Patient Blood Management Guidelines: Module 6

Neonatal and Paediatrics

Technical report

Volume 1
Review of the evidence

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 normalised 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

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
TAGVHD	transfusion-associated graft-versus-host-disease

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

1 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	1 – Critical Bleeding/Massive Transfusion
	2 – Perioperative
II	3 – Medical
	4 – Critical Care
III	5 – Obstetrics and Maternity
	6 – Neonatal and Paediatrics

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.

2 Methods

2.1 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.

2.1.1 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 neonates/paediatric patients, what is the effect of red blood cell (RBC) (allogeneic) transfusion on patient outcomes? (Interventional question)
- *Question 2* – In neonates/paediatric 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 neonates/paediatric 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 neonates/paediatric 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.

2.1.2 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-pharmacological strategies for minimisation of blood loss from sampling reduce the incidence of red cell transfusion?
- *Background question 4* – In perioperative neonatal and paediatric patients needing cardiac surgery, do strategies to minimise blood loss reduce the incidence of transfusion?
- *Background question 5* – What recommendations should be made for the detection, diagnosis and management of iron deficiency anaemia in neonates and children?

2.1.3 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.

2.1.4 Scheduled review and update

This module will be reviewed and amended in 2021 unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need for an earlier review.

2.2 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.

2.2.1 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 2014, 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 rigour 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.

2.2.2 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).

2.2.3 Expert sources

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

2.2.4 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.

2.2.5 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.

2.2.6 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.

2.3 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.

2.4 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	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort study
III–1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	All or none[e]	All or none[e]
III–2	A comparative study with concurrent controls: • non-randomised, experimental trial[f] • cohort study • case–control study • interrupted time series with a control group	Analysis of prognostic factors 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 studies[g] • interrupted time series without a parallel control group	A retrospective cohort study	A case–control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

Source: 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 versus B and B versus C to determine A versus C).

g Comparing single-arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A versus B and B versus C to determine A versus 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]

2.4.1 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).

2.4.2 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).

2.5 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).

2.5.1 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 I^2 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).

2.5.2 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' was 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.

2.6 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.

2.7 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.

3 Findings of systematic review

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

3.1 Question 1

Question 1 (Interventional)

In neonates/paediatric 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 is suggested.[a, b, c] [a] See PP6 for guidance on a restrictive transfusion strategy. [b] Higher Hb thresholds may be appropriate in very low birth weight and preterm neonates. [c] See PP2, PP3 and Appendix F for guidance for preterm neonates.
R2 (Grade A)	In children and adolescents with sickle cell disease who have been assessed to be at increased risk of stroke.[a, b] A program of prophylactic RBC transfusions should be used in order to reduce stroke occurrence. [a] Assessed by transcranial Doppler ultrasonography[12] 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 guideline[a] for RBC transfusion in preterm infants that includes the following: • age of infant • age-specific Hb reference ranges • Hb or haematocrit • level of respiratory support • ongoing or anticipated red cell loss • nutritional status. [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 G (*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: • age-specific Hb reference ranges • volume of transfusion and rate of administration • patient monitoring during and after transfusion • transfusion technique (e.g. use of syringe pumps) • recognition and reporting of adverse events.
PP6	In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[a] suggests that, with a: • Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. • Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate. [a] See PP3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[15]
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 G (*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*.[16]
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 sickle cell disease should be assessed for stroke

	risk using both transcranial Doppler ultrasonography[12] 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; MRI, magnetic resonance imaging; PP, practice point; R, recommendation; RBC, red blood cell	

Evidence gaps and areas for future research

There is a need for further research on:

- the effect on RBC transfusion on morbidity (including bronchopulmonary dysplasia) 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.

3.1.1 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.

3.1.2 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.

3.1.3 Preterm and low birth weight infants

Evidence statements – preterm and low birth weight infants (RBC transfusion)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES1.1	In very low birth weight infants (<1500 g), the effect of RBC transfusion compared with no transfusion on mortality is uncertain. (See evidence matrix D1.A in Volume 2 of the technical report.)	√	NA	√	√√√	√
ES1.2	In preterm infants, the effect of RBC transfusion compared with no transfusion on a composite of mortality and severe morbidity is unknown.	NA	NA	NA	NA	NA
ES1.3	In preterm infants, the effect of RBC transfusion compared with no transfusion on NEC is uncertain. (See evidence matrix D1.B in Volume 2 of the technical report.)	√	X	X	√√	√
ES1.4	In preterm infants, the effect of RBC transfusion compared with no transfusion on ROP is uncertain. (See evidence matrix D1.C in Volume 2 of the technical report.)	X	√	X	√√	√
ES1.5	In very low birth weight infants (<1500 g), the effect of RBC transfusion compared with no transfusion on IVH is uncertain. (See evidence matrix D1.D in Volume 2 of the technical report.)	√	NA	√	√√√	√
ES1.6	In very low birth weight infants (<1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is uncertain. (See evidence matrix D1.E in Volume 2 of the technical report.)	√√	√√√	NA	√√	√√
ES1.7	In very low birth weight infants (<1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on a composite outcome of mortality and severe morbidity is uncertain. (See evidence matrix D1.F in Volume 2 of the technical report.)	√√	√√	X	√√	√
ES1.8	In very low birth weight infants (<1500 g), there is no difference between restrictive RBC transfusion or liberal RBC transfusion on the incidence of NEC, ROP or BPD. (See evidence matrix D1.G in Volume 2 of the technical report.)	√√	√√√	NA	√√	√√
ES1.9	In very low birth weight infants (<1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on brain injury is uncertain. (See evidence matrix D1.H in Volume 2 of the technical report.)	√√	√√	NA	√√	√√

Evidence statements – preterm and low birth weight infants (RBC transfusion)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES1.10	In very low birth weight infants (<1500 g), liberal RBC transfusion may reduce cognitive delays compared with restrictive RBC transfusion. (See evidence matrix D1.I in Volume 2 of the technical report.)	√√	NA	√	√√	√√
ES1.11	In very low birth weight infants (<1500 g), the effect of restrictive RBC transfusion compared with liberal RBC transfusion on neurosensory impairment, cerebral palsy, and visual and hearing impairments is uncertain. (See evidence matrix D1.I in Volume 2 of the technical report.)	√√	NA	√	√√	√√
BPD, bronchopulmonary dysplasia; ES, evidence statement; NEC, necrotising enterocolitis; RBC, red blood cell; ROP, retinopathy of prematurity √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendation – preterm and low birth weight infants (RBC transfusion)	
R1 (Grade C)	In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a, b, c] [a] See PP6 for guidance on a restrictive transfusion strategy. [b] Higher Hb thresholds are appropriate in very low birth weight and preterm neonates. [c] See PP2, PP3 and Appendix F 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 guideline[a] for RBC transfusion in preterm infants that includes the following: • age of infant • age-specific Hb reference ranges • Hb or haematocrit • level of respiratory support • ongoing or anticipated red cell loss • nutritional status.

