome of severe ROP (stage 3–4) when analysed according to subgroups (rHuEPO dose or timing of administration) (see **Table 3.2.7**).

Ohlsson (2014) and Aher (2014) reported on the rate of severe ROP (≥ stage 3) in preterm infants according to the timing of administration of ESA treatment. Ohlsson (2014) included data from seven RCTs involving 801 neonates, and found no significant difference on the incidence of severe ROP (≥ stage 3) (RR 1.37; 95% CI 0.87, 2.17) in preterm infants administered rHuEPO within the first week of life. There was no heterogeneity for this outcome (I2=0%). Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with sham injections, which reported the proportion of subjects who had severe ROP (≥ stage 3). Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 0.47; 95% CI 0.09, 2.37).

Aher (2014) included data from three RCTs involving 442 neonates, and found no significant difference on the incidence of severe ROP (≥ stage 3) (RR 1.73; 95% CI 0.92, 3.24) in preterm infants administered rHuEPO between days 8 and 28 of life. There was no heterogeneity for this outcome (I2=18%).

The systematic review by Ohlsson (2014) conducted a post-hoc analysis on the rate of severe ROP (≥ stage 3) in neonates that were administered rHuEPO, regardless of the timing of administration. The meta-analysis included 10 RCTs involving 1303 neonates, and found a statistically significant increased risk of severe ROP (≥ stage 3) in infants who received rHuEPO treatment (RR 1.48; 95% CI 1.02, 2.13). There was no heterogeneity for this outcome (I2=0%).

A meta-analysis was conducted to update the Ohlsson (2014) and Aher (2014) reviews with data from the review by Xu (2014), and to evaluate the effect of ESA therapy compared with no ESA therapy on the incidence of severe ROP (≥ stage 3) in preterm neonates, regardless of the age at which the neonates received ESA therapy (see **Figure 3.2.6**). The analysis showed a nonsignificant increase in risk of severe ROP (≥ stage 3) (RR 1.22; 95% CI 0.88, 1.68) in preterm infants administered ESAs. There was moderate heterogeneity (I2=46%) for this outcome. A sensitivity analysis restricted to RCTs also showed a nonsignificant increase risk for rate of ROP (all stages or stage not reported) (64/661 versus 44/644; RR 1.40; 95% CI 0.97, 2.03; *P =*0.07) in preterm infants administered ESAs. There was no significant heterogeneity for this outcome (I2=0%).

Table 3.2.7 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – ROP

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA + iron  n/N (%) | Iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Xu 201492  Level I  *Good* | 11 studiesc  5 RCTs (Ohls 2013, Fauchere 2008, Maier 2002, Romagnoli 2000, Shannon 1995)100; 106; 114; 139; 143  6 cohort or case–control studies (Mehmet 2011, Zayed 2010, Shah 2010, Figueras-Aloy 2010, Suk 2008, Dani 2001)155-160  N=2355 | Preterm neonates | USA, Turkey, Spain, Germany, Italy, Europe | rHuEPO or DAR (± iron) versus placebo or no treatment (± iron)  *\*early or late* | ROP | 563/1221 (46.1%) | 420/1134 (37.0%) | OR 1.59 [0.90, 2.81] | *No significant difference*  *P >*0.05  Substantial heterogeneity  I2 = 82.9% |
| 5 RCTsc (Ohls 2013, Fauchere 2008, Maier 2002, Romagnoli 2000, Shannon 1995)100; 106; 114; 139; 143  N=777 | USA, Germany, Europe, Italy | ROP | Sensitivity analysis: RCTs only | | |  |
|  | 151/430 (35.1%) | 92/347 (26.5%) | OR 1.11 [0.61, 2.01] | *No significant difference*  *P =*0.742  Substantial heterogeneity  I2 = 55.4% |
| 4 RCTsc (Ohls 2013, Fauchere 2008, Maier 2002, Romagnoli 2000)100; 106; 114; 139  4 cohort or case–control studies (Shah 2010, Figueras-Aloy 2010, Suk 2008, Dani 2001)155-156; 158-159  N=1670 | USA, Germany, Europe, Italy, Spain |  | Subgroup analysis: dosing | | |  |
| high-dose rHuEPO or DAR (>500units/kg/week) | 456/996 (45.8%) | 170/674 (25.2%) | OR 1.74 [0.84, 3.61] | *No significant difference*  *P =*0.14d  Substantial heterogeneity  I2 = 87.7% |
| 2 RCTsc (Ohls 2013, Shannon 1995)114; 139; 143  N=222 | USA | low-dose rHuEPO or DAR (<500units/kg/week) | 11/109 (10.1%) | 15/113 (13.3%) | OR 0.69 [0.27, 1.76] | *No significant difference*  *P =*0.50d  No significant heterogeneity  I2 = 0% |
|  |  |  | Subgroup analysis: timing of administration | | |  |
| 1 RCTc (Fauchere 2008)100  2 cohort studies (Figueras-Aloy 2010, Suk 2008)156; 159  N=1021 | Germany , USA, Spain | Early rHuEPO (administered at 0–7 days) | 288/615 (46.8%) | 78/406 (19.2%) | OR 2.70 [0.75, 9.79] | No significant difference  *P =*0.13d  Substantial heterogeneity  I2 = 90.5% |
| 2 RCTsc (Maier 2002, Romagnoli 2000)106; 139  N=449 | Europe, Italy | late rHuEPO (administered at 8–28 days) | 126/263 (47.9%) | 63/186 (33.9%) | OR 1.59 [0.54, 4.70] | No significant difference  *P =*0.40d  Substantial heterogeneity  I2 = 86.1% |
| 9 studiesc  4 RCTs (Ohls 2013, Fauchere 2008, Ohls 2001, Romagnoli 2000)100; 112; 114; 139  5 cohort or case–control studies (Zayed 2010, Figueras-Aloy 2010, Schneider 2008, Suk 2008, Manzoni 2005)156; 159-162  N=2497 | USA, Germany , Italy, Spain | Severe ROP (stage 3–4) | 192/1298 (14.8%) | 166/1199 (13.8%) | OR 1.20 [0.76, 1.90] | *No significant difference*  *P >*0.05  Substantial heterogeneity  I2 = 63.8% |
|  |  | Severe ROP (stage 3–4) | Sensitivity analysis: RCTs only | | |  |
| 4 RCTsc (Ohls 2013, Fauchere 2008, Ohls 2001, Romagnoli 2000) 100; 112; 114; 139  N=692 | USA, Germany, Italy | 51/352 (14.5%) | 37/340 (10.9%) | OR 1.35 [0.76, 2.40] | *No significant difference*  *P =*0.301  No significant heterogeneity  I2 = 18.3% |
|  |  |  | Subgroup analysis: dosing | | |  |
| 4 RCTsc (Ohls 2013, Ohls 2001, Fauchere 2008, Romagnoli 2000) 100; 112; 114; 139  2 cohort studies (Figueras-Aloy 2010, Suk 2008)156; 159  N=1607 | USA, Germany, Italy, Spain | high-dose rHuEPO or DAR (>500units/kg/week) | 96/883 | 77/724 | OR 1.31 [0.58, 2.96] | No significant difference  *P =*0.52d  Substantial heterogeneity  I2 = 75.6% |
| 1 RCTc (Ohls 2013)114  N=67 | USA | low-dose rHuEPO or DAR (<500units/kg/week) | 2/34 | 4/33 | OR 0.45 [0.08, 2.66] | No significant difference  *P =*0.38  Heterogeneity not applicable |
|  |  |  | Subgroup analysis: timing of administration | | |  |
| 1 RCTc (Fauchere 2008)100  2 cohort studies (Figueras-Aloy 2010, Suk 2008)156; 159  N=1021 | Germany, USA, Spain | Early rHuEPO (administered at 0–7 days) | 48/589 (8.15%) | 44/432 (10.19%) | OR 1.37 [0.21, 8.89] | No significant difference  *P =*0.74d  Substantial heterogeneity  I2 = 86.8% |
| 1 RCTc (Romagnoli 2000)139  1 cohort study (Schneider 2008)  N=502 | Italy, USA | late rHuEPO (administered at 8–28 days) | 46/252 | 36/250 | OR 1.46 [0.56, 3.77] | No significant difference  *P =*0.44d  Substantial heterogeneity  I2 = 71.0% |
| Ohlsson 201490  Level I  *Good* | 8 trialse (Arif 2005, Carnielli 1998, Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Ohls 2013, Yeo 2001)95; 98; 100-101; 105-106; 114; 120  N=982 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Austria x1, Europe x2, Italy x1, Singapore x1, Switzerland x1, Turkey x1, USA x1 | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | ROP (all stages or not reported) | 131/505 (26.0%) | 129/477 (27.0%) | RR 0.99 [0.81, 1.21] | *No significant difference*  *P =*0.94  No significant heterogeneity  I2 = 0% |
| 7 trialse (Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013)100-101; 105-106; 112; 114  N=801 | Austria x1, Europe x2, Switzerland x1, USA x3 | Severe ROP (≥ stage 3) | 38/410 (9.3%) | 26/391 (6.6%) | RR 1.37 [0.87, 2.17] | *No significant difference*  *P =*0.18  No significant heterogeneity  I2 = 0% |
|  | 10 trialse (Al-Kharfy 1996, Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Romagnoli 2000, Shannon 1995)100-101; 105-106; 112; 114; 123; 139; 143  N=1303 |  | Austria x1, Canada x1, Europe x2, Italy x1, Switzerland x1, USA x4 | rHuEPO + iron versus placebo/no treatment + iron  *\*early or late* | Severe ROP (≥ stage 3) | 70/689 (10.2%) | 40/614 (6.5%) | RR 1.48 [1.02, 2.13] | *Favours iron alone*  *P =*0.04  No significant heterogeneity  I2 = 0% |
| RD 0.03 [0.00, 0.06], | *P =*0.03  Moderate heterogeneity  I2 = 50%  NNTH 33 [17–∞] |
| Aher 201487  Level I  *Good* | 3 trialsf (Maier 2002, Pollak 2001, Romagnoli 2000)106; 137; 139  N=404 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | Single centre, Austria, Italy  Multicentre, Europe | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | ROP (all stages or not reported) | 84/209 (40.2%) | 64/195 (32.8%) | RR 1.27 [0.99,1.64] | *No significant difference*  P = 0.063  Substantial heterogeneity  I2 = 83% |
| 3 trialsf (Al-Kharfy 1996, Romagnoli 2000, Shannon 1995)123; 139; 143  N=442 | Single centre, Canada, Italy  Multicentre, USA | Severe ROP (≥ stage 3) | 24/219 (11.0%) | 14/223 (6.3%) | RR 1.73 [0.92,3.24] | *No significant difference*  *P =*0.087  No significant heterogeneity  I2 = 18% |
| Level II evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trial (Ohls 2013)114  N=62 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | USA | DAR + iron versus placebo + iron | ROP (all stages) | 12/32 (37.5%) | 12/30 (40.0%) | RR 0.94 [0.50, 1.75] | *No significant difference*  *P =*0.84 |
| Severe ROP (≥ stage 3) | 2/32 (6.3%) | 4/30 (13.3%) | RR 0.47 [0.09, 2.37] | *No significant difference*  *P =*0.36 |

CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; LBW, low birth weight; NNTH, number needed to treat to harm; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference; rHuEPO, recombinant human epoetin; ROP, retinopathy of prematurity; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one study (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned), one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group), one trial (Ohls 2013) that contributed two datasets: rHuEPO versus no rHuEPO and DAR versus no DAR, and one trial (Shannon 1995) that reported threshold ROP, which was considered under ROP (stage ≥3) by Ohlsson (2014) and Aher (2014).

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** Analysis includes one study (Carnielli 1998) that compared rHuEPO + iron versus placebo (no iron in control group) and one study (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned) and one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group).

**f.** Analysis includes one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group).

Figure 3.2.4 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – ROP (all stages or stage not reported)



Figure 3.2.5 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – ROP (all stages or stage not reported – RCTs only)



Figure 3.2.6 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – severe ROP (stage 3–4)



Figure 3.2.7 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – severe ROP (stage 3–4 – RCTs only)



###### Bronchopulmonary dysplasia

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the incidence of BPD in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. **Table 3.2.8** summarises the results from these studies.

Our literature search identified no additional Level II studies that reported on this outcome.

Early rHuEPO or DAR

Ohlsson (2014) identified 11 RCTs that reported the incidence of BPD (supplemental oxygen at 28 days of life or at 36 weeks postmenstrual age, or age at diagnosis not stated) in preterm infants administered rHuEPO within the first week of life. Ohlsson (2014) also noted that two RCTs (Ohls 1995, Ohls 1997) reported no difference in BPD rates between treatment groups, but data were not provided by the trial authors.

One RCT (Yeo 2001) involving 100 neonates reported no significant difference between treatment groups (RR 0.75; 95% CI 0.35, 1.62) for use of supplemental oxygen at 28 days. A meta-analysis of five RCTs involving 542 neonates found no significant difference between treatment groups (RR 0.99; 95% CI 0.81, 1.21) for the use of supplemental oxygen at 36 weeks postmenstrual age. There was no heterogeneity for this outcome (I2=0%). Similarly, a meta-analysis of five RCTs involving 528 neonates that reported the incidence of BPD (age not specified) also found no significant difference between treatment groups (RR 0.98; 95% CI 0.61, 1.56), with no heterogeneity for this outcome (I2=0%).

Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with sham injections that reported the proportion of subjects who had BPD (supplemental oxygen at 36 weeks postmenstrual age). Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 1.03; 95% CI 0.73, 1.46).

Late rHuEPO

Aher (2014) identified five RCTs that reported the incidence of BPD (supplemental oxygen at 28 days of life or at 36 weeks postmenstrual age) in preterm infants administered rHuEPO between days 8 and 28 of life. A meta-analysis of two RCTs involving 285 neonates showed a borderline significant increased risk of BPD (supplemental oxygen at 28 days) (RR 1.25; 95% CI 1.00, 1.55; *P =*0.05) in infants administered late rHuEPO. There was substantial heterogeneity for this outcome (I2=97%). When analysed using a random-effects model, the effect was nonsignificant (RR 1.21; 95% CI 0.35, 4.24; *P =*0.76). A meta-analysis of three RCTs involving 216 neonates reported the incidence of BPD (supplemental oxygen at 36 weeks postmenstrual age), with no significant difference (RR 0.89; 95% CI 0.59, 1.35) between treatment groups reported. There was substantial heterogeneity for this outcome (I2=56%).

Early or late ESAs

A meta-analysis was conducted to combine the Ohlsson (2014) and Aher (2014) reviews, and to evaluate the effect of ESA therapy compared with no ESA therapy on the incidence of BPD in preterm neonates, regardless of BPD definition or the age at which the neonates received ESA therapy (see **Figure 3.2.8**). The analysis showed no significant difference between treatment groups (RR 1.00; 95% CI 0.94, 1.07) for the outcome of BPD in preterm infants administered ESAs compared with no ESA or placebo. There was no heterogeneity (I2=0%) for this outcome.

Table 3.2.8 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – BPD

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA + iron  n/N (%) | Iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | |
| Ohlsson 201490  Level I  *Good* | 5 trialsc (Fauchere 2008, Maier 2002, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013)100; 106; 112; 114  N=542 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Switzerland x1, Europe x1, USA x3 | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | BPD (supplemental oxygen at 36 weeks postmenstrual age) | 107/282 (37.9%) | 98/260 (37.7%) | RR 0.99 [0.81, 1.21] | *No significant difference*  *P =*0.94  No significant heterogeneity  I2 = 0% |
| 5 trialsd (Arif 2005, Carnielli 1998, Haiden 2005, Lima-Rogel 1998, Obladen 1991)98; 101; 104; 109; 123  N=528 | Turkey x1, Italy x1, Austria x1, Mexico x1, Europe x1 | BPD (age at diagnosis not stated) | 30/269 (11.2%) | 25/259 (9.7%) | RR 0.98 [0.61, 1.56] | *No significant difference*  *P =*0.92  No significant heterogeneity  I2 = 0% |
| Aher 201487  Level I  *Good* | 2 trialse (Al-Kharfy 1996; Romagnoli 2000)123; 139  N=285 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8– 28 days | Canada, Italy | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | BPD (supplementary oxygen at 28 days) | 70/142 (49.3%) | 57/143 (39.9%) | RR 1.25 [1.00, 1.55] | *No significant difference (borderline)*  *P =*0.051f  Substantial heterogeneity  I2 = 97% |
| 3 trials (Griffiths 1997, Maier 2002, Pollak 2001)106; 132; 137  N=216 | England, Europe Austria | BPD (supplementary oxygen at 36 weeks postmenstrual age) | 30/115 (26.1%) | 31/101 (30.7%) | RR 0.89 [0.59, 1.35] | *No significant difference*  *P =*0.57  Substantial heterogeneity  I2 = 56% |
| Level II evidence | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trial (Yeo 2001)120  N=100 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Singapore | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | BPD (supplemental oxygen at 28 days) | 9/50 (18%) | 12/50 (24%) | RR 0.75 [0.35, 1.62] | *No significant difference*  *P =*0.46 |
| 1 trial (Ohls 2013)114  N=62 | USA | DAR + iron versus placebo + iron | BPD (supplemental oxygen at 36 weeks postmenstrual age) | 22/32 (68.8%) | 20/30 (66.7%) | RR 1.03 [0.73, 1.46] | *No significant difference*  *P =*0.86 |

BPD, bronchopulmonary dysplasia; CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; LBW, low birth weight; NR, not reported; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one trial (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned).

**d.** Analysis includes one study (Carnielli 1998) that compared rHuEPO + iron versus placebo (no iron in control group).

**e.** Analysis includes one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group).

**f.** Nonsignificant (*P =*0.76) when analysed using RevMan 5.1.2 using a random-effects model (RR 1.21; 95% CI 0.35, 4.24)

Figure 3.2.8 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – BPD



###### Necrotising enterocolitis

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the incidence of necrotising enterocolitis (NEC) in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. One additional Level II study (El-Ganzoury 2014) was identified in our literature search that also reported on this outcome in preterm infants administered enteral rHuEPO. **Table 3.2.9** summarises the results from these studies.

Early rHuEPO or DAR

Ohlsson (2014) included data from 11 RCTs involving 1347 neonates that reported any outcome stated as NEC in their analysis. Ohlsson (2014) also noted that one RCT (Ohls 1995) reported no difference in the rate of NEC between treatment groups, but data were not provided. A meta-analysis found no significant difference on the rate of NEC (RR 1.07; 95% CI 0.73, 1.57) in preterm infants administered rHuEPO within the first week of life. There was no significant heterogeneity for this outcome (I2=0%).

Ohlsson (2014) also identified one RCT (Ohls 2013) comparing early DAR with sham injections that reported the proportion of subjects who had NEC (> stage 2). Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 0.94; 95% CI 0.14, 6.24).

The RCT by El-Ganzoury (2014) aimed to assess the safety and efficacy of enteral rHuEPO and G-CSF in preventing feeding intolerance and/or NEC in preterm infants. The authors reported a nonsignificant reduced risk (RR 0.21; 95% CI 0.01, 3.87) of NEC in preterm infants administered oral rHuEPO (or oral rHuEPO plus G-CSF) compared with placebo.

Late rHuEPO

Aher (2014) included data from six RCTs involving 656 neonates that reported NEC (≥ stage 2). A meta-analysis found no significant difference on the rate of NEC (≥ stage 2) (RR 0.88; 95% CI 0.46, 1.69) in preterm infants administered rHuEPO between days 8 and 28 of life. There was no significant heterogeneity (I2=0%) for this outcome.

Early or late ESAs

A meta-analysis was conducted to combine the Ohlsson (2014) and Aher (2014) reviews, and to evaluate the effect of ESA therapy compared with no ESA therapy on the incidence of NEC in preterm neonates, regardless of the age at which the neonates received ESA therapy (see **Figure 3.2.9**). The analysis showed no significant difference between treatment groups (69/1038 versus 64/1027; RR 0.98; 95% CI 0.70, 1.38) for the outcome of NEC in preterm infants administered ESAs compared with no ESAs or placebo. There was no significant heterogeneity (I2=0%) for this outcome.

Table 3.2.9 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – NEC

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA + iron  n/N (%) | Iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | |
| Ohlsson 201490  Level I  *Good* | 11 trialsc (Arif 2005, Fauchere 2008, Haiden 2005, Lima-Rogel 1998, Maier 1994, Maier 2002, Obladen 1991, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Yeo 2001)95; 100-101; 104; 106; 109; 112; 114; 120  N=1347 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Austria x1, Europe x3, Mexico x1, Singapore x1, Switzerland x1, Turkey x1, USA x3 | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | NEC | 52/678 (7.7%) | 45/669 (6.7%) | RR 1.07 [0.73, 1.57] | *No significant difference*  *P =*0.73  No significant heterogeneity  I2 = 0% |
| Aher 201487  Level I  *Good* | 6 trialsd (Maier 2002, Meyer 1994, Romagnoli 2000, Samanci 1996, Shannon 1991, Shannon 1995)106; 136; 139-141; 143  N=656 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged 8–28 days | Single centre, South Africa x1, Italy x1, Turkey x1,  Multicentre, Europe x1, USA x2 | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | NEC (≥Bell’s stage 2) | 15/328 (4.6%) | 17/328 (5.2%) | RR 0.88 [0.46, 1.69] | *No significant difference*  *P =*0.70  No significant heterogeneity  I2 = 0% |
| Level II evidence | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trial (Ohls 2013)114  N=62 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | USA | DAR + iron versus placebo + iron | NEC (>Bell’s stage 2) | 2/32 (6.3%) | 2/30 (6.7%) | RR 0.94 [0.14, 6.24] | *No significant difference*  *P =*0.95  No significant heterogeneity  I2 = 0% |
| Feeding intolerance | | | | | | | | | |
| El-Ganzoury 2014e 150  Level II  Fair | N=50 | Preterm infants (≤33 weeks gestation) | Multiple NICUs, Egypt | Oral rHuEPO versus placebo | NEC | 0/20 (0%) | 3/30 (10%) | RR 0.21 [0.01, 3.87]f | *No significant difference*  *P =*0.29f  *P =*0.165g |
| N=40 | Oral rHuEPO + G-CSF versus G-CSF | 0/20 (0%) | 0/20 (0%) | Not estimable | *Not applicable* |

CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; LBW, low birth weight; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one study (Fauchere 2008) that compared ESAs to no ESAs (use of iron not mentioned).

**d.** Analysis includes one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group).

**e.** El-Ganzoury (2014) was a four-armed trial comparing G-CSF versus rHuEPO versus G-CSF plus rHuEPO versus placebo. Data for rHuEPO versus placebo and rHuEPO + G-CSF versus G-CSF is presented here.

**f.** Calculated post-hoc using RevMan 5.1.2.

**g.** *P-*value as reported by trial authors (calculated using Chi-squared test).

Figure 3.2.9 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – NEC



###### Mortality

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed the incidence of mortality in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. One additional Level II study (El-Ganzoury 2014) was identified in our literature search that also reported on this outcome in preterm infants administered enteral rHuEPO. **Table 3.2.10** summarises the results from these studies.

Early rHuEPO or DAR

Ohlsson (2014) included data from 16 RCTs involving 1656 neonates that reported all-cause mortality during initial hospital stay. A meta-analysis found no significant difference between treatment groups for the incidence of mortality (RR 0.91; 95% CI 0.68, 1.22) in these preterm infants administered rHuEPO within the first week of life. There was no significant heterogeneity for this outcome (I2=0%).

Ohlsson (2014) also identified one RCT (Ohls 2013) involving 66 preterm infants comparing early DAR with sham injections that reported all-cause mortality during their initial hospital stay. Ohls (2013) found no significant difference between treatment groups comparing DAR with sham injections (RR 1.33; 95% CI 0.04, 3.04).

The RCT by El-Ganzoury (2014) aimed to assess the safety and efficacy of enteral rHuEPO and G-CSF in preventing feeding intolerance and/or NEC in preterm infants. There was no significant difference between treatment groups (RR 1.00; 95% CI 0.18, 5.46) for the incidence of mortality in preterm infants administered oral rHuEPO compared with placebo or in preterm infants administered rHuEPO plus G-CSF compared with G-CSF alone (RR 0.50; 95% CI 0.05, 5.08).

Late rHuEPO

Aher (2014) included data from 13 RCTs involving 767 neonates that reported all-cause mortality during initial hospital stay. A meta-analysis found no significant difference on the incidence of mortality (RR 0.82; 95% CI 0.49, 1.39) in preterm infants administered rHuEPO between days 8 and 28 of life. There was no significant heterogeneity (I2=0%) for this outcome.

Early or late ESAs

A meta-analysis was conducted to combine the Ohlsson (2014) and Aher (2014) reviews, and to evaluate the effect of ESA therapy compared with no ESA therapy on the incidence of mortality in preterm neonates, regardless of the age at which the neonates received ESA therapy (see **Figure 3.2.10**). The analysis showed no significant difference between treatment groups (RR 0.90; 95% CI 0.70, 1.17) on the outcome of mortality in preterm infants administered ESAs compared with no ESAs or placebo. There was no heterogeneity (I2=0%) for this outcome.

Table 3.2.10 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA ± iron  n/N (%) | ± iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I  *Good* | 16 trialsc (Arif 2005, Avent 2002, Carnielli 1992, Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Obladen 1991, Ohls 1997, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013, Soubasi 1993, Soubasi 1995, Yasmeen 2012, Yeo 2001)95-96; 98; 100-101; 105-106; 109; 111-112; 114; 116-117; 119-120  N=1656 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates, aged less than 8 days | Austria x1, Bangladesh x1, Europe x3, Greece x2, Italy x1, South Africa x1, Singapore x1, Switzerland x1, Turkey x1, USA x4 | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | All-cause mortality during initial hospital stay | 79/864 (9.1%) | 80/792 (10.1%) | RR 0.91 [0.68, 1.22] | *No significant difference*  *P =*0.53  No significant heterogeneity  I2 = 0% |
| Aher 201487  Level I  *Good* | 13 trials (Al-Kharfy 2005, Bechensteen 1993, Chen 1995, Donato 1996, Emmerson 1993, Giannakopoulou 1998, Griffiths 1997, Maier 2002, Meyer 1994, Pollak 2001, Shannon 1991, Shannon 1995, Whitehall 1999)106; 123; 126-127; 129-132; 136-137; 141; 143-144  N=767 | Preterm (<37 weeks gestation) and/or LBW (<2500g) neonates, aged 8–28 days | Argentina x1, Australia x1, Austria x1, Canada x1,Europe x1, Greece x1, Norway x1, South Africa x1, Taiwan x1, UK x2, USA x2 | Late rHuEPO + iron versus placebo/no intervention + iron  \*Initiation of rHuEPO 8 to 28 days after birth | All-cause mortality during hospital stay | 20/403 (5.0%) | 23/364 (6.3%) | RR 0.82 [0.49,1.39] | *No significant difference*  *P =*0.47  No significant heterogeneity  I2 = 0% |
| Level II evidence | | | | | | | | | |
| Anaemia of prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trial (Ohls 2013)114  N=66 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates | USA | DAR + iron versus placebo+ iron | All-cause mortality during initial hospital stay | 1/33 (3.0%) | 3/33 (9.1%) | RR 0.33 [0.04, 3.04] | *No significant difference*  *P =*0.33 |
| Feeding intolerance | | | | | | | | | |
| El-Ganzoury 2014d 150  Level II  Fair | N=50 | Preterm infants (≤33 weeks gestation) | Multiple NICUs, Egypt | rHuEPO versus placebo | Mortality | 2/20 (10%)  \*both due to early onset sepsis | 3/30 (10%)  \*due to NEC (grade III/IV) | RR 1.00 [0.18, 5.46]e | No significant difference  *P =*1.0e  *P =*0.92f |
| N=40 | rHuEPO + G-CSF versus G-CSF | 1/20 (5%)  \*due to respiratory distress syndrome (grade IV) | 2/20 (10%)  \*one due to early onset septicaemia and one due to respiratory distress syndrome (grade III) | RR 0.50 [0.05, 5.08]e | No significant difference  *P =*0.56e |

CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; LBW, low birth weight; NICU, neonatal intensive care unit; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one study (Carnielli 1992) that compared rHuEPO + iron to placebo (no iron in control group) and one study (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned).

**d.** El-Ganzoury (2014) was a four-armed trial comparing G-CSF versus rHuEPO versus G-CSF plus rHuEPO versus placebo. Data for rHuEPO versus placebo and rHuEPO + G-CSF versus G-CSF is presented here.

**e.** Calculated post-hoc using RevMan 5.1.2.

**f.** *P-*value as reported by trial authors (calculated using Chi-squared test).

Figure 3.2.10 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – mortality



###### Secondary outcomes[[24]](#footnote-24)

Functional/performance status

The systematic reviews by Ohlsson (2014) and Aher (2014) assessed long-term outcomes in preterm infants administered ESAs compared with no ESA or placebo, stratified according to the age at which ESA treatment was initiated. These outcomes were specified to be those assessed at any age beyond 1 year of age by a validated cognitive, motor, language, or behavioural, school, social interaction or adaptation test. Ohlsson (2014) reported data from three RCTs (Ohls 2001a, He 2008, Ohls 2013) (four comparisons) that reported functional/performance measures in preterm infants administered ESAs within the first week of life. Aher (2014) did not identify any RCTs that reported long-term outcomes on preterm infants administered ESAs between days 8 and 28 of life. There was one additional long-term follow-up report (Newton 1999) identified in our literature search that reported on functional/performance status in preterm infants. **Table 3.2.11** summarises the results from these studies.

Ohls (2004) reported long-term follow-up data for preterm infants enrolled in an RCT initially described by Ohls (2001a). The authors found no significant difference between treatment groups for MDI <70 at 18–22 months corrected age (RR 0.88; 95% CI 0.49, 1.57) or for any neurodevelopmental impairment at 18–22 months corrected age (RR 0.97; 95% CI 0.62, 1.51), but reported that infants administered rHuEPO had a borderline significant increased risk of having a psychomotor development index <70 at 18–22 months corrected age (RR 2.33; 95% CI 0.98, 5.53) when compared to placebo.

He (2008) was reported to show a statistically significant higher short-term neonatal behavioural assessment score at 40 weeks postmenstrual age in infants administered rHuEPO (MD 1.80; 95% CI 1.23, 2.34) compared with placebo.

Ohls (2013) was reported to show a statistically significant higher Bayley Scales of Infant Development-III score at 18–22 months corrected age in infants administered rHuEPO (MD 10.0; 95% CI 3.06, 16.94) and DAR (MD 9.0; 95% CI 3.33, 14.67) when compared with placebo.

Newton (1999) reported long-term follow-up data for 40 preterm infants administered rHuEPO after the first week of life that were enrolled in one of three RCTs initially described by Shannon (1991, 1992, 1995). Data were available for 33 infants that completed BSID assessments at 18 months (number in treatment and placebo groups not reported), with no significant difference in test scores reported. There were no significant neurosensory deficits (blindness and/or deafness) reported in either group. The authors also reported no significant difference between treatment groups for any impairment in neurodevelopmental or cognitive development outcomes at last assessment.

Table 3.2.11 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Functional / performance status (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA + iron  n/N (%)  Mean ± SD | Iron only  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | |
| Ohlsson 201490  Level I/II  *Good* | 1 trialc (Ohls 2001a)112  N=99 | Preterm (<37 weeks gestation) and/or LBW (<2500 g) neonates | USA | Early rHuEPO + iron versus placebo + iron  \*Initiation of rHuEPO <8 days after birth | MDI <70 at 18–22 months corrected age (N=90) | 14/45 (31.1%) | 16/45 (35.6%) | RR 0.88 [0.49, 1.57] | *No significant difference*  *P =*0.66 |
| RD –0.04 [–0.24, 0.15] | *No significant difference*  *P =*0.65d |
| PDI <70 at 18–22 months corrected age (N=90) | 14/45 (31.1%) | 6/45 (13.3%) | RR 2.33 [0.98, 5.53] | *Borderline favours placebo + iron*  *P =*0.054 |
| RD 0.18 [0.01, 0.35] | *Favours placebo + iron*  *P =*0.04  NNTH 6 [3–100] |
| Any neuro-developmental impairment at 18–22 months corrected age (N=99) | 21/48 (43.8%) | 23/51 (45.1%) | RR 0.97 [0.62, 1.51] | *No significant difference*  *P =*0.89 |
| RD –0.01 [–0.21, 0.18] | *No significant difference*  *P =*NR |
| 1 triale (He 2008)102  N=44 | China | Early rHuEPO ± iron (n=22) versus placebo ± iron (n=22)  \*Initiation of rHuEPO <8 days after birth | Neonatal Behavioural Neurological Assessment score at 40 weeks postmenstrual age | 36.2 ± 0.75 | 34.4 ± 1.05 | MD 1.80 [1.26, 2.34] | *Favours early rHuEPO ± iron*  *P <*0.00001 |
| 1 trialf (Ohls 2013)114  N=54 | USA | Early rHuEPO + iron (n=30) versus placebo + iron (n=24)  \*Initiation of rHuEPO <8 days after birth | BSID-III cognitive score at 18–22 months | 98 ± 14 | 88 ± 12 | MD 10.0 [3.06, 16.94] | *Favours rHuEPO + iron*  *P =*0.0047 |
| 1 trial (Ohls 2013)114  N=51 | DAR + iron (n=27) versus placebo + iron (n=24)  \*Initiation of DAR <8 days after birth | BSID-III cognitive score at 18–22 monthsf | 97 ± 8 | 88 ± 12 | MD 9.0 [3.33, 14.67] | *Favours DAR + iron*  *P =*0.0019 |
| Newton 1999163  Level II | N=50 | Preterm infants (<32 weeks gestation) with VLBW (<1500 g) | Single centre, USA | Late rHuEPO ± iron versus placebo ± iron  \*Initiation of rHuEPO 8–35 days after birth | MDI at 12–18 months (mean adjusted age 17 months)  N=33 | 94.6 ± 18.7 (n=NR) | 95.4 ± 9.9 (n=NR) | MD 0.8 [NR] | *No significant difference*  *P =*0.878 |
| Neurosensory deficits (blindness and/or deafness) | 0/20 (0%) | 0/20 (0%) | *Not estimable* | *Not applicable* |
| Any ‘suspect’ neurologic impairment at last assessmenth | 1/20 (5%) | 0/20 (0%) | RR 3.00 [0.13, 69.52]d | *No significant difference*  *P =*0.49d |
| Any ‘abnormal’ neurologic impairment at last assessmenth | 1/20 (5%) | 0/20 (0%) | RR 3.00 [0.13, 69.52]d | *No significant difference*  *P =*0.49d |
| Any cognitive development impairment assessed as ‘borderline’ at last assessmenth | 5/20 (25%) | 5/20 (25%) | RR 1.00 [0.34, 2.93]d | *No significant difference*  *P =*1.0d |
| Any cognitive development impairment assessed as ‘deficient’ at last assessmenth | 2/20 (10%) | 0/20 (0%) | RR 5.00 [0.26, 98.00]d | *No significant difference*  *P =*0.29d |

BSID-III, Bayley Scales of Infant Development; CI, confidence interval; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; LBW, low birth weight; MDI, Mental Developmental Index; MD, mean difference; NNTH, number needed to treat to harm; NR, not reported; PDI, psychomotor developmental index; RD, risk difference; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Long-term outcomes for participants in this trial reported by Ohls et al (2004).

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** Study published in Chinese; review authors obtained data from abstract only. Unclear if iron administered to participants.

**f.** Long-term outcomes published in abstract form only.

**g.** Preterm infants enrolled in one of three RCTs described by Shannon (1991, 1992, 1995). Mean adjusted age (months) at last follow-up rHuEPO group 45.1 ± 20, placebo group 48.2 ± 32

**h.** One infant had persistent low tone (suspect) and one infant had spastic diplegia (abnormal)

**i.** Development and cognitive scores that were 1–2 SDs below the mean were considered borderline; scores >2 SDs below the mean were considered deficient.

Laboratory measures

Four RCTs (Jim 2000, Kremenopoulos 1997, El-Ganzoury 1997, Ovali 1996) were identified that reported laboratory measures (Hb, Hct, ferritin) in preterm infants administered ESAs compared with no ESA or placebo. **Table 3.2.12** summarises the results from these studies.

Jim (2000) assessed the effectiveness of rHuEPO in maintaining Hb values in preterm infants after birth and reported a statistically significant increase in Hb (g/dL), Hct (%), and serum ferritin (ng/mL) favouring rHuEPO treatment; however, the data were incomplete (no SDs provided).

Kremenopoulos (1997) assessed the effectiveness of rHuEPO in reducing the need for RBC transfusions and improving haematological values in two groups of preterm infants – group A (high-dose, initiated at age 3–7 days) and group B (low-dose, initiated at age >3 weeks). The authors reported a significant increase in Hb (g/dL) at end of treatment in infants in group A without complications (MD 13.00; 95% CI 4.21, 21.79), and in infants in group A with complications (MD 19.00; 95% CI 5.17, 32.83) but not infants in group B (MD –6.00, 95% CI –19.42, 7.42). A significant increase in Hct (%) at end of treatment favouring rHuEPO was also reported in all groups: group A without complications (MD 0.06; 95% CI 0.03, 0.09), group A with complications (MD 0.07; 95% CI 0.02, 0.12), group B (MD 0.03; 95% CI 0.01, 0.05). Serum ferritin levels were not significantly different in any group: group A without complications (MD –120.00; 95% CI –247.05, 7.05), group A with complications (MD –136.00; 95% CI –292.91, 20.91), group B (MD –30.00; 95% CI 144.35, 84.35).

El-Ganzoury (2014) assessed the safety and efficacy of enteral rHuEPO and G-CSF in preventing feeding intolerance and/or NEC in preterm infants. There was no significant difference between treatment groups on Hb (g/dL) levels comparing rHuEPO with no rHuEPO (MD 2.30; 95% CI –0.32, 4.92) or rHuEPO plus G-CSF compared with G-CSF (MD –0.20; 95% CI –3.12, 2.72).

Ovali (1996) examined the safety and effectiveness of ESA therapy in reducing the need for RBC transfusion in preterm infants with Rh haemolytic disease, but did not report sufficient data for any analysis (no SDs provided).

Table 3.2.12 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESA + iron  Mean ± SD  median (IQR) | Iron only  Mean ± SD  median (IQR) | Risk estimate (95% CI) | | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | |
| Anaemia of Prematurity | | | | | | | | | | |
| Jim 2000151  Level II  *Poor* | N=23 | Preterm infants (<33 weeks gestation) with VLBW (<1500 g) | Taiwan | Late rHuEPO + iron (n=12) versus placebo + iron (n=11)  \*Initiation of rHuEPO ≥7 days of age | Hb (g/dL) after week 4 | 11.1 ± NR | 8.9 ± NR | NR | | *Favours late rHuEPO + iron P <*0.05e |
| Hct (%) after week 5 | 34.1 ± NR | 26.6 ± NR | NR | | *Favours late rHuEPO + iron P <*0.05e |
| Serum ferritin (ng/mL) | NR ± NR | NR ± NR | NR | | *Favours iron only*  *P <*0.05e |
| Kremenopoulos 1997152  Level II  *Poor* | N=85  \*Group A (N=50)  \*Group B (N=35) | Preterm infants (≤31 weeks gestation) with VLBW (≤1500 g) | Greece | rHuEPO + oral iron versus oral iron  \*Group A (rHuEPO750) initiation of rHuEPO 3–7 days after birth  \*Group B (rHuEPO600) initiation of rHuEPO >3 weeks after birth | Mean Hb (g/dL) at end of treatment  \*Group A  \*Group B | NR | NR | NR | | NR |
| 96 ± 13 (n=20) | 102 ± 24 (n=15) | MD –6.00 [–19.42, 7.42]e | | *No significant difference*  *P =*0.38e |
| infants without complications | Secondary analysis (Group A only): complications (mechanical ventilation, sepsis) | | | | |
| 100 ± 9 (n=10) | 87 ± 12 (n=12) | MD 13.00 [4.21, 21.79]d | | Favours early rHuEPO + iron  *P <*0.05e |
| infants with complications | 111 ± 16 (n=14) | 92 ± 21 (n=14) | MD 19.00 [5.17, 32.83]d | | Favours early rHuEPO + iron  *P <*0.05e |
| Hct at end of treatment  \*Group A  \*Group B | NR | NR | NR | | NR |
| 0.29 ± 0.04 | 0.26 ± 0.03 | MD 0.03 [0.01, 0.05]d | | *Favours late rHuEPO + iron*  *P <*0.01e |
| infants without complications | Secondary analysis (Group A only): complications (mechanical ventilation, sepsis) | | | | |
| 0.32 ± 0.03 | 0.26 ± 0.04 | MD 0.06 [0.03, 0.09]d | *Favours early rHuEPO + iron*  *P <*0.01 | |
| infants with complications | 0.36 ± 0.05 | 0.29 ± 0.07 | MD 0.07 [0.02, 0.12]d | *Favours early rHuEPO + iron*  *P <*0.01 | |
| Ferritin (µg/L) at end of treatment  \*Group A  \*Group B | NR | NR | NR | NR | |
| 237 ± 184 | 267 ± 185 | MD –30.00 [144.35, 84.35]d | *No significant difference*  *P =*0.61d | |
| infants without complications | Secondary analysis (Group A only): complications (mechanical ventilation, sepsis) | | | | |
| 193 ± 161 | 313 ± 139 | MD –120.00 [–247.05, 7.05]d | *No significant difference*  *P =*0.06d | |
| infants with complications | 334 ± 165 | 470 ± 250 | MD –136.00 [–292.91, 20.91]d | *No significant difference*  *P =*0.09d | |
| Feeding intolerance | | | | | | | | | | |
| El-Ganzoury 2014c 150  Level II  *Fair* | N=50 | Preterm infants (≤33 weeks gestation) | Multiple NICUs, Egypt | rHuEPO versus placebo | Hb (g/dL) | 17.7 ± 5.5 (n=20) | 15.4 ± 2.9 (n=30) | MD 2.30 [–0.32, 4.92]d | | *No significant difference*  *P =*0.09d  *P =*0.27e |
| N=40 | rHuEPO + G-CSF versus G-CSF | Hb (g/dL) | 16.6 ± 5.1 | 16.8 ± 4.3 | MD –0.20 [–3.12, 2.72]d | | *No significant difference*  *P =*0.89 |
| Rh haemolytic disease of the fetus and newborn | | | | | | | | | | |
| Ovali 1995153  Level II  Fair | N=20 | Preterm infants with RhHDFN | Single NICU, Turkey | rHuEPO + iron versus placebo + iron | Hb (mmol/L) at 10 weeks | ~1.8 ± NR | ~1.6 ± NR | MD –0.2 [NR] | | NR |

CI, confidence interval; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony factor; Hb, haemoglobin; Hct, haematocrit; IQR, interquartile range; MD, mean difference; NICU, neonatal intensive care unit; NR, not reported; RhHDFN, Rh haemolytic disease of the fetus and newborn; rHuEPO, recombinant human epoetin; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** El-Ganzoury (2014) was a four-armed trial comparing G-CSF versus rHuEPO versus G-CSF plus rHuEPO versus placebo. Data for rHuEPO versus placebo and rHuEPO + G-CSF versus G-CSF are presented here.

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** *P-*value as reported by study authors.

* + - 1. Oral and/or parenteral iron therapy

| Evidence statements – preterm and low birth weight infants (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | 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 | √√ | √ |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| 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

Preterm and low birth weight infants are at risk of developing iron-deficiency anaemia as a result of smaller iron stores at birth and a higher demand for iron during the first few months of life than that of infants born at term. This is because most iron stores present at birth are accumulated during the last 10 weeks of gestation. Blood sampling and blood loss during surgery may also contribute to anaemia in the first few weeks of life. Iron supplementation is therefore often administered to preterm and low birth weight infants to prevent iron deficiency or iron-deficiency anaemia. Iron supplementation is also thought to be beneficial in improving growth and development in the longer term; however, there are safety concerns about excess iron, which can cause or exacerbate oxidative injury to surrounding tissues and may increase the risk of infection.

##### Summary of evidence

###### Level I evidence

Two Level I studies (Long 2012,164 Mills 2012165) identified from the systematic review and hand-searching process examined the use of iron in preterm or low birth weight infants (see **Appendix C, Volume 2**). The reviews by Mills (2012) and Long (2012) did not specifically assess the effect of iron on transfusion volume or incidence[[25]](#footnote-25) and did not report any usable data for other outcomes; therefore, data from the primary Level II studies deemed eligible for inclusion in our systematic review were obtained and assessed individually.

Mills (2012) assessed the prophylactic use of enteral iron supplementation on growth and neurodevelopment in preterm and low birth weight infants; however, reported high heterogeneity of participants, methods and results that precluded any extensive quantitative synthesis. Mills (2012) also reported haematological parameters and morbidity and mortality.

The systematic review by Long (2012) assessed the effects of iron supplementation on haematological parameters, growth and neurodevelopment but presented much of their results as a narrative, with no data or pooled analyses reported.

###### Level II evidence

Four Level II studies (Taylor 2013, Sankar 2009, Berseth 2004, Franz 2000) identified from the systematic review and hand-searching process examined the use of oral iron in preterm or low birth weight infants (see **Appendix C, Volume 2**).

There were no Level II studies identified in the systematic review and hand-searching process that compared different modes of administration of iron or compared parenteral iron with no parenteral iron in preterm or low birth weight infants.

All included studies enrolled infants with VLBW (<1500 g) or ELBW (<1000 g) who had reached 100–120 mL/kg/day of oral feeds. Three of the four included RCTs (Taylor 2013, Sankar 2009, Franz 2000) compared enteral intakes of iron in addition to the recommended nutrient intake (RNI) for preterm infants as defined by The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (2 mg/kg/day)166 whereas control infants in the remaining RCT (Berseth 2004) received a lower iron dose. The main characteristics of these RCTs are summarised in **Table 3.2.13**.

The RCT by Taylor (2013) was conducted at a single centre in the USA; it examined the safety and effectiveness of iron supplementation in addition to routine iron fortified formula or mother’s milk in increasing the haematocrit at 36 weeks postmenstrual age. Sankar (2009) was conducted in a single neonatal care unit in India; it assessed the safety and effectiveness of iron supplementation administered from 14 days of life on haematological parameters. Berseth (2004) was a multicentre study conducted in Canada and the USA that examined the safety and effectiveness of an iron fortified human milk fortifier compared to a control product (not fortified with iron). The RCT by Franz (2000) was conducted at a single neonatal referral centre in Germany; it assessed the safety and effectiveness of iron supplementation (2–6 mg/kg/day) during feeding on serum ferritin status at 2 months postnatal age.

Table 3.2.13 Characteristics and quality of Level II evidence – iron in preterm and LBW infants

| Study ID | Study type  *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Taylor 2013167 | Level II  Good | Preterm infants with VLBW (<1500 g) who reached 120 mL/kg/day of feedings before 32 weeks postmenstrual age  N=150  \*restrictive transfusion guidelines were in place | Multivitamin with iron (2 mg/kg/day) versus multivitamin without iron  \*Administered independent of feedings  \*All infants received iron fortified formula or iron fortified mothers milk (equivalent to ≥2 mg/kg/day iron) | Transfusion incidence  BPD  NEC  Mortality  Laboratory measures |
| Sankar 2009168 | Level II  Fair | Preterm infants with VLBW (1000–1500 g) or ELBW (<1000 g) who reached at least 100 mL/kg/day of oral feeds by day 14  N=44  \*restrictive transfusion guidelines were in place | Early iron (3 or 4 mg/kg/day) versus late iron (no iron until day 61)  \*Administered independent of feedings  \*Intervention also contained folic acid (200 µg/mL) and vitamin B12 (5 µg/mL)  \*All infants received HMF mothers milk (no supplemental iron) or iron fortified formula (equivalent to ≥2 mg/kg/day iron) | Transfusion incidence  ROP  BPD  NEC  Laboratory measures |
| Berseth 2004169 | Level II  *Poor* | Preterm infants (≤33 weeks gestational age) with VLBW (1000–1500 g) or ELBW (<1000 g) who reached at least 100 mL/kg/day of oral feeds  N=181 | Iron fortified HMF versus HMF control (not iron fortified)  \*Administered as supplement during feeding  \*Approximate iron dose: 1.53 mg/100 mL milk versus 0.44 mg/100 mL milk | Transfusion incidence  BPD  NEC  Mortality  Laboratory measures |
| Franz 2000170 | Level II  *Poor* | Preterm infants with VLBW (≤1300 g) who reached at least 100 mL/kg/day of oral feeds  ITT=204  P*P =*135  \*restrictive transfusion guidelines were in place | Early iron (2 mg/kg/day) versus late iron (no iron until day 61)  \*Administered as supplement during feeding  \*All infants received protein and energy enriched mothers milk (no supplemental iron) or iron fortified formula (equivalent to ≥2 mg/kg/day iron)  \*Increased to 4 mg/kg/day if haematocrit fell below 0.30 | Transfusion incidence and volume  Mortality  Laboratory measures |

BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; HMF, human milk fortifier; ITT, intent-to-treat; LBW, low birth weight; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; PP, per protocol; VLBW, very low birth weight

##### Results

###### Transfusion incidence and volume

Four RCTs were identified (Taylor 2013, Sankar 2009, Berseth 2004, Franz 2000) that reported the proportion of preterm infants with VLBW or ELBW who received a RBC transfusion and had received oral iron supplements compared with no additional iron supplements. A summary of the results from these studies is provided in **Table 3.2.14** and **Figure 3.2.11**.

Taylor (2013) and Sankar (2009) reported no significant difference between treatment groups (RR 0.86; 95% CI 0.69, 1.08 and RR 0.73; 95% CI 0.13, 3.95, respectively) for the number of infants that received a RBC transfusion; whereas Berseth (2004) and Franz (2000) both report an effect favouring oral iron supplementation (borderline statistical significance) for a reduction in the number of infants transfused after 14 days of receiving iron supplements (RR 0.53; 95% CI 0.28, 1.02 and RR 0.63; 95% CI 0.46, 0.87, respectively). Franz (2000) also reported a statistically significant reduction in the mean/median volume of RBCs transfused but data were insufficient to interpret further (no SDs provided).

Figure 3.2.11 Meta-analysis of iron versus no iron in preterm infants – transfusion incidence



Table 3.2.14 Preterm infants: Results for oral and/or parenteral iron versus no iron – Transfusion incidence or volume

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%)  Median (IQR) | Placebo/no iron therapy  n/N (%)  Median (IQR) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Taylor 2013167  Level II  Good | N=150 | Preterm infants with VLBW (<1500 g) who reached 120 mL/kg/day of oral feeds before 32 weeks postmenstrual age | Single hospital, USA | Oral iron supplement versus placebo  \*All infants received iron fortified formula or iron fortified mothers milk | Number of infants transfused | 47/76 (61.8%) | 53/74 (71.6%) | RR 0.86 [0.69, 1.08]c | *No significant difference*  *P =*0.21c |
| Median number of transfusions per patient | 1 (0–2) | 1 (0–2) | Difference between medians 0 (0–1) | *No significant difference*  *P =*0.64 |
| Sankar 2009168  Level II  Fair | N=44 | Preterm infants with VLBW (<1500 g) who reached at least 100 mL/kg/day of oral feeds by day 14 | Single tertiary care unit, India | Oral iron supplement versus no iron supplement (until 60 days)  \*Intervention also contained folic acid and vitamin B12 | Number of infants transfused | 2/21 (9.5%) | 3/23 (13.0%) | RR 0.73 [0.13, 3.95]c | No significant difference  *P =*0.72c  *P =*0.63d |
| Berseth 2004169  Level II  *Poor* | N=181 | Preterm infants with VLBW (≤1500 g) who reached at least 100 mL/kg of oral feeds per day | Multicentre, Canada, USA | Oral iron supplement versus no iron supplement  \*Administered as supplement during feeding | Number of infants transfused, day 0–14 | 30/96 (31.3%) | 27/85 (31.8%) | RR 0.98 [0.64, 1.51]c | No significant difference  *P =*0.94c |
| Number of infants transfused, day 15–28 | 12/96 (12.5%) | 20/85 (23.5%) | RR 0.53 [0.28, 1.02]c | Favours iron  *P =*0.06c  *P =*0.014d |
| Franz 2000170  Level II  *Poor* | ITT=204  P*P =*135 | Infants with VLBW (≤1300 g) who tolerated at least 100 mL/kg of oral feeds per day | Single centre, Germany | Oral iron supplement versus no iron supplement (until day 61)  \*Administered as supplement during feeding | Number of infants transfused, days 14 to 68 (ITT) | 41/105 (39.0%) | 53/99 (53.5%) | RR 0.73 [0.54, 0.99]c | No significant difference  *P =*0.04c  *P =*0.068d |
| Number of infants transfused, day 14 to 68 (PP) | 29/68 (42.6%) | 44/65 (67.7%) | RR 0.63 [0.46, 0.87]c | Borderline favours iron  *P =*0.0052 |
| Volume transfused (mL/kg) days 14–68 (ITT)  \*mean / median (min-max) | 15.4 ± NR  0 (0–99) | 25.7 ± NR  21 (0–128) | MD 10.3 [NR]  Difference between medians 21 | Favours iron  *P =*0.023e |
| Volume transfused (mL/kg) days 14–68 (PP)  \*mean / median (min-max) | 15.8 ± NR  0 (0–78) | 31.7 ± NR  27 (0–108) | MD 15.9 [NR]  Difference between medians 27 | Favours iron  *P =*0.0014e |

CI, confidence interval; IQR, interquartile range; ITT, intent-to-treat; MD, mean difference; NR, not reported; PP, per protocol; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value as reported by study authors.

**e.** Not clear which value (mean / median) the *P-*value refers.

###### ROP, BPD and NEC

Three RCTs were identified (Taylor 2013, Sankar 2009, Berseth 2004) in the systematic review and hand-searching process that reported the proportion of preterm infants with VLBW or ELBW who had ROP, BPD or NEC, and had received oral iron supplements compared with no additional iron supplements. A summary of the results from these studies is provided in **Table 3.2.15** and **Figure 3.2.12**.

Sankar (2013) did not find any significant difference between treatment groups on the incidence of ROP (RR 0.73; 95% CI 0.13, 3.95) comparing oral iron administered from day 14 of life with no iron supplements.

For the incidence of BPD, both Taylor (2013) and Sankar (2009) reported no significant difference between treatment groups (RR 0.96; 95% CI 0.63, 1.46 and RR 1.10; 95% CI 0.07, 16.43, respectively). Berseth (2009) also reported that the percentage of patients that required supplemental oxygen did not significantly differ between treatment groups (no data provided).

Similarly, Taylor (2013), Sankar (2009), and Berseth (2004) each reported no significant difference between treatment groups for the incidence of NEC (≥ Bell’s stage 2) or NEC (suspected or surgical) in preterm infants with VLBW who had received oral iron supplements compared with no iron supplements.

Table 3.2.15 Preterm infants: Results for oral and/or parenteral iron versus no iron – ROP, BPD and NEC

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%) | Placebo/no iron therapy  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Taylor 2013167  Level II  Good | N=150 | Preterm infants with VLBW (<1500 g) who reached 120 mL/kg/day of oral feeds before 32 weeks postmenstrual age | Single hospital, USA | Oral iron supplement versus placebo  \*All infants received iron fortified formula or iron fortified mothers milk | BPD  \*oxygen dependence at 36 weeks postmenstrual age | 27/74 (36%) | 27/71 (38%) | RR 0.96 [0.63, 1.46] | *No significant difference*  *P =*0.85 |
| Medical NEC  \*≥Bell’s stage II | 7/76 (9%) | 6/74 (8%) | RR 1.14 [0.40, 3.22] | *No significant difference*  *P =*0.81 |
| Surgical NEC  \*exploratory laparotomy or surgical drain for perforation | 5/76 (7%) | 2/74 (3%) | RR 2.43 [0.49, 12.16] | *No significant difference*  *P =*0.26 |
| Sankar 2009168  Level II  Fair | N=44 | Preterm infants with VLBW (<1500 g) who reached at least 100 mL/kg/day of oral feeds by day 14 | Single tertiary care unit, India | Oral iron supplement versus no iron supplement (until 60 days)  \*Intervention also contained folic acid and vitamin B12 | ROP | 2/21 (9.5%) | 3/23 (13.0%) | RR 0.73 [0.13, 3.95]c | No significant difference  *P =*0.72c  *P =*0.57d |
| Chronic lung disease | 1/21 (4.8%) | 1/23 (4.3%) | RR 1.10 [0.07, 16.43]c | No significant difference  *P =*0.95c  *P =*0.88d |
| NEC | 1/21 (4.8%) | 0/21 (%) | RR 3.00 [0.13, 69.70]c | No significant difference  *P =*0.49 |
| Berseth 2004169  Level II  *Poor* | N=181 | Preterm infants with VLBW (≤1500 g) who reached at least 100 mL/kg of oral feeds per day | Multicentre, Canada, USA | Oral iron supplement versus no iron  \*Administered as supplement during feeding | BPD | NR | NR | NR | No significant difference  *P =*NR |
| Confirmed NEC  \*≥Bell’s stage II | 1/96 (1.0%) | 1/85 (1.2%) | 0.89 [0.06, 13.94] c | No significant difference  *P =*0.93c |
| Suspected NEC | 6/96 (6.3%) | 4/85 (4.7%) | 1.33 [0.39, 4.55] c | No significant difference  *P =*0.65 c |

BPD, bronchopulmonary dysplasia; CI, confidence interval; NEC, necrotising enterocolitis; NR, not reported; ROP, retinopathy of prematurity; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value as reported by study authors.

Figure 3.2.12 Meta-analysis of iron versus no iron in preterm infants – ROP, BPD and NEC



###### Mortality

Two RCTs were identified (Taylor 2013, Franz 2000) that reported all-cause mortality in preterm infants with VLBW or ELBW who had received oral iron supplements compared with no additional iron supplements. Neither study was sufficiently powered to detect differences in mortality. A summary of the results from these studies is provided in **Table 3.2.16**.

Taylor (2013) reported two deaths (one in each group) before 36 weeks postmenstrual age (RR 0.97; 95% CI 0.06, 15.28); both deaths were attributed to NEC.

Franz (2000) reported four deaths (two in each group) (RR 0.94; 95% CI 0.14, 6.57) but no further details were provided.

Table 3.2.16 Preterm infants: Results for oral and/or parenteral iron versus no iron – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%) | Placebo/no iron therapy  n/N (%) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Taylor 2013167  Level II  *Good* | N=150 | Preterm infants with VLBW (<1500 g) who reached 120 mL/kg/day of oral feeds before 32 weeks postmenstrual age | Single hospital, USA | Oral iron supplement versus placebo  \*All infants received iron fortified formula or iron fortified mothers milk | Mortality (all-cause)  \*both deaths attributed to NEC | 1/76 (1.3%) | 1/74 (1.4%) | RR 0.97 [0.06, 15.28]c | *No significant difference*  *P =*0.98c |
| Franz 2000170  Level II  *Poor* | N=204 | Infants with VLBW (≤1300 g) who tolerated at least 100 mL/kg of oral feeds per day | Single centre, Germany | Oral iron supplement versus no iron supplement (until day 61)  \*Administered as supplement during feeding | Mortality (all-cause) | 2/105 (1.9%) | 2/99 (2.0%) | RR 0.94 [0.14, 6.57] | *No significant difference*  *P =*0.95c |

CI, confidence interval; NEC, necrotising enterocolitis; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Secondary outcomes[[26]](#footnote-26)

Functional/performance status

None of the RCTs included in our systematic review reported the effect of iron supplementation compared to no additional iron supplementation on functional and performance status in preterm infants with VLBW or ELBW. It was also noted that neurodevelopmental and growth measures were the primary outcomes of the systematic review by Mills (2012) (excluded here for no usable data) who reported no RCTs comparing iron supplementation with no additional iron supplementation reported the neurodevelopment outcomes of the participants (out of 21 identified trials).

Laboratory measures

Four RCTs were identified (Taylor 2013, Sankar 2009, Berseth 2004, Franz 2000) that reported laboratory measures (Hb, Hct, ferritin) in preterm infants with VLBW or ELBW who had received oral iron supplements compared with no additional iron supplements. There was no significant difference reported between treatment groups for any laboratory measure. A summary of the results from these studies is provided in **Table 3.2.17**.

Taylor (2013) reported no significant difference in the mean haematocrit at 36 weeks postmenstrual age (MD 0.9; 95% CI –0.5, 2.3) of infants administered iron compared with infants who had no additional iron supplement. Sankar (2009) reported no significant difference in the mean Hb (MD 0.60; 95% CI –0.55, 1.75), mean haematocrit at 60 days (MD 1.70; 95% CI –1.73, 5.13) or mean ferritin at 14 (MD –3.30; 95% CI –10.46, 3.86) or 60 days (MD 5.50; 95% CI –1.42, 12.42) in infants administered iron compared with infants who had no additional iron supplement.

Berseth (2004) reported no difference in haematocrit or ferritin levels at either day 14 or day 28 for infants who received additional iron supplements but only reported median values. Similarly, Franz (2000) reported no significant difference in mean /median haematocrit and ferritin levels at day 61 but did not provide complete data for further analysis (no SDs reported).

Haematological iron status was a primary outcome of the systematic review by Long (2012) and a secondary outcome of the review by Mills (2012). Both Long (2012) and Mills (2012) reported that iron supplementation appears to increase haematologic measures of iron status relative to control but the optimum timing and duration of treatment is unclear. The authors also noted that there was significant heterogeneity among the included studies.

Table 3.2.17 Preterm infants: Results for oral and/or parenteral iron versus no iron – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron  Mean ± SD  Median (IQR) | Placebo/no iron  Mean ± SD  Median (IQR) | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Taylor 2013167  Level II  *Good* | N=150 | Preterm infants with VLBW (<1500 g) who reached 120mL/kg/day of oral feeds before 32 weeks postmenstrual age | Single hospital, USA | Oral iron versus no iron  \*All infants received iron fortified formula or iron fortified mothers milk | Hct (%) at 36 weeks postmenstrual age | 29.2 ± 4.0 (n=73) | 28.3 ± 4.5 (n=75) | MD 0.9 (–0.5, 2.3) | *No significant difference*  *P =*0.21 |
| Sankar 2009168  Level II  Fair | N=46 | Preterm infants with VLBW (<1500 g) who reached at least 100 mL/kg/day of oral feeds by day 14 | Single tertiary care unit, India | Oral iron versus control (no iron until 60 days)  \*Intervention also contained folic acid and vitamin B12 | Hb (g/dL) at 60 days | 10.8 ± 1.8 | 10.2 ± 2.1 | NR | No significant difference  *P =*0.36 |
| Hct (%) at 60 days | 32.5 ± 5.3 | 30.8 ± 6.3 | NR | No significant difference  *P =*0.35 |
| Serum ferritin at 14 days (µg/L) | 55.7 ± 12.1 | 59.0 ± 12.1 | NR | No significant difference  *P =*0.37 |
| Serum ferritin at 60 days (µg/L) | 50.8 ± 11.5 | 45.3 ± 11.9 | NR | No significant difference  *P =*0.12 |
| Berseth 2004169  Level II  *Poor* | N=181 | Preterm infants with VLBW (≤1500 g) who reached at least 100 mL/kg/day of oral feeds | Multicentre, Canada, USA | Iron supplement versus no iron  \*Administered as supplement during feeding | Hct (%) at day 14 | 30.0 (26.2–34.0)  (n=67) | 29.4 (25.1–34.0)  (n=55) | NR | No significant difference  *P =*NR |
| Hct (%) at day 28 | 27.0 (24.0–29.6)  (n=43) | 26.0 (24.0–31.0)  (n=32) | NR | No significant difference  *P =*NR |
| Ferritin (ng/mL) at day 14 | 100.0 (54–200)  (n=66) | 120.0 (68–205)  (n=53) | NR | No significant difference  *P =*NR |
| Ferritin (ng/mL) at day 28 | 77.0 (37–155)  (n=22) | 92.0 (33–110)  (n=19) | NR | No significant difference  *P =*NR |
| Franz 2000170  Level II  *Poor* | N=135 | Infants with VLBW (≤1300 g) | Single centre, Germany | Oral iron versus control (no iron until 61 days)  \*Administered as soon as 100mL/kg/day of oral feeds were tolerated | Ferritin at day 61 (mean) | 87.8 ± NR (n=65) | 74.2 ± NR (n=60) | NR | *No significant difference*  *P =*0.98c |
| Ferritin at day 61 (median, min-max) | 45 (9–478) | 51 (9–682) |
| Hct (L/L) at day 61 (mean) | 0.291 ± NR (n=67) | 0.295 ± NR (n=63) | NR | No significant difference  *P =*0.77c |
| Hct (L/L) at day 61 (median, min-max) | 0.28 (0.21–0.44) | 0.28 (0.20–0.42) |

CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; IQR, interquartile range; MD, mean difference; NR, not reported; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Not clear which value (mean / median) the *P-*value refers.

### Infants, children and adolescents at risk of anaemia

* + - 1. ESAs (with or without iron)

| Evidence statements – infants, children and adolescents (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of ESA treatment (with or without iron supplementation) in infants, children, or adolescents at risk of anaemia.

* + - 1. Oral and/or parenteral iron

| Evidence statements – infants, children and adolescents (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 | | | | | | |

| 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)85 and Pottie *et al* (2011)86  b See Section 3.6 and Section 4.5 *Patient Blood Management Guidelines: Module 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

All infants, children and adolescents are at risk of developing anaemia, with the most common cause being iron deficiency. Inadequate iron intake can occur because of a lack of availability of iron-rich foods, poor diet choice (e.g. due to poverty, culture or lack of education), or inadequate gastrointestinal absorption. Iron supplementation is therefore often administered to infants and children to prevent or treat iron-deficiency anaemia and to provide additional longer term benefits of improved growth and development. The evidence base for these benefits is uncertain and concerns exist about the adverse effects of iron supplementation, which include gastrointestinal side effects and increased the risk of infection.

##### Summary of evidence

###### Level I evidence

Two Level I studies (Pasricha 2013, Okebe 2011) identified from the systematic review and hand-searching process examined the use of oral iron in infants, children or adolescents at risk of developing anaemia (see **Appendix C, Volume 2**). The main characteristics of these reviews are summarised in **Table 3.2.18**.

There were no Level I studies identified from the systematic review and hand-searching process that examined the use of parenteral iron or compared different modes of administration of iron in infants, children or adolescents at risk of developing anaemia (see **Appendix C, Volume 2**).

The good-quality review by Pasricha (2013) assessed the safety and effectiveness of daily oral iron supplements compared to control in children aged 4–23 months on haematologic measures (Hb, ferritin, anaemia, iron status and iron deficiency anaemia), cognitive and psychomotor development, and physical growth. Of the 35 RCTs included in the review by Pasricha (2013), 33 trials involving 42 015 infants provided usable data (see **Table 3.2.19**). These trials were conducted in a wide variety of countries and involved infants of variable socioeconomic or nutritional status. Iron was usually provided as ferrous salts and was compared with placebo or no iron in all but three RCTs (Sazawal 2006, Siegel 2005, Tielsch 2006), which all assessed iron in combination with folic acid. In some studies, infants also received multivitamins (three RCTs), vitamin A (three RCTs), vitamin C (three RCTs), zinc (five RCTs), or malaria prophylaxis (two RCTs). Only nine studies were assessed by Pasricha (2013) to be of overall low risk of bias.

There were 32 976 infants enrolled in one of two large cluster randomised trials (Sazawal 2006, Tielsch 2006) that reported the outcome of mortality; however, complete data from these two trials were not reported by Pasricha (2013). These Level II studies were therefore retrieved for further analysis. All other trials identified by Pasricha (2013) reported secondary outcomes only (functional and performance status, and laboratory measures).

The good-quality review by Okebe (2011) assessed the safety and efficacy of daily oral iron supplements (with and without folic acid) compared to control in children aged less than 18 years that were living in areas with malaria endemicity. Trials that were conducted in non-malaria areas or those that were conducted during periods of malaria inactivity were specifically excluded. The review was focused on the outcome of malaria, severe malaria and mortality, and included 71 RCTs involving 45 353 children. Death was not defined as an outcome in 70 of these trials, but was reported in 16 and obtained from 14 others by the systematic review authors. Four of the trials assessed iron use during an acute attack of malaria (van Hensbroek 1995, Nwanyanwu 1996, van den Hombergh 1996, Gara 2010) and are reported separately in this review (see **Section 3.2.7**). All other trials assessed the use of iron or iron plus folic acid in otherwise healthy children. In some studies, infants in both groups also received micronutrients (13 RCTs), malaria prophylaxis (five RCTs), or antihelminths (18 RCTs).

The main characteristics of the RCTs included in the review are summarised in **Table 3.2.19**.

Fifteen trials involving 29 232 participants were cluster randomised, using households (5 trials) or schools/classes (10 trials) as the unit of randomisation. Nine of these cluster randomised trials did not adjust the main outcomes for clustering, rather reported results per individual. To account for this potential bias, Okebe (2011) adjusted the reported results using design effects or estimated intracluster correlation coefficients in their meta-analyses.

###### Level II evidence

No additional Level II studies identified from the systematic review and hand-searching process examined the use of oral iron in infants aged 1 – 35 months or children aged less than 18 years at risk of developing anaemia (see **Appendix C, Volume 2**).

There were no Level II studies identified from the systematic review and hand-searching process that examined the use of parenteral iron or compared different modes of administration of iron in infants, children, or adolescents at risk of developing anaemia (see **Appendix C, Volume 2**).