	[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 G (*Transfusion volume calculation for neonates, infants and small children*).
Hb, haemoglobin; 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.

3.1.3.1 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)[17]	Systematic review of observational studies *Good*	Preterm infants or neonates 12 studies, N>2000	RBC transfusion versus no transfusion	NEC
Kirpalani (2012)[18]	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)[19]	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)[20]	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)[21]	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)[22]	Retrospective cohort *Fair*	Preterm infants with VLBW N=1077	RBC transfusion (n=574) versus no transfusion (n=503)	Mortality
Elabaid (2013)[23]	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)[24]	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)[25]	Prospective cohort *Fair*	Preterm infants with ELBW N=157	RBC transfusion (n=124) versus no transfusion (n=33)	ROP (≥stage 3)
Hakeem (2012)[26]	Prospective cohort *Fair*	Preterm infants (≤32 weeks gestational age) with VLBW; Infants (>32 weeks gestational age or >1500 g birth weight)	>1 RBC transfusion (n=23) versus 1 RBC transfusion (n=25) versus no transfusion (n=124)	ROP (stage 1–3)

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		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		
Kabatas (2013)[27]	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)[28]	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)[29]	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)[30]	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)[31]	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)[32]	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)	RBC transfusion (n=135) versus no transfusion (n=30)	ROP (≥stage 3)

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		with VLBW, without ROP N=165 (cases, n=55; controls, n=110)		

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)[17] and/or (2) Kirpalani (2012)[18]			
Blau (2011)[a 33]	(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 34]	(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 35]	(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 36]	(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)[37]	(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)[38]	(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

Study	Study type *Study quality*	Population N	Comparison
Mally (2006)[a] [39]	(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] [40]	(1) Not included (2) Case–control *High risk of bias in 1 out of 5 measures*	NR	
Paul (2011)[41]	(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] [42]	(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)[43]	(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] [44]	(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] [45]	(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] [46]	(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[a]. 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.

[a] 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**).

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Dos Santos 2011[22] 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 2010[29] Level III-2	Retrospective cohort study N=194	Preterm infants (≤30 weeks gestation) with VLBW (≤1500 g)	2 NICUs, Iran	RBC transfusion versus 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

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

d. Only variables 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[b]

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 BPD.[c]

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 (I^2=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 (I^2=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).

[b] 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.

[c] 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**).

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 (I^2= 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 (I^2= 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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Mohamed 2012[17] Level I/III *Good*	5 trials (Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Wan-Huen 2011)[34-35; 41; 43] 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 I^2 = 58%
	4 trials (Harsono 2011, Paul 2011, Stritzke 2011, Wan-Huen 2011)[36; 41; 44-45] N=3863				NEC *studies that adjusted for potential confounders	NR	NR	OR 2.01 [1.61, 2.50]	*Favours no transfusion* p < 0.0001[c] I^2 = 91%
	3 trials (Paul 2011, Stritzke 2011, Wan-Huen 2011)[41; 44-45] 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 I^2 = 0%
Kirpalani 2012[18] Level I/III *Poor*	6 cohort studies (Blau 2011, Christensen 2009, Holder 2009, Mally 2006, Paul 2011, Valieva 2009)[33-34; 37; 39; 41; 46] 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 I^2 = 98%
	4 cohort studies (Christensen 2009, Holder 2009, Paul 2011, Valieva 2009)[34; 37; 41; 46] N=22,155					135/2940 (4.6%)	144/19215 (0.7%)	RR 4.55 [0.78, 26.45][d]	*No significant difference* p = 0.09[e] I^2 = 97%

Study Level of evidence[a] *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** **Heterogeneity[b]**
	4 case–control studies (El-Dib 2011, Josephson 2010, McGrady 1987, Singh 2011)[35; 38; 40; 43] N=567					129/186 (69.4%)	129/381 (33.9%)	OR 2.19 [1.52, 3.17]	*Favours no transfusion* p < 0.0001 I^2 = 92%
	3 case–control studies (El-Dib 2011, Josephson 2010, Singh 2011)[35; 38; 43] N=567					105/186 (56.5%)[d]	124/381 (32.5%)[d]	RR 1.66 [0.75, 3.64][d]	*No significant difference* p = 0.21[f] I^2 = 94%
Additional Level III–2 cohort studies									
AlFaleh 2014[19] 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 2012[21] 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 = 0.64[d]
					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 2013[23] Level III–2	Retrospective cohort study	Preterm infants with VLBW	Single NICU, USA	RBC transfusion versus no	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

Study Level of evidence[a] *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 Heterogeneity[b]
Fair	N=3060	(≤1500 g) or ELBW (≤1000 g)		transfusion		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

Study Level of evidence[a] *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 Heterogeneity[b]
					>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 2013[30] 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 < 0.00001[d]
						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 2013[31] 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 2011[41] Level III–2 *Poor*	Retrospective cohort study N=2311	Preterm infants with VLBW (<1500 g)	Single NICU, USA	RBC transfusion versus no transfusion	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 < 0.00001[d]

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention versus comparator *RBC transfusions after NEC diagnosis were excluded	Outcome	Results RBC transfusion N/N (%)	No transfusion N/N (%)	Risk estimate (95% CI)	*Statistical significance* p- value Heterogeneity[b]
						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 = 0.52[d]
					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 < 0.0001[d]
Singh 2011[43] 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 < 0.00001[d]
						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 < 0.00001[d]
						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

Study Level of evidence[a] *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 Heterogeneity[b]
						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 < 0.00001[d]
						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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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