Table 3.2.18 Characteristics and quality of Level I evidence – iron in paediatric patients at risk of anaemia

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Pasricha (2013)171 | Level I  *Good* | Children aged 4–23 months living in community or outpatient setting and otherwise well  33 RCTs, N=42 015 | Oral iron versus no iron | Mortality  Functional and performance status  Laboratory measures (Hb, ferritin) |
| Okebe (2011)172 | Level I  *Good* | Children aged <18 years living in areas with malaria endemicity  71 RCTs, N=45 353 | Oral iron ± folic acid versus placebo or no iron ± folic acid | Mortality  Laboratory measures (Hb) |

Hb, haemoglobin; RCT, randomised controlled trial

Table 3.2.19 Characteristics and quality of Level II evidence – iron in paediatric patients at risk of anaemia

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Studies identified and assessed by Pasricha (2013) | | | | |
| Akman (2004)173 | Level II | Infants and children aged 6–30 months  N=40 | Oral iron (3 mg/kg, bid) versus placebo for 3 months | Functional and performance status  Laboratory measures (Hb, ferritin) |
| Aukett (1986)174 | Level II | Infants aged 17–19 months  N=110 | Oral iron (24 mg/day) versus no iron for 2 months  \*All infants received vitamin C (10 mg/day) | Laboratory measures (Hb, ferritin) |
| Berger (2000)175 | Level II | Infants aged 4–7 months  N=197 | Oral iron (2–3 mg/kg) versus placebo for 3 months | Laboratory measures (Hb, ferritin) |
| Berger (2006)176 | Level II | Infants aged 4–7 months  N=915 | Oral iron (10 mg) ± zinc (10 mg) versus no iron ± zinc for 6 months  \*All infants received vitamin A (100 000 IU) | Laboratory measures (Hb, ferritin) |
| Desai (2003)177 | Level II | Infants and children aged 2–36 months  N=546 | Oral iron (3–6 mg/kg) versus placebo for 12 weeks  \*All infants received intermittent malaria prophylaxis (sulphadoxine / pyrimethamine) | Laboratory measures (Hb) |
| Dijkhuizen (2001)178 | Level II | Infants aged 4 months  N=478 | Oral iron (10 mg) ± zinc (10 mg) versus zinc versus placebo for 6 months | Laboratory measures (Hb, ferritin) |
| Domellof (2001)179 | Level II | Infants aged 4–9 months  N=232 | Oral iron (1 mg/kg) versus placebo for 3 or 5 months | Laboratory measures (Hb, ferritin) |
| Dossa (2001)180 | Level II | Infants and children aged 18–30 months  N=154 | Oral iron (66 mg) ± multivitamins versus multivitamins versus placebo for 6 weeks | Laboratory measures (Hb) |
| Ermis (2002)181 | Level II | Infants aged 5 months  N=83 | Oral iron (2 mg/kg) versus oral iron (1 mg/kg) versus placebo for 4 months | Laboratory measures (Hb, ferritin) |
| Fahmida (2007)182 | Level II | Infants aged 3–6 months  N=392 | Oral iron (10 mg) + zinc versus zinc alone for 6 months | Laboratory measures (Hb, ferritin) |
| Fuerth (1972)183 | Level II | Infants aged 1 month  N=602 | Oral iron (30 mg) versus placebo for 11 months | Laboratory measures (Hb, Hct)  (data not usable) |
| Geltman (2001)184 | Level II | Infants aged 6 months  N=310 | Oral iron (10 mg) versus no iron for 3 months  \*All infants received multivitamins | Laboratory measures (anaemia, ID) |
| Geltman (2004)185 | Level II | Infants aged 5–7 months  N=376 | Oral iron (10 mg) versus no iron for 3 months  \*All infants received multivitamins | Laboratory measures (Hb, ferritin) |
| Idjradinata (1993)186 | Level II | Infants aged 12–18 months  N=129 | Oral iron (4 mg/kg) versus placebo for 4 months | Functional and performance status  Laboratory measures (Hb, ferritin) |
| Irigoyen (1991)187 | Level II | Infants aged 6 months  N=334 | Oral iron (3 or 6 mg/kg) versus placebo for 3 months | No relevant outcomes for this review |
| Lind (2003)188 | Level II | Infants aged 6 months  N=680 | Oral iron (10 mg) ± zinc (10 mg) versus no iron ± zinc for 6 months  \*All infants received vitamin C | Functional and performance status (Bayley’s MDI, PDI)  Laboratory measures (Hb, ferritin) |
| Lozoff (1982)189 | Level II | Infants aged 6–24 months  N=68 | Oral iron (5 mg/kg) versus placebo for 1 week | Functional and performance status |
| Lozoff (1996)190 | Level II | Infants aged 12–13 months  N=50 | Oral iron (6 mg/kg) versus placebo for 6 months | Functional and performance status  (data not usable) |
| Majumdar (2003)191 | Level II | Infants aged 6–24 months  N=126 | Oral iron (2 mg/kg) versus placebo for 4 months | Laboratory measures (Hb, ferritin) |
| Massaga (2003)192 | Level II | Infants aged 3–4 months  N=291 | Oral iron (7.5 mg) ± amadioquine versus placebo ± amadioquine for 6 months | No relevant outcomes for this review |
| Nagpal (2004)193 | Level II | Infants aged 4–6 months  N=100 | Oral iron (2 mg/kg) versus placebo for 8 weeks | Laboratory measures (Hb, ferritin) |
| Ninh (2002)194 | Level II | Infants aged 5–12 months  N=205 | Oral iron (15mg) versus placebo for 3 months | Laboratory measures (Hb, anaemia) |
| Northrop-Clewes (1996)195 | Level II | Infants and children aged <2 years  N=191 | Oral iron (15mg) versus placebo for 3 months | Laboratory measures (Hb, ferritin) |
| Reeves (1985)196 | Level II | Infants aged 11–14 months  N=278 | Oral iron (3 mg/kg) versus placebo for 3 months | No relevant data for this review |
| Sazawal (2006)b197 | Level II  *Fair* | Infants and children aged 1–35 months  N=15 956 | Oral iron (12.5 mg) + folic acid (50 µg) versus placebo up to 14 months  \*Infants aged <1 year old received half-tablet  \*All infants and children aged over 6 months received vitamin A | Mortality  Laboratory measures (Hb) |
| Siegel (2005)198 | Level II | Infants aged 4–12 months  N=362 | Oral iron (6.25 mg) + folic acid (25 µg) ± zinc versus zinc versus placebo up to 37 weeks | Functional and performance status |
| Thibault (1993)199 | Level II | Infants and children aged 6–36 months  N=75 | Oral iron (30–45 mg, depending on weight) versus placebo for 2 months | Laboratory measures (Hb, ferritin) |
| Tielsch (2006)c200 | Level II  *Good* | Infants and children aged 1–36 months  N=17 020 | Oral iron (12.5 mg) + folic acid (50 µg) versus placebo up to 18 months  \*Infants aged <1 year old received half-tablet  \*All infants and children aged over 6 months received vitamin A | Mortality  Laboratory measures (Hb, ferritin) |
| Walter (1989)201 | Level II | Infants aged 12 months  N=196 | Oral iron (15 mg, tid) versus placebo for 10 days | Functional and performance status |
| Wasantwisut (2006)202 | Level II | Infants aged 4–6 months  N=674 | Oral iron (10 mg) ± zinc versus no iron ± zinc for 6 months  \*All infants received vitamin C | Laboratory measures (Hb, ferritin) |
| Wieringa (2003)203 | Level II | Infants aged 4 months  N=258 | Oral iron (10 mg) ± zinc (10 mg) versus zinc versus placebo for 6 months | Laboratory measures (Hb, ferritin) |
| Yalcin (2000)204 | Level II | Infants aged 6 months  N=24 | Oral iron (1 mg/kg) versus no iron for 3 months | Functional and performance status  Laboratory measures (Hb, ferritin, Hct) |
| Yurdakok (2004)205 | Level II | Infants aged 4 months  N=52 | Oral iron (1 mg/kg) versus no iron for 3 months | Laboratory measures (Hb, ferritin) |
| Ziegler (2009)206 | Level II | Infants aged 4 months  N=107 | Oral iron (7.5 mg) versus no iron for 5 months | Laboratory measures (Hb, ferritin) |
| Zlotkin (2003)207 | Level II | Infants aged 8–20 months  N=230 | Oral iron (12.5 mg) versus placebo for 6 months | Laboratory measures (Hb) |

bid, twice daily; tid, three times daily; Hb, haemoglobin; Hct, haematocrit; ID, iron deficiency; IU, international units; MDI, mental and development index; PDI, psychomotor developmental index

**a.** Studies were conducted in a wide variety of countries, including Turkey x4, UK, Togo, Vietnam x2, Kenya, Indonesia x5, Sweden, Honduras, Benin, USA x6, Guatemala, Costa Rica, India x2, Tanzania x2, Pakistan, Nepal x2, France, Chile, Thailand, and Ghana**.**

**b.** Sazawal (2006) was a three-arm trial comparing i) iron + folic acid ii) iron + folic acid + zinc iii) placebo. Only the iron + folic acid group results compared with placebo are reported here.

**c.** Tielsch (2006) was a three-arm trial comparing i) iron + folic acid ii) iron + folic acid + zinc iii) placebo. Only the iron + folic acid group results compared with placebo are reported here.

##### Results

###### Transfusion volume or incidence

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of oral and/or parenteral iron in infants, children, or adolescents at risk of anaemia and reported the outcome of transfusion volume or incidence.

###### Mortality

Two Level I studies (Pasricha 2013, Okebe 2011) identified from the systematic review and hand-searching process reported mortality in infants, children or adolescents at risk of developing anaemia administered oral iron (with or without folic acid). These results are summarised in **Table 3.2.20**.

Infants aged less than 2.5 years

The review by Pasricha (2013) assessed the safety and effectiveness of daily oral iron supplements in children aged 4–23 months, and identified two trials (Sazawal 2006, Tielsch 2006) that reported the outcome of mortality. A meta-analysis revealed a nonsignificant increased risk of mortality in children that received iron and folic acid compared with placebo (RR 1.10; 95% CI 0.91, 1.34). There was no significant heterogeneity for this outcome (I2=0%).

All-cause mortality was a primary outcome of the RCTs by both Tielsch (2006) and Sazawal (2006); however, infants receiving iron and folic acid in both trials stopped receiving these supplements early on the recommendation of the data and safety monitoring board. This is because higher rates of severe adverse events (hospital admissions and death) were found in infants in the trial by Sazawal (2006). Tielsch (2006) also reported that there was no evidence of a beneficial effect in the infants receiving iron and folic acid, and the statistical power to detect a significant benefit between treatment groups was considered too small by the time recruitment and follow-up were to be completed.

The RCT by Tielsch (2006) reported no difference in all-cause mortality in infants and children aged 1–36 months comparing iron and folic acid with placebo (HR 1.03; 95% CI 0.78, 1.37). There was also no evidence of between-group differences when analysed by gender or age, although the authors noted a nonsignificant decline in the hazard ratio with increasing age. Cause-specific analysis revealed a significant increase risk of mortality due to ‘other infections’ in infants receiving iron plus folic acid (HR 3.58; 95% CI 1.02, 13.52); nonsignificant increased risks for diarrhoea (HR 1.21; 95% CI 0.66, 2.11) and malnutrition (HR 1.10, 95% CI 0.46, 2.81); and nonsignificant lower risk for acute lower respiratory illness, dysentery, SIDS, injury or other causes.

The RCT by Sazawal (2006) reported a nonsignificant increased risk of mortality over time in children that received iron and folic acid compared with placebo (RR 1.16; 95% CI 0.92, 1.47). The authors noted that there was an increased risk of mortality among infants admitted to hospital and administered iron and folic acid compared with placebo (RR 1.31; 95 % CI 0.79, 2.18, *P =*NR). This effect was significant in infants who died of cerebral malaria (RR 1.70; 95% CI 1.08, 2.68; *P =*0.02).

In contrast, Sazawal (2006) reported a reduced risk of mortality over time among infants enrolled in a substudy of the trial (RR 0.88; 95% CI 0.34, 2.28; *P =*NR). The objectives of the substudy were to assess the effects of the intervention in haematological and zinc status, infectious disease morbidity and malaria prevalence. Children in the substudy were older that those in the main study and more likely to sleep; those with severe anaemia (Hb <7 g/dL) were excluded. Importantly, the substudy monitored the children and offered treatment for malaria at home throughout the trial period.

Children less than 18 years

The review by Okebe (2011) identified 22 RCTs involving 8644 infants administered iron that reported mortality among infants or children aged less than 18 years living in areas with malaria. A meta-analysis found no significant increased risk of mortality among children administered iron compared with no iron or placebo (RD 0.00; 95% CI –0.00, 0.00). There was no significant heterogeneity for this outcome (I2=0%). Subgroup analyses according to malaria endemicity also found no difference between treatment groups.

Four RCTs reported by Okebe (2011) reported mortality and compared iron plus folic acid with placebo or no iron in infants or children aged less than 18 years living in areas with malaria. A meta-analysis found no significant between-group differences for all-cause mortality (RD 1.19 per 1000 children; 95% CI –1.76, 5.59). This analysis included unpublished data from the independent substudy of infants enrolled in the RCT reported by Sazawal (2006).

Table 3.2.20 Neonatal and paediatric patients at risk of anaemia: Results for oral and/or parenteral iron versus no iron – Mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%)  Rate per 1000 person-years | No iron therapy  n/N (%)  Rate per 1000 person-years | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Children <2.5 years | | | | | | | | | |
| Pasricha 2013171  Level I  *Good* | 2 trialsc (Sazawal 2006, Tielsch 2006)197; 200  N=32,976 | Community or outpatient children aged 4–23 months | Tanzania, Nepal | Oral iron plus folic acid versus placebo | Mortality | NR | NR | RR 1.10 [0.91, 1.34] | *No significant difference*  *P =*0.33  No significant heterogeneity  I2 = 0% |
| Children <18 Years | | | | | | | | | |
| Okebe 2011172  Level I  *Good* | 22 trials (Aggarwal 2005, Baqui 2003, Fahmida 2007, Gebresellassie 1996, Lind 2004, Nagpal 2004, Richard 2006, Roschnik 2004, Wasantwisut 2006, Ayoya 2009, Desai 2003, Dossa 2001a, Dossa 2001b, Latham 1990, Massaga 2003, Mebrahtu 2004, Menendez 1997, Olsen 2006, Powers 1983, Smith 1989, Verhoef 2002, Zlotkin 2003)177; 180; 182; 192-193; 202; 207-221  N=8644 | Children <18 years living in malaria-endemic areas | Various countries in Africa, South America, Asia and the Middle East with active malaria | Oral iron versus placebo / no treatment | Mortality (all-cause) | 38/4294 (0.9%) | 36/4350 (0.8%) | RD 0.00 [–0.00, 0.00]  Absolute RD per 1000 children NR | *No significant difference*  *P =*0.87  No significant heterogeneity  I2 = 0% |
| \*13 trials conducted in hyper- or holo-endemic settings  N=4846 | Subgroup analysis: malaria endemicity | | |  |
| 2/2377 | 5/2469 | RD –0.00 [–0.00, 0.00]  Absolute RD per 1000 children 2.42 [–6.47, 11.34] | *No significant difference*  *P =*0.44  No significant heterogeneity  I2 = 0% |
| \*9 trials conducted in hypo- or meso-endemic settings  N=3798 | 36/1917 | 31/1881 | RD 0.00 [–0.01, 0.01]  Absolute RD per 1000 children –1.24 [–4.37, 1.88] | *No significant difference*  *P =*0.59  No significant heterogeneity  I2 = 0% |
| 4 trials (Shah 2002, Greisen 1986, Hall 2002, Sazawal 2006)197; 222-224  N=18,107 | Oral iron plus folic acid versus placebo / no treatment | Mortality (all-cause) | 153/9045 (1.69%) | 137/9062 (1.51%) | RD 0.00 [–0.00, 0.01]  Absolute RD per 1000 children 1.19 (–1.76, 5.59] | *No significant difference*  *P =*0.31  No significant heterogeneity  I2 = 0% |
| \*3 trials conducted in hyper- or holo-endemic settings  N=17,898 | Subgroup analysis: malaria endemicity | | |  |
| 153/8908 | 137/8990 | RD 0.00 [–0.00, 0.01]  Absolute RD per 1000 children 1.93 (–1.78, 5.64] | *No significant difference*  *P =*0.31  No significant heterogeneity  I2 = 0% |
| \*1 trial conducted in hypo- or meso-endemic settings  N=209 | 0/137 | 0/72 | RD 0.00 [–0.02, 0.02] | *No significant difference*  *P =*1.0 |
| Level II evidence | | | | | | | | | |
| Children <2.5 years | | | | | | | | | |
| Tielsch 2006d 200  Level II  *Good* | N=16,811 | Children aged 1–36 months | Nepal  \*cluster randomised | Oral iron plus folic acid versus placebo | Mortality (all-cause) | 112/8128 (1.38%)  12.16 | 115/8683 (1.32%)  11.74 | HR 1.03 [0.78, 1.37] | *No significant difference*  *P >*0.10 |
| Treatment groups were compared by baseline household, maternal, and child characteristics to assess imbalances after randomisation. To account for the clustered randomisation, estimates of standard error were adjusted using the generalised estimating equations approach. Mortality was assessed using two approaches: the first based on person-time and the second using survival analysis. Cox proportional hazard models were used to adjust for potential confounders. | | |
|  | Subgroup analysis: gender | | |  |
| Male | 41/4244  8.49 | 52/4239  10.59 | HR 0.80 [0.52, 1.22] | No significant difference  *P >*0.10 |
| Female | 71/3884  16.20 | 63/4172  12.88 | HR 1.25 [0.87, 1.79] | No significant difference  *P >*0.10 |
| 1–5 months | Subgroup analysis: age | | |  |
| 34/3814  28.07 | 28/3978  21.83 | HR 1.28 [0.79, 2.08] | No significant difference  *P >*0.10 |
| 6–11 months | 24/966  14.89 | 24/961  14.00 | HR 1.06 [0.59, 1.92] | No significant difference  *P >*0.10 |
| 12–23 months | 34/1784  10.47 | 37/1758  10.79 | HR 0.97 [0.57, 1.64] | No significant difference  *P >*0.10 |
| 24–36 months | 20/1564  6.37 | 26/1714  7.72 | HR 0.82 [0.45, 1.51] | No significant difference  *P >*0.10 |
| Mortality (cause-specific) |  | | |  |
| Acute lower respiratory illness | 24/8128  2.61 | 29/8411  2.97 | HR 0.88 [0.50, 1.46] | No significant difference  *P =*NR |
| Diarrhoea | 24/8128  2.61 | 21/8411  2.15 | HR 1.21 [0.66, 2.11] | No significant difference  *P =*NR |
| Dysentery | 11/8128  1.20 | 12/8411  1.23 | HR 0.98 [0.42, 2.14] | No significant difference  *P =*NR |
| Malnutrition | 9/8128  0.98 | 9/8411  0.92 | HR 1.10 [0.46, 2.81] | No significant difference  *P =*NR |
| SIDS | 7/8128  0.76 | 10/8411  1.02 | HR 0.75 [0.25, 1.69] | No significant difference  *P =*NR |
| Injuries | 1/8128  0.11 | 5/8411  0.51 | HR 0.22 [0.02, 1.76] | No significant difference  *P =*NR |
| Other infections  \*sepsis, hepatitis, meningitis, GI infections | 10/8128  1.11 | 3/8411  0.31 | HR 3.58 [1.05, 13.52] | Favours placebo  *P =*NR |
| Other  \*premature birth, congenital heart defects, rabies, retinoblastoma, other miscellaneous) | 5/8128  0.44 | 0/8411 | Not estimable | No significant difference  *P =*NR |
| Uncertain/missing | 21/8128  2.28 | 26/8411  2.66 | HR 0.86 | No significant difference  *P =*NR |
| Sazawal 2006e 197  Level II  *Fair* | N=15,956 | Children aged 1–35 months without severe malnutrition | Island of Pemba, Tanzania  \*cluster randomised | Oral iron plus folic acid versus placebo | Mortality (all-cause) | 149/7950 (1.87%) | 130/8006 (1.62%) | RR 1.16 [0.92, 1.47] | No significant difference  P = 0.21 |
| Mortality in infants admitted to hospital | NR (n=887) | NR (n=835) | RR 1.31 [0.79, 2.18] | Significance NR  P = NR |
| Mortality (cause-specific)  Cerebral malaria | NR | NR | RR 1.70 [1.08, 2.68] | Favours placebo  P = 0.02 |
| Substudy  N=2413 | Children aged 1–35 months without severe malnutrition and Hb ≥70 g/L | Island of Pemba, Tanzania  \*cluster randomised | Oral iron plus folic acid versus placebo | Mortality (all-cause) | NR | NR | RR 0.88 [0.34, 2.28] | Significance NR  P = NR |

CI, confidence interval; GI, gastrointestinal; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RD, risk difference; RR, risk ratio;

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%

**c.** The RCTs by Sazawal et al (2006) and Tielsch et al (2006) were cluster randomised.

**d.** Tielsch et al (2006) was a three-arm trial comparing i) iron + folic acid ii) iron + folic acid + zinc iii) placebo. All children received vitamin A. Only the iron + folic acid group results compared with placebo are reported her**e.**

**e.** Sazawal et al (2006) was a four-arm trial comparing i) iron + folic acid ii) iron + folic acid + zinc iii) placebo iv) zin**c.** All children received vitamin A. Only the iron + folic acid group results compared with placebo are reported here.

###### Secondary outcomes[[27]](#footnote-27)

Functional and performance status

One Level I study (Pasricha 2013) identified from the systematic review and hand-searching process reported functional and performance measures in infants, children or adolescents at risk of developing anaemia administered oral iron (with or without folic acid). These studies are summarised in **Table 3.2.21**.

Pasricha (2013) identified 6 RCTs (Akman 2004, Idjradinata 1993, Walter 1989, Yalcin 2000, Lind 2003, Lozoff 1982) involving over 1000 infants or children aged less than 2.5 years that reported Bayley’s scores for mental and psychomotor development. The authors reported no significant difference between treatment groups assessed using the MDI (MD 1.65; 95% CI –0.63, 3.94) or psychomotor development index (PDI) (MD 1.05; 95% CI –1.36, 3.46) comparing infants administered iron with placebo or infants who did not receive iron. There was substantial heterogeneity for these outcomes (I2=66% and 67%, respectively).

The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline Hb, baseline iron status, dose and duration of treatment, inclusion of other supplements, and malaria endemicity. Two analyses for MDI approached statistical significance for subgroup differences with a significant effect favouring iron reported in infants who were iron deficient at enrolment (3 trials, MD 5.90; 95% CI 1.81, 10.00) and in infants administered 12.5–30 mg iron (1 trial, MD 6.26; 95% CI 1.54, 10.98). No subgroup differences approached statistical significance for the outcome of PDI.

Table 3.2.21 Neonatal and paediatric patients at risk of anaemia: Results for oral and/or parenteral iron versus no iron – Functional/performance status (secondary outcome)

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron  Mean ± SD | No iron  Mean ± SD | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Children <2.5 years | | | | | | | | | |
| Pasricha 2013171  Level I  *Good* | 6 trialsc (Akman 2004, Idjradinata 1993, Walter 1989, Yalcin 2000, Lind 2003, Lozoff 1982)173; 186; 188-189; 201; 204  N=1093 | Community or outpatient children aged 4–23 months | Chile, Guatemala, Indonesia, Turkey | Daily oral iron supplementation versus no iron / placebo | Bayley’s mental development index score | NR | NR | MD 1.65 [–0.63, 3.94]d | *No significant difference*  *P =*0.16  Substantial heterogeneity  I2 = 66% |
| Iron deficient children  3 trials (Akman 2004, Idradinata 1993, Walter 1989)  N=281 | The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline haemoglobin, baseline iron status, dose and duration of treatment, inclusion of other supplements, and malaria endemicitye.  Two analyses approached statistical significance for subgroup difference and are reported below. | | |  |
| Subgroup analysis: baseline iron status | | |  |
| NR | NR | MD 5.90 [1.81, 10.00] | *Favours iron*  *P =*0.005  Moderate heterogeneity  I2 = 34% |
| Iron replete children  2 trials (Idradinata 1993, Walter 1989, Yalcin 2000)  N=90 | NR | NR | MD 0.65 [–1.59, 2.88] | *No significant difference*  *P =*0.57  No significant heterogeneity  I2 = 0% |
| Mixed/ not reported  2 trials (Lind 2003, Lozoff 1982)  N=722 | NR | NR | MD –0.14 [–3.14, 2.85] | *No significant difference*  *P =*0.93  Substantial heterogeneity  I2 = 66% |
| ≤12.5 mg  3 trials (NR)  N=790 | Subgroup analysis: dose | | |  |
| NR | NR | MD 1.49 [–0.95, 3.94] | *No significant difference*  *P =*0.23  Substantial heterogeneity  I2 = 73% |
| 12.6 to 30 mg  1 trial (Akman 2004)  N=40 | NR | NR | MD 6.26 [1.54, 10.98] | *Favours iron*  *P =*0.009  Heterogeneity not applicable |
| 31 – 60mg  2 trials (NR)  N=63 | NR | NR | MD –1.84 [–7.70, 4.01] | *No significant difference*  *P =*0.54  No significant heterogeneity  I2 = 16% |
| 6 trialsc (Akman 2004, Idradinata 1993, Walter 1989, Yalcin 2000, Lind 2003, Lozoff 1982)173; 186; 188-189; 201; 204  N=1,086 | Chile, Guatemala, Indonesia, Turkey | Bayley’s PDI score | NR | NR | MD 1.05 [–1.36, 3.46] | *No significant difference*  *P =*0.39  Substantial heterogeneity  I2 = 67% |
| The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline haemoglobin, baseline iron status, dose and duration of treatment, inclusion of other supplements, and malaria endemicitye.  No subgroup differences approached statistical significanc**e.** | | |  |

CI, confidence interval; MD, mean difference; NR, not reported; PDI, psychomotor developmental index; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%

**c.** Analysis includes one trial (Lind 2003) that included vitamin C ± zinc in the treatment and comparator arms.

**d.** Reported in supplementary Figure 3 of appendix as MD 1.73 [–0.44, 3.90]; *P =*0.12; I2=60%

**e.** Refer to **Appendix F, Volume 2** of the technical report.

Laboratory measures

Two Level I studies (Pasricha 2013, Okebe 2011) identified from the systematic review and hand-searching process reported laboratory measures (Hb, Hct, ferritin) in infants, children or adolescents at risk of developing anaemia, administered oral iron (with or without folic acid). A summary of the results from these studies is provided in **Table 3.2.22**.

Infants aged less than 2.5 years

Pasricha (2013) identified 26 RCTs involving 5479 infants and children aged less than 2.5 years that reported Hb levels as an outcome. The authors reported a statistically significant increase in mean Hb levels in infants administered oral iron compared with placebo or no iron (MD 7.22; 95% CI 4.87, 9.57). There was substantial heterogeneity for this outcome (I2=94%).

The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline Hb, baseline iron status, dose and duration of treatment, inclusion of other supplements and malaria endemicity. Two analyses approached statistical significance for subgroup differences (infants who were anaemic at baseline and iron dose).

There were 24 RCTs involving 4526 infants and children aged less than 2.5 years identified by Pasricha (2013) that reported Hb levels as an outcome. The authors reported a statistically significant increase in mean ferritin levels in infants administered oral iron compared with placebo or no iron (MD 20.94; 95% CI 16.84, 25.04). There was substantial heterogeneity for this outcome (I2=98%).

The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline Hb, baseline iron status, dose and duration of treatment, inclusion of other supplements and malaria endemicity. Three analyses approached statistical significance for subgroup differences: dose, duration and malaria endemicity.

Children aged less than 18 years

Okebe (2011) identified 35 RCTs involving 8544 infants and children aged less than 18 years that reported mean Hb levels at the end of treatment, and 20 RCTs involving 4205 infants and children that reported the mean change from baseline. A significant effect favouring oral iron compared with placebo or no iron was reported for both outcomes (MD 0.87; 95% CI 0.64, 1.09 and MD 0.61; 95% CI 0.41, 0.80, respectively). There was substantial heterogeneity for these outcomes (I2=95% and 88%, respectively). Subgroup analyses according to anaemia status at baseline or malaria endemicity also showed a significant effect favouring iron.

Six RCTs involving 1140 infants and children aged less than 18 years identified by Okebe (2011) reported mean Hb levels at the end of treatment comparing oral iron and folic acid with placebo or no treatment. A significant effect favouring the intervention was reported (MD 1.03; 95% CI 0.56, 1.49). There was substantial heterogeneity for this outcome (I2=88%).

Table 3.2.22 Neonatal and paediatric patients at risk of anaemia: Results for oral and/or parenteral iron versus no iron – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron  n/N (%)  Mean ± SD | No iron  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Children <2.5 years | | | | | | | | | |
| Pasricha 2013171  Level I  *Good* | 26 trials (Akman 2004, Aukett 1986, Berger 2000, Berger 2006, Desai 2003, Dijkhuizen 2001, Domellof 2001, Dossa 2001, Ermis 2002, Fahmida 2007, Fuerth 1972, Geltman 2004, Idjradinata 1993, Lind 2003, Majumdar 2003, Nagpal 2004, Ninh 2002, Northrop*-*Clewes 1996, Sazawal 2006, Thibault 1993, Wasantwisut 2006 Wieringa 2003, Yalcin 2000, Yurdakok 2004, Ziegler 2009, Zlotkin 2003)173-176; 178-183; 185-186; 188; 191; 193; 195; 197; 199; 202-207  N=5479 | Community or outpatient children aged 4–23 months. | Low and middle-income settings | Daily oral iron supplementation versus no iron / placebo | Hb (g/dL) | NR | NR | MD 7.22 [4.87, 9.57] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 94% |
| The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline Hb, baseline iron status, dose and duration of treatment, inclusion of other supplements, and malaria endemicity**c.**  Two analyses approached statistical significance for subgroup differences and are reported below. | | |
| Anaemic  3 trials (NR)  N=635 | Subgroup analysis: baseline Hb | | | Favours iron  *P <*0.0001  Substantial heterogeneity  I2 = 94% |
| NR | NR | MD 14.14 [7.36, 20.92] |
| Non-anaemic  4 trials (NR)  N=228 | NR | NR | MD 11.64 [–5.00, 28.28] | No significant difference  *P =*0.17  Substantial heterogeneity  I2 = 99% |
| Mixed / not reported  20 trials  N=4616 | NR | NR | MD 5.81 [3.96, 7.66] | Favours iron  *P <*0.00001  Substantial heterogeneity  I2 = 88% |
| ≤12.5 mg  16 trials (NR)  N=3889 | Subgroup analysis: dose | | | Favours iron  *P <*0.00001  Substantial heterogeneity  I2 = 93% |
| NR | NR | MD 5.72 [3.48, 7.96] |
| 12.6 to 30 mg  6trials (NR)  N=796 | NR | NR | MD 12.77 [3.30, 22.24] | Favours iron  *P =*0.008  Substantial heterogeneity  I2 = 98% |
| 31–60 mg  1 trial (NR)  N=491 | NR | NR | MD 8.76 [6.81, 10.72] | Favours iron  *P <*0.00001  Heterogeneity not applicable |
| >61 mg  1 trial (NR)  N=150 | NR | NR | MD 8.06 [3.79, 12.33] | Favours iron  *P =*0.0002  Heterogeneity not applicable |
| Mixed dose / not specified  2 trials  N=153 | NR | NR | MD 2.35 [–0.66, 5.36] | No significant difference  *P =*0.13  Moderate heterogeneity  I2 = 48% |
| 24 trialsd (Akman 2004, Aukett 1986, Berger 2000, Berger 2006, Dijkhuizen 2001, Domellof 2001, Ermis 2002, Fahmida 2007, Geltman 2004, Idjradinata 1993, Lind 2003, Majumdar 2003, Nagpal 2004, Northrop*-*Clewes 1996, Thibault 1993, Wasantwisut 2006, Wieringa 2003, Yalcin 2000, Yurdakok 2004, Ziegler 2009)173-176; 178-179; 181-182; 185-186; 188; 191; 193; 195; 199; 202-206  N=4526 | Low and middle-income settings | Ferritin (ng/mL) | NR | NR | MD 20.94 [16.84, 25.04] | *Favours iron*  *P <*0.0001  Substantial heterogeneity  I2 = 98% |
|  | The authors conducted subgroup analyses on a variety of measures to explore the heterogeneity that included breastfeeding, baseline Hb, baseline iron status, dose and duration of treatment, inclusion of other supplements, and malaria endemicity**c.**  Three analyses approached statistical significance for subgroup differences (see **Appendix F, Volume 2** for details). | | |  |
| Children <18 years | | | | | | | | | |
| Okebe 2011172  Level I  *Good* | 35 trials (Adam 1997, Bhatia 1993, Chwang 1988, Dossa 2001a, Dossa 2001b, Fahmida 2007, Gebresellassie 1996, Idjradinata 1993, Mebrahtu 2004, Soemantri 1989, Soewondo 1989, Verhoef 2002, Aggarwal 2005, Aguayo 2000, Angeles 1993, Ayoya 2009, Baqui 2003, Berger 1997, Berger 2000, Berger 2006, Devaki 2007, Harvey 1989, Kapur 2003, Kashyap 1987, Lawless 1994, Lind 2004, Mejia 1988, Nagpal 2004, Olsen 2006, Palupi 1997, Richard 2006, Rosado 1997, Smuts 2005, Wasantwisut 2006, Zlotkin 2003)175-176; 180; 182; 186; 193; 202; 207-211; 213-214; 216; 218; 221; 225-242  N=8544 | Children <18 years living in malaria-endemic areas | Various countries in Africa, South America, Asia and the Middle East | Oral iron versus placebo / no treatment | Mean Hb (g/dL), end of treatment | NR | NR | MD 0.87 [0.64, 1.09] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 95% |
| Anaemic  11 trials  N=2692 | Subgroup analysis: baseline anaemia | | | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 98% |
| NR | NR | MD 1.59 [0.93, 2.26] |
| Non-anaemic  29 trials  N=5852 | NR | NR | MD 0.64 [0.48, 0.80] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 86% |
| Hypo- or meso-endemic  34 trials  N=4335 | Subgroup analysis: by location | | | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 96% |
| NR | NR | MD 0.85 [0.54, 1.16] |
| Hyper- or holo-endemic  17 trials  N=4209 | NR | NR | MD 0.90 [ 0.59, 1.21] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 86% |
| 20 trials (Aggarwal 2005, Aguayo 2000, Angeles 1993, Charoenlarp 1973, de Silva 2003, Fahmida 2007, Kianfar 2000, Mejia 1988, Nagpal 2004, Olsen 2006, Palupi 1997, Smuts 2005, Berger 1997, Berger 2000, Berger 2006, Dossa 2001a, Lawless 1994, Mwanri 2000, Powers 1983, Zlotkin 2003)175-176; 182; 193; 207-208; 216-217; 226-228; 232; 236-238; 240; 243-246  N=4205 | Hb, mean change from baseline, end of treatment | NR | NR | MD 0.61 [0.41, 0.80] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 88% |
| Hypo- or meso-endemic  12 trials  N=2595 | Subgroup analysis: by location | | | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 78% |
| NR | NR | MD 0.40 [0.22, 0.58] |
| Hyper- or holo-endemic  8 trials  N=1610 | NR | NR | MD 0.91 [0.56, 1.26] | *Favours iron*  *P <*0.00001  Substantial heterogeneity  I2 = 87% |
| 6 trials(Gopaldas 1983, Sarma 1977, Seshadri 1984a, Seshadri 1984b, Seshadri 1982b, Hettiarachchi 2008)247-252  N=1140 | Oral iron plus folic acid versus placebo / no treatment | Mean Hb (g/dL), end of treatment | NR | NR | MD 1.03 [0.56, 1.49] | *Favours iron + folic acid*  *P =*0.000018  Substantial heterogeneity  I2 = 88% |
| Anaemic  4 trials (Gopaldas 1983, Sarma 1977, Seshadri 1982b, Seshadri 1984b)  N=273 | Subgroup analysis: baseline anaemia | | | *Favours iron + folic acid*  *P =*0.0074  Substantial heterogeneity  I2 = 89% |
| NR | NR | MD 1.10 [0.30, 1.91] |
| Non-anaemic  2 trials (Hettiarachchi 2008, Seshadri 1984a)  N=867 | NR (474) | NR (393) | MD 0.95 [ 0.32, 1.59 ] | *Favours iron + folic acid*  *P =*0.0032  Substantial heterogeneity  I2 = 90% |

CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; MD, mean difference; NR, not reported; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%

**c.** Refer to **Appendix F, Volume 2** of the technical report.

**d.** This data retrieved from corrected supplementary appendix, published Feb 7, 2014. Still, only 20 trials listed as reporting ferritin. The published article reported: 23 trials, MD 21.42 [17.25, 25.58].

### Neonatal and paediatric patients with cancer

* + - 1. ESAs (with or without iron)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Evidence statements – cancer (ESA with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
|  | 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 |
|  | 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.) | √√ | √√ | √ | √√ | √ |
|  | 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.) | √ | √√ | √ | √√ | √ |
|  | In neonatal patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
|  | 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 | √√ | √ |
|  | In neonatal patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Practice point – cancer (erythropoiesis stimulating agents) | |
| 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*14 |
| ESA, erythropoiesis stimulating agent; PP, practice point; R, recommendation | |

##### Background

People with cancer often have anaemia, which develops either as a result of their malignancy or chemotherapy. One option for treating this cancer- or chemotherapy-induced anaemia is RBC transfusions, which quickly help to correct the symptoms of anaemia, but can place patients at risk of infection, allergic reactions, iron overload and other adverse transfusion reactions. Another treatment option is ESAs, which act to increase the production of RBCs and help treat the symptoms of anaemia. There is consistent evidence that ESAs reduce the probability of having a RBC transfusion in adult cancer patients; however, ESAs are associated with an increased risk for thromboembolic events and reduced survival.

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified in the systematic review and hand-searching process that examined the use of ESAs in neonatal patients with cancer.

Nine Level I studies identified from the systematic review and hand-searching process examined the use of ESAs in children with cancer (see **Appendix C, Volume 2**). From these nine Level I studies, five systematic reviews provided the most comprehensive data to form the basis of this review (Grant 2013, Tonia 2012, Mystakidou 2007, Ross 2006, Feusner 2002). The main characteristics of these reviews are summarised in **Table 3.2.23**.

The good-quality reviews by Grant (2013) and Tonia (2012) evaluated the use of erythropoietin or darbepoetin in cancer patients (adults and children) who had anaemia or where at risk for anaemia. The authors updated previous reviews and integrated the result of a separate meta-analysis conducted by the Cochrane Collaboration based on individual patient data with recently published trials. Grant (2013) identified a total of 59 RCTs involving 17,552 participants, three of which involved children <18 years (Razzouk 2006, Wagner 2004, Porter 1996). Tonia (2012) identified 91 RCTs involving 20,102 participants; however, only one RCT in children <18 years (Razzouk 2006) was included in their analysis.

The fair-quality review by Ross (2006) examined the safety and efficacy of ESAs for the treatment of chemotherapy-induced anaemia in adults and children, and included data from three RCTs involving children <18 years (Wagner 2004, Varan 1999, Porter 1996).

The poor-quality reviews by Mystakidou (2007) and Feusner and Hastings (2002) both specifically reviewed the evidence for the use of ESA in paediatric oncology patients and included data from both randomised and non-randomised trials. In addition to the trials identified in the more recent or higher quality reviews, Mystakidou (2007) identified one additional RCT (Csaki 1998), and Feusner and Hastings (2002) identified a further two RCTs (Bennetts 1995, Ragni 1998).

The RCTs by Porter (1996), Varan (1999), and Wagner (2004) were identified in the systematic review by Tonia (2012); however, they were considered too small for inclusion in their meta-analysis or did not provide usable data. Varan (1999) was excluded from the evidence evaluation report by Grant (2013) because communication with the trial authors suggested treatment allocation was not concealed.[[28]](#footnote-28)

The RCT by Csaki (1998) was not identified in the larger systematic reviews; however, as it was a small, pilot study it is likely to have been too small for inclusion. The RCTs described by Bennetts (1995) and Ragni (1998) were published in abstract form only; therefore, the data from these should be interpreted with caution.

The main characteristics of the six Level II studies (Razzouk 2006, Varan 1999, Csaki 1998, Ragni 1998, Porter 1996, Bennetts 1995) identified in the included Level I studies are presented in **Table 3.2.24**. In each of the Level I studies, the results from the identified RCTs were presented individually for each study, with no post-hoc or pooled analyses provided (except when pooled with studies that included adults). Therefore, data from the published RCTs was sought if additional information about the study was deemed necessary (e.g. study design).

###### Level II evidence

There were no Level II studies identified in the systematic review and hand-searching process that examined the use of ESAs in neonatal patients with cancer.

No additional Level II studies examining the effectiveness of ESAs in children with cancer were identified in our literature search.

Table 3.2.23 Characteristics and quality of Level I evidence – ESAs in paediatric patients with cancer

| Study | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Grant (2013)253 | Level I  *Good* | Any patient diagnosed with malignant disease (all types/stages), regardless of previous therapy  59 RCTs, N=17,552  *Paediatric/neonatal*  3 RCTs, N=286 | rHuEPO or DAR (iv or sc) versus placebo or no treatment or any active head-to-head | Transfusion incidence  Overall survival  On-study mortality  Thromboembolic events  Laboratory measures (haematological response, change in Hb values)  QoL |
| Tonia (2012)254 | Level I  *Good* | Patients diagnosed with malignant disease (all types/stagesa) with anaemia or at risk for anaemia, regardless of previous therapy  91 RCTs, N=20,102  *Paediatric/neonatal*  1 RCT, N=224 | rHuEPO or DAR (iv or sc) versus placebo or no treatmentb | Transfusion incidence and volume  Overall survival  On-study mortality  Thromboembolic events  Laboratory measures (haematological response, change in Hb values) |
| Mystakidou (2007)255 | Level I  *Poor* | Paediatric cancer patients  5 RCTs, N=316 | rHuEPO or DAR versus placebo or no treatment | Transfusion incidence  Transfusion volume  Laboratory measures (haematological response, change in Hb values)  QoL  Adverse events |
| Ross (2006)256 | Level I  *Fair* | Patients with chemotherapy-induced anaemia (baseline Hb <11 g/dL)  28 RCTs, N=8323  6 non-RCTs, N=9771 | rHuEPO or DAR versus placebo or no treatment | Transfusions  QoL  Venous thromboembolism  Mortality (all-cause, treatment associated) |
| Feusner (2002)257 | Level I  *Poor* | Paediatric cancer patients  4 RCTs, N=68 | rHuEPO versus placebo or no treatment | Clinical efficacy  Adverse events |
| DAR, darbepoetin; rHuEPO, erythropoietin; Hb, haemoglobin; iv, intravenous; QoL, health-related quality of life; RCT, randomised controlled trial; sc, subcutaneous  **a.** Trials were excluded if more than 80% of participants were diagnosed with acute leukaemia.  **b.** Concomitant supportive treatments (e.g. G-CSF) were allowed if given equally to both treatment arms; trials using iron supplementation in the experimental group but not the control arm were also allowed. | | | | |

Table 3.2.24 Characteristics and quality of Level II evidence – ESAs in paediatric patients with cancer

| Study | Study type  Study qualitya | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Razzouk (2006)258 | Level II  *High* | Paediatric cancer patients with anaemiab receiving myelosuppressive chemotherapy for non-myeloid malignanciesc  N=224 | rHuEPO (600 U/kg per week) for 16 weeks versus placebo  \*dose adjustments allowed and iron supplementation given as neededd  \*Transfusion given if Hb fell below 7 g/dL | Transfusion needs  Haematological response (Hct, Hb)  QoL |
| Wagner (2004)259 | Level II  *Low* | Children with high risk neuroblastoma receiving intensive chemotherapy  N=38 | rHuEPO (200 U/kg) plus G-CSF versus G-CSF alone  \*rHuEPO administered daily if Hb <10 g/dL or tiw if Hb >10 g/dL  \*Transfusion given if Hb fell below 8 g/dL | Transfusion incidence  Tumour response |
| Varan (1999)260 | Level II  *NR* | Children receiving chemotherapy for solid tumours at risk for anaemia  N=34 | rHuEPO (150 U/kg, tiw) for 2 months versus control (not further described)  \*rHuEPO administered when Hb fell below 10 g/dL | Transfusion needs  Haematological response |
| Csaki (1998)261 | Level II  \*pilot study | Children aged 4–8 years with solid tumours and Hb <12g/dL  N=20 | rHuEPO (150 U/kg, tiw) for 12 weeks or over three chemotherapy cycles versus no rHuEPO | Transfusion needs Haematological response (Hct, Hb) |
| Ragni (1998)262 | Level II  \*Abstract only | Children receiving chemotherapy for a variety of tumour types | rHuEPO (150 U/kg, tiw) for 16 weeks versus placebo  \*Oral iron supplements given (details not provided) | Transfusion needs  Haematological response (Hct, Hb) |
| Porter (1996)263 | Level II  *Low* | Children receiving chemotherapy for sarcoma  N=24 | rHuEPO (150 U/kg, tiw) for 16 weeks versus placebo  \*Dose adjustments allowed every 4 weeks and iron supplements given to both groupse | Transfusion volume and incidence (RBC, platelets) |
| Bennetts (1995)264 | Level II  \*Abstract only | Children newly diagnosed with ALL  N=37 | rHuEPO (150 U/kg, tiw) versus no rHuEPO over three courses of chemotherapy  \*Transfusion given if Hb fell below 7.5 g/dL | Transfusion volume and incidence (RBC)  Safety  Iron deficiency |

ALL, acute lymphocytic leukaemia; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; Hct, haematocrit; NR, not reported; QoL, health-related quality of life; rHuEPO, recombinant human epoetin; tiw, three times per week

**a.** Assessed and reported by Grant (2013).

**b.** Hb ≤10.5 g/dL if aged 5–12 years, Hb ≤11 g/dL for girls aged more than 12 years, Hb ≤12 for boys aged more than 12 years.

**c.** Solid tumours, Hodgkin’s disease, non-Hodgkin’s disease, ALL. Children with brain tumours were excluded.

**d.** Increased if Hb increase <1 g/dL within 4 weeks, withheld if Hb >15 g/dL; oral iron administered when transferrin saturation <20 % or ferritin <100 ng/mL.

**e.** To maintain a target Hb of >11.5 g/dL, rHuEPO increased by 50 U/kg/dose until transfusion independent or a maximum dose of 300 U/kg reached. Oral iron (6 mg/kg/day) discontinued if serum ferritin >1000 ng/mL.

##### Results

###### Transfusion incidence and volume

Four RCTs (Razzouk 2006, Porter 1996, Csaki 1998, Varan 1999) identified by the systematic review and hand-searching process reported transfusion incidence in paediatric patients with cancer that were administered ESAs (with or without iron) compared with no ESAs or placebo. Two RCTs (Porter 1996, Bennetts 1995) were identified that reported transfusion volume. **Table 3.2.25** summarises the results from these studies.

Number of infants transfused

Two RCTs (Razzouk 2006, Varan 1999) reported a significant reduction in the number of infants that received a RBC transfusion favouring ESA therapy (RR 0.84; 95% CI 0.71, 0.99 and RR 0.13; 95% CI 0.02, 0.89, respectively). A subgroup analysis reported by Razzouk (2006) showed that the effect was nonsignificant in infants who had acute lymphocytic leukaemia (RR 1.03; 95% CI 0.73, 1.45).

The RCTs by Porter (1996) and Csaki (1998) both reported no significant difference between treatment groups on the incidence of RBC transfusion (RR 0.90; 95% CI 0.69, 1.18 and RR 1.17; 95% CI 0.39, 3.51), but the studies were small (≤25 children enrolled in each trial) and likely to be underpowered to detect significance.

Porter (1996) also reported significant reduction in the number of infants that received a platelet transfusion favouring ESA therapy (RR 0.33; 95% CI 0.13, 0.88).

A meta-analysis was conducted to evaluate the effectiveness of ESA therapy compared with no ESA therapy on reducing the incidence of RBC transfusion in children receiving chemotherapy for cancer (see **Figure 3.2.13**). The analysis showed that administration of ESAs reduced the incidence of transfusions (RR 0.86; 95% CI 0.69, 1.09) but the effect was nonsignificant. There was moderate heterogeneity (I2=42%) for this outcome.

Transfusion volume

The RCT by Porter (1996) reported a significant reduction in the median number of units transfused (median difference 8.5, *P =*0.01) and in the median volume of RBCs transfused (median difference 57, *P =*0.02) (no SEs or SDs provided).

Bennetts (1995) was reported to show no significant difference between treatment groups in the total volume of RBCs transfused (MD –8.00; 95% CI –16.42, 0.42) or in the mean volume transfused per patient (MD –0.85, 95% CI –1.92, 0.22). The authors noted a significant effect favouring ESA therapy in a subgroup of ‘low-risk’ children with acute lymphocytic leukaemia. Bennetts (1995) was reported in abstract form only; therefore, these data should be interpreted with caution.

Table 3.2.25 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%)  Mean ± SD  Median (IQR) | No ESAs ± iron  n/N (%)  Mean ± SD  Median (IQR) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Transfusion incidence | | | | | | | | | |
| Grant 2013253  Level I/II  *Good* | 1 RCT (Razzouk 2006)258  N=222 | Any patient diagnosed with malignant disease (all types/stages), regardless of previous therapy  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAc | rHuEPO versus placebo  \*Iron supplementation given as needed | Number of patients receiving RBC transfusions | 72/111 (64.86%) | 86/111 (77.48%) | RR 0.84 [0.71, 0.99] | *Favours rHuEPO*  *P =*0.04d |
|  | Subgroup analysis: cancer type | | | |
| Non-myeloid malignancies other than ALL | 46/71 (64.79%) | 64/76 (84.2%) | RR 0.77 [0.63, 0.94]d | *Favours rHuEPO*  *P =*0.009d |
| ALL patients | 26/40 (65.0%) | 22/35 (62.9%) | RR 1.03 [0.73, 1.45]d | No significant difference  *P =*0.85d |
| 1 RCT (Porter 1996)263  N=20 | \*children receiving chemotherapy for sarcoma | Single centre, USAc | rHuEPO versus placebo  \*All patients received oral iron supplementation | Number of patients receiving RBC transfusion | 9/10 (90.0%) | 10/10 (100.0%) | RR 0.90 [0.69, 1.18]d | No significant difference  *P =*0.46d |
| Mystakidou 2007255  Level I/II  *Poor* | 1 RCT (Razzouk 2006)258  N=222 | Children aged 0–18 years with cancer and receiving chemotherapy  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAC | rHuEPO versus placebo  \*Iron supplementation given as needed | Transfusion independent | NR (38.7%) | NR (22.5%) | NR | *Favours rHuEPO*  *P =*0.01 |
| 1 RCT (Csaki 1998)261  N=15 | \*children aged 4–8 years with solid tumours and Hb <12g/dL | Single centre, Hungaryc | rHuEPO versus control | Number of patients requiring blood transfusions | 4/8 (50.0%) | 3/7 (42.9%) | RR 1.17 [0.39, 3.51]c | *No significant difference*  *P =*0.78c |
| 1 RCT (Varan 1999)260  N=34 | \*children receiving chemotherapy for solid tumours at risk for anaemia | Single centre, Turkeyc | rHuEPO versus placebo | Number of patients requiring blood transfusions | 1/17 (5.9%) | 8/17 (47.1%) | RR 0.13 [0.02, 0.89]c | *Favours rHuEPO*  *P =*0.008 |
| Porter 1996263  Level II  *Good* | N=20 | Paediatric patients aged 6 months to 18 years with malignant sarcomas | Single centre, USA | rHuEPO versus placebo  \*All patients received oral iron supplementation | Number of patients receiving a platelet transfusion | 3/10 (30%) | 9/10 (90%) | RR 0.33 [0.13, 0.88]d | *Favours rHuEPO*  *P =*0.03d |
| Transfusion volume | | | | | | | | | |
| Feusner 2002257  Level I/II  *Poor* | 1 RCT (Porter 1996)263  N=20 | Paediatric cancer patients  \*children receiving chemotherapy for sarcoma | Single centre, USAc | rHuEPO versus placebo  \*All patients received oral iron supplementation | Median units RBC transfused | 4.5 (0–9) | 13.0 (2–22) | Difference in medians 8.5 [NR] | *Favours rHuEPO*  *P =*0.01e |
| Median volume of RBC transfused (mL/kg) | 23 (0–118) | 80 (18–226) | Difference in medians 57 [NR] | *Favours rHuEPO*  *P =*0.02e |
| 1 RCT (Bennetts 1995)264  N=37 | Paediatric cancer patients  \*children newly diagnosed with ALL | NR | rHuEPO versus placebo | Total amount RBC transfused (cc/kg) | 27 ± 18 (n=19) | 35 ± 5 (n=18) | MD –8.00 [–16.42, 0.42]d | *No significant difference*  *P =*0.06d  *P =*0.11e |
| low risk ALL patients (n=NR) | Subgroup analysis | | | Favours rHuEPO  *P =*0.02 |
| 16.8 ± 12.7 | 69.5 ± 36.1 | NR |
| Mean amount RBC transfused per patient (cc/kg) | 2.21 ± 1.58 | 3.06 ± 1.69 | MD –0.85 [–1.92, 0.22]d | *No significant difference*  *P =*0.12d  *P =*0.39e |
| Porter 1996263  Level II  *Good* | N=20 | Paediatric patients aged 6 months to 18 years with malignant sarcomas | Single centre, USA | rHuEPO + oral iron versus placebo + oral iron | Median number of platelet units transfused | 0 (0–3) | 4 (0–17) | NR | *Favours rHuEPO + iron*  *P =*0.005 |

ALL, acute lymphocytic leukaemia; CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; IQR, interquartile range; MD, mean difference; NR, not reported; RBC, red blood cells; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Not reported in systematic review; retrieved from Level II study.

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** *P-*value reported by trial authors.

Figure 3.2.13 Meta-analysis of ESAs versus no ESAs in paediatric patients receiving chemotherapy for cancer – number of infants requiring RBC transfusions (by type of cancer)



###### Thromboembolic events

One RCT (Razzouk 2006) identified by the systematic review and hand-searching process that reported thromboembolic events in children with cancer that were administered ESAs (with or without iron). **Table 3.2.26** summarises the results from this study.

Razzouk (2006) reported no significant difference between treatment groups comparing ESA therapy with placebo on the incidence of thromboembolism (RR 0.98; 95% CI 0.60, 1.60). A nonsignificant increased risk of ‘clinically relevant’ thromboembolic events was also observed (RR 2.95; 95% CI 0.61, 14.28) (see **Figure 3.2.14**).

Figure 3.2.14 Analysis of ESAs versus no ESAs in paediatric patients receiving chemotherapy for cancer – thromboembolic events



Table 3.2.26 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Thromboembolic events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%) | No ESAs ± iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Grant 2013253  Level I/II  *Good* | 1 RCT (Razzouk 2006)258  N=222 | Any patient diagnosed with malignant disease (all types/stages), regardless of previous therapy.  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAc | rHuEPO versus placebo  \*Iron supplementation given as needed | Thromboembolism (any) | 25/112 (22.3%) | 25/110 (22.7%) | RR 0.98 [0.60, 1.60]d | *No significant difference*  *P =*0.94 d |
| Thromboembolism (clinically relevant) | 6/112 (5.4%) | 2/110 (1.8%) | RR 2.95 [0.61, 14.28]d | *No significant difference*  *P =*0.18 d |

CI, confidence interval; ESA, erythropoiesis stimulating agent; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Not reported in systematic review; retrieved from Level II study.

**d.** Calculated post-hoc using RevMan 5.1.2.

###### Mortality

Three RCTs (Razzouk 2006, Porter 1996, Varan 1999) identified by the systematic review and hand-searching process reported all-cause mortality in paediatric patients with cancer that were administered ESAs (with or without iron) compared with no ESAs or placebo. **Table 3.2.27** summarises the results from these studies.

The RCTs by Razzouk (2006), Porter (1996) and Varan (1999) each reported no significant difference between treatment groups comparing ESAs with placebo or no ESAs for the outcome of all-cause mortality in infants and children receiving chemotherapy for cancer.

A meta-analysis was conducted to evaluate the effectiveness of ESA therapy compared with no ESA therapy on reducing the incidence of in-study mortality in children receiving chemotherapy for cancer (see **Figure 3.2.15**). The analysis showed no significant difference between treatment groups on the incidence of in-study mortality (RR 1.02; 95% CI 0.21, 4.88). There was no significant heterogeneity for this outcome (I2=0%).

One RCT (Wagner 2004) was identified that reported the probability of 5 year progression-free survival in children with high risk neuroblastoma receiving intensive chemotherapy. Wagner (2004) reported that children administered ESAs with G-CSF compared with G-CSF alone had a significantly increased probability of progression-free survival (MD 13.90; 95% CI 7.34, 20.46).

Figure 3.2.15 Meta-analysis of ESAs versus no ESAs in paediatric patients receiving chemotherapy for cancer – mortality



Table 3.2.27 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | | Intervention versus comparator | | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%)  Mean ± SD | No ESAs ± iron  n/N (%)  Mean ± SD | | Risk estimate (95% CI) | | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | | | | |
| Grant 2013253  Level I/II  *Good* | 1 RCT (Razzouk 2006)258  N=222 | Any patient diagnosed with malignant disease (all types/stages), regardless of previous therapy  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAc | rHuEPO versus placebo  \*Iron supplementation given as needed | | In-study mortality | | 2/112 (1.8%) | 2/110 (1.8%) | OR 0.98 [0.14, 7.10]d | | *No significant difference*  *P =*0.99d | |
| 1 RCT (Wagner 2004)259  N=38 | \*children with high risk neuroblastoma receiving intensive chemotherapy | NR | rHuEPO plus G-CSF versus G-CSF | | Probability of 5 year progression-free survival (%) | | 38.9 ± 11.5 (n=18) | 25.0 ± 8.8 (n=20) | MD 13.90 [7.34, 20.46]d | | Favours rHuEPO plus G-CSF  P < 0.0001d | |
| Ross 2006256  Level I/II  *Fair* | 1 RCT (Porter 1996)  N=21 | Patients with chemotherapy-induced anaemia (baseline Hb <11 g/dL)  \*children receiving chemotherapy for sarcoma | Single centre, USAc | rHuEPO versus placebo  \*All patients received oral iron supplementation | | In-study mortality (all-cause) | | 1/10 (10%) | 1/11 (9.1%) | OR 1.11 [0.06, 20.49] | | *No significant difference*  *P =*0.944 | |
| 1 RCT (Varan 1999)260  N=34 | \*children receiving chemotherapy for solid tumours at risk for anaemia | Single centre, Turkeyc | rHuEPO versus control | | 0/17 (0%) | 0/17 (0%) | OR 1.00 [0.01, 84.36] | | *No significant difference*  *P =*1.000 | |

CI, confidence interval; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factors; Hb, haemoglobin; MD, mean difference; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Not reported in systematic review; retrieved from Level II study.

**d.** Calculated post-hoc using RevMan 5.1.2.

###### Secondary outcomes[[29]](#footnote-29)

Functional and performance status

None of the RCTs included in our systematic review reported the effect of ESAs compared to placebo or no ESAs (with or without iron) on functional and performance status in infants, children or adolescents with cancer.

Laboratory measures

Five RCTs (Razzouk 2006, Varan 1999, Csaki 1998, Ragni 1998, Bennetts 1995) identified by the systematic review and hand-searching process reported laboratory measures in paediatric patients with cancer, and examined the effectiveness of ESA therapy (with or without iron) compared to placebo or no ESAs. **Table 3.2.28** summarises the results from these studies.

Razzouk (2006) reported a significant effect favouring ESA therapy for an overall haematological response (increase in Hb levels of ≥2 g/dL or a ≥6 % point increase in Hct) in children administered ESAs compared to placebo (RR 1.62; 95% CI 1.20, 2.18), but the effect was not significant for mean change in Hb from baseline (MD 0.30; 95% CI –0.27, 0.87).

The RCTs by Varan (1999), Csaki (1998) and Ragni (1998) were reported to show a significant increase in mean Hb post-treatment (g/dL) in children administered ESAs compared to placebo but data were incomplete so no further analysis was possible (no SDs provided). Csaki (1998) was also reported to show a significant increase in haematocrit (%) favouring ESA therapy compared with placebo.

The RCT by Bennetts (1995) reported no difference in the number of children with iron deficiency comparing ESA therapy with placebo (RR 1.58; 95% CI 0.44, 5.67).

Table 3.2.28 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%)  Mean ± SD | No ESAs ± iron  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | |
| Tonia 2012254  Level I/II  *Good* | 1 RCT (Razzouk 2006)258  N=222 | Patients diagnosed with malignant disease (all types/stages) with anaemia or at risk of anaemia  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAc | rHuEPO versus placebo  \*Iron supplementation given as needed | Haematologic response  \*Increase in Hb of ≥2 g/dL or ≥6 % point increase in Hct | | 63/111 (56.8%) | 39/111 (35.1%) | RR 1.62 [1.20, 2.18] | *Favours rHuEPO*  *P =*0.0018 |
| Mean change in Hb level | | 1.3 ± 2.38 | 1 ± 1.9 | MD 0.30 [–0.27, 0.87] | *No significant difference*  *P =*0.30 |
| Mystakidou 2007255  Level I/II  *Poor* | 1 RCT (Razzouk 2006)258  N=222 | Children aged 0–18 years with cancer and receiving chemotherapy  \*Anaemic children receiving myelosuppressive chemotherapy for non-myeloid malignancies | Multicentre, USAc | rHuEPO versus placebo  \*Iron supplementation given as needed | Mean Hb post-treatment (g/dL) | | 11.2 ± NR | 10.5 ± NR | MD –0.7 [NR] | *P =*NR |
| Hb increase of at least 2 g/dL | | NR (56%) | NR (35%) | NR | *Favours rHuEPO*  *P =*0.002 |
| children aged 5–7 years | | Subgroup analysis: age | | | Favours rHuEPO  *P =*NR |
| NR (92%) | NR (41%) | NR |
| 1 RCT (Varan 1999)260  N=34 | \*children receiving chemotherapy for solid tumours at risk for anaemia | Single centre, Turkeyc | rHuEPO v control | Mean Hb post-treatment (g/dL) | | 10.21 ± NR | 8.41 ± NR | MD –1.8 [NR] | *Favours rHuEPO*  *P =*NR |
| 1 RCT (Csaki 1998)261  N=15 | \*children aged 4–8 years with solid tumours and Hb <12 g/dL | Single centre, Hungaryc | rHuEPO versus no rHuEPO | Mean Hb at week 8 (g/dL) | | 13.11 ± NR | 11.06 ± NR | MD –2.05 [NR] | *Favours rHuEPO*  *P =*NR |
| Hct at week 8 (%) | | 39.3 ± NR | 33.2 ± NR | MD –6.0 [NR] | *Favours rHuEPO*  *P =*NR |
| Feusner 2002257  Level I/II  *Poor* | 1 RCT (Ragni 1998)262  N=82\*  \*number of chemotherapy courses | Paediatric cancer patients  \*children receiving chemotherapy for a variety of tumour types | NR | rHuEPO versus placebo | Mean nadir Hb (g/dL) | | 10.36 (range 7.7–13.8) | 8.7 (range 5.5–13.5) | MD –1.66 [NR] | *Favours rHuEPO*  *P <*0.05 |
| Number of chemotherapy courses where Hb decreased to <9 g/dL | | 4/22 (18.2%) | 36/60 (60%) | RR 0.30 [0.12, 0.75]d | *Favours rHuEPO*  *P =*0.01d |
| Mean time (days) to Hb recovery | | 3.5 (3–5) | 7.3 (3–23) | NR | *P =*NR |
| 1 RCT (Bennetts 1995)264  N=37 | \*children newly diagnosed with ALL | NR |  | Number of patients with iron deficiency | | 5/19 (26.3%) | 3/18 (16.7%) | RR 1.58 [0.44, 5.67]d | *No significant difference*  *P =*0.48d |

ALL, acute lymphocytic leukaemia; CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; MD, mean difference; NR, not reported; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Not reported in systematic review; retrieved from Level II study.

**d.** Calculated post-hoc using RevMan 5.1.2.

Tumour progression or recurrence

One RCT (Wagner 2004) was identified by the systematic review and hand-searching process that reported the outcome of tumour progression or recurrence in paediatric patients with cancer. Wagner (2004) was reported by Grant (2013) to show no significant difference between treatment groups on tumour response (complete or partial) comparing ESA plus G-CSF to G-CSF alone (RR 1.06; 95%CI 0.68, 1.66). **Table 3.2.29** summarises the results from this study.

Table 3.2.29 Paediatric patients with cancer: Results for ESAs versus no ESAs – Tumour progression or recurrence (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%) | No ESAs ± iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Grant 2013253  Level I/II  *Good* | 1 RCT (Wagner 2004)259  N=35 | Any patient diagnosed with malignant disease (all types/stages), regardless of previous therapy | NR | rHuEPO plus G-CSF versus G-CSF | Tumour response (complete + partial response) | 12/17 (70.6%) | 12/18 (66.7%) | RR 1.06 [0.68, 1.66]c | *No significant difference*  *P =*0.80c |

CI, confidence interval; ESA, erythropoiesis stimulating agent; G-CSF, granulocyte colony-stimulating factor; NR, not reported; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2. Reported by Grant (2013) as RR 0.94 [0.60, 1.48]; *P-*value NR.

* + - 1. Oral and/or parenteral iron

| Evidence statements – cancer (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of oral and/or parenteral iron compared with no iron or placebo in neonatal and/or paediatric patients with cancer.

### Neonatal and paediatric patients with kidney disease

* + - 1. ESAs (with or without iron)

| Evidence statements – kidney disease (ESA with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 | √√ | √√ |
|  | In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion volume is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 | | | | | | |

| Practice points – chronic kidney disease (erythropoiesis stimulating agents) | |
| --- | --- |
| 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*14  b The KDIGO guidelines82 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 guidelines83 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*14 |
| 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*14 |
| 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; R, recommendation; RBC, red blood cell | |

##### Background

People with kidney disease often have anaemia, primarily due to an inability of the kidneys to stimulate the production of erythropoietin. Iron deficiency through blood loss, nutritional deficits or other causes may also contribute to this anaemia. As kidney function declines, the severity of anaemia increases. Left untreated, anaemia in people with CKD can cause substantial morbidity because it exacerbates symptoms of tiredness, shortness of breath and lethargy, and increases the risk of heart complications. In adult patients with CKD, ESAs have been used to correct anaemia and reduce the need for blood transfusions; however, there is little evidence relating to the management of CKD in children.

##### Summary of evidence

###### Level I evidence

Three Level I studies (Cody 2005, KDIGO 2012, NICE 2011) identified from the systematic review and hand-searching process examined the use of ESAs in children with CKD but provided no usable data for inclusion in this review (see **Appendix C, Volume 2**).

The good-quality review by Cody (2005) searched for RCTs or quasi-RCTs comparing rHuEPO with either placebo or no rHuEPO in patients (adults or children) with anaemia due to CKD; however, no studies in children were included in their analysis. The authors identified two RCTs in children awaiting assessment, but neither RCT met the criteria for inclusion in our review. Jabs (1994) reported results of a Phase III study published in abstract form only, and Brandt (1999) assessed dosing requirements for ESAs (no placebo arm).

Clinical practice guidelines published by the Kidney Disease Improving Global Outcomes (KDIGO) (KDIGO 2012) and NICE (2011) 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 to guide monitoring and treatment adjustments so as to avoid adverse outcomes.

###### Level II evidence

One Level II study (Pape 2009) identified from the systematic review and hand-searching process examined the use of ESAs in children with acute kidney disease (see **Appendix C, Volume 2**). The RCT by Pape (2009) was a single centre pilot study conducted in Germany and examined the safety and effectiveness of rHuEPO in reducing the need for RBC transfusion in children with acute renal failure due to haemolytic uremic syndrome. The main characteristics of this RCT are summarised in **Table 3.2.30**.

Table 3.2.30 Characteristics and quality of Level II evidence – ESAs in paediatric patients with kidney disease

| Study | Study type  *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Pape 2009265 | Level II  *Poor* | Children aged 1–6 years with EHEC-positive HUS or likely EHEC infection and bloody diarrhoea  N=10 | rHuEPO (33 IU/dose/kg, tiw) for 4 weeks versus conservative therapy without rHuEPO  \*early administration of rHuEPO within 3 hours of hospital admission  \*RBC transfusions given when Hb fell below 5 mg/dL | Transfusion incidence |

EHEC, enterohaemorrhagic Escherichia coli; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; HUS, haemolytic uremic syndrome; IU, international units; RBC, red blood cells; rHuEPO, recombinant human epoetin; tiw, three times per week

##### Results

###### Transfusion incidence and volume

One RCT (Pape 2009) identified by the systematic review and hand-searching process reported transfusion incidence in paediatric patients with haemolytic uremic syndrome (HUS) that were administered ESAs. **Table 3.2.31** summarises the results from these studies.

The RCT by Pape (2009) reported a nonsignificant reduction in the number of infants that received one or more RBC transfusions comparing rHuEPO with no rHuEPO (RR 0.25; 95% CI 0.04, 1.52) and a significant reduction in the mean number of transfusions (MD 1.2; *P =*0.04) but data were incomplete (no SDs provided). The study was small and underpowered.

Table 3.2.31 Paediatric patients with kidney disease: Results for ESAs versus no ESAs – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Haemolytic uremic syndrome | | | | | | | | | |
| Pape 2009265  Level II  *Poor* | N=10 | Children aged 1–6 years with EHEC-positive HUS or likely EHEC infection and bloody diarrhoea | Single centre, Germany | rHuEPO versus standard therapy without rHuEPO  \*early administration of rHuEPO within 3 hours of hospital admission | Number of children who received 1 or more RBC transfusions | 1/5 (20%) | 4/5 (80%) | RR 0.25 [0.04, 1.52]c | *No significant difference*  *P =*0.13c |
| Mean number of RBC transfusions per child | 0.2 ± NR | 1.4 ± NR | MD 1.2 [NR] | *Favours early rHuEPO*  *P =*0.04 |

CI, confidence interval; EHEC, enterohaemorrhagic *Escherichia coli*; ESA, erythropoiesis stimulating agent; HUS, haemolytic uremic syndrome; MD, mean difference; NR, not reported; RBC, red blood cells; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Thromboembolic events

There were no studies identified in the systematic review and hand-searching process that reported on the outcome of thromboembolic events when assessing the safety and effectiveness of ESAs compared to no ESAs in paediatric patients with kidney disease.

###### Mortality

There were no studies identified in the systematic review and hand-searching process that reported on the outcome of mortality when assessing the safety and effectiveness of ESAs compared to no ESAs in paediatric patients with kidney disease.

###### Secondary outcomes[[30]](#footnote-30)

Functional and performance status

None of the RCTs included in our systematic review reported the effect of ESAs compared to placebo or no ESAs (with or without iron) on functional and performance status in paediatric patients with kidney disease.

Laboratory measures

The RCT by Pape (2009) reported no significant difference on the level of Hb at discharge in children aged 1–6 years with HUS administered rHuEPO compared to no rHuEPO (MD –0.8), but data were incomplete (no SDs provided). **Table 3.2.32** summarises the results from this study.

Table 3.2.32 Paediatric patients with kidney disease: Results for ESAs versus no ESAs – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  Mean ± SD | No ESAs  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Haemolytic uremic syndrome | | | | | | | | | |
| Pape 2009265  Level II  *Poor* | N=10 | Children aged 1–6 years with EHEC-positive HUS, or likely EHEC infection and bloody diarrhoea | Single centre, Germany | rHuEPO versus standard therapy without rHuEPO  \*early admission of rHuEPO within 3 hours of hospital admission | Hb (mg/dL) at discharge | 9.2 ± NR | 8.4 ± NR | MD –0.8 [NR] | *No significant difference*  *P =*NR |

CI, confidence interval; EHEC, enterohemorrhagic *Escherichia coli*; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; HUS, haemolytic uremic syndrome; MD, mean difference; NR, not reported; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Oral and/or parenteral iron

| Evidence statements – kidney disease (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 epoetin; IV, intravenous  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

##### Summary of evidence

###### Level I evidence

One Level I study (Albaramki 2012) identified from the systematic review and hand-searching process examined the use of iron in children with CKD during ESA therapy, but provided no usable data for inclusion in this review (see **Appendix C, Volume 2**).

The good-quality review by Albaramki (2012) searched for RCTs or quasi-RCTs comparing oral and IV routes of administration of iron in patients (adults or children) with anaemia due to CKD. The authors identified 28 trials, but only one RCT (Warady 2004) was in children and no data for our primary outcomes were reported. The authors concluded that there is strong evidence that intravenous (IV) iron increases ferritin and transferrin saturation levels in adult patients with CKD compared with oral iron, and that there is a small increase in Hb levels. A significant reduction in ESA requirements in patients treated with IV iron was also reported. There was no significant difference in mortality.

Warady (2004) was a small multicentre trial conducted in the USA that compared IV iron with oral iron in infants and children aged less than 20 years on dialysis and receiving maintenance rHuEPO therapy. The main characteristics of this RCT are summarised in **Table 3.2.33**.

###### Level II evidence

No additional Level II studies were identified in the systematic review and hand-searching process that examined the use of iron in paediatric patients with CKD (see **Appendix C, Volume 2**).

Table 3.2.33 Characteristics and quality of Level II evidence – IV iron versus oral iron in paediatric patients with CKD

| Study | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Warady 2004266 | Level II  *Poor* | Paediatric patients aged between 1 and 20 years with ESRD on chronic haemodialysis for >2 months and with baseline serum transferrin saturation >20 %  N=35 | iv iron dextran (25–100 mg/weeka) for 12 weeks versus oral iron (4–6 mg/kg/day)  \*All patients were on maintenance rHuEPO therapy (iv or sc) | Transfusion incidence  Laboratory measures (Hb, Hct) |

CKD, chronic kidney disease; ESRD, end-stage renal disease; Hb, haemoglobin; Hct, haematocrit; iv, intravenous; rHuEPO, recombinant human epoetin; sc, subcutaneous

**a.** Weight based dosing: patients <20 kg = 25 mg/week; 20–40 kg = 50 mg/week; >40 kg = 100 mg/week

##### Results

###### Transfusion incidence and volume

One RCT (Warady 2004) identified by the systematic review and hand-searching process reported transfusion incidence in paediatric patients with end-stage renal disease, and compared IV iron with oral iron during ESA maintenance therapy. The study was small (total N=35) and no transfusions were reported in either group. **Table 3.2.34** summarises the results from this study.

Table 3.2.34 Paediatric patients with kidney disease: Results for IV iron versus oral iron – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Chronic kidney disease | | | | | | | | | |
| Warady 2004266 | N=35 | Paediatric patients with end-stage renal disease receiving haemodialysis | Multicentre, USA | rHuEPO + iv iron versus rHuEPO + oral iron | Transfusion incidence | 0/17 | 0/18 | Not estimable | *Not applicable* |

CI, confidence interval; ESA, erythropoiesis stimulating agent; iv, intravenous; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Thromboembolic events

No studies identified in the systematic review and hand-searching process reported on the outcome of thromboembolic events when assessing the safety and effectiveness of IV iron compared to oral iron in paediatric patients with CKD during haemodialysis and rHuEPO therapy.

###### Mortality

No studies identified in the systematic review and hand-searching process reported on the outcome of mortality when assessing the safety and effectiveness of IV iron compared to oral iron in paediatric patients with CKD during haemodialysis and rHuEPO therapy.

###### Secondary outcomes[[31]](#footnote-31)

Functional and performance status

None of the RCTs included in our systematic review that examined the effectiveness of IV iron compared with oral iron reported on functional and performance status in paediatric patients with CKD during haemodialysis and rHuEPO therapy.

Laboratory measures

The RCT by Warady (2004) assessed the effectiveness of IV iron compared to oral iron in correcting anaemia in children with end-stage renal disease receiving chronic haemodialysis and rHuEPO therapy. The trial found no significant difference between treatment groups on the mean change in Hb (g/dL) or Hct (%) from baseline (MD 0.02; 95% CI –1.47, 1.51 and MD 0.33; 95% CI –4.26, 4.92, respectively). A significant effect in favour of IV iron was reported for mean change in ferritin (ng/mL) (MD 137.30; 95% CI 60.25, 214.35).