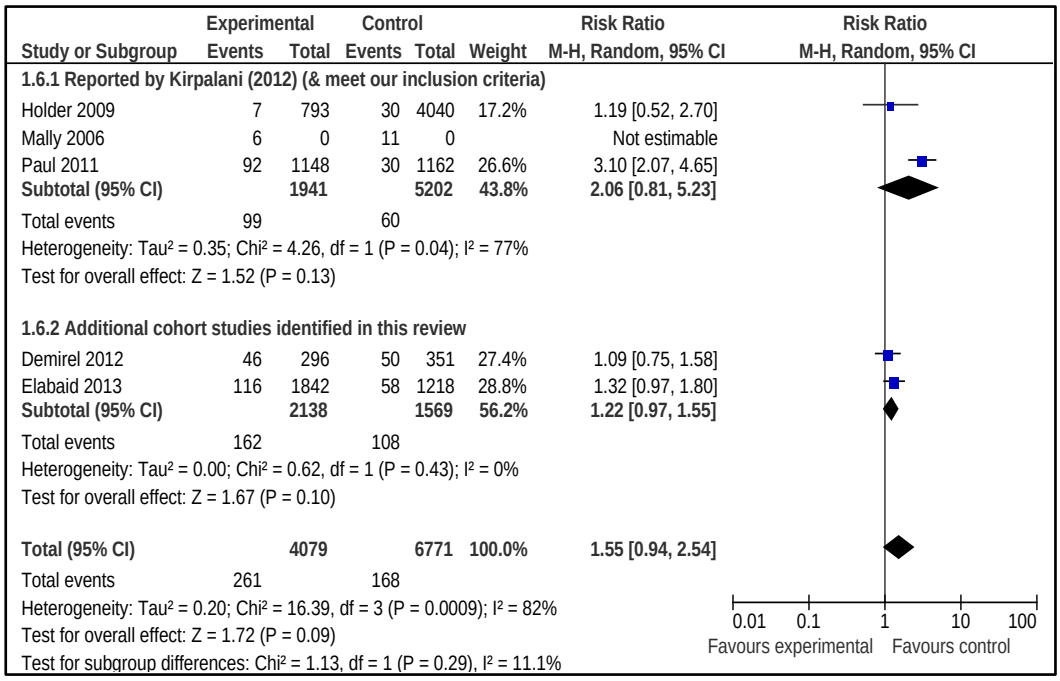
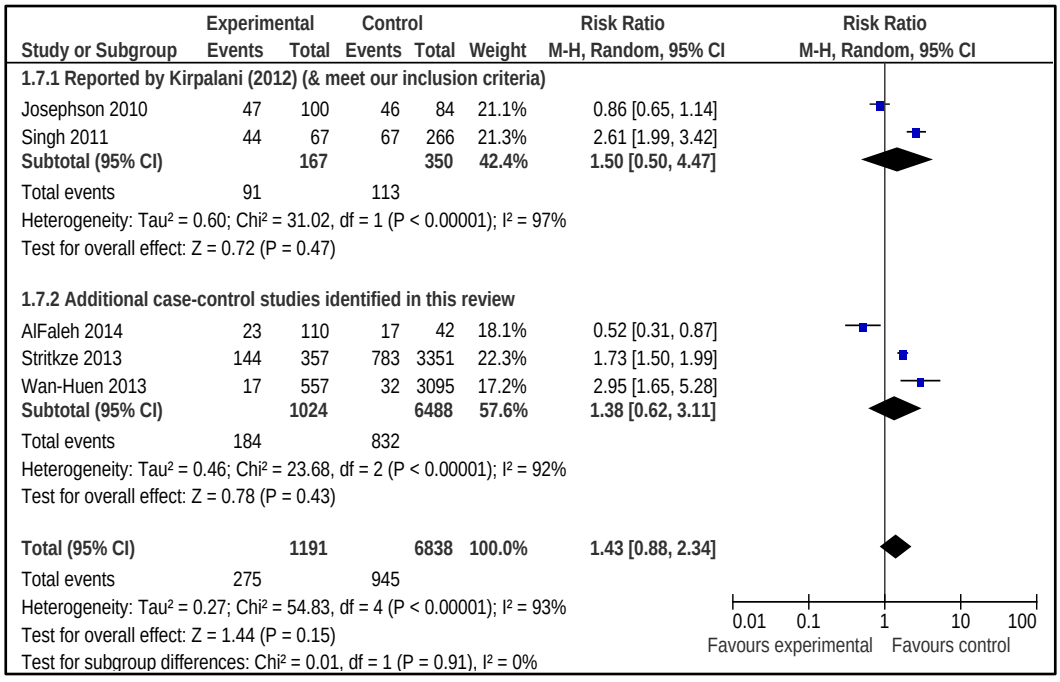


Figure 3.1.2 Pooled data from case–control studies assessing the association between RBC transfusions and NEC in preterm and/or low birth weight infants



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.[d] 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

[d] 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**).

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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Feghhi 2012[24] 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 < 0.00001[c]
						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 2013[25] 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 = 0.11[c]
Hakeem 2012[26] 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 = 0.22[c]
						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 = 0.55[c]
					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 therapy[d]		OR 2.483 [1.182, 5.222]	*Favours no transfusion* p = 0.016
Kabatas 2013[27] 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	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 = 0.006[c]
					ROP requiring laser photocoagulation	18/87 (20.7%)	4/26 (15.4%)	RR 1.34 [0.50, 3.62][c]	*No significant difference* p = 0.56[c]
				RBC 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 < 0.0001[c]

Study Level of evidence[a] *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** **Heterogeneity[b]**
		sepsis requiring prolonged mechanical ventilation		versus no transfusion in first 10 days of life		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 = 0.78[c]
Li 2013[28] 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 2011[32] 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 = 0.01[c]
						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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Baer 2011[20] 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 = 0.003[c]
						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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 serious adverse event (SAEs) (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, transfusion-associated graft-versus-host disease (TAGVHD), anaphylactic reactions).

3.1.3.2 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)[e] or Whyte (2009).[f]

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)[g] 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.

[e] Follow-up of Bell (2005).
[f] Follow-up of Kirpalani (2006).
[g] Ransome (1989) did not report any outcome measures that met our inclusion criteria.

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)[47]	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)[48]	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)[49]	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)[50]	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)[51]	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)[52]	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	RCT	Preterm infants (<31 weeks gestational	Restrictive RBC transfusion (n=223)	Mortality

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
(2006)[53] *also known as PINT 2006	*Good*	age) with ELBW (<1000 g) and <48 hours old N=451	versus liberal RBC transfusion (n=228)	Composite of mortality and severe morbidity Severe morbidity (BPD, ROP, NEC, brain injury)
Included and assessed by Venkatesh (2012)				
Brooks (1999)[54]	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)[55] *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)[56]	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 57] *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)[58] *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)[59] *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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Ibrahim 2014[47] Level I *Good*	3 trials (Bell 2005, Chen 2009, Kirpalani 2006)[51-53] 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 I^2 = 0%
Venkatesh 2012[48] Level I *Good*	4 trials[c] (Bell 2005, Brooks 1999, Chen 2009, Kirpalani 2006)[51-54] 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 I^2 = 0%
Whyte 2011[49] Level I *Good*	4 trials[d] (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)[51-53; 57] 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 I^2 = 0%
LEVEL II EVIDENCE									
Venkatesh 2012[48] Level I/II *Good*	1 trial (Mukhopadhyay 2004[55]) 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 2011[49] 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

Study Level of evidence[a] *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 Heterogeneity[b]
Whyte 2011[e 49] Level I/II *Fair*	1 trial (Whyte 2009)[59] 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.

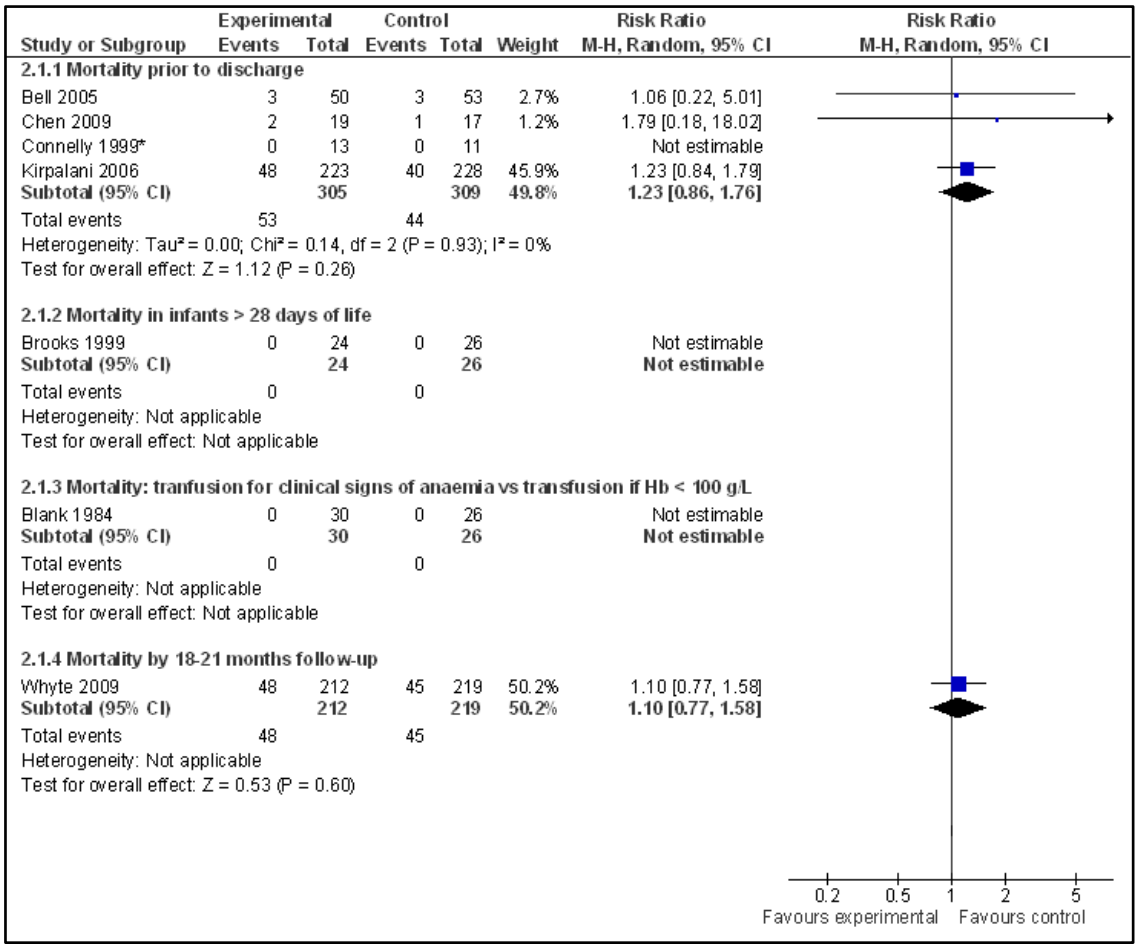
b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

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 evidence[a] *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 Heterogeneity[b]**
LEVEL I EVIDENCE									
Whyte 2011[49] Level I *Good*	3 trials[c] (Kirpalani 2006, Chen 2009, Connelly 1998)[52-53; 57] 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 I^2 = 0%
	4 trials[c] (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1998)[51-53; 57] 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 I^2 = 6%
LEVEL II EVIDENCE									
Whyte 2011[49] Level I/II Good	1 trial (Whyte 2009)[59] 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
					Mortality or severe morbidity 18–21 months post-transfusion with MDI <85 (>1 SD below age norm)	Post-hoc analysis			
						125/208 (60.1%)	106/213 (49.8%)	RR 1.21 [1.01, 1.44]	*Favours liberal RBC transfusion* p = 0.034