Table 3.2.35 Paediatric patients with kidney disease: Results for IV iron versus oral iron – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  Mean ± SD | No ESAs  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Chronic kidney disease | | | | | | | | | |
| Warady 2004266 | N=35 | Paediatric patients with end-stage renal disease receiving haemodialysis | Multicentre, USA | rHuEPO + iv iron versus rHuEPO + oral iron | Hb (g/dL) change from beginning to end of study | –0.15 ± 2.55 | –0.17 ± 1.89 | MD 0.02 [–1.47, 1.51] c | *No significant difference*  *P =*0.98c |
| Hct (%) change from beginning to end of study | –0.48 ± 7.71 | –0.81 ± 5.98 | MD 0.33 [–4.26, 4.92] c | *No significant difference*  *P =*0.89c |
| Ferritin (ng/mL) change from beginning to end of study | 120.6 ± 133.7 | –16.7 ± 94.3 | 137.30 [60.25, 214.35]c | Favours iv iron  *P =*0.001 |

CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; iv, intravenous; MD, mean difference; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

### Neonatal and paediatric patients with malaria

* + - 1. ESA (with or without iron)

| Evidence statements – malaria (ESAs with or without iron) | | **Evidence** | | **Consistency** | | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal and paediatric patients with malaria, the effect of ESA therapy (with or without iron) compared with no ESA therapy on transfusion volume or incidence is unknown. | | NA | | NA | NA | NA | NA |
|  | In neonatal and paediatric patients with malaria, the effect of ESA therapy (with or without iron) compared with no ESA therapy on thromboembolic events is unknown. | | NA | | NA | NA | NA | NA |
|  | In neonatal and paediatric patients with malaria, the effect of ESA therapy (with or without iron) compared with no ESA therapy on mortality is unknown. | | NA | | NA | NA | NA | NA |
| ES, evidence statement; ESA, erythropoiesis stimulating agent  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | | | |

* + - 1. Oral and/or parenteral iron

| Evidence statements – malaria (oral and/or parenteral iron) | | **Evidence** | **Consistency** | | | **Clinical impact** | | **Generalisability** | | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal and paediatric patients with malaria, the effect of oral iron plus folic acid compared with folic acid alone on transfusion volume or incidence is uncertain.  (See evidence matrix D2.R in Volume 2 of the technical report.) | √ | | NA | NA | | √√ | | √ | |
|  | In neonatal and paediatric patients with malaria, the effect of oral iron plus folic acid compared with folic acid alone on mortality is uncertain.  (See evidence matrix D2.S in Volume 2 of the technical report.) | √√√ | | √√√ | NA | | √ | | X | |
| ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | | | | | |

Recommendations and practice points concerning the use of iron in children with clinical malaria were not made because this topic was judged by the CRG to be outside the scope of these guidelines.

Neonatal and paediatric patients with malaria are therefore not discussed in Module 6.

The evidence identified during the systematic review and hand-searching process is presented here for completeness.

##### Background

Iron supplements are often given to infants and children to treat or prevent anaemia; however, iron deficiency is thought to be protective of clinical malaria and other infections. This is because free iron can be used by pathogens for their own survival or to mediate pathogenesis. Malaria contributes to anaemia by the increased clearance and destruction of RBCs infected with the malaria parasite. It is important to balance the effect of iron supplements against potential harms.

##### Summary of evidence

###### Level I evidence

One Level I study (Okebe 2011) identified in the systematic review and hand-searching process examined the use of oral iron (with or without folic acid) in infants, children or adolescents with malaria-associated anaemia (see **Appendix C, Volume 2**). The main characteristics of this review have been summarised in **Section 3.2.4.2** and **Table 3.2.18**.

###### Level II evidence

The good- quality systematic review by Okebe (2011) identified four RCTs (Gara 2010, Nwanyanwu 1996, van den Hombergh 1996, van Hensbroek 1995) involving 1004 infants that assessed the safety and effectiveness of oral iron supplementation (with or without folic acid) during treatment for an acute attack of malaria.

The RCTs by van Gara (2010), Nwanyanwu (1996), van den Hombergh (1996) and Hensbroek (1995) were open-label RCTs conducted at single centres each in Nigeria (Gara 2010), Malawi (Nwanyanwu 1996), Tanzania (van den Hombergh 1996) and The Gambia (van Hensbroek 1995). All infants were administered malaria treatment and in two trials (Gara 2010, van den Hombergh 1996) infants also received folic acid. The main characteristics of these RCTs are shown in **Table 3.2.36.**

No additional Level II studies assessing the safety and effectiveness of oral iron supplements during an acute attack of malaria were identified in the systematic review and hand-searching process.

Table 3.2.36 Characteristics and quality of Level II evidence – iron in neonatal and paediatric patients with clinical malaria

| Study ID | Study type  *Study qualitya* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Gara 2010267 | Level II  *Low to high risk of bias* | Infants with clinical malaria and anaemia aged 6–60 months  N=82 | Oral iron syrup (2 mg/kg/day) versus no iron  \*All infants were administered folic acid (5 mg/day), chloroquine and SP | Mortality  Laboratory measures (Hb, anaemia) |
| Nwanyanwu 1996268 | Level II  *Unclear/high risk of bias* | Infants with malaria and Hb >5 g/dL, mean age 26 months  N=222 | Oral iron syrup (6 mg/kg/day) versus oral iron (0.85 mg/kg/day)  \*All infants were administered SP | Mortality  Laboratory measures (Hb) |
| van den Hombergh 1996269 | Level II  *Unclear/high risk of bias* | Infants with severe *P. falciparum* malaria aged <30 months and Hb <5 g/dL  N=100 | Oral iron tablets (200 mg/day) versus no iron  \*All infants were administered folic acid (100 µg/day) and quinine and SP | Transfusion incidenceb  Mortality  Laboratory measures (Hb, anaemia) |
| Van Hensbroek 1995270 | Level II  *Unclear/high risk of bias* | Infants with uncomplicated *P. falciparum* malaria aged 6–9 months and Hb <11 g/dL  N=600 | Oral iron syrup (6 mg/kg/day) versus placebo c  \*All infants were administered SP | Mortality  Laboratory measures (Hb) |

Hb, haemoglobin; SP, sulphadoxine-pyrimethamine

**a.** Assessed by Okebe (2011).

**b.** Data retrieved from RCT, not reported by Okebe (2011).

**c.** Van Hensbroek (1995) was a four-arm trial comparing oral iron plus SP versus placebo plus SP versus folic acid plus chloroquine versus placebo plus chloroquine. Only oral iron plus SP versus placebo plus SP is reported in this review.

##### Results

###### Transfusion incidence and volume

One RCT (van den Hombergh 1996) identified by the systematic review and hand-searching process reported transfusion incidence in 100 paediatric patients aged less than 30 months with severe malaria due to *P. falciparum* compared oral iron with no iron supplements, given together with folic acid and antimalarial treatment. The author reported no difference between treatment groups on the incidence of transfusions (RR 1.00; 95% CI 0.64, 1.56). There was also no significant difference between groups on the incidence of transfusion given one to two days after randomisation (RR 1.0; 95% CI 0.15, 6.82). **Table 3.2.37** summarises the results from this study.

Table 3.2.37 Neonatal and paediatric patients with anaemia associated with malaria-: Results for oral and/or parenteral iron versus no iron – Transfusion volume or incidence

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%) | No iron therapy  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Van den Hombergh 1996269  Level II  *Poor* | N=100 | Children <30 months with severe malaria-associated anaemia (Hb ≤5 g/dL) | Single hospital, Tanzania | Oral iron plus folic acid versus folic acid  \*All children received antimalarial therapy | Transfusion incidence | 22/50 | 22/50 | RR 1.00 [0.64, 1.56]c | No significant difference  *P =*1.00c |
| Transfusion later than day one or two | 2/50 | 2/50 | RR 1.00 [0.15, 6.82]c | No significant difference  *P =*1.00c |

CI, confidence interval; Hb, haemoglobin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Mortality

Okebe (2011) assessed the incidence of mortality (all-cause) in children administered iron (with or without folic acid) during an acute attack of malaria and included data from four RCTs involving 664 children. The pooled risk difference was reported to be 2.66 per 1000 children.

The meta-analysis showed no significant difference on the incidence of mortality (RD 0.00; 95% CI –0.01, 0.02) in these children; however, there were no deaths in two trials and the outcome is likely to be underpowered to detect a significant difference (see **Figure 3.2.16**). There was no heterogeneity for this outcome (I2=0%). **Table 3.2.38** summarises the results from this study.

Figure 3.2.16 Meta-analysis of iron versus no iron in neonatal and paediatric patients with anaemia associated with malaria – mortality



Table 3.2.38 Neonatal and paediatric patients with anaemia associated with malaria: Results for oral and/or parenteral iron versus no iron – Mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  n/N (%) | No iron therapy  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Okebe 2011172  Level I  *Good* | 4 trials (Gara 2010, Nwanyanwu 1996, van den Hombergh 1996, van Hensbroek 1995)267-270  N=664 | Children with clinical malaria | Nigeria, Malawi, Tanzania, The Gambia | Oral iron ± folic acid versus placebo / no treatment ± folic acid  \*All children received antimalarial therapy | Mortality (all-cause) | 3/370 | 2/294 | RD 0.00 [–0.01, 0.02]  RD per 1000 children 2.66 [–13.34, 18.67] | *No significant difference*  *P =*0.74  No significant heterogeneity  I2 = 0% |

CI, confidence interval; RD, risk difference

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%

###### Secondary outcomes[[32]](#footnote-32)

Functional and performance status

None of the RCTs included in the systematic review reported on functional and performance status that examined the effectiveness of iron supplements (with or without folic acid) compared to placebo or no iron in paediatric patients with clinical malaria.

Laboratory measures

The review by Okebe (2011) assessed the effectiveness of iron supplements (with or without folic acid) compared to no iron in improving Hb levels in children with clinical malaria receiving antimalarial treatment. **Table 3.2.39** summarises the results from this study.

The review identified two RCTs (Gara 2010, van den Hombergh 1996) that reported Hb levels at end of treatment, with the analysis showing a nonsignificant increase in Hb (g/dL) (MD 0.32; 95% CI –0.01, 0.64) in children administered iron plus folic acid compared with folic acid alone. One RCT (Gara 2010) was reported to show significantly lower incidence of anaemia at the end of treatment (RR 0.84; 95% CI 0.72, 0.98) in children administered iron plus folic acid compared with folic acid alone.

Table 3.2.39 Neonatal and paediatric patients with anaemia associated with malaria: Results for oral and/or parenteral iron versus no iron – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Iron therapy  Mean ± SD | No iron therapy  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | |
| Okebe 2011172  Level I  *Good* | 2 trials (Gara 2010, van den Hombergh 1996)267; 269  N=176 | Children with clinical malaria | Nigeria, Tanzania | Oral iron + folic acid versus folic acid  \*All children received antimalarial treatment | Mean Hb (g/dL), end of treatment | NR | NR | MD 0.32 [–0.01, 0.64] | *Borderli*ne favours iron  *P =*0.058  No significant heterogeneity  I2 = 0.0% |
| Level II evidence | | | | | | | | | |
| Okebe 2011172  Level I  *Good* | 1 trial (Gara 2010)267  N=80 | Children with clinical malaria | Outpatient setting, Nigeria | Oral iron + folic acid versus folic acid  \*All children received antimalarial treatment | Anaemia, end of treatment | 32/39 | 40/41 | RR 0.84 [0.72, 0.98] | *Favours iron*  *P =*0.03d |
| Van den Hombergh 1996269  Level II  *Poor* | N=100 | Children aged <30 months with severe malaria-associated anaemia (Hb ≤5 g/dL) | Single hospital, Tanzania  \*holo-endemic | Oral iron + folic acid versus folic acid  \*All children received antimalarial treatment | Mean Hb (g/dL) | NR | NR | NR | NR |
|  | Subgroup analysis: baseline transfusions  children who had received blood transfusion at baseline (N=40) | | |  |
| at week 2  at week 4  at week 8  at week 12 | 9.4 ± 1.1  9.7 ± 1.5  8.6 ± 2.8  10.1 ± 1.5 | 9.6 ± 2.1  9.9 ± 1.5  8.4 ± 1.8  9.4 ± 2.1 | MD –0.20 [–1.24, 0.84] d  MD –0.20 [–1.13, 0.73] d  MD –0.20 [–1.26, 1.66] d  MD 0.70 [–0.43, 1.83] d | *P =*0.71d  *P =*0.67d  *P =*0.79d  *P =*0.23d |
|  | children who did not receive blood transfusion at baseline (N=56)c | | |  |
| at week 2  at week 4  at week 8  at week 12 | 8.1 ± 1.4  8.9 ± 1.2  9.0 ± 1.8  9.2 ± 1.5 | 8.1 ± 1.4  8.7 ± 1.8  8.1 ± 1.9  9.0 ± 1.5 | MD 0.00 [–0.73, 0.73] d  MD 0.20 [–0.60, 1.00] d  MD 0.90 [–0.07, 1.87] d  MD 0.20 [–0.59, 0.99] d | *P =*1.00d  *P =*0.62d  *P =*0.07d  *P =*0.62d |

CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; MD, mean difference; NR, not reported; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%

**c.** There were four children (two in each arm) that received a transfusion later than day 1 or 2 that were removed from the analysis.

**d.** Calculated post-hoc using RevMan 5.1.2.

### Neonatal and paediatric patients with HIV or AIDS

* + - 1. ESAs (with or without iron)

| Evidence statements – HIV (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal and paediatric patients with HIV, the effect of ESA therapy (with or without iron) compared with no ESA therapy on transfusion volume or incidence is unknown. | NA | NA | NA | NA | NA |
|  | In neonatal and paediatric patients with HIV, the effect of ESA therapy (with or without iron) compared with no ESA therapy on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
|  | In neonatal and paediatric patients with HIV, the effect of ESA therapy (with or without iron) compared with no ESA therapy on mortality is uncertain.  (See evidence matrix D2.T in Volume 2 of the technical report.) | X | NA | NA | √ | √ |
| ES, evidence statement; ESA, erythropoiesis stimulating agent; HIV, human immunodeficiency virus  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

* + - 1. Oral and/or parenteral iron

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

Recommendations and practice points concerning the use of ESAs in HIV-positive children were not made because there was insufficient evidence to support the use of ESAs in this population.

Neonatal and paediatric patients with HIV or AIDS are therefore not discussed Module 6.

The evidence identified during the systematic review and hand-searching process is presented here for completeness.

##### Summary of evidence

###### Level I evidence

One Level I study (Marti-Carvajal 2011) identified from the systematic review and hand-searching process examined the use of ESAs in anaemic patients (no age restrictions) with HIV or AIDS (see **Appendix C, Volume 2**). The authors concluded that rHuEPO compared to placebo does not reduce mortality, transfusion needs or Hb levels (6 RCTs with high risk of bias) anaemic patients with HIV or AIDS. The main characteristics of this review are summarised in **Table 3.2.40**.

Table 3.2.40 Characteristics and quality of Level I evidence – ESAs in paediatric patients with anaemia associated with HIV or AIDS

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Marti-Carvajal 2011271 | Level I  *Good* | People with HIV or AIDS who also have anaemia (Hb <12 g/dL in men, Hb <11 g/dL in women)  6 RCTs, N=537 | rHuEPO or DAR or androgen replacement or vitamin B12 or folic acid versus placebo or other comparator | Transfusion incidence Mortality  Laboratory Measures  QoL |

AIDS, acquired immunodeficiency syndrome; DAR, darbepoetin alpha; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; HIV, human immunodeficiency virus; QoL, health-related quality of life; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin

###### Level II evidence

The systematic review by Marti-Carvajal (2011) identified one Level II study (Rendo 2001) involving 21 children that examined the efficacy of rHuEPO in anaemic HIV-infected children receiving antiretroviral therapy. No additional Level II studies assessing the safety and effectiveness of ESAs in paediatric patients with HIV were identified in the systematic review and hand-searching process.

Rendo (2001) was a multicentre trial conducted in Argentina comparing rHuEPO with placebo. The study was small and had high risk of reporting bias. The main characteristics of this RCT are summarised in **Table 3.2.41**.

Table 3.2.41 Characteristics and quality of Level II evidence – ESAs in paediatric patients with anaemia associated with HIV or AIDS

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Rendo (2001)272 | Level II  *Poor* | Children aged 6 months to 15 years with anaemia (Hb <10.5 g/dL), infected with HIV and receiving antiretroviral therapy  N=21 | rHuEPO (150–250 U/kg, tiw, sc) versus placebo (albumin)  \*All infants administered folic acid (1 mg/day)  \*oral iron (6 mg/kg) administered if serum ferritin fell below 50 ng/dL | Mortality  Laboratory measures (haemoglobin, haematocrit) |

AIDS, acquired immunodeficiency syndrome; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; HIV, human immunodeficiency virus; rHuEPO, recombinant human epoetin; sc, subcutaneous; tiw, three times weekly

##### Results

###### Transfusion incidence or volume

The RCT by Rendo (2001) did not report any usable data for transfusion incidence. This is because responders were reported as those who reached an Hb level of 11.5 g/dL or more and did not receive a transfusion in two consecutive assessments. A response rate of 6/10 (60%) for the rHuEPO group and 1/11 (9%) for the placebo group (*P <*0.02) was reported.

###### Thromboembolic events

There we no RCTs identified in the systematic review or hand-searching process examining the safety or effectiveness of ESAs in paediatric patients with HIV that reported the outcome of thromboembolic events. The RCT by Rendo (2001) reported that ‘no significant side effects were observed in either group’, but further details were not provided.

###### Mortality

One RCT (Rendo 2001) identified in the systematic review and hand-searching process examining the safety or effectiveness of ESAs reported the incidence of mortality in paediatric patients with HIV. **Table 3.2.42** summarises the results from this study.

Mortality was not an outcome of the RCT by Rendo (2001), but the authors reported two deaths (one in each intervention group) when comparing rHuEPO with placebo in children with anaemia due to HIV infection (RR 1.10; 95% CI 0.08, 15.36). The study was small (N=21) and not powered to detect a significant between-group difference for this outcome.

Table 3.2.42 Neonatal and paediatric patients with anaemia associated with HIV or AIDS: Results for ESAs versus no ESAs – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%) | No ESAs ± iron  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Anaemic children with HIV | | | | | | | | | |
| Marti-Carvajal 2011271  Level I/II  *Good* | 1 RCT (Rendo 2001)272  N=21 | Anaemic children with HIV or AIDS receiving antiretroviral therapy | Multicentre, Argentina | rHuEPO + folic acid versus placebo + folic acid  \*oral iron was administered if serum ferritin dropped below 50 ng/dL | Mortality | 1/10 (10.0%) | 1/11 (9.1%) | RR 1.10 [0.08, 15.36] | *No significant difference*  *P =*0.94c |

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; ESA, erythropoiesis stimulating agent; HIV, human immunodeficiency virus; RCT, randomised controlled trial; rHuEPO, recombinant human epoetin; RR, risk ratio.

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Secondary outcomes[[33]](#footnote-33)

Functional or performance status

There we no RCTs identified in the systematic review or hand-searching process examining the safety or effectiveness of ESAs in paediatric patients with HIV that reported functional or performance measures.

Laboratory measures

The RCT by Rendo (2001) reported a significant effect favouring rHuEPO compared to placebo for mean Hb (MD –1.9) and haematocrit (MD –4.3) levels in children with anaemia due to HIV infection but data were incomplete (no SDs provided) (see **Table 3.2.43**).

Table 3.2.43 Neonatal and paediatric patients with anaemia associated with HIV or AIDS: Results for ESAs versus no ESAs – Laboratory measures (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  Mean ± SD | No ESAs ± iron  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Anaemic children with HIV | | | | | | | | | |
| Rendo 2001d 272  Level II  *Poor* | N=21 | Anaemic children with HIV or AIDS receiving antiretroviral therapy | Multicentre, Argentina | rHuEPO + folic acid versus placebo + folic acid  \*oral iron administered if serum ferritin dropped below 50 ng/dL | Mean Hb (g/dL) | 11.7 ± NR | 9.8 ± NR | MD –1.9 [NR] | *Favours rHuEPO*  *P <*0.05c |
| Hct (%) | 36.0 ± NR | 31.7 ± NR | MD –4.3 [NR] | *Favours rHuEPO*  *P <*0.05c |

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; HIV, human immunodeficiency virus; MD, mean difference; NR, not reported; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** *P-*value reported by trial authors.

**d.** Data extracted from abstract only.

### Neonatal and paediatric patients with sickle cell disease

* + - 1. Hydroxyurea

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

|  |  |
| --- | --- |
| Recommendation – sickle cell disease (hydroxyurea) | |
| R4  (Grade B) | In paediatric patients withSCD, 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 R2 and PP22 |
| Practice point – sickle cell disease (hydroxyurea) | | |
| PP22 | In paediatric patients over 9 months of age with sickle cell disease, hydroxyurea may be used to reduce vaso-occlusive pain crises and acute chest syndromes. | |
| PP, practice point; R, recommendation; SCD, sickle cell disease  Note: 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 transcranial Doppler 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 the current recommendations (R2 and R4) and practice points (PP11) can be reassessed. | |

##### Background

People with sickle cell disease have increased blood viscosity and abnormal interactions between the sickled RBCs and other blood components (e.g. leukocytes, platelets and clotting factor); this results in haemolytic anaemia, tissue and organ damage, and vaso-occlusive events that may include painful crises caused by local infarcts or ischaemia. Ultimately, people with sickle cell disease are at increased risk for stroke and acute chest syndrome, and have a lower life expectancy than the general population.

##### Summary of evidence

###### Level I evidence

Three Level I studies (Mulaku 2013,273 Jones 2001,274 Segal 2008275) identified from the systematic review and hand-searching process examined the use of hydroxyurea in children with sickle cell disease, but none provided any usable data for inclusion in this review (see **Appendix C, Volume 2**).

The review by Mulaku (2013)273 was an evidence review of hydroxyurea in people with sickle cell disease, with a view to provide guidance on the use of hydroxyurea in children aged less than 5 years from the perspective of low-income countries. The authors reported data from two RCTs (Wang 2011, Ware 2012) and 16 observational studies; however, due to significant heterogeneity of the studies and outcomes reported, the results were presented as a narrative only (statistical pooling of the results was considered inappropriate). The RCT by Wang (2011) was included in our review but the RCT by Ware (2012) was deemed ineligible for inclusion in our review because it compared hydroxyurea plus phlebotomy with RBC transfusions plus chelation therapy (wrong comparator).

The review by Jones (2001)274 assessed the effects of hydroxyurea in people (adults and children) with sickle cell disease and included two RCTs in their analysis, only one of which was conducted in children (Ferster 1996). This small RCT (N=25) did not report any outcomes included in our review (reported hospitalisation rates, length of stay and fetal Hb levels); therefore, it did not provide any usable data for this review. The authors concluded that hydroxyurea appears to be both effective and safe in adults severely affected by sickle cell disease.

The good-quality review by Segal (2008)275 was a technology assessment report prepared for the Agency for Healthcare Research and Quality that searched for Level I–IV studies that evaluated the effectiveness of hydroxyurea in people with sickle cell disease (adults and children). The authors included the same small RCT in children identified by Jones (2001); therefore, it did not provide any usable data for this review.

###### Level II evidence

Two Level II studies (Jain 2012277, Wang 2011278) identified in the systematic review and hand-searching process examined the use of hydroxyurea compared with no hydroxyurea in infants or children with sickle cell disease (see **Appendix C, Volume 2**). The main characteristics of these RCTs are summarised in **Table 3.2.44**.

The RCT by Jain (2012)277 was a single centre trial conducted in India over a period of 18 months that assessed the safety and efficacy of hydroxyurea compared with placebo in 60 children aged 5 to 18 years with severe sickle cell anaemia.

The RCT by Wang (2011)278 was a multicentre trial conducted in the USA (BABY HUG) that assessed the safety and efficacy of hydroxyurea in infants aged 9–18 months with sickle cell disease, regardless of severity of illness.

One additional report by Thornburg (2012)276 was also identified that provided additional data and subgroup analyses of infants enrolled on the BABY HUG trial.

Table 3.2.44 Characteristics and quality of Level II evidence – hydroxyurea in paediatric patients with sickle cell disease

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Jain (2012)277 | Level II  *Fair* | Children (aged 5–18 years) with severe sickle cell anaemia (more than three episodes of vaso-occlusive crises or blood transfusions per year)  N=60 | Hydroxyurea (10 mg/kg/day) for 18 months versus placebo (powdered glucose capsules) | Transfusion incidence  Laboratory measures (Hb)  Vaso-occlusive events |
| Wang (2011)278 | Level II  *Good* | Infants (aged 9–18 months) with sickle cell anaemia (HbSS) or Hb Sβ⁰thalassemia of all clinical severities  N=193 | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | Transfusion incidence  Stroke  Functional/performance status  Laboratory measures (Hb)  Vaso-occlusive events |

Hb, haemoglobin

##### Results

###### Transfusion incidence and volume

Two RCTs (Jain 2012, Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported on transfusions in paediatric patients with sickle cell disease. **Table 3.2.45** summarises the results from these studies.

The RCT by Jain (2012) reported a significant reduction in the mean number of transfusions per patient per year comparing hydroxyurea with placebo in children aged 5–18 years with sickle cell disease (MD –1.85; 95% CI –2.18, 1.52)

The RCT by Wang (2011) reported a significant reduction in the number of infants aged 9–18 months that required a RBC transfusion over a 2-year period comparing hydroxyurea with placebo (HR 0.55; 95% CI 0.32, 0.96). Further subgroup analysis by Thornburg (2012) showed the effect was significant among infants who were asymptomatic at enrolment (HR 2.7; 95% CI 1.0, 6.9) but not among infants who were symptomatic at enrolment (see **Figure 3.2.17**).

Figure 3.2.17 Subgroup analysis of hydroxyurea versus placebo in paediatric patients with sickle cell disease – one or more RBC transfusions



Table 3.2.45 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  n/N (%)  Mean ± SD | No hydroxyurea  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Jain 2012277  Level II  *Fair* | N=60 | Children aged 5–18 years with severe sickle cell anaemia | Single tertiary care hospital, India | Hydroxyurea (10 mg/kg/day) for 18 months versus placebo (powdered glucose capsules) | Mean number of blood transfusion per patient per year at 18 months (end of study) | 0.13 ± 0.43 (n=30) | 1.98 ± 0.82 (n=30) | MD –1.85 [–2.18, –1.52]c | *Favours hydroxyurea*  *P <*0.001 |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=193 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | Number of children who received a transfusion | 20/96 (20.8%) | 33/97 (34.0%) | RR 0.61 [0.38, 0.99]c  HR 0.55 [0.32, 0.96]d | *Favours hydroxyurea*  *P =*0.04c  *P =*0.03e |
| Total number of transfusions | 35 | 63 |
| Number of transfused children who received two or more transfusions | 7/20 (35%) | 17/33 (52%) | RR 0.68 [0.34, 1.34]c | *No significant difference*  *P =*0.27c |
| Number of children who received a transfusion | Subgroup analysis: cohort of infants from the BABY HUG trial who were asymptomatic at enrolment reported in Thornburg 2012 (N=101) | | | Favours hydroxyurea  *P =*0.04 |
| 6/52 (11.5%) | 14/49 (28.6%) | HR 2.7 [1.0, 6.9]c |
| Transfusions associated with ACS events  \*data displayed as per ACS event (not per patient) | 2/8 (25%) | 12/27 (44%) | RR 0.56 [0.16, 2.01]c | *No significant difference*  *P =*0.38c |

ACS, acute chest syndrome; CI, confidence interval; HR, hazard ratio; MD, mean difference; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Hazard ratios and 95% CIs were generated using a Cox model. *P-*values were generated from log-rank life tests comparing the time to first event between the two treatment groups.

**e.** The authors reported transfusions were marginally more common in the placebo group. It is assumed that transfusion were a secondary endpoint as the level of significance was set at 0.05 for primary endpoints and 0.01 for secondary endpoints.

###### Stroke

One RCT (Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported on the incidence of stroke in paediatric patients with sickle cell disease. **Table 3.2.46** summarises the results from this study.

Wang (2011) reported no significant difference on the incidence of clinical stroke in infants aged 9–18 months that received hydroxyurea over a 2-year period compared with placebo (RR 0.34; 95% CI 0.01, 8.17).

Table 3.2.46 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Stroke

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  n/N (%)  Mean ± SD | No hydroxyurea  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=193 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | Stroke (clinical) | 0/96 (0%) | 1/97 (1.0%) | RR 0.34 [0.01, 8.17]c | *No significant difference*  *P =*0.50c  *P =*0.31d |

CI, confidence interval; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*values reported by trial authors, generated from log-rank life tests comparing the time to first event between the two treatment groups.

###### Secondary outcomes[[34]](#footnote-34)

Functional and performance status

One RCT (Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported functional performance measures in paediatric patients with sickle cell disease. **Table 3.2.47** summarises the results from this study.

Wang (2011) assessed neurodevelopment in infants aged 9–18 months that received hydroxyurea over a 2-year period compared with placebo using the Bayley Development and Vineland Adaptive Behaviour Scales and reported no significant difference between treatment groups for Bayley MDI scores (MD 3; 95% CI –2, 8) and PDI scores (MD 2, 95% CI –3, 7).

Table 3.2.47 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Functional/performance status (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | | Intervention versus comparator | | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  Mean ± SD | No hydroxyurea  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | | |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=158 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | | Mean change in Bayley MDI from baseline at study exit (% difference) | | 1% | –3% | MD 3 [–2, 8] | *No significant difference*  *P =*0.22 |
| Bayley MDI score at 2 years | | 97 ± NR | 94 ± NR |
| Mean change in Bayley PDI from baseline at study exit | | 5% | 2% | MD 2 [–3, 7] | *No significant difference*  *P =*0.37 |
| Bayley PDI score at 2 years | | 101 ± NR | 99 ± NR |

CI, confidence interval; MD, mean difference; MDI, mental and development index; NR, not reported; PDI, psychomotor development index; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

Laboratory measures

Two RCTs (Jain 2012, Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported laboratory measures in paediatric patients with sickle cell disease. **Table 3.2.48** summarises the results from these studies.

Jain (2012) reported a significant increase in Hb levels in children aged 5–18 years with severe sickle cell anaemia who were administered hydroxyurea for 18 months compared with placebo (MD 1.39; 95% CI 1.10, 1.68). A significant increase in mean fetal Hb levels were also reported (MD 5.08, 95% CI 2.13, 8.03).

Wang (2011) reported a significant increase in Hb levels (comparing exit versus entry values) in infants aged 9–18 months with sickle cell anaemia who received hydroxyurea for 2 years compared with placebo (MD 0.9; 95% CI 0.5, 1.3). A significant increase in mean fetal Hb levels were also reported (MD 6.7, 95% CI 4.8, 8.7).

Table 3.2.48 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | | Intervention versus comparator | | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  Mean ± SD | No hydroxyurea  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | | | |
| Jain 2012277  Level II  Fair | N=60 | Children aged 5–18 years with severe sickle cell anaemia and more than 3 episodes of vaso-occlusive crises or blood transfusions per year | Single tertiary care hospital, India | Oral hydroxyurea (10 mg/kg/day) versus placebo (powdered glucose capsules) | | Mean Hb (g/dL) at 18 months (end of study) | | 9.29 ± 0.55 | 7.90 ± 0.58 | MD 1.39 [1.10, 1.68]c | Favours hydroxyurea  *P <*0.001 |
| Mean Hb F (%) at 18 months (end of study) | | 24.00 ± 5.90 | 18.92 ± 5.77 | MD 5.08 [2.13, 8.03]c | Favours hydroxyurea  *P <*0.001 |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=158 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | | Mean difference in Hb (g/dL) from baseline (% difference) | | 3% | –7% | MD 0.9 [0.5, 1.3] | Favours hydroxyurea  *P <*0.0001 |
| Mean Hb (g/dL) at study exit | | 91 ± NR | 86 ±NR | MD –5 [NR] | NR |
| Mean difference in Hb F (%) from baseline (% difference) | | –13% | –37% | MD 6.7 [4.8, 8.7] | Favours hydroxyurea  *P <*0.0001 |
| Mean Hb F (%) at study exit | | 22.4 ± NR | 17.1 ± NR | MD –5.3 [NR] | NR |

CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; Hb F, fetal haemoglobin; MD, mean difference; NR, not reported; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Chronic pain

One RCT (Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported pain events in paediatric patients with sickle cell disease. **Table 3.2.49** summarises the results from this study.

Wang (2011) reported a significant reduction in the number of infants aged 9–18 months who received hydroxyurea over a 2-year period and experienced pain (all reports) compared with placebo (HR 0.59; 95% CI 0.42, 0.83), and in those who experienced pain alone (HR 0.54, 95% CI 0.36, 0.83). The subgroup analysis by Thornburg (2012) revealed that there was no significant difference for these outcomes among those who were asymptomatic at baseline. However, a significant effect favouring hydroxyurea was reported among infants who had more than four pain events (RR 0.32, 95% CI 0.18, 0.56) but not those with two or three pain events (RR 1.06, 95% CI 0.61, 1.86) and favouring placebo in infant who experienced one pain event (RR 1.95; 95% CI 1.12, 3.41) (see **Figure 3.2.18**).

Figure 3.2.18 Subgroup analysis of hydroxyurea versus placebo in paediatric patients with sickle cell disease – chronic pain



Table 3.2.49 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Chronic pain (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  n/N (%)  Mean ± SD | No hydroxyurea  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=193 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | Patients who experienced pain (all reports) | 62/96 (64.6%) | 75/97 (77.3%) | HR 0.59 [0.42, 0.83]c | *Favours hydroxyurea*  *P =*0.002d |
| Number of pain events (all reports) | 177 | 375 |
| Patients who experienced pain alone | 37/96 (38.5%) | 55/97 (56.7%) | HR 0.54 [0.36, 0.83] c | *Favours hydroxyurea*  *P =*0.004d |
| Number of pain alone events | 63 | 121 |
|  | Secondary analysis: cohort of infants from the BABY HUG trial reported in Thornburg 2012 | | |  |
| Incidence of pain events per 100 patient years | 94 | 203 | HR 0.59 | *Favours hydroxyurea*  *P =*0.002d |
| Subjects with 0 pain events | 34/96 (35%) | 22/97 (23%) | RR 1.56 [0.99, 2.46]e | *No significant difference*  *P =*0.06e |
| Subjects with 1 pain event | 29/96 (30%) | 15/97 (15%) | RR 1.95 [1.12, 3.41]e | *Favours placebo*  *P =*0.02e |
| Subjects with 2 or 3 pain events | 20/96 (21%) | 19/97 (20%) | RR 1.06 [0.61, 1.86] e | *No significant difference*  *P =*0.83e |
| Subjects with 4+ pain events | 13/96 (14%) | 41/97 (42%) | RR 0.32 [0.18, 0.56] e | *Favours hydroxyurea*  *P <*0.0001e |
| Pain associated with ACS  \*Data displayed as pain per ACS event (not per patient) | 4/8 (50%) | 7/27 (26%) | RR 1.93 [0.75, 4.95] e | *No significant difference*  *P =*0.17e  *P =*0.23d |
|  | Subgroup analysis: cohort of infants from the BABY HUG trial who were asymptomatic at enrolment reported in Thornburg 2012 (N=101) | | |  |
| Patients who experienced pain (all reports) | 30/52 (57.7%) | 31/49 (63.3%) | HR 1.3 [0.8, 2.1] | *No significant difference*  *P =*0.35 |
| Patients who experienced pain alone | 17/52 (32.7%) | 24/49 (49.0%) | HR 1.6 [0.9, 3.0] | *No significant difference*  *P =*0.14 |

ACS, acute chest syndrome; CI, confidence interval; HR, hazard ratio; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Hazard ratios and 95% CIs were generated using a Cox model.

**d.** *P-*values were generated from log-rank life tests comparing the time to first event between the two treatment groups.

**e.** Calculated post-hoc using RevMan 5.1.2.

Vaso-occlusive events

Two RCTs (Jain 2012, Wang 2011) identified by the systematic review and hand-searching process comparing hydroxyurea with placebo reported vaso-occlusive events in paediatric patients with sickle cell disease. **Table 3.2.50** summarises the results from these studies.

Jain (2012) reported a significant decrease in the mean number of vaso-occlusive crises in children aged 5–18 years with severe sickle cell anaemia who were administered hydroxyurea for 18 months compared with placebo (MD –9.60; 95% CI –10.86, –8.34).

Wang (2011) reported a significant decrease in the number of infants aged 9–18 months with sickle cell anaemia who experienced acute chest syndrome compared to those who received hydroxyurea for 2 years with placebo (HR 0.36; 95% CI 0.15, 0.87). Among those who were asymptomatic at baseline, Thornburg (2012) reported that there was no significant difference between treatment groups for the incidence of acute chest syndrome (HR 2.5; 95% CI 0.7, 9.7), but there was a significant effect favouring hydroxyurea among infants who experienced multiple (2 or 3) acute chest syndrome events (RR 0.13, 95% CI 0.02, 0.99) but not those with one acute chest syndrome event (RR 0.61, 95% CI 0.23, 1. 60) and favouring placebo in infants who experienced zero acute chest syndrome events (RR 1.14; 95% CI 1.02, 1.27) (see **Figure 3.2.19**).

Figure 3.2.19 Subgroup analysis of hydroxyurea versus placebo in paediatric patients with sickle cell disease – acute chest syndrome



Table 3.2.50 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Vaso-occlusive events (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Hydroxyurea  n/N (%)  Mean ± SD | No hydroxyurea  n/N (%)  Mean ± SD | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Jain 2012277  Level II  *Fair* | N=60 | Children aged 5–18 years with severe sickle cell anaemia and more than 3 episodes of vaso-occlusive crises or blood transfusions per year | Single tertiary care hospital, India | Oral hydroxyurea (10 mg/kg/day) versus placebo (powdered glucose capsules) | Mean number of vaso-occlusive crises at 18 months (end of study) | 0.60 ±1.37 | 10.2 ± 3.24 | MD –9.60 [–10.86, –8.34]c | *Favours hydroxyurea*  *P <*0.001d |
| Wang 2011278 (BABY HUG)  Level II  *Good* | N=193 | Infants aged 9–18 months with sickle cell anaemia (HbSS) or sickle beta thalassemia of all clinical severities | 13 centres, USA | Hydroxycarbamide (20 mg/kg/day) for 2 years versus placebo | Patients with ACS | 7/96 (7.3%) | 18/97 (18.6%) | HR 0.36 [0.15, 0.87]c | *Favours hydroxyurea*  *P =*0.02d |
| Number of ACS events | 8 | 27 |
|  | Secondary analysis: infants from the BABY HUG trial reported in Thornburg 2012 | | |  |
| Incidence of ACS events per 100 patient years | 4.2 | 14.6 | HR 0.36C | *Favours hydroxyurea*  *P =*0.02d |
| Subjects with 0 ACS events | 89/96 (93%) | 79/97 (82%) | RR 1.14 [1.02, 1.27]e | *Favours placebo*  *P =*0.02e |
| Subjects with 1 event of ACS | 6/96 (6%) | 10/97 (10%) | RR 0.61 [0.23, 1.60]e | *No significant difference*  *P =*0.31e |
| Subjects with 2 or 3 events of ACS | 1/96 (1%) | 8/97 (8%) | RR 0.13 [0.02, 0.99]e | *Borderline favours hydroxyurea*  *P =*0.05e |
|  | Subgroup analysis: cohort of infants from the BABY HUG trial who were asymptomatic at enrolment reported in Thornburg 2012 (N=101) | | |  |
| Patients with ACS | 3/52 (5.8%) | 7/49 (14.3%) | HR 2.5 [0.7, 9.7]c | *No significant difference*  *P =*0.17d |

ACS, acute chest syndrome; CI, confidence interval; HR, hazard ratio; MD, mean difference; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Hazard ratios and 95% CIs were generated using a Cox model.

**d.** *P-*values were generated from log-rank life tests comparing the time to first event between the two treatment groups.

**e.** Calculated post-hoc using RevMan 5.1.2.

### Neonatal and paediatric patients requiring surgery

* + - 1. ESAs (with or without iron)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Evidence statements – surgical (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
|  | 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 | √ | √√ | √ |
|  | 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 | √ | √√ | √ |
|  | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on transfusion volume is unknown. | NA | NA | NA | NA | NA |
|  | 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 | √ | √ |
|  | 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 |
|  | In paediatric patients undergoing surgery, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
|  | 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 | √ | √ |
|  | In neonatal patients undergoing noncardiac surgery, the effect of ESA therapy (with or without iron) on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Practice point – surgical (erythropoiesis stimulating agents) | |
| 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 | |

##### Background

Blood loss during surgery often necessitates the use of RBC transfusions to assist in recovery. Iron supply may be a limiting factor in erythropoiesis following surgery. This is because iron is one of the main regulators of erythropoiesis. It is therefore essential that preoperative iron stores are adequate, so that patients can respond to the increase in erythropoiesis stimulated by blood loss during surgery.

Where preoperative anaemia is identified, it is important to determine its aetiology, so that appropriate therapy can be given. For example, in iron-deficiency anaemia, iron therapy will correct anaemia, whereas, in anaemia of chronic disease (also known as anaemia of inflammation) and anaemia of renal impairment, the addition of ESAs (e.g. rHuEPO or DAR) may be used. These agents may also be used as a way of raising circulating RBCs either before or after surgery.

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified from the systematic review and hand-searching process that examined the use of ESAs in neonatal and/or paediatric patients requiring surgery (see **Appendix C, Volume 2**).

###### Level II evidence

Three Level II studies (Andropoulos 2013279, Bierer 200994, Fearon 2002) identified in the systematic review and hand-searching process examined the use of ESAs in neonates and infants aged less than 8 years requiring surgery (see **Appendix C, Volume 2**). The main characteristics of these RCTs are summarised in **Table 3.2.51**. None of the RCTs identified assessed the use of ESAs in children aged over 8 years requiring surgery.

The RCT by Androupolous (2013)279 was a single centre Phase I/II trial conducted in the USA that assessed the safety of rHuEPO in 62 neonates scheduled for complex neonatal cardiac surgery. The neuroprotective effect of rHuEPO in the perioperative period was also assessed. The study was limited by changes in rHuEPO dose and antifibrinolytics used during the study.

The RCT by Bierer (2009)94 was a single centre trial conducted in the USA that assessed the safety and efficacy of rHuEPO in stimulating erythropoiesis in neonates scheduled for major surgery (defined as surgery requiring at least 15-minutes of general anaesthesia or surgery where anticipated blood loss was 10 mL/kg or greater). Four out of 20 enrolled neonates had necrotising enterocolitis (an acquired condition related to prematurity) requiring surgical exploration, whereas all others required surgery due to major congenital anomalies. Bierer (2009) was removed from the analysis reported by Aher (2014) for reasons described in **Section 3.2.3**.

The RCT by Fearon (2001)280 was a single centre study conducted in the USA that assessed the safety and efficacy of rHuEPO in reducing the rate of RBC transfusion in infants and small children requiring craniosynostosis repair. A total of 29 children aged less than 8 years were randomised to either receive rHuEPO administered preoperatively for three weeks prior to surgery or no intervention.

Table 3.2.51 Characteristics and quality of Level II evidence – ESAs in neonatal and paediatric patients requiring surgery

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Andropoulos (2013)279 | Level II  *Good* | Neonates (aged <30 days) scheduled for cardiac surgery with hypothermic CPB for >60 minutes  N=59 | rHuEPO (1000 U/kg, iv qd) or rHuEPO (500 U/kg, iv, qad)a versus placebo (normal saline)  \*All infants received antifibrinolytics (aprotinin or ε-aminocaproic acid) | Thromboembolic events  Mortality  Functional or performance status |
| Bierer (2009)94 | Level II  *Poor* | Neonates (aged <28 days) with diagnosis of disease requiring major surgeryb  \*requiring at least 15 minutes of general anaesthesia or where anticipated blood loss was ≥10 mL/kg body weight  N=20 | rHuEPO (200 U/kg/day, iv) or rHuEPO (400 U/kg, sc tiw) for 14 days or until discharge versus placebo (saline or sham)  \*All infants received oral iron supplements (dose not reported) when enteral feeds reached 60 mL/kg/day  \*strict transfusion guidelines were in place | Transfusion incidence and volume  Laboratory measures (Hct) |
| Fearon (2002)280 | Level II  *Poor* | Paediatric patients (aged <8 years) scheduled for primary cranial vault remodelling  N=31 | rHuEPO (600 U/kg, sc qw) for 3 weeks before surgery versus no rHuEPO  \*All infants received oral elemental iron (4 mg/kg/day)  \*strict transfusion guidelines were in place | Transfusion incidence  Laboratory measures (Hb) |

CPB, cardiopulmonary bypass; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; iv, intravenous; NEC, necrotising enterocolitis; qd, once daily; qad, every other day; qw, once per week; rHuEPO, recombinant human epoetin; sc, subcutaneous; tiw, three times weekly

**a.** Initial protocol of rHuEPO 1000 U/kg administered 12–24 hours preoperatively, immediately after CPB, then 24 hours after dose 2 (n=33) was changed to rHuEPO 500 U/kg administered preoperatively and on postoperative days 1 and 3 (n=26) after the Food and Drug Administration (FDA) mandated a dosing regimen change. Similarly, aprotinin was administered to the first 21 patients, but was subsequently suspended so the final 38 patients received ε-aminocaproic acid.

**b.** NEC (n=3 rHuEPO group, n= 1 placebo group), gastroschisis (3, 5), congenital diaphragmatic hernia (2, 1), intestinal atresia (2, 2), tracheoesophageal fistula (0, 1).

##### Results

###### Transfusion incidence and volume

Two RCTs (Bierer 2009, Fearon 2002) identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo reported on transfusion incidence or volume in neonates and infants requiring surgery. **Table 3.2.52** summarises the results from these studies.

Bierer (2009) showed a significant effect favouring placebo for the mean number of transfusions per patient during the 2-week study period (MD 0.70; 95% CI 0.39, 1.01) and also for the mean number of transfusions per patient until discharge (MD 1.60, 95% CI 1.27, 1.93) when comparing rHuEPO with placebo in neonates requiring major surgery (see **Figure 3.2.20** and **Figure 3.2.21**). The authors noted that infants in the rHuEPO group were assessed as more critical that those in the placebo group and that the pilot study was too small to test for between-group differences in transfusions.

Fearon (2002) reported a significant reduction in the number of infants aged less than 8 years that received a transfusion (RR 0.61; 95% CI 0.38, 0.98) and had received rHuEPO and iron in the weeks before craniosynostosis repair compared with those that received iron alone (see **Figure 3.2.22**).

Table 3.2.52 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs (with or without iron) – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs ± iron  n/N (%)  Mean ± SD | No ESAs ± iron  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Bierer 200994  Level II  *Poor* | N=20 | Neonates aged <28 days requiring major surgery | Single hospital, USA | rHuEPO versus placebo  \*Administered for 14 days or until discharge  \*All infants received oral iron supplements when enteral feeds reached 60 mL/kg/day | Mean number of transfusions per patient during study | 0.8 ± 0.3 | 0.1 ± 0.4 | MD 0.70 [0.39, 1.01]c | *Favours placebo*  *P <*0.00001c  *P =*0.07d |
| Mean number of transfusions per patient during hospitalisation | 2.1 ± 0.5 | 0.5 ± 0.2 | MD 1.60 [1.27, 1.93] c | *Favours placebo*  *P <*0.00001c |
| Volume transfused during study (mL/kg) | 17 ± 4 | 4 ± 4 | MD 13.00 [9.49, 16.51] c | *Favours placebo*  *P <*0.00001c |
| Volume transfused during hospitalisation (mL/kg) | 43 ± 15 | 16 ± 7 | MD 27.00 [16.74, 37.26]c | *Favours placebo*  *P <*0.00001c |
| Fearon 2002280  Level II  *Poor* | N=31 | Infants and children aged <8 years scheduled for primary cranial vault remodelling | Single hospital, USA | rHuEPO versus no rHuEPO  \*Administered 3 weeks before surgery  \*All children received oral elemental iron (4 mg/kg/day) | Patients who received a blood transfusion | 8/14 (57.1%) | 14/15 (93.3%) | RR 0.61 [0.38, 0.98]c | *Favours rHuEPO + iron*  *P =*0.03 |

CI, confidence interval; ESA, erythropoiesis stimulating agent; MD, mean difference; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Reported as nonsignificant (*P =*0.07) by Bierer (2009). The authors noted that infants in the rHuEPO group were more critical that those in the placebo group and that the study was too small to test for between-group differences in transfusions.

Figure 3.2.20 ESAs versus no ESAs in neonates requiring major surgery – mean number of transfusions



Figure 3.2.21 ESAs versus no ESAs in neonates requiring major surgery – transfusion volume (mL/kg)



Figure 3.2.22 ESA with iron versus iron alone in infants aged <8 years scheduled for primary cranial vault remodelling – transfusion incidence



###### Thromboembolic events

One RCT (Andropoulos 2013) identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo reported on thromboembolic event in neonates requiring cardiac surgery. **Table 3.2.53** summarises the results from this study.

No studies identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo reported on thromboembolic event in infants, children or adolescents requiring surgery.

Andropoulos (2013) reported no significant between-group differences for the incidence of preoperative (RR 2.53; 95% CI 0.56, 11.53) or postoperative (RR 0.51; 95% CI 0.13, 1.93) cerebral infarction in neonates scheduled for cardiac surgery. There was also no significant between-group differences for the incidence of preoperative (no events in either group) or postoperative (RR 0.84; 95% CI 0.19, 3.84) dural sinovenous thrombosis in in patient population (see **Figure 3.2.23**).

Figure 3.2.23 ESAs versus no ESAs in neonates requiring cardiac surgery – thromboembolic events



Table 3.2.53 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Thromboembolic events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Andropoulos 2013279  Level II  *Good* | N=59 | Neonates aged ≥35 weeks gestation and <30 days, scheduled for cardiac surgery with hypothermic CPB for >60 minutes | USA | rHuEPO versus placebo (normal saline)  \*Administered preoperatively and on postoperative days 1 and 3 | Preoperative cerebral infarction (all) | 6/32 (18.8%) | 2/27 (7.4%) | RR 2.53 [0.56, 11.53]c | No significant difference  *P =*0.23c  *P =*0.269d |
|  | Subgroup analysis: severity | | | *No significant difference* |
| Mild  Moderate  Severe | 4/32 (12.5%)  1/32 (3.1%)  1/32 (3.1%) | 2/27 (7.4%)  0/27 (0%)  0/27 (0%) | RR 1.69 [0.33, 8.51]c  RR 2.55 [0.11, 60.04]c  RR 2.55 [0.11, 60.04]c | *P =*0.53c  *P =*0.56c  *P =*0.56c |
| Postoperative cerebral infarction (all) | 3/32 (9.4%) | 5/27 (18.5%) | RR 0.51 [0.13, 1.93]c | No significant difference  *P =*0.32c  *P =*0.450d |
|  | Subgroup analysis: severity | | | *No significant difference* |
| Mild  Moderate  Severe | 3/32 (9.4%)  0/32 (0%)  0/32 (0%) | 5/27 (18.5%)  0/27 (0%)  0/27 (0%) | RR 0.51 [0.13, 1.93]c  Not estimable  Not estimable | *P =*0.32c  *P =*NA  *P =*NA |
| Preoperative DSVT (all) | 0/32 (0%) | 0/27 (0%) | Not estimable | *No significant difference*  *P =*NA |
| Postoperative DSVT (all) | 3/32 (9.4%) | 3/27 (11.1%) | RR 0.84 [0.19, 3.84] c | *No significant difference*  *P =*0.83c  *P =*0.997d |
|  | Subgroup analysis: severity | | | *No significant difference* |
| Mild  Moderate  Severe | 2/32 (6.3%)  1/32 (3.1%)  0/32 (0%) | 2/27 (7.4%)  1/27 (3.7%)  0/27 (0%) | RR 0.84 [0.13, 5.60]c  RR 0.84 [0.06, 12.86]c  Not estimable | *P =*0.86c  *P =*0.90c  *P =*NA |

CI, confidence interval; CPB, cardiopulmonary bypass; DSVT, dural sinovenous thrombosis; ESA, erythropoiesis stimulating agent; NA, not applicable; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value reported by trial authors.

###### Mortality

One RCT (Andropoulos 2013) identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo reported mortality in neonates requiring cardiac surgery. **Table 3.2.54** summarises the results from this study.

There were no studies identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo that reported on mortality in infants, children or adolescents requiring surgery.

Andropoulos (2013) reported no significant between-group differences for the incidence of mortality (RR 0.84; 95% CI 0.19, 3.84), but the study was small and not powered to detect a significant difference for this outcome.

Table 3.2.54 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Andropoulos 2013279  Level II  *Good* | N=59 | Neonates aged ≥35 weeks gestation and <30 days, scheduled for cardiac surgery with hypothermic CPB for >60 minutes | USA | rHuEPO versus placebo (normal saline)  \*Administered preoperatively and on postoperative days 1 and 3 | Mortality | 3/32 (9.4%) | 3/27 (11.1%) | RR 0.84 [0.19, 3.84]c | *No significant difference*  *P =*0.83c |

CI, confidence interval; CPB, cardiopulmonary bypass; ESA, erythropoiesis stimulating agent; NR, not reported; rHuEPO, recombinant human epoetin; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Secondary outcomes[[35]](#footnote-35)

Functional/performance status

One RCT (Andropoulos 2013) identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo reported functional/performance measures in neonates requiring cardiac surgery. **Table 3.2.55** summarises the results from this study.

There were no studies identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo that reported functional/performance measures in infants, children or adolescents requiring surgery.

Andropoulos (2013) assessed neurodevelopment in neonates administered rHuEPO compared to no rHuEPO using the Bayley Scales of Infant and Toddler Development (Third Edition) but the study was not powered to detect a significant difference for this outcome. The authors reported both the primary composite scores (cognitive, language and motor development) and the social-emotional and adaptive behavioural composite scores (social-emotional, behavioural, conceptual, social and practical) and reported no significant between-group differences at 12 months follow-up for any measure (see **Figure 3.2.24**).

Andropoulos (2013) also reported subgroup analyses for 12-month Bayley III scores for the primary composite scores (cognitive, language, and motor) according to anatomic/surgical group (data not shown), use of aprotinin (see **Figure 3.2.25**) and rHuEPO dose (see **Figure 3.2.26**), and found no statistically significant differences between treatment groups apart from a higher Bayley III cognitive score in the placebo group in patients who did not receive aprotinin.

Table 3.2.55 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Functional / performance status (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  Mean ± SD  Median (IQR) | No ESAs  Mean ± SD  Median (IQR) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Andropoulos 2013279  Level II  Good | N=42 | Neonates aged ≥35 weeks gestation and <30 days, scheduled for cardiac surgery with hypothermic CPB for >60 minutes | USA | rHuEPO versus placebo (normal saline)  \*Administered preoperatively and on postoperative days 1 and 3 | Bayley III composite score at 12 months follow-up |  |  |  |  |
| cognitive | 101.1 ± 13.6 | 106.3 ± 10.8 | MD –5.20 [–12.60, 2.20]c | *No significant difference*  *P =*0.187 |
| language | 88.5 ± 12.8 | 92.4 ± 12.4 | MD –3.90 [–11.53, 3.73]c | *No significant difference*  *P =*0.329 |
| motor | 89.9 ± 12.3 | 92.6 ± 14.1 | MD –2.70 [–10.74, 5.34]c | *No significant difference*  *P =*0.506 |
| social-emotionald | 95.0 (92.5, 105.0) | 100.0 (96.3, 108.8) | NR | *No significant difference*  *P =*0.249 |
| behavioural | 93.2 ± 10.7 | 97.3 ± 15.7 | MD –4.10 [–12.31, 4.11]c | *No significant difference*  *P =*0.342 |
| conceptual | 98.7± 13.6 | 99.2 ± 13.1 | MD –0.50 [–8.58, 7.58]c | *No significant difference*  *P =*0.906 |
| social | 97.2 ± 11.4 | 100.7 ± 15.6 | MD –3.50 [–11.83, 4.83]c | *No significant difference*  *P =*0.423 |
| practical | 89.5 ± 9.1 | 92.8 ± 12.6 | MD –3.30 [–10.00, 3.40]c | *No significant difference*  *P =*0.352 |
|  | The authors reported a subgroup analysis of 12-month Bayley III scores for measures of cognitive, language, and motor skill by anatomic/surgical group (HLHS, D-TGA, AA+VSD/other), use of aprotinin, and rHuEPO dose. No statistically significant differences between treatment groups were observed except a higher Bayley III cognitive score in the placebo group in patients who did not receive aprotinin. | | |  |

AA+VSD, hypoplastic aortic arch/ventricular septal defect; CI, confidence interval; CPB, cardiopulmonary bypass; D-TGA, dextrotransposition of the great arteries; ESA, erythropoiesis stimulating agent; HLHS, hypoplastic left heart syndrome; IQR, interquartile range; MD, mean difference; NR, not reported; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Data not normally distributed.

Figure 3.2.24 ESAs versus no ESAs in neonates requiring cardiac surgery – Bayley III scores at 12-months follow-up



**a.** Authors reported the median (IQR) for this outcome as data were not normally distributed.

Figure 3.2.25 ESAs versus no ESAs in neonates requiring cardiac surgery – Bayley III scores at 12-months follow-up (subgroup analysis by use of aprotinin)



Figure 3.2.26 ESAs versus no ESAs in neonates requiring cardiac surgery – Bayley III scores at 12-months follow-up (subgroup analysis by rHuEPO dose)



Laboratory measures

One RCT (Fearon 2002) identified in the systematic review and hand-searching process comparing rHuEPO plus iron with iron alone reported laboratory measures in neonates requiring cardiac surgery. Fearon (2002) reported a statistically significant mean change in Hb level (g/dL) from baseline observed in the rHuEPO group (MD 1.0) compared with no change in Hb level from baseline in the control group (MD 0.0); however, a comparison between treatment groups was not reported and data were incomplete, preventing further analysis (no SDs provided). **Table 3.2.56** summarises the results from this study.

Table 3.2.56 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Laboratory measures (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Fearon 2002280  Level II  *Poor* | N=31 | Infants and children aged <8 years scheduled for primary cranial vault remodelling | Single hospital, USA | rHuEPO versus no rHuEPO  \*Administered 3 weeks before surgery  \*All children received oral elemental iron (4mg/kg/day) | Mean Hb (g/dL) post-treatment | 13.1 ± NR | 11.8 ± NR | MD –1.3 [NR] | NR |
| Mean change in Hb (g/dL) pre- and post-treatment | 1.0 ± NR | 0.0 ± NR | MD 1.0 [NR] | NR |

CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; MD, mean difference; NR, not reported; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

* + - 1. Oral and/or parenteral iron

| Evidence statements – surgical (oral and/or parenteral iron) | | **Evidence** | **Consistency** | | | **Clinical impact** | | **Generalisability** | | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 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 | |
|  | 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 | | | | | | | | | | |

|  |  |  |
| --- | --- | --- |
| Recommendation – surgical (oral and/or parenteral iron) | | |
| R5  (Grade C) | In surgical paediatric patients with or at risk of iron-deficiency anaemia, preoperative iron therapy is recommended.a  a See R4 in *Patient Blood Management Guidelines: Module 2 – Perioperative*15 | |
| 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 haemoglobin b See Appendix G(*Paediatric Hb 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 haemoglobin and iron stores. |
| AI, adequate intake; PP, practice point; R, recommendation; RBC, red blood cell; RDI, recommended daily intake; RNI, recommended nutrient intake | | |

##### Summary of evidence

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of oral and/or parenteral iron compared with no iron or placebo in neonatal and/or paediatric patients requiring surgery.

### Critically ill neonatal and paediatric patients

* + - 1. ESAs (with or without iron)

| Evidence statements – critically ill (ESAs with or without iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Practice point – critically ill (erythropoiesis stimulating agents) | |
| 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*84 |
| ESA, erythropoiesis stimulating agent; PP, practice point; R, recommendation; | |

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified from the systematic review and hand-searching process that examined the use of ESAs compared with placebo or no ESAs in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**).

###### Level II evidence

There were no RCTs identified in the systematic review and hand-searching process that assessed the use of ESAs in critically ill neonates.

Two Level II studies 281,282 identified in the systematic review and hand-searching process examined the use of ESAs in critically ill infants, children or adolescents (see **Appendix C, Volume 2**). The main characteristics of these RCTs are summarised in **Table 3.2.57**.

The RCT by Chicella (2006)281 was a single centre study conducted in the USA that assessed the safety and efficacy of rHuEPO in reducing the rate of RBC transfusion in critically ill infants and children admitted to a single paediatric intensive care unit (PICU) and diagnosed with anaemia (defined as Hct <30%). A total of 27 patients aged 1 month to 13 years were randomised to receive either rHuEPO (mean age 23 months) or placebo (mean age 29 months). All infants received iron.

The RCT by Jacobs (2003)282 was a single centre study conducted in the USA that assessed the safety and efficacy of rHuEPO in reducing the rate of RBC transfusion in critically ill infants who were diagnosed with bronchiolitis, acute respiratory failure and anaemia (defined as Hct <2 SD below normal for age). A total of 44 patients aged 1 month to 2 years were randomised to receive either rHuEPO (mean age 3.5 months) or placebo (mean age 2.7 months). All infants were administered iron. The study was stopped early after an interim analysis revealed that significantly higher enrolment target was needed to detect a significant difference between treatment groups for the primary outcome measure.

Table 3.2.57 Characteristics and quality of Level II evidence – ESAs in critically ill paediatric patients

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Chicella (2006)281 | Level II  *Poor* | Critically ill children (aged ≤18 years) admitted to PICU with anaemia (defined as Hct ≤30 %)  N=27 | rHuEPO (300 U/kg/day, iv) versus placebo (saline)  \*All infants received oral iron (6 mg/kg/day, ferrous sulphate)  \*no specified transfusion protocol | Transfusion incidence  Laboratory measures (Hct) |
| Jacobs (2003)282 | Level II  *Fair* | Critically ill infants (aged 1 month to 2 years) diagnosed with bronchiolitis, acute respiratory failure and anaemia  N=44 | rHuEPO (200 U/kg/day, iv) versus placebo (albumin)  \*All infants received enteral elemental iron (3 mg/kg/day)  \*Transfusion guidelines were in place | Transfusion incidence and volume  Mortality  Laboratory measures (Hct, ferritin) |

ESA, erythropoiesis stimulating agent; Hct, haematocrit; iv, intravenous; PICU, paediatric intensive care unit; rHuEPO, recombinant human epoetin; U, unit

##### Results

###### Transfusion incidence and volume

Two RCTs 281,282 identified in the systematic review and hand-searching process comparing rHuEPO with placebo reported on transfusion incidence or volume in critically ill infants and children. **Table 3.2.58** summarises the results from these studies.

Both Chicella (2006)281 and Jacobs (2003)282 reported no significant difference between treatment groups for the incidence of RBC transfusions (RR 0.70; 95% CI 0.19, 2.54 and RR 0.91; 95% CI 0.49, 1.69, respectively) or the mean number of transfusions per patient (MD –0.40; 95% CI –1.09, 0.29 and MD –0.10; 95% CI –0.22, –0.02, respectively) when comparing rHuEPO with placebo in critically ill paediatric patients.

The study by Jacobs (2003)282 may not be sufficiently powered to detect a significant difference for this outcome, given that the study was stopped early after the interim analysis revealed no difference between groups for the primary outcome of number of RBC transfusions. The authors calculated that a total of 98 patients would be required to detect a significant difference between groups for this outcome; however, the interim results suggested that more than 3000 patients would be needed.

Jacobs (2003)282 also reported no significant difference between treatment groups for the mean volume of RBC transfused (*P =*NR); however, our analysis using the values reported suggests a significant effect in favour of rHuEPO (with iron) for reducing the volume of RBC transfused (MD –0.80; 95% CI –1.13, 0.47) in critically ill paediatric patients. The reasons for this discrepancy were not determined.

A meta-analysis was conducted to evaluate the effectiveness of rHuEPO compared with placebo on reducing the need for RBC transfusion in critically ill infants and children (see **Figure 3.2.27** and **Figure** **3.2.28**). The analysis showed that the administration of ESAs did not significantly alter the incidence of RBC transfusions (RR 0.86; 95% CI 0.49, 1.51) or affect the mean number of RBC transfusions per patient (MD –0.11; 95% CI –0.23, 0.01) in critically ill infants and children. There was no significant heterogeneity for either outcome (I2=0%).

Table 3.2.58 Critically ill paediatric patients: Results for ESAs versus no ESAs – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | Statistical significance  P-value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Chicella 2006281  Level II  *Poor* | N=27 | Critically ill children aged ≤18 years with Hct ≤30 % | Single PICU, USA | rHuEPO versus placebo (normal saline)  \*All children received oral ferrous sulphate (6 mg elemental iron/kg/day) | Patients who received a RBC transfusion | 3/14 (21%) | 4/13 (31%) | RR 0.70 [0.19, 2.54]c | *No significant difference*  *P =*0.68 |
| Mean number RBC transfusions per patient | 0.2 ± 0.4 | 0.6 ± 1.2 | MD –0.40 [–1.09, 0.29]c | *No significant difference*  *P =*0.49 |
| Jacobs 2003282  Level II  Fair | N=44 | Critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure and anaemia | Single PICU, USA | rHuEPO versus placebo (albumin)  \*All children received enteral elemental iron (3 mg/kg/day) | Patients who received one or more RBC transfusions | 10/22 (45.5%) | 11/22 (50.0%) | RR 0.91 [0.49, 1.69]c | *No significant difference*  *P =*0.76c |
| Mean number RBC transfusions per patient | 0.6 ± 0.2 | 0.7 ± 0.2 | MD –0.10 [–0.22, 0.02]c | *No significant difference*  *P =*0.10c |
| Mean volume RBC transfused (mL/kg) | 9.6 ± 0.5 | 10.4 ± 0.6 | MD –0.80 [–1.13, –0.47]c | *No significant difference*  *P >*0.05d |

CI, confidence interval; ESA, erythropoiesis stimulating agent; Hct, haematocrit; MD, mean difference; PICU, paediatric intensive care unit; RBC, red blood cell; rHuEPO, recombinant human epoetin; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value as reported by trial authors.

Figure 3.2.27 Meta-analysis: ESAs versus no ESAs in critically ill paediatric patients – transfusion incidence



Figure 3.2.28 Meta-analysis: ESAs versus no ESAs in critically ill paediatric patients – mean number of transfusions



###### Thromboembolic events

There were no studies identified in the systematic review and hand-searching process that assessed the safety or effectiveness of ESA treatment (with or without iron supplementation) in critically ill paediatric patients and reported thromboembolic events.

###### Mortality

One RCT (Jacobs 2003) identified in the systematic review and hand-searching process reported the incidence of mortality in critically ill infants comparing rHuEPO with placebo. **Table 3.2.59** summarises the results from this study.

There were no studies identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo that reported on mortality in critically ill neonates, children or adolescents.

Mortality was not an outcome of the RCT by Jacobs (2003), but the authors reported that there were no deaths in either group when comparing rHuEPO with placebo in critically ill infants (0/22 versus 0/22). The study was too small (N=44) and not powered to detect a significant between-group difference for this outcome.

Table 3.2.59 Critically ill paediatric patients: Results for ESAs versus no ESAs – Mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Jacobs 2003282  Level II  Fair | N=44 | Critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure and anaemia. | Single PICU, USA | rHuEPO versus placebo (albumin)  \*All children received enteral elemental iron (3 mg/kg/day) | Mortality | 0/22 (0%) | 0/22 (0%) | NA | *Not estimable*  *P =*NA |

CI, confidence interval; ESA, erythropoiesis stimulating agent; NA, not applicable; PICU, paediatric intensive care unit; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Secondary outcomes[[36]](#footnote-36)

Functional or performance status

There were no studies identified in the systematic review and hand-searching process comparing rHuEPO with no rHuEPO or placebo that reported on functional or performance status in critically ill neonatal and/or paediatric patients.

Laboratory measures

Two RCTs (Chicella 2006, Jacobs 2003) identified in the systematic review and hand-searching process comparing rHuEPO with placebo reported laboratory measures (Hct, ferritin) in critically ill infants and children. **Table 3.2.60** summarises the results from these studies.

Chicella (2006) reported no significant difference between treatment groups for mean change in Hct (%) from baseline to discharge (MD 2.70; 95% CI –0.44, 5.84) or the final Hct (MD 3.50; 95% CI 0.28, 6.72) when comparing rHuEPO with placebo in critically ill infants and children aged <18 years.

Jacobs (2003) reported an effect favouring rHuEPO for mean change in Hct (%) from admission to discharge (MD 2.70; 95% CI 2.15, 3.25) but not serum ferritin (MD –5.20; 95% CI –18.73, 8.33) when comparing rHuEPO with placebo in critically ill infants aged <2 years.

Table 3.2.60 Critically ill paediatric patients: Results for ESAs versus no ESAs – Laboratory measures (Hb, Hct, ferritin) (secondary outcome)

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ESAs  n/N (%)  Mean ± SD | No ESAs  n/N (%)  Mean ± SD | Risk estimate (95% CI) | Statistical significance  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Chicella 2006281  Level II  *Poor* | N=27 | Critically ill children aged ≤18 years with Hct ≤30% | Single PICU, USA | rHuEPO versus placebo (normal saline)  \*All children received oral ferrous sulphate (6 mg elemental iron/kg/day) | % Hct change | 3.9 ± 4 | 1.2 ± 4.3 | MD 2.70 [–0.44, 5.84]c | *No significant difference*  *P =*0.14 |
| Final Hct | 30.3 ± 3.6 | 26.8 ± 4.8 | MD 3.50 [0.28, 6.72]c | *No significant difference*  *P =*0.06 |
| Jacobs 2003282  Level II  *Fair* | N=44 | Critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure and anaemia | Single PICU, USA | rHuEPO versus placebo (albumin)  \*All children received enteral elemental iron (3 mg/kg/day) | Mean change in Hct (%) from admission to discharge | 7.1 ± 1.0 | 4.4 ± 0.85 | MD 2.70 [2.15, 3.25]c | *Favours rHuEPO + iron*  *P <*0.00001c |
| Mean change in serum ferritin from admission to discharge (ng/mL) | 16.3 ± 20.15 | 21.5 ± 25.35 | MD –5.20 [–18.73, 8.33]c | *No significant difference*  *P =*0.45c |

CI, confidence interval; ESA, erythropoiesis stimulating agent; Hb, haemoglobin; Hct, haematocrit; MD, mean difference; PICU, paediatric intensive care unit; rHuEPO, recombinant human epoetin; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Oral and/or parenteral iron

| Evidence statements – critically ill (oral and/or parenteral iron) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| Practice point – oral and/or parenteral iron | |
| PP27 | Critically ill paediatric patients should receive iron supplementation as necessary to achieve the RNI. |

##### Summary of evidence

There were no studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of oral and/or parenteral iron in critically ill neonatal and/or paediatric patients.

## Question 3

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

|  |  |
| --- | --- |
| Recommendation –FFP, cryoprecipitate, fibrinogen concentrate, and/or platelets | |
| R6 (Grade C) | In neonatal and paediatric patients requiring cardiac surgery, the *routine* use of an FF*P-*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 –FFP, cryoprecipitate, fibrinogen concentrate, and/or platelets | |
| 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 toa   * *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011)283 * *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*15 * *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis* (2004)284 * *AHCDO guidelines for patients with specific factor deficiencies* (www.ahcdo.org.au) * TTP: *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant* (2004)285   a See PP17 from *Patient Blood Management Guidelines: Module 3 – Medical*14 |
| 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 x 109/L in the absence of risk factors, and at <20 x 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*14 |
| FFP, fresh frozen plasma; PP, practice point; R, recommendation | |

|  |  |
| --- | --- |
| Expert opinion points – FFP, cryoprecipitate, fibrinogen concentrate, and/or platelets | |
| 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. |
| 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. |
| EOP3 | In general, neonatal and paediatric patients with a platelet count ≥ 50 X 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 *Patient Blood Management Guidelines: Module 2 – Perioperative*15 |
| EOP, expert opinion point; FFP, fresh frozen plasma; INR, international normalised ratio; POC, point of care; PP, practice point | |

|  |
| --- |
| Evidence gaps and areas for future research |
| In the neonatal and paediatric population in general there is a need for further research on:   * 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. |

### Background

The systematic review examined the evidence for 5 interventions that aim to improve haemostasis in neonatal and paediatric patients: (1) FFP; (2) cryoprecipitate; (3) fibrinogen concentrate; (4) platelets; and (5) a combination of these products.

FFP contains all the coagulation factors present in normal plasma and is primarily transfused in neonatal or paediatric patients who have abnormal coagulation test results, under the assumption that these tests accurately predict bleeding and that transfusion will reduce that risk. FFP may also be used in patients requiring medical care for oncology, cardiac, transplantation, orthopaedic, burns, c**r**aniofacial surgery, ECMO (extracorporeal membrane oxygenation) or ECLS (extracorporeal life support) and trauma.

Fibrinogen (also called factor I) is a blood plasma protein produced by the liver that is important in blood coagulation. Assessment of fibrinogen deficiency is made through a fibrinogen level blood test that measures the concentration (g/L) of fibrinogen in the blood. Both cryoprecipitate and fibrinogen concentrate are used in patients with hypofibrinogenaemia, under the assumptions that low fibrinogen levels accurately predict bleeding, and that transfusion will reduce that risk. Primary triggers for transfusion of cryoprecipitate are haemostatic support during massive blood loss episode, low fibrinogen and active bleeding before or during an invasive procedure, dysfibrinogenaemia and active bleeding before or during an invasive procedure.

Platelet transfusions are frequently used to correct thrombocytopenia in critically ill patients. The pretransfusion platelet count is the primary measure in initiating a transfusion episode. Primarytriggers for transfusion of platelets are low platelet count and active bleeding prior to or during an invasive procedure, prophylaxis post chemotherapy or bone marrow transplant, known or suspected disorder (acquired or inherited) affecting platelet function and active bleeding before or during an invasive procedure.