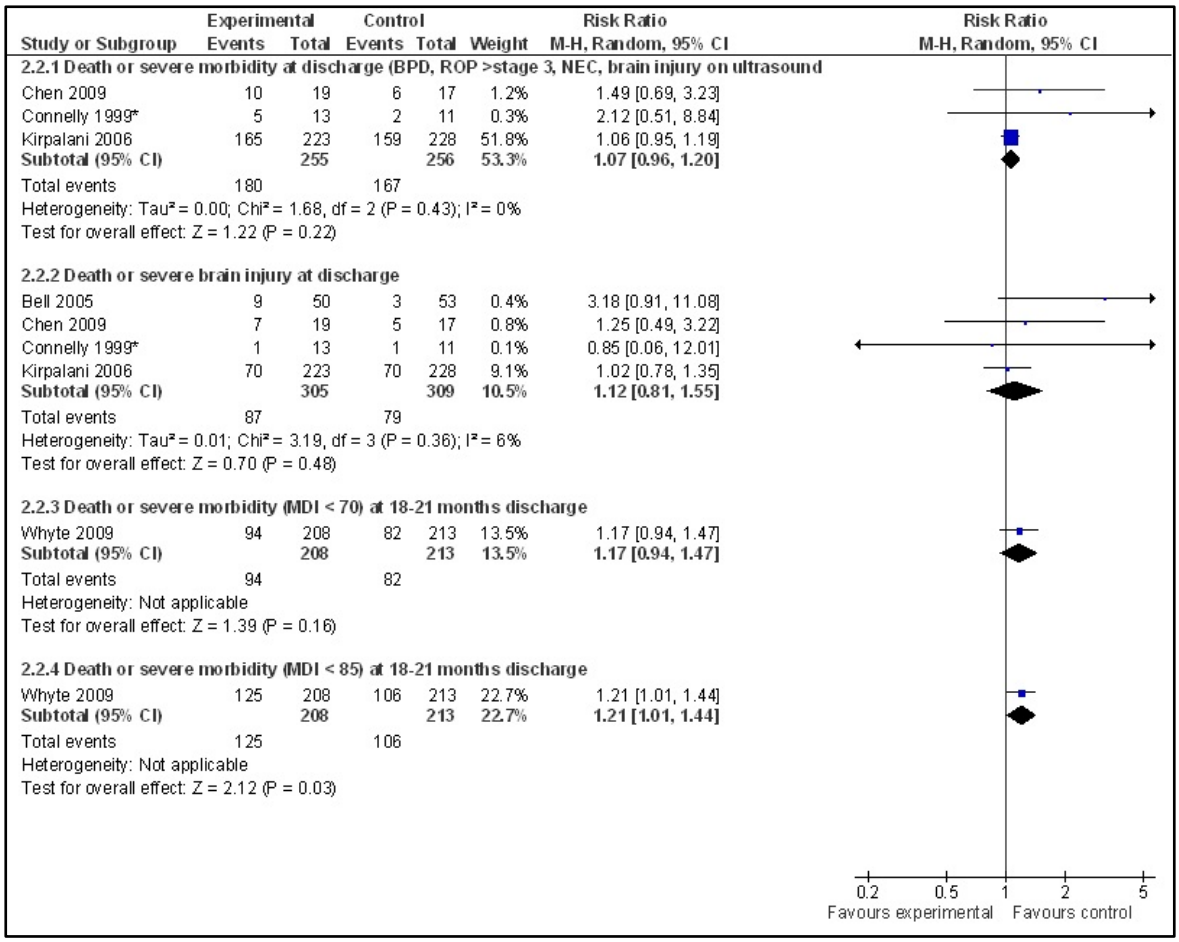
BPD, bronchopulmonary dysplasia; CI, confidence interval; ELBW, extremely low birth weight; MDI, mental developmental index; NEC, necrotising enterocolitis, NICU, neonatal intensive care unit; RBC, red blood cell; ROP, retinopathy of prematurity; RR, risk ratio; SD, standard deviation; VLBW, very low 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[h]

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**.

[h] 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.

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

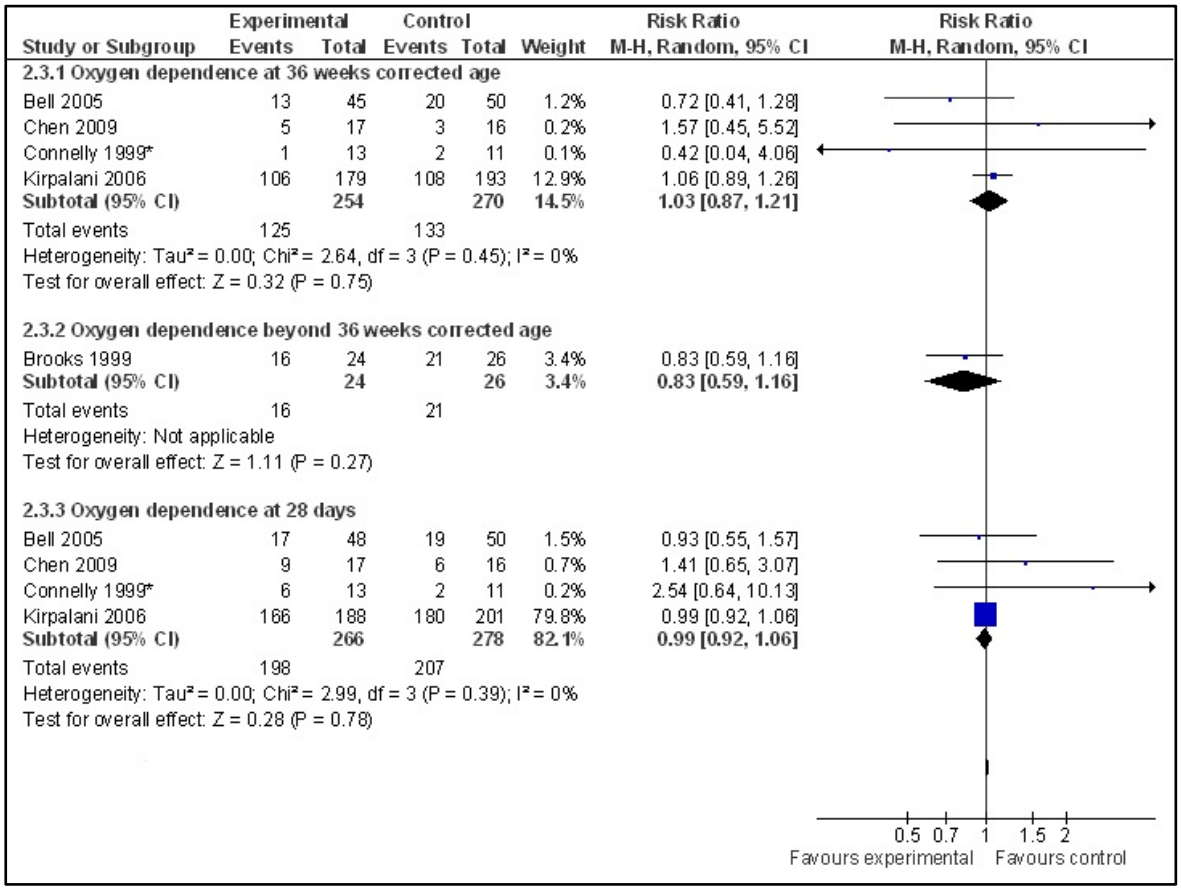


Table 3.1.11 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – severe morbidity (BPD)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Ibrahim 2014[47] Level I *Good*	3 trials (Bell 2005, Chen 2009, Kirpalani 2006)[51-53] 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 I^2 = 0%
Venkatesh 2012[48] Level I *Good*	4 trials[c] (Bell 2005, Brooks 1999, Chen 2009, Kirpalani 2006)[51-54] 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 I^2 = NR
Whyte 2011[49] Level I *Good*	4 trials[d] (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)[51-53; 57] 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 I^2 = 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 I^2 = 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

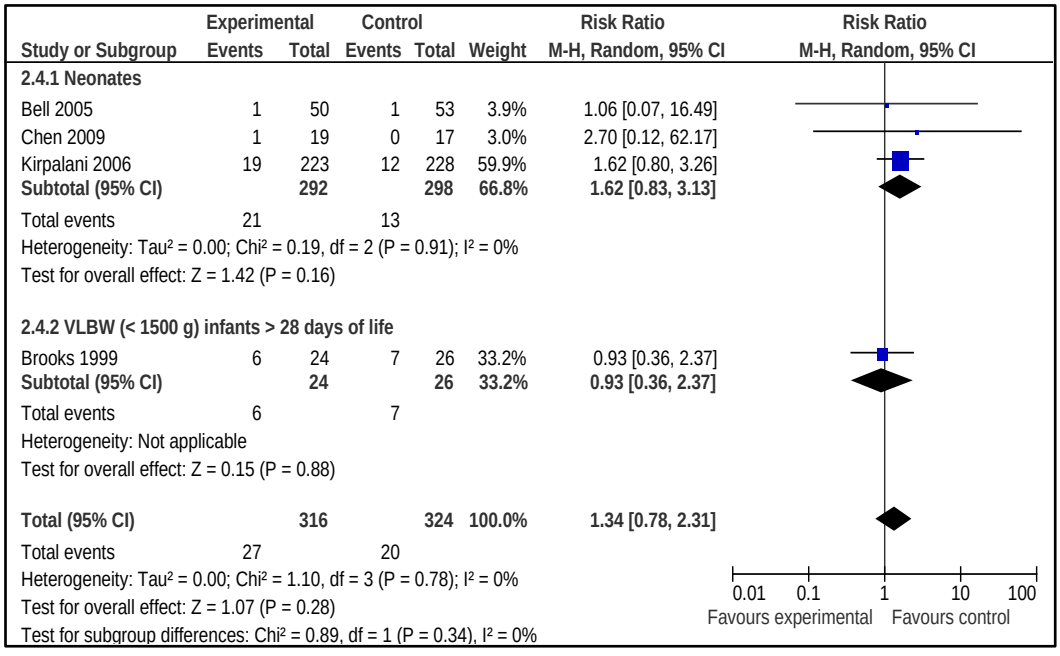


Table 3.1.12 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (NEC)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Ibrahim 2014[47] Level I *Good*	3 trials (Bell 2005, Chen 2009, Kirpalani 2006)[51-53] 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 I^2 = 0%
LEVEL II EVIDENCE									
Bassler 2008[50] Level I/II *Good*	1 trial (Brooks 1999)[54] 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 = 0.88[c] I^2 = 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

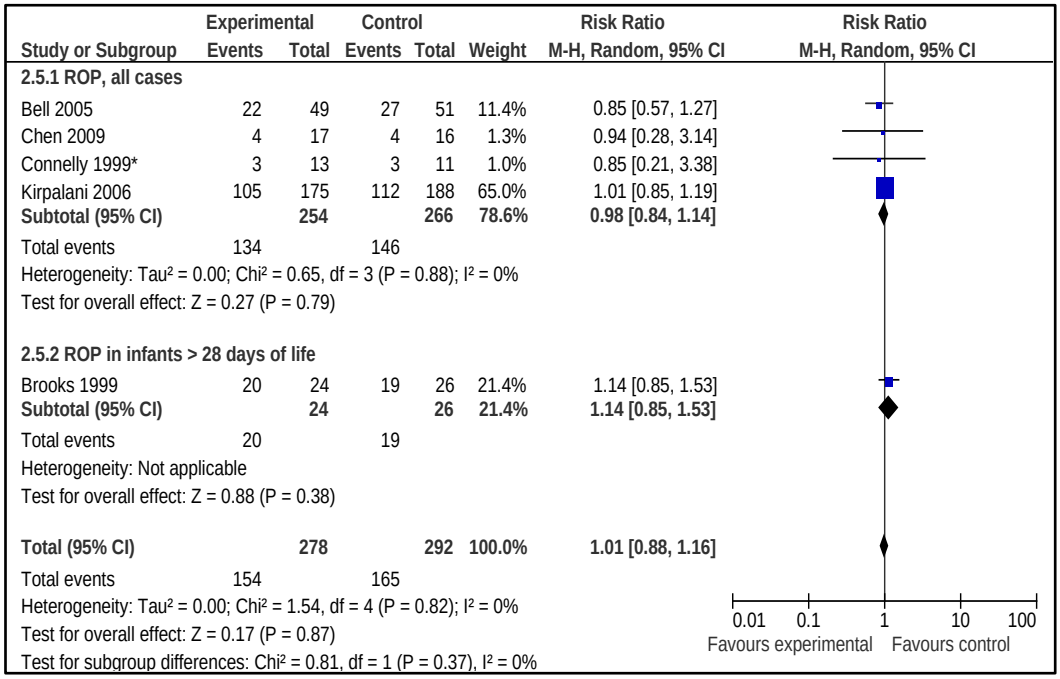


Figure 3.1.8 Meta-analysis: restrictive RBC transfusion versus liberal RBC transfusion in preterm infants – severe morbidity (ROP – by stage)