A combination of FFP, cryoprecipitate, platelet and fibrinogen in bleeding patients may be used if bleeding continues after attempted surgical haemostasis fails, and when the coagulation tests are abnormal or the platelet count reduced.

There is controversy over the benefits of using these blood products to improve haemostasis in both procedural and nonprocedural settings. The use of these interventions may be associated with infection, allergic reactions, haemolysis, transfusion-related circulatory overload (TACO) and transfusion-related acute lung injury (TRALI). The review aimed to establish whether such products provide a clinical benefit on patient outcomes.

### Methods

The systematic review examined the evidence for FFP, cryoprecipitate, fibrinogen concentrate, and platelet concentrates in neonatal and paediatric patients, with a focus on four specific population groups: (1) preterm infants (aged <37 weeks gestational age) and infants (aged 0–23 months); (2) a general population of neonatal and paediatric patients undergoing medical care; (3) neonatal and paediatric patients undergoing surgery; and (4) critically ill neonatal and paediatric patients (see **Section 4.1**).

In preterm infants and infants, two separate comparisons were assessed: (1) FFP compared with no FFP (or a different FFP transfusion strategy); and (2) platelet transfusion compared with no platelet transfusion (or a different platelet transfusion strategy).

In neonatal and paediatric patients under medical care, one comparison was assessed: (1) platelet transfusion compared with no platelet transfusion (or a different platelet transfusion strategy).

In neonatal and paediatric patients undergoing surgery and in critically ill neonatal and paediatric patients, five separate comparisons were assessed: (1) FFP compared with no FFP (or a different FFP transfusion strategy); (2) cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate transfusion strategy); (3) platelet transfusion compared with no platelet transfusion (or a different platelet transfusion strategy); (4) fibrinogen concentrate compared with no fibrinogen concentrate (or a different fibrinogen transfusion strategy); and (5) a combination of FFP, cryoprecipitate, fibrinogen concentrate of platelets compared with a different combination.

For this question, the only evidence that was considered was Level III–2 or higher, published after 1995 (see **Section 3.1.2** for details on the levels of evidence for intervention studies). Articles published before 1995 that had been included in a Level I study were included in the review. A search of lower level evidence was only conducted for primary outcomes not addressed in higher level evidence (see **Section 2.3**). Secondary outcomes were only extracted from studies that reported one or more primary outcomes.

Overall, the systematic review and hand-searching process identified two Level I studies, six Level II studies and seven Level III studies that evaluated the use of FFP, cryoprecipitate, fibrinogen concentrate or platelet transfusion in neonatal and paediatric patients and reported primary outcomes relevant to our research questions.

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

### Preterm and low birth weight infants

* + - 1. Fresh frozen plasma

| Evidence statements – preterm and low birth weight infants (fresh frozen plasma) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √ |
|  | 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 | √√√ | √ |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study 286 that reported the effect of FFP transfusion strategies in preterm and term infants (see **Appendix C, Volume 2**). The main characteristics of this review are summarised in **Table 3.3.1.**

Osborn (2004)286 was a good-quality systematic review that examined the effect of early volume expansion on morbidity and mortality in very preterm infants. Four RCTs (Beverley 1985287; Ekblad 1992288; Gottuso 1976289; NNNI 1996a290) and one 2-year follow-up report (NNNI 1996b291) were identified that were relevant to our research question, and compared FFP with control (either no treatment or maintenance fluid). The included studies enrolled patients on the basis of prematurity, not haemodynamic compromise, and were generally small, single centre studies; with three RCTs each enrolling between 40–80 patients. The largest study was the Northern Neonatal Nursing Initiative (NNNI) trial290 that was conducted in 18 maternity units across the UK. As this trial contributed the majority of the data, the published reports of this study 290,291 were retrieved for further assessment.

**Table 3.3.2** summarises the main characteristics of the Level II studies assessed by Osborn (2004). The review authors concluded that there was no evidence to support the routine use of early volume expansion in preterm infants on the basis of gestational age or birth weight in the first days after birth.

Table 3.3.1 Characteristics and quality of Level I evidence – FFP in preterm and low birth weight infants

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Osborn  (2004)286 | Level I  *Good* | Preterm infants (≤32 weeks gestational age) or VLBW infants (≤1500 g), aged <72 hours old  8 RCTs, N=940 | Early volume expansion versus no volume expansion or another form of volume expansion  \*includes normal saline, FFP, albumin, plasma substitutes or blood | Mortality  Bleeding events |

FFP, fresh frozen plasma; RCT, randomised controlled trial; VLBW, very low birth weight.

###### Level II evidence

The systematic review and hand-searching process identified no additional Level II studies that examined the effect of FFP transfusion strategies in preterm infants (see **Appendix C, Volume 2**).

###### Level III evidence

The systematic review and hand-searching process identified no Level III studies that examined the use of FFP transfusion strategies in preterm infants (see **Appendix C, Volume 2**).

Table 3.3.2 Characteristics and quality of Level II evidence – FFP in preterm and low birth weight infants

| Study ID | Study type  *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Identified and assess by Osborn (2004) | | | | |
| Beverly (1985)287 | Level II  *Adequate* | Preterm infants (<32 weeks gestational age) or <1500 g  N=80 | FFP (10 mL/kg) on admission and at 24 hours of age (n=38) versus control (no treatment) (n=42) | Bleeding events |
| Ekblad (1991)288 | Level II  *Unclear* | Preterm infants (<30 and 30–34 weeks gestational age) and <5 hours old  N=40 | FFP (10 mL/kg) over 2 hours, daily for 3 days (n=21) versus control (no treatment) (n=19) | Bleeding events |
| Gottuso (1976)289 | Level II  *Adequate* | Preterm infants  Group 1: 700–1000 g, < 24 hours old  Group 2: 1001–2000 g, < 24 hours old  Group 3: >1000 g, any age with partial thromboplastin time > 60 s, and acidosis or hypoxia in 60% inspired oxygen  N=59 | FFP (15 mL/kg) (n=26) versus control (supportive care only) (n=33) | Mortality  Bleeding events |
| NNNI (1996a)290 | Level II  *Adequate* | Preterm infants (<32 weeks gestational age), <2 hours old  N=515a | FFP (20 mL/kg over 15 minutes then 10 mL/kg at 24 hours) (n=257) versus gelatin plasma substitute (n=261) versus control (maintenance fluids) (n=258) | Mortality  Bleeding events |
| NNNI (1996b)291  \*2-year follow-up | Level II  *Adequate* | Preterm infants (<32 weeks gestational age), <2 hours old  N=515a | FFP (20 mL/kg over 15 minutes then 10 mL/kg at 24 hours) (n=257) versus gelatin plasma substitute (n=261) versus control (maintenance fluids) (n=258) | Mortality  Bleeding events |

FFP, fresh frozen plasma; NNNI, Northern Neonatal Nursing Initiative

**a.** NNNI (1996) was a three-arm trial. Only FFP versus control **(**glucose as 10% dextrose or dextrose saline) is reported here.

##### Results

###### Mortality

The systematic review and hand-searching process identified one good-quality Level I study (Osborn 2004) that assessed the incidence of mortality in preterm infants administered FFP compared with no FFP or placebo. Additional data from the RCT conducted by the NNNI (NNNI 1996a, NNNI 1996b) was retrieved and included in our review. **Table 3.3.3** summarises the results from these studies.

The systematic review by Osborn (2004) conducted a meta-analysis of three RCTs (Beverley 1985, Gottuso 1976, NNNI 1996a) involving 654 preterm infants and reported no significant difference between treatment groups comparing FFP with no FPP (RR 1.05; 95%CI 0.81, 1.36). There were 76 (23.7%) deaths in the FFP group compared with 78 (23.4%) deaths in the control group. There was no significant heterogeneity for this outcome (I2=0%).

The large multicentre trial conducted by the NNNI (NNNI 1996a) reported no significant difference in mortality before 6 weeks (RR 1.00; 95%CI 0.68, 1.48) or before discharge (RR 1.05; 95%CI 0.73, 1.50). Subgroup analyses were performed for cause-specific mortality before discharge, which also showed no significant difference in mortality due to respiratory distress (RR 0.97; 95%CI 0.59, 1.60), IVH (RR 1.88; 95%CI 0.81, 4.36), NEC (RR 0.72; 95%CI 0.23, 2.23) or other (RR 0.50; 95%CI 0.09, 2.72).

NNNI (1996b) was a follow-up of survivors from NNNI (1996a) 2 years post intervention. There were no significant differences in overall mortality before 2 years of age (RR 1.02; 95%CI 0.73, 1.43); neonatal mortality before 4 weeks of age (RR 0.93; 95%CI 0.63, 1.39) or infant mortality between 1 and 23 months (RR 1.41; 95%CI 0.64, 3.11). Subgroup analyses were performed for cause-specific mortality in infants aged 1–23 months. There were no significant difference in mortality due to chronic lung disease (RR 1.41; 95%CI 0.45, 4.37), sudden unexpected death (RR 4.02; 95%CI 0.45, 35.68), infection (RR 1.00; 95%CI 0.14, 7.07) or other causes (RR 0.50; 95%CI 0.05, 5.50).

Table 3.3.3 Preterm infants: Results for FFP versus no FFP – mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%) | No FFP  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| **Level I evidence** | | | | | | | | | |
| Osborn 2004286  Level I  *Good* | 3 trials (Beverley 1985,287 Gottuso 1976,289 NNNI 1996a290)  N=654 | Preterm infants (≤ 32 weeks gestation) or ≤ 1500 g and aged ≤ 72 hours | NR | FFP versus no FFP | Mortality | 76/321 (23.7%) | 78/333 (23.4%) | RR 1.05 [0.81, 1.36] | *No significant difference*  *P =*0.69  No significant heterogeneity  I2 = 0% |
| **Level II evidence** | | | | | | | | | |
| NNNI 1996a290  Level II  *Fair* | N=515 | Preterm infants (≤ 32 weeks gestation), aged ≤ 2 hours | Multicentre, UK | FFP versus dextrose c | Mortality before 6 weeks | 43/257 (16.7%) | 43/258 (16.7%) | RR 1.00 [0.68, 1.48]d | *No significant difference*  *P =*0.98d |
| Mortality before discharge (all patients) | 49/257 (19.1%) | 47/258 (18.2%) | RR 1.05 [0.73, 1.50]d | *No significant difference*  *P =*0.80d |
|  | *Subgroup analysis: Cause-specific mortality before discharge* | | | |
| due to respiratory distress (no IVH) | 27/257 (10.5%) | 28/258 (10.9%) | RR 0.97 [0.59, 1.60]d | *No significant difference*  *P =*0.90d |
| due to IVH | 15/257 (5.8%) | 8/258 (3.1%) | RR 1.88 [0.81, 4.36]d | *No significant difference*  *P =*0.14d |
| due to NEC | 5/257 (1.9%) | 7/258 (2.7%) | RR 0.72 [0.23, 2.23]d | *No significant difference*  *P =*0.57d |
| due to other reasons | 2/257 (0.8%) | 4/258 (1.6%) | RR 0.50 [0.09, 2.72]d | *No significant difference*  *P =*0.42d |
| NNNI 1996b291  Level II  *Fair*  \*2-year follow-up of NNNI 1996a290 | N=515 | Preterm infants (≤ 32 weeks gestation), aged ≤ 2 hours at 2 years follow-up | Multicentre, UK | FFP versus dextrose c | Mortality before 2 years of age | 54/257 (21.0%) | 53/258 (20.5%) | RR 1.02 [0.73, 1.43]d | *No significant difference*  *P =*0.90d |
| Neonatal mortality (aged < 4 weeks) | 40/257 (15.6%) | 43/258 (16.7%) | RR 0.93 [0.63, 1.39]d | *No significant difference*  *P =*0.73d |
| Infant mortality (aged 1–23 months) | 14/257 (5.4%) | 10/258 (3.9%) | RR 1.41 [0.64, 3.11]d | *No significant difference*  *P =*0.40d |
|  | *Subgroup analysis: Cause-specific mortality (age 1–23 months)* | | | |
| due to chronic lung disease | 7/257 (2.7%) | 5/258 (1.9%) | RR 1.41 [0.45, 4.37]d | *No significant difference*  *P =*0.56d |
| due to sudden unexpected death | 4/257 (1.6%) | 1/258 (0.4%) | RR 4.02 [0.45, 35.68]d | *No significant difference*  *P =*0.21d |
| due to infection | 2/257 (0.8%) | 2/258 (0.8%) | RR 1.00 [0.14, 7.07]d | *No significant difference*  *P =*1.00d |
| due to other reasons | 1/257 (0.4%) | 2/258 (0.8%) | RR 0.50 [0.05, 5.50]d | *No significant difference*  *P =*0.57d |

CI, confidence interval; FFP, fresh frozen plasma; NNNI, Northern Neonatal Nursing Initiative; NR, not reported; OR, odds ratio; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** NNNI 1996a was a three-armed RCT comparing FFP with either a gelatin plasma substitute or control (maintenance infusion of 10% dextrose or dextrose saline). Only the FFP versus dextrose results are presented here.

**d.** Calculated post-hoc using RevMan 5.1.2.

###### Bleeding events

The systematic review and hand-searching process identified one good-quality Level I study (Osborn 2004) that provided evidence for bleeding events in preterm infants administered FFP compared with no FFP. Additional data from the RCT conducted by the NNNI (NNNI 1996a) was retrieved for this outcome to clarify the data reported by Osborn (2004). **Table 3.3.4** summarises the results from these studies.

The review by Osborn (2004) identified two RCTs (Beverley 1985, Ekblad 1991) involving 120 preterm infants born before 32 weeks gestation that examined the association between FFP and bleeding events in preterm infants. A meta-analysis of the data found that 11 infants (18.6%) in the FFP group experienced P/IVH (any grade) compared with 20 infants (32.8%) in the control group. This trend towards reduced P/IVH in infants receiving FFP was not statistically significant (RR 0.58, 95%CI 0.30, 1.11). There was moderate heterogeneity (I2=33%) for this outcome.

Osborn (2004) also reported the individual trials results according to the grade of P/IVH. The RCT by Beverley (1985) reported a nonsignificant trend towards reduced P/IVH grade 2–4 (one trial; RR 0.43, 95%CI 0.17, 1.08) and P/IVH grade 3–4 (one trial; RR 0.55, 95%CI 0.21, 1.47). In a secondary analysis of patients from one trial (NNNI 1996a), it was reported that there was no significant difference in P/IVH (any grade) (RR 1.20, 95%CI 0.83, 1.74) or P/IVH grade 2–4 (RR 0.93, 95%CI 0.45, 1.95) among infants surviving 6 weeks in maternity units with routine scanning facilities.

The complete data for all infants enrolled in the NNNI study was retrieved from the published report (NNNI 1996a) to further understand the missing data. Among 515 preterm infants randomised to the FFP or control group, 429 survived 6 weeks, and 308 of these had available scans (including patients in unit without routine scanning facilities). Among these infants, there was no significant difference in IVH (any grade) (RR 1.15 95%CI 0.80, 1.64), subependymal IVH (RR 1.31 95%CI 0.82, 2.09) or severe IVH (RR 0.89 95%CI 0.44, 1.79).

The data from the NNNI (1996a) study are likely to overstate the incidence of IVH as not all infants received scans.

Table 3.3.4 Preterm infants: Results for FFP versus no FFP – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%) | No FFP  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level I evidence** | | | | | | | | | |
| Osborn 2004286  Level I  *Good* | 2 trials (Beverley 1985,287 Ekblad 1991288)  N=120 | Preterm infants (≤ 32 weeks gestation) or ≤ 1500g and aged ≤ 72 hours | NR | FFP versus no FFP | P/IVH (any) | 11/59 (18.6%) | 20/61 (32.8%) | RR 0.58 [0.30, 1.11] | *No significant difference*  *P =*0.099  Moderate heterogeneity  I2 = 33% |
| **Level II evidence** | | | | | | | | | |
| Osborn 2004286  Level I/II  *Good* | 1 trial (Beverley 1985287)  N=80 | Preterm infants (≤ 32 weeks gestation) or ≤ 1500g and aged ≤ 72 hours | NR | FFP versus no FFP | P/IVH (grade 2–4) | 5/38 (13.2%) | 13/42 (31.0%) | RR 0.43 [0.17, 1.08] | *No significant difference*  *P =*0.072 |
| P/IVH (grade 3–4) | 5/38 (13.2%) | 10/42 (23.8%) | RR 0.55 [0.21, 1.47] | *No significant difference*  *P =*0.24 |
| 1 trial (NNNI 1996a)  N=282 | Multicentre, UK (maternity units from 18 hospitals) | P/IVH (any) in infants surviving 6-weeks and cared for in a unit with routine scan facilities e | 42/135 (31.1%) | 38/147 (25.9%) | RR 1.20 [0.83, 1.74] | *No significant difference*  *P =*0.33 |
| P/IVH grade 2–4 in infants surviving 6-weeks and cared for in a unit with routine scan facilities e | 12/135 (8.9%) | 14/147 (9.5%) | RR 0.93 [0.45, 1.95] | *No significant difference*  *P =*0.85 |
| NNNI 1996a290  Level II  *Fair* | N=308 | Preterm infants (≤ 32 weeks gestation), aged ≤ 2 hours | Multicentre, UK (maternity units from 18 hospitals) | FFP versus dextrose c | IVH (any) in infants surviving 6-weeks and scanned e | 44/147 (29.9%) | 42/161 (26.1%) | RR 1.15 [0.80, 1.64]d | *No significant difference*  *P =*0.45d |
| Subependymal only | 31/147 (21.1%) | 26/161 (16.1%) | RR 1.31 [0.82, 2.09]d | *No significant difference*  *P =*0.27d |
| Severe IVH | 13/147 (8.8%) | 16/161 (9.9%) | RR 0.89 [0.44, 1.79]d | *No significant difference*  *P =*0.74d |

CI, confidence interval; FFP, fresh frozen plasma; IVH, intraventricular haemorrhage; NNNI, Northern Neonatal Nursing Initiative; NR, not reported; OR, odds ratio; P/IVH, peri/intraventricular haemorrhage; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** NNNI 1996a was a three-armed RCT comparing FFP with either a gelatin plasma substitute or control (maintenance infusion of 10% dextrose or dextrose saline). Only the FFP versus dextrose results are presented here.

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** There were 214 and 258 infants in the intervention and control groups respectively that survived 6-weeks however not all units provided routine cerebral ultrasounds and not all infants received scans. The data reported by Osborn (2004) refers to those infants that received care in one of eight maternity units reported to provide routine screening and had received a scan. These data were also reported by the NNNI Trial Group (1996a) along with the complete data for all infants scanned (also provided here for completeness).

###### Transfusion-related serious adverse events

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness and FFP compared with no FPP (or a different FFP transfusion strategy) in preterm infants that reported the incidence of transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness and FFP compared with no FPP (or a different FFP transfusion strategy) in preterm infants and reported transfusion volume or incidence.

* + - 1. Platelet transfusion

| Evidence statements – preterm and low birth weight infants (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | In neonates with thrombocytopenia 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 | √√ | √ |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

| Evidence statements – preterm and low birth weight infants (platelet transfusion using a different platelet transfusion strategy) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √√ |
|  | 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 | √√ | √√ |
|  | 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 |
|  | 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; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; RBC, red blood cell  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of platelet transfusions compared with no platelet transfusion (or a different platelet transfusion strategy) in preterm infants.

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that assessed the safety and effectiveness of platelet transfusions compared with no platelet transfusion (or a different platelet transfusion strategy) in preterm infants.

###### Level III evidence

The systematic review and hand-searching process identified three Level III studies (Baer 2007, Bonifacio 2007, Christensen 2006) comparing platelet transfusion with no platelet transfusion in preterm infants and one Level III study (von Lindern 2012) comparing different platelet transfusion strategies in preterm infants (see **Appendix C, Volume 2**). **Table 3.3.5** summarises the main characteristics of these studies.

Baer (2007) conducted a good-quality retrospective cohort study that investigated the association between platelet transfusion and mortality among 1600 neonates with thrombocytopenia. The study was conducted in multiple NICUs in the USA.

Bonifacio (2007) conducted a poor-quality nested case–control study in a single NICU in the USA involving 164 preterm infants born at or before 32 weeks gestation. Cases were defined as participants with thrombocytopenia (platelet count ≤150x109/L) and controls as those without thrombocytopenia. Of the 94 included cases, 12 were defined as having mild thrombocytopenia (100–150x109/L), 34 with moderate (50–100x109/L), and 48 with severe (<50x109/L). The authors investigated the association between thrombocytopenia and platelet transfusion-related morbidity (IVH, sepsis, NEC, and bleeding) and mortality.

Christensen (2006) conducted a poor-quality retrospective cohort study of 284 preterm infants with extremely low birth weight (≤1000 g) from multiple NICUs in the USA. The authors examined the association between platelet transfusion and mortality during and after thrombocytopenia. Data was collected from electronic medical records, case mix, pharmacy, and laboratory systems. Trained clinical personnel entered additional data, with data managed by authorised data analysts. Patient medical records were also reviewed by the authors to determine reasons for ordering each platelet transfusion.

Von Lindern (2012) was a fair-quality retrospective cohort study conducted in two NICUs in the Netherlands that followed different platelet transfusion guidelines during the study period. The authors included data on 679 premature infants born before 32 weeks gestation with thrombocytopenia (platelet count <150 x109/L) and examined the effect of restrictive platelet transfusion strategy (transfused when active haemorrhage and platelet count <50x109/L) compared with a liberal platelet transfusion strategy (transfused according to predefined platelet count threshold) on mortality, IVH (all grades) and major haemorrhage.

Table 3.3.5 Characteristics and quality of Level III evidence – platelet transfusions in preterm infants (<37 weeks gestational age)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Study type  *Study quality* | Population  N | Comparison | Outcomes |
| Platelet transfusion compared with no transfusion | | | | |
| Baer  (2007)292 | Retrospective cohort  *Good* | Neonates with thrombocytopenia  N=1600 | Platelet transfusion versus no transfusion | Mortality  Bleeding events |
| Bonifacio  (2007)293 | Nested case–control study  *Poor* | Preterm infants (≤32 weeks gestational age) with thrombocytopenia (platelet count ≤150 x109/L (cases) or without thrombocytopenia (controls)  N=164 | Platelet transfusion versus no transfusion | Mortality  Bleeding events |
| Christensen (2006)294 | Retrospective cohort study  *Fair* | Preterm infants with ELBW (≤1000 g)  N=284 | Platelet transfusion versus no transfusion | Mortality |
| Platelet transfusion compared with a different platelet transfusion strategy | | | | |
| Von Lindern (2012)295 | Retrospective cohort  *Fair* | Preterm infants (<32 weeks gestational age) with thrombocytopenia (platelet count <150 x109/L)  N=679 | Restrictive platelet transfusiona versus liberal platelet transfusionb | Mortality  Bleeding events |

ELBW, extremely low birth weight

**a.**Transfused when active haemorrhage and platelet count <50x109/L.

**b.** Transfused according to predefined platelet count threshold.

##### Results

###### Mortality

Platelet transfusion compared with no platelet transfusion

The systematic review and hand-searching process identified three Level III studies (Baer 2007, Bonifacio 2007, Christensen 2006) of variable quality that examined the association between platelet transfusion and mortality among preterm infants. **Table 3.3.6** summarises the results of these studies.

Baer (2007) assessed mortality among 1600 neonatal patients and reported transfusion of platelets to be a significant predictor of mortality (unadjusted; RR 9.18; 95%CI 5.70, 14.79). The analysis revealed an increasing number of platelet transfusions to be associated with a significant increased risk of death with a linear regression analysis reported to show an increasing risk of mortality with each additional platelet transfusion (OR 1.14; 95%CI 1.10, 1.18). In a logistic regression analysis of patients who received ≤10 platelet transfusions only, there was also an increased association between platelet transfusion and mortality reported (OR 1.45, 95% CI NR).

Baer (2007) also conducted a sensitivity analyses to test 48 hypothetical scenarios combining the risk of additional platelet transfusions and unmeasured variables on mortality. Known and unknown predictors of mortality were considered. The observed OR of 1.14 (95%CI 1.10, 1.18) occurred when r=0. Results of the sensitivity analysis showed that for all 24 scenarios with *P <*0.6, there was a statistically significant adverse effect of additional platelet transfusions on mortality, beyond the effect of the observed variable.

The authors concluded that “*the number of platelet transfusions administered in the NICU predicts the mortality rate”* and that “*the present data and the sensitivity analysis both suggest that some of this correlation is due to harmful effects of multiple platelet transfusions in this group of patients”.*

Bonifacio (2007) was a nested case–control study of 94 preterm infants with thrombocytopenia and 70 preterm infants without thrombocytopenia. The authors found a significant difference in mortality that favoured no platelet transfusion (RR 2.66; CI 1.05, 6.70); however in a subgroup analyses according age the effect was not significant (<28 weeks gestational age; RR 3.57; CI 0.57, 22.38 and gestational age 28–32 weeks; RR 1.82; CI 0.51, 6.53).

Christensen (2006) found no significant difference in mortality between platelet transfusion and no platelet transfusion in all patients, regardless of platelet count (RR 1.44; 95%CI 0.89, 2.35). However in thrombocytopenic patients, there was a significant difference favouring no platelet transfusion for all-cause mortality (RR 2.54; 95%CI 1.17, 5.51).The authors conducted a subgroup analyses stratified by number of platelet transfusions received. Infants who received 1–5 platelet transfusions were significantly more likely to die (all-cause mortality; RR 2.26; 95%CI 1.00, 5.09 and mortality during thrombocytopenia; RR 2.49; 95%CI 1.04, 5.98); but there was no association between the number of platelets transfused and mortality after thrombocytopenia had resolved (RR 0.83; 95%CI 0.05, 13.08). A similar trend was seen in infants who received >5 platelet transfusions. That is, there were significant between-group differences for all-cause mortality (RR 3.32; 95%CI 1.38, 7.99) and mortality during thrombocytopenia (RR 3.10; 95%CI 1.16, 8.25) that favoured no platelet transfusion, but there was no difference in the incidence of mortality after thrombocytopenia had resolved (RR 4.65; 95%CI 0.44, 49.54).

Table 3.3.6 Preterm infants: Results for platelet transfusion versus no platelet transfusion – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%) | No platelet transfusion  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level III evidence** | | | | | | | | | |
| Baer 2007292  Level III–2  *Good* | N=1600 | Neonates with thrombocytopenia who had survived >48 hours and were admitted to the NICU | Multiple NICUs, USA | Platelet transfusion versus no platelet transfusion | Mortality (unadjusted) | 82/494 (16%) | 20/1106 (2%) | RR 9.18 [5.70, 14.79]c | *Favours no platelet transfusion*  P < 0.00001 |
|  | *Subgroup analysis: number of platelet transfusions versus no platelet transfusions* | | | |
| Infants who received 1–2 platelet transfusions versus control | 31/278 (11%) | 20/1106 (2%) | RR 6.17 [3.57, 10.65]c | *Favours no platelet transfusion*  P < 0.00001 |
| Infants who received 3–10 platelet transfusions versus control | 34/167 (20%) | 20/1106 (2%) | RR 11.26 [6.64, 19.09]c | *Favours no platelet transfusion*  P < 0.00001 |
| Infants who received >10 platelet transfusions versus control | 17/49 (35%) | 20/1106 (2%) | RR 19.19 [10.74, 34.26]c | *Favours no platelet transfusion*  P < 0.00001 |
| Mortality with each additional platelet transfusion | NA | NA | OR 1.14 [1.10, 1.18]  \*linear regression model | *Favours no platelet transfusions*  *P =*NR |
| OR 1.45 [NR]  \*logistic regression model; patients who received ≤10 platelet transfusions only | *Favours no platelet transfusions*  *P =*NR |
| The authors conducted a sensitivity analysis tested 48 hypothetical scenarios combining the risk of additional platelet transfusions and unmeasured variables on mortality, using the linear logistic regression model with observed OR of 1.14 (95%CI 1.10, 1.18). Results of the sensitivity analysis showed that for 30 scenarios there was a statistically significant adverse effect of additional platelet transfusions on mortality, beyond the effect of the observed variable. In 13 scenarios, platelet transfusions neither significantly increased nor decreased mortality rate, and in 5 scenarios the OR was significantly below 1, indicating a beneficial effect of platelet transfusions on mortality rate | | | |
| Bonifacio 2007293  Level III–2  *Poor* | N=164 | Preterm infants (≤ 32 weeks gestational age) with thrombocytopenia | Single NICU, USA | Platelet transfusion versus no platelet transfusion | Mortality | 29/60 (48.3%) | 4/22 (18.2%) | 2.66 [1.05, 6.70]c | *Favours no platelet transfusion*  *P =*0.04c |
|  | *Subgroup analysis: gestational age* | | | |
| Infants with gestational age <28 weeks | 25/49 (51.0%) | 1/7 (14.3%) | RR 3.57 [0.57, 22.38]c | *No significant difference*  *P =*0.17c |
| Infants with gestational age 28–32 weeks | 4/11 (36.4%) | 3/15 (20.0%) | RR 1.82 [0.51, 6.53]c | *No significant difference*  *P =*0.36c |
| Christensen 2006294  Level III–2  *Poor* | N=284 | Preterm infants with ELBW (≤ 1000 g) | Multiple NICUs, USA | Platelet transfusion versus no platelet transfusion | Mortality in all patients regardless of platelet count | 29/129 (23%) | 24/154 (16%) | RR 1.44 [0.89, 2.35] | *No significant difference*  *P =*0.14 |
| Mortality in thrombocytopenic patients (all-cause) | 29/129 (23%) | 7/79 (9%) | RR 2.54 [1.17, 5.51]c | *Favours no platelet transfusion*  *P =*0.02c |
|  | *Subgroup analysis: number of platelet transfusions* | | | |
| Infants who received 1–5 platelet transfusions | 19/95 (20%) | 7/79 (9%) | RR 2.26 [1.00, 5.09]c | *Favours no platelet transfusion*  *P =*0.05c |
| Infants who received > 5 platelet transfusions | 10/34 (29%) | 7/79 (9%) | RR 3.32 [1.38, 7.99]c | *Favours no platelet transfusion*  *P =*0.007c |
| Mortality during thrombocytopenia | 26/129 (20%) | 6/79 (7.6%) | RR 2.65 [1.14, 6.16] | *Favours no platelet transfusion*  *P =*0.02c |
|  | *Subgroup analysis: number of platelet transfusions* | | | |
| Infants who received 1–5 platelet transfusions | 18/95 (18.9%) | 6/79 (7.6%) | RR 2.49 [1.04, 5.98]c | *Favours no platelet transfusion*  *P =*0.04c |
| Infants who received >5 platelet transfusions | 8/34 (23.5%) | 6/79 (7.6%) | RR 3.10 [1.16, 8.25]c | *Favours no platelet transfusion*  *P =*0.02c |
| Mortality after thrombocytopenia had resolved | 3/129 (2.3%) | 1/79 (1.3%) | RR 1.84 [0.19, 17.36]c | *No significant difference*  *P =*0.60c |
|  | *Subgroup analysis: number of platelet transfusions* | | | |
| Infants who received 1–5 platelet transfusions | 1/95 (1.1%) | 1/79 (1.3%) | RR 0.83 [0.05, 13.08]c | *No significant difference*  *P =*0.90c |
| Infants who received > 5 platelet transfusions | 2/34 (5.9%) | 1/79 (1.3%) | RR 4.65 [0.44, 49.54]c | *No significant difference*  *P =*0.20c |

CI, confidence interval; ELBW, extremely low birth weight; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** The authors reported a higher proportion of infants with gestational age <28 weeks that received platelet transfusions died compared with the non-transfused group, but did not provide *P-*values.

Platelet transfusion compared with a different platelet transfusion protocol

One fair-quality Level III study (von Lindern 2012) identified in the systematic review and hand-searching process assessed the association between different platelet transfusion strategies and IVH among preterm infants and provided evidence for mortality in this patient group. **Table 3.3.7** summarises the results from this study.

Von Lindern (2012) reported no significant difference in overall mortality between restrictive and liberal platelet transfusion groups (RR 1.05; 95%CI 0.60, 1.82). Data should be interpreted with caution because bias may have been introduced due to the retrospective nature of the study.

Table 3.3.7 Preterm infants: Results for platelet transfusion versus different platelet transfusion strategy – mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%) | Different platelet transfusion strategy  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| **Level III evidence** | | | | | | | | | |
| von Lindern 2012295  Level III–2  *Fair* | N=679 | Preterm infants (<32 weeks gestational age) with or without thrombocytopenia | 2x NICUs, The Netherlands | Restrictive platelet transfusion (when active haemorrhage and platelet count <50 x109/L) versus liberal platelet transfusion (predefined platelet count threshold)d | Mortality (overall) | 25/353 (7%) | 22/326 (7%) | RR 1.05 [0.60, 1.82] | *No significant difference*  *P =*0.86 |
| The authors noted that there was no difference in death rate in infants who received a platelet transfusions compared with those who did not receive a platelet transfusion, but no data were reported. | | |

CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** The data is reported according to NICU transfusion policy, not specifically infants who received platelet transfusions.

**e.** Two infants in the restrictive transfusion unit also had pulmonary haemorrhage managed by mechanical ventilation with positive end-expiratory pressure and endotracheal xylomethazoline

###### Bleeding events

Platelet transfusion compared with no transfusion

The systematic review and hand-searching process identified two Level III studies (Baer 2007, Bonifacio 2007) of variable quality that examined the association between platelet transfusion and morbidity among preterm infants and provided evidence for bleeding events. **Table 3.3.8** summarises the results from these studies.

Baer (2007) was a retrospective cohort study of 1600 neonates with thrombocytopenia. The authors reported a significant difference in severe IVH (grade 3–4) that favoured no platelet transfusions (RR 5.04; 95%CI 3.59, 7.07); however, these data were not adjusted for confounding variables. In an assessment according to the number of platelet transfusions administered, there were significant differences favouring no platelet transfusion in infants who received 1–2 platelet transfusions (RR 3.53; 95%CI 2.34, 5.32), 3–10 platelet transfusions (RR 7.53; 95%CI 5.19, 10.91) and >10 platelet transfusions (RR 5.13; 95%CI 2.75, 9.58). Again, these data were not adjusted for confounding variables and no assessment comparing the number of platelet transfusions received was performed (such as 1–2 versus 3–10).

The study by Bonifacio (2007) was a nested case–control study that investigated thrombocytopenia and platelet transfusion-related IVH. The diagnosis of IVH (any grade) was based on the results of cranial ultrasound examinations on days 7 and 14 of life. The authors reported a significant increased risk of IVH among preterm infants administered platelets (RR 1.94; 95%CI 1.02, 3.69) and observed that IVH occurred more frequently in cases than controls; irrespective of the severity and age of onset of thrombocytopenia. In subgroup analyses by gestational age, there was no significant difference in IVH among infants aged <28 weeks gestation (RR 1.21; 95%CI 0.62, 2.37) or infants aged 28–32 weeks gestation (RR 1.36; 95%CI 0.34, 5.52).

Table 3.3.8 Preterm infants: Results for platelet transfusion versus no platelet transfusion – bleeding events

| Study  Level of evidence a  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%) | No platelet transfusion or different strategy  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level III evidence** | | | | | | | | | |
| Baer 2007292  Level III–2  *Good* | N=1600 | Neonates with thrombocytopenia who had survived > 48 hours and were admitted to the NICU | Multiple NICUs, USA | Platelet transfusion versus no platelet transfusion | IVH (grade 3–4) | 99/494 (20%) | 44/1106 (4%) | RR 5.04 [3.59, 7.07]c | *Favours no platelet transfusion*  *P <*0.00001 |
|  | *Subgroup analysis: number of platelet transfusions* | | | |
| Infants who received 1–2 platelet transfusions versus control | 39/278 (14%) | 44/1106 (4%) | RR 3.53 [2.34, 5.32]c | *Favours no platelet transfusion*  *P <*0.001 |
| Infants who received 3–10 platelet transfusions versus control | 50/167 (30%) | 44/1106 (4%) | RR 7.53 [5.19, 10.91]c | *Favours no platelet transfusion*  *P <*0.001 |
| Infants who received >10 platelet transfusions versus control | 10/49 (20%) | 44/1106 (4%) | RR 5.13 [2.75, 9.58]c | *Favours no platelet transfusion*  *P <*0.001 |
| Bonifacio 2007293  Level III–2  *Poor* | N=164 | Preterm infants (≤ 32 weeks gestational age) with thrombocytopenia | Single NICU, USA | Platelet transfusion versus no platelet transfusion | IVH (any grade) | 37/60 (61.7%) | 7/22 (31.8%) | RR 1.94 [1.02, 3.69]c | *Favours no platelet transfusions*  *P =*0.04c |
|  | *Subgroup analysis: gestational age* | | | |
| Infants with gestational age <28 weeks | 34/49 (69.4%) | 4/7 (57.2%) | RR 1.21 [0.62, 2.37]c | *No significant difference*  *P =*0.57c |
| Infants with gestational age 28–32 weeks | 3/11 (27.3%) | 3/15 (20.0%) | RR 1.36 [0.34, 5.52]c | *No significant difference*  *P =*0.66c |

CI, confidence interval; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Platelet transfusion compared with a different platelet transfusion protocol

The systematic review and hand-searching process identified one Level III study (von Lindern 2012) that assessed the association between different platelet transfusion strategies and IVH among preterm infants (< 32 weeks gestational age). **Table 3.3.9** summarises the results from this study.

The study by von Lindern (2012) reported the incidence of IVH among preterm infants admitted to a NICU with a restrictive platelet transfusions strategy compared with those admitted to a NICU with a liberal platelet transfusions strategy. Among infants in whom cranial ultrasounds were available, the study found no significant difference between treatment groups (RR 1.17; 95%CI 0.87, 1.57). In a logistic regression analysis to assess for potential confounders, the authors reported a significant association between IVH (all grades) and thrombocytopenia irrespective of severity, and gestational age before 28 weeks, but not platelet transfusions.

Among infants with thrombocytopenia, von Lindern (2012) reported no significant difference between restrictive and liberal platelet transfusions strategies on the severity of IVH: IVH (grade 1 or 2) (RR 1.24; 95%CI 0.78, 1.99) or severe IVH (grade 3 or 4) (RR 0.73; 95%CI 0.36, 1.49). However, a significant difference in IVH (grade 1) was noted, favouring a liberal platelet transfusion strategy (RR 1.94; 95%CI 1.09, 3.46), and a significant difference in IVH (grade 2), favouring a restrictive platelet transfusion strategy (RR 0.19; 95%CI 0.04, 0.87). There were no significant between-group differences for IVH (grade 3) (RR 0.24; 95%CI 0.05, 1.12), IVH (grade 4) (RR 1.22; 95%CI 0.49, 2.99) or major haemorrhage other than IVH requiring one or more platelet transfusions(RR 1.39; 95%CI 0.23, 8.24).

Table 3.3.9 Preterm infants: Results for platelet transfusion versus different platelet transfusion strategy – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%) | Different platelet transfusion strategy  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level III evidence** | | | | | | | | | | |
| von Lindern 2012295  Level III–2  *Fair* | N=653 | Preterm infants (< 32 weeks gestational age) with or without thrombocytopenia | | 2x NICUs, The Netherlands | Restrictive platelet transfusion (when active haemorrhage and platelet count < 50 x109/L) versus liberal platelet transfusion (predefined platelet count threshold)d | IVH (all infants with available cranial ultrasound) (N=653) | 75/330 (23%) | 63/323 (20%) | RR 1.17 [0.87, 1.57]c | *No significant difference*  *P =*0.31 |
| The authors conducted logistic regression analysis to assess confounders for IVH including: gestational age at birth (<28 weeks or 28–32 weeks), thrombocytopenia (by severity), sepsis, intrauterine growth retardation, NEC, platelet transfusion, NICU (restrictive or liberal), and PDA and reported a significant association between IVH (all grades) and thrombocytopenia (irrespective of severity) and gestational age <28 weeks. | | |
| IVH (grade 1 or 2) in thrombocytopenic patients (N=286) | 32/145 (22%) | 25/141 (18%) | RR 1.24 [0.78, 1.99]c | *No significant difference*  *P =*0.36 |
| IVH (grade 1) | 30/145 (21%) | 15/141 (11%) | RR 1.94 [1.09, 3.46]c | *Favours liberal transfusion*  *P =*0.02 |
| IVH (grade 2) | 2/145 (1%) | 10/141 (7%) | RR 0.19 [0.04, 0.87]c | *Favours restrictive transfusion*  *P =*0.02 |
| IVH (grade 3 or 4) in thrombocytopenic patients (N=286) | 12/145 (8%) | 16/141 (11%) | RR 0.73 [0.36, 1.49]c | *No significant difference*  *P =*0.38 |
| IVH (grade 3) | 2/145 (1%) | 8/141 (6%) | RR 0.24 [0.05, 1.12]c | *No significant difference*  *P =*0.06 |
| IVH (grade 4) | 10/145 (7%) | 8/141 (6%) | RR 1.22 [0.49, 2.99]c | *No significant difference*  *P =*0.67 |
| Major haemorrhage other than IVH requiring one or more platelet transfusions e | 3/353 (0.85%)  \*gastrointestinal, adrenal post-surgery | 2/326 (0.6%)  \*pulmonary | RR 1.39 [0.23, 8.24]c | *No significant difference*  *P =*0.72c |

CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** The data is reported according to NICU transfusion policy, not specifically infants who received platelet transfusions.

**e.** Two infants in the restrictive transfusion unit also had pulmonary haemorrhage managed by mechanical ventilation with positive end-expiratory pressure and endotracheal xylomethazoline.

###### Transfusion-related serious adverse events

The systematic review and hand-searching process identified no studies that compared platelet transfusion with no platelet transfusion (or a different platelet transfusion strategy) in preterm infants and reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process identified no studies that compared platelet transfusion with no platelet transfusion (or a different platelet transfusion strategy) in preterm infants and reported on transfusion volume or incidence.

It was noted that the Level III study by von Lindern (2012) reported no significant difference in the number of RBC transfusions administered to patients admitted to the liberal transfusion unit compared with the restrictive transfusion unit (RR 0.90; CI 0.77, 1.06). This data did not differentiate between patients with thrombocytopaenia who received platelets compared with those who did not, therefore was not an appropriate comparison for inclusion in this review. It was also noted that thrombocytopaenic patients in the restrictive transfusion unit were administered significantly fewer platelets compared with those patients in the liberal transfusion unit.

### Neonatal and paediatric patients with cancer

* + - 1. Platelet transfusion

| Evidence statements – cancer (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study (Estcourt 2012) that examined the safety and effectiveness of platelet transfusions in neonatal and paediatric patients with cancer (see **Appendix C, Volume 2**). **Table 3.3.10** summarises the main characteristics of this review.

Estcourt (2012) was a good-quality Cochrane review of RCTs that examined the use of platelet transfusion for the prevention of bleeding in patients of all ages with haematological disorders receiving treatment with myelosuppressive chemotherapy and/or stem cell transplantation. Of the 13 included studies, two were conducted in paediatric populations (Murphy 1982, Roy 1973) and involved children hospitalised with previously untreated acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL). The study by Roy (1973) did not meet our inclusion criteria because it compared two different doses of prophylactic platelet transfusions. Three studies were conducted in both adults and children (Diedrich 2005, Sensebe 2004, Slichter 2010); however, results were pooled for both age groups.

The RCT by Murphy (1982) was conducted in a single centre in the USA and investigated the effect of therapeutic platelet transfusions (administered only in presence of bleeding) compared with a prophylactic platelet transfusion PPT (administered to maintain platelet count above 20 x109/L) on mortality, all causes and from bleeding. The study was assessed by Estcourt (2012) to be of unclear risk of bias as no description of the method of random allocation was provided. Details for allocation concealment and blinding (patient, clinician or assessor) were not reported and loss to follow-up and outcome data was not reported. Primary (survival) outcomes were reported. The review authors noted high risk of bias for selective reporting and ‘*poorly backed up statements*’*.*

Table 3.3.10 Characteristics and quality of Level I evidence – platelet transfusion in neonatal and paediatric patients with cancer

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Estcourt (2012)296 | Level I  *Good* | Children hospitalised with previously untreated AML or ALL  13 RCTs, N=2331  Paediatric RCTs  2 RCTs, N=56 | Platelet transfusion versus different platelet transfusion strategy | Mortality  Bleeding events  Transfusion volume and incidence |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that assessed the safety and effectiveness of platelet transfusion in neonatal and paediatric patients with cancer.

###### Level III evidence

The systematic review and hand-searching process identified no Level III studies that assessed the safety and effectiveness of platelet transfusion in neonatal and paediatric patients with cancer.

##### Results

###### Mortality

The systematic review and hand-searching process identified one Level I study (Estcourt 2012) that assessed the incidence of mortality in neonatal and paediatric patients with cancer who were administered platelets. **Table 3.3.11** summarises the results from this study.

Estcourt (2012) identified one RCT (Murphy 1982) that compared prophylactic and therapeutic platelet transfusion regimes in paediatric patients with AML of ALL. The study reported no significant difference in the incidence of all-cause mortality (RR 0.97; CI 0.46, 2.08) or mortality due to bleeding (RR 3.33; CI 0.32, 34.56). The study was not powered to detect differences for this outcome.

Table 3.3.11 Neonatal and paediatric patients with cancer: Results for platelet transfusion versus different platelet transfusion strategy – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%)  Mean ± SD | Different strategy  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level II evidence** | | | | | | | | | |
| Estcourt 2012296  Level I/II  *Good* | 1 trial (Murphy 1982)297  N=56 | Children hospitalised with previously untreated AML or ALL | Children’s Hospital of Philadelphia, USA | TPT (administered only in presence of bleeding) versus PPT (administered to maintain platelet count above 20 x109/L) | Mortality (all causes) | 7/21 (33.3%) | 12/35 (34.3%) | RR 0.97 [0.46, 2.08] | *No significant difference*  *P =*0.94c |
| Mortality (from bleeding) | 2/21 (9.5%) | 1/35 (2.9%) | RR 3.33  [0.32, 34.56] | *No significant difference*  *P =*0.31c |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; PPT, prophylactic platelet transfusion; RR, risk ratio; TPT, therapeutic platelet transfusion

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Bleeding events

The systematic review and hand-searching process identified one Level I study (Estcourt 2012) that assessed the effect of platelet transfusions in neonatal and paediatric patients with cancer on bleeding events. **Table 3.3.12** summarises the results from this study.

Estcourt (2012) identified one RCT (Murphy 1982) that compared prophylactic and therapeutic platelet transfusion regimes in paediatric patients with AML of ALL. The study reported 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 x109/L on children with ≥1 significant bleeding event (patients with ALL and AML) (RR 1.66; CI 0.9, 3.04).

In a subgroup analysis according to type of cancer, there was a trend towards less bleeding in children with ALL administered prophylactic platelet transfusions (RR 2.61; CI 1.00, 6.83), but the authors reported no significant difference between treatment groups in children with AML (RR 0.93; CI 0.45, 1.95). The power of the studies was generally inadequate to detect differences.

Table 3.3.12 Neonatal and paediatric patients with cancer: Results for platelet transfusion versus different platelet transfusion strategy – Bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%)  Mean ± SD | Different strategy  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level II evidence** | | | | | | | | | |
| Estcourt 2012296  Level I/II  *Good* | 1 trial (Murphy 1982297)  N=56 | Children hospitalised with previously untreated AML or ALL | Children’s Hospital of Philadelphia, USA | TPT (administered only in presence of bleeding) versus PPT (administered to maintain platelet count above 20 x109/L) | Children with ≥1 significant bleeding event (patients with ALL and AML) | 11/21 (52%) | 10/35 (29%) | RR 1.66 [0.9, 3.04] | *No significant difference*  *P =*0.10 |
|  | *Subgroup analysis: cancer type* | | | |
| Children with ALL | 7/15 (47%) | 5/28 (18%) | RR 2.61 [1.00, 6.83] | *Borderline favours prophylactic platelet transfusion*  *P =*0.05 |
| Children with AML | 4/6 (67%) | 5/7 (71%) | RR 0.93 [0.45, 1.95] | *No significant difference*  *P =*0.85 |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; PPT, prophylactic platelet transfusion; RR, risk ratio; TPT, therapeutic platelet transfusion

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level II evidence. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Transfusion-related serious adverse events

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of platelet transfusions in neonatal or paediatric patients with cancer that reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process identified one Level I study (Estcourt 2012) that assessed the effect of platelet transfusions in neonatal and paediatric patients with cancer and reported on transfusion incidence. **Table 3.3.13** summarises the results from this study.

Estcourt (2012) identified one RCT (Murphy 1982) that compared prophylactic and therapeutic platelet transfusion regimes in paediatric patients with AML of ALL. The study reported no significant difference between therapeutic and prophylactic platelet transfusion strategies on the mean number of platelet transfusions per course of chemotherapy (MD 0.0; CI 0.0, 0.0). The study was small and likely to be underpowered to detect significant differences for this outcome.

Table 3.3.13 Neonatal and paediatric patients with cancer: Results for platelet transfusion versus different platelet transfusion strategy – transfusion volume or incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  Mean ± SD | Different strategy  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| **Level II evidence** | | | | | | | | | |
| Estcourt 2012296  Level I/II  *Good* | 1 trial (Murphy 1982297)  N=56 | Children hospitalised with previously untreated AML or ALL | Children’s Hospital of Philadelphia, USA | TPT (administered only in presence of bleeding) versus PPT (administered to maintain platelet count above 20 x109/L) | Mean number of platelet transfusions per course of chemotherapy | 1.0 ± 0 (n=21) | 2.2 ± 0 (n=35) | MD 0.0 [0.0, 0.0] | *No significant difference*  *P =*not estimable |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; PPT, prophylactic platelet transfusion; RR, risk ratio; TPT, therapeutic platelet transfusion

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level II evidence. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

### Neonatal and paediatric patients undergoing surgery

* + - 1. Fresh frozen plasma

| Evidence statements – surgical (fresh frozen plasma) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √√ |
|  | 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 |
|  | In neonatal patients undergoing surgery, the effect of FFP compared with no FFP on mortality is unknown. | NA | NA | NA | NA | NA |
|  | In neonatal and paediatric patients undergoing cardiac surgery, the use of an FF*P-*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 | √√ | √ |
|  | 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 |
|  | 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 |
|  | In neonatal and paediatric patients undergoing cardiac surgery, the use of an FF*P-*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 | √√√ | √ |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study (Yang 2012) that assessed the safety and efficacy FFP transfusions in any population (see **Appendix C, Volume 2**). The study did not provide any usable data because it reported and assessed results across all populations. Therefore, Level II studies conducted in paediatric populations that were identified in the review by Yang (2012) were retrieved for further analysis.

###### Level II evidence

The systematic review and hand-searching process identified three Level II studies (Lee 2013, McCall 2004, Oliver 2003) that assessed the safety and effectiveness of FFP transfusions in neonatal and paediatric patients undergoing cardiac surgery (see **Appendix C, Volume 2**). **Table 3.3.14** summarises the main characteristics of these studies.

Lee (2013) was a fair-quality RCT conducted in South Korea involving 123 paediatric patients aged 1 month to 16 years who required cardiac surgery with cardiopulmonary bypass (CPB). Infants (<12 months age) and children (>12 months) were analysed separately for all outcomes. The authors examined the effect of FFP compared with 20% albumin in pump priming for bleeding after heparin reversal, and intraoperative and postoperative transfusion requirements.

McCall (2004) was a fair-quality RCT conducted in a single centre in the USA involving 20 infants weighing <8 kg who required CPB surgery. Patients were excluded if they had a pre-existing coagulopathy, were receiving a medication known to alter coagulation, or were patients for whom CPB was a re-operation. The authors examined the effect of FFP compared with no FFP for reducing transfusion requirements and hypofibrinogenaemia.

Oliver (2003) was a poor-quality RCT conducted in a single hospital in the USA. The authors included 56 paediatric patients weighing ≤10 kg who required CPB surgery. Patients with haematologic diseases, coagulation defects, severe liver dysfunction, or who had received a blood transfusion within 24 hours of operation were excluded. The authors examined the effect of FFP compared with 5% albumin for reducing blood loss in the ICU 24 hours postoperatively, recorded as mediastinal chest tube drainage (MCTD).

Table 3.3.14 Characteristics and quality of Level II evidence – FFP in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Lee (2013)298 | RCT  *Fair* | Paediatric patients aged 1 month to 16 years scheduled for cardiac surgery with CPB  N=123 | FFP in pump prime versus 20% albumin in pump prime | Bleeding events  Transfusion volume and incidence |
| McCall (2004)299 | RCT  *Fair* | Infants weighing <8 kg scheduled for cardiac surgery with CPB  N=20 | FFP (1U) in pump prime versus no FFP in pump prime (more albumin) | Transfusion volume and incidence |
| Oliver (2003)300 | RCT  *Poor* | Paediatric patients weighting ≤10 kg scheduled for cardiac surgery with CPB  N=56 | FFP (1U) in pump prime versus 200ml 5% albumin in pump prime | Bleeding events  Transfusion volume and incidence |

CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; MCTD, mediastinal chest tube drainage; U, unit

###### Level III evidence

The systematic review and hand-searching process identified one Level III study (Nacoti 2012) that assessed the association between FFP transfusions and mortality in neonatal and paediatric patients undergoing liver transplant (see **Appendix C, Volume 2**). The main characteristics of this study is summarised in **Table 3.3.15.**

Nacoti (2012) was a fair-quality retrospective cohort study conducted in Italy that involved 243 paediatric patients aged <18 years undergoing liver transplant from deceased brain-dead donors. Combined organ transplantations were excluded. The authors examined the association between various blood components (including RBC, FFP, platelets and fibrinogen) on patient survival after liver transplant and reported the effect of postoperative and perioperative FFP on mortality. Seven hepatobiliary surgeons performed all liver transplants, with two surgeons involved for each procedure. The transfusion policy was based on clinical assessment.

Table 3.3.15 Characteristics and quality of Level III evidence – FFP in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparisons | Outcomes |
| --- | --- | --- | --- | --- |
| Nacoti (2012)69 | Retrospective cohort study  *Fair* | Paediatric patients (<18 years) undergoing liver transplant  N=243 | FFP versus platelet versus fibrinogen versus no blood product | Mortality |

FFP, fresh frozen plasma

##### Results

###### Mortality

The systematic review and hand-searching process identified one fair-quality Level III study (Nacoti 2012) that assessed the association between FFP and mortality in paediatric patients undergoing liver transplant. **Table 3.3.16** summarises the results from this study.

The study by Nacoti (2012) reported a significant difference in cumulative patient survival at 1 year comparing postoperative FFP transfusion (≥1 unit) with no postoperative FFP transfusion. Patients transfused with FFP were significantly more likely to die than those who did not receive FFP (RR 2.21; 95% CI 1.08, 4.54). However, the authors reported that the effect did not remain significant when analysed using a multivariate Cox regression model (data not reported).

FFP use during surgery was reported by Nacoti (2012) to be a significant predictor for cumulative patient survival at 1 year. This effect was dose-related and remained significant when analysed using a multivariate Cox regression model for at least three units FFP (HR 3.35; 95%CI 1.20, 9.36), but not two units FFP transfused (HR 1.124; 95% CI 0.341, 3.705). When assessed using a propensity score adjusted analysis, the effect was not significant for at least units FFP transfused (HR 2.808; 95% CI 0.927, 8.505) or two units FFP transfused (HR 1.111; 95% CI 0.336, 3.680).

The authors noted that although a relationship between number of units transfused and infant survival was observed, it may just be a surrogate marker for sicker patients. The study did not completely distinguish that survival was related to massive transfusion for low levels of haemoglobin and coagulation factor or for over-transfusion of blood products.

Table 3.3.16 Neonatal and paediatric patients requiring cardiac surgery: Results for FFP versus no FFP – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%)  Mean ± SD | | Low /no FFP  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | |
| FFP versus no FFP | | | | | | | | | | |
| Nacoti 201269  Level III–2  Fair | N=243 | Paediatric liver transplant patients aged < 18 years | Riuniti Hospital, Italy | Postoperative FFP (≥ 1 unit) versus no FFP  \*within 48 hours after liver transplant | Mortality at 1 yearc | 10/51 (20.3%) | | 17/192 (8.7%) | RR 2.21 [1.08, 4.54]d | *Favours no FFP*  *P =*0.03d  *P =*0.022e |
| Forty-one potential risk factors were assessed for predicting 1-year patient survival. When analysed using a multivariate Cox regression model the effect of FFP administered within 48 hours after liver transplant was not a predictor for 1-year patient survival. | | | |  |
| FFP versus different volume FFP | | | | | | | | | | |
| Nacoti 201269  Level III–2  Fair | N=243 | Paediatric liver transplant patients aged < 18 years | Riuniti Hospital, Italy | FFP (≥ 3 units) versus FFP (2 units) versus FFP (≤ 1 unit)  \*during surgery | Mortality at 1 yearc | 15/63 (24.2%) | 5/60 (8.7%) | 7/120 (6%) | NR | *Favours low FFP P =*0.001e |
| Cumulative patient survival at 1-year was significantly associated with FFP usage during surgery (*P =*0.001) (data shown in Kaplan–Meier curves).  Of 41 risk factors investigated, 5 were identified as predicting 1-year patient survival when analysed using a multivariate Cox regression model\* and included: recipients age, total ischaemia time, number of RBC units transfused during surgery, number of FFP units transfused during surgery, and biliary complications.  To control for confounding factors that could potentially influence the use of blood product, propensity score analysis was also used. Variables included that influence the risk of transfusion were: recipient and donor sex, platelets received before liver transplant, INR before liver transplant, PELD, graft type, equivalent dose of norepinephrine, and total ischaemia time.  \*reference value = FFP (≤ 1 unit) | | | |  |
| FFP (2 units)  \*during surgery | Multivariate analysis: 1-year patient survival | | | HR 1.124 [0.341, 3.705] | *No significant difference*  *P =*0.848 |
| Propensity score adjusted: 1-year patient survival | | | HR 1.111 [0.336, 3.680] | *No significant difference*  *P =*0.863 |
| FFP (≥ 3 units)  \*during surgery | Multivariate analysis: 1-year patient survival | | | HR 3.346 [1.196, 9.364] | *Favours low FFP*  *P =*0.021 |
| Propensity score adjusted: 1-year patient survival | | | HR 2.808 [0.927, 8.505] | *No significant difference*  *P =*0.068 |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval; FFP, fresh frozen plasma; INR, international normalised ratio; PELD; paediatric end-stage liver disease; PPT, prophylactic platelet transfusion; RR, risk ratio; TPT, therapeutic platelet transfusion

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level II evidence. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Mortality back-calculated from reported % patient survival data 1 year.

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** *P-*value reported by study authors using log-rank test.

###### Bleeding events

The systematic review and hand-searching process identified three Level II studies (Lee 2013, McCall 2004, Oliver 2003) that assessed the effect of FFP transfusions in neonatal and paediatric patients undergoing surgery and provided evidence for bleeding events. **Table 3.3.17** summarises the results from these studies.

The fair-quality RCT by Lee (2013) reported no significant difference between the use of FFP (1–2 units) in the pump prime compared with no FFP on the median volume of bleeding (mL/kg) after heparin reversal in infants (<12 months) or children (12 months to 16 years) (MD NR).

The fair-quality RCT by McCall (2004) also reported no significant difference between the use of FFP (1 unit) in the pump prime compared with no FFP on 24-hour postoperative blood loss (mL/kg) in infants weighing less than 8 kg (MD 0.00; 95% CI –5.33, 5.33) or total volume 24 hour blood loss (mL) (MD 0.00; 95% CI –23.06, 23.06).

The poor-quality RCT by Oliver (2003) reported no significant difference between the use of FFP (1 unit) in the pump prime compared with no FFP on 24-hour postoperative blood loss (mL/kg) in infants weighing less than 10 kg (MD –18.60; 95% CI –34.21, –2.99). However, in secondary analyses reported by Oliver (2003) a significantly reduced volume of postoperative blood loss was observed in patients undergoing complex surgery and in cyanotic patients who were administered FFP in the pump prime (complete data NR). The study was rated as poor-quality because the method of randomisation was not reported. In addition, the author’s conclusions did not align with the data presented. Results of this study should be interpreted with caution.

Table 3.3.17 Neonatal and paediatric patients requiring cardiac surgery: Results for FFP versus no FFP – bleeding events (major and minor)

| Study  Level of evidence a  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%)  Median (IQR)  Mean ± SD | No FFP  n/N (%)  Median (IQR)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| FFP versus no FFP | | | | | | | | | |
| Lee 2013298  Level II  *Fair* | N=123 | Infants and children (aged > 1 month to 16 years) requiring CPB surgery | Single centre, South Korea | FFP (1–2 units) in the pump prime versus no FFP | Bleeding (mL/kg) after heparin reversal | NR | NR | NR | NR |
|  | Subgroup analysis: age | | | |
| Infants (aged < 12 months)  N=55 | 12.3 (7.8, 16.7) | 12.2 (9.6, 18.3) | NR | *No significant difference*  *P =*0.677 |
| Children (aged 12 months to 16 years)  N=68 | 10 (6, 13.1) | 10 (6.4, 16.1) | NR | *No significant difference*  *P =*0.893 |
| McCall 2004299  Level II  *Fair* | N=20 | Infants (< 8 kg) requiring CPB surgery | Single unit, USA | FFP (1 unit) in the pump prime versus no FFP | Postoperative (0–24 hr) blood loss (mL/kg) | 10 ± 7 (n=10) | 10 ± 5 (n=10) | MD 0.00 [–5.33, 5.33]c | *No significant difference*  *P =*1.0c |
| Postoperative (0–24 hr) blood loss (mL)d | 43 ± 30 (n=10) | 43 ± 22 (n=10) | MD 0.00  [–23.06, 23.06] | *No significant difference*  *P =*1.0c |
| Oliver 2003300  Level II  *Poor* | N=56 | Infants and children (≤ 10 kg) requiring CPB surgery | Single hospital, Minnesota, USA | FFP (1 unit) in the pump prime versus no FFP | Postoperative (0–24 hr) blood loss (mL/kg) | 32.4 ± 17.6 (n=28) | 51.0 ± 38.3 (n=28) | MD –18.60 [–34.21, –2.99]c | *No significant difference*  *P =*0.152e |
|  | Subgroup analysis: surgical grade | | | |
| Simple | 36 ± NR (n=8)  \*estimated from graph | 22 ± NR (n=11)  \*estimated from graph | NR | *No significant difference*  *P =*0.21 |
| Complex | 30 ± NR (n=20)  \*estimated from graph | 68 ± NR (n=17)  \*estimated from graph | NR | *Favours FFP*  *P =*0.003 |
|  | *Subgroup analysis: presence of cyanosis* | | | |
| cyanotic patients | 35 ± NR (n=15)  \*estimated from graph | 70 ± NR (n=11)  \*estimated from graph | NR | Favours FFP  *P =*0.035 |
| acyanotic patients | 32 ± NR (13)  \*estimated from graph | 40 ± NR (17)  \*estimated from graph | NR | No significant difference  *P =*0.933 |

CCHD, cyanotic congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass: FFP, fresh frozen plasma; GEL, gelofusine; HES, hydroxyethyl starch; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity if I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** Data reported by Yang (2012), calculated using the reported mean blood loss (mL/kg) and mean weight (kg) in each group.

**e.** *P-*value reported by trial authors.

###### Transfusion-related serious adverse events

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of FFP in neonatal or paediatric patients undergoing surgery that reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process identified three Level II studies (Lee 2013, McCall 2004, Oliver 2003) that assessed the effect of FFP in neonatal and paediatric patients undergoing surgery and provided evidence for transfusion volume or incidence. The RCTs by Lee (2013) and McCall (2004) were fair-quality and the RCT by Oliver (2003) was poor-quality. **Table 3.3.18** summarises the results from these studies.

The fair-quality RCT reported by Lee (2013) found that infants (aged < 12 months) administered 1–2 units of FFP in the pump prime received a significantly greater median volume of blood products (mL/kg) transfused intraoperatively, but the volume difference was not significant when the FFP used in the pump prime was not included in the analysis. Infants who received FFP in the pump prime required significantly more RBCs in the CPB circuit and after heparin reversal, but required significantly less FFP after heparin reversal. In children (aged 12 months to 16 years) who were administered 1–2 units of FFP in the pump prime, there was no significant difference on the median volume of blood products (mL/kg) transfused intraoperatively. Only FFP requirements after heparin reversal were reported to be significantly less in those who had received FFP in the pump prime. When assessing the total volume of blood products transfused during the first 24 hours in ICU, Lee (2013) reported that there were no significant differences between treatment groups in both infants and children (see **Table 3.3.18**)**.**

The fair-quality RCT reported by McCall (2004) found that total donor exposures were reduced among infants undergoing cardiac surgery when FFP was administered in the pump prime (MD –1.30; 95% CI –2.57, –0.03). For individual blood products, only donor exposures to cryoprecipitate were significantly lower in infants who received FFP (MD –1.60; 95% CI –2.35, –0.85). There was no significant difference for RBC or platelet donor exposures. The authors concluded that the use of FFP in the pump prime decreases the transfusion of cryoprecipitate after CPB, and tends to decrease the overall mean patient exposure to blood products. The study was underpowered and the authors noted the small size did not allow for detection of differences between cyanotic and acyanotic patients, or those undergoing simple and complex operations.

The poor-quality RCT reported by Oliver (2003) found patients who received FFP in the pump prime were more likely to have more total blood products transfused intraoperatively and 24 hours postoperatively (MD 1.90; 95CI% –0.38, 4.18), but the effect was not significant when the FFP used in the pump prime was not included in the analysis. For individual blood product requirements, there was no significant difference between patients who received FFP in the pump prime and those who did not for RBCs (MD 0.10; 95% CI –0.24, 0.44), platelet concentrate (MD 0.80; 95% CI –0.06, 1.66) or cryoprecipitate (MD 0.00; 95% CI –0.33, 0.33]. The use of FFP in the pump prime resulted in a significantly increased total amount of FFP administered to patients (MD 0.70 95% CI 0.38, 1.02). The study was rated as being poor-quality because the method of randomisation was not reported. In addition, the author’s conclusions did not align with the data presented. Results of this study should be interpreted with caution.

Table 3.3.18 Neonatal and paediatric patients requiring cardiac surgery: Results for FFP versus no FFP – transfusion volume or incidence

| Study  Level of evidence a  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%)  Median (IQR)  Mean ± SD | | No FFP  n/N (%)  Median (IQR)  Mean ± SD | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | | | |
| FFP versus no FFP | | | | | | | | | | | |
| Lee 2013298  Level II  *Fair* | N=123 | Infants and children (aged > 1 month to 16 years) requiring CPB surgery | Single centre, South Korea | FFP (1–2 units) in the pump prime versus no FFP | **Infants (aged < 12 months)** | | | | | |  |
| Total intraoperative transfusion requirements (mL/kg) | 94.2 (76.1, 128.4) | | 61.7 (47.4, 83.6) | | NR | *Favours no FFP*  *P =*0.001 |
| Total intraoperative transfusion requirements (mL/kg)  \*excluding FFP in the pump prime | 64 (52.5, 86.3) | | | 61.7 (47.4, 83.6) | NR | *No significant difference*  *P =*0.497 |
| RBC in pump priming (mL) | 125 (125, 125) | | | 125 (125, 125) | NR | *No significant difference*  *P =*1.000 |
| additional RBC into CPB circuit (mL) | 125 (125, 250) | | | 125 (125, 125) | NR | *Favours no FFP*  *P =*0.002 |
| RBC after heparin reversal (mL) | 40 (0, 70) | | | 2.5 (0, 37.5) | NR | *Favours no FPP*  *P =*0.047 |
| FFP after heparin reversal (mL) | 0 (0, 0) | | | 0 (0, 43.1) | NR | *Favours FFP*  *P =*0.042 |
| Platelets after heparin reversal (mL) | 0 (0, 0) | | | 0 (0, 0) | NR | *No significant difference*  *P =*0.342 |
| Total transfusion requirements (mL) during 24 hours in the ICU | 7.9 (0.4, 14.4) | | | 15.9 (4.6, 33.5) | NR | *No significant difference*  *P =*0.065 |
| RBC (mL) | 5 (0, 42.5) | | | 12.5 (0, 66.8) | NR | *No significant difference*  *P =*0.567 |
| FFP (mL) | 0 (0, 38.8) | | | 32.5 (0, 50) | NR | *No significant difference*  *P =*0.102 |
| platelets (mL) | 0 (0, 31.3) | | | 0 (0, 36) | NR | *No significant difference*  *P =*0.944 |
| pump blood (mL) | 0 (0, 3.8) | | | 0 (0, 18.8) | NR | *No significant difference*  *P =*0.386 |
| **Infants and children (aged > 12 months to 16 years)** | | | | | |  |
| Total intraoperative transfusion requirements (mL/kg) | | 32.4 (20.2, 52.8) | | 34.4 (20.1, 65.7) | NR | *No significant difference*  *P =*0.857 |
| Total intraoperative transfusion requirements (mL/kg)  \*excluding FFP in the pump prime | | 21.8 (12.9, 41.3) | | 34.4 (20.1, 65.7) | NR | *No significant difference*  *P =*0.060 |
| RBC in pump priming (mL) | | 125 (0, 250) | | 250 (0, 250) | NR | *No significant difference*  *P =*0.203 |
| additional RBC into CPB circuit (mL) | | 0 (0, 125) | | 0 (0, 250) | NR | *No significant difference*  *P =*0.742 |
| RBC after heparin reversal (mL) | | 5 (0, 375) | | 125 (0, 412.5) | NR | *No significant difference*  *P =*0.302 |
| FFP after heparin reversal (mL) | | 0 (0, 11.3) | | 150 (0, 300) | NR | *Favours FFP*  *P =*0.002 |
| Platelets after heparin reversal (mL) | | 0 (0, 0) | | 0 (0, 0) | NR | *No significant difference*  *P =*0.717 |
| Total transfusion requirements (mL) during 24 hours in the ICU | | 6.3 (1.9, 15.3) | | 10 (0, 14.6) | NR | *No significant difference*  *P =*0.863 |
| RBC (mL) | | 0 (0, 120) | | 0 (0, 125) | NR | *No significant difference*  *P =*0.975 |
| FFP (mL) | | 0 (0, 242.5) | | 0 (0, 157) | NR | *No significant difference*  *P =*0.598 |
| platelets (mL) | | 0 (0, 20) | | 0 (0, 30) | NR | *No significant difference*  *P =*0.955 |
| pump blood (mL) | | 0 (0, 145) | | 0 (0, 15) | NR | *No significant difference*  *P =*0.718 |
| McCall 2004299  Level II  Fair | N=20 | Infants (< 8 kg) requiring CPB surgery | Single unit, USA | FFP (1 U) in the pump prime versus no FFP | Total donor exposures per patient | | 4.1 ± 1.5 (n=10) | | 5.4 ± 1.4 (n=10) | MD –1.30 [–2.57, –0.03]c | *Borderline favours FFP*  *P =*0.05c  *P =*0.06d |
| RBC | | 1.8 ± 0.4 | | 2.1 ± 0.3 | MD–0.30 [–0.61, 0.01]c | *No significant difference*  *P =*0.06c  *P =*0.09d |
| platelets | | 0.9 ± 0.7 | | 1.0 ± 0.7 | MD –0.10 [–0.71, 0.51]c | *No significant difference*  *P =*0.75c  *P =*0.8d |
| cryoprecipitate | | 0.4 ± 0.8 | | 2.0 ± 0.9 | MD –1.60 [–2.35, –0.85]c | *Favours FFP*  *P <*0.0001c  *P <*0.001d |
| FFP | | 1.0 ± 0.0 | | 0.3 ± 0.5 | MD 0.70 [0.39, 1.01]c | *Favours no FFP*  *P <*0.0001c  *P <*0.001d |
| Blood products administered postoperatively, prior to ICU admission (no. patients) | | | | | | |
| platelets | | 1/10 (10%) | | 1/10 (10%) | RR 1.00 [0.07, 13.87]c | *No significant difference*  *P =*1.00c |
| cryoprecipitate | | 2/10 (20%) | | 0/10 (0%) | RR 5.00 [0.27, 92.62]c | *No significant difference*  *P =*0.28 |
| FFP | | 0/10 (0%) | | 3/10 (30%) | RR 0.14 [0.01, 2.45]a | *No significant difference*  *P =*0.18 |
| Oliver 2003300  Level II  Poor | N=56 | Infants and children (≤ 10 kg) requiring CPB surgery | Single hospital, Minnesota, USA | FFP (1 U) in the pump prime versus no FFP | Total blood products (units) transfused (intraoperative and initial 24 hours in ICU)  \*including FFP (1U) used in prime pump | | 8.0 ± 4.2 (n=28) | | 6.1 ± 4.5 (n=28) | MD 1.90 [–0.38, 4.18]c | *Favours no FFP*  *P =*0.10c  *P =*0.035d |
| Total blood products (units) transfused (intraoperative and initial 24 hours in ICU)  \*excluding FFP (1U) used in prime pump | | 7.0 ± 4.2 (n=28) | | 6.1 ± 4.5 (n=28) | MD 0.90 [–1.38, 3.18]c | *No significant difference*  *P =*0.44c  *P >*0.10d |
| RBC | | 2.6 ± 0.7 | | 2.5 ± 0.6 | MD 0.10 [–0.24, 0.44]C | *No significant difference*  *P =*0.57c, *P >*0.10d |
| FFP  \*including FFP (1U) used in prime pump | | 1.3 ± 0.5 | | 0.6 ± 0.7 | MD 0.70 [0.38, 1.02]c | *Favours no FFP*  *P <*0.0001c  *P =*<0.001d |
| FFP  \*excluding FFP (1U) used in prime pump | | 0.3 ± 0.5 | | 0.6 ± 0.7 | MD –0.30 [–0.62, 0.02]C | *Favours FFP*  *P =*0.06c  *P =*0.038d |
| Platelet concentrate | | 2.1 ± 1.7 | | 1.3 ± 1.6 | MD 0.80 [–0.06, 1.66]c | *No significant difference*  *P =*0.07c  *P =*0.069d |
| Cryoprecipitate | | 0.1 ± 0.8 | | 0.1 ± 0.4 | MD 0.00 [–0.33, 0.33]c | *No significant difference*  *P =*1.00c  *P >*0.10d |

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; GEL, gelofusine; HES, hydroxyethyl starch; ICU, intensive care unit; MD, mean difference; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value reported by trial authors.