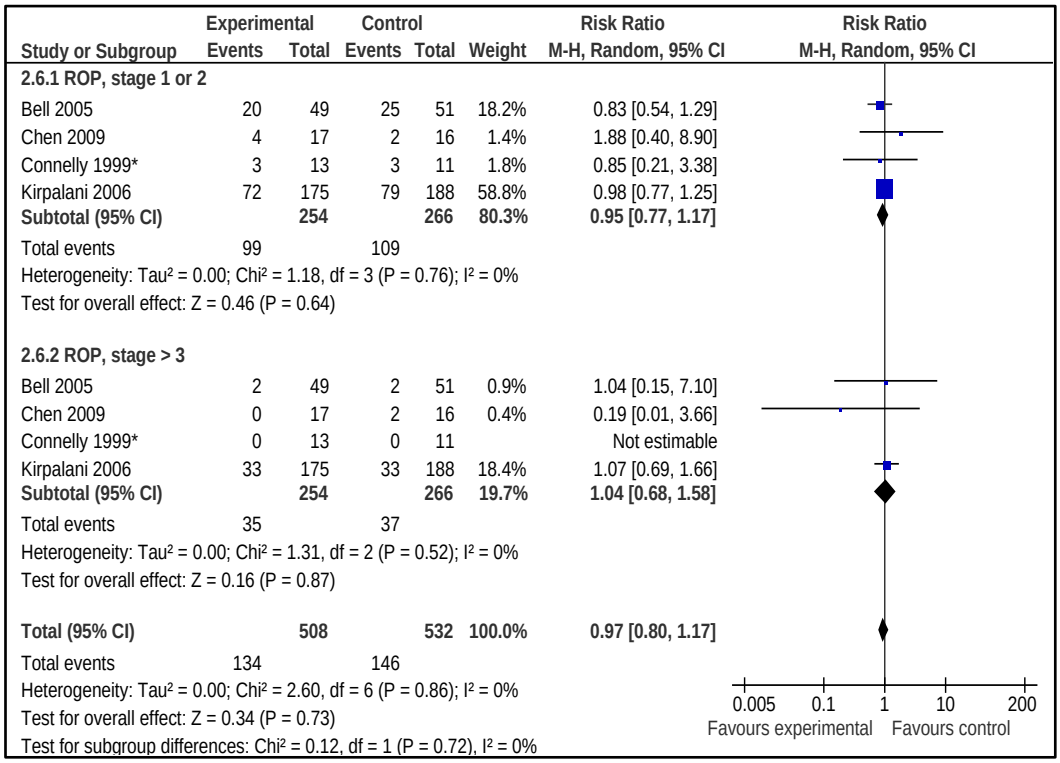


Table 3.1.13 Preterm infants: Results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (ROP)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Ibrahim 2014[47] Level I *Good*	3 trials (Bell 2005, Chen 2009, Kirpalani 2006)[51-53] 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 I^2 = 0%
Whyte 2011[49] Level I *Good*	4 trials[c] (Bell 2005, Chen 2009, Connelly 1998, Kirpalani 2006)[51-53; 57] 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 I^2 = 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 I^2 = 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 I^2 = 0%
LEVEL II EVIDENCE									
Bassler 2008[50] Level I/II *Good*	1 trial (Brooks 1999)[54] 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 = 0.87[f] I^2 = NA
Brooks 1999[54] 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 = 0.20[d]
					751–1000 g	9/11 (81.8%)	10/13 (76.9%)	RR 1.06 [0.71, 1.60][d]	*No significant difference* p = 0.77[d]
					1001–1250 g	4/7 (57.1%)	6/8 (75.0%)	RR 0.76 [0.36, 1.62][d]	*No significant difference* p = 0.48[d]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

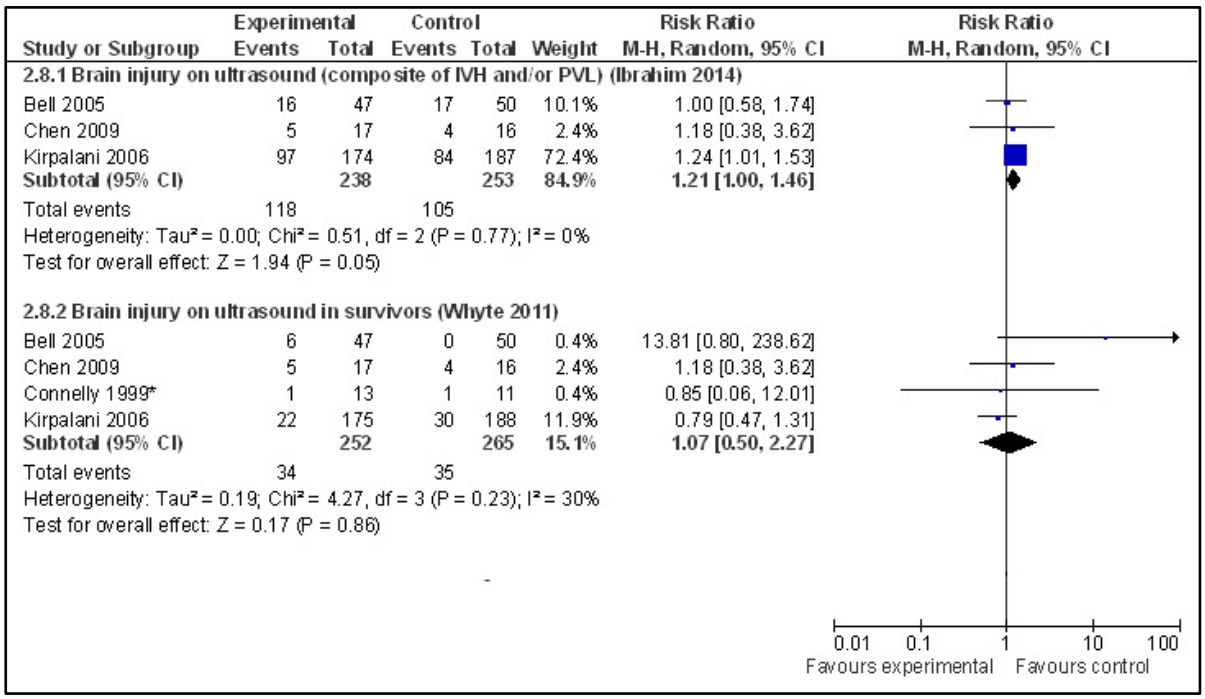


Table 3.1.14 Preterm infants: results for restrictive RBC transfusion versus liberal RBC transfusion – Severe morbidity (brain injury on ultrasound)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Ibrahim 2014[47] Level I *Good*	3 trials (Bell 2005, Chen 2009, Kirpalani 2006)[51-53] 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 I^2 = 0%
Whyte 2011[49] Level I *Good*	4 trials[c] (Bell 2005, Chen 2009, Connelly 1998; Kirpalani 2006)[51-53; 57] 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 I^2 = 30%
LEVEL II EVIDENCE									
Bell 2005[51] 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 2009[52] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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,[i] 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[j] (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 automatised 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).

[i] Defined as Mental Developmental Index (MDI) <70 and >2 SDs below age norm.
[j] Defined as MDI <85 and >1 SD below age norm.

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Whyte 2011[49] Level I/II *Good*	1 trial (Whyte 2009)[59] 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
					MDI <85 (>1 SD below age norm)	*Post-hoc analysis*			
						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

Study Level of evidence[a] *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 Heterogeneity[b]
McCoy 2011[d 58] 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 = 0.047[e]
					VCI	93.85 ± 26.0 (n=33)	104.78 ± 15.7 (n=23)	0.238 [NR]	*No significant difference* p = 0.078[e]
					PRI	91.67 ± 18.1 (n=33)	99.70 ± 15.5 (n=23)	0.229 [NR]	*No significant difference* p = 0.089[e]
					WRAT-III (reading ability)	93.94 ± 15.0	105.83 ± 10.2 (23)	0.410 [NR]	*Favours restrictive RBC transfusion* p = 0.002[e]
					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 = 0.003[f]
					RAN	0.08 ± 1.70 (n=33)	0.59 ± 1.02 (n=23)	0.189 [NR]	*No significant difference* p = 0.167[f]
					JOL (visual spatial reasoning)	–1.06 ± 1.54 (n=33)	–0.81 ± 1.23 (n=23)	0.091 [NR]	*No significant difference* p = 0.593[g]
					GPB (fine motor coordination)	–0.75 ± 2.00 (n=33)	–0.24 ± 0.97 (n=23)	0.152 [NR]	*No significant difference* p = 0.152[g]
					Bender-II (visual-motor integration)	0.12 ± 1.19 (n=33)	0.75 ± 0.90 (n=23)	0.279 [NR]	*No significant difference* p = 0.037[g]
					Visual memory	–3.05 ± 1.75 (n=33)	–1.95 ± 1.38 (n=23)	0.324 [NR]	*Favours restrictive RBC transfusion* p = 0.015[f]
					Verbal memory	–1.41 ± 1.42 (n=33)	–0.92 ± 0.96 (n=23)	0.192 [NR]	*No significant difference* p = 0.157[f]