###### Secondary outcomes[[37]](#footnote-37)

Thromboembolic events

The systematic review and hand-searching process identified no studies that assessed FFP in neonatal and paediatric patients undergoing surgery and reported thromboembolic events (stroke, myocardial infection, deep vein thrombosis, or pulmonary embolism).

* + - 1. Cryoprecipitate

| Evidence statements – surgical (cryoprecipitate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In neonatal and paediatric patients undergoing surgery, the effect of cryoprecipitate compared with no cryoprecipitate on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that assessed the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that assessed the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

###### Level III evidence

The systematic review and hand-searching process did not identify any Level III studies that assessed the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

* + - 1. Platelets

| Evidence statements – surgical (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √√ |
|  | 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 |
|  | In neonatal patients undergoing surgery, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that assessed the safety and effectiveness of platelet transfusions compared with no platelet transfusions (or a different platelet transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that assessed the safety and effectiveness of platelet transfusions compared with no platelet transfusions (or a different platelet transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

###### Level III evidence

The systematic review and hand-searching process identified one Level III study Nacoti (2012) that assessed the safety and effectiveness of platelet transfusions compared with no platelet transfusions (or a different platelet transfusion strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**). The main characteristics of this study is summarised in **Table 3.3.19.**

Nacoti (2012) was a fair-quality retrospective cohort study conducted in Italy that involved 243 paediatric patients aged <18 years undergoing liver transplant from deceased brain-dead donors. Combined organ transplantations were excluded. The authors examined the association between various blood components (including RBC, FFP, platelets and fibrinogen) on patient survival after liver transplant and reported the effect of different doses of pre-, peri- and postoperative platelet transfusions on mortality. Seven hepatobiliary surgeons performed all the liver transplants, with two surgeons involved for each procedure. The transfusion policy was based on clinical assessment.

Table 3.3.19 Characteristics and quality of Level III evidence – platelet transfusion in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Nacoti (2012)69 | Retrospective cohort study  *Fair* | Paediatric patients (<18 years) undergoing liver transplant  N=243 | FFP versus platelet versus fibrinogen versus no blood component | Mortality |

FFP, fresh frozen plasma

##### Results

###### Mortality

The systematic review and hand-searching process identified one Level III study of fair-quality (Nacoti 2012) that examined the association between platelet transfusion and mortality in neonatal and paediatric patients undergoing surgery. **Table 3.3.20** summarises the results from this study.

The study by Nacoti (2012) reported an increased risk of mortality at 1 year in patients transfused with ≥1 unit of intraoperative platelets, but the effect was not significant compared with patients who did not receive intraoperative platelets (RR 1.69; 95% CI 0.46, 6.24). A similar result was reported for patients who were transfused with platelets within 48 hours after liver transplant (RR 1.90; 95% CI 0.64, 5.60). Nacoti (2012) also examined the association between mortality and preoperative platelet transfusions, and reported no significant difference comparing high (≥181 × 1000/cc), medium (91–180 × 1000/cc), or low (≤90 × 1000/cc) volumes of platelets transfused. .

Table 3.3.20 Neonatal and paediatric patients requiring surgery: Results for platelet transfusion versus no platelet transfusion – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelets  n/N (%)  Median (IQR)  Mean ± SD | | No platelets  n/N (%)  Median (IQR)  Mean ± SD | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | | |
| Platelet transfusion versus no platelet transfusion | | | | | | | | | | | |
| Nacoti 201269  Level III  Fair | N=243 | Paediatric liver transplant patients aged <18 years | Single hospital, Italy | Intraoperative platelets (≥1 unit) versus no platelets | Mortality at 1 yearc | 2/11 (18.2%) | | 25/232 (10.9%) | | RR 1.69 [0.46, 6.24]d | *No significant difference*  *P =*0.342e |
| Postoperative platelets (≥ 1 unit) versus no platelets  \*within 48 hours after liver transplant | Mortality at 1 yearc | 3/15 (20.6%) | | 24/228 (10.6%) | | RR 1.90 [0.64, 5.60]d | *No significant difference*  *P =*0.237e |
|  | \*Univariate analysis nonsignificant  Of 41 risk factors investigated, 5 were identified as predicting 1-year patient survival when analysed using a multivariate Cox regression model and included: recipients age, total ischaemia time, number of RBC units transfused during surgery, number of FFP units transfused during surgery, and biliary complications. | | | | |
| Platelet transfusion versus different platelet transfusion volume | | | | | | | | | | | |
| Nacoti 201269  Level III  Fair | N=243 | Paediatric liver transplant patients aged <18 years | Single hospital, Italy | Preoperative platelets (high-dose, ≥181x1000/cc ) versus medium dose (91–180x1000/cc) versus low-dose (≤90x1000/cc) | Mortality at 1 yearc | 9/79 (11.9%) | 9/82 (11.5%) | | 7/76 (9.8%) | NR | No significant difference  *P =*0.929e |

CI, confidence interval; FFP, fresh frozen plasma; RBC, red blood cells; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Mortality back-calculated from reported % patient survival data at 1year.

**d.** Calculated post-hoc using RevMan 5.1.2.

**e.** *P-*value reported by study authors using log-rank test.

###### Bleeding events

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of platelet transfusions on bleeding events (major or minor) in neonatal and paediatric patients undergoing surgery.

###### Transfusion-related serious adverse events

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of platelet transfusions in neonatal and paediatric patients undergoing surgery and reported on transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process did not identify any studies that assessed the effectiveness of platelet transfusions in reducing RBC transfusion volume or incidence in neonatal and paediatric patients undergoing surgery.

* + - 1. Fibrinogen concentrate

| Evidence statements – surgical (fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | 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 |
|  | In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | √√√ | √ |
|  | 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 | √√√ | √ |
|  | 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 |
|  | 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 |
|  | 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 | √√√ | √ |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study (Wikkelso 2013) that evaluated the safety and effectiveness of fibrinogen concentrate in bleeding patients. The review did not provide any usable data because the analysis included studies conducted in both adult and paediatric populations (see **Appendix C, Volume 2**). The authors identified 2 RCTs conducted in a paediatric patients undergoing cardiac surgery with CPB (Cui 2010, Galas 2012). These studies were retrieved for further analysis. It was subsequently determined that the RCTs by Cui (2010) and Galas (2012) did not meet our inclusion criteria. This was because Cui (2010) assessed the effect of fibrinogen used in combination with transfusions guided by thromboelastography compared with transfusions guided by clinical experience (wrong comparator) and Galas (2012) was published in abstract form only.

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that examined the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**).

The systematic review and hand-searching process identified one Level II study (Galas 2014) that examined the safety and effectiveness of fibrinogen concentrate compared with a different fibrinogen strategy (cryoprecipitate) in neonatal and in paediatric patients undergoing surgery. **Table 3.3.21** summarises the main characteristics of this study.

The good-quality RCT by Galas (2014) was conducted in at a single hospital in Brazil and included 63 children aged <7 years who underwent cardiac surgery with CPB. Patients were eligible after heparin neutralisation if they had diffuse bleeding from capillary beds at wound surfaces requiring haemostatic therapy, and a plasma fibrinogen concentration <1 g/L. The authors examined the effect of fibrinogen concentrate (60 mg/kg) compared with cryoprecipitate (10 mL/kg) on mortality, bleeding, transfusion requirements and thromboembolic events. It was noted that the selected subset of cardiac patients (already bleeding and with low fibrinogen levels) in this study showed higher complication rates and length of stay than would be seen in Australian practice.

Table 3.3.21 Characteristics and quality of Level II evidence – fibrinogen concentrate in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Galas (2014)301 | RCT  *Good* | Paediatric patients < 7 years scheduled for elective cardiac surgery with CPB  N=63 | Fibrinogen concentrate (60 mg/kg) versus cryoprecipitate (10 mL/kg) | Mortality  Transfusion incidence Thromboembolic events |

CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; FFP, fresh frozen plasma; MI, myocardial infarction; PE, pulmonary embolism; RBC, red blood cell

###### Level III evidence

The systematic review and hand-searching process identified one Level III study (Nacoti 2012) that assessed the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate (or a different fibrinogen concentrate strategy) in neonatal and paediatric patients undergoing surgery (see **Appendix C, Volume 2**). **Table 3.3.22** summarises the main characteristics of this study.

Nacoti (2012) was a fair-quality retrospective cohort study conducted in Italy that involved 243 paediatric patients aged <18 years undergoing liver transplant from deceased brain-dead donors. Combined organ transplantations were excluded. The authors examined the association between various blood components (including RBC, FFP, platelets and fibrinogen) on patient survival after liver transplant and reported the effect of fibrinogen concentrate on mortality. Seven hepatobiliary surgeons performed all the liver transplants, with two surgeons involved for each procedure. The transfusion policy was based on clinical assessment.

Table 3.3.22 Characteristics and quality of Level III evidence – fibrinogen concentrate in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Nacoti (2012)69 | Retrospective cohort study  *Fair* | Paediatric patients (<18 years) undergoing liver transplant  N=243 | FFP versus platelet versus fibrinogen versus no blood component | Mortality |

FFP, fresh frozen plasma

##### Results

###### Mortality

Fibrinogen concentrate compared with no fibrinogen concentrate

The systematic review and hand-searching process identified one Level III study of fair-quality (Nacoti 2012) that examined the association between fibrinogen concentrate and mortality in neonatal and paediatric patients undergoing liver transplant. **Table 3.3.23** summarises the results from this study.

The study by Nacoti (2012) reported a dose-related increased risk of mortality at 1 year comparing high (≥ 221 mg/dL), medium (141–220 mg/dL), and low (≤ 140 mg/dL) volumes of fibrinogen concentrate, but the effect was not significant.

Fibrinogen concentrate compared with a different fibrinogen strategy

The systematic review and hand-searching process identified one Level II study of good-quality (Galas 2014) that compared fibrinogen concentrate with cryoprecipitate in paediatric patients undergoing cardiac surgery with CPB and reported mortality. Error! Reference source not found. summarises the results from this study.

Galas (2014) reported no deaths in the study cohort. The study was not powered to detect between-group differences for this outcome.

Table 3.3.23 Neonatal and paediatric patients requiring surgery: Results for fibrinogen concentrate compared with no fibrinogen concentrate – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fibrinogen  n/N (%) | | | No fibrinogen  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | | | |
| Fibrinogen versus a different fibrinogen volume | | | | | | | | | | | |
| Nacoti 201269  Level III  Fair | N= 243 | Paediatric liver transplant patients aged <18 years | Single hospital, Italy | Preoperative fibrinogen: high (≥ 221 mg/dL) versus medium (141–220 mg/dL) versus low (≤ 140 mg/dL) | Mortality at 1 yearc | 12/82 (15.1%) | 9/80 (11.6%) | 5/79 (6.6%) | | NR  (univariate analysis) | *No significant difference*  *P =*0.308d |
| Of 41 risk factors investigated, 5 were identified as predicting 1-year patient survival when analysed using a multivariate Cox regression model and included: recipients age, total ischaemia time, number of RBC units transfused during surgery, number of FFP units transfused during surgery, and biliary complications | | | | |

CI, confidence interval; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Mortality back-calculated from reported % patient survival data at 1 year.

**d.** *P-*value reported by study authors using log-rank test.

Table 3.3.24 Neonatal and paediatric patients requiring surgery: Results for fibrinogen concentrate compared with cryoprecipitate – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fibrinogen concentrate  n/N (%) | Cryoprecipitate  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Fibrinogen concentrate versus cryoprecipitate | | | | | | | | | |
| Galas (2014)301  Level II  *Good* | N=63 | Paediatric patients aged <7 years undergoing cardiac surgery with CPB | Single hospital, Brazil | Fibrinogen concentrate (60 mg/kg) versus cryoprecipitate (10 mL/kg) | Mortality | 0/30 (0%) | 0/33 (0%) | not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; NA, not applicable

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Bleeding events

Fibrinogen concentrate compared with no fibrinogen concentrate

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of fibrinogen concentrate on bleeding events (major or minor) in neonatal and paediatric patients undergoing surgery.

Fibrinogen concentrate compared with a different fibrinogen strategy

The systematic review and hand-searching process identified one Level II study of good-quality (Galas 2014) that compared fibrinogen concentrate with cryoprecipitate in paediatric patients undergoing cardiac surgery with CPB and provided evidence for bleeding events **Table 3.3.25** summarises the results from this study.

The RCT by Galas (2014) reported the median volume (mL) of 48 hour blood loss (intraoperative and 46 hour drainage) and found no significant difference between patients administered fibrinogen concentrate compared with cryoprecipitate (*P =*0.672). The authors concluded that the use of fibrinogen concentrate is as efficient and safe as cryoprecipitate in the management of bleeding children undergoing cardiac surgery. The study was limited by small sample size and single centre design.

Table 3.3.25 Neonatal and paediatric patients requiring surgery: Results for fibrinogen concentrate compared with cryoprecipitate – bleeding events

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fibrinogen concentrate  Median (IQR) | Cryoprecipitate  Median (IQR) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Fibrinogen concentrate versus cryoprecipitate | | | | | | | | | |
| Galas (2014)301  Level II  *Good* | N=63 | Paediatric patients aged <7 years undergoing cardiac surgery with CPB | Single hospital, Brazil | Fibrinogen concentrate (60 mg/kg) versus cryoprecipitate (10 mL/kg) | 48 hr blood loss (intraoperative and 48 hr drainage) (mL) | 320 (157–750) | 410 (215–510) | NR | *No significant difference*  *P =*0.672 |

CI, confidence interval; IQR, interquartile range; NR, not reported

a. Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Transfusion-related serious adverse events

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrates (or a different fibrinogen strategy) in neonatal and paediatric patients undergoing surgery and reported on transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

Fibrinogen concentrate compared with no fibrinogen concentrate

The systematic review and hand-searching process did not identify any studies that assessed the effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate in reducing RBC transfusion volume or incidence in neonatal and paediatric patients undergoing surgery.

Fibrinogen concentrate compared with a different fibrinogen strategy

The systematic review and hand-searching process identified one Level II study of good-quality (Galas 2014) that compared the use of fibrinogen concentrate with cryoprecipitate in neonatal and paediatric patients undergoing cardiac surgery with CPB and reported transfusion incidence. There was no evidence for transfusion volume. **Table 3.3.26** summarises the results from this study.

The RCT by Galas (2014) reported a reduced risk of postoperative transfusions in children who received fibrinogen concentrate (86.7%) compared with those who received cryoprecipitate (100.0%) (RR 0.87; 95% CI 0.75, 1.01). For individual blood products, there was a reduced risk for receiving a RBC transfusion (RR 0.86, 95% CI 0.72, 1.02), but the effect was not statistically significant. There was no significant differences between treatment groups for the transfusion incidence of platelets (RR 0.16; 95% CI 0.01, 2.91), FFP (RR 0.41; 95% CI 0.12, 1.41), or cryoprecipitate (RR 1.02; 95% CI 0.58, 1.81).

Table 3.3.26 Neonatal and paediatric patients requiring cardiac surgery: Results for fibrinogen concentrate compared with cryoprecipitate – transfusion volume or incidence

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fibrinogen concentrate  n/N (%) | Cryoprecipitate  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Fibrinogen concentrate versus cryoprecipitate | | | | | | | | | |
| Galas (2014)301  Level II  *Good* | N=63 | Paediatric patients aged <7 years undergoing cardiac surgery with CPB | Single hospital, Brazil | Fibrinogen concentrate (60 mg/kg) versus cryoprecipitate (10 mL/kg) | Postoperative transfusion | 26/30 (86.7%) | 33/33 (100.0%) | RR 0.87 [0.75, 1.01]c | *Favours fibrinogen concentrate*  *P =*0.06c  *P =*0.046d |
| RBC transfusion | 25/30 (83.3%) | 32/33 (97.0%) | RR 0.86 [0.72, 1.02]c | *No significant difference*  *P =*0.094 |
| Platelet transfusion | 0/30 (0%) | 3/33 (9.1%) | RR 0.16 [0.01, 2.91]c | *No significant difference*  *P =*0.240 |
| FFP transfusion | 3/30 (10.0%) | 8/33 (24.2%) | RR 0.41 [0.12, 1.41]c | *No significant difference*  *P =*0.137 |
| Cryoprecipitate transfusion | 13/30 (43.3%) | 14/33 (42.4%) | RR 1.02 [0.58, 1.81]c | *No significant difference*  *P =*0.942 |

CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; RBC, red blood cell

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** *P-*value reported by trial authors.

###### Secondary outcomes[[38]](#footnote-38)

Thromboembolic events

The systematic review and hand-searching process identified one Level II study of good-quality (Galas 2014) that compared the use of fibrinogen concentrate with cryoprecipitate in neonatal and paediatric patients undergoing cardiac surgery with CPB, and provided evidence for thromboembolic events. **Table 3.3.27** summarises the results from this study.

The RCT by Galas (2014) found no significant difference between treatment groups for any thromboembolic event reported; including stroke, acute myocardial infarction, deep venous thrombosis and pulmonary embolism. Incidence rates were low and the study was not powered to detect between-group differences.

Table 3.3.27 Neonatal and paediatric patients requiring cardiac surgery: Results for fibrinogen concentrate compared with cryoprecipitate – thromboembolic events

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fibrinogen concentrate  n/N (%) | Cryoprecipitate  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Fibrinogen concentrate compared with cryoprecipitate | | | | | | | | | |
| Galas (2014)301  Level II  *Good* | N=63 | Paediatric patients aged <7 years undergoing cardiac surgery with CPB | Single hospital, Brazil | Fibrinogen concentrate (60mg/kg) versus cryoprecipitate (10ml/kg) | Stroke | 0/30 (0%) | 0/33 (0%) | NA | *No significant difference*  *P =*NA |
| Acute myocardial infarction | 2/30 (6.7%) | 5/33 (15.2%) | NR | *No significant difference*  *P =*0.429 |
| Deep venous thrombosis | 0/30 (0%) | 0/33 (0%) | NA | *No significant difference*  *P =*NA |
| Pulmonary embolism | 0/30 (0%) | 0/33 (0%) | NA | *No significant difference*  *P =*NA |

CI, confidence interval; NA, not applicable; NR, not reported

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

* + - 1. Combination of FFP, cryoprecipitate, platelet or fibrinogen concentrate

| Evidence statements – surgical (combination FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in neonatal and paediatric patients undergoing surgery.

###### Level III evidence

The systematic review and hand-searching process did not identify any Level III studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in neonatal and paediatric patients undergoing surgery.

### Critically ill neonatal and paediatric patients

* + - 1. Fresh frozen plasma

| Evidence statements – critically ill (fresh frozen plasma) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √√ |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that assessed the safety and effectiveness of FFP compared with no FFP (or a different FFP strategy) in critically ill neonatal and/or paediatric patients.

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that assessed the safety and effectiveness of FFP compared with no FFP (or a different FFP strategy) in critically ill neonatal or paediatric patients.

###### Level III evidence

The systematic review and hand-searching process identified two Level III studies (Church 2009302, Karam 2013303) that examined the safety and effectiveness of FFP compared with no FFP in critically ill neonatal and paediatric patients. The main characteristics of these studies are summarised in **Table 3.3.28.**

Church (2009)302 was a good-quality retrospective analysis of 315 paediatric patients with acute lung injury (ALI) conducted in two PICUs in the USA. Patients were excluded if they received an exchange transfusion or plasmapheresis within the first 72 hours after diagnosis of ALI. The authors compared mortality and ventilation outcomes among patients who received transfusions of blood products (including FFP), and those who did not. Only transfusions administered in the first 72 hours after diagnosis of ALI were included in the analysis.

Karam (2013)303 was a good-quality prospective cohort study conducted at a single PICU in Canada. The authors included 831 paediatric patients aged less than 18 years, to examine the effect of FFP transfusion on a number of clinical outcomes including mortality. Patients were enrolled prospectively over a 1-year period. Exclusion criteria included need for plasma exchange therapy, born prematurely (<40 weeks gestational age), age <3 days or brain death at PICU admission.

Table 3.3.28 Characteristics and quality of Level III evidence – FFP in critically ill neonatal and paediatric patients

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Church (2009)302 | Retrospective cohort  *Fair* | Paediatric patients aged from 36 weeks corrected age to 18 years in ICU with ALI  N=315 | FFP versus no FFP | Mortality |
| Karam (2013)303 | Prospective cohort  *Fair* | Paediatric patients aged <18 years in ICU  N=831 | FFP versus no FFP | Mortality |

ALI, acute lung injury; FFP, fresh frozen plasma; ICU, intensive care unit; MODs, multiple organ dysfunction syndrome.

##### Results

###### Mortality

The systematic review and hand-searching process identified two Level III studies of good-quality (Church 2009, Karam 2013) that assessed the association between FFP and mortality in critically ill neonatal and paediatric patients. **Table 3.3.29** summarises the results from these studies.

The study by Church (2009) reported a significant association between FFP transfusion and mortality in a univariate analysis. The authors used statistical analyses to identify potential confounding variables, and included all those with a *P-*value <0.1 in backward, stepwise multivariate model. The multivariate analyses, which adjusted for organ system dysfunction, Pao2/FIo2 and disseminated intravascular coagulation, showed that the association between the use of FFP in critically ill paediatric patients and mortality remained significant (OR 1.08; 95% CI 1.00, 1.18; p = 0.04). However, in a multivariate analysis which adjusted for PRISM III scores (paediatric risk of mortality) and disseminated intravascular coagulation, the result was no longer significant (OR 1.08; 95% CI 0.98, 1.19; p = 0.09). One limitation of the study was that some patients were transfused with blood products other than FFP, making it difficult to establish the individual effect of FFP on mortality. Still, the authors concluded that FFP transfusion is associated with an increased risk of mortality in children with ALI.

The study by Karam (2013) reported 15 deaths in the FFP transfusion group (16.0%) and 13 deaths in the control group (1.8%), which was a significant difference in favour of the control (p < 0.0001). All deaths were considered to be related to progressive MODs. The authors noted that patient characteristics varied significantly between groups in terms of age, weight and illness severity, with those receiving transfusions being younger, smaller and with more severe illness. The authors attempted to control for this by including several clinically significant covariables in a logistic regression model. After adjusting for weight, severity score and coagulopathy at admission, plasma prior to admission, need for extracorporeal life support, RBC and platelet transfusions, the difference in mortality originally observed was no longer significant. Study limitations included that there were no formal transfusion guidelines in the PICU.

Table 3.3.29 Critically ill neonatal and paediatric patients: Results for FFP compared with no FFP – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FFP  n/N (%) | No FFP  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | |
| Church 2009302  Level III–2  *Good* | N=203 | Paediatric intensive care patients aged 36 weeks corrected gestational age to 18 years with ALI | PICUs at two children’s hospitals, USA | FFP transfusion versus no transfusion | Mortality in PICU | NR/40 (50%)  (estimated from graph) | NR/163 (17%)  (estimated from graph) | NR | *Favours no FFP*  *P <*0.001 |
| NR | NR | OR 1.08 [1.00, 1.18]  (adjusted analysis) | *Favours no FFP*  *P =*0.04 |
| Multivariate analysis that considered organ system dysfunction, PaO2/FIO2 and disseminated intravascular coagulation. | | |  |
| NR | NR | OR 1.08 [0.98, 1.19] | *No significant difference*  *P =*0.09 |
| Multivariate analysis that considered PRISM III scores (paediatric risk of mortality) and disseminated intravascular coagulation. | | |  |
| Karam 2013303  Level III–2  *Good* | N=831 | Paediatric intensive care patients aged <18 years | Single PICU, Canada | FFP or FP transfusion (leukoreduced) versus no transfusion | 28-day mortality | 15/94 (16.0%) | 13/737 (1.8%) | OR 10.6 [4.9, 23.1]  (univariate analysis) | *Favours no FFP*  *P <*0.0001c |
| 15/94 (16.0%) | 13/737 (1.8%) | AR 2.2 [0.5, 8.6]  (adjusted analysis) | *No significant difference*  *P =*NR |
| Adjusted for weight, severity score and coagulopathy at admission, plasma prior to admission, need for ECLS, RBC and platelet transfusions. | | |  |

ALI, acute lung injury: CI, confidence interval; ECLS, extracorporeal life support; FFP, fresh frozen plasma; OR, odds ratio; PICU, paediatric intensive care unit; PRISM, paediatric risk of mortality; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Bleeding events

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of FFP compared with no FFP (or a different FFP strategy) in critically ill neonatal and paediatric patients that reported on bleeding events (major or minor).

###### Transfusion-related serious adverse events

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of FFP compared with no FFP (or a different FFP strategy) in critically ill neonatal and paediatric patients that reported on transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process did not identify any studies that assessed the safety and effectiveness of FFP compared with no FFP (or a different FFP strategy) in critically ill neonatal and paediatric patients that reported on transfusion volume or incidence.

* + - 1. Cryoprecipitate

| Evidence statements – critically ill (cryoprecipitate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In critically ill neonatal and paediatric patients, the effect of cryoprecipitate compared with no cryoprecipitate on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that examined the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate strategy) in critically ill neonatal or paediatric patients.

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that examined the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate strategy) in critically ill neonatal or paediatric patients.

###### Level III evidence

The systematic review and hand-searching process did not identify any Level III studies that examined the safety and effectiveness of cryoprecipitate compared with no cryoprecipitate (or a different cryoprecipitate strategy) in critically ill neonatal or paediatric patients.

* + - 1. Platelets

| Evidence statements – critically ill (platelet transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that examined the safety and effectiveness of platelet transfusions compared with no platelet transfusions (or a different platelet transfusion protocol) in critically ill neonatal or paediatric patients.

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that examined safety and effectiveness of platelet transfusions compared with no platelet transfusions (or a different platelet transfusion protocol) in critically ill neonatal or paediatric patients.

###### Level III evidence

The systematic review and hand-searching process identified one Level III study (Church 2009) that examined the effect of platelet transfusion compared with no platelet transfusions in critically ill paediatric patients. The main characteristics of this study is summarised in **Table 3.3.30**.

Church (2009) was a good-quality retrospective analysis of 315 paediatric patients with ALI conducted in two PICUs in the USA. Patients were excluded if they received an exchange transfusion or plasmapheresis within the first 72 hours after diagnosis of ALI. The authors compared mortality and ventilation outcomes among patients who received transfusions of blood products (including platelets), and those who did not. Only transfusions administered in the first 72 hours after diagnosis of ALI were included in the analysis.

Table 3.3.30 Characteristics and quality of Level III evidence – platelet transfusion in critically ill neonatal and paediatric patients

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Church (2009)302 | Retrospective cohort  *Fair* | Paediatric patients aged from 36 weeks corrected age to 18 years with ALI admitted to ICU  N=315 | Any transfusion (FFP, platelets, RBC) versus no transfusion | Mortality |

ALI, acute lung injury; FFP, fresh frozen plasma; ICU, intensive care unit; RBC, red blood cell.

##### Results

###### Mortality

The systematic review and hand-searching process identified one Level III study of good-quality (Church 2009) that assessed the association between platelet transfusions and mortality among critically ill paediatric patients. **Table 3.3.31** summarises the results from this study.

Church (2009) reported a significant association between mortality and platelet transfusions in a univariate analysis involving 216 patients. The authors used statistical analyses to identify potential confounding variables, and included all those with a *P-*value <0.1 in backward, stepwise multivariate models. After performing a multivariate analysis that adjusted for organ system dysfunction, Pao2/FIo2 and disseminated intravascular coagulation, the difference in mortality was no longer significant (OR 1.85; 95% CI 0.63, 5.46; *P =*0.26). A limitation of the study was that some patients were transfused with blood products other than platelets, making it difficult to establish the individual effect of platelet transfusion on mortality.

Table 3.3.31 Critically ill neonatal and paediatric patients: Results for platelet transfusion compared with no platelet transfusion – mortality

| Study  Level of evidencea  Quality | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Platelet transfusion  n/N (%) | No platelet transfusion  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level III evidence | | | | | | | | | |
| Church 2009302  Level III–2  *Good* | N=216 | Paediatric intensive care patients aged 36 weeks corrected gestational age to 18 years with ALI | PICUs at two children’s hospitals, USA | Platelet transfusion versus no transfusion | Mortality in PICU | NR/53 (36%) | NR/163 (18%) | NR  (univariate analysis) | *Favours no transfusion*  *P <*0.005 |
| NR | NR | OR 1.85 [0.63, 5.46]  (multivariate analysis) | *No significant difference*  *P =*0.26 |
| Multivariate analysis that considered organ system dysfunction, Pao2/FIo2 and disseminated intravascular coagulation. | | |  |

ALI, acute lung injury; CI, confidence interval; OR, odds ratio; PICU, paediatric intensive care unit; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Bleeding events

The systematic review and hand-searching process did not identify any studies that examined the use of platelet transfusion in critically ill neonatal and/or paediatric patients and reported bleeding events (see **Appendix C, Volume 2**).

###### Transfusion-related serious adverse events

The systematic review and hand-searching process did not identify any studies that examined the use of platelet transfusion in critically ill neonatal and/or paediatric patients and reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions).

###### Transfusion volume or incidence

The systematic review and hand-searching process did not identify any studies that examined the use of platelet transfusion in critically ill neonatal and/or paediatric patients and reported transfusion volume or incidence.

* + - 1. Fibrinogen concentrate

| Evidence statements – critically ill (fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process did not identify any Level I studies that examined the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate (or a different fibrinogen concentrate strategy) in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**).

###### Level II evidence

The systematic review and hand-searching process did not identify any Level II studies that examined the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate (or a different fibrinogen concentrate strategy) in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**).

###### Level III evidence

The systematic review and hand-searching process did not identify any Level III studies that examined the safety and effectiveness of fibrinogen concentrate compared with no fibrinogen concentrate (or a different cryoprecipitate strategy) in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**).

* + - 1. Combination of FFP, cryoprecipitate, platelet or fibrinogen concentrate

| Evidence statements – critically ill (combination of fresh frozen plasma, cryoprecipitate, platelet transfusion or fibrinogen concentrate) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 |
|  | 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 | | | | | | |

##### Summary of evidence

The systematic review and hand-searching process identified no studies that examined the use of a combination of blood products (FFP, cryoprecipitate, platelet or fibrinogen concentrate) in critically ill neonatal and/or paediatric patients

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in critically ill neonatal and/or paediatric patients (see **Appendix C, Volume 2**).

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in critically ill neonatal and/or paediatric patients.

###### Level III evidence

The systematic review and hand-searching process identified no Level III studies that examined the effect of a combination of FFP, cryoprecipitate, platelets, or fibrinogen concentrate compared with a difference combination in critically ill neonatal and/or paediatric patients.

## Question 4

Question 4 (Interventional)

In paediatric/neonatal patients, what is the effect of strategies that aim to minimise blood loss on morbidity, mortality, or the need for RBC transfusion?

RBC, red blood cell

### Methods

The systematic review examined the evidence for a variety of strategies that aim to minimise blood loss, and reduce or avoid the need for blood transfusions in a general population of neonatal and paediatric patients, and in subsets of patients in whom a different management strategy might be appropriate (see **Section 4.1**).

Three different populations were considered for this question: (1) preterms (aged <37 weeks gestational age) and infants (aged 0–23 months); (2) neonatal and paediatric patients requiring surgery; and (3) critically ill neonatal and paediatric patients.

For preterms and infants, two comparisons were assessed: (1) placental transfusion compared with no placental transfusion; and (2) intravenous immunoglobulin (IVIg) for haemolytic disease compared with no IVIg.

For neonatal and paediatric patients requiring surgery, eight comparisons were assessed: (1) prevention of hypothermia compared with no prevention of hypothermia; (2) controlled induced hypotension compared with no induced hypotension; (3) acute normovolemic haemodilution (ANH) compared with no ANH; (4) intraoperative cell salvage compared with no cell salvage; (5) viscoelastometric point of care (POC) testing compared with no viscoelastometric POC testing; (6) antifibrinolytics compared with no antifibrinolytics; (7) recombinant activated factor VII (rFVIIa) compared with no rFVIIa (cardiac and extracorporeal membrane oxygenation (ECMO) patients only); and (8) miniaturised CPB systems compared with standard-sized systems.

For critically ill paediatric patients, two comparisons were assessed: (1) rFVIIa compared with no rFVIIa (cardiac and ECMO patients only); and (2) viscoelastometric POC testing compared with no viscoelastometric POC testing.

For this question, only Level II or higher evidence published after 1995 was considered(see **Section 3.1.2** for details on the levels of evidence for intervention studies). Articles published before 1995 that had been included in a Level I study were included in the review. A search of lower level evidence was conducted only for primary outcomes not addressed in higher level evidence (see **Section 2.3**). Secondary outcomes were only extracted from studies that reported one or more primary outcomes.

Overall, the systematic review and hand-searching process identified 13 Level I studies that included 62 Level II studies, and an additional 22 Level II studies that evaluated a strategy aiming to minimise blood loss in neonatal and paediatric patients, and reported primary outcomes relevant to our research questions (**Appendix C, Volume 2**).

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

### Preterm and term infants

* + - 1. Placental transfusion

| Evidence statements – preterm and term infants (placental transfusion) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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.) | √ | √√√ | √√ | √√ | √√ |
|  | 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).304 |
| IVH, intraventricular haemorrhage; PP, practice point | |

|  |
| --- |
| Evidence gaps and areas for future research |
| Further research is needed on:   * the role of the *routine use* of deferred cord clamping in preterm infants. * the use of deferred cord clamping where there is limited access to safe blood for transfusion or phototherapy for jaundice (NB: particularly relevant to Indigenous community because of high level of iron-deficiency anaemia). * alternatives to deferred cord clamping (e.g. cord stripping or milking). |

##### Background

In newborn infants, the number of RBCs in circulation decreases after birth. Infants born before term have a more marked decrease in RBCs due to frequent withdrawal of blood, which may be necessary to monitor the infant's clinical condition. As a result, preterm infants are likely to require RBC transfusions. Placental transfusion can provide the infant with additional blood volume and red cell mass, and thus protect against anaemia and reduce the need for RBC transfusions. The amount of blood returned to the infant depends on when the cord is clamped and at what level the infant is held (above or below the mother’s abdomen) before clamping.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified five Level I studies (Backes 2014, Ghavam 2013, Mathew 2011, McDonald 2013, Rabe 2012) that examined the effect of placental transfusion in preterms and infants (**Appendix C, Volume 2**). **Table 3.4.1** summarises the main characteristics of these reviews.

Backes (2014) and Rabe (2012) were good-quality reviews and provided the most comprehensive evidence for preterm infants. Backes (2014) included 12 RCTs involving 531 very preterm infants (born before 32 weeks gestation). The review provided evidence for the effect of placental transfusion achieved through delayed cord clamping (DCC) compared with early cord clamping (ECC) on transfusion volume and incidence, mortality and IVH. Rabe (2012) assessed 15 RCTs involving 738 preterm infants born before 37 weeks gestation. The review provided evidence for the effect of DCC or cord milking compared to immediate cord clamping (ICC) on transfusion volume and incidence, mortality before discharge, and IVH.

Ghavam (2013) was a poor-quality review that examined the effect of placental transfusion in extremely low birth weight (<1000 g) infants born before 30 weeks gestation. The review compared DCC or cord milking with ICC and included evidence from 10 RCTs involving 199 preterm infants for the outcomes of RBC transfusion incidence and IVH.

Mathew (2011) was a fair-quality review of term and preterm neonates; however, only preterm neonates had outcomes of interest for this overview. The authors examined the effect of DCC compared to ECC on transfusion volume and incidence, mortality and IVH.

McDonald (2013) was a good-quality review that assessed the effectiveness of placental transfusion in term infants born after 37 weeks gestation. The review included data from 15 RCTs involving more than 3911 infants; however, only one outcome of interest (mortality) was relevant for this review.

Table 3.4.1 Characteristics and quality of Level I evidence – placental transfusion in preterm and term infants

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Backes (2014)305 | Systematic review  *Good* | Preterm infants (<32 weeks gestation)  12 RCTs, N=531 | Placental transfusion (DCC or cord milking) versus no placental transfusion (ECC) | Transfusion incidence  Mortality  IVH |
| Ghavam (2013)306 | Systematic review  *Poor* | Preterm neonates (<30 weeks gestation) with ELBW (<1000 g)  10 RCTs, N=199 | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | Transfusion incidence  IVH |
| Mathew (2011)307 | Systematic review  *Fair* | Terma and preterm neonates  27 RCTs (15 term, 14 preterm); N=NR | Placental transfusion (DCC) versus no placental transfusion (ECC) | Transfusion incidence  Mortality  IVH |
| McDonald (2013)304 | Systematic review  *Good* | Term infants (>37 weeks gestation)  15 RCTs, N=3911 | Placental transfusion (DCC) versus no placental transfusion (ECC) | Mortality |
| Rabe (2012)308 | Systematic review  *Good* | Preterm infants (<37 weeks gestation)  15 RCTs, N=738 | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | Transfusion incidence  Mortality  IVH |

DCC, delayed cord clamping; ECC, early cord clamping; ELBW, extremely low birth weight; ICC, immediate cord clamping; IVH, intraventricular haemorrhage, NR, not reported; RCT, randomised controlled trial

**a.** None of the term studies reported outcomes of interest for this review.

###### Level II evidence

Twenty of the Level II studies assessed by the included Level I studies reported outcomes relevant to our research question. The systematic review and hand-searching process identified two additional Level II studies (Alan 2014, Katheria 2014) that examined the effect of placental transfusion in preterms and term infants, and had been published after the literature search dates of the included Level I studies (**Appendix C, Volume 2**). **Table 3.4.2** summarises the main characteristics of the Level II studies relevant to this evidence review.

Alan (2014) was a fair-quality RCT conducted in a single NICU in Turkey that involved 48 very low birth weight (<1500 g) preterm infants born at or before 32 weeks gestation. The authors examined the effect of cord milking compared with ICC on the need for RBC transfusion in the first 3 days of life and during the NICU stay, the number and volume of RBC transfusions during the NICU stay and in the first 14 and 35 days of life, major bleeding or death in the delivery room or in days 2–7 of life, and severe IVH.

Katheria (2014) was a fair-quality RCT conducted in a single tertiary hospital in the USA that enrolled 60 preterm infants born between 23–32 weeks gestation. The authors compared the effect of placental transfusion (achieved through cord milking) with ICC on transfusion incidence, age when transfusion given, mortality, IVH and severe IVH.

The included studies were largely of unclear risk of bias, with many having some risk of selection bias. For this type of intervention, it is not possible to blind the staff present at delivery.

Table 3.4.2 Characteristics and quality of Level II evidence – placental transfusion in preterm and term infants

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Identified and assessed for this review | | | | |
| Alan (2014)309 | RCT  *Fair* | Preterm infants (≤32 weeks gestation) with VLBW (≤1500 g)  N=48 | Cord milking (n=24) versus ICC (n=24) | Transfusion volume and incidence  Mortality  IVH |
| Katheria (2014)310 | RCT  *Fair* | Preterm infants (aged between 23–32 weeks gestation)  N=60 | Cord milking (n=30) versus ICC (n=30) | Transfusion incidence  Mortality  IVH |
| Identified and assessed by included Level I studiesa,b | | | | |
| Baenziger (2007)311 | RCT  *modified Jadad score 9/10*  *Moderate risk of bias* | Preterm infants (aged between 24–32 weeks gestation)  N=39  \*stratified by GA and vaginal/caesarean birth | DCC (delay time 60–90 s) (n=15) versus ECC (delay time <20 s) (n=24) | Mortality |
| Ceriani-Cernadas (2006)312 | RCT  *Low to unclear risk of bias* | Term infants (>36 weeks gestation)  N=276 | DCC (delay time 60 s) (n=91) versus DCC (delay time 3 mins) (n=92) versus ECC (delay time <15 s) (n=93) | Mortality |
| Gokmen (2011)313 | RCT  *modified Jadad score 9/10*  *High risk of bias* | Preterm infants (<32 weeks gestation, mean 29.3–29.4 weeks)  N=42 | DCC (delay time 30–45 s) (n=21) versus ECC (delay time >10 s) (n=21) | Transfusion incidence  IVH |
| Hofmeyr (1988)314 | RCT  *Moderate risk of bias* | Preterm infants (<35 weeks gestation)  N=38  \*included vaginal and caesarean births | DCC (delay time 60 s) (n=24) versus ICC (n=14)  \*some infants (n=NR) in the DCC group had ergometrine given at delivery | Mortality  IVH |
| Hofmeyr (1993)315 | RCT  *Low to unclear risk of bias* | Preterm infants (<35 weeks gestation) and expected weight <2000 g  N=86  \*included vaginal and caesarean births | DCC (delay time 60–120 s) versus ICC | Mortality  IVH |
| Hosono (2008)316 | RCT  *modified Jadad score 10/10* | Preterm infants (aged between 24–28 weeks gestation)  N=40  \*included vaginal and caesarean births | Cord milking (20 cm/s, 2–3 times) (n=20) versus ICC (n=20) | Transfusion incidence  Mortality  IVH |
| Ibrahim (2000)c317 | RCT  *modified Jadad score 10/10* | Preterm infants (aged between 24–29 weeks gestation) with VLBW (501–1250 g)  N=32  \*vaginal birth only | DCC (delay time 20 s) (n=16) versus ICC (n=16) | Transfusion incidence  IVH |
| Kinmond (1993)318 | RCT  *modified Jadad score 10/10*  *Unclear risk of bias* | Preterm infants (aged between 27–33 weeks gestation)  N=36  \*vaginal birth only | DCC (delay time 25–35 s) (n=17) versus ICC (mean delay time 10 s) (n=19) | Transfusion incidence  Mortality |
| Kugelman (2007)319 | RCT  *Unclear risk of bias* | Preterm infants (aged between 24–35 weeks gestation)  N=65  \*included vaginal and caesarean births | DCC (delay time 30–45 s) (n=30) versus ECC (delay time <10 s) (n=35) | Transfusion incidence  Mortality  IVH |
| March (2013)320 | RCT  *modified Jadad score 10/10* | Preterm infants (aged between 24 and <29 weeks gestation)  N=75 | Cord milking (20 cm before clamping) (n=36) versus ICC (n=39) | Transfusion incidence  Mortality  IVH |
| McDonnell (1997)321 | RCT  *modified Jadad score 10/10*  *Moderate risk of bias* | Preterm infants (aged between 26–33 weeks gestation)  N=46  \*included vaginal and caesarean births | DCC (delay time 31±4 s) (n=23) versus ICC (delay time 7±4 s) (n=23)  \*syntocinon administered at birth | Transfusion volume  Mortality  IVH |
| Mercer (2003)322 | RCT  *modified Jadad score 10/10*  *Low to unclear risk of bias* | Preterm infants (aged between 24–32 weeks gestation)  N=32  \*included vaginal and caesarean births | DCC (delay time 32±12 s) (n=16) versus ICC (delay time 5–10 s) (n=16) | Mortality  IVH |
| Mercer (2006)323 | RCT  *modified Jadad score 10/10*  *Low to unclear risk of bias* | Preterm infants (aged between 24–32 weeks gestation)  N=72  \*stratified by GA  \*included vaginal and caesarean births | DCC (delay time 32.1±12.6 s) (n=36) versus ECC (delay time 6.9±4.3 s) (n=36) | Transfusion incidence  Mortality  IVH |
| Oh (2002)d 324  \*pilot study \*abstract only | RCT  *Not assessed* | Preterm infants (aged between 24–28 weeks gestation) with ELBW  N=33  \*included vaginal and caesarean births | DCC (delay time 30–45 s) (n=16) versus ICC (delay time <5 s) (n=17) | Transfusion incidence  Mortality  IVH |
| Oh (2011)325 | RCT  *modified Jadad score 8/10* | Preterm infants (aged between 24–28 weeks gestation)  N=33 | DCC (delay time 35.2±10.1 s) (n=16) versus ECC (delay time 7.9±5.2 s) (n=17) | IVH |
| Rabe (2000)e326 | RCT  *Moderate risk of bias* | Preterm infants (<33 weeks gestation)  N=40  \*included vaginal and caesarean births | DCC (delay time 45 s) (n=20) versus ECC (delay time <20 s) (n=20) | Transfusion incidence  Mortality  IVH |
| Strauss (2008) 327 | RCT  *Moderate risk of bias* | Preterm infants (aged between 30–36 weeks gestation)  N=105  \*stratified by GA  \*included vaginal and caesarean births | DCC (delay time 60 s) (n=45) versus ICC (n=60) | Transfusion incidence  Mortality  IVH |
| Ultee (2008)328 | RCT  *High risk of bias* | Preterm infants (aged between 34–36 weeks gestation)  N=41  \*vaginal birth only | DCC (n=21) (delay time 180 s) versus ECC (delay time <30 s, mean 13.4 s) | Mortality |
| van Rheenen (2007)329 | RCT  *Low to unclear risk of bias* | Term infants (>37 weeks gestation) and weight >2500 g  N=105 | DCC (delay until cord stopped pulsating, mean 305 s) (n=55) versus ECC (delay time <20 s) (n=50) | Mortality |
| Windrim (2011)330  \* pilot study | RCT | Preterm infants (aged between 24–32 weeks gestation) | DCC (mean delay time 39.7s) versus ICC (mean delay time 5.4 s) | IVH |

DCC, delayed cord clamping; ECC, early cord clamping; ELBW, extremely low birth weight; GA, gestational age; ICC, immediate cord clamping; IVH, intraventricular haemorrhage; NR, not reported; RCT, randomised controlled trial; VLBW, very low birth weight

**a.** Studies reported by Backes (2014) assessed using modified Jadad score (maximum out of 10).

**b.** Mathew (2011), McDonald (2013) and Rabe (2012) reported an overall assessment for risk of bias in included studies.

**c.** Ibrahim (2000) excluded from the review by Rabe (2012) as the intervention did not meet their inclusion criteria (delay time minimum <30 s).

**d**. Oh (2002) was published several years later as Oh (2011). Some systematic reviews double counted the data from this study in their meta-analyses. Where this has occurred, it has been noted.

**e.** Rabe (2000) not included in the review by Backes (2014) as the comparator group (delay time <20 s) not considered to be ECC by the review authors.

**f.** Strauss (2008) enrolled 158 neonates but did not report data for infants aged <30 weeks gestation due to problems with the delayed clamping techniques used in this population.

##### Results

###### Transfusion incidence and volume

The systematic review and hand-searching process identified four Level I studies (Backes 2014, Ghavam 2013, Mathew 2011, Rabe 2012) and two additional Level II studies (Alan 2014, Katheria 2014) that assessed the effect of placental transfusions on the incidence of transfusions, the mean number of transfusions per infant or transfusion volume in preterm and term infants. **Table 3.4.3** summarises the results from these studies.

Transfusion incidence

Backes (2014) identified six trials (Hosono 2008, Ibrahim 2000, Kinmond 1993, March 2013, McDonnell 1997, Mercer 2006) involving 301 preterm infants born before 32 weeks gestation comparing DCC (or cord milking) with ECC that reported the proportion of subjects who received a transfusion. A meta-analysis of the data showed that, in the placental transfusion group, 73 infants (49.3%) required a transfusion compared with 101 infants (66.0%) in the control group. This difference was statistically significant favouring placental transfusion (RR 0.75, 95% CI 0.63, 0.90).

Ghavam (2013) measured RBC transfusion incidence among extremely low birth weight (<1000 g) preterm neonates. In a meta-analysis of five trials (Hosono 2008, Ibrahim 2000, Kugelman 2007, March 2011, Rabe 2000), a significant difference was observed in favour of placental transfusion (MD –2.22, 95% CI –2.52, –1.92, *P <*0.01).

Matthew (2011) conducted a meta-analysis of six trials with 358 preterm infants examining transfusion incidence, and reported a significant difference in favour of placental transfusion (RR 0.72, 95% CI 0.54, 0.96).

Rabe (2012) conducted a meta-analysis of seven trials (Hosono 2008, Kinmond 1993, Kugelman 2007, McDonnell 1997, Mercer 2006, Rabe 2000, Strauss 2008) involving 392 preterm infants born before 37 weeks gestation. In the placental transfusion group, 44 infants (23.7%) required a transfusion for anaemia compared to 75 infants (36.4%) in the control group. This was a significant difference favouring placental transfusion (RR 0.61, 95% CI 0.46, 0.81, *P =*0.00053).

Two additional RCTs provided evidence for transfusion incidence.

Alan (2014) measured transfusion incidence in 42 very low birth weight (<1500 g) infants. No differences were reported for any RBC transfusion in the first 3 days of life (RR 0.50, 95% CI 0.10, 2.44, *P =*0.384) or during NICU stay (RR 0.88, 95% CI 0.67, 1.17, *P =*0.380).

Katheria (2014) assessed transfusion incidence among 60 preterm infants aged 23 to <32 weeks gestation. In the placental transfusion group, 11 infants (37%) received a transfusion compared to 22 infants (73%) in the control group. This was a significant difference which favoured placental transfusion (*P =*0.004). A subgroup analysis of infants aged <29 weeks gestation was conducted, with the results also favouring placental transfusion (RR 0.66, 95% CI 0.44, 0.97, *P =*0.04). There was no significant difference in the age when transfusion was given (MD 0.00, 95% CI –6.09, 6.09, *P =*1.00).

A meta-analysis was conducted to evaluate all studies that reported transfusion incidence in preterm infants (born <37 weeks gestation), and to evaluate the effectiveness of placental transfusion in this population (**Figure 3.4.1**). Studies were stratified by gestational age at birth. The analysis showed that placental transfusion significantly reduced the mean number of RBC transfusions (RR 0.76; 95% CI 0.65, 0.88). There was no significant heterogeneity (I2=17%).

Mean number of transfusions per infant

Backes (2014) conducted a meta-analysis of six trials (Gokmen 2011, Hosono 2008, Ibrahim 2000, Kinmond 1993, Mercer 2006, Oh 2002) involving 245 preterm infants born before 32 weeks gestation. There was a significant difference in the mean number of transfusions per infant, favouring placental transfusion (MD –1.14, 95% CI –2.01, –0.27).

Rabe (2012) conducted a meta-analysis of five trials (Hosono 2008, Kinmond 1993, Mercer 2006, Oh 2002, Rabe 2000) involving 210 preterm infants born before 37 weeks gestation and reported a statistically significant difference favouring placental transfusion for the number of transfusions administered (MD –1.26, 95% CI –1.87, –0.64).

Matthew (2011) also conducted a meta-analysis of four trials (NR) involving 144 preterm infants examining the mean number of transfusions administered. A significant difference favouring placental transfusion was reported (MD –0.92, 95% CI –1.78, –0.05).

One additional RCT provided evidence for number of transfusions. Alan (2014) reported the median number of RBC transfusions in very low birth weight (<1500 g) infants in the first 14 days of life (1 versus 1, *P =*0.828), first 35 days of life (2 versus 2, *P =*0.840) and during NICU stay (3 versus 3, *P =*0.813), and reported no significant differences between groups.

A meta-analysis was conducted to evaluate all studies that reported the mean number of transfusions in preterm infants (born <37 weeks gestation), and to evaluate the effectiveness of placental transfusion in this population (**Figure** **3.4.2**). Results were to be stratified by degree of prematurity, but all studies were in preterms born <32 weeks gestation. The analysis showed that placental transfusion significantly reduced the mean number of RBC transfusions (MD –1.16; 95% CI –1.93, –0.40); however, there was substantial heterogeneity for this outcome (I2=60%).

Transfusion volume

The RCT by Alan (2014) reported the median volume of RBC transfusions in the first 14 days of life (10 versus 10, *P =*0.773), first 35 days of life (25 versus 25, *P =*0.885) and during NICU stay (45 versus 42, *P =*0.872). No statistically significant differences were reported between groups at any time point.

Table 3.4.3 Preterm and term infants: Results for placental transfusion versus no placental transfusion – Transfusion volume or incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Placental transfusion  n/N (%)  Mean ± SD (n)  Median (range) | | No placental transfusion  n/N (%)  Mean ± SD (n)  Median (range) | | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | | | | |
| Backes 2014305  Level I  *Good* | 6 trials (Hosono 2008,316 Ibrahim 2000,317 Kinmond 1993,318 March 2013,320 McDonnell 1997,321 Mercer 2006323)  N=301 | Preterm infants (<32 weeks gestation) | NR | Placental transfusion (DCC or cord milking) versus no placental transfusion (ECC) | Transfusion incidence | 73/148 (49.3%) | 101/153 (66.0%) | | RR 0.75 (0.63, 0.90) | | | *Favours placental transfusion*  *P =*0.002  No significant heterogeneity  I2 = 0% |
| 6 trials (Gokmen 2011,313 Hosono 2008c,316 Ibrahim 2000,317 Kinmond 1993,318 Mercer 2006,323 Oh 2002)324  N=245 | Mean no. of transfusions | NR (n=122) | | NR (n=123) | | | MD –1.14 (–2.01, –0.27) | *Favours placental transfusion*  *P =*0.010  Substantial heterogeneity  I2 = 64% |
| Ghavam 2013306  Level I  *Poor* | 5 trials (Hosono 2008,316 Ibrahim 2000,317 Kugelman 2007,319 March 2011,331 Rabe 2000326)  N=NR | Preterm neonates (<30 weeks gestation) with ELBW (<1000 g) | NR | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | RBC transfusion | 70/NR | | 79/NR | | | MD –2.22 (–2.52, –1.92) | *Favours placental transfusion*  *P <*0.001  Heterogeneity NR  I2 = NR |
| Mathew 2011307  Level I  *Fair* | 6 trials(NRd)  N=358 | Preterm neonates | UK, USA, Germany, 2 trials NR | Placental transfusion (DCC) versus no placental transfusion (ECC) | Transfusion incidence | NR | | NR | | | RR 0.72 (0.54, 0.96) | *Favours placental transfusion*  *P =*NR  Heterogeneity NR  I2 = NR |
| 4 trials (NRd)  N=144 | Mean no. of transfusions administered | NR | | NR | | | MD –0.92 (–1.78, –0.05) | *Favours placental transfusion*  *P =*NR  Heterogeneity NR  I2 = NR |
| Rabe 2012308  Level I  *Good* | 7 trials (Hosono 2008,316 Kinmond 1993e,318 Kugelman 2007,319 McDonnell 1997,321 Mercer 2006,323 Rabe 2000,326 Strauss 2008327)  N=392 | Preterm infants (<37 weeks gestation) | Scotland, England, Israel, Australia, USA x2 | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | Transfusion for anaemia | 44/186 (23.7%) | | 75/206 (36.4%) | | | RR 0.61 (0.46, 0.81) | *Favours placental transfusion*  *P =*0.00053  No significant heterogeneity  I2 = 0% |
| 5 trials (Hosono 2008,316 Kinmond 1993,318 Mercer 2006,323 Oh 2002,324 Rabe 2000326)  N=210 | Scotland, England, USA x2, Japan | Mean no. of transfusions | NR (n=104) | | NR (n=106) | | | MD –1.26 (–1.87, –0.64) | *Favours placental transfusion*  *P =*0.000061  No significant heterogeneity  I2 = 0% |
| Level II evidence | | | | | | | | | | | | |
| Alan 2014309  Level II  *Fair* | N=42 | Preterm infants (≤32 weeks gestation) with VLBW (≤1500 g) | Single NICU, Turkey | Placental transfusion (cord milking) versus no placental transfusion (ICC) | No. of infants undergoing RBC transfusion in first 3 days of life | 2/21 (9.5%) | | 4/21 (19.0%) | | RR 0.50 (0.10, 2.44)c | | *No significant difference*  *P =*0.384 |
| No. of infants undergoing RBC transfusion during study period | 15/19 (78.9%) | | 17/19 (89.5%) | | RR 0.88 (0.67, 1.17)c | | *No significant difference*  *P =*0.380 |
| Median no. of RBC transfusions in first 14 days of life | 1 (0–3) | | 1 (0–4) | | NR | | *No significant difference*  *P =*0.828 |
| Median no. of RBC transfusions in first 35 days of life | 2 (0–6) | | 2 (0–7) | | NR | | *No significant difference*  *P =*0.840 |
| Median no. of RBC transfusions during NICU stay | 3 (0–7) | | 3 (0–8) | | NR | | *No significant difference*  *P =*0.813 |
| Volume of RBC transfusions in first 14 days of life (mL/kg) | 10 (0–40) | | 10 (0–45) | | NR | | *No significant difference*  *P =*0.773 |
| Volume of RBC transfusions in first 35 days of life (mL/kg) | 25 (0–78) | | 25 (0–75) | | NR | | *No significant difference*  *P =*0.885 |
| Volume of RBC transfusions during NICU stay (mL/kg) | 45 (0–103) | | 42 (0–116) | | NR | | *No significant difference*  *P =*0.872 |
| Katheria 2014310  Level II  *Fair* | N=60 | Preterm infants (23 to <32 weeks gestation) | Single hospital, USA | Placental transfusion (cord milking) versus no placental transfusion (ICC) | Transfusion incidence | 11/30 (37%) | | 22/30 (73%) | | 0.50 [0.30, 0.84]f | | *Favours placental transfusion*  *P =*0.004 |
|  | *Subgroup analysis: gestational age* | | | | | |  |
| infants <29 weeks gestation | 9/14 (64%) | | 14/14 (100%) | | RR 0.66 (0.44, 0.97)f | | *Favours placental transfusion*  *P =*0.04 |
| Age (days) when transfusion given | 12 ± 11 (n=30) | | 12 ± 13 (n=30) | | MD 0.00 (–6.09, 6.09)f | | *No significant difference*  *P =*1.00f |

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; ELBW, extremely low birth weight; ICC, immediate cord clamping; MD, mean difference; NICU, neonatal intensive care unit; NR, not reported; RBC, red blood cell; RR, risk ratio; SD, standard deviation; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Data used in the meta-analysis by Backes (2014) for Hosono (2008) does not match the published report. Not clear if this is corrected data retrieved from the authors, or error in reporting.

**d.** The studies included in the meta-analysis by Mathew (2011) were not able to be verified.

**e.** Data used in the meta-analysis by Rabe (2012) for Kinmond (1993) does not match that in the review by Backes (2014). Kinmond (1993) reported RBC transfusion incidence for ventilated patients only (1/13 vs 7/13) whereas Backes (2014) is assumed to report data retrieved from the authors, that included all patients (5/17 vs 9/19).

**f.** Calculated post-hoc using RevMan 5.1.2.

Figure 3.4.1 Meta-analysis: placental transfusion versus control in preterm infants by gestational age at birth – transfusion incidence



Figure 3.4.2 Meta-analysis: placental transfusion versus control in preterm infants by gestational age at birth – mean number of transfusions per infant



###### Mortality

The systematic review and hand-searching process identified four Level I studies (Backes 2014, Matthew 2011, McDonald 2013, Rabe 2012) and two additional Level II studies (Alan 2014, Katheria 2014) that assessed the effect of placental transfusions on mortality in preterm and term infants. **Table 3.4.4** summarises the results from these studies.

Backes (2014) conducted a meta-analysis of eight trials (Baenziger 2007, Hosono 2008, Kinmond 1993, March 2013, McDonnell 1997, Mercer 2003, Mercer 2006, Oh 2002) involving 373 preterm infants born before 32 weeks gestation. Mortality before discharge favoured placental transfusion, with six deaths (3.4%) recorded in the placental transfusion group compared with 18 deaths (9.3%) in the control group (RR 0.42, 95% CI 0.19, 0.95).

Matthew (2011) conducted a meta-analysis of nine trials (details NR) involving 503 preterm neonates and found no significant difference in mortality when comparing DCC with ECC (RR 0.55, 95% CI 0.21, 1.46).

McDonald (2013) conducted a meta-analysis of two trials (Cernadas 2006, van Rheenen 2007) involving 381 term infants that reported mortality. Three deaths (1.3%) were recorded in the placental transfusion (DCC) group compared with one death (0.47%) in the control group (ECC). All events occurred in the van Rheenen (2007) study, and the difference was not statistically significant (RR 2.73, 95% CI 0.29, 25.38).

Rabe (2012) assessed mortality in preterm infants and conducted several subgroup and sensitivity analyses. The first meta-analysis included 13 trials involving 668 infants (Baenziger 2007, Hofmeyr 1988, Hofmeyr 1993, Hosono 2008, Kinmond 1993, Kugelman 2007, McDonnell 1997, Mercer 2003, Mercer 2006, Oh 2002, Rabe 2000, Strauss 2008, Ultee 2008) and assessed mortality before discharge. No difference was reported between groups, with 10 deaths (3.1%) recorded in the placental transfusion group compared with 17 deaths (4.9%) in the control group (RR 0.63, 95% CI 0.31, 1.28). A subgroup analysis (by intervention) found no significant difference with DCC (12 trials; RR 0.62, 95% CI 0.28, 1.36, *P =*0.23) or cord milking patients (1 trial; RR 0.67, 95% CI 0.12, 3.57, *P =*0.64).

Rabe (2012) also conducted two sensitivity analyses, the first including studies with a low risk of bias for allocation concealment and the second including studies with a high or unclear risk of bias in this domain. The first meta-analysis included two trials (Oh 2002, Mercer 2006) and recorded two deaths (3.8%) in the placental transfusion group compared with six deaths (11.3%) in the control group. This difference was not significant (RR 0.40, 95% CI 0.10, 1.59, *P =*0.19). The second meta-analysis included 11 trials (Baenziger 2007, Hofmeyr 1988, Hofmeyr 1993, Hosono 2008, Kinmond 1993, Kugelman 2007, McDonnell 1997, Mercer 2003, Rabe 2000, Strauss 2008, Ultee 2008) and recorded eight deaths (3.0%) in the placental transfusion group and 11 deaths (3.7%) in the control group. This difference was also not significant (RR 0.74, 95% CI 0.32, 1.73, *P =*0.49).

Two additional RCTs provided evidence for mortality; however neither study was sufficiently powered to detect a statistically significant difference between groups for this outcome.

Alan (2014) reported a composite outcome of major bleeding or death at two time points (in the delivery room or in days 2–7 of life) among 48 very low birth weight (<1500 g) infants. The first analysis reported no deaths in the placental transfusion group and two deaths (8.3%) in the control group (RR 0.20, 95% CI 0.01, 3.96, *P =*0.29). The second analysis reported three deaths (13.6%) in the placental transfusion group and three deaths (13.6%) in the control group (RR 1.00, 95% CI 0.23, 4.42, *P =*1.00). Neither analysis showed a statistically significant difference between comparator groups.

Katheria (2014) assessed mortality in 60 preterm infants and reported no significant difference between groups (RR 2.00, 95% CI 0.19, 20.90, *P =*0.56).

A meta-analysis was conducted to include all 17 studies[[39]](#footnote-39) that evaluated the effect of placental transfusion on mortality in preterm infants (**Figure 3.4.3**). Studies were stratified by age of gestation at birth. The analysis showed no statistically significant between-group difference on the outcome of mortality (RR 0.73; 95% CI 0.38, 1.42). There was no significant heterogeneity (I2=0%).

Figure 3.4.3 Meta-analysis: placental transfusion versus control in preterm and term infants by gestational age at birth – mortality



Table 3.4.4 Preterm and term infants: Results for placental transfusion versus no placental transfusion – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Placental transfusion  n/N (%) | No placental transfusion  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Backes 2014305  Level I  *Good* | 8 trials (Baenziger 2007,311 Hosono 2008,316 Kinmond 1993318, March 2013,320 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002324)  N=373 | Preterm infants (<32 weeks gestation) | NR | Placental transfusion (DCC or cord milking) versus no placental transfusion | Mortality before discharge | 6/179 (3.4%) | 18/194 (9.3%) | RR 0.42 (0.19, 0.95) | *Favours placental transfusion*  *P =*0.04  No significant heterogeneity  I*2* = 0% |
| Mathew 2011307  Level I  *Fair* | 9 trials (Baenziger 2007,311 Hofmeyr 1988,314 Kugelman 2007,319 McDonnell 1997,321 Mercer 2006,323 Strauss 2007,332 3 trials NR)  N=503 | Preterm neonates | Switzerland, South Africa, Israel, Australia, USA x2 | Placental transfusion (DCC) versus no placental transfusion (ECC) | Mortality | NR | NR | RR 0.55 (0.21, 1.46) | *No significant difference*  *P =*NR  Heterogeneity NR  I2 = NR |
| McDonald 2013304  Level I  *Good* | 2 trials (Cernadas 2006,312 van Rheenen 2007329)  N=381 | Term infants (>37 weeks gestation) | Central/South America, Africa | Placental transfusion (DCC) versus no placental transfusion (ECC) | Mortality  \*all events occurred in van Rheenen 2007 | 3/239 (1.3%) | 1/142 (0.7%) | RR 2.73 (0.29, 25.38) d | *No significant difference*  *P =*0.38  No significant heterogeneity  I2 = 0% |
| Rabe 2012308  Level I  *Good* | 13 trials (Baenziger 2007,311 Hofmeyr 1988,314 Hofmeyr 1993,315 Hosono 2008,316 Kinmond 1993,318 Kugelman 2007,319 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002,324 Rabe 2000,326 Strauss 2008,327 Ultee 2008328)  N=668 | Preterm infants (<37 weeks gestation) | Scotland x2, England, South Africa x2, The Netherlands, Israel, Australia, USA x4, Japan | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | Mortality before discharge | 10/319 (3.1%) | 17/349 (4.9%) | RR 0.63 (0.31, 1.28) | *No significant difference*  *P =*0.20  No significant heterogeneity  I2 = 0% |
| 12 trials (Baenziger 2007,311 Hofmeyr 1988,314 Hofmeyr 1993,315 Kinmond 1993,318 Kugelman 2007,319 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002,324 Rabe 2000,326 Strauss 2008,327 Ultee 2008328)  N=628 | Scotland, England, South Africa, The Netherlands, Israel, Australia, USA | *DCC patients only* | *Subgroup analysis: by intervention* | | |  |
| 8/299 (2.7%) | 14/329 (4.3%) | RR 0.62 (0.28, 1.36) | *No significant difference*  *P =*0.23  No significant heterogeneity  I2 = 0% |
| 1 trial (Hosono 2008316)  N=40 | Japan | Cord milking only | 2/20 (10.0%) | 3/20 (15.0%) | RR 0.67 (0.12, 3.57) | *No significant difference*  *P =*0.64 |
|  |  |  | *Sensitivity analysis: risk of bias for allocation concealment* | | |  |
| 2 trials (Oh 2002,324 Mercer 2006323)  N=105 | USA | Studies with low risk of bias | 2/52 (3.8%) | 6/53 (11.3%) | RR 0.40 (0.10, 1.59) | *No significant difference*  *P =*0.19  No significant heterogeneity  I2 = 0% |
| 11 trials (Baenziger 2007,311 Hofmeyr 1988,314 Hofmeyr 1993,315 Hosono 2008,316 Kinmond 1993,318 Kugelman 2007,319 McDonnell 1997,321 Mercer 2003,322 Rabe 2000,326 Strauss 2008,327 Ultee 2008328)  N=563 | Scotland, England, South Africa, The Netherlands, Israel, Australia, USA, Japan | Studies with high/unclear risk of bias | 8/267 (3.0%) | 11/296 (3.7%) | RR 0.74 (0.32, 1.73) | *No significant difference*  *P =*0.49  No significant heterogeneity  I2 = 0% |
| Level II evidence | | | | | | | | | |
| Alan 2014309  Level II  *Fair* | N=48 | Preterm infants (≤32 weeks gestation) with VLBW (≤1500 g) | Single NICU, Turkey | Placental transfusion (cord milking) versus no placental transfusion (ICC) | Major bleeding or death in the delivery room | 0/24 (0%) | 2/24 (8.3%) | RR 0.20 (0.01, 3.96)c | *No significant difference*  *P =*0.29c |
| Major bleeding or death in days 2–7 of life | 3/22 (13.6%) | 3/22 (13.6%) | RR 1.00 (0.23, 4.42)c | *No significant difference*  *P =*1.000 |
| Katheria 2014310  Level II  *Fair* | N=60 | Preterm infants (23 to <32 weeks gestation) | Single hospital, USA | Placental transfusion (cord milking) versus no placental transfusion (ICC) | Mortality | 2/30 (7%) | 1/30 (3%) | RR 2.00 (0.19, 20.90)c | *No significant difference*  *P =*0.56c |

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; ICC, immediate cord clamping; NICU, neonatal intensive care unit; NR, not reported; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** McDonald (2012) compared early with late cord clamping (RR 0.37, 95% CI 0.04 to 3.41), therefore the data were re-calculated post-hoc using RevMan 5.1.2 to reverse the intervention/comparator arms.

###### Secondary outcomes[[40]](#footnote-40)

Intraventricular haemorrhage

The systematic review and hand-searching process identified four Level I studies (Backes 2014, Ghavam 2013, Matthew 2011, Rabe 2012) and two additional Level II studies (Alan 2014, Katheria 2014) that assessed the effect of placental transfusions on IVH in preterm and term infants. **Table 3.4.5** summarises the results from these studies.

Backes (2014) conducted a meta-analysis of nine trials (Gokmen 2011, Hosono 2008, Ibrahim 2000, March 2013, McDonnell 1997, Mercer 2003, Mercer 2006, Oh 2002, Oh 2011) involving 390 preterm infants born before 32 weeks gestation. A statistically significant effect was reported for IVH (all grades), favouring placental transfusion (RR 0.62, 95% CI 0.43, 0.91, *P =*0.01); however, the analysis included duplicate data (both Oh 2002 and Oh 2011 were included). Severe IVH (grades 3 or 4) was reported to be assessed by six trials (Hosono 2008, McDonnell 1997, March 2013, Mercer 2003, Mercer 2006, Oh 2002), and a meta-analysis showed that the effect was not statistically significant (RR 0.64, 95% CI 0.34, 1.21, *P =*0.17). However in the RCT by Oh (2002), the same number of infants had IVH (all grades) and severe IVH (grades 3 or 4) suggesting that the number of infants with IVH (all grades) is underestimated, or the number of infants with severe IVH (grades 3 or 4) is overestimated.[[41]](#footnote-41)

Ghavam (2013) assessed the effect of placental transfusion on IVH in preterm neonates with extremely low birth weight (<1000 g). A meta-analysis of six trials (Ibrahim 2000, Kugelman 2007, Mercer 2006, Oh 2011, Rabe 2000, Windrim 2011 ) involving 196 neonates showed no significant difference between groups (6 trials; RR 0.56, 95% CI 0.29, 1.07, *P =*0.08).

Matthew (2011) conducted a meta-analysis of seven trials (details NR) involving 408 preterm neonates, and reported a significant effect favouring placental transfusion on the incidence of IVH (RR 0.49, 95% CI 0.32, 0.74).

Rabe (2012) assessed IVH in preterm infants born before 37 weeks gestation and conducted several subgroup and sensitivity analyses. The first meta-analysis included 10 trials (Kugelman 2007, Hosono 2008, Hofmeyr 1993, Hofmeyr 1988, McDonnell 1997, Mercer 2003, Mercer 2006, Oh 2002, Rabe 2000, Strauss 2008) involving 539 infants and assessed the effect of placental transfusion on IVH (all grades). A significant effect favouring placental transfusion was reported (RR 0.59, 95% CI 0.41, 0.85, *P =*0.0048). A second meta-analysis involving six trials (Hofmeyr 1988, Hofmeyr 1993, Hosono 2008, Mercer 2003, Mercer 2006, Rabe 2000) that examined the effect of placental transfusion on severe IVH (grades 3 or 4) showed no significant difference between groups (RR 0.68, 95% CI 0.23, 1.96, *P =*0.47).

A subgroup analysis was conducted by Rabe (2012) based on the type of intervention assessed in the included studies. Five RCTs (Hofmeyr 1988, Hofmeyr 1993, Mercer 2003, Mercer 2006, Rabe 2000) assessed DCC, with no significant difference for severe IVH reported between groups (RR 0.85, 95% CI 0.20, 3.66, *P =*0.83). One RCT (Hosono 2008) assessed cord milking and again, no significant difference in severe IVH was reported (RR 0.50, 95% CI 0.10, 2.43, *P =*0.39).

Rabe (2012) also conducted two sensitivity analyses, the first including studies with a low risk of bias for allocation concealment and the second including studies with a high or unclear risk of bias in this domain. One RCT (Mercer 2006) with a low risk of bias reported no significant difference between groups for severe IVH (RR 0.33, 95% CI 0.01, 7.92, *P =*0.50). A meta-analysis of five trials (Hofmeyr 1988, Hofmeyr 1993, Hosono 2008, Mercer 2003, Rabe 2000) with a high risk of bias also showed no significant difference (RR 0.76, 95% CI 0.24, 2.36, *P =*0.63).

The RCT by Alan (2014) assessed severe IVH (grade 3 or 4) in 42 preterm infants (<32 weeks gestation) with VLBW (<1500 g) and reported no significant difference between groups. However, the number of infants who developed IVH was reported as percentage points (13.6% versus 0%), which could not be accurately re-calculated to incident numbers.

The RCT by Katheria (2014) assessed IVH (all grades) and severe IVH in 60 preterm infants (23–32 weeks gestation). It reported no statistically significant difference between groups for either outcome (RR 0.73; 95% CI 0.34, 1.55 and RR 0.50; 95% CI 0.10, 2.53, respectively).

A meta-analysis was conducted to include all RCTs identified in this review that assessed the effect of placental transfusion in preterm infants on IVH (all grades) (**Figure 3.4.4**) and severe (IVH) (**Figure 3.4.5**). Studies were grouped by gestational age at birth. The analyses showed a significant effect favouring placental transfusion on the outcome of IVH (all grades) (RR 0.59; 95% CI 0.41, 0.85) but not severe IVH (RR 0. 56, 95% 0.32, 1.32).

Table 3.4.5 Preterm and term infants: Results for placental transfusion versus no placental transfusion – IVH (secondary outcome)

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | | Setting  Location | | Intervention versus comparator | | Outcome | | Results | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Placental transfusion  n/N (%) | | No placental transfusion  n/N (%) | | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b | |
| Level I evidence | | | | | | | | | | | | | | | | | |
| Backes 2014305  Level I  *Good* | 9 trialsc (Gokmen 2011,313 Hosono 2008,316 Ibrahim 2000,317 March 2013,320 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002,324 Oh 2011325)  N=390 | Preterm infants (<32 weeks gestation) | | NR | | Placental transfusion (DCC or cord milking) versus no placental transfusion | | IVH (all grades) | | 32/192 (16.7%) | | 54/198 (27.3%) | | | RR 0.62 (0.43, 0.91) | *Favours placental transfusion*  *P =*0.01  No significant heterogeneity  I2 = 0% | |
| 6 trialsd (Hosono 2008,316 March 2013,320 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002324)  N=283 | Severe IVH (grade 3 or 4) | | 12/139 (8.6%) | | 20/144 (13.9%) | | | RR 0.64 (0.34, 1.21) | *No significant difference*  *P =*0.17  No significant heterogeneity  I2 = 0% | |
| Ghavam 2013306  Level I  *Poor* | 6 trials (Ibrahim 2000,317 Kugelman 2007,319 Mercer 2006,323 Oh 2011,325 Rabe 2000,326 Windrim 2011330)  N=196 | Preterm neonates (<30 weeks gestation) with ELBW (<1000 g) | | NR | | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | | IVH | | NR | | NR | | | OR 0.56 (0.29, 1.07) | *No significant difference*  *P =*0.08  Heterogeneity NR  I2 = NR | |
| Mathew 2011307  Level I  *Fair* | 7 trials (Kugelman 2007,319 Mercer 2003,322 Mercer 2006,323 Oh 2002,324 Rabe 2000,326 Strauss 2007, 1 trial NR)  N=408 | Preterm neonates | | Israel, USA x3, UK, Germany | | Placental transfusion (DCC) versus no placental transfusion (ECC) | | IVH | | NR | | NR | | | RR 0.49 (0.32, 0.74) | *Favours placental transfusion*  *P =*NR  Heterogeneity NR  I2 = NR | |
| Rabe 2012308  Level I  *Good* | 10 trials (Hofmeyr 1993,315 Hofmeyr 1988,314 Hosono 2008,316 Kugelman 2007,319 McDonnell 1997,321 Mercer 2003,322 Mercer 2006,323 Oh 2002,324 Rabe 2000,326 Strauss 2008327)  N=539 | Preterm infants <37 weeks gestation | | England, South Africa x2, Israel, Australia, USA x4 Japan | | Placental transfusion (DCC or cord milking) versus no placental transfusion (ICC) | | IVH (all grades) | | 35/260 (13.5%) | | 56/279 (20.1%) | | | RR 0.59 (0.41, 0.85) | *Favours placental transfusion*  *P =*0.0048  No significant heterogeneity  I2 = 0% | |
| 6 trials (Hofmeyr 1988,314 Hofmeyr 1993,315 Hosono 2008,316 Mercer 2003,322 Mercer 2006,323 Rabe 2000326)  N=305 | England, USA, South Africa, Japan | | Severe IVH (grade 3 or 4) | | 5/154 (3.2%) | | 7/151 (4.6%) | | | RR 0.68 (0.23, 1.96) | *No significant difference*  *P =*0.47  No significant heterogeneity  I2 = 0% | |
|  |  | |  | | *Subgroup analysis: intervention* | | | | | |  | |
| 5 trials (Mercer 2003,322 Rabe 2000,326 Hofmeyr 1988,314 Mercer 2006,323 Hofmeyr 1993315)  N=265 | England, USA, South Africa | | DCC patients only | | 3/134 (2.2%) | | 3/131 (2.3%) | | | RR 0.85 (0.20, 3.66) | *No significant difference*  *P =*0.83  No significant heterogeneity  I2 = 0% | |
| 1 trial (Hosono 2008316)  N=40 | Japan | | Cord milking patients only | | 2/20 (10.0%) | | 4/20 (20.0%) | | | RR 0.50 (0.10, 2.43) | *No significant difference*  *P =*0.39 | |
|  |  | |  | | *Sensitivity analysis: risk of bias for allocation concealment* | | | | | |  | |
| 1 trial (Mercer 2006323)  N=72 | USA | | Studies with low risk of bias | | 0/36 (0%) | | 1/36 (2.8%) | | | RR 0.33 (0.01, 7.92) | *No significant difference*  *P =*0.50 | |
| 5 trials (Hofmeyr 1988,314 Hofmeyr 1993,315 Hosono 2008,316 Mercer 2003,322 Rabe 2000326)  N=233 | England, USA, South Africa, Japan. | | Studies with high/unclear risk of bias | | 5/118 (4.2%) | | 6/115 (5.2%) | | | RR 0.76 (0.24, 2.36) | *No significant difference*  *P =*0.63  No significant heterogeneity  I2 = 0% | |
| Level II evidence | | | | | | | | | | | | | | | | | |
| Alan 2014309  Level II  *Fair* | N=42 | | Preterm infants (≤32 weeks gestation) with VLBW (≤1500 g) | | Single NICU, Turkey | | Placental transfusion (cord milking) versus no placental transfusion (ICC) | | Severe IVH (grade 3 or 4) | | 3/22 (13.6%) | | 0/22 (0%) | RR 7.00 [0.38, 128.02]e | | | *No significant difference*  *P =*0.19e |
| Katheria 2014310  Level II  *Fair* | N=60 | | Preterm infants (23 to <32 weeks gestation) | | Single hospital, USA | | Placental transfusion (cord milking) versus no placental transfusion (ICC) | | IVH (all grades) | | 8/30 (27%) | | 11/30 (37%) | RR 0.73 [0.34, 1.55]e | | | *No significant difference*  *P =*0.29 |
| Severe IVH | | 2/30 (7%) | | 4/30 (13%) | RR 0.50 [0.10, 2.53]e | | | *No significant difference*  *P =*0.40e |

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; ELBW, extremely low birth weight; ICC, immediate cord clamping; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; RR, risk ratio; VLBW, very low birth weight

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes duplicate data (Oh 2002 and Oh 2011 are the same study).

**d.** The same number of infants in the RCT by Oh (2002) had IVH (all grades) and severe IVH (grades 3 or 4) suggesting that the number of infants with IVH (all grades) is underestimated, or the number of infants with severe IVH (grades 3 or 4) is overestimated.

**e.** Calculated post-hoc using RevMan 5.1.2.

Figure 3.4.4 Meta-analysis: placental transfusion versus control in preterm infants by gestational age at birth – IVH (all grades)



Figure 3.4.5 Meta-analysis of placental transfusion versus control in preterm infants by gestational age at birth – severe IVH (grades 3 and 4)



* + - 1. IVIg for haemolytic disease

| Evidence statements – preterm and term infants (IVIg for haemolytic disease) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √ |
|  | 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 G  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| Recommendation – preterm and term infants (IVIg for haemolytic disease) | |
| R7  (Grade B) | In infants with HDFN, the *routine* use of IVIg is not recommended. |
| Practice point – preterm and term infants (IVIg for haemolytic disease) | |
| 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 – preterm and term infants (IVIg for haemolytic disease) | |
| 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; IVIg, intravenous immunoglobulin G; PP, practice point, R, recommendation | |

|  |
| --- |
| Evidence gaps and areas for future research |
| There is a need for further research on the use of IVIg in maternity patients to prevent HDFN |

##### Background

Haemolytic disease of the fetus and newborn (HDFN) is characterised by a breakdown of red blood cells by maternal antibodies. During pregnancy, some of the mother’s antibodies are transported across the placenta and enter the fetal circulation. HDFN occurs if there is incompatibility of the Rh or ABO blood groups between the mother and fetus. It often leads to anaemia and hyperbilirubinaemia, which require multiple exchange transfusions. Exchange transfusions are associated with an increased risk of neonatal morbidity and mortality. IVIg blocks Fc receptor cells that mediate RBC breakdown and may be effective in treating HDFN, thereby reducing the incidence of exchange transfusions.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study that examined the effect of IVIg for alloimmune haemolytic disease in preterm and term infants (**Appendix C, Volume 2**). **Table 3.4.6** summarises the main characteristics of this study.

Louis (2014) was a good-quality systematic review of 12 RCTs involving 236 preterm and term neonates with alloimmune haemolytic disease (AHD) secondary to Rh incompatibility. The authors examined the effect of IVIg (used therapeutically or prophylactically) compared with placebo on the need for exchange transfusion, number of exchange transfusions per infant and mortality.

**Table 3.4.7** summarises the main characteristics of the Level II studies identified and assessed by Louis (2014). Nine of the 12 Level II studies were reported to have a high risk of bias due to lack of blinding and no rigorous decision criteria on when to give an exchange transfusion. Therefore, sensitivity analyses on pooled data were conducted by Louis (2014) where required.

Table 3.4.6 Characteristics and quality of Level I evidence – IVIg for haemolytic disease in preterm and term infants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| Louis (2014)333 | Systematic review  *Good* | Preterm and term neonates with alloimmune haemolytic disease secondary to Rh incompatibility  12 RCTs, N=236 | IVIg (therapeutic or prophylactic) versus placebo | Exchange transfusion incidence  Mortality |

IVIg, intravenous immunoglobulin; RCT, randomised controlled trial; Rh, rhesus

###### Level II evidence

The systematic review and hand-searching process identified no additional Level II studies that assessed IVIg compared with no IVIg in preterm and term infants with alloimmune haemolytic disease.

Table 3.4.7 Characteristics and quality of Level II evidence – IVIg for haemolytic disease in preterm and term infants

| **Study ID** | **Study type *Study quality*** | **Population**  **N** | **Comparison** | **Outcomes** |
| --- | --- | --- | --- | --- |
| ***Identified and assessed by Louis 2014a*** | | | | |
| Alpay (1999)334 | RCT  *High risk of bias* | Rh and ABO haemolytic disease  Neonates (gestational age NR) with significantly elevated bilirubin levels (>204 μmol/L), positive DAT and reticulocyte count ≥ 10 %  N=116 (ABO n=93, Rh n=16) | IVIg (1 g/kg) over 4 hours at diagnosis (n=58) versus no IVIg (n=58)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Dagoglu (1995)335 | RCT  *High risk of bias* b | Rh haemolytic disease  Neonates (mean 36 weeks gestation) with a positive direct Coombs test  N=45  \*neonates who received IUTs were included  \*mothers were Rh negative | IVIg (0.5 g/kg) as soon as possible after birth within 2 hours (n=22) versus no IVIg (n=19)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Elalfy (2011)336 | RCT  *High risk of bias* | Rh haemolytic disease  Neonates (>38 weeks gestation) with positive direct Coomb’s test requiring phototherapy in the first 12 hours of birth and or rising by 0.5 mg/dL/hr while still below exchange.  N=90  \*mothers were Rh negative | IVIg (0.5 g/kg) administered at 12 hours of life (n=25) versus IVIg (1 g/kg) administered at 12 hours of life (n=15) versus no IVIg (n=50)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Garcia (2004)337 | RCT  *Low risk of bias* | Neonates (mean 33–35 weeks gestation) with haemolytic disease according to modified Liley charts. Neonates receiving IUTs were included.  N=18  \*mothers were Rh negative | IVIg (0.75 g/kg) daily for 3 days (n=11) versus placebo (normal saline 15 mL/kg) (n=7)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Huang (2006)338 | RCT  *High risk of bias* | ABO haemolytic disease  Full term neonates with A or B blood group and positive DAT  N=121  \*mothers were blood group O with Anti-A or Anti-B antibody titre >1:128 | IVIg (dose NR) (n=61) versus placebo (1 g/kg/day of albumin) for 3 days (n=60)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Miqdad (2004)339 | RCT  *High risk of bias* | ABO haemolytic disease  Neonates (mean 38 weeks gestation) with a positive direct Coomb’s test  N=112 | IVIg (0.5 g/kg) when bilirubin rising >0.5 mg/dL/hr (n=56) versus no IVIg (n=56)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Nasseri (2006)340 | RCT  *High risk of bias* | Rh and ABO haemolytic disease  Neonates (≥ 37 weeks gestation) with positive direct Coomb’s test, bilirubin rising ≥ 0.5 mg/dL/hr and below exchange transfusion upon admission  N=34 (ABO n=21, Rh n=13) | IVIg (0.5 g/kg) every 12 hours for 3 doses after admission to NICU (n=17) versus no IVIg (n=17)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Pishva (2000)341 | RCT  *High risk of bias* | Rh or ABO haemolytic disease  Neonate (gestational age NR) with positive direct Coomb’s test  N=40  \*neonates with a history of IUTs were excluded | IVIg (0.5 g/kg) administered over 4–6 hours during first 24 hours of life (n=20) versus no IVIg (n=20)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Rubo (1992)342 | RCT  *High risk of bias* | Rh haemolytic disease  Neonates (gestational age NR) with positive direct Coomb’s test  N=34c  \*mothers were Rh negative | IVIg (0.5 g/kg) administered over 2 hours at diagnosis (n=16) versus no IVIg (n=16)  \*all infants received conventional phototherapy | Exchange transfusion incidence  Mortality |
| Santos (2013)343 | RCT  *Low risk of bias* | Rh haemolytic disease  Neonates (≥ 32 weeks gestation) with positive DAT  N=92  \*neonates who received IUTs were included | IVIg (0.5 g/kg) administered within the first 6 hours of age (n=46) versus no IVIg (n=46)  \*all infants received prophylactic high intensity phototherapy | Exchange transfusion incidence  Mortality |
| Smits-Wintjens (2011)344 | RCT  *Low risk of bias* | Rh haemolytic disease, neonates (≥ 35 weeks gestation) with positive DAT  N=80  \*neonates who received IUTs were included | IVIg (0.75 g/kg) administered within the first 4 hours of life (n=41) versus no IVIg (n=39)  \*all infants received prophylactic high intensity phototherapy | Exchange transfusion incidence  Mortality |
| Voto (1995)345 | RCT  *High risk of bias* | Rh haemolytic disease  Neonates (mean 37–37.5 weeks gestation) with a positive direct Coomb’s test  N=40  \*neonates who received prenatal therapy (maternal IVIg or IUT) were excluded | IVIg (0.8 g/kg/day) for 3 days (n=20) versus no IVIg (n=20)  \*all infants received conventional phototherapy | Exchange transfusion incidenced  Mortality |

DAT, direct antiglobulin test; IVIg, intravenous immunoglobulin; IUT, intrauterine transfusion; NR, not reported; RCT, randomised controlled trial; Rh, rhesus

**a.** Risk of bias assessed using the Cochrane Collaborations ‘risk of bias’ tool.

**b.** Consent withheld for 4 randomised patients (2 in each group).

**c.** Two infants excluded from the analysis post randomisation (1 in each group) due to ‘protocol violations’.

**d.** Voto (1995) reported the rate of exchange transfusion combined with blood transfusions for late-onset anaemia, therefore was not included in the meta-analysis reported by Louis (2014).

##### Results

###### Exchange transfusion incidence

The systematic review by Louis (2014) assessed the effect of IVIg (therapeutic or prophylactic) on the incidence of exchange transfusion in term and preterm neonates with AHD and performed separate meta-analyses in Rh and ABO incompatible patients. **Table 3.4.8** summarises the results from this study.

Haemolytic disease secondary to Rh incompatibility

Nine RCTs (Alpay 1999, Dagoglu 1995, Elalfy 2011, Garcia 2004, Nasseri 2006, Pishva 2000, Rubo 1992, Santos 2013, Smits-Wintjens 2011) involving 426 neonates reported exchange transfusion incidence. A meta-analysis showed an effect favouring IVIg (RR 0.43; 95% CI 0.25, 0.74) but heterogeneity was high (I2=84%). A sensitivity analysis revealed a statistically significant effect favouring IVIg (RR 0.23, 95% CI 0.13, 0.40) in the six RCTs that were assessed by Louis (2014) to have an overall high risk of bias (Alpay 1999, Dagoglu 1995, Elalfy 2011, Nasseri 2006, Pishva 2000, Rubo 1992). Whereas, in the three RCTs assessed to have an overall low risk of bias (Garcia 2004, Santos 2013, Smits-Wintjens 2011), the difference was no longer significant (RR 0.82, 95% CI 0.53, 1.26) (**Figure 3.4.6**). All three RCTs with a low risk of bias evaluated the role of prophylactic IVIg, whereas three of the six RCTs with a high risk of bias evaluated the role of therapeutic IVIg. Removal of these three RCTs (Alpay 1999, Elalfy 2011, Nasseri 2006) from the analysis showed IVIg did not provide a statistically significant (*P =*0.06) beneficial effect in reducing the need for exchange transfusion (RR 0.53; 95% CI 0.27, 1.03) (**Figure 3.4.7**).

Louis (2014) reported pooled data from two RCTs (Garcia 2004, Santos 2013) that provided separate evidence for preterm neonates and found IVIg did not provide a significant benefit in reducing the need for exchange transfusions (RR 0.73; 95% CI 0.44, 1.19).

The review authors also reported pooled results for the mean number of exchange transfusions per infant. In the RCTs assessed to have an overall low risk of bias, there was no significant difference on the number of exchange transfusions per infant (MD –0.02, 95% CI –0.14, 0.10). However, studies assessed to have an overall high risk of bias showed a significant effect in favour of IVIg (MD –0.9, 95% CI –1.5, –0.3).

Haemolytic disease secondary to ABO incompatibility

Louis (2014) reported a meta-analysis of five RCTs (Alpay 1999, Huang 2006, Miqdad 2004, Nasseri 2006, Pishva 2000) involving 350 neonates that demonstrated a beneficial effect of IVIg on the number of infants requiring exchange transfusion (RR 0.31, 95% CI 0.18, 0.55, *P <*0.0001). All studies were assessed by Louis (2014) to have an overall high risk of bias. Pooled results of three RCTs involving 226 neonates showed that IVIg significantly reduced the mean number of exchange transfusions per infant (MD –0.2, 95% CI –0.3, –0.1).

Figure 3.4.6 Meta-analysis: IVIg for haemolytic disease due to Rh isoimmunisation in preterm and term infants – exchange transfusion incidence



Figure 3.4.7 Meta-analysis: IVIg for haemolytic disease due to Rh isoimmunisation (prophylactic only) in preterm and term infants – exchange transfusion incidence



Figure 3.4.8 Meta-analysis: IVIg for haemolytic disease due to ABO isoimmunisation in preterm and term infants – exchange transfusion incidence



Table 3.4.8 Preterm and term infants: Results for IVIg versus no IVIg – exchange transfusion incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IVIg  n/N (%)  Mean ± SD (n) | No IVIg  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Louis 2014333  Level I  *Good* | 9 trials (Alpay 1999,334 Dagoglu 1995,335 Elalfy 2011,336 Garcia 2004,337 Nasseri 2006,340 Pishva 2000,341 Rubo 1992,342 Santos 2013,343 Smits-Wintjens 2011344)  N=426 | Term and preterm neonates with alloimmune haemolytic disease secondary to Rh incompatibility | Turkey (Alpay 1999, Dagoglu 1995), Germany (Rubo 1992) NR (Elalfy 2011, Nasseri 2006, Pishva 2000) | IVIg (therapeutic or prophylactic) versus placebo | No. of infants requiring exchange transfusion | 31/214 | 68/212 | RR 0.43 [0.25, 0.74]  RD –0.27 [–0.45, –0.10] | *Favours IVIg*  *P =*0.002c  Significant heterogeneity  I2 = 86% |
|  | *Sensitivity analysis: risk of bias of included studies* | | |  |
| Studies with a low risk of bias  3 trials (Garcia 2004, Santos 2013, Smits-Wintjens 2011)  N=190 | 20/98 (20.4%) | 19/92 (20.7%) | RR 0.82 (0.53, 1.26) | *No significant difference*  *P =*0.37  No significant heterogeneity  I2 = 0% |
| Studies with a high risk of bias  6 trials (Alpay 1999, Dagoglu 1995, Elalfy 2011, Nasseri 2006, Pishva 2000, Rubo 1992)  N=236 | 11/116 (9.5%) | 49/120 (40.8%) | RR 0.23 (0.13, 0.40) | *Favours IVIg*  *P <*0.0001  No significant heterogeneity  I2 = 0% |
|  | *Subgroup analysis: prophylactic IVIg only d* | | |  |
| Studies with a low risk of bias  3 trials (Garcia 2004, Santos 2013, Smits-Wintjens 2011)  N=190 | 20/98 (20.4%) | 19/92 (20.7%) | RR 0.82 (0.53, 1.26) | *No significant difference*  *P =*0.37  No significant heterogeneity  I2 = 0% |
| Studies with a high risk of bias  3 trials (Dagoglu 1995, Pishva 2000, Rubo 1992)  N=110 | 6/57 (10.5%) | 26/53 (49.1%) | RR 0.21 [0.10, 0.45] | *Favours IVIg*  *P <*0.0001c  No significant heterogeneity  I2 = 0% |
|  | *Subgroup analysis: gestational age at birth* | | |  |
| Preterm infant studies  2 trials (Garcia 2004, Santos 2013)  N=64  \*both studies had a low risk of bias | 10/31 (32.3%) | 12/33 (36.4%) | RR 0.73 (0.44, 1.19) | *No significant difference*  *P =*0.21  No significant heterogeneity  I2 = 0% |
| Mean no. exchange transfusions per infant | *Subgroup analysis: risk of bias of included studies* | | |  |
| studies with a low risk of bias  3 trials (Garcia 2004, Santos 2013, Smits-Wintjens 2011)  N=190 | NR | NR | MD –0.02 (–0.14, 0.10) | *No significant difference*  *P =*NR  No significant heterogeneity  I2 = 0% |
| studies with a high risk of bias  5 trials (NR)  N=199 | NR | NR | MD –0.9 (–1.5, –0.3) | *Favours IVIg*  *P =*NR  Substantial heterogeneity  I2 = 92% |
| 5 trials (Alpay 1999,334 Huang 2006,338 Miqdad 2004,339 Nasseri 2006,340 Pishva 2000341)  N=350 | Term and preterm neonates with alloimmune haemolytic disease secondary to ABO incompatibility | NR | IVIg (therapeutic or prophylactic) versus placebo | No. of infants requiring exchange transfusion  \*all studies had a high risk of bias | 13/174 (7.5%) | 46/176 (26.1%) | RR 0.31 (0.18, 0.55) | *Favours IVIg*  *P <*0.0001  No significant heterogeneity  I2 = 0% |
| 3 trials (NR)  N=226 | No. of exchange transfusions per infant  \*all studies had a high risk of bias | NR | NR | MD –0.2 (–0.3, –0.1) | *Favours IVIg*  *P =*NR  No significant heterogeneity  I2 = 0% |

CI, confidence interval; IVIg, intravenous immunoglobulin; MD, mean difference; NR, not reported; Rh, rhesus; RD, risk difference; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

**d.** IVIg administered within first few hours of birth or before the development of significant hyperbilirubinaemia.

###### Mortality

The systematic review by Louis (2014) provided evidence for mortality in term and preterm neonates with AHD secondary to Rh or ABO incompatibility. **Table 3.4.9** summarises the results from this studies.

There was no deaths reported in the 12 RCTs (Alpay 1999, Dagoglu 1995, Rubo 1992, Santos 2013, Smits-Wintjens 2011, Garcia 2004, Elalfy 2011, Nasseri 2006, Huang 2006, Miqdad 2004, Pishva 2000, Voto 1995) identified by Louis (2014) that compared the effectiveness of IVIg with no IVIg in 236 neonates with AHD secondary to Rh or ABO incompatibility.

Table 3.4.9 Preterm and term infants: Results for IVIg versus no IVIg – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IVIg  n/N (%) | No IVIg  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Louis 2014333  Level I  *Good* | 12 trials (Alpay 1999,334 Dagoglu 1995,335 Elalfy 2011,336 Garcia 2004,337 Huang 2006,338 Miqdad 2004,339 Nasseri 2006,340 Pishva 2000341, Rubo 1992,342 Santos 2013,343 Smits-Wintjens 2011,344 Voto 1995345)  N=236 | Term and preterm neonates with isoimmune haemolytic disease secondary to Rh or ABO incompatibility | Turkey, Germany, NR | IVIg (therapeutic or prophylactic) versus placebo | Mortality | 0/NR | 0/NR | Not estimable | *No significant difference*  *P =*NA  Heterogeneity NR  I2 = NR |

CI, confidence interval; IVIg, intravenous immunoglobulin; NA, not applicable; NR, not reported; Rh, rhesus

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

### Neonatal and paediatric patients undergoing surgery

* + - 1. Prevention of hypothermia

| ***Evidence statements – neonatal and paediatric patients undergoing surgery (prevention of hypothermia)*** | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √√ |
|  | 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 |
|  | 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 | √√√ | √√ |
|  | 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 | | | | | | |

|  |  |
| --- | --- |
| 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.*15 |
| R, recommendation | |

##### Background

In patients undergoing surgery, anaesthesia alters thermoregulatory mechanisms, which can lead to hypothermia if warming mechanisms are not in place. Up to 20% of adult surgical patients experience unintended perioperative hypothermia, defined as a core temperature below 36°C. Even mild hypothermia can cause adverse effects in adults surgical patients, including substantial increases in adverse cardiac outcomes, surgical blood loss, allogeneic transfusion and surgical site infections (see Section 3.6.2 Module 2 – Perioperative). Paediatric patients are more vulnerable to perioperative hypothermia because they have reduced weight to surface area ration, less stores of subcutaneous fat and greater loss of heat from the head compared with adults, and require vigilant proactive approach to maintenance of normothermia. In paediatric patients undergoing surgery, methods for preventing hypothermia may be associated with reduced transfusion volume or incidence, and risk of mortality.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of preventing of hypothermia compared with no prevention of hypothermia in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

The systematic review and hand-searching process identified one Level II study (Caputo 2011) that assessed the safety and effectiveness of preventing hypothermia compared with no prevention of hypothermia in neonatal and paediatric patients undergoing surgery. (**Appendix C, Volume 2**). **Table 3.4.10** summarises the main characteristics of this study**.**

Caputo (2011) was a good-quality RCT of 59 paediatric patients undergoing cardiac surgery with CPB. 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, transfusion volume and incidence of RBCs, platelet and FFP.

Table 3.4.10 Characteristics and quality of Level II evidence – prevention of hypothermia in paediatric patients undergoing surgery

| **Study ID** | **Study type *Study quality*** | **Population**  **N** | **Comparison** | **Outcomes** |
| --- | --- | --- | --- | --- |
| Caputo 2011346 | RCT  *Good* | Paediatric patients (median age 6.5 years) undergoing cardiac surgery with CPB  N=59 | Normothermia (35–37°C) (n=28) versus hypothermia (28°C) (n=31) | Mortality  Transfusion volume and incidence |

CPB, cardiopulmonary bypass; RCT, randomised controlled trial

##### Results

###### Mortality

The systematic review and hand-searching process identified one good-quality Level II study (Caputo 2011) comparing normothermia with hypothermia in paediatric patients undergoing surgery that provided evidence for mortality. **Table 3.4.11** summarises the results from this study.

The RCT by Caputo (2011) assessed all-cause mortality among 59 paediatric patients undergoing cardiac surgery with CPB. No deaths were recorded during the study, but the study was not sufficiently powered to detect a statistically significant difference between groups for this outcome.

Table 3.4.11 Neonatal and paediatric patients undergoing surgery: Results for prevention of hypothermia versus no prevention of hypothermia – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Prevention of hypothermia  n/N (%) | Hypothermia  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Caputo 2011346  Level II  *Good* | N=59 | Paediatric patients (median age 6.5 years) undergoing cardiac surgery with CPB | Single hospital, England | Normothermia (35–37°C) versus hypothermia (28°C) | All-cause in-hospital mortality | 0/28 (0%) | 0/31 (0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; CPB, cardiopulmonary bypass; NA, not applicable

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Transfusion volume and incidence

The systematic review and hand-searching process identified one good-quality Level II study (Caputo 2011) comparing normothermia with hypothermia in paediatric patients undergoing surgery that provided evidence for transfusion volume or incidence. **Table 3.4.12** summarises the results from this study.

Caputo (2011) assessed transfusion volume (mL/kg) and incidence among 59 paediatric patients undergoing cardiac surgery with CPB. No significant differences between groups were reported for RBC transfusion incidence (RR 1.11, 95% CI 0.48, 2.55, *P =*0.81), median RBC transfusion volume (9.6 versus 9.5), platelet/FFP transfusion incidence (RR 1.33, 95% CI 0.46, 3.88, *P =*0.60) or median platelet/FFP transfusion volume (9.9 versus 5.2).

Table 3.4.12 Neonatal and paediatric patients undergoing surgery: Results for prevention of hypothermia versus no prevention of hypothermia – transfusion volume or incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Prevention of hypothermia  n/N (%)  Median (IQR) | Hypothermia  n/N (%)  Median (IQR) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Caputo 2011346  Level II  *Good* | N=59 | Paediatric patients (median age 6.5 years) undergoing cardiac surgery with CPB | Single hospital, England | Normothermia (35–37°C) versus hypothermia (28°C) | RBC transfusion incidence | 8/28 (29%) | 8/31 (26%) | RR 1.11 [0.48, 2.55]c | *No significant difference*  *P =*0.81c |
| RBC transfusion volume (mL/kg) | 9.6 (6.8–19.7) | 9.5 (6.8–16.6) | NR | *No significant difference*  *P =*NR |
| Platelet/FFP transfusion incidence | 6/28 (21%) | 5/31 (16%) | RR 1.33 [0.46, 3.88]c | *No significant difference*  *P =*0.60c |
| Platelet/FFP transfusion volume (mL/kg) | 9.9 (4.9–10.0) | 5.2 (4.9–5.5) | NR | *No significant difference*  *P =*NR |

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IQR, interquartile range; NR, not reported; RBC, red blood cell; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Deliberate/controlled induced hypotension

| Evidence statements – neonatal and paediatric patients undergoing surgery (deliberate/controlled induced hypotension) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 | √√ | √√ |
|  | 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 |
|  | 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 | | | | | | |

|  |
| --- |
| Evidence gaps and areas for future research |
| Further research is needed on:   * the role of reduced hypotension in paediatric spinal surgery |

##### Background

Controlled induced hypotension involves deliberately lowering a patient's mean arterial blood pressure to below normal, with the aim of limiting blood loss and improving the surgical field. In paediatrics, it is commonly used in scoliosis surgery and may help to reduce blood loss and the subsequent need for blood transfusions. The use of controlled hypotension needs to be balanced against the risks of causing reduced perfusion of the spinal cord and other organs.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of controlled induced hypotension compared with no controlled induced hypotension in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

One Level II study (Previous 1996) identified in the systematic review and hand-searching process assessed the safety and effectiveness of controlled induced hypotension compared with no controlled induced hypotension in neonatal and paediatric patients undergoing surgery (**Appendix C, Volume 2**). **Table 3.4.13** summarises the main characteristics of this study.

Precious (1996) was a poor-quality RCT of 50 adolescent patients aged 13–15 years who were undergoing osteotomy or genioplasty. The authors examined the effect of induced hypotensive anaesthesia where blood pressure was maintained within 75% of baseline systolic values, compared with no hypotensive anaesthesia (blood pressure maintained within 10 mm Hg of baseline systolic values). The authors reported transfusion incidence, estimated blood loss and rating of the surgical field.

Table 3.4.13 Characteristics and quality of Level II evidence – deliberate/controlled induced hypotension in paediatric patients undergoing surgery

| **Study ID** | **Study type *Study quality*** | **Population**  **N** | **Comparison** | **Outcomes** |
| --- | --- | --- | --- | --- |
| Precious (1996)347 | RCT  *Poor* | Adolescents (aged 13–15 years) undergoing osteotomy or genioplasty  N=50 | Induced hypotensive anaesthesia (blood pressure maintained within 75% of baseline systolic values) (n=25) versus no hypotensive anaesthesia (blood pressure maintained within 10 mm Hg of baseline systolic values) (n=25) | Transfusion incidence  Bleeding events |

Hg, mercury; RCT, randomised controlled trial

##### Results

###### Mortality

The systematic review and hand-searching process identified no studies that assessed controlled induced hypotension compared with no controlled induced hypotension and reported mortality in neonatal and paediatric patients undergoing surgery.

###### Transfusion volume or incidence

The systematic review and hand-searching process identified one poor-quality Level II study (Precious 1996) comparing induced hypotensive anaesthesia with no hypotensive anaesthesia in paediatric patients undergoing surgery that provided evidence for transfusion incidence. **Table 3.4.14** summarises the results from this study.

Precious (1996) assessed transfusion incidence in 50 adolescent patients undergoing osteotomy or genioplasty, and reported no transfusions in either treatment group.

Table 3.4.14 Neonatal and paediatric patients undergoing surgery: Results for deliberate/controlled induced hypotension versus no deliberate/controlled induced hypotension – transfusion volume or incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Induced hypotension  n/N (%) | No induced hypotension  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Precious 1996347  Level II  *Poor* | N=50 | Adolescents (aged 13–15 years) undergoing osteotomy or genioplasty | Single hospital, Canada | Induced hypotensive anaesthesia (blood pressure maintained within 75% of baseline systolic values) versus no hypotensive anaesthesia (blood pressure maintained within 10 mm Hg of baseline systolic values) | Transfusion incidence | 0/25 (0%) | 0/25 (0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; Hg, mercury; NA, not applicable

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Bleeding events

One Level II study of poor-quality (Precious 1996) provided evidence for bleeding events. **Table 3.4.15** summarises the results from these studies.

Precious (1996) assessed bleeding events in 50 adolescent patients undergoing osteotomy or genioplasty. A significant difference favouring induced hypotension was reported for estimated blood loss by surgeon (MD –1.80, 95% CI –3.19, –0.41, *P <*0.017), by anaesthetist (MD –3.00, 95% CI –4.96, –1.04, *P <*0.003), and by haematocrit (MD –2.60, 95% CI –4.75, –0.45, *P <*0.02). A significant difference favouring induced hypotension was also reported for average estimated blood loss (MD –2.50, 95% CI –3.98, –1.02, *P <*0.002) and surgical field rating (MD –0.5, 95% CI –0.78, –0.22, *P <*0.001).

Table 3.4.15 Neonatal and paediatric patients undergoing surgery: Results for deliberate/controlled induced hypotension versus no deliberate/controlled induced hypotension – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Induced hypotension  Mean ± SD (n) | No induced hypotension  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Precious 1996347  Level II  *Poor* | N=50 | Adolescent patients aged 13–15 years undergoing osteotomy or genioplasty | Single hospital, Canada | Induced hypotensive anaesthesia (blood pressure maintained within 75% of baseline systolic values) versus no hypotensive anaesthesia (blood pressure maintained within 10 mm Hg of baseline systolic values) | Estimated blood loss by surgeon (mL/kg) | 5.0 ± 1.9 (n=25) | 6.8 ± 3.0 (n=25) | MD –1.80 [–3.19, –0.41]c | *Favours induced hypotension*  *P <*0.017 |
| Estimated blood loss by anaesthetist (mL/kg) | 4.9 ± 2.4 (n=25) | 7.9 ± 4.4 (n=25) | MD –3.00 [–4.96, –1.04]c | *Favours induced hypotension*  *P <*0.003 |
| Estimated blood loss by Hct (mL/kg) | 6.3 ± 3.4 (n=25) | 8.9 ± 4.3 (n=25) | MD –2.60 [–4.75, –0.45]c | *Favours induced hypotension*  *P <*0.02 |
| Average estimated blood loss (mL/kg) | 5.4 ± 2.0 (n=25) | 7.9 ± 3.2 (n=25) | MD –2.50 [–3.98, –1.02]c | *Favours induced hypotension*  *P <*0.002 |
| Surgical field rating | 1.2 ± 0.4 (n=25) | 1.7 ± 0.6 (n=25) | MD –0.5 [–0.78, –0.22]c | *Favours induced hypotension*  *P <*0.001 |

CI, confidence interval; Hct, haematocrit; Hg, mercury; MD, mean difference; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Acute normovolaemic haemodilution

| Evidence statements – neonatal and paediatric patients undergoing surgery (acute normovolemic haemodilution) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In paediatric patients undergoing surgery, the effect of ANH compared with no ANH on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 normovolemic haemodilution; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

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| Practice points – surgical (acute normovolemic haemodilution) | |
| 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 normovolemic haemodilution; PP, practice point, | |

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| Evidence gaps and areas for future research |
| * Further research is needed on the role of ANH in paediatric patients undergoing surgery in which substantial blood loss is anticipated. |

##### 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 haematocrit and decreasing the risk of allogenic transfusion.

In infants, particularly those 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

###### Level I evidence

The systematic review and hand-searching process identified no Level I that assessed the safety and effectiveness of ANH compared with no ANH in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

The systematic review and hand-searching process identified three Level II studies (Friesen 2006, Hans 2000, Lisander 1996) that examined the safety and effectiveness of ANH in paediatric patients undergoing surgery (**Appendix C, Volume 2**). **Table 3.4.16** summarises the main characteristics of these studies.

The fair-quality RCT by Friesen (2006) was conducted in the USA and enrolled 32 paediatric patients aged >1 month and <15 kg scheduled for noncomplex open cardiac surgery with CPB. The authors examined the effect of ANH compared with no ANH, and reported on transfusion incidence of homologous blood components during the intraoperative and 24 hr postoperative periods.

The poor-quality RCT by Hans (2000) was conducted in Belgium and involved 34 infants scheduled for craniofacial repair surgery. The authors examined the effect of ANH on blood loss and homologous transfusion volume and incidence.

Lisander (1996) was a poor-quality pilot study conducted in Sweden that involved 24 adolescents undergoing surgery for scoliosis to examine the effect of various blood-saving methods on blood loss and transfusion volume and incidence. One of the treatment arms included in the pilot study was preoperative haemodilution to achieve a haemoglobin concentration of 8 g/L. This was compared with the control arm that included colloids for volume replacement.

Table 3.4.16 Characteristics and quality of Level II evidence – ANH in paediatric patients undergoing surgery

| **Study ID** | **Study type *Study quality*** | **Population**  **N** | **Comparison** | **Outcomes** |
| --- | --- | --- | --- | --- |
| Friesen (2006)348 | RCT  *Fair* | Paediatric patients (weight 5–12 kg) undergoing noncomplex cardiac surgery with CPB  N=32 | ANH (15 mL/kg whole blood withdrawal, with isovolaemia maintained by infusion of 1 mL of 5% albumin solution for each mL of blood withdrawn) (n= 16) versus no ANH (n=16)  \*autologous blood was re-transfused postoperatively | Transfusion incidence |
| Hans (2000)349 | RCT  *Poor* | Paediatric patients (mean age 7 months) scheduled for surgical repair for scaphocephaly or pachycephaly  N=34 | ANH to achieve a Hct of 25% (n=17) versus no ANH (n=17) | Transfusion volume and incidence |
| Lisander (1996)a 350  \*pilot study | RCT  *Poor* | Paediatric patients (mean age 14.5 years) undergoing scoliosis surgery  N=24 | PHD to achieve Hb concentration of 80 g/L (n=10) versus intraoperative haemodilution (dextran, n=13)  \*blood was withdrawn in standard citrated bags (450 mL), with simultaneous volume replacement achieved with 500 mL 6% dextran 70 and later 3% dextran | Transfusion volume |

ANH, acute normovolemic haemodilution; CPB, cardiopulmonary bypass; Hb, haemoglobin; Hct, haematocrit; IAT, intraoperative autotransfusion; PHD, preoperative haemodilution; RCT, randomised controlled trial

**a.** Lisander (1996) was a five armed trial comparing: (1) PHD (2) IAT (3) PHD + IAT (4) PHD + IAT + hypotensive anaesthesia and (5) colloids for volume replacement. The PHD and the control group are reported here.

##### Results

###### Mortality

The systematic review and hand-searching process identified no studies that assessed ANH compared with no ANH that reported mortality in neonatal and paediatric patients undergoing surgery.

###### Transfusion volume and incidence

The systematic review and hand-searching process identified three Level II studies (Friesen 2006, Hans 2000, Lisander 1996) comparing ANH with no ANH in paediatric patients undergoing surgery that provided evidence for transfusion volume or incidence. **Table 3.4.17** summarises the results from these studies.

The RCT by Friesen (2006) assessed transfusion incidence of a number of blood products in 32 infants undergoing noncomplex cardiac surgery with CPB. The authors reported no significant difference in RBC transfusion incidence during surgery with CPB (RR 1.08; 95% CI 0.80, 1.45; *P =*0.63) or after surgery with CPB (RR 1.00; 95% CI 0.24, 4.23; *P =*1.00). There was also no significant difference in transfusion incidence of FFP (RR 0.33; 95% CI 0.04, 2.87; *P =*0.32), platelets (RR 0.14; 95% CI 0.01, 2.56, *P =*0.19) or cryoprecipitate (no events).

The RCT by Hans (2000) 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 (RR 1.07, 95% CI 0.81, 1.42, *P =*0.63) or transfusion volume (MD –2.60, 95% CI –6.34, 1.14, *P =*0.17).

Lisander (1996) assessed transfusion volume in 23 adolescents undergoing scoliosis surgery and found no significant difference in the number of donor blood units transfused (MD   
–0.60; 95% CI –2.61, 1.41; *P =*0.56).

Table 3.4.17 Neonatal and paediatric patients undergoing surgery: Results for ANH versus no ANH – transfusion volume and incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ANH  n/N (%)  Mean ± SD (n) | No ANH  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Friesen (2006)348  Level II  *Fair* | N=32 | Infants (5–12 kg) undergoing noncomplex open cardiac surgery with CPB | Single hospital, USA | ANH to maintain isovolaemia using 5% albumin solution after 15 mL/kg autologous blood withdrawn and re-transfused postoperatively versus no ANH | RBC transfusion during CPB | 14/16 (87.5%) | 13/16 (81.3%) | RR 1.08 [0.80, 1.45]c | *No significant difference*  *P =*0.63c |
| RBC transfusion post CPB | 3/16 (18.8%) | 3/16 (18.8%) | RR 1.00 [0.24, 4.23]c | *No significant difference*  *P =*1.00c |
| FFP transfusion incidence | 1/16 (6.3%) | 3/16 (18.8%) | RR 0.33 [0.04, 2.87]c | *No significant difference*  *P =*0.32c |
| Platelet transfusion incidence | 0/16 (0.0%) | 3/16 (18.8%) | RR 0.14 [0.01, 2.56]c | *No significant difference*  *P =*0.19c |
| FFP or platelet transfusion incidence | 1/16 (6.2%) | 5/16 (31%) | RR 0.20 [0.03, 1.53]c | *No significant difference*  *P =*0.12c |
| Cryoprecipitate transfusion incidence | 0/16 (0.0%) | 0/16 (0.0%) | Not estimable | *No significant difference*  *P =*NA |
| Hans 2000349  Level II  *Poor* | N=34 | Paediatric patients (mean age 7 months) scheduled for surgical repair for scaphocephaly or pachycephaly | Belgium | ANH to achieve a Hct of 25% versus no ANH | Transfusion incidence | 15/17 (88.2%) | 14/17 (82.4%) | RR 1.07 [0.81, 1.42]c | *No significant difference*  *P =*0.63c |
| Transfusion volume | 17.0 ± 4.7 (n=17) | 19.6 ± 6.3 (n=17) | MD –2.60 [–6.34, 1.14]c | *No significant difference*  *P =*0.17c |
| Lisander 1996350  Level II  *Poor*  \*pilot study | N=23 | Paediatric patients (mean age 14.5 years) undergoing scoliosis surgery (ASA class I) | Single hospital, Sweden | ANH to a dilution of Hb 80 g/L versus intraoperative volume replacement with plasma substitute | Donor blood units transfused | 4.9 ± 2.6 (n=10) | 5.5 ± 2.2 (n=13) | MD –0.60 [–2.61, 1.41]c | *No significant difference*  *P =*0.56c |

ANH, acute normovolaemic haemodilution; ASA, American Society of Anesthesiologists; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hb, haemoglobin; Hct, haematocrit; MD, mean difference; NA, not applicable; RR, risk ratio; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Intraoperative cell salvage

| Evidence statements – neonatal and paediatric patients undergoing surgery (intraoperative cell salvage) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √ |
|  | 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 |
|  | 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.) | √ | √√ | √ | √√√ | √ |
|  | 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 points – 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 | |

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| --- |
| Evidence gaps and areas for future research |
| * Further research is needed on the role of intraoperative cell salvage in paediatric patients undergoing surgery in which substantial blood loss is anticipated. |

##### 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 red blood cells suspended in saline. One of the key aims of intraoperative cell salvage is to reduce allogeneic transfusion incidence and volume and associated risks.

##### Summary of evidence

###### Level I evidence

There were no Level I studies identified in the systematic review and hand-searching process that assessed the safety and effectiveness of intraoperative cell salvage compared with no intraoperative cell salvage in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

Three Level II studies (Cholette 2013, Ye 2013, Lisander 2013) were identified in the systematic review and hand-searching process that assessed the safety and effectiveness of intraoperative cell salvage compared with no intraoperative cell salvage in neonatal and paediatric patients undergoing surgery (**Appendix C, Volume 2**). **Table 3.4.18** summarises the main characteristics of these studies.

The good-quality RCT by Cholette (2013) was a pilot study conducted in the USA that involved 106 children weighing <20 kg and scheduled for cardiac surgery with CPB. The authors examined the effect of cell salvaged blood (including use of residual CPB circuit volume) compared with crystalloid, colloid or albumin for volume replacement. Outcomes of interest included mortality, need for RBC transfusion within one, two and seven days post-surgery, and need for platelet, FFP or cryoprecipitate transfusion within two days post-surgery. As this was a pilot study, it was not powered to assess differences in clinical outcomes.

The poor-quality RCT by Ye (2013) was conducted in a single hospital in China and involved 309 paediatric patients scheduled for open-heart surgery with CPB. Patients were aged 6 days to 13 years and weighed 2 to 36 kg. The authors examined the effect of reinfusing washed residual CPB blood on mortality and need for perioperative allogeneic RBC transfusion.

Lisander (1996) was a poor-quality RCT conducted in Sweden that involved 24 adolescents undergoing surgery for scoliosis to examine the effect of various blood-saving methods on blood loss and transfusion volume and incidence. One of the treatment arms included in the pilot study used cell salvaged blood. This was compared with the control arm that included colloids for volume replacement. As this was a pilot study, it was not powered to assess differences in clinical outcomes.

Table 3.4.18 Characteristics and quality of Level II evidence – intraoperative cell salvage in neonatal and paediatric patients undergoing surgery

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Cholette (2013)351  \*pilot study | RCT  *Good* | Paediatric patients weighing <20 kg scheduled for cardiac surgery with CPB  N=106 | Cell salvaged blood (n=53) versus crystalloid, colloid or albumin for volume replacement (n=53) | Mortality  Transfusion incidence |
| Lisander (1996)a 350  \*pilot study | RCT  *Poor* | Paediatric patients (mean age 14.5 years) undergoing scoliosis surgery  N=24 | Cell salvaged blood (n=11) versus intraoperative haemodilution (dextran, n=13)  \*normovolaemia maintained with 6% dextran 70 (up to 500 mL), then 3% dextran (equal volume with Ringer’s acetate) up to a maximum of 1.5 g/kg/bw | Transfusion volume |
| Ye (2013)352 | RCT  *Poor* | Paediatric patients (aged 6 days to 13 years) weighing 2–36 kg scheduled for open-heart surgery with CPB  N=309 | Reinfusion of washed residual CPB circuit blood (n=217) versus no cell salvage (n=92) | Mortality  Transfusion incidence |

CPB, cardiopulmonary bypass; IAT, intraoperative autotransfusion; PHD, preoperative haemodilution; RCT, randomised controlled trial

**a.** Lisander (1996) was a five armed trial comparing: (1) PHD (2) IAT (3) PHD + IAT (4) PHD + IAT + hypotensive anaesthesia and (5) colloids for volume replacement. The IAT and the control group are reported here.

##### Results

###### Mortality

The systematic review and hand-searching process identified two Level II studies (Cholette 2013, Ye 2013) comparing intraoperative cell salvage with no intraoperative cell salvage in paediatric patients undergoing surgery that provided evidence for mortality. **Table 3.4.19** summarises the results from these studies.

Cholette (2013) assessed mortality among 106 children scheduled for cardiac surgery with CPB. Three deaths (5.7%) were recorded in the cell salvage group compared with one in the no cell salvage group (1.9%), but this difference was not significant (RR 3.00, 95% CI 0.32, 27.93, *P =*0.31). The study was not sufficiently powered to detect any differences between groups for this outcome.

Ye (2013) assessed mortality in 309 paediatric patients scheduled for open-heart surgery with CPB. No significant difference was observed between groups (RR 0.21, 95% CI 0.02, 2.31, *P =*0.212), with one death (0.5%) recorded in the cell salvage group and two deaths in the control group (2.2%). The study was not sufficiently powered to detect any differences between groups for this outcome.

Table 3.4.19 Neonatal and paediatric patients undergoing surgery: Results for intraoperative cell salvage versus no intraoperative cell salvage – mortality

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Intraoperative cell salvage  n/N (%) | No cell salvage  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Cholette 2013351  Level II  *Good*  \*pilot study | N=106 | Children weighing <20 kg scheduled for cardiac surgery with CPB | Single hospital, USA | Cell salvaged blood versus crystalloid, colloid or albumin for volume replacement | Mortality | 3/53 (5.7%) | 1/53 (1.9%) | RR 3.00 [0.32, 27.93]c | *No significant difference*  *P =*0.310 |
| Ye 2013352  Level II  *Poor* | N=309 | Paediatric patients (aged 6 days to 13 years) weighing 2–36 kg scheduled for open-heart surgery with CPB | Single hospital, China | Reinfusion of washed residual CPB circuit blood versus no cell salvage | Mortality | 1/217 (0.5%) | 2/92 (2.2%) | RR 0.21 [0.02, 2.31]c | *No significant difference*  *P =*0.212 |

CI, confidence interval; CPB, cardiopulmonary bypass; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Transfusion volume and incidence

The systematic review and hand-searching process identified three Level II studies (Cholette 2013, Lisander 1996, Ye 2013) comparing intraoperative cell salvage with no intraoperative cell salvage in paediatric patients undergoing surgery that provided evidence for transfusion volume or incidence. **Table 3.4.20** summarises the results from these studies.

Cholette (2013) assessed transfusion needs among 106 children scheduled for cardiac surgery with CPB. Cell salvage reduced the mean number of RBCs transfused within 24 hours post-surgery (MD –0.47; 95% CI –0.72, –0.22) and 48 hours post-surgery (MD –0.56; 95% CI –0.90, –0.22); but the effect did not remain statistically significant within 7 days post-surgery (MD –0.46; 95% CI –0.96, 0.04, *P =*0.07). A statistically significant effect on the mean number of platelets (0 ± 0 versus 0.11 ±0.38, *P =*0.03), FFP (0 ± 0 versus 0.15 ± 0.46, *P =*0.02) and cryoprecipitate (0 ± 0 versus 0.08 ± 0.27, *P =*0.04) within 48 hours post-surgery was also reported, but the data were small and underpowered.

The small pilot study by Lisander (1996) reported no significant difference in the mean number of donor blood units transfused among 24 adolescents undergoing surgery for scoliosis (MD –1.40, 95% CI –2.89, 0.09, *P =*0.07). As this was a pilot study, it was not powered to assess differences in clinical outcomes.

Ye (2013) 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).

Table 3.4.20 Neonatal and paediatric patients undergoing surgery: Results for intraoperative cell salvage versus no intraoperative cell salvage – transfusion volume and incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Intraoperative cell salvage  Mean ± SD (n)  Median (IQR) | No cell salvage  Mean ± SD (n)  Median (IQR) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | | |
| Cholette 2013351  Level II (pilot)  *Good* | N=106 | Children weighing <20 kg scheduled for cardiac surgery with CPB | | Single hospital, USA | Cell salvaged blood versus crystalloid, colloid or albumin for volume replacement | Mean no. RBC transfused within 24 hrs post-surgery | 0.04 ± 0.19 (n=53) | 0.51 ± 0.91 (n=53) | MD –0.47 [–0.72, –0.22]c | *Favours cell salvage*  *P =*0.001 |
| Mean no. RBC transfused within 48 hrs post-surgery | 0.19 ± 0.44 (n=53) | 0.75 ± 1.2 (n=53) | MD –0.56 [–0.90, –0.22]c | *Favours cell salvage*  *P =*0.003 |
| Mean no. RBC transfused within 7 days post-surgery | 0.64 ± 1.24 (n=53) | 1.1 ± 1.4 (n=53) | MD –0.46 [–0.96, 0.04]c | *No significant difference*  *P =*0.07 |
| Mean no. PLT transfused within 2 days post-surgery | 0 ± 0 (n=53) | 0.11 ± 0.38 (n=53) | NR | *Favours cell salvage*  *P =*0.03 |
| Mean no. FFP transfused within 2 days post-surgery | 0 ± 0 (n=53) | 0.15 ± 0.46 (n=53) | NR | *Favours cell salvage*  *P =*0.02 |
| Mean no. cryoprecipitate transfused within 2 days post-surgery | 0 ± 0 (n=53) | 0.08 ± 0.27 (n=53) | NR | *Favours cell salvage*  *P =*0.04 |
| Lisander 1996350  Level II (pilot)  *Poor* | N=24 | Paediatric patients (mean age 14.5 years) undergoing scoliosis surgery (ASA class I) | | Single hospital, Sweden | Cell salvaged blood versus intraoperative volume replacement with plasma substitute | Donor blood units transfused | 4.1 ± 1.5 (n=11) | 5.5 ± 2.2 (n=13) | MD –1.40 [–2.89, 0.09] c | *No significant difference*  *P =*0.07 c |
| Ye 2013352  Level II  *Poor* | N=309 | Paediatric patients (aged 6 days to 13 years) weighing 2–36 kg who were scheduled for open-heart surgery with CPB | | Single hospital, China | Reinfusion of washed residual CPB circuit blood versus no cell salvage | Perioperative allogeneic RBC transfusion volume or incidence (units) | 1.5 (1.5–2.5) | 2.5 (2.5–3.0) | NR | *Favours cell salvage*  *P =*0.000 |

ASA, American Society of Anesthesiologists; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; IQR, interquartile range; NR, not reported; MD, mean difference; PLT, platelet; RBC, red blood cell; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Viscoelastometric point-of-care testing

| Evidence statements – neonatal and paediatric patients undergoing surgery (viscoelastometric point-of-care testing) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 points – surgical (viscoelastometric POC) | |
| 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 | |

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| Evidence gaps and areas for future research |
| Further research is needed on:   * the role of viscoelastometric testing in paediatric patients undergoing other types of surgery in which substantial blood loss is anticipated. * the role of viscoelastometric testing in neonates and infants. |

##### Background

Viscoelastometric point-of-care (POC) testing includes thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These are whole-blood coagulation analysers that measure clot development, stabilisation and dissolution (fibrinolysis), which reflect *in vivo* haemostasis. In paediatric patients requiring surgery, these techniques offer improvements over traditional laboratory testing in monitoring changes of haemostasis and may help clinicians to assess the cause of bleeding and improve the care of patients with unexplained blood loss.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of viscoelastometric POC testing compared with no viscoelastometric POC testing in neonatal and paediatric patients undergoing surgery.

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that assessed the safety and effectiveness of viscoelastometric POC testing compared with no viscoelastometric POC testing in neonatal and paediatric patients undergoing surgery.[[42]](#footnote-42).

* + - 1. Antifibrinolytics (aprotinin, TXA or EACA)

| Evidence statements – neonatal and paediatric patients undergoing surgery (antifibrinolytics) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√ | √ |
|  | 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.) | √√ | √√ | √ | √√ | √ |
|  | 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.) | √√ | √√ | √ | √√√ | √√ |
|  | 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 | √√√ | √√ |
|  | 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.) | √√ | √√ | √ | √√ | √√ |
|  | 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 | √√ | √√ |
|  | In paediatric patients undergoing primary adenoidectomy, the effect of topical tranexamic acid compared with no tranexamic acid on transfusion incidence is uncertain.  (See evidence matrix D4.P in Volume 2 of the technical report.) | √√ | NA | NA | √√√ | √ |
|  | 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 | √√ | √ |
|  | 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 | √√ | √ |
|  | 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.) | √√ | √√ | √ | √√√ | √√ |
|  | 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.) | √√ | √√√ | √ | √√ | √ |
|  | 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 throat; ES, evidence statement  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

|  |  |
| --- | --- |
| 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, TXA should be administered within 3 hours of injury.a  a See R3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*84 |
| PP38 | In paediatric trauma patients aged under 12 years, a TXA 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.354 |
| CPB, cardiopulmonary bypass ; EACA, epsilon aminocaproic acid; PP, practice point; R, recommendation; TXA, tranexamic acid | |

|  |
| --- |
| Evidence gaps and areas for future research |
| Further research is needed on:   * the use of antifibrinolytics in patients with congenital or acquired bleeding disorders undergoing surgery. * the pharmacokinetics and dosing of antifibrinolytics in paediatric patients of different age groups and in different surgical settings. |

##### Background

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

Aprotinin is a natural proteinase inhibitor that slows the breakdown of blood clots by inhibiting trypsin and other proteolytic enzymes. Aprotinin is injected during complex surgery, such as heart and liver surgery, to reduce bleeding. The aim is to decrease the need for blood transfusions, as well as end-organ damage due to marked blood loss and hypotension. Aprotinin was withdrawn from the market on 6 November 2007 after preliminary results from the BART clinical trial355 suggested that cardiac surgery patients who received aprotinin had an increased risk of death compared to patients who received TXA or EACA. Aprotinin remains on the Australian Register of Therapeutic Goods but is not being supplied or marketed by the Australian sponsor. It is available for use under the Special Access Scheme. After reviewing the evidence, therapeutic goods regulators in Canada and Europe allowed aprotinin back into the marketplace for cardiac bypass surgery in 2012.

TXA is a synthetic derivative of the amino acid lysine, which competitively inhibits the activation of plasminogen to plasmin, thus reducing fibrin degradation. In Australia, TXA tablets and solution for injection are approved for a number of indications including cardiac surgery and traumatic hyphaema, as well as for patients with coagulopathies undergoing minor surgery. There is strong evidence supporting the use of TXA in adult surgical patients to reduce blood loss (refer to *Patient Blood Management Guidelines: Module 2 – Perioperative*15).

EACA is a derivative and analogue of the amino acid lysine that reduces fibrinolysis by inhibiting proteolytic enzymes. It has not been found to be as effective in reducing postoperative blood loss in orthopaedic surgery as it has in cardiac surgery. It is not available for use in Australia.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified six Level I studies (Arnold 2006, Faraoni 2012, Ker 2013, Schouten 2009, Song 2013, Tzortzopoulou 2008) that assessed the safety and effectiveness of antifibrinolytics (aprotinin, TXA or EACA) compared with no antifibrinolytics in paediatric patients undergoing surgery. A further two Level I studies (Badeaux 2014,356 Basta 2012357) were identified but did not provide any data additional to the included Level I studies (**Appendix C, Volume 2**). The included studies reviewed the evidence in paediatric patients undergoing a variety of surgeries including: cardiac, scoliosis, craniofacial and ear, nose and throat (ENT) surgery. **Table 3.4.21** summarises the main characteristics of the Level I studies included in this review.

Cardiac surgery

Two good-quality Level I studies (Arnold 2006, Faraoni 2012) provided the most comprehensive and recent evidence for paediatric patients undergoing cardiac surgery.

Arnold (2006) assessed aprotinin in paediatric patients aged <18 years with congenital heart disease (CHD) undergoing open-heart surgery with CPB, and included 12 RCTs involving 626 infants and children. Faraoni (2012) assessed TXA in paediatric patients aged <18 years undergoing cardiac surgery, and included data from eight RCTs involving 848 patients in the analysis. One additional Level I study (Schouten 2009) assessed the effect of antifibrinolytics (aprotinin, TXA or EACA) in paediatric patients undergoing cardiac surgery, and provided some additional data not reported by Arnold (2006) or Faraoni (2012).

Scoliosis surgery

One good-quality Level I study (Tzortzopoulou 2008) provided the most comprehensive evidence for paediatric patients aged <18 years undergoing surgery for scoliosis. Tzortzopoulou (2008) assessed the effect of antifibrinolytics (aprotinin, TXA or EACA) on mortality, transfusion incidence, total blood transfused, postoperative deep vein thrombosis (DVT) and total blood loss. The review by Schouten (2009) also included paediatric patients undergoing surgery for scoliosis, but did not report any data additional to that that provided by Tzortzopoulou (2008).

Craniofacial surgery

One fair-quality Level I study (Song 2013) provided evidence for the effect of antifibrinolytics in paediatric patients undergoing craniofacial surgery. The authors examined the effect of intravenous TXA in children undergoing craniosynostosis surgery on RBC transfusion volume and perioperative blood loss, and included data from two RCTs and one retrospective comparative study in their analysis.

ENT surgery

Ker (2013) was a good-quality Level I study that assessed the effect of topical administration of TXA in subjects of all ages with bleeding of any severity. The review identified 29 RCTs, only one of which was in paediatric patients. The study involved 400 children undergoing primary isolated adenoidectomy, and provided evidence for the effect of TXA in ENT surgery on transfusion incidence and blood loss.

Table 3.4.21 Characteristics and quality of Level I evidence – antifibrinolytics in paediatric patients undergoing surgery

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Cardiac surgery | | | | |
| Arnold (2006)358 | Systematic review  *Good* | Paediatric patients (aged <18 years) with CHD undergoing open-heart surgery with CPB  12 RCTs, N=626 | Aprotinin versus placebo | Transfusion volume and incidence  Bleeding events |
| Faraoni (2012)359 | Systematic review  *Good* | Paediatric patients (aged <18 years) undergoing cardiac surgery  8 RCTs, N=710 | TXA versus placebo | Transfusion volume and incidence  Bleeding events |
| Schouten (2009)360 | Systematic review  *Good* | Paediatric patients (aged <18 years) undergoing cardiac surgerya  23 RCTs, N=1893 | Antifibrinolytics (aprotinin, EACA, TXA) versus placebo | Transfusion volume  Bleeding events |
| Scoliosis surgery | | | | |
| Tzortzopoulou (2008)361 | Systematic review  *Good* | Paediatric patients (aged <18 years) undergoing scoliosis surgery  6 RCTs, N=254 | Antifibrinolytics (aprotinin, EACA, TXA) versus placebo | Mortality  Thromboembolic events  Bleeding events  Transfusion volume and incidence |
| Craniofacial surgery | | | | |
| Song (2013)362 | Systematic review  *Fair* | Children undergoing craniosynostosis surgery  3 studies, N=138  \*Included 2 RCTs and 1 Level III study | IV TXA versus placebo | Transfusion volume  Bleeding events |
| ENT surgery | | | | |
| Ker (2013)363 | Systematic review  *Good* | Children undergoing primary isolated adenoidectomy  29 RCTsb, N=2612  *Paediatric/neonatal*  1 RCT, N=400 | Topical TXA versus placebo | Transfusion incidence  Bleeding events |

CHD, congenital heart disease; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; ENT, ear nose throat; IV, intravenous; RCT, randomised controlled trial; TXA, tranexamic acid

**a.** Schouten (2009) also assessed antifibrinolytics in paediatric patients undergoing scoliosis surgery. Five RCTs involving 207 patients met their inclusion criteria. The review did not provide any data additional to that reported by Tzortzopoulou (2008).

**b.** Ker (2013) assessed the topical use of TXA in the control of bleeding for any population: 28 RCTs involved patients undergoing surgery and one RCT involved patients with nosebleed. Only one RCT was conducted in neonatal and/or paediatric patients.

###### Level II evidence

**Table 3.4.22** summarises the main characteristics of the 30 Level II studies identified and assessed by the included Level I studies.

Table 3.4.22 Characteristics and quality of Level II evidence identified and assessed by included Level I studies – antifibrinolytics in neonatal and paediatric patients undergoing surgery

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Identified and assessed by included Level I studies | | | | |
| *Cardiac surgery* | | | | |
| Boldt (1993a)a | RCT  *Jadad scoreb 2/6* | Infants and children (mean age 1 year) with CHD undergoing cardiac surgery with CPB  N=42 | IV aprotinin 35,000 KIU/kg + 10,000 KIU/kg/min during surgery + 35,000 KIU/kg prime versus IV aprotinin 20,000 KIU/kg + 20,000 KIU/kg/min during surgery + 20,000 KIU/kg prime versus no treatment | Transfusion volume  Blood loss |
| Boldt (1993b) a | RCT  *Jadad scoreb 2/6* | Infants and children (mean age 2 years) with CHD undergoing cardiac surgery with CPB  N=48 | IV aprotinin 25,000 KIU/kg + 25,000 KIU/kg/hr during CPB + 25,000 KIU/kg prime versus no treatment | Blood loss |
| Boldt (1994)a 364 | RCT  *Jadad scoreb 2/6* | Children (mean age 3 years) with CHD undergoing cardiac surgery with CPB  N=30 | IV aprotinin 30,000 KIU/kg + 30,000 KIU/kg/hr during CPB + 30,000 KIU/kg prime versus no treatment | Transfusion incidence  Blood loss |
| Bulutcu (2005)365 | RCT  Poor c | Children (mean age 4 years) with cyanotic CHD undergoing cardiac surgery with CPB  N=50 | Aprotinin 3x doses 30,000 KIU/kg versus TXA 3x 100mg/kg doses versus aprotinin + TXA versus no treatment | Transfusion volume  Blood loss |
| Chauhan (2000)366 | RCT  *Jadad scoreb 5/6* | Children (mean age 4 years) with CHD undergoing cardiac surgery with CPB  N=180 | IV aprotinin 10,000 KIU/kg + 10,000 KIU/kg prime + 10,000 KIU/hr x3hr post CPB versus EACA versus aprotinin + EACA versus no treatment | Transfusion volume  Blood loss |
| Chauhan (2003)367 | RCT  *Fair* | Children aged 2 months to 15 years with cyanotic CHD undergoing corrective surgery with CPB  N=120 | TXA 3x 10 mg/kg doses versus no treatment | Transfusion volume  Blood loss |
| Chauhan (2004 a)368 | RCT  *Jadad scoreb 1/6* | Children aged 2 months to 15 years (mean age 4 years) with cyanotic CHD undergoing corrective surgery with CPB  N=150 | IV TXA 3x 10 mg/kg doses versus EACA 3x 100 mg/kg doses versus no treatment | Transfusion volume  Blood loss |
| Chauhan (2004b)369 | Five armed RCT  *Jadad scoreb 1/6* | Children aged 2 months to 15 years (mean age 4 years) with cyanotic CHD undergoing corrective surgery with CPB  N=150 | IV TXA 50 mg/kg versus IV TXA 10 mg/kg + 1 mg/kg infusion for 8hrs versus IV TXA 10 mg/kg after anaesthesia + 10 mg/kg on CPB + 10 mg/kg after protamine versus IV TXA 20 mg/kg after anaesthesia + 20 mg/kg after protamine versus no treatment | Transfusion volume  Blood loss |
| Davies (1997)370 | RCT  Good c | Children (mean age 3.5 years) with CHD undergoing cardiac surgery with CPB  N=39 | IV aprotinin 140,000 KIU/m2 + 56,000 KIU/m2/hr until skin closure + 240,000 KIU/m2 prime (BSA <1.16 m2) OR 250,000 KIU/m2 + 70,000 KIU/m2/hr until skin closure + 280,000 KIU/m2 prime (BSA >1.16 m2) versus placebo | Transfusion volume and incidence  Blood loss |
| D’Errico (1996)371 | RCT  *Jadad scoreb 4/6* | Infants and children aged <1 to 12 years (median age 2.5 years) with CHD undergoing cardiac surgery with CPB  N=57 | IV aprotinin 120 mg/m2 + 28 mg/m2 continuous infusion + 120 mg/m2 prime versus IV aprotinin 240 mg/m2 + 56 mg/m2 continuous infusion + 240 mg/m2 prime versus placebo | Transfusion volume and incidence  Blood loss |
| Dietrich (1993)372 | RCT  *Jadad scoreb 3/6* | Infants (mean age 9 months) with CHD undergoing cardiac surgery with CPB  N=60 | IV aprotinin 30,000 KIU/kg + 30,000 KIU/kg prime versus IV aprotinin 15,000 KIU/kg + 15,000 KIU/kg prime versus no treatment | Blood loss |
| Gomar (1995)373 | RCT  *Quality not assessed* | Children >10 kg with CHD undergoing cardiac surgery with CPB  N=25 | IV aprotinin 240 mg/m2 + 50 mg/m2/hr until end of surgery + 50 mg KIU/m2 prime versus placebo | Blood loss |
| Herynkopf (1994)374 | RCT  *Jadad scoreb 3/6* | Infants and children aged <1 to 11 years with CHD undergoing cardiac surgery with CPB  N=30 | IV aprotinin 2.8 mg/kg + 1.4 mg/kg by continuous infusion during CPB + 1.4 mg/kg prime versus placebo | Transfusion volume and incidence |
| Levin (2000)375 | RCT  *Jadad score b 3/6* | Infants and children aged 3 months to 16 years undergoing major cardiac bypass surgery  N=56 | TXA 50 mg/kg versus placebo | Blood loss |
| Miller (1998)376 | RCT  *Jadad scoreb* 4/6 | Children (mean age 4.5 years) with CHD undergoing cardiac surgery with CPB  N=30 | IV aprotinin 20,000 KIU/kg + 10,000 KIU/kg/hr until skin closure + 20,000 KIU/kg prime versus IV aprotinin 40,000 KIU/kg + 20,000 KIU/kg/hr until skin closure + 40,000 KIU/kg prime versus no treatment | Transfusion incidence  Blood loss |
| Mossinger (2003)377 | RCT  *Jadad scoreb* 5/6 | Infants (median age 4.8 months) with CHD undergoing cardiac surgery with CPB  N=60 | IV aprotinin 30,000 KIU/kg + 50,000 KIU prime versus placebo | Transfusion incidence  Blood loss |
| Rao (2000)378 | RCT  Poor c | Infants and children aged 2 months to 14 years with cyanotic CHD scheduled for corrective surgery with CPB  N=170 | EACA 3x 100 mg/kg doses versus placebo | Transfusion volume |
| Reid (1997)379 | RCT  Fair c | Infants and children aged 6 months to 12 years who had undergone 1+ previous sternotomies and who were scheduled for elective repeat cardiac surgery via sternotomy with CPB  N=41 | IV TXA 100 mg/kg infused over 15 minutes + 100 mg/kg bolus injected at start of surgery versus placebo | Transfusion volume  Blood loss |
| Seghaye (1996)380 | RCT  *Jadad scoreb* 3/6 | Infants and children aged <1 to 12 years (mean age 6.5 years) with CHD undergoing cardiac surgery with CPB  N=25 | IV aprotinin versus no treatment | Transfusion volume |
| Shimizu (2011)381 | RCT  *Blinded, adequate randomisation* | Children <18 years (mean age 2.5 years) scheduled for elective cardiac surgery with CPB  N=160 | IV TXA 50 mg/kg before skin incision followed by 50 mg/kg into CPB circuit prior to CPB until skin closure versus placebo | Transfusion volume  Blood loss |
| Zonis (1996)382 | RCT  *Jadad score b 6/6* | Children (mean age 5 years) undergoing cardiac surgery with CPB  N=88 | IV TXA 50 mg/kg versus placebo | Blood loss |
| *Scoliosis surgeryb* | | | | |
| Cole (2002)383  \*abstract only | RCT  Unclear c | Children undergoing surgical correction of idiopathic scoliosis  N=47 | IV EACA loading dose 150 mg/kg pre-incision followed by continuous infusion 15 mg/kg to 4hrs postoperative versus placebo | Mortality  Transfusion volume  Blood loss |
| Cole (2003)384 | RCT  Adequate c | Children undergoing surgical correction of primary or secondary scoliosis  N=44 | IV aprotinin loading dose 240 mg/m2 followed by 56 mg/m2/hr continuous infusion (max 280 mg/m2) versus placebo | Mortality  Transfusion volume  Thromboembolic events  Blood loss |
| Florentino-Pineda (2004)385 | RCT  Adequate c | Children undergoing surgery for correction of idiopathic scoliosis  N=36 | IV EACA loading dose 100 mg/kg followed by continuous infusion 10 mg/kg/hr versus placebo | Mortality  Transfusion volume and incidence  Blood loss |
| Khoshhal (2003)386 | RCT  Adequate c | Adolescents undergoing surgery for correction of idiopathic scoliosis  N=43 | IV aprotinin loading dose 4 mg/kg followed by continuous infusion 1 mg/kg/hr versus placebo | Mortality  Transfusion volume and incidence  Blood loss |
| Neilipovitz (2001)387 | RCT  *Double-blinded, adequate randomisation, allocation concealment unclear* | Adolescents undergoing surgery for correction of primary or secondary scoliosis  N=40 | IV TXA loading dose 10 mg/kg followed by continuous infusion 1 mg/kg/hr versus placebo | Mortality  Transfusion volume and incidence  Blood loss |
| Sethna (2005)388 | RCT  Double-blinded, adequate randomisation, unclear allocation concealment | Children and adolescents undergoing surgery for correction of primary or secondary scoliosis  N=44 | IV TXA loading dose 100 mg/kg followed by continuous infusion 10 mg/kg/hr versus placebo | Mortality  Transfusion volume and incidence  Blood loss |
| *Craniofacial surgery* | | | | |
| Dadure (2011)389 | RCT  Jadad composite scale d 5/5 | Infants (median age 6.5 months) scheduled for surgical correction of craniosynostosis  N=40 | IV TXA 15 mg/kg after induction of general anaesthesia + continuous infusion 1 mg/kg until skin closure versus placebo | Transfusion volume  Blood loss |
| Goobie (2011)390 | RCT  *Jadad composite scaled* 5/5 | Infants and children aged 2 months to 6 years undergoing craniosynostosis reconstruction surgery  N=43 | IV TXA 50 mg/kg followed by infusion of 5 mg/kg/hr versus placebo | Transfusion volume  Blood loss |
| ENT surgery | | | | |
| Albirmawy (2013)391 | RCT  *Unclear allocation concealment* | Children undergoing primary isolated adenoidectomy  N=400 | Topical TXA (100 mg diluted in 10 mL saline) (n=200) versus placebo (n=200) | Transfusion incidence  Blood loss |

BSA, bovine serum albumin; CHD, congenital heart disease; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; ENT, ear nose throat; FFP, fresh frozen plasma; IV, intravenous; KIU, kilo international unit; RCT, randomised controlled trial; TXA, tranexamic acid

**a.** A number of studies by Boldt have been retracted due to research misconduct, including lack of ethics approval and false data. While the included studies have not been formally retracted, care should be taken in the interpretation of analysis involving this study.

**b.** Jadad score (maximum out of 6). Good quality trials scored 5 or 6 out of 6.

**c.** Overall assessment using Cochrane Collaboration ‘Risk of Bias’ Tool.

**d.** Jadad composite scale (maximum out of 5). Good quality trials scored 3–5 out of 5.

The systematic review and hand-searching process identified 13 additional Level II studies that assessed the safety and effectiveness of antifibrinolytics (aprotinin, TXA or EACA) compared with no antifibrinolytics in paediatric patients undergoing surgery (**Appendix C, Volume 2**). Studies were in patients undergoing either cardiac, scoliosis, craniofacial or ENT surgery. **Table 3.4.23** summarises the main characteristics of the additional Level II studies identified and assessed in this review.

Cardiac surgery

Seven additional Level II studies (Aggarwal 2012, Coniff 1998, Ferreira 2010, Flaujac 2007, Sarupria 2013, Singh 2001, Vacharaksa 2002) provided evidence for paediatric patients undergoing cardiac surgery. Four studies assessed the effects of aprotinin (Coniff 1998, Ferreira 2010, Flaujac 2007, Singh 2001), two studies assessed TXA (Aggarwal 2012, Vacharaksa 2002) and one study assessed EACA (Sarupria 2013).

Arrgarwall (2012) was a fair-quality RCT conducted in a single centre in India that involved 80 paediatric patients aged 1–12 years with tetralogy of Fallot undergoing intracardiac repair. The study aimed to examine the effect of TXA on blood loss and coagulation parameters.

Coniff (1998) was a compassionate-use study that compared aprotinin (high-dose, low-dose and pump prime only) with placebo in 116 paediatric patients undergoing surgery with CPB and an increased risk of bleeding. The method of randomisation and blinding were not reported, and there were only three patients aged ≤1 year randomised to high-dose aprotinin, which may have distorted results. Also, as a compassionate-use study, the methods for monitoring the trial were not as formal as a conventional RCT; therefore, care should be taken when interpreting results.

Ferreira (2010) was a poor-quality RCT conducted in a single centre in Brazil. The study enrolled 19 paediatric patients aged 1 month to 4 years scheduled for cardiac surgery with CPB, and aimed to examine the effect of aprotinin compared with no aprotinin on clinical outcomes, including transfusion volume and incidence. The method of randomisation was not reported and the study was not blinded.

Flaujac (2007) was a poor-quality RCT conducted in a single centre in France that included nine newborns aged ≤1 month and 11 infants aged 2–36 months undergoing primary corrective cardiac surgery with CPB. The study aimed to assess the effect of high-dose aprotinin compared with no aprotinin on platelet function, postoperative blood loss and transfusion requirements.

Sarupria (2013) enrolled 120 paediatric patients undergoing cardiac surgery with CPB for tetralogy of Fallot. The authors examined the effect of high-dose EACA, compared to low-dose EACA, compared to placebo.

Singh (2001) was a fair-quality RCT conducted in India that examined the effect of aprotinin (two doses or one dose) compared with no aprotinin on total blood loss and transfusion requirement. The study enrolled 75 paediatric cyanotic patients tetralogy of Fallot undergoing cardiac surgery with CPB.

Vacharaksa (2002) enrolled 62 paediatric patients with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery. The authors examined the effect of TXA administered at the end of CPB with placebo at the end of CPB. All patients were treated with TXA after induction of anaesthesia.

Scoliosis surgery

Two additional Level II studies (Thompson 2005, Verma 2014) provided evidence for paediatric patients undergoing scoliosis surgery. Thompson (2005) was a poor-quality RCT of 36 children aged 11–18 years with idiopathic scoliosis who were scheduled for posterior spinal fusion. The authors examined the effect of EACA compared to no treatment on transfusion volume or incidence and blood loss. Verma (2014) was a good-quality three-armed RCT of 125 patients with adolescent idiopathic scoliosis who were scheduled for posterior spinal arthrodesis. The authors examined the effect of TXA or EACA compared to placebo on blood loss and drain output.

The RCT by Thompson (2005) examined the effect of EACA in paediatric patients aged 11–18 years with idiopathic scoliosis who were scheduled for posterior spinal fusion.

Craniofacial surgery

Three additional Level II studies (Ahmed 2014, D’Errico 2003, Hanna 2010) provided evidence for paediatric patients undergoing craniofacial surgery. Two studies (Ahmed 2014, D’Errico 2003) examined the effect of intravenous aprotinin compared to placebo. Ahmed (2014) was a fair-quality RCT of 26 paediatric patients aged 1 month to 3 years undergoing major reconstructive craniofacial surgery. Outcomes included mortality, blood product transfusion incidence and volume, thrombotic complications and drain output. D’Errico (2003) was a good-quality RCT conducted in the USA that involved 39 paediatric patients aged 1 month to 12 years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement.

The third study (Hanna 2010) was not included in the analysis as the full text article was not able to be retrieved. Hanna (2010) enrolled 45 paediatric patients of ASA class I and II with congenital craniofacial malformations scheduled for reconstructive surgery. Children were randomly allocated into one of three groups comparing rFVIIa with either TXA or control.

ENT surgery

Two additional Level II studies (Brum 2012, Eldaba 2013) provided evidence for paediatric patients undergoing ENT surgery. Both studies examined the effect of intravenous TXA compared to placebo. Brum (2012) was a good-quality RCT of 95 children aged 4–12 years who were scheduled for adenotonsillectomy. Outcomes of interest included intraoperative and postoperative bleeding. Eldaba (2013) was a fair-quality RCT of 100 children aged 5–10 years with chronic rhinosinusitis undergoing endoscopic sinus surgery. The authors reported bleeding volume and surgical field grade.

Table 3.4.23 Characteristics and quality of Level II evidence identified and assessed in this review – antifibrinolytics

| Study ID | Study type *Study quality* | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Cardiac surgery | | | | |
| Aggarwal (2012)392 | RCT  Fair | Children aged 1–12 years with tetralogy of Fallot undergoing intracardiac repair  N=80 | IV TXA (3x 10 mg/kg doses) versus placebo | Bleeding events |
| Coniff (1998)393  \*Compassionate-use study | RCT  Poor | Paediatric patients (aged ≤16 years) undergoing cardiac surgery with CPB and an increased risk of bleeding  N=116 | Aprotinin high-dose (n=31) versus aprotinin low-dose (n=33) versus aprotinin in pump prime only (n=18) versus placebo (n=34) | Mortality  Transfusion volume and incidence |
| Ferreira (2010)394 | RCT  Poor | Paediatric patients (aged 1 month to 4 years) with CHD undergoing cardiac surgery with CPB  N=19 | IV aprotinin (240 mg/m2 infusion and in perfusate oxygenator + 56 mg/m2 infusion) (n=10) versus placebo (n=9) | Mortality  Transfusion volume and incidence  Bleeding events |
| Flaujac (2007)395 | RCT  Poor | Infants (aged 4 days to 36 months) undergoing primary corrective cardiac surgery with CPB  N=20 | IV aprotinin (2x 30,000 KIU/kg boluses + 8,000 KIU/kg infusion) (n=10) versus placebo (n=10) | Transfusion volume and incidence  Thromboembolic events |
| Sarupria (2013)396 | RCT  Fair | Paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB for tetralogy of Fallot  N=115 | EACA (1x 100 mg/kg infusion, + 2x 100 mg/kg boluses) (n=38) versus EACA (2x 75 mg/kg infusions + 1x 75 mg/kg bolus) (n=40) versus placebo (n=37) | Mortality  Transfusion volume and incidence  Bleeding events |
| Singh (2001)397 | RCT  Fair | Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot undergoing total correction with CPB  N=75 | Aprotinin (20,000 KIU/kg bolus) + 20,000 KIU/kg infusion (n=25) versus aprotinin (20,000 KIU/kg bolus) (n=25) versus placebo (n=25) | Mortality  Transfusion volume  Bleeding events |
| Vacharaksa (2002)398 | RCT  *Fair* | Paediatric patients (aged ≤14 years) with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery  N=62 | IV TXA (15 mg/kg) at the end of CPB (n=33) versus placebo (saline) at the end of CPB (n=29)  \*both groups administered IV TXA (15 mg/kg) after induction of anaesthesia | Mortality  Transfusion volume  Thromboembolic events  Bleeding events |
| Scoliosis surgery | | | | |
| Thompson (2005)381 | RCT  Poor | Children aged 11–18 years with idiopathic scoliosis scheduled for posterior spinal fusion with segmental spinal instrumentation  N=36 | IV EACA 100 mg/kg before skin incision followed by maintenance infusion 10 mg/kg/hr until skin closure versus no treatment | Transfusion volume and incidence  Blood loss |
| Verma (2014)399 | RCT  Good | Patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis  N=125 | TXA (10 mg/kg infusion + 1 mg/kg maintenance infusion) (n=36) versus EACA (100 mg/kg infusion + 10 mg/kg maintenance infusion) (n=42) versus placebo (n=47) | Bleeding events |
| Craniofacial surgery | | | | |
| Ahmed (2014)400 | RCT  *Fair* | Paediatric patients (aged 1 month to 3 years) undergoing major reconstructive craniofacial surgery  N=26 | IV aprotinin (n=13) versus placebo (n=13) | Mortality  Transfusion volume and incidence  Thromboembolic events  Bleeding events |
| D’Errico (2003)401 | RCT  Good | Paediatric patients (aged 1 month to 12 years) undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement  N=39 | IV aprotinin versus placebo | Mortality |
| *ENT surgery* |  |  |  |  |
| Brum (2012)402 | RCT  Good | Children (aged 4–12 years) scheduled for adenotonsillectomy  N=95 | IV TXA (n=47) versus placebo (n=48) | Bleeding events |
| Eldaba (2013)403 | RCT  *Fair* | Children (aged 5–10 years) with chronic rhinosinusitis undergoing endoscopic sinus surgery  N=100 | IV TXA (n=50) versus placebo (n=50) | Bleeding events |

CHD, congenital heart disease; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; ENT, ear nose throat; IV, intravenous; RCT, randomised controlled trial; TXA, tranexamic acid

##### Results

###### Mortality

The systematic review and hand-searching process identified 13 Level II studies that reported the incidence of mortality among paediatric patients undergoing surgery that were administered antifibrinolytics compared with no antifibrinolytics. **Table 3.4.24** summarises the results from these studies.

Cardiac surgery

Five Level II studies (Coniff 1998, Ferreira 2010, Sarupria 2013, Singh 2001, Vacharaksa 2002) provided evidence for mortality in paediatric patients undergoing cardiac surgery. No study reported a significant difference in mortality, but the studies were not powered to detect between-group differences for this outcome.

The RCT by Coniff (1998) involving 116 paediatric patients reported a total of four deaths in those administered aprotinin: one death (3.2%) in the high-dose group, two deaths (6.1%) in the low-dose group, and one death (5.6%) in the pump prime only group. There were five deaths (14.7%) in the control group. The difference between groups was not significant (RR 0.33, 95% CI 0.09, 1.16).

The RCT by Sarupria (2013) involving 120 paediatric patients reported a total of five deaths in those administered aprotinin: two deaths (5.3%) in the high-dose group and three deaths (7.5%) in the low-dose group. There were three deaths (8.1%) in the control group. The difference between groups was not significant (RR 0.79; 95% CI 0.20, 3.13).

No deaths were recorded in the studies reported by Ferreira (2010), Singh (2001) and Vacharaksa (2002).

Scoliosis surgery

The systematic review by Tzortzopoulou (2008) assessed mortality among paediatric patients undergoing surgery for scoliosis. No deaths were reported in six trials involving 163 patients (Cole 2002, Cole 2003, Khoshhal 2003, Neilipovitz 2001, Sethna 2005, Florentino-Pineda 2004).

Craniofacial surgery

Two RCTs (Ahmed 2014, D’Errico 2003) provided evidence for mortality in paediatric patients scheduled for major craniofacial reconstruction. Neither study reported any deaths during the study period.

Table 3.4.24 Surgical paediatric/neonatal patients: Results for antifibrinolytics versus no antifibrinolytics – mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%) | No antifibrinolytics  n/N (%) | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | | |
| Scoliosis surgery | | | | | | | | | | |
| Tzortzopoulou 2008361  Level I  *Good* | 6 trials (Cole 2002c,383 Cole 2003,384 Florentino-Pineda 2004,385 Khoshhal 2003,386 Neilipovitz 2001,387 Sethna 2005388)  N=163 | Paediatric patients aged <18 years undergoing scoliosis surgery | Canada, USA | IV antifibrinolytic (aprotinin, TXA, EACA) versus placebo | Mortality | 0/NR (0%) | | 0/NR (0%) | Not estimable | *No significant difference*  *P =*NA  Heterogeneity NR  I2 = NR |
| Level II evidence | | | | | | | | | | |
| Cardiac surgery | | | | | | | | | | |
| Coniff 1998d393  Level II  *Poor* | N=116 | Paediatric patients (aged ≤16 years) undergoing surgery with CPB and an increased risk of bleeding | Multicentre, USA | Aprotinin (high-dose, low-dose or pump prime only) versus placebo | Mortality | 4/82 (4.9%) | 5/34 (14.7%) | | RR 0.33 [0.09, 1.16]e | *No significant difference*  *P =*0.08e |
| High-dose | 1/31 (3.2%) |
| Low-dose | 2/33 (6.1%) |
| Pump prime only | 1/18 (5.6%) |
| Ferreira 2010394  Level II  *Poor* | N=19 | Paediatric patients (aged 1 month to 4 years) with CHD undergoing cardiac surgery with CPB | Single hospital, Brazil | IV aprotinin (3x doses) versus placebo | Mortality | 0/10 (0%) | 0/9 (0%) | | Not estimable | *No significant difference*  *P =*NA |
| Sarupria 2013396  Level II  *Fair* | N=120 | Paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB for tetralogy of Fallot | Single hospital, India | IV EACA (high or low-dose) versus placebo | Mortality | 5/78 (6.4%) | 3/37 (8.1%) | | NR | *No significant difference*  *P =*0.88 |
| High-dose | 2/38 (5.3%) |
| Low-dose | 3/40 (7.5%) |
| Singh 2001397  Level II  *Fair* | N=75 | Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot undergoing total correction with CPB | India | IV aprotinin (2x doses or 1x dose) versus placebo | Mortality | 2x: 0 (0%)  1x: 0 (0%) | 0 (0%) | | Not estimable | *No significant difference*  *P =*NA |
| Vacharaksa 2002398  Level II  *Fair* | N=62 | Paediatric patients (aged ≤14 years) with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery | Single hospital, Thailand | IV TXA (2x doses) versus IV TXA (1x dose) + placebo | Mortality | 0/33 (0%) | 0/29 (0%) | | Not estimable | *No significant difference*  *P =*NA |
| Craniofacial surgery | | | | | | | | | | |
| Ahmed 2014400  Level II  *Fair* | N=26 | Paediatric patients (aged 1 month to 3 years) undergoing major reconstructive craniofacial surgery | Single hospital, USA | IV aprotinin versus placebo | Mortality | 0/13 (0%) | 0/13 (0%) | | Not estimable | *No significant difference*  *P =*NA |
| D’Errico 2003401  Level II  *Good* | N=39 | Paediatric patients aged 1 month to 12 years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement | Single hospital, USA | IV aprotinin versus placebo | Mortality | 0/18 (0%) | 0/21 (0%) | | Not estimable | *No significant difference*  *P =*NA |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; IV, intravenous; NA, not applicable; NR, not reported; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Abstract only.

**d.** Compassionate-use study.

**e.** Calculated post-hoc in RevMan 5.1.2.

###### Transfusion volume and incidence

Cardiac surgery

The systematic review and hand-searching process identified three Level I studies (Arnold 2006, Faraoni 2012, Schouten 2009) and six additional Level II studies (Coniff 1998, Ferreira 2010, Flaujac 2007, Sarupria 2013, Singh 2001, Vacharaksa 2002) that assessed the effect of antifibrinolytics on transfusion volume and incidence in paediatric patients undergoing cardiac surgery. **Table 3.4.25** summarises the results from these studies.

Overall, the evidence suggested a significant trend towards a reduction in the volume of blood products transfused in paediatric patients undergoing cardiac surgery, but the effect on the number of patients transfused was not significantly different. Results could not be pooled because of large heterogeneity between studies and quality of the outcomes reported.

Transfusion volume

*Aprotinin*

The systematic review by Arnold (2006) identified six RCTs (Boldt 1993a, Chauhan 2000, Davies 1997, D’Errico 1996, Herynkopf 1994, Seghaye 1996) that examined the effect of aprotinin on the volume (mL/kg) of blood transfused in 404 paediatric patients undergoing cardiac surgery. A meta-analysis of the data was reported to show no significant difference between treatment groups (WMD –8.42, 95% –19.86, 3.02), but heterogeneity was high I2=96% and reasons for heterogeneity were not explored.[[43]](#footnote-43)

A significant difference in RBC transfusion volume that favoured aprotinin (WMD –4, 95% CI –7, –2) was reported in a meta-analysis of three RCTs involving 250 patients (Davies 1997, Chauhan 2000, Bulutcu 2005) by Schouten (2009). This result differed to that reported by Arnold (2006), who reported no significant difference for transfusion volume comparing aprotinin with placebo. Full details of the data used in both reviews were not available. Schouten (2009) also pooled data from two RCTs involving 228 patients (Chauhan 2000, Bulutcu 2005) that reported plasma transfusion volume, and showed an effect that favoured aprotinin (WMD –5, 95% CI –8, –2).

The RCT by Coniff (1998) reported a trend towards a reduction in the mean number of units transfused of both donor blood *or* blood products (platelets, cryoprecipitate and FFP) that favoured high-dose aprotinin over placebo (2.9 versus 11.3 units), but the effect was not statistically significant when assessing donor blood only (2.6 versus 4.8 units). The authors also explored the relationship between aprotinin and volume of blood transfused in patients undergoing repeat procedures, those aged <1 year, and those aged between 1 and 17 years; however, no statistically significant between-group differences were observed at any dose.

The RCT by Ferreira (2010) assessed transfusion volume in 19 paediatric patients. It reported no significant difference between groups in the mean volume of intraoperative RBC transfused (MD –27.00; 95% CI –85.62, 31.62) or the mean volume of albumin transfused postoperatively (MD 14.63; 95% CI –7.72, 36.98).

The RCT by Flaujac (2007) assessed postoperative transfusion volume and incidence in 20 infants. It reported a significant difference in 24 hour postoperative transfusion requirements (mL/kg) that favoured aprotinin.

Singh (2001) compared aprotinin (two doses or one dose) with placebo and reported a significant effect favouring aprotinin for a reduction in the volume of blood transfused, the volume of FFP transfused, and the volume of platelets transfused.

*Tranexamic acid*

Faraoni (2012) conducted several meta-analyses investigating the effect of TXA on 24-hour postoperative transfusion volumes for RBC, platelets and FFP. Sensitivity analyses were conducted that excluded studies by Chauhan and colleagues. This was to reduce possible bias introduced by these authors, whose studies dominated the primary meta-analysis.

For RBC transfusion volume, a meta-analysis of six RCTs involving 710 patients (Bulutcu 2005, Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Reid 1997, Shimizu 2011) demonstrated a statistically significant reduction in RBC transfusion volume, favouring TXA (MD –6.38, 95% CI –8.28, –4.47). The effect remained statistically significant in two sensitivity analyses excluding studies with potential bias. For platelet transfusion volume, a statistically significant effect favouring TXA was reported (4 trials, MD –3.70, 95% CI –5.40, –2.00). However, in a sensitivity analyses the excluded potential bias, the result was no longer significant. A statistically significant effect favouring TXA was also reported for a reduction in FFP transfusion volume (5 trials, MD –5.52, 95% CI –7.54, –3.50). The effect remained significant in the first sensitivity analysis that excluded one study by Chauhan (2004a), but not the second sensitivity analysis excluding all studies by Chauhan and colleagues.

The systematic review by Schouten (2009) reported a meta-analysis involving 370 patients administered TXA, which showed an effect that favoured TXA for a reduction in thrombocyte transfusion volume (WMD –5, 95% CI –7, –3).

The RCT by Vacharaksa (2002) assessed transfusion volume in 62 paediatric patients with cyanotic CHD. It reported no significant differences between treatment groups for postoperative transfusion volume of RBCs, FFP, or platelets.

*EACA*

The systematic review by Shouten (2009) conducted a meta-analysis of three RCTs involving 410 patients (Chauhan 2000, Chauhan 2004, Rao 2000) that reported plasma transfusion volume in patients administered EACA compared with placebo. A significant reduction favouring EACA was reported (WMD –3, 95% CI –5, –1).

The RCT by Sarupria (2013) examined the effect of EACA (high and low doses) compared to placebo in 120 paediatric patients. It reported a significant difference favouring EACA (high and low-dose) compared with placebo for intraoperative transfusion volumes (mL/kg) of RBCs and FFP. A significant effect favouring EACA (high and low-dose) was also reported for total transfusion volumes (mL/kg) for RBCs and FFP. However, no significant differences were reported for intraoperative and total platelet concentrate transfusion volume. Low-dose EACA (but not high-dose EACA) was favoured over placebo for transfusion incidence of RBCs and FFP.

Transfusion incidence

The systematic review by Arnold (2006) identified six RCTs (Boldt 1994, Davies 1997, D’Errico 1996, Herynkopf 1994, Miller 1998, Mossinger 2003) that examined the effect of aprotinin on transfusion incidence. A meta-analysis of these trials found no significant difference in RBC or whole blood transfusion incidence (RR 0.67, 95% CI 0.51, 0.89).[[44]](#footnote-44) However, in a sensitivity analyses involving four good-quality RCTs (Davies 1997, D’Errico 1996, Herynkopf 1994, Mossinger 2003) a statistically significant effect favouring aprotinin was reported (RR 0.60, 95% CI 0.38, 0.95). Studies that had an objective transfusion protocol (Davies 1997, D’Errico 1996, Herynkopf 1994) also reported a significant effect favouring aprotinin (RR 0.72, 95% CI 0.58, 0.89). Significant differences favouring aprotinin were also reported in subgroup analyses that involved patients undergoing primary sternotomy (3 trials, RR 0.44, 95% CI 0.26, 0.76), patients with mean weight >10 kg (5 trials, RR 0.73, 95% CI 0.59, 0.89) and patients with mean weight <10 kg (1 trial, data NR).

The RCT by Coniff (1998) also found no significant difference between groups for the incidence of donor blood or blood product transfusion, or patients requiring ≥20 units of donor blood or blood products.

The RCT by Ferreira (2010) assessed transfusion incidence in 19 paediatric patients. It reported no significant difference between groups for postoperative RBC transfusion incidence (10% versus 0%), postoperative platelet concentrate transfusion incidence (0% versus 22%), or number of postoperative donor exposures (20% versus 22.2%).

The RCT by Flaujac (2007) assessed postoperative transfusion incidence in 20 infants and reported no significant between group differences for 24 hour postoperative transfusion incidence of RBCs, platelets, FFP, albumin or prothrombin complex concentrate.

*Tranexamic acid*

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of TXA compared with no TXA and reported transfusion incidence in neonatal or paediatrics patients undergoing cardiac surgery.

*EACA*

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of EACA compared with no EACA and reported transfusion incidence in neonatal or paediatrics patients undergoing cardiac surgery.

Table 3.4.25 Neonatal and paediatric patients undergoing cardiac surgery: Results for antifibrinolytics versus no antifibrinolytics – transfusion volume and incidence

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%)  Mean ± SD (n)  Median (IQR) | No antifibrinolytics  n/N (%)  Mean ± SD (n)  Median (IQR) | | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level I evidence | | | | | | | | | | | |
| Transfusion volume | | | | | | | | | | | |
| Arnold 2006c358  Level I  *Good* | 6 trialsd (Boldt 1993 a,404 Chauhan 2000,366 Davies 1997,370 D’Errico 1996,371 Herynkopf 1994,374 Seghaye 1996380)  N=404 | Paediatric patients aged <18 years with CHD undergoing open-heart surgery with CPB | NR | IV aprotinin versus placebo | Volume of blood transfused (mL/kg) | NR | NR | | | WMD –8.42 [–19.86, 3.02] | *No significant difference*  *P =*NR  Substantial heterogeneity  I2 = 96% |
| Faraoni 2012e359  Level I  *Fair* | 6 trialsf (Bulutcu 2005,365 Chauhan 2003,367 Chauhan 2004 a,368 Chauhan 2004b,369 Reid 1997,379 Shimizu 2011381)  N=710 | Paediatric patients aged <18 years undergoing cardiac surgery | India, Turkey, USA or NR | TXA versus placebo | 24 hr postoperative RBC transfusion volume (mL/kg) | NR | NR | | | MD –6.38 [–8.28, –4.47]e | *Favours TXA*  *P <*0.00001  No significant heterogeneity  I2 = 0% |
| 4 trialsf (Chauhan 2003,367 Chauhan 2004 a,368 Chauhan 2004b,369 Shimizu 2011381)  N=520 | India or NR | 24 hr postoperative PLT transfusion volume (mL/kg) | NR | NR | | | MD –3.70 [–5.40, –2.00]e | *Favours TXA*  *P <*0.0001  No significant heterogeneity  I2 = 0% |
| 5 trialsf (Bulutcu 2005,365 Chauhan 2003,367 Chauhan 2004 a,368 Chauhan 2004b,369 Shimizu 2011381)  N=669 | India, Turkey, or NR | 24 hr postoperative FFP transfusion volume (mL/kg) | NR | NR | | | MD –5.52 [–7.54, –3.50]e | *Favours TXA*  *P <*0.00001  No significant heterogeneity  I2 = 0% |
|  |  |  | *Sensitivity analyses: excluding Chauhan 2004 a due to potential bias* | | | | |  |
| 24 hr postoperative RBC transfusion volume (mL/kg)  5 trials (NR)  N=470 | NR | NR | | | MD –7.57 [–10.17, –4.98] | *Favours TXA*  *P =*NR  No significant heterogeneity  I2 = 0% |
| 24 hr postoperative PLT transfusion volume (mL/kg)  3 trials (NR)  N=180 | NR | NR | | | MD –3.12 [–7.09, 0.96] | *No significant difference*  *P =*NR  Substantial heterogeneity  I2 = 53% |
| 24 hr postoperative FFP transfusion volume (mL/kg)  4 trials (NR)  N=429 | NR | NR | | | MD –6.19 [–8.87, –3.52] | *Favours TXA*  *P =*NR  Mild heterogeneity  I2 = 4% |
|  | *Sensitivity analysis excluding all studies by Chauhan et al due to potential bias* | | | | | |
| 24 hr postoperative RBC transfusion volume (mL/kg)  3 trials (NR)  N=250 | NR | NR | | | MD –8.83 [–13.48, –4.19] | *Favours TXA*  *P =*NR  Moderate heterogeneity  I2 = 39% |
| 24 hr postoperative FFP transfusion volume (mL/kg)  2 trials (NR)  N=209 | NR | NR | | | MD –4.48 [–10.27, 1.31] | *No significant difference*  *P =*NR  Moderate heterogeneity  I2 = 40% |
| Schouten 2009360  Level I  *Good* | 3 trials (Davies 1997,370 Chauhan 2000,366 Bulutcu 2005365)  N=250 | Paediatric patients aged <18 years undergoing cardiac surgery | NR | Aprotinin versus placebo | RBC transfusion volume | NR | NR | | | WMD –4 (–7, –2) | *Favours aprotinin*  *P =*NR  No significant heterogeneity  I2 = 0% |
| 2 trials (Chauhan 2000,366 Bulutcu 2005365)  N=228 | Plasma transfusion volume | NR | NR | | | WMD –5 (–8, –2) | *Favours aprotinin*  *P =*NR  No significant heterogeneity  I2 = 0% |
| No. of trials NR  N=370 | TXA versus placebo | Thrombocyte transfusion volume | NR | NR | | | WMD –5 (–7, –3) | *Favours TXA*  *P =*NR  No significant heterogeneity  I2 = 0% |
| 3 trials (Chauhan 2000,366 Chauhan 2004,368-369 Rao 2000378)  N=410 | EACA versus placebo | Plasma transfusion volume | NR | NR | | | WMD –3 (–5, –1) | *Favours EACA*  *P =*NR  Mild heterogeneity  I2 = 20% |
| Transfusion incidence | | | | | | | | | | | |
| Arnold 2006c358  Level I  *Good* | 6 trialsd (Mossinger 2003,377 Miller 1998,376 Davies 1997,370 D’Errico 1996,371 Herynkopf 1994,374 Boldt 1994364)  N=362 | Paediatric patients aged <18 years with CHD undergoing open-heart surgery with CPB | NR | IV aprotinin versus placebo | RBC or whole blood transfusion incidence | NR | NR | | | RR 0.67 [0.51, 0.89] | *Favours aprotinin*  *P =*NR  Mild heterogeneity  I2 = 15% |
|  | *Sensitivity analyses* | | | | | |
| Good quality studies  4 trials (Mossinger 2003, Davies 1997, D’Errico 1996, Herynkopf 1994)  N=186 | NR | NR | | | RR 0.60 [0.38, 0.95] | *Favours aprotinin*  *P =*NR  Heterogeneity NR  I2 = NR |
| Studies with an objective transfusion protocol  3 trials (Davies 1997, D’Errico 1996, Herynkopf 1994)  N=126 | NR | NR | | | RR 0.72 [0.58, 0.89] | *Favours aprotinin*  *P =*NR  Heterogeneity NR  I2 = NR |
| Patients undergoing primary sternotomy  3 trials (Mossinger 2003, Boldt 1994, Herynkopf 1994)  N=120 | NR | NR | | | RR 0.44 [0.26, 0.76] | *Favours aprotinin*  *P =*NR  Heterogeneity NR  I2 = NR |
|  | *Subgroup analysis: weight* | | | | | |
| Patients with mean weight >10 kg  5 trials (Boldt 1994, D’Errico 1996, Davies 1997, Herynkopf 1994, Miller 1998)  N=186 | NR | NR | | | RR 0.73 [0.59, 0.89] | *Favours aprotinin*  *P =*NR  Heterogeneity NR  I2 = NR |
| Patients with mean weight <10 kg  1 trial (Mossinger 2003)  N=60 | NR | NR | | | NR | *Favours aprotinin*  *P =*NR |
| Level II evidence | | | | | | | | | | | |
| Transfusion volume | | | | | | | | | | | |
| Coniff 1998g393  Level II  *Poor* | N=116 | Paediatric patients (aged ≤16 years) undergoing surgery with CPB and an increased risk of bleeding | Multicentre, USA | Aprotinin (high-dose [H], low-dose [L] or pump prime only [P]) versus placebo | Donor blood *or* blood products transfused (units) | All patients | | | | | |
| High-dose  Low-dose  Pump prime only | 2.9 ± 8.5 (n=31)  6.0 ± 5.1 (n=33)  9.1 ± 12.6 (n=18) | 11.3 ± 23.7 (n=34)  11.3 ± 23.7 (n=34)  11.3 ± 23.7 (n=34) | | MD –8.40 [–16.91, 0.11]h  MD –5.30 [–13.45, 2.85]h  MD –2.20 [–12.07, 7.67]h | | *No significant difference*  *P =*0.05h  *P =*0.20h  *P =*0.66h |
|  | *Subgroup analyses: patients undergoing redo operations (more prone to bleeding)* | | | | | |
| High-dose  Low-dose  Pump prime only | 7.1 ± 10.4 (n=19)  7.4 ± 5.4 (n=22)  11.9 ± 16.3 (n=10) | | 5.2 ± 28.6 (n=22)  15.2 ± 28.6 (n=22)  15.2 ± 28.6 (n=22) | MD –8.10 [–20.93, 4.73]h  MD –7.80 [–19.96, 4.36]h  MD –3.30 [–18.95, 12.35]h | | *No significant difference*  *P =*0.22h  *P =*0.21h  *P =*0.68h |
|  | *Subgroup analysis: age* | | | | | |
| Patients aged ≤1 year |  |  | | |  | *No significant difference* |
| High-dose  Low-dose  Pump prime only | 7.3 ± 3.2 (n=3)  5.0 ± 3.1 (n=14)  14.1 ± 17.6 (n=8) | 9.0 ± 6.5 (n=6)  9.0 ± 6.5 (n=6)  9.0 ± 6.5 (n=6) | | | MD –1.70 [–8.04, 4.64]h  MD –4.00 [–9.45, 1.45]h  MD 5.10 [–8.16, 18.36]h | *P =*0.60h  *P =*0.15h  *P =*0.45h |
| Patients aged 1–17 years |  |  | | |  | *No significant difference* |
| High-dose  Low-dose  Pump prime only | 5.0 ± 8.9 (n=28)  6.8 ± 6.1 (n=19)  5.1 ± 4.5 (n=10) | 11.8 ± 26.0 (n=28)  11.8 ± 26.0 (n=28)  11.8 ± 26.0 (n=28) | | | NR  NR  NR | NR  NR  NR |
| Donor blood transfused (units) | *Subgroup analysis: patients aged >1 and <17 years* | | | | | |
| High-dose  Low-dose  Pump prime only | 2.6 ± 1.8 (n=28)  3.7 ± 2.3 (n=19)  2.8 ± 2.2 (n=10) | 4.8 ± 6.5 (n=28)  4.8 ± 6.5 (n=28)  4.8 ± 6.5 (n=28) | | | MD –2.20 [–4.70, 0.30]h  MD –1.10 [–3.72, 1.52]h  MD –2.00 [–4.77, 0.77]h | *No significant difference*  *P =*0.08  *P =*0.41  *P =*0.16 |
| Ferreira 2010394  Level II  *Poor* | N=19 | Paediatric patients aged 1 month to 4 years with CHD undergoing cardiac surgery with CPB | Single hospital, Brazil | IV aprotinin (3x doses) versus placebo | Intraoperative RBC transfusion volume (mL) | 221 ± 55 (n=10) | 248 ± 73 (n=9) | | | MD –27.00 [–85.62, 31.62]h | *No significant difference*  *P =*0.37h |
| Postoperative platelet transfusion volume | 0 ± 0 (n=10) | 12 ± NR (n=9) | | | not estimable | NR |
| Postoperative albumin transfusion volume | 27.58 ± 30.27 (n=10) | 12.95 ± 18.58 (n=9) | | | 14.63 [–7.72, 36.98]h | *No significant difference*  *P =*0.20c |
| Flaujac 2007395  Level II  *Poor* | N=20 | Infants aged 4 days to 36 months undergoing primary corrective cardiac surgery with CPB | Single hospital, France | IV aprotinin (2x doses) versus placebo | 24 hr postoperative transfusion volume (mL/kg) | 18 (9.0–25.8) | 30 (25.8–39.3) | | | NR | *Favours aprotinin*  *P =*0.01 |
| Sarupria 2013396  Level II  *Fair* | N=120 | Paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB for tetralogy of Fallot | Single hospital, India | IV EACA (high or low-dose) versus placebo | Intraoperative RBC transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | 22.47 ± 12.32 (n=38) | 32.38 ± 13.01 (n=37) | | | MD –9.91 [–15.65, –4.17]h | *Favours high-dose EACA*  *P <*0.01 |
| Low-dose EACA | 16.56 ± 12.49 (n=40) | 32.38 ± 13.01 (n=37) | | | MD –15.82 [–21.53, –10.11]h | *Favours low-dose EACA*  *P <*0.01 |
| Intraoperative FFP transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | 10.33 ± 7.96 (n=38) | 17.00 ± 5.08 (n=37) | | | NR | *Favours high-dose EACA*  *P <*0.01 |
| Low-dose EACA | 10.19 ± 7.63 (n=40) | 17.00 ± 5.08 (n=37) | | | NR | *Favours low-dose EACA*  *P <*0.01 |
| Intraoperative platelet concentrate transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | 2.08 ± 1.054 (n=38) | 2.30 ± 0.82 (n=37) | | | NR | *No significant difference*  *P =*0.47 |
| Low-dose EACA | 2.31 ± 0.86 (n=40) | 2.30 ± 0.82 (n=37) | | | NR | *No significant difference*  *P =*0.47 |
| Total RBC transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | 54.35 ± 27.42 (n=38) | 69.86 ± 23.91 (n=37) | | | NR | *Favours high-dose EACA* *P <*0.05 |
| Low-dose EACA | 24.47 ± 19.62 (n=40) | 69.86 ± 23.91 (n=37) | | | NR | *Favours low-dose EACA*  *P <*0.01 |
| Total FFP transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | 27.60 ± 16.36 (n=38) | 42.98 ± 13.91 (n=37) | | | NR | *Favours high-dose EACA*  *P <*0.01 |
| Low-dose EACA | 12.80 ± 9.82 (n=40) | 42.98 ± 13.91 (n=37) | | | NR | *Favours low-dose EACA*  *P <*0.01 |
| Total platelet concentrate transfusion volume (mL/kg) | | | | | |  |
| High-dose EACA | NR (n=38) | NR (n=37) | | | NR | *No significant difference*  *P >*0.05 |
| Low-dose EACA | NR (n=40) | NR (n=37) | | | NR | *No significant difference*  *P >*0.05 |
| Singh 2001397  Level II  *Fair* | N=75 | Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot undergoing total correction with CPB | India | IV aprotinin (2x doses or 1x dose) versus placebo | Blood transfusion (units) | 2x: 1.1 ± 1.1 (n=25)  1x: 0.91 ± 0.75 (n=25) | 2.2 ± 1.0 (n=25) | | | NR | *Favours aprotinin*  *P <*0.05 |
| FFP transfusion (units) | 2x: 2.0 ± 2.5 (n=25)  1x: 1.8 ± 1.3 (n=25) | 4.8 ± 1.0 (n=25) | | | NR | *Favours aprotinin*  *P <*0.05 |
| Platelet transfusion (units) | 2x: 1.4 ± 3.8 (n=25)  1x: 1.6 ± 1.8 (n=25) | 2.6 ± 2.0 (n=25) | | | NR | *Favours aprotinin*  *P <*0.05 |
| Vacharaksa 2002398  Level II  *Fair* | N=62 | Paediatric patients aged ≤14 years with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery | Single hospital, Thailand | IV TXA (2x doses) versus IV TXA (1x dose) + placebo | Total postoperative RBC transfusion volume (mL) | 395.82 ± 160.50 (n=33) | 434.04 ± 200.82 (n=29) | | | SMD –0.21 [–0.71, 0.29]h | *No significant difference*  *P =*0.4 |
| Postoperative RBC transfusion volume (mL/kg/24 hr) | 23.72 ± 10.61 (n=33) | 27.05 ± 11.28 (n=29) | | | SMD –0.30 [–0.80, 0.20]h | *No significant difference*  *P =*0.2 |
| Total postoperative FFP transfusion volume (mL) | 294.22 ± 139.62 (n=33) | 276.18 ± 152.80 (n=29) | | | SMD 0.12 [–0.38, 0.62]h | *No significant difference*  *P =*0.6 |
| Postoperative FFP transfusion volume (mL/kg/24 hr) | 19.39 ± 9.98 (n=33) | 16.21 ± 6.98 (n=29) | | | SMD 0.36 [–0.14, 0.86]h | *No significant difference*  *P =*0.4 |
| Postoperative platelet transfusion volume (units/kg/24 hr) | 0.12 ± 0.05 (n=33) | 0.11 ± 0.05 (n=29) | | | SMD 0.20 [–0.30, 0.70]h | *No significant difference*  *P =*0.4 |
| Transfusion incidence | | | | | | | | | | | |
| Coniff 1998f393Level II  *Poor* | N=116 | Paediatric patients (aged ≤16 years) undergoing surgery with CPB and an increased risk of bleeding | Multicentre, USA | Aprotinin (high-dose [H], low-dose [L] or pump prime only [P]) versus placebo | Donor blood *or* blood product transfusion incidence | All patients | | | | |  |
| High-dose  Low-dose  Pump prime only | NR (93.5%)  NR (93.9%)  NR (88.9%) | NR (85.3%)  NR (85.3%)  NR (85.3%) | | | NR  NR  NR | NR  NR  NR |
|  | *Subgroup analysis: patients undergoing redo operations (more prone to bleeding)* | | | | | |
| High-dose  Low-dose  Pump prime only | NR (94.7%)  NR  NR | NR (90.9%)  NR  NR | | | NR  NR  NR | NR  NR  NR |
|  | *Subgroup analysis: age* | | | | |  |
| Patients aged ≤1 year |  |  | | |  |  |
| High-dose  Low-dose  Pump prime only | NR  NR (92.9%)  NR | NR  NR  NR | | | NR  NR  NR | NR  NR  NR |
| Patients aged >1 and <17 years |  |  | | |  |  |
| High-dose  Low-dose  Pump prime only | NR (92.9%)  NR (94.7%)  NR (80.0%) | NR (82.1%)  NR (82.1%)  NR (82.1%) | | | NR  NR  NR | NR  NR  NR |
| Patients requiring ≥ 20 units of donor blood *or* blood products | All patients | | | | |  |
| High-dose  Low-dose  Pump prime only | NR (3.2%)  NR (3.0%)  NR (5.6%) | NR (11.8%)  NR (11.8%)  NR (11.8%) | | | NR  NR  NR | NR  NR  NR |
|  | *Subgroup analysis: patients undergoing redo operations (more prone to bleeding)* | | | | |  |
| High-dose  Low-dose  Pump prime only | NR (5.3%)  NR (4.5%)  NR (10.0%) | NR (13.6%)  NR (13.6%)  NR (13.6%) | | | NR  NR  NR | NR  NR  NR |
|  | *Subgroup analysis: age* | | | | |  |
| Patients aged ≤1 year |  |  | | |  |  |
| High-dose  Low-dose  Pump prime only | NR  NR  NR (12.5%) | NR (16.7%)  NR (16.7%)  NR (16.7%) | | | NR  NR  NR | NR  NR  NR |
| Patients aged >1 and <17 years |  |  | | |  |  |
| High-dose  Low-dose  Pump prime only | NR (3.6%)  NR (5.3%)  NR | NR (10.7%)  NR (10.7%)  NR (10.7%) | | | NR | NR |
| Patients requiring ≥ 20 units of donor blood | *Subgroup analysis: patients aged >1 and <17 years* | | | | |  |
| High-dose  Low-dose  Pump prime only | NR (14.3%)  NR (31.6%)  NR (30.0%) | NR (28.6%)  NR (28.6%)  NR (28.6%) | | | NR  NR  NR | NR  NR  NR |
| Ferreira 2010394  Level II  *Poor* | N=19 | Paediatric patients aged 1 month to 4 years with CHD undergoing cardiac surgery with CPB | Single hospital, Brazil | IV aprotinin (3x doses) versus placebo | Postoperative RBC transfusion incidence | 1/10 (10%) | 0/9 (0%) | | | RR 2.73 [0.12, 59.57]h | *No significant difference*  *P =*0.52h |
| Postoperative platelet concentration transfusion incidence | 0/10 (0%) | 2/9 (22%) | | | RR 0.18 [0.01, 3.35]h | *No significant difference*  *P =*0.25h |
| No. of postoperative donor exposures | 2/10 (20%) | 2/9 (22.2%) | | | RR 0.90 [0.16, 5.13]h | *No significant difference*  *P =*0.91h |
| Flaujac 2007395  Level II  *Poor* | N=20 | Infants aged 4 days to 36 months undergoing primary corrective cardiac surgery with CPB | Single hospital, France | IV aprotinin (2x doses) versus placebo | 24 hr postoperative RBC transfusion incidence | 6/10 (60%) | 10/10 (100%) | | | NR | *No significant difference*  *P =*0.06h |
| 24 hr postoperative platelet transfusion incidence | 3/10 (30%) | 6/10 (60%) | | | NR | *No significant difference*  *P =*0.21h |
| 24 hr postoperative FFP transfusion incidence | 2/10 (20%) | 3/10 (30%) | | | NR | *No significant difference*  *P =*0.61h |
| 24 hr postoperative albumin transfusion incidence | 0/10 (0%) | 4/10 (40%) | | | NR | *No significant difference*  *P =*0.12 h |
| 24 hr postoperative prothrombin complex concentrate (prepared from FFP) transfusion incidence | 4/10 (40%) | 7/10 (70%) | | | NR | *No significant difference*  *P =*0.20 h |
| Sarupria 2013396  Level II  *Fair* | N=120 | Paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB for tetralogy of Fallot | Single hospital, India | IV EACA (high [H] or low [L] dose) versus placebo | RBC transfusion incidence | | | | | |  |
| High-dose EACA | 34/38 (89.5%) | 36/37 (97.3%) | | | NR | *No significant difference*  *P =*NR |
| Low-dose EACA | 30/40 (75.0%) | 36/37 (97.3%) | | | NR | *Favours low-dose EACA*  *P =*0.01 |
| FFP transfusion incidence | | | | | |  |
| High-dose EACA | 34/38 (89.5%) | 37/37 (100%) | | | NR | *No significant difference*  *P =*NR |
| Low-dose EACA | 29/40 (72.5%) | 37/37 (100%) | | | NR | *Favours low-dose EACA*  *P =*0.01 |
| Platelet concentrate transfusion incidence | | | | | |  |
| High-dose EACA | 37/38 (97.4%) | 37/37 (100%) | | | NR | *No significant difference*  *P =*1.00 |
| Low-dose EACA | 40/40 (100%) | 37/37 (100%) | | | NR | *No significant difference*  *P =*1.00 |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; FFP, fresh frozen plasma; IQR, interquartile range; IV, intravenous; MD, mean difference; NR, not reported; PLT, platelet; RBC, red blood cell; SD, standard deviation; SMD, standard mean difference; TXA, tranexamic acid; WMD, weighted mean difference

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes studies reported by Boldt. A number of studies by Boldt have been retracted due to research misconduct, including lack of ethics approval and false data. Although the included studies have not been formally retracted, care should be taken in the interpretation of this analysis.

**d.** Boldt 1993a was included twice (infants >10 kg and infants <10 kg). Chauhan 2000 was a four-armed RCT comparing aprotinin to EACA to a combination to placebo. Only data for aprotinin versus placebo was presented in the analysis (the author did not present data for EACA versus placebo).

**e.** Meta-analyses using fixed-effects models were included where heterogeneity was low, and random-effects models were included where heterogeneity was high.

**f.** Includes Chauhan 2004 a four times for different doses of TXA versus placebo.

**g.** Compassionate-use study.

**h.** Calculated post-hoc using RevMan 5.1.2.

Scoliosis surgery

The systematic review and hand-searching process identified two Level I studies (Tzortzopoulou 2008, Schouten 2009) and one additional Level II study (Thompson 2005) that provided evidence for the effect of antifibrinolytics on transfusion volume or incidence in paediatric patients undergoing surgery for scoliosis. **Table 3.4.26** summarises the results from these studies.

Transfusion volume

Tzortzopoulou (2008) conducted a meta-analysis of five trials involving 207 paediatric patients (Cole 2003, Florentino-Pineda 2004, Khoshhal 2003, Neilipovitz 2001, Sethna 2005) that reported the effect of antifibrinolytics (aprotinin, TXA or EACA) on transfusion volume. The authors combined both intraoperative and postoperative periods of evaluation, and reported a significant reduction in the total volume (mL) of blood transfused in patients administered antifibrinolytics (MD –327.41, 95% CI –469.04, –185.78). There was no significant heterogeneity (I2= 0%). The same effect was observed when the analysis was assessed by product type (**Table 3.4.26**). .

Schouten (2009) reported one additional outcome for TXA not reported in the review by Tzortzopoulou (2008). In a meta-analysis of two trials (Sethna 2005, Neilipovitz 2001), the authors reported no significant difference in plasma transfusion volume (WMD –15, 95% CI   
–127, 98).

One additional RCT (Thompson 2005) provided evidence for transfusion volume. The authors reported a significant difference in the mean number of autologous blood units transfused that favoured EACA (MD –1.00; 95% CI –1.76, –0.24).

Transfusion incidence

The systematic review by Tzortzopoulou (2008) reported a meta-analysis of four trials involving 163 patients (Florentino-Pineda 2004, Khoshhal 2003, Neilipovitz 2001, Sethna 2005,) that showed there was no significant difference between treatment groups for the number of patients transfused (RR 0.87, 95% CI 0.67, 1.12). The subgroup analyses for different antifibrinolytic agents also demonstrated no significant difference for the number of patients transfused, regardless of product type.

Tzortzopoulou (2008) also reported that one RCT (Khoshhal 2003) showed there were fewer allogenic blood transfusions among patients administered aprotinin (RR 0.71, 95% CI 0.53, 0.90) compared with those who did not receive aprotinin but no data were provided and the statistical significance of the effect was not reported. There was no allogenic blood transfusion reported in the RCTs that assessed the effectiveness of TXA (Neilipovitz 2001, Sethna 2005,) or EACA (Florentino-Pineda 2004).

The RCT by Thompson (2005) also reported no difference in the incidence of allogenic blood transfusions for patients administered EACA (no events in either group).

Table 3.4.26 Neonatal and paediatric patients undergoing scoliosis surgery: Results for antifibrinolytics versus no antifibrinolytics – transfusion requirements

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%)  Mean ± SD (n) | No antifibrinolytics  n/N (%)  Mean ± SD (n) | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | | |
| Tzortzopoulou 2008361  Level I  *Good* | 5 trials (Cole 2003,384 Khoshhal 2003,386 Neilipovitz 2001,387 Sethna 2005,388 Florentino-Pineda 2004385)  N=207 | Paediatric patients aged <18 years undergoing scoliosis surgery | Canada (Khoshhal 2003, Neilipovitz 2001), USA (Cole 2003, Sethna 2005, Florentino-Pineda 2004) | IV antifibrinolytic (aprotinin, TXA, EACA) versus placebo | Total blood transfused (mL) | NR | NR | | MD –327.41  [–469.04, –185.78] | *Favours antifibrinolytic*  *P <*0.00001  No significant heterogeneity  I2 = 0% |
| 4 trials (Khoshhal 2003,386 Neilipovitz 2001,387 Sethna 2005,388 Florentino-Pineda 2004385)  N=163 | Transfusion incidence | 42/79 (53.2%) | 53/84 (63.1%) | | RR 0.87 [0.67, 1.12] | *No significant difference*  *P =*0.28  No significant heterogeneity  I2 = 0% |
| 2 trials (Cole 2003,384 Khoshhal 2003386)  N=87 | IV aprotinin versus placebo | Total blood transfused (mL) | NR | NR | | MD –361.42  [–583.88, –138.96] | *Favours aprotinin*  *P =*0.0015  No significant heterogeneity  I2 = 0% |
| 1 trial (Khoshhal 2003386)  N=43 | Transfusion incidence | 8/15 (53.3%) | 20/28 (71.4%) | | RR 0.75 [0.44, 1.27] | *No significant difference*  *P =*0.28 |
| Transfusion incidence (allogeneic blood only) | NR | NR | | RR 0.71 [0.53, 0.90] | *Favours aprotinin*  *P =*NR |
| 2 trials (Neilipovitz 2001,387 Sethna 2005388)  N=84 | IV TXA versus placebo | Transfusion incidence | 20/45 (44.4%) | 21/39 (53.8%) | | RR 0.84  [0.56, 1.27] | *No significant difference*  *P =*0.41  No significant heterogeneity  I2 = 0% |
| Transfusion incidence (allogeneic blood only) | 0 | 0 | | Not estimable | *No significant difference*  *P =*NA  Heterogeneity NR  I2 = NR |
| Total blood transfused (mL) | NR | NR | | MD –395.14  [–687.55, –102.73] | *Favours TXA*  *P =*0.0081  No significant heterogeneity  I2 = 0% |
| 1 trial (Florentino-Pineda 2004385)  N=36 | IV EACA versus placebo | Transfusion incidence | 14/19 (73.7%) | 12/17 (70.6%) | | RR 1.04 [0.69, 1.57] | *No significant difference*  *P =*0.84 |
| Transfusion incidence (allogeneic blood only) | 0 | 0 | | Not estimable | *No significant difference*  *P =*NA |
| Total blood transfused (mL) | NR | NR | | MD –245.00  [–481.03, –8.97] | *Favours EACA*  *P =*0.042 |
| Schouten 2009360  Level I  *Good* | 2 trials (Sethna 2005,388 Neilipovitz 2001387)  N=84 | Paediatric patients aged <18 years undergoing scoliosis surgery |  | TXA versus placebo | Plasma transfusion volume | NR | NR | | WMD –15 (–127, 98) | *No significant difference*  *P =*NR  Mild heterogeneity  I2 = 24% |
| Level I evidence | | | | | | | | | | |
| Thompson 2005405  Level II  *Poor* | N=36 | Paediatric patients aged 11 to 18 years with idiopathic scoliosis scheduled for posterior spinal fusion with segmental spinal instrumentation | USA | IV EACA versus no treatment | Autologous units transfused | 1.1 ± 1.0 (n=19) | | 2.1 ± 1.3 (n=17) | MD –1.00 [–1.76, –0.24] | *Favours EACA*  *P =*0.002 |
| Allogeneic transfusion incidence | 0/19 (0.02%) | | 0/17 (0.0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; EACA, epsilon-aminocaproic acid; IV, intravenous; MD, mean difference; NA, not applicable; NR, not reported; SD, standard deviation; RR, risk ratio; TXA, tranexamic acid; WMD, weighted mean difference

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Craniofacial surgery

The systematic review and hand-searching process identified one Level I study (Song 2013) and an additional two Level II studies (Ahmed 2014, D’Errico 2003) that provided evidence for the effect of antifibrinolytics on transfusion volume or incidence in paediatric patients undergoing craniofacial surgery. **Table 3.4.27** summarises the results from these studies.

Transfusion volume

The systematic review by Song (2013) conducted a meta-analysis involving 138 children undergoing craniosynostosis surgery to assess the effect of TXA on RBC transfusion volume. Two RCTs (Dadure 2011, Goobie 2011) and one Level III study (Maugans 2011) (that involved two groups of patients) were included in the analysis. A statistically significant reduction in the volume of RBCs transfused, favouring TXA, was reported (MD –10.81, 95% CI –16.84, –4.78).

The RCT by Ahmed (2014) reported a statistically significant reduction in the mean intraoperative volume (mL) of RBCs transfused (MD –170.00; 95% CI –289.22, –50.78) and the mean intraoperative volume by weight (mL/g) of RBCs transfused (MD –20.00, 95% CI –32.16, –7.84), favouring aprotinin. There were no significant differences between treatment groups in the total intraoperative transfusion volume (mL) of FFP (MD –120.00; 95% CI –255.90, 15.90), FFP intraoperative transfusion volume by weight (mL/kg) (MD –10.00; 95% CI –25.38, 5.38) or intraoperative albumin transfusion volume (mL) (MD –10.00, 95% CI –86.88, 66.880).

The RCT by D’Errico (2003) also reported a statistically significant effect that favoured aprotinin for the reduction in intraoperative blood transfusions (mL/kg) (MD –20.00; 95% CI –38.57, –1.43) and postoperative RBC transfusion volume (MD –24.00, 95% CI –43.67, –4.33).

Since Level III evidence did not meet the inclusion criteria for this review, a meta-analysis of included Level II studies was conducted to assess the effect of antifibrinolytics on perioperative RBC transfusion volume in paediatric patient undergoing craniofacial surgery (**Figure 3.4.9**). The analysis showed a significantly reduced volume of RBCs (mL/kg) transfused in patients treated with antifibrinolytics, compared with control (MD –24.00, 95% CI –43.67, –4.33). There was moderate heterogeneity for this outcome (I2=32%).

Transfusion incidence

The RCT by Ahmed (2014) reported transfusion incidence in 26 paediatric patients undergoing major reconstructive craniofacial surgery. There was no significant difference between treatment groups for postoperative RBC and/or platelet transfusion incidence (RR 0.67 95% CI 0.13, 3.35) or FFP transfusion incidence (RR 0.56, 95% CI 0.26, 1.21).

The RCT by D’Errico (2003) reported the proportion of patients requiring transfusions of platelets, FFP or cryoprecipitate. Analysis of the data showed that aprotinin does not significantly reduce the incidence of blood components transfusions (Table 3.4.27).

Table 3.4.27 Neonatal and paediatric patients undergoing craniofacial surgery: Results for antifibrinolytics versus no antifibrinolytics – transfusion requirements

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%)  Mean ± SD (n) | No antifibrinolytics  n/N (%)  Mean ± SD (n) | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | | |
| Song 2013362  Level I/III  *Fair* | 3 trialsc (Dadure 2011,389 Goobie 2011,390 Maugans 2011406)  N=138 | Children undergoing craniosynostosis surgery | USA, France | IV tranexamic acid versus placebo | RBC transfusion volume (mL/kg) | NR | | NR | MD –10.81 (–16.84, –4.78) | *Favours TXA*  *P =*0.0004  No significant heterogeneity  I2 = 0% |
| Level II evidence | | | | | | | | | | |
| Ahmed 2014400  Level II  *Fair* | N=26 | Paediatric patients aged 1 month to 3 years undergoing major reconstructive craniofacial surgery | Single hospital, USA | IV aprotinin versus placebo | Intraoperative RBC transfusion volume (mL) | 380 ± 90 (n=13) | | 550 ± 200 (n=13) | MD –170.00 [–289.22, –50.78]d | *Favours aprotinin*  *P =*0.004 |
| Intraoperative RBC transfusion volume (mL/kg) | 40 ± 10 (n=13) | | 60 ± 20 (n=13) | MD –20.00 [–32.16, –7.84]d | *Favours aprotinin*  *P <*0.05 |
| Intraoperative FFP transfusion volume (mL) | 100 ± 150 (n=13) | | 220 ± 200 (n=13) | MD –120.00 [–255.90, 15.90]d | *No significant difference*  *P =*0.08d |
| Intraoperative FFP transfusion volume (mL/kg) | 10 ± 20 (n=13) | | 20 ± 20 (n=13) | MD –10.00 [–25.38, 5.38]d | *No significant difference*  *P =*0.20d |
| Intraoperative albumin transfusion volume (mL) | 110 ± 100 (n=13) | | 120 ± 100 (n=13) | MD –10.00 [–86.88, 66.88]d | *No significant difference*  *P =*0.8d |
| Postoperative RBC and/or platelet transfusion incidence | 2/13 (15.4%) | | 3/13 (23.1%) | RR 0.67 [0.13, 3.35]d | *No significant difference*  *P =*0.62d |
| FFP transfusion incidence | 5/13 (38.5%) | | 9/13 (69.2%) | RR 0.56 [0.26, 1.21] | *No significant difference*  *P =*0.14 |
| D’Errico 2003401  Level II  *Good* | N=39 | Paediatric patients aged 1 month to 12 years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement | Single hospital, USA | IV aprotinin versus placebo | Intraoperative blood transfusion volume (mL/kg) | 32 ± 25 (n=18) | | 52 ± 34 (n=21) | MD –20.00 [–38.57, –1.43] | *Favours aprotinin*  *P =*0.04 |
| Postoperative RBC transfusion volume (mL/kg) | 33 ± 24 (n=18) | | 57 ± 38 (n=21) | MD –24.00 [–43.67, –4.33]d | *Favours aprotinin*  *P =*0.03 |
| Platelet transfusion incidence | 1/18 (5.6%) | | 0/21 (0%) | RR 3.47 [0.15, 80.35]d | *No significant difference*  *P =*0.44d |
| FFP transfusion incidence | 2/18 (11.1%) | | 5/21 (23.8) | RR 0.47 [0.10, 2.12]d | *No significant difference*  *P =*0.32d |
| Cryoprecipitate transfusion incidence | 0/18 (0%) | | 0/21 (0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; FFP, fresh frozen plasma; IV, intravenous; MD, mean difference; NA, not applicable; NR, not reported; RR, risk ratio; SD, standard deviation; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** The analysis included one Level III study (Maugans 2011).

**d.** Calculated post-hoc using RevMan 5.1.2.

Figure 3.4.9 Meta-analysis: antifibrinolytics versus no antifibrinolytics in paediatric patients undergoing craniofacial surgery – perioperative RBC transfusion volume (mL/kg)



Ear, nose and throat surgery

The systematic review and hand-searching process identified one Level I study (Ker 2013) that provided evidence for the effect of antifibrinolytics on transfusion volume or incidence in paediatric patients undergoing ENT surgery. **Table 3.4.28** summarises the results from these studies.

Transfusion incidence

The systematic review by Kerr (2013) identified one RCT (Albirmawy 2013) that assessed the use of topical TXA in 400 paediatric patients undergoing primary isolated adenoidectomy. The RCT reported no significant difference between treatment groups for the incidence of transfusions (RR 0.20, 95% CI 0.01, 4.14).

Table 3.4.28 Neonatal and paediatric patients undergoing ENT surgery: Results for antifibrinolytics versus no antifibrinolytics – transfusion requirements

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%) | No antifibrinolytics  n/N (%) | | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | | |
| Ker 2013363  Level I/II  *Good* | 1 trial (Albirmawy 2013391)  N=400 | Children undergoing primary isolated adenoidectomy | Egypt | Topical TXA versus placebo | Transfusion incidence | 0/200 (0%) | | 2/200 (1%) | RR 0.20 (0.01, 4.14) | *No significant difference*  *P =*NR |

CI, confidence interval; ENT, ear nose throat; NR, not reported; RR, risk ratio; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Thromboembolic events

The systematic review and hand-searching process identified one Level I study (Tzortzopoulou 2008) and four additional Level II studies (Ahmed 2014, Flaujac 2007, Thompson 2005, Vacharaksa 2002) that assessed the effect of antifibrinolytics in neonatal and paediatric patients undergoing surgery that reported thromboembolic events. **Table 3.4.29** summarises the results from these studies.

Overall, the event rate of thromboembolic events in paediatric patients undergoing surgery who were treated with antifibrinolytics was too small to detect any between-group differences.

Cardiac surgery

Two RCTs (Flaujac 2007, Vacharaksa 2002) were identified that assessed the incidence of thromboembolic events in 82 paediatric patients undergoing cardiac surgery; however, no thrombotic events were reported in either study.

Scoliosis surgery

Two RCTs (Cole 2003, Thompson 2005) were identified that assessed the incidence of thromboembolic events in 80 paediatric patients undergoing scoliosis surgery. The RCT by Cole (2003) reported no DVT events in the aprotinin group (0%) compared with three events in the placebo group (13%). The result was not significant (*P =*0.21). The RCT by Thompson (2005) reported no events of venous thrombosis or thromboemboli during the study period.

Craniofacial surgery

The RCT by Ahmed (2014) measured thrombotic complications in 26 paediatric patients undergoing major reconstructive craniofacial surgery, but no events were reported.

Table 3.4.29 Neonatal and paediatric patients undergoing surgery: Results for antifibrinolytics versus no antifibrinolytics – thromboembolic events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%) | No antifibrinolytics  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Cardiac surgery | | | | | | | | | |
| Flaujac 2007395  Level II  *Poor* | N=20 | Infants aged 4 days to 36 months undergoing primary corrective cardiac surgery with CPB | Single hospital, France | IV aprotinin (2x doses) versus placebo | Thrombotic events | 0/10 (0%) | 0/10 (0%) | Not estimable | *No significant difference*  *P =*NA |
| Vacharaksa 2002398  Level II  *Fair* | N=62 | Paediatric patients aged ≤14 years with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery | Single hospital, Thailand | IV TXA (2x doses) versus IV TXA (1x dose) + placebo | Thrombotic complications | 0/33 (0%) | 0/29 (0%) | Not estimable | *No significant difference*  *P =*NA |
| Scoliosis surgery | | | | | | | | | |
| Tzortzopoulou 2008361  Level I/II  *Good* | 1 trial (Cole 2003384)  N=44 | Paediatric patients aged <18 years undergoing scoliosis surgery | USA | IV aprotinin versus placebo | Postoperative DVT | 0/21 (0%) | 3/23 (13.0%) | RR 0.16 [0.01, 2.85]c | *No significant difference*  *P =*0.21c |
| Thompson 2005405  Level II  *Poor* | N=36 | Paediatric patients aged 11 to 18 years with idiopathic scoliosis scheduled for posterior spinal fusion with segmental spinal instrumentation | USA | IV Amicar (EACA) 100 mg/kg over 15 mins before skin incision + maintenance infusion 10 mg/kg/hr until wound closure versus no treatment | Venous thrombosis or thromboemboli | 0/19 (0.0%) | 0/17 (0.0%) | Not estimable | *No significant difference*  *P =*NA |
| Craniofacial surgery | | | | | | | | | |
| Ahmed 2014400  Level II  *Fair* | N=26 | Paediatric patients aged 1 month to 3 years undergoing major reconstructive craniofacial surgery | Single hospital, USA | IV aprotinin versus placebo | Thrombotic complications | 0/13 (0%) | 0/13 (0%) | Not estimable | *No significant difference*  *P =*NA |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; EACA, epsilon-aminocaproic acid; IV, intravenous; NA, not applicable; RR, risk ratio; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

###### Bleeding events

Cardiac surgery

The systematic review and hand-searching process identified two Level I studies (Arnold 2006, Faraoni 2012) and an additional five Level II studies (Aggarwal 2012, Ferreira 2010, Sarupria 2013, Singh 2001, Vacharaksa 2002) that assessed the effect of antifibrinolytics in paediatric patients undergoing cardiac surgery and provided evidence for bleeding events. **Table 3.4.30** summarises the results from these studies.

Aprotinin

Arnold (2006) identified 11 RCTs (Boldt 1994, Boldt 1993 a x2, Boldt 1993b, Chauhan 2000, Davies 1997, Dietrich 1993, D’Errico 1996, Gomar 1995, Miller 1998, Mossinger 2003) that assessed the effect of aprotinin in 571 paediatric patients and reported the volume of chest tube drainage as an outcome. A meta-analysis of the data from these RCTs found no significant difference between treatment groups (WMD –0.97, 95% CI –4.94, 2.99). Heterogeneity was substantial (I2=77%).

The RCT by Ferreira (2010) assessed the effect of aprotinin in 19 paediatric patients with CHD undergoing cardiac surgery with CPB. No significant difference between treatment groups was reported for 48-hour postoperative blood loss (mL/kg) (17.6 versus 18.1), but the data were incomplete (no SDs provided).

The RCT by Singh (2001) assessed the effect of one or two doses of aprotinin among 75 paediatric patients, and reported total blood loss (mL) and 24 hour chest tube drainage. A significant reduction in the total volume of blood loss favouring aprotinin was reported, regardless of the dose (two doses, MD –204.60, 95% CI –247.72; one dose, MD –171.80, 95% CI –208.94, –134.66). A similar result favouring aprotinin was reported for 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) which favoured aprotinin.

Tranexamic acid

Faraoni (2012) conducted a meta-analysis of eight RCTs involving 848 paediatric patients (Bulutcu 2005, Chauhan 2003, Chauhan 2004 a, Chauhan 2004b x4, Levin 2000, Reid 1997, Shimizu 2011, Zonis 1996) that assessed the effect of TXA on 24-hour postoperative blood loss. The authors found no significant difference between treatment groups (MD –3.61; 95% CI –8.08, 0.85; *P =*0.11). Faraoni (2012) conducted two sensitivity analyses to explore the possible bias introduced by Chauhan and colleagues, whose studies dominated the primary meta-analysis. The first sensitivity analysis excluded Chauhan 2004a and the second excluded all studies by Chauhan and colleagues. Both sensitivity analyses showed an effect that favoured TXA (7 trials, MD –7.82, 95% CI –11.54, –4.10 and 5 trials, MD –5.22, 95% CI –8.16, –2.28; respectively). Faraoni (2012) also conducted a subgroup analysis involving 298 acyanotic patients, and reported no significant effect of TXA on 24-hour postoperative blood loss difference in this patient group (*P =*0.47); however, complete data for this analysis were not provided.

The RCT by Aggarwal (2012) assessed the effect of TXA in 80 children, and reported a significant difference in 24-hour postoperative blood loss that favoured TXA (MD –9.00, 95% CI –10.55, –7.45). In the TXA group, there were two cases (5.0%) of excessive bleeding (>25 ml/kg) due to hyperfibrinolysis, compared with five cases (12.5%) in the control group; however, this result was not statistically significant (RR 0.40, 95% CI 0.08, 1.94).

The RCT by Vacharaksa (2002) measured blood loss in 62 paediatric patients administered TXA. It reported no significant difference in total (mL) postoperative blood loss (MD 9.33, 95% CI –78.24, 96.90) or 24-hour postoperative blood loss by weight (mL/kg) (MD 1.83, 95% CI –3.24, 6.90).

EACA

The RCT by Sarupria (2013) assessed the effect of two doses of EACA on cumulative postoperative blood loss (mL) in 120 paediatric patients, and reported a significant effect favouring low-dose EACA at 6, 12 and 24 hours (**Table 3.4.30**). For high-dose EACA, only 6-hour postoperative blood loss reached statistical significance in favour of EACA, with no significant difference in cumulative blood loss reported at 12 or 24 hours.

Table 3.4.30 Neonatal and paediatric patients undergoing cardiac surgery: results for antifibrinolytics versus no antifibrinolytics – bleeding events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%)  Mean ± SD (n) | No antifibrinolytics  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Arnold 2006358  Level I  *Good* | 11 trialsc (Boldt 1994,364 Boldt 1993 a,404 Boldt 1993b,407 Chauhan 2000,366 Davies 1997,370 D’Errico 1996,371 Dietrich 1993,372 Gomar 1995,373 Miller 1998,376 Mossinger 2003377)  N=571 | Paediatric patients aged <18 years with CHD undergoing open-heart surgery with CPB | NR | IV aprotinin versus placebo | Chest tube drainage (mL/kg) | NR | NR | WMD –0.97 [–4.94, 2.99] | *No significant difference*  *P =*NR  Substantial heterogeneity  I2 = 77% |
| Faraoni 2012d359  Level I  *Fair* | 8 trialse (Bulutcu 2005,365 Chauhan 2003,367 Chauhan 2004 a,368 Chauhan 2004b,369 Levin 2000,375 Reid 1997,379 Shimizu 2011,381 Zonis 1996382)  N=848 | Paediatric patients aged <18 years undergoing cardiac surgery | Canada, India, Turkey, USA or NR | TXA versus placebo | 24 hr postoperative blood loss (mL/kg) | NR | NR | MD –3.61 [–8.08, 0.85]e | *No significant difference*  *P =*0.11  Substantial heterogeneity  I2 = 82% |
|  | *Sensitivity analyses:* | | | |
| excluding Chauhan 2004 a  7 trials (NR)  N=608 | NR | NR | MD –7.82 [–11.54, –4.10] | *Favours TXA*  *P =*NR  Substantial heterogeneity  I2 = 57% |
| excluding all studies by Chauhan et al  5 trials (NR)  N=388 | NR | NR | MD –5.22 [–8.16, –2.28] | *Favours TXA*  *P =*NR  No significant heterogeneity  I2 = 0% |
|  | *Subgroup analysis of acyanotic patients* | | | |
| 3 trials (NR)  N=298 | NR | NR | NR | *No significant difference*  *P =*0.47  Heterogeneity NR  I2 = NR |
| Level II evidence | | | | | | | | | |
| Aggarwal 2012392  Level II  *Fair* | N=80 | Children (aged 1–12 years) with tetralogy of Fallot undergoing intracardiac repair | India | IV TXA (3x 10 mg/kg doses) versus placebo | 24 hr postoperative blood loss (mL/kg) | 12 ± 3 (n=40) | 21 ± 4 (n=40) | MD –9.00 [–10.55, –7.45]f | *Favours TXA*  *P <*0.01 |
| Excessive bleeding (>25 mL/kg) due to hyperfibrinolysis | 2/40 (5.0%) | 5/40 (12.5%) | RR 0.40 [0.08, 1.94]f | *No significant difference*  *P =*0.26e |
| Ferreira 2010394  Level II  *Poor* | N=19 | Paediatric patients aged 1 month to 4 years with CHD undergoing cardiac surgery with CPB | Single hospital, Brazil | IV aprotinin (3x doses) versus placebo | 48 hr postoperative bleeding (mL/kg) | 17.6 ± NR (n=10) | 18.1 ± NR (n=9) | NR | *No significant difference*  *P =*NR |
| Sarupria 2013396  Level II  *Fair* | N=120 | Paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB for tetralogy of Fallot | Single hospital, India | IV EACA (high [H] or low [L] dose) versus placebo | 6 hr postoperative blood loss (mL) | | | |  |
| High-dose | 108.45 ± 61.45 (n=38) | 137.84 ± 52.50 (n=37) | MD –29.39 [–55.23, –3.55]f | *Favours high-dose EACA*  *P <*0.05 |
| Low-dose | 32.75 ± 26.02 (n=40) | 137.84 ± 52.50 (n=37) | MD –105.10 [–123.84, –86.36]f | *Favours low-dose EACA*  *P <*0.0001 |
| Cumulative 12 hr postoperative blood loss (mL) | | | |  |
| High-dose | 172.37 ± 71.56 (n=38) | 192.16 ± 66.67 (n=37) | MD –19.79 [–51.08, 11.50] | *No significant difference*  *P >*0.05 |
| Low-dose | 50.50 ± 42.30 (n=40) | 192.16 ± 66.67 (n=37) | MD –141.66 [–166.83, –116.49] | *Favours low-dose EACA*  *P <*0.0001 |
| Cumulative 24 hr postoperative blood loss (mL) | | | |  |
| High-dose | 223.95 ± 83.36 (n=38) | 235.41 ± 79.88 (n=37) | MD –11.46 [–48.41, 25.49]f | *No significant difference*  *P >*0.05 |
| Low-dose | 69.00 ± 50.01 (n=40) | 235.41 ± 79.88 (n=37) | MD –166.41 [–196.45, –136.37]f | *Favours low-dose EACA*  *P <*0.0001 |
| Singh 2001397  Level II  *Fair* | N=75 | Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot undergoing total correction with CPB | India | IV aprotinin (2x doses or 1x dose) versus placebo | Total blood loss (mL) | | | |  |
| 2x doses | 221.4 ± 60.3 (n=25) | 426.0 ± 92.0 (n=25) | MD –204.60 [–247.72, –161.48] f | *Favours aprotinin*  *P <*0.05 |
| 1x dose | 254.2 ± 22.6 (n=25) | 426.0 ± 92.0 (n=25) | MD –171.80 [–208.94, –134.66]f | *Favours aprotinin*  *P <*0.05 |
| 24 hr chest tube drainage (mL) | | | |  |
| 2x doses | 164.3 ± 25.7 (n=25) | 321.0 ± 23.0 (n=25) | MD –175.80 [–187.88, –163.72]f | *Favours aprotinin*  *P <*0.05 |
| 1x dose | 145.2 ± 20.5 (n=25) | 321.0 ± 23.0 (n=25) | MD –156.70 [–170.22, –143.18]f | *Favours aprotinin*  *P <*0.05 |
| Vacharaksa 2002398  Level II  *Fair* | N=62 | Paediatric patients aged ≤14 years with cyanotic CHD and a right-to-left shunt undergoing open-heart surgery | Single hospital, Thailand | IV TXA (2x doses) versus IV TXA (1x dose) + placebo | Total postoperative blood loss (mL) | 195.63 ± 188.03 (n=33) | 186.30 ± 163.78 (n=29) | MD 9.33 [–78.24, 96.90]f | *No significant difference*  *P =*0.5 |
| 24 hr postoperative blood loss (mL/kg) | 12.51 ± 13.20 (n=33) | 10.68 ± 6.38 (n=29) | MD 1.83 [–3.24, 6.90] | *No significant difference*  *P =*0.5 |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; EACA, epsilon-aminocaproic acid; IV, intravenous; MD, mean difference; NR, not reported; RR, risk ratio; SD, standard deviation; TXA, tranexamic acid; WMD, weighted mean difference

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes studies reported by Boldt. A number of studies by Boldt have been retracted due to research misconduct, including lack of ethics approval and false data. While the included studies have not been formally retracted, care should be taken in the interpretation of this analysis.

**d.** Data for meta-analyses using fixed-effects models were included where heterogeneity was low and random-effects models where heterogeneity was high.

**e.** Includes Chauhan 2004 a four times for different doses of TXA versus placebo.

**f.** Calculated post-hoc using RevMan 5.2.1.

Scoliosis surgery

One Level I study (Tzortzopoulou 2008) and two additional Level II studies (Thompson 2005, Verma 2014) were identified in the systematic review that assessed the effect of antifibrinolytics in paediatric patients undergoing surgery for scoliosis and provided evidence for blood loss. **Table 3.4.31** summarises the results from these studies.

Tzortzopoulou (2008) conducted a meta-analysis of five trials (Cole 2003, Khoshhal 2003, Neilipovitz 2001, Sethna 2005, Florentino-Pineda 2004) involving 163 paediatric patients, and found that patients administered antifibrinolytics (aprotinin, TXA or EACA) had significantly less volume (mL) of blood loss during surgery compared with patients who did not receive antifibrinolytics (MD –426.53, 95% CI –602.51, –250.56). Individual assessments of each intervention also showed an effect favouring aprotinin (2 trials, MD –450.32, 95% CI –726.35, –174.29), TXA (2 trials, MD –681.81, 95% CI –1149.12, –214.49) and EACA (1 trial, MD –325.00; 95% CI –586.83, –63.17).

The RCT by Thompson (2005) reported no significant difference in intraoperative blood loss among 36 patients administered EACA compared with no EACA (MD –59.00, 95% CI –221.23, 103.23). However, patients who received EACA were significantly more likely to have a lower volume of blood loss postoperatively (mL), measured by chest tube drainage (MD –266.00, 95% CI –423.17, –108.83) and less total perioperative blood loss (mL) (MD –325.00, 95% CI –586.83, –63.17).

The RCT by Verma (2014) assessed the effect of TXA or EACA compared to placebo among 125 patients. It reported a lower mean volume of intraoperative estimated blood loss (mL) (MD –304, 95% CI NR) among patients treated with antifibrinolytics. A similar, statistically significant effect was reported for total blood loss (MD –453.00, 95% CI –848.48, –57.52), but the effect was not statistically significant for mean volume (mL) of chest tube drainage (MD –122.00, 95% CI –309.98, 65.98).

Verma (2014) also reported the results for each intervention (TXA or EACA) compared with placebo. For TXA, a reduction in intraoperative estimated blood loss was observed among patients administered TXA, but the effect was not statistically significant (MD –295, 95% CI NR). Still, Verma (2014) reported that TXA was associated with significantly less intraoperative estimated blood loss with mean arterial pressure <75 mmHg, drain volume and total blood loss (**Table 3.4.31**). For EACA, the results were reversed. Patients administered EACA had significantly lower intraoperative estimated blood loss (MD –311, 95% CI NR), but no significant differences were reported for intraoperative estimated blood loss with mean arterial pressure <75 mmHg, drain volume (MD –18.00, 95% CI –222.52, 186.52) or total blood loss (MD –341.00, 95% CI –770.47, 88.47).

Table 3.4.31 Neonatal and paediatric patients undergoing scoliosis surgery: Results for antifibrinolytics versus no antifibrinolytics – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  Mean ± SD (n) | No antifibrinolytics  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Tzortzopoulou 2008361  Level I  *Good* | 5 trials (Cole 2003,384 Khoshhal 2003,386 Neilipovitz 2001,387 Sethna 2005,388 Florentino-Pineda 2004385)  N=163 | Paediatric patients aged <18 years undergoing scoliosis surgery | Canada (Khoshhal 2003, Neilipovitz 2001), USA (Cole 2003, Sethna 2005, Florentino-Pineda 2004385) | IV antifibrinolytic (aprotinin, TXA, EACA) versus placebo | Total blood loss (mL) | NR | NR | MD –426.53  [–602.51, –250.56] | *Favours antifibrinolytic*  *P <*0.00001  No significant heterogeneity  I2 = 0% |
|  | *Subgroup analysis: type of product* | | |  |
| IV aprotinin  2 trials (Cole 2003, Khoshhal 2003)  N=87 | NR | NR | MD –450.32  [–726.35, –174.29] | *Favours aprotinin*  *P =*0.0014  No significant heterogeneity  I2 = 0% |
| IV TXA  2 trials (Neilipovitz 2001, Sethna 2005)  N=84 | NR | NR | MD –681.81  [–1149.12, –214.49] | *Favours TXA*  *P =*0.0042  Mild heterogeneity  I2 = 24% |
| IV EACA  1 trial (Florentino-Pineda 2004)  N=36 | NR | NR | MD –325.00  [–586.83, –63.17] | *Favours EACA*  *P =*0.015  Heterogeneity NA |
| Level II evidence | | | | | | | | | |
| Thompson 2005405  Level II  *Poor* | N=36 | Paediatric patients aged 11 to 18 years with idiopathic scoliosis scheduled for posterior spinal fusion with segmental spinal instrumentation | USA | IV EACA versus no treatment | Intraoperative blood loss (mL) | 893 ± 166 (n=19) | 952 ± 303 (n=17) | MD –59.00 [–221.23, 103.23]c | *No significant difference*  *P =*0.48c |
| Postoperative chest tube drainage (mL) | 498 ± 179 (n=19) | 764 ± 284 (n=17) | MD –266.00 [–423.17, –108.83]c | *Favours EACA*  *P =*0.0009c |
| Total perioperative blood loss (mL) | 1391 ± 212 (n=19) | 1716 ± 513 (n=17) | MD –325.00 [–586.83, –63.17]c | *Favours EACA*  *P =*0.03 |
| Verma 2014399  Level II  *Good* | N=125 | Patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis | Single centre, USA | IV TXA or EACA versus placebo | Intraoperative estimated blood loss (mL) | 776 ± NR (n=78) | 1080 ± NR (n=47) | MD –304 [NR] | *Favours TXA or EACA*  *P =*0.019 |
| Drain volume (mL) | 912.0 ± 446 (n=78) | 1034.0 ± 559 (n=47) | MD –122.00 [–309.98, 65.98]c | *No significant difference*  *P =*0.187 |
| Total blood losses (mL) | 1663.0 ± 882 (n=78) | 2116.0 ± 1202 (n=47) | MD –453.00 [–848.48, –57.52] c | *Favours TXA or EACA*  *P =*0.019 |
| IV TXA versus placebo | Intraoperative estimated blood loss (mL) | 785 ± NR (n=36) | 1080 ± NR (n=47) | MD –295 [NR] | *No significant difference*  *P =*0.058 |
| Intraoperative estimated blood loss with MAP <75 mm Hg (mL) | 715 ± NR (n=36) | 1124 ± NR (n=47) | MD –409 [NR] | *Favours TXA*  *P =*0.042 |
| Drain volume (mL) | 789 ± 449 (n=36) | 1034 ± 559 (n=47) | MD –245.00 [–461.92, –28.08]c | *Favours TXA*  *P =*0.027 |
| Total blood losses (mL) | 1531 ± 911 (n=36) | 2116 ± 1201 (n=47) | MD –585.00 [–1039.37, –130.63]c | *Favours TXA*  *P =*0.015 |
| IV EACA versus placebo | Intraoperative estimated blood loss (mL) | 769 ± NR (n=42) | 1080 ± NR (n=47) | MD –311 [NR] | *Favours EACA*  *P =*0.037 |
| Intraoperative estimated blood loss with MAP <75 mm Hg (mL) | 761 ± NR (n=42) | 1124 ± NR (n=47) | MD –363 [NR] | *No significant difference*  *P =*0.061 |
| Drain volume (mL) | 1016 ± 422 (n=42) | 1034 ± 559 (n=47) | MD –18.00 [–222.52, 186.52]c | *No significant difference*  *P =*0.867 |
| Total blood losses (mL) | 1775 ± 853 (n=42) | 2116 ± 1201 (n=47) | MD –341.00 [–770.47, 88.47]c | *No significant difference*  *P =*0.161 |

CI, confidence interval; EACA, epsilon-aminocaproic acid; Hg, mercury; IV, intravenous; MAP, mean arterial pressure; MD, mean difference; NA, not applicable; NR, not reported; SD, standard deviation; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

Craniofacial surgery

The systematic review and hand-searching process identified one Level I study (Song 2013) and two additional Level II studies (Ahmed 2014, D’Errico 2003) that assessed the effect of antifibrinolytics in paediatric patients undergoing craniofacial surgery and provided evidence for blood loss. **Table 3.4.32** summarises the results from these studies.

Song (2013) pooled the results of two Level II studies (Dadure 2011, Goobie 2011) and one Level III study (Maugans 2011) to assess the effect of TXA on perioperative blood loss among 138 children undergoing craniosynostosis surgery. The analysis showed a significant reduction on the volume of blood loss, favouring TXA (MD –20.53, 95% CI –32.26, –8.80); however, in a sensitivity analysis including only RCTs, the effect was not significant (2 RCTs, MD –30.79, 95% CI –71.72, 10.14).

The RCT by Ahmed (2014) assessed the effect of aprotinin in 26 paediatric patients undergoing major reconstructive craniofacial surgery. It reported a reduction in the volume (mL) of drain output at 1 day post-surgery, 2 days post-surgery and the average of the 2 days; but the effect was not statistically significant at any time point (1–2 days, MD –21.00, 95% CI –44.06, 2.06).

The RCT by D’Errico (2003) also reported no statistically significant effect of aprotinin on the estimated volume of blood loss (mL/kg) among 39 paediatric patients undergoing surgery for undergoing craniofacial reconstruction (MD –11.00, 95% CI –25.44, 3.44).

A meta-analysis of all included Level II studies was conducted to assess the effect of antifibrinolytics (TXA or aprotinin) on perioperative blood loss (**Figure 3.4.10**). The analysis showed a significant reduction in the volume of blood loss favouring the use of antifibrinolytics in craniofacial surgery (SMD –0.67, 95% CI –1.00, –0.33). There was no significant heterogeneity for this outcome (I2=0%)

Table 3.4.32 Neonatal and paediatric patients undergoing craniofacial surgery: Results for antifibrinolytics versus no antifibrinolytics – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  Mean ± SD (n) | No antifibrinolytics  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level I evidence | | | | | | | | | |
| Song 2013362  Level I/III  *Fair* | 3 studiesc (Dadure 2011,389 Goobie 2011,390 Maugans 2011)  N=138 | Children undergoing craniosynostosis surgery | USA, France | IV TXA versus placebo | Perioperative blood loss (mL) | NR | NR | MD –20.53 (–32.26, –8.80) | *Favours TXA*  *P =*0.0006  Substantial heterogeneity  I2 = 56% |
|  | *Sensitivity analysis: RCTs only* | | |  |
| 2 RCTs (Dadure 2011, Goobie 2011)  N=82 | NR | NR | MD –30.79 [–71.72, 10.14] | *No significant difference*  *P =*0.14  Substantial heterogeneity  I2 = 82% |
| Level II evidence | | | | | | | | | |
| Ahmed 2014400  Level II  *Fair* | N=26 | Paediatric patients (aged 1 month to 3 years) undergoing major reconstructive craniofacial surgery | Single hospital, USA | IV aprotinin versus placebo | Drain output 1 day post-surgery (mL) | 60 ± NR (n=13) | 103 ± NR (n=13) | MD –43.0 [NR] | *No significant difference*  *P =*NR |
| Drain output 2 days post-surgery (mL) | 100 ± NR (n=13) | 99 ± NR (n=13) | MD 1.0 [NR] | *No significant difference*  *P =*NR |
| Average drain output, days 1–2 (mL) | 80 ± 30 (n=13) | 101 ± 30 (n=13)d | MD –21.00 [–44.06, 2.06]e | *No significant difference*  *P =*0.07e |
| D’Errico 2003401  Level II  *Good* | N=39 | Paediatric patients aged 1 month to 12 years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement | Single hospital, USA | IV aprotinin versus placebo | Estimated blood loss (mL/kg) | 28 ± 21 (n=18) | 39 ± 25 (n=21) | MD –11.00 [–25.44, 3.44]e | *No significant difference*  *P =*0.14 |

CI, confidence interval; IV, intravenous; MD, mean difference; NR, not reported; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Analysis includes one Level III study (Maugans 2011).

**d.** Reported in paper as 101 ± 3; however, this believed to be a typo due to result also being reported as nonsignificant.

**e.** Calculated post-hoc using RevMan 5.1.2.

Figure 3.4.10 Meta-analysis: antifibrinolytics versus placebo in paediatric patients undergoing craniofacial surgery – perioperative blood loss



Ear, nose and throat surgery

The systematic review and hand-searching process identified one Level I study (Ker 2013) and two additional Level II studies (Brum 2012, Eldaba 2013) that assessed the effect of antifibrinolytics in paediatric patients undergoing ENT surgery and provided evidence for blood loss. **Table 3.4.33** summarises the results from these studies.

The systematic review by Ker (2013) assessed the topical application of TXA and identified one Level II study (Albirmawy 2013) involving 400 children undergoing primary isolated adenoidectomy that reported a significant reduction in in blood loss among patients administered topical TXA compared with placebo (MD 0.73; 95% CI 0.71, 0.76).

The RCT by Brum (2012) assessed blood loss in 95 children scheduled for adenotonsillectomy. It reported no significant difference between treatment groups for total intraoperative bleeding (mL), total intraoperative bleeding by weight (mL/kg), or primary and secondary postoperative bleeding. **Table 3.4.33** summarises the results.

The RCT by Eldaba (2013) assessed surgical field ratings among children with chronic rhinosinusitis undergoing endoscopic sinus surgery, and reported a significant reduction in total bleeding volume (mL) among patients administered TXA compared with placebo (MD –51, 95% CI –59.27, –42.73). However, there was no significant difference in the number of patients with surgical field rating grade II (mild bleeding) 15 minutes after beginning surgery (70.0% versus 52.0%) or 30 minutes after beginning surgery (74.0% versus 56.0%). A nonsignificant effect was also reported for surgical field rating grade IV or V (severe or massive bleeding) 15 minutes after beginning surgery (0% versus 0%) or 30 minutes after beginning surgery (0% versus 0%). In contrast, a significant effect favouring the use of TXA was reported for the number of patients with a surgical field rating grade III (moderate bleeding) 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).

Table 3.4.33 Neonatal and paediatric patients undergoing ENT surgery: Results for antifibrinolytics versus no antifibrinolytics – bleeding events

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Antifibrinolytics  n/N (%)  Mean ± SD (n) | No antifibrinolytics  n/N (%)  Mean ± SD (n) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Ker 2013363  Level I/II  *Good* | 1 trial (Albirmawy 2013391)  N=400 | Children undergoing primary isolated adenoidectomy | Egypt | Topical TXA versus placebo | Blood loss (mL) | NR (200) | NR (200) | MD 0.73 (0.71, 0.76) | *Favours TXA*  *P =*NR |
| Brum 2012402  Level II  *Good* | N=95 | Children (aged 4–12 years) scheduled for adenotonsillectomy | Single hospital, Brazil | IV TXA versus placebo | Total intraoperative bleeding (mL) |  | | |  |
| Intent-to-treat analysis | 135.1 ± 71.4 (n=47) | 158 ± 88.1 (n=48) | NR | *No significant difference*  *P =*0.197 |
| Per protocol analysis | 131.92 ± 64.04 (n=39) | 155 ± 86.2 (n=39) | NR | *No significant difference*  *P =*0.184 |
| Intraoperative bleeding (mL/kg) |  | | |  |
| Intent-to-treat analysis | 5.84 ± 3.4 (n=47) | 5.23 ± 3.29 (n=48) | NR | *No significant difference*  *P =*0.381 |
| Per protocol analysis | 5.71 ± 3.44 (n=39) | 5.46 ± 3.39 (n=39) | NR | *No significant difference*  *P =*0.742 |
| Primary postoperative bleeding | NR | NR | NR | *No significant difference*  *P =*0.85 |
| Secondary postoperative bleeding | 0 | 0 | Not estimable | *No significant difference*  *P =*NA |
| Eldaba 2013403  Level II  *Fair* | N=100 | Children (aged 5–10 years) with chronic Rhinosinusitis undergoing endoscopic sinus surgery | Egypt | IV TXA versus placebo | Bleeding volume (mL) | 102 ± 19 | 153 ± 23 | MD –51.00 [–59.27, –42.73] | *Favours TXA*  *P <*0.0001 |
| Surgical field grade II (mild bleeding) 15 minutes after beginning surgery | 35/50 (70.0%) | 26/50 (52.0%) | NR | *No significant difference*  *P =*0.064 |
| Surgical field grade III (moderate bleeding) 15 minutes after beginning surgery | 8/50 (16.0%) | 24/50 (48.0%) | NR | *Favours TXA*  *P =*0.0006 |
| Surgical field grade IV or V (severe or massive bleeding) 15 minutes after beginning surgery | 0/50 (0%) | 0/50 (0%) | Not estimable | *No significant difference*  *P =*NA |
| Surgical field grade II (mild bleeding) 30 minutes after beginning surgery | 37/50 (74.0%) | 28/50 (56.0%) | NR | *No significant difference*  *P =*0.059 |
| Surgical field grade III (moderate bleeding) 30 minutes after beginning surgery | 2/50 (4.0%) | 21/50 (42.0%) | NR | *Favours TXA*  *P <*0.0001 |
| Surgical field grade IV or V (severe or massive bleeding) 30 minutes after beginning surgery | 0/50 (0%) | 0/50 (0%) | Not estimable | *No significant difference*  *P =*NA |

CI, confidence interval; IV, intravenous; MD, mean difference; NA, not applicable; NR, not reported; SD, standard deviation; TXA, tranexamic acid

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1.2.

* + - 1. Recombinant activated factor VII

| Evidence statements – neonatal and paediatric patients undergoing surgery (recombinant factor VIIa) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √√√ |
|  | 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 |
|  | 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 | √√√ | √√√ |
|  | 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 |
|  | 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 | √√√ | √√√ |
|  | 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 |
|  | 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 factor VIIa  √√√=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 points – 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*.15 |
| CPB, cardiopulmonary bypass ; PP, practice point, R, recommendation; rFVIIa, recombinant factor VIIa | |

##### Background

Recombinant activated factor VII (rFVIIa) is a synthetic form of blood factor VII that activates the formation of prothrombinase complex. It has a local mode of action in areas where tissue factor or phospholipid is 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. Without systemic activation of the coagulation cascade, the risk of thromboembolic events is minimised. In paediatric patients undergoing cardiac surgery, rFVIIa may control severe bleeding at the wound site and reduce the need for blood transfusions.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified one Level I study (Simpson 2012) that assessed the safety and effectiveness of rFVIIa compared with no rFVIIa neonatal in paediatric patients undergoing cardiac surgery (**Appendix C, Volume 2**). **Table 3.4.34** summarises the main characteristics of this study.

Simpson (2012) was a good-quality systematic review that aimed to assess the effectiveness of rFVIIa when used therapeutically to control active bleeding, or prophylactically to prevent (excessive) bleeding in patients without haemophilia. The author identified 29 RCTs involving 4290 patients, of which three RCTs were conducted in children. Only one RCT (Ekert 2006) met the inclusion criteria for this review.[[45]](#footnote-45) Simpson (2012) concluded that the effectiveness of rFVIIa remains unproven and that there is an increased risk of arterial events in patients receiving rFVIIa. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

Ekert (2006) was a single centre RCT conducted in Australia that enrolled 76 infants aged <1 year with CHD who required surgery with CPB. Outcomes reported were mortality, transfusion incidence and thromboembolic events. The study was assessed by Simpson (2012) to have an overall unclear risk of bias. Details on method of randomisation and allocation concealment were not provided, transfusion protocols were not reported, and some outcomes were not reported or were available only as mean or standard deviation.

Table 3.4.34 Characteristics and quality of Level I and Level II evidence – rFVIIa in neonatal and paediatric patients undergoing surgery

| Study ID | Study type  Study quality | Population  N | Comparison | Outcomes |
| --- | --- | --- | --- | --- |
| Level I evidence | | | | |
| Simpson (2012)408 | Systematic review  Good | Patients without haemophilia who are actively bleeding (therapeutic) or patients with possible excessive bleeding (prophylactic)  29 RCTs, N=4290  *Paediatric studies*  3 RCTsa, N=134 | rFVIIa versus placebo | Mortality  Transfusion incidence  Thromboembolic events |
| Level II evidence | | | | |
| Ekert (2006)409 | Level II  *Unclear* | Infants aged <1 year with CHD requiring surgery with CPB  N=76 | rFVIIa versus placebo | Mortality  Transfusion incidence  Thromboembolic events |

CHD, congenital heart disease; CPB, cardiopulmonary bypass; RCT, randomised controlled trial; rFVIIa, recombinant activated factor VII

**a.** Two RCTs did not meed out inclusion criteria (wrong population, not cardiac or ECMO). One RCT (Hanna 2010) enrolled paediatric patients of ASA class I and II with congenital craniofacial malformations scheduled for reconstructive surgery (n=45, 3 arm trial comparing rFVIIa and TXA with control) and one RCT (Chuansumrit 2005) examined the role of rFVIIa in the control of bleeding in children with Dengue haemorrhagic fever (n=28).

###### Level II evidence

The systematic review and hand-searching process identified no additional Level II studies that assessed the safety and effectiveness of rFVIIa compared with no rFVIIa in neonatal and paediatric patients undergoing cardiac surgery.

##### Results

###### Mortality

The systematic review and hand-searching process identified one Level I study (Simpson 2012) that reported the effect of rFVIIa in paediatric patients undergoing cardiac surgery and provided evidence for mortality. **Table 3.4.35** summarises the results from this study.

Simpson (2012) included data from one RCT (Ekert 2006) conducted in 76 infants aged <1 year with CHD who were undergoing cardiac surgery with CPB. The authors did not report data for this outcome; therefore, Simpson (2012) assumed there were no deaths during the study period.

Table 3.4.35 Neonatal and paediatric patients undergoing surgery: Results for rFVIIa versus no rFVIIa – mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| rFVIIa  n/N (%) | No rFVIIa  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Simpson 2012408  Level I  *Good* | 1 trial (Ekert 2006409)  N=76 | Infants aged <1 year with CHD requiring surgery with CPB. | Australia | Prophylactic rFVIIa versus placebo | Mortality | 0/40 (0%) | 0/36 (0%) | Not estimable | *No significant difference*  P = NA |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; NA, not applicable; rFVIIa, recombinant activated factor VII

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Transfusion volume and incidence

The systematic review and hand-searching process identified one Level I study (Simpson 2012) that reported the effect of rFVIIa in paediatric patients undergoing cardiac surgery and provided evidence for transfusion incidence. **Table 3.4.36**summarises the results from this study.

The review by Simpson (2012) included data from one RCT (Ekert 2006) that was conducted in 76 infants aged <1 year with CHD who were undergoing cardiac surgery with CPB. Thirty patients (75%) administered rFVIIa group received a transfusion, compared with 29 patients (80.6%) in the control group. This result was not statistically significant (RR 0.93, 95% CI 0.73, 1.18).

Table 3.4.36 Surgical paediatric/neonatal patients: Results for rFVIIa versus no rFVIIa – transfusion requirements

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| rFVIIa  n/N (%) | No rFVIIa  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Simpson 2012408  Level I/II  *Good* | 1 trial (Ekert 2006409)  N=76 | Infants aged <1 year with CHD requiring surgery with CPB | Australia | Prophylactic rFVIIa versus placebo | Transfusion incidence | 30/40 (75%) | 29/36 (80.6%) | RR 0.93 [0.73, 1.18] | *No significant difference*  P = 0.56c |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; rFVIIa, recombinant activated factor VII; RR, risk ratio

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

**c.** Calculated post-hoc using RevMan 5.1. 2.

###### Thromboembolic events

The systematic review and hand-searching process identified one Level I study (Simpson 2012) that reported the effect of rFVIIa in paediatric patients undergoing cardiac surgery and provided evidence for thromboembolic events. **Table 3.4.37** summarises the results from this study.

The review by Simpson (2012) identified one RCT (Ekert 2006) that was conducted in 76 infants aged <1 year with CHD who were undergoing cardiac surgery with CPB. No thromboembolic events were reported.

Table 3.4.37 Neonatal and paediatric patients undergoing surgery: Results for rFVIIa versus no rFVIIa – thromboembolic events

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| rFVIIa  n/N (%) | No rFVIIa  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II Evidence | | | | | | | | | |
| Simpson 2012408  Level I  *Good* | 1 trial (Ekert 2006409)  N=76 | Infants aged <1 year with CHD requiring surgery with CPB | Australia | Prophylactic rFVIIa versus placebo | Thromboembolic events | 0/40 (0%) | 0/36 (0%) | Not estimable | *No significant difference*  P = NA |

CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; NA, not applicable; rFVIIa, recombinant activated factor VII

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Bleeding events

The systematic review and hand-searching process identified no studies that assessed the safety and effectiveness of rFVIIa compared with no rFVIIa and reported bleeding events in surgical neonatal or paediatric patients.

* + - 1. Miniaturised cardiopulmonary bypass systems

| Evidence statements – neonatal and paediatric patients undergoing surgery (miniaturised cardiopulmonary bypass systems) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 | √√√ | √ |
|  | 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 |
|  | 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 | √ | √√√ | √ |
|  | 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 |
|  | 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 | | | | | | |

|  |
| --- |
| Evidence gaps and areas for future research |
| * The use of miniaturised CPB in paediatric patients is limited to single-unit experiences (arguable methods and low-quality papers). |

##### Background

Miniaturised CPB systems are thought to 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 increased risk of mortality.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of miniaturised CPB systems compared with standard-sized systems in neonatal or paediatric patients undergoing surgery.

###### Level II evidence

The literature search identified one Level II study (Mozol 2008) that examined the effect of miniaturised CPB systems in paediatric patients undergoing surgery (**Appendix C, Volume 2**). **Table 3.4.38** summarises the main characteristics of this study.

Mozol 2008 was a poor-quality RCT of 60 paediatric patients <1 year of age who were scheduled for cardiac surgery with CPB and extracorporeal circulation support. The authors examined the effect of a miniaturised CPB system compared to a conventional-sized CPB system on mortality, perioperative RBC transfusion volume and total blood products transfused.

Table 3.4.38 Characteristics and quality of Level II evidence – miniaturised CPB systems in neonatal and paediatric patients undergoing surgery

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Study type *Study quality* | Population  N | Comparison | Outcomes |
| Mozol (2008)410 | RCT  *Poor* | Paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support  N=60 | Miniaturised CPB system (n=30) versus conventional CPB system (n=30) | Mortality  Transfusion volume |

CPB, cardiopulmonary bypass; RCT, randomised controlled trial

##### Results

###### Mortality

The systematic review and hand-searching process identified one poor-quality RCT (Mozol 2008) that compared miniaturised CPB systems with standard-sized systems and reported on mortality in paediatric patients undergoing surgery. **Table 3.4.39** summarises the results from this study.

Mozol (2008) assessed mortality among 60 paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support. No deaths were reported during the study.

Table 3.4.39 Surgical paediatric/neonatal patients: Results for miniaturised CPB systems versus standard-sized systems – mortality

| Study  Level of evidencea  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Miniaturised CPB systems  n/N (%) | Standard-sized systems  n/N (%) | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneityb |
| Level II evidence | | | | | | | | | |
| Mozol 2008410  Level II  *Poor* | N=60 | Paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support | Poland | Miniaturised CPB system versus conventional CPB system | Mortality | 0 | 0 | Not estimable | *No significant difference*  P = NA |

CI, confidence interval; CPB, cardiopulmonary bypass; NA, not applicable

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

###### Transfusion volume and incidence

The systematic review and hand-searching process identified one poor-quality RCT (Mozol 2008) that compared miniaturised CPB systems with standard-sized systems and reported on transfusion incidence or volume in paediatric patients undergoing surgery. **Table 3.4.40** summarises the results from these studies.

Mozol (2008) reported transfusion volume (mL) among 60 paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support. Results for perioperative RBC transfusion volume (318 ± 128 versus 415 ± 97, P = 0.001), plasma transfusion volume (192 ± 140 versus 285 ± 129, *P =*0.01) and total blood products transfused (635 versus 800, *P =*0.0007) favoured the miniaturised CPB system. No statistically significant difference between groups was reported for volume of RBCs transfused (14 ±31 versus 32 ± 47) or albumin transfused (113 ±83 versus 139 ±109).

Table 3.4.40 Neonatal and paediatric patients undergoing surgery: Results for miniaturised CPB systems versus standard-sized systems – transfusion volume and incidence

| Study  Level of evidence a  *Quality* | No. of trials / sample size included in analysis | Patient population / Surgical procedure | Setting  Location | Intervention versus comparator | Outcome | Results | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Miniaturised CPB systems  n/N (%)  Mean ± SD | Standard-sized systems  n/N (%)  Mean ± SD | Risk estimate (95% CI) | *Statistical significance*  *P-*value  Heterogeneity b |
| Level II evidence | | | | | | | | | |
| Mozol 2008410  Level II  *Poor* | N=60 | Paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support | Poland | Miniaturised CPB system versus conventional CPB system | Perioperative RBC transfused (mL) | 318 ± 128 | 415 ± 97 | NR | *Favours miniaturised CPB*  *P =*0.001 |
| RBC transfused (mL) | 14 ± 31 | 32 ± 47 | NR | *No significant difference*  *P =*NR |
| Plasma transfused (mL) | 192 ± 140 | 285 ± 129 | NR | *Favours miniaturised CPB*  *P =*0.01 |
| Albumin transfused (mL) | 113 ± 83 | 139 ± 109 | NR | *No significant difference*  *P =*NR |
| Total blood products transfused (mL) | 635 ± NR | 800 ± NR | NR | *Favours miniaturised CPB*  *P =*0.0007 |

CI, confidence interval; CPB, cardiopulmonary bypass; NR, not reported; SD, standard deviation

**a.** Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

**b.** Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25–50%; substantial heterogeneity I2 >50%.

### Critically ill neonatal and paediatric patients

* + - 1. Recombinant activated factor VII

| Evidence statements –critically ill neonatal and paediatric patients (recombinant factor VIIa) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on mortality is unknown. | NA | NA | NA | NA | NA |
|  | 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 |
|  | In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is unknown. | NA | NA | NA | NA | NA |
|  | 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 factor VIIa  √√√=A; √√=B; √=C; X=D; NA, not applicable | | | | | | |

##### Background

Recombinant activated factor VII (rFVIIa) is a synthetic form of blood factor VII that activates the formation of prothrombinase complex. The intervention has a local mode of action in areas where tissue factor or phospholipids 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. Without systemic activation of the coagulation cascade, the risk of thromboembolic events is minimised. In paediatric patients with traumatic injuries, rFVIIa may control severe bleeding at the wound site and reduce the need for blood transfusions.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of rFVIIa compared with no rFVIIa in critically ill neonatal and paediatric patients.

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that assessed the safety and effectiveness of rFVIIa compared with no rFVIIa in critically ill neonatal and paediatric patients.

* + - 1. Viscoelastometric point-of-care testing

| Evidence statements – critically ill neonatal and paediatric patients (viscoelastometric point-of-care testing) | | **Evidence** | **Consistency** | **Clinical impact** | **Generalisability** | **Applicability** |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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 |
|  | 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 |
|  | 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 thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These are whole-blood coagulation analysers that monitor dynamic changes in haemostasis and may help guide patient care. In paediatric patients with traumatic injuries, monitoring changes of haemostasis may help clinicians to assess the cause of bleeding and improve the care of patients with unexplained blood loss.

##### Summary of evidence

###### Level I evidence

The systematic review and hand-searching process identified no Level I studies that assessed the safety and effectiveness of viscoelastometric POC testing compared with no viscoelastometric POC testing in critically ill neonatal and paediatric patients.

###### Level II evidence

The systematic review and hand-searching process identified no Level II studies that assessed the safety and effectiveness of viscoelastometric POC testing compared with no viscoelastometric POC testing in critically ill neonatal and paediatric patients.

# Appendixes

## Appendix 1 Research question structure

The structures of the foreground research questions developed for this module are presented in **Table 4.1.1** (generic questions relevant to all modules of the patient blood management guidelines) and **Table 4.1.2** (question specific to the neonatal and paediatric patient blood management guidelines).

The research questions were all intervention-based and structured according to the PICO criteria. Use of the PICO framework facilitates the systematic review process as it improves conceptual clarity of the clinical problem, allows more complex search strategies, results in more precise search results, and allows evidence to be selected appropriately.

The population element of the framework (subgroups and stratification) is intended to provide the systematic reviewers with logical datasets for presentation and analysis of the available data. The systematic reviewers examined for all evidence in children aged <18 years and searched down to the lowest level of evidence to find studies relating to each of the specified subgroups shown in bold (for example, bleeding and non-bleeding patients), but not the minor subgroups (not shown in bold) within those. The systematic review process stopped at the highest level of evidence available to address the primary outcomes and subgroups shown in bold, irrespective of what minor subgroups were covered.

When describing the patient population of interest through the module and technical reports, the term ‘neonate’ was used to reflect the evidence when referring to the newborn; it specifically refers to a defined period of time up to 28 days following birth. The term ‘preterm’ was used to describe patients born before 37 weeks gestational age. The specific gestational age of the preterms was reported where available. In some cases, the evidence refers to both preterm and term infants. This population is discussed according to birth weight. The term ‘infants’ was used to refer to those aged between 1 and 24 months, ‘children’ were those aged between 2 and 12 years, and ‘adolescents’ were those aged between 13 and 18 years. The term ‘paediatric’ was used to encompass all infants, children and adolescents.

Table 4.1.1 Structure of generic research questions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 1. What is the effect of RBC (allogeneic) transfusion on patient outcomes?  Intervention vs. Comparator = (1) vs. (1), (2) vs. (2) [Intervention Foreground Question] | | | | |
| Populationa | Intervention | Comparison | Outcomes | Other SR considerations |
| **Preterm (<37 wks)**  **Infant**   * Newborn (<1 mo) * Infant * 1-6 mo * 7-12 mo * 13-23 mo   **Child/adolescent**   * Preschool (2-5 yrs) * Child (6-12 yrs) * Adolescent (13-18 yrs)   **Medical**   * Oncology * Renal * Chronic anaemia * Anaemias as a result of ineffective erythropoiesis * Haemolytic anaemias   **Surgical**   * Cardiac (cyanotic vs non-cyanotic) * Transplantation * Orthopaedic * Burns   **Critical** **illness**   * ECMO/ECLS * Trauma   Stratify by:   * Anaemia status according to Hb level | **1.** RBC (allogeneic) transfusion (including dose)  **2.** Restrictive transfusion (by study definition) | **1.** No transfusion (or alternative doses)  **2.** Liberal transfusion (by study definition) | **Preterm**  Primary   * Mortality * Composite of mortality & severe morbidity (BPD, ROP, brain injury on ultrasound, etc.)   Secondary   * Bronchopulmonary dysplasia (BPD) * Necrotising enterocolitis (NEC) * ROP * Neurodevelopmental disability * Transfusion-related SAEs (TACO, TRALI, othera)   **Infant/child/adolescent/Medical/Surgical**  Primary   * Mortality * Stroke - *sickle cell disorder subgroups only* * New or progressive M/ failure -*surgical patient subgroup only*   Secondary   * Transfusion-related SAEs (TACO, TRALI, otherb) * Functional/performance status   **Critical illness**  Primary   * New or progressive multiple organ dysfunction/failure   Secondary   * Mortality * Transfusion-related SAEs (TACO, TRALI, otherb) | * Identify any evidence in Indigenous populations * Must find evidence for each of the **6 bold population groups** * Clearly define age groups, and term/preterm status * Extract information on ‘anaemia’ status (as defined, symptomatic anaemia etc.), or Hb or Hct levels at baseline, by age * Note special RBC requirements for patients with immunodeficiency * Restrictive vs liberal studies may also use other terminology (e.g. protocol, algorithm, threshold)   **Limits:**   * Studies published after 1995c * Restrict to Level III-2 studies (N>100) and higher for RBC (allogeneic) transfusion * Restrict to Level II studies for restrictive transfusion intervention * Check previous module tech reports for paediatric studies   **Notes:**   * BPD, NEC, ROP for preterm only. * Use ‘ROP Stage III’ & ‘threshold ROP’ to clarify the level of severity * Specific functional/performance status tools will not be specified *a priori* for secondary outcomes * Exchange transfusions not included (wrong intervention). |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 2. What is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?  [Intervention Foreground Question] | | | | |
| Populationa | Intervention | Comparison | Outcomes | Other SR considerations |
| **Preterm (<37 wks)**  **Infant**   * Newborn (<1 mo) * Infant * 1-6 mo * 7-12 mo * 13-23 mo   **Child/adolescent**   * Preschool (2-5 yrs) * Child (6-12 yrs) * Adolescent (13-18 yrs)   **Medical**   * Oncology * Renal * Chronic anaemia * Anaemias as a result of ineffective erythropoiesis * Haemolytic anaemias   **Surgical**   * Cardiac (cyanotic vs non-cyanotic) * Transplantation * Orthopaedic * Burns   **Critical illness**   * ECMO/ECLS * Trauma   Stratify by:   * Level and type of anaemia/ baseline Hb | **1.** ESAs  **2.** Oral and/or parenteral iron therapy (IV or IM)  **3.** Combination of above  [Nb. Include all ESA and iron dose regimens]  **4.** Hydroxyurea (*sickle cell disorders only*) | **1.** No intervention or any active head-to-head (e.g. 1 vs. 2, 1 vs. 3)  **2.** No intervention or any active head-to-head (e.g. 1 vs. 2, 2 vs. 3)  **3.** Different combination of above  **4.** No hydroxyurea | Primary   * Transfusion volume (in transfused patients only), or transfusion incidence * Thromboembolic events (stroke, DVT [including line vein thrombosis], PE) *– ESA intervention only (including ESAs combined with iron therapy)* * ROP, BPD & NEC *– preterm subgroup only* * Mortality – *ESA and iron interventions only (including combinations)* * Stroke – *hydroxyurea intervention only*   Secondary   * Functional/performance status (e.g. Bayley score, MDI, Denver Scale, GMFCS) * Laboratory measures: Hb, Hct, ferritin * Chronic pain – *hydroxyurea intervention for sickle cell disorders subgroup only* * Vaso-occlusive events – *hydroxyurea intervention only* * Tumour progression or recurrence – *oncology subgroup only* | * Identify any evidence in Indigenous populations * Include studies that compare modes of administration of iron therapy (i.e. oral vs parenteral) * Include studies with non-anaemic patients at baseline (i.e. prophylaxis and treatment) * Hydroxyurea is particularly used for sickle cell anaemia, thalassaemia major, etc. * Use ‘ROP Stage III’ & ‘threshold ROP’ to clarify the level of severity * Vaso-occlusive events includes painful crises caused by local infarcts or ischaemia secondary to sickling   **Limits:**   * Studies published after 1995c * Restrict to Level II evidence   **Notes:**   * Hydroxyurea use in this group is ‘off label’, may only be able to develop a Practice Point * Practice tip: hormonal therapy for reducing blood loss in menstruating females * Include comment in guidance chapter regarding tumour progression/recurrence |
| 3. What is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?  *Intervention vs. Comparator* = (1) vs. (1), (2) vs. (2), etc. [Intervention Foreground Question] | | | | |
| Populationa | Intervention | Comparison | Outcomes | Other SR considerations |
| **Preterm (<37 wks)**  Infant   * Newborn (<1 mo) * Infant * 1-6 mo * 7-12 mo * 13-23 mo   Child/adolescent   * Preschool (2-5 yrs) * Child (6-12 yrs) * Adolescent (13-18 yrs)   **Medical**   * Oncology   **Surgical**   * Cardiac (cyanotic vs non-cyanotic) * Transplantation * Orthopaedic * Burns * Craniofacial surgery   **Critical illness**   * ECMO/ECLS * Trauma   Stratify by:   * Bleeding/non-bleeding (prophylaxis and treatment) | **1.** FFP (preterm, surgical and critical illness subgroups)  **2.** Cryoprecipitate (*surgical, critical illness subgroups only*)  **3.** Platelet transfusion  **4.** Fibrinogen concentrate (*surgical, critical illness subgroups only*)  5. Combination of above -(surgical, critical illness – *bleeding patient subgroups* *only)* | **1.** No FFP or FFP using a different FFP transfusion protocol  **2.** No cryoprecipitate or cryoprecipitate using a different cryoprecipitate transfusion protocol  **3.** No platelet transfusion or platelet transfusion using a different platelet transfusion protocol  **4.** No fibrinogen concentrate or fibrinogen using a different fibrinogen transfusion protocol  **5.** Different combination –  *bleeding patients only* | Primary   * Mortality * Bleeding events (major and minor) * Transfusion-related SAEs (TACO, TRALI, otherb) * Transfusion volume or transfusion incidence   Secondary   * Thromboembolic events (stroke, MI, DVT, PE) – *Surgical-cardiac & ECMO subgroup only* | * Identify any evidence in Indigenous populations * TTP/HUS or anticoagulated patients will be a relevant lower level subgroup for the medical patients   **Limits:**   * studies published after 1995c * Restrict to Level III-2 studies and higher * May apply study size limits after examining the body of evidence   **Notes:**   * TTP population could refer to other guideline (as per Medical module PP19) |

BDP, bronchopulmonary dysplasia; DVT, deep vein thrombosis; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; g/L, grams per litre; GMFCS, Gross Motor Function Classification System; Hb, haemoglobin; Hct, haematocrit; HIV, human immunodeficiency virus; HUS, haemolytic-uraemic syndrome; IM, intramuscular; IV, intravenous; MDI, Major Depression Inventory; MI, myocardial infarction; mo, month; NEC, necrotising enterocolitis; PE, pulmonary embolism; RBC, red blood cell; ROP, retinopathy of prematurity; SAE, serious adverse event; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TTP, thrombotic thrombocytopenic purpura; vs, versus; wks, weeks; yrs, years

**a**. The systematic reviewers will search down to the lowest level of evidence to find studies relating to each of the specified subgroups shown in **bold**, but not the minor subgroups (not shown in bold) within those.

**b.** Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions, iron overload

**c.** Studies published prior to 1995 will be excluded (except primary studies if they are included as part of a systematic review published after this date). The decision to make this change was based on several factors including the fact that around 1985 the approach to transfusion therapy in all age groups changed because of recognition of the risks of HIV and hepatitis C. Although those risks have since subsided, with the development of better screening questionnaires for donors and tests, papers published since that time consider risks of transfusion differently and are more likely to explore parsimonious approaches to transfusion. During the 1980s, paediatric and neonatal care were evolving rapidly, and there was increasing understanding of the hazards of extrapolating from adult diagnosis and treatment to children and infants. Papers published before 1995 are more likely to be of historical interest than to be useful as a basis for current practice. Also, a systematic review of papers published between 1985 and 1995 for this question in the adult population has been conducted in previous modules which will be used for reference. For Question 3, choice of this date is related to the relatively recent development of a range of blood component therapies to prevent bleeding and their application to paediatric/neonatal medicine. Due to advances in paediatric and neonatal critical and perioperative care, papers published before 1995 are unlikely to reflect the current context of care.

Table 4.1.2 Structure of the research question specific to neonatal and paediatric patient blood management

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 4. In all paediatric patients, what is the effect of strategies that aim to minimise blood loss on morbidity, mortality, or the need for RBC transfusion?  *Intervention vs. comparator =* (1) vs. (1), (2) vs. (2), (3) vs. (3), (2) vs. (3) [Intervention Foreground Question] | | | | |
| Populationa | Intervention | Comparison | Outcomes | Other SR considerations |
| **Preterm (<37 wks)**  Infant   * Newborn (< 1 mo) * Infant * 1-6 mo * 7-12 mo * 13-23 mo   Child/adolescent   * Preschool (2-5 yrs) * Child (6-12 yrs) * Adolescent (13-18 yrs)   **Surgical**   * Cardiac (cyanotic vs non-cyanotic) * Transplantation * Orthopaedic * Burns   **Critical illness**   * ECMO/ECLS * Trauma | **Preterm and infant only**  **1.** Placental transfusion  **2.** IVIg for haemolytic disease  **Infant/child/adolescent**  **Surgical**  **1.** Prevention of hypothermia  **2.** Deliberate/controlled induced hypotension  **3.** ANH  **4.** Intraoperative cell salvage  **5.** POC testing (thromboelastometry, thromboelastography)  **6.** Antifibrinolytics (aprotinin, TXA, EACA)  **7.** rFVIIa (cardiac & ECMO only)  **8.** Miniaturised CPB systems  **Infant/child/adolescent**  **Critical illness**  **1.** rFVIIa (cardiac & ECMO only)  **2.** POC testing (thromboelastometry, thromboelastography) | **Preterm and infant only**  **1.** No placental transfusion  **2.** No IVIg transfusion  **Infant/child/adolescent**  **Surgical**  **1.** No prevention of hypothermia  **2.** No deliberate induced hypotension  **3.** No ANH  **4.** No ICS  **5.** No POC testing  **6.** No antifibrinolytics  **7.** No rFVIIa  **8.** Standard-sized systems  **Infant/child/adolescent**  **Critical illness**  **1.** No rFVIIa (cardiac & ECMO only)  **2.** No POC testing (TEG, ROTEM) | **Preterm and infant only**  Primary   * Transfusion volume (in transfused patients only) or transfusion incidence *– placental transfusion only* * Exchange transfusion incidence – IVIg for haemolytic disease intervention only * Mortality   Secondary   * Intracranial/IVH –*placental transfusion intervention only*   **Infant/child/adolescent**  **Surgical/critical illness**  Primary   * Mortality * Thromboembolic events – antifibrinolytics and rFVIIa interventions only * Bleeding events – *induced hypotension, POC testing, antifibrinolytics, rFVIIa interventions only* * Transfusion volume (in transfused patients only) or transfusion incidence | * Identify any evidence in Indigenous populations * Cochrane review update on preterm/infant intervention 2, expected soon.   **Limits:**   * Limit to studies published after 1995b * Restrict to Level I evidence for preterm and infant only * Restrict to Level II studies and higher for Surgical/Critical illness   **Surgical:**   * Conduct literature search update and use existing data from Module 2 technical report for prevention of hypothermia intervention (all populations) and antifibrinolytics interventions (paediatric population only)   **Notes:**   * Evidence in paediatric population included in Module 2 Technical Report includes aprotinin, TXA, EACA (cardiac and scoliosis). No other paediatric evidence for the surgical (perioperative) interventions. * For CPB intervention, three citations provided by EWG; reconcile with lit search. * *Retrograde priming of bypass system* is a separate modality for surgical population that may need to be addressed as ‘Expert Opinion’ * Strategies (e.g. protocols) to minimise iatrogenic blood loss: Provide example of a protocol in the module (potential background question) * Refer to Perioperative Module for appropriate patient positioning |

ANH, acute normovolemic haemodilution; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; EACA, Epsilon-aminocaproic acid; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; EWG, Expert Working Group; IVH, intraventricular haemorrhage; IVIg, intravenous immunoglobulin; MI, myocardial infarction; mo, month; PE, pulmonary embolism; POC, point of care; RBC, red blood cell; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; vs, versus; wks, weeks; yrs, years

**a.** The systematic reviewers will search down to the lowest level of evidence to find studies relating to each of the specified subgroups shown in bold, but not the minor subgroups (not shown in bold) within those; that is Pre-term, Surgical, and Critical illness (not infant/child/adolescent as separate populations).

**b.** Studies published prior to 1995 were excluded (except primary studies if they are included as part of a systematic review published after this date). Due to advances in paediatric and neonatal critical and perioperative care, papers published before 1995 are unlikely to reflect the current context of care.

## Appendix 2 Quality assessment

Each included study was assessed using the quality criteria for the relevant study type, as shown below (see **Volume 2, Appendix E**).

Studies were considered:

* good quality, with a low risk of bias, if they met all, or all but one, of the criteria
* fair quality, with a moderate risk of bias, if they did not meet two or three criteria
* poor quality, with a high risk of bias, if they did not meet four or more criteria

### Systematic reviews

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study type:** | | | | Systematic review |  |
| **Citation:** | | | |  |  |
| Y | N | NR | NA | Quality criteria | Error ratinga |
|  | | | | A. Was an adequate search strategy used? |  |
| ✓ |  |  |  | * Was a systematic search strategy reported? | I |
|  |  |  |  | * Were the databases searched reported? | III |
|  |  |  |  | * Was more than one database searched? | III |
|  |  |  |  | * Were search terms reported? | IV |
|  |  |  |  | * Did the literature search include hand searching? | IV |
|  | | | | B. Were the inclusion criteria appropriate and applied in an unbiased way? |  |
|  |  |  |  | * Were inclusion/exclusion criteria reported? | II |
|  |  |  |  | * Was the inclusion criteria applied in an unbiased way? | III |
|  |  |  |  | * Was only Level II evidence included? | I-IV |
|  | | | | C. Was a quality assessment of included studies undertaken? |  |
|  |  |  |  | * Was the quality of the studies reported? | III |
|  |  |  |  | * Was a clear, pre-determined strategy used to assess study quality? | IV |
|  | | | | D. Were the characteristics and results of the individual studies appropriately summarised? |  |
|  |  |  |  | * Were the characteristics of the individual studies reported? | II-III |
|  |  |  |  | * Were baseline demographic and clinical characteristics reported for patients in the individual studies? | IV |
|  |  |  |  | * Were the results of the individual studies reported? | III |
|  | | | | E. Were the methods for pooling the data appropriate? |  |
|  |  |  |  | * If appropriate, was a meta-analysis conducted? | III-IV |
|  | | | | F. Were the sources of heterogeneity explored? |  |
|  |  |  |  | * Was a test for heterogeneity applied? | III-IV |
|  |  |  |  | * If there was heterogeneity, was this discussed or the reasons explored? | III-IV |
| **Commentsb:** | | | |  |  |
| **Quality rating:**  **[Good/Fair/Poor]** | | | | Systematic review: |  |
| Included studies: |  |

Source: Quality criteria were adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Rules for assigning quality rating were adapted from SIGN (2008) SIGN 50: a guideline developer’s handbook. SIGN, Edinburgh.

**a.** Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

**b.** Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality. For quality assessment of systematic reviews, this should include a statement regarding the methodological quality of the studies included in the systematic review.

### Randomised controlled trials

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study type:** | | | | Randomised controlled trial |  |
| **Citation:** | | | |  |  |
| Y | N | NR | NA | Quality criteria | Error ratinga |
|  | | | | A. Was assignment of subjects to treatment group randomised? |  |
| ✓ |  |  |  | * Was the use of randomisation reported? | I |
|  |  |  |  | * Was the method of randomisation reported? | III |
|  |  |  |  | * Was the method of randomisation appropriate? | I-III |
|  | | | | A. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |  |
|  |  |  |  | * Was a method of allocation concealment reported? | III |
|  |  |  |  | Was the method of allocation concealment adequate? | III |
|  | | | | B. Was the study double-blinded? |  |
|  |  |  |  | * Were subjects and investigators blinded to treatment arm? | II-IV |
|  | | | | C. Were patient characteristics and demographics similar between treatment arms at baseline? |  |
|  |  |  |  | * Were baseline patient characteristics and demographics reported? | III |
|  |  |  |  | * Were the characteristics similar between treatment arms? | III-IV |
|  | | | | D. Were all randomised participants included in the analysis? |  |
|  |  |  |  | * Was loss to follow-up reported? | II |
|  |  |  |  | * Was loss to follow-up appropriately accounted for in the analysis? | III-IV |
|  | | | | E. Was outcome assessment likely to be subject to bias? |  |
|  |  |  |  | * Were all relevant outcomes measured in a standard, valid, and reliable way? | III-IV |
|  |  |  |  | * Was outcome assessment blinded to treatment allocation? | III |
|  |  |  |  | * If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? | III |
|  | | | | F. Were the statistical methods appropriate? |  |
|  |  |  |  | * Were the methods used for comparing results between treatment arms appropriate? | III |
|  |  |  |  | * If the study was carried out at more than one site, are the results comparable for all sites? | IV |
|  | | | | G. If appropriate, were any subgroup analyses carried out? |  |
|  |  |  |  | * Were subgroup analyses reported? | III-IV |
|  |  |  |  | * Were subgroup analyses appropriate? | III-IV |
| **Commentsb:** | | | |  |  |
| **Quality rating:**  **[Good/Fair/Poor]** | | | |  |  |

Source: Quality criteria were adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Rules for assigning quality rating were adapted from SIGN (2008) SIGN 50: a guideline developer’s handbook. SIGN, Edinburgh.

**a.** Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

**b.** Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

### Cohort studies/ Concurrent control

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study type:** | | | | Cohort study |  |
| **Citation:** | | | |  |  |
| Y | N | NR | NA | Quality criteria | Error ratinga |
|  | | | | A. Was the selection of subjects appropriate? |  |
| ✓ |  |  |  | * Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation? | II-IV |
|  |  |  |  | * Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis? | III |
|  | | | | B. Were all recruited participants included in the analysis? |  |
|  |  |  |  | * Does the study report whether all people who were asked to take part did so, in each of the groups being studied? | III |
|  |  |  |  | * Was loss to follow-up and exclusions from analysis reported? | II |
|  |  |  |  | * Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis? | III-IV |
|  | | | | C. Does the study design/analysis adequately control for potential confounding variables? |  |
|  |  |  |  | * Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis? | II-IV |
|  | | | | D. Was outcome assessment subject to bias? |  |
|  |  |  |  | * Were all relevant outcomes measured in a standard, valid, and reliable way? | III-IV |
|  |  |  |  | * Was outcome assessment blinded to exposure status? | III |
|  |  |  |  | * If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? | III |
|  | | | | E. Was follow-up adequate? |  |
|  |  |  |  | * Was follow-up long enough for outcomes to occur? | III |
| **Commentsb:** | | | |  |  |
| **Quality rating:**  **[Good/Fair/Poor]** | | | |  |  |

Source: Quality criteria were adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Rules for assigning quality rating were adapted from SIGN (2008) SIGN 50: a guideline developer’s handbook. SIGN, Edinburgh.

**a.** Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

**b.** Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

### Case–control studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study type:** | | | | Case–control study |  |
| **Citation:** | | | |  |  |
| Y | N | NR | NA | Quality criteria | Error ratinga |
|  | | | | A. Was the definition and selection of cases and controls appropriate? |  |
|  |  |  |  | * Were the cases and controls taken from comparable populations? | III |
|  |  |  |  | * Were the same exclusion criteria used for both cases and controls? | III |
|  |  |  |  | * Was a comparison made between participants and non-participants to establish their similarities or differences? | III |
|  |  |  |  | * Were cases clearly defined and differentiated from controls? | III |
|  |  |  |  | * Was it clearly established that controls were non-cases? | III |
|  | | | | B. Was the analysis subject to bias? |  |
|  |  |  |  | * Were all selected subjects included in the analysis? | III |
|  | | | | C. Was exposure assessment likely to be subject to bias? |  |
|  |  |  |  | * Were sufficient measures taken to prevent knowledge of primary exposure influencing case ascertainment? | III |
|  |  |  |  | * Was exposure status measured in a standard, valid, and reliable way? | III |
|  | | | | D. Was outcome assessment likely to be subject to bias? |  |
|  |  |  |  | * Were all relevant outcomes measured in a standard, valid, and reliable way? | III |
|  |  |  |  | * Were the main potential confounders identified and taken into account in the design and analysis? | II-III |
| **Commentsb:** | | | |  |  |
| **Quality rating:**  **[Good/Fair/Poor]** | | | |  |  |

Source: Quality criteria were adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Rules for assigning quality rating were adapted from SIGN (2008) SIGN 50: a guideline developer’s handbook. SIGN, Edinburgh.

**a.** Each quality criterion was associated with an error category designed to reflect the relative weight that should be assigned to each criterion. These error categories were defined as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (e.g. good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

**b.** Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

## Appendix 3 Modified NHMRC evidence statement form

### Evidence statement form

|  |  |  |  |
| --- | --- | --- | --- |
| **Key question(s):** | | | **Evidence table ref:** |
| **1. Evidence base** *(number of studies, level of evidence and risk of bias in the included studies)* | | | |
|  | A | **One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias** | |
| B | **One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias** | |
| C | **One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias** | |
| D | **Level IV studies or Level I to III studies/SRs with a high risk of bias** | |
| **2. Consistency** *(if only one study was available, rank this component as ‘not applicable’)* | | | |
|  | A | **All studies consistent** | |
| B | **Most studies consistent and inconsistency can be explained** | |
| C | **Some inconsistency, reflecting genuine uncertainty around question** | |
| D | **Evidence is inconsistent** | |
| NA | **Not applicable (one study only)** | |
| **3. Clinical impact** *(Indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)* | | | |
|  | A | **Very large** | |
| B | **Substantial** | |
| C | **Moderate** | |
| D | **Slight/Restricted** | |
| NA | **Not applicable/no difference/underpowered** | |
| **4. Generalisability** *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)* | | | |
|  | A | **Evidence directly generalisable to target population** | |
| B | **Evidence directly generalisable to target population with some caveats** | |
| C | **Evidence not directly generalisable to the target population but could be sensibly applied** | |
| D | **Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply** | |
| **5. Applicability** *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)* | | | |
|  | A | **Evidence directly applicable to Australian health-care context** | |
| B | **Evidence applicable to Australian health-care context with few caveats** | |
| C | **Evidence probably applicable to Australian health-care context with some caveats** | |
| D | **Evidence not applicable to Australian health-care context** | |

|  |  |  |
| --- | --- | --- |
| **Other factors** *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)* | | |
|  | | |
| **EVIDENCE STATEMENT MATRIX**  *Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account.* | | |
| **Component** | **Rating** | **Description** |
| 1. Evidence base |  |  |
| 1. Consistency |  |  |
| 1. Clinical impact |  |  |
| 1. Generalisability |  |  |
| 1. Applicability |  |  |
| **EVIDENCE STATEMENT**  *Indicate any dissenting opinions* | | |

### Recommendation form

|  |  |  |
| --- | --- | --- |
| **RECOMMENDATION**  *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* | **GRADE OF RECOMMENDATION** | **RELEVANT ESF(S)** |
| *Indicate any dissenting opinions* | | |
| **UNRESOLVED ISSUES**  *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.* | | |
|  | | |
| **IMPLEMENTATION OF RECOMMENDATION**  *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.* | | |
| Will this recommendation result in changes in usual care? | | YES |
| NO |
| Are there any resource implications associated with implementing this recommendation? | | YES |
| NO |
| Will the implementation of this recommendation require changes in the way care is currently organised? | | YES |
| NO |
| Are the guideline development group aware of any barriers to the implementation of this recommendation? | | YES |
| NO |

## Appendix 4 Consensus process for development of practice points

### Background

Often, there are insufficient high-quality data in the contemporary clinical literature to produce clinical guidelines with an evidence-based recommendation. Thus, there remains a role for expert opinion and consensus in guidelines development. The use of expert opinion as a form of ‘evidence’ requires a formal consensus development process among the guidelines developers, with rigorous rules that will lead to the same attributes of validity, reliability and applicability demanded for more rigorous evidence-based practice methodology.

### Role of the Clinical/Consumer Reference Group

The CRG provided expert opinion for the development of practice points relevant to the recommendation being considered under the consensus process.

The consensus process was followed only for recommendations where:

* the systematic review has found no Level I to III-2 evidence to address the relevant clinical question, or where recommendations developed by the systematic review process were ranked with a Grade D (poor) quality evidence base
* the CRG determines that additional clinical practice guidance is required for recommendations developed by the systematic review process that are graded above D
* the development of ‘expert opinion’ is required (e.g. for the background research questions)

Applying the consensus process to recommendations with Grade D (poor) evidence could result in:

* the rejection of the recommendation
* the confirmation of the recommendation
* the development of a ‘practice point’ to supplement the recommendation, or
* rejection of the recommendation and the development of a practice point on its own.

### Chair of CRG meetings

The Chair of CRG meetings facilitated and guided the process of reaching a consensus decision on practice points. Specifically, the Chair’s role was to:

* assist the CRG to define decisions that need to be made
* help the CRG through the stages of reaching an agreement
* keep the meeting moving
* focus discussion to the point at hand
* ensure that everyone has the opportunity to participate
* test whether consensus has been reached

The Chair helped to direct the consensus process, not its content, and did not make decisions for the CRG.

### Development of practice points: overview of consensus decision-making process

The following process was used to develop practice points through consensus.

##### Stage 1 – Introduction

* **Describe the process.** The Chair described the consensus process, participants’ roles and responsibilities, ground rules and guiding principles.
* **State where there is a need for practice point development.** The Chair described where evidence was not found or was considered inadequate to develop recommendations above Grade D, or where a practice point may be required to supplement recommendations.

##### Stage 2 – Open discussion

* **Clarify the practice point.** The Chair opened the floor to a general discussion and suggestions for practice point content. This time will not be used for raising objections or concerns, but to suggest content for the practice point. Suggestions were recorded in the relevant section of the draft results report.
* **State concerns.** When the CRG was satisfied that the practice point is complete, the Chair provided an opportunity for concerns or issues to be raised.

##### Stage 3 – Resolve concerns

* **Review concerns.** The group reviewed any concerns raised. If the concerns were many and the time was short, the discussion on practice point development was carried over to a later meeting.
* **Resolve concerns.** The Chair had the first option to resolve the listed concerns by:
* clarifying the wording of the practice point
* changing the wording of the practice point or adding a practice point to supplement the recommendation
* explaining why the recommendation as stated is not in conflict with the CRG’s values
* seeing whether those with concerns will stand aside (i.e. “had concerns, but could live with them”).

##### Stage 4 – First call for consensus

* When all concerns had been resolved, the Chair called for consensus.

##### Stage 5 – Consideration of CRG principles and values and second call for consensus

* When concerns had been adequately discussed but remained unresolved, the CRG assessed how the unresolved concerns related to CRG principles and values.
* After considering these principles, the Chair made one of the following conclusions:
* the member withdrew the concern, consensus was reached and a practice point could be made (or a Grade D evidence-based recommendation confirmed)
* the member stood aside so that a practice point could be made (or Grade D evidence-based recommendation confirmed), 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 recommendation or practice point was not accepted.

### Guiding principles and values

These principles and values were used throughout the development of consensus-based practice points:

* Consensus is reached where all members of the CRG strongly agree, or agree with the practice point. Consensus is not achieved on the basis of a ‘majority’.
* The opinions of all members of the CRG are equally valid/important, notwithstanding that some members may have discipline-specific expert opinion.
* Where consensus is not reached (one or more members disagree or strongly disagree with the practice point), the dissenting members are allowed to present their case. This may be done immediately in the current meeting, or be carried over to the subsequent meeting to allow the members to succinctly formulate their concerns or provide other documentation/research.
* Issues of semantics, language or content, while recognised as important, should preferably not absorb discussion time within the CRG meetings.
* CRG members are respectfully asked to reflect upon their own values and conflicts of interests, and be mindful of the extent to which these may influence their opinions.

### Ground rules

* Members agree to take turns speaking and not interrupt each other.
* Members agree to call each other by their first names, not ‘he’ or ‘she’.
* Members agree to not blame, attack, or engage in put-downs and will ask questions of each other for the purposes of gaining clarity and understanding.
* Members agree to stay away from establishing hard positions and express themselves in terms of personal needs and interests and the outcomes that they wish to realise.
* Members agree to listen respectfully and sincerely try to understand the other person’s needs and interests.
* Members recognise that, even when they do not agree, each of them is entitled to their own perspective.
* Members will not dwell on things that did not work in the past, but instead will focus on the future they would like to create.
* Members agree to make a conscious, sincere effort to refrain from unproductive arguing, venting, or narration, and agree to use their time during the meeting to work towards what they perceive to be their fairest and most constructive agreement possible.
* Members will speak up when something is not working for them during the consensus process.
* Members will request a break when they need to.
* Members will point out when they feel the Chair is not being impartial as to person and neutral as to result.
* CRG members not present at the meeting have the opportunity to provide feedback via an agreed electronic format (e.g. GovDex or email) when developed practice points are circulated to the entire CRG after the meeting.

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1. One additional Level III study (Boo 1997) was identified and excluded by the systematic review authors as the study was deemed to be of historical interest only (See **Volume 2, Appendix B**). [↑](#footnote-ref-1)
2. Note: 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. One Level III study (Demirel 2009) published prior to 2011 was identified that assessed risk factors for the development of BPD in VLBW infants. This study is awaiting assessment (See **Volume 2, Appendix B**) [↑](#footnote-ref-3)
4. Eight Level III studies (Al-Essa 1999, Bayat-Mokhtari 2010, Dutta 2004, Ebrahim 2010, Fortes-Filho 2009, Fortes-Filho 2010, Hesse 1997, Lad 2009) published prior to 2011 were identified that assessed risk factors for the development of ROP in ELBW or VLBW infants. These studies are awaiting assessment (See **Volume 2, Appendix B**). [↑](#footnote-ref-4)
5. Follow-up of Bell (2005) [↑](#footnote-ref-5)
6. Follow-up of Kirpalani (2006) [↑](#footnote-ref-6)
7. Ransome (1989) did not report any outcome measures that met our inclusion criteria. [↑](#footnote-ref-7)
8. Note: 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. Defined as Mental Developmental Index (MDI) <70 and >2 SDs below age norm. [↑](#footnote-ref-9)
10. Defined as MDI <85 and >1 SD below age norm. [↑](#footnote-ref-10)
11. As determined by neuroimaging, clinical evidence of permanent neurologic injury or both. [↑](#footnote-ref-11)
12. An event that resulted in focal neurologic deficits that lasted less than 24 hours did not result in abnormalities that were indicative of an acute infarct, and had no other reasonable medical explanation. [↑](#footnote-ref-12)
13. Note: 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-13)
14. Note: 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-14)
15. Note: 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-15)
16. Note: 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-16)
17. Multivariate analysis using logistic regression adjusted for GCD score, age category, gender, and ISS. [↑](#footnote-ref-17)
18. Note: 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-18)
19. Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, and anaphylactic reactions. [↑](#footnote-ref-19)
20. Note: 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-20)
21. A systematic review (Aher 2012) comparing early administration of rHuEPO to late administration of rHuEPO was identified in our literature search, but was excluded from this review as it did not meet the PICO criteria (comparator out of scope).93 [↑](#footnote-ref-21)
22. Not used or not clear in four RCTs (Chang 1998, Fauchere 2008, He 2008, Yasmeen 2012). [↑](#footnote-ref-22)
23. Not used or not clear in two RCTs (Akisu 2001, Shannon 2001). [↑](#footnote-ref-23)
24. Note: 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-24)
25. RBC transfusions were permitted in four of the 21 RCTs included in the by review Mills (2012), 9 RCTs excluded infants that received a transfusion or did not permit them during the study period and 8 RCTs did not mention transfusions. The review by Long (2012) reported RBCs transfusions among the adverse events. [↑](#footnote-ref-25)
26. Note: 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-26)
27. Note: 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-27)
28. This reason for exclusion was reported in superseded AHRQ report (Seidenfeld, 2006). [↑](#footnote-ref-28)
29. Note: 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-29)
30. Note: 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-30)
31. Note: 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-31)
32. Note: 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-32)
33. Note: 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-33)
34. Note: 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-34)
35. Note: 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-35)
36. Note: 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-36)
37. Note: 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-37)
38. Note: 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-38)
39. Alan (2014)309 was not included in the meta-analysis as a composite outcome was reported. [↑](#footnote-ref-39)
40. Note: 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-40)
41. Note: The systematic review by Rabe (2012) included Oh (2002) in a meta-analysis for IVH (all grades) only. [↑](#footnote-ref-41)
42. One RCT353) published after the systematic review literature search was identified that confirms current practice for thromboelastometry-guided intraoperative haemostatic management in reducing bleeding and red cell transfusion after paediatric cardiac surgery. The published results by Nakayma (2015) will be included in the technical report when the module is reviewed and updated. [↑](#footnote-ref-42)
43. Analysis included studies reported by Boldt. A number of studies by Boldt have been retracted due to research misconduct, including lack of ethics approval and false data. Although the included studies have not been formally retracted, care should be taken in the interpretation of the analysis. [↑](#footnote-ref-43)
44. Analysis included studies reported by Joachim Boldt. A number of studies by Boldt have been retracted due to research misconduct, including lack of ethics approval and false data. Although the included studies have not been formally retracted, care should be taken in the interpretation of the analysis. [↑](#footnote-ref-44)
45. Only studies that assessed the use of rFVIIa in neonatal and paediatric patients undergoing cardiac surgery or receiving ECMO were included. [↑](#footnote-ref-45)