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 automatised 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 $r=\sqrt{[t2/(t2+df)]}$. P <0.01 was considered statistically significant.
f. Effect sizes (r) were calculated by $r=\sqrt{[t2/(t2+df)]}$. P <0.025 was considered statistically significant.
g. Effect sizes (r) were calculated by $r=\sqrt{[t2/(t2+df)]}$. 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, TAGVHD, 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 evidence**[a] ***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** **Heterogeneity**[b]
LEVEL II EVIDENCE									
Bell 2005[51] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.1.4 Infants, children and adolescents

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

Recommendation – infants, children and adolescents (RBC transfusion)	
R1 (Grade C)	In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a, b, c] [a] See PP6 for guidance on a restrictive transfusion strategy. [b] Higher Hb thresholds are appropriate in very low birth weight and preterm neonates. [c] See PP2,PP3 and Appendix F 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: • age-specific Hb reference ranges • volume of transfusion and rate of administration • patient monitoring during and after transfusion • transfusion technique (e.g. use of syringe pumps) • recognition and reporting of adverse events.
PP6	In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[a] suggests that, with a: • Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where

	other specific therapy is available. • Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. • Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate. [a] See PP3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[15]
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 G (*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.*[16]
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	

3.1.4.1 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.

3.1.4.2 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.

3.1.5 Neonatal and paediatric patients with sickle cell disease

Evidence statements – sickle cell disease (RBC transfusion)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES1.14	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
ES1.15	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	√√	√√
ES1.16	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
ES1.17	In children and adolescents with sickle cell anaemia or sickle beta thalassemia who have been assessed to be at increased risk of stroke,[a] ongoing prophylactic RBC transfusion compared with no RBC transfusion (or cessation of RBC transfusions) reduces stroke occurrence. (See evidence matrix D1.K in Volume 2 of the technical report.)	√√	√√√	√√√	√√√	√√
ES1.18	In neonatal and paediatric patients with sickle cell disease, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is unknown.	NA	NA	NA	NA	NA
ES1.19	In neonatal and paediatric patients with 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 as assessed by transcranial Doppler ultrasonography[12] or MRI[13].

Recommendation – sickle cell disease (RBC transfusion)	
R2 (Grade A)	In children and adolescents with sickle cell disease who have been assessed to be at increased risk of stroke.[a] a program of prophylactic RBC transfusions should be used in order to reduce stroke occurrence.[b] [a] Assessed by transcranial Doppler ultrasonography[12] and MRI.[13] [b] See PP11 for methods of assessment.
Practice points – sickle cell disease (RBC transfusion)	
PP7	In paediatric patients with beta thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90–100 g/L.[a]

	[a] See PP23 in *Patient Blood Management Guidelines: Module 3 – Medical.*[14]
PP11	Children and adolescents with sickle cell disease should be assessed for stroke risk using both transcranial Doppler ultrasonography[12] and MRI.[13]
MRI, magnetic resonance imaging; PP, practice point; R, recommendation; RBC, red blood cell	

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.

3.1.5.1 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)[60]	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)[61]	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**).[k] 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.

[k] Note: The Phase III TWiTCH trial did not meet the inclusion criteria for our review as it is a non-inferiority trial comparing RBC transfusion to hydroxyurea in paediatric patients with sickle cell disease. The study 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.

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)[62] 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)[63] *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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Wang 2013[61] 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)[62] 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 2014[13] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[l] 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[m] compared with three patients (3.1%) in the standard care group. Adding these transient ischaemic attack 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.

[l] As determined by neuroimaging, clinical evidence of permanent neurologic injury or both.

[m] 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.

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Wang 2013[61] 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 1998[62] 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 = 0.03[c]
					Intracerebral haematoma	0/63 (0%)	1/67 (1.5%)	RR 0.35 [0.01, 8.54][c]	*No significant difference* p = 0.52
Pegelow 2001[63] Level II *Poor* *follow-up of Adams 1998	N=124	Children (2–16 years) with HbSS or Sβ^0 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 = 0.02[c]
					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 = 0.23[c]
					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 = 0.08[c]
Cherry 2012[60] Level I/II *Good*	1 trial (Adams 2005)[62] 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 = 0.32[c] p = 0.31[e]
					Reversion to abnormal TCD	0/38 (0%)	14/41 (34.1%)	RR 0.04 [0.00, 0.60][c]	*Favours continued RBC transfusion* p = 0.02[c] p = 0.01[e]
					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 = 0.02[c] p < 0.001[e]
Debaun 2014[13] Level II	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 = 0.04[f]

Study **Level of evidence**[a] ***Quality*** *Fair*	**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** **Heterogeneity**[b]
					TIA	0/99 (0%)	3/97 (3.1%)	RR 0.14 [0.01, 2.67][c]	*No significant difference* p = 0.19[c]
					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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[n]

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, TAGVHD, 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.

[n] 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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Cherry 2012[60] 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)[62] 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 2014[13] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

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

3.1.5.2 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.

3.1.6 Neonatal and paediatric patients with cancer

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

Practice points – anaemia associated with cancer (RBC transfusion)	
PP5	For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes the following: • age-specific Hb reference ranges • volume of transfusion and rate of administration • patient monitoring during and after transfusion • transfusion technique (e.g. use of syringe pumps) • recognition and reporting of adverse events.
PP6	In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[a] suggests that, with a: • Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. • Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate. [a] See PP3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[15]

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 G (*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*.[16]
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.

3.1.6.1 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)[64]	Retrospective longitudinal *Poor*	Children (aged <15 years) diagnosed with acute lymphoblastic leukaemia N=108	Transfusion of >5 units leukoreduced[a] 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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE										
Jaime-Perez 2011[64] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Leukoreduced RBCs are not available in Australia.

Secondary outcomes[o]

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, TAGVHD 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.

3.1.6.2 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.

[o] 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.

3.1.7 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**
ES1.23	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
ES1.24	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
ES1.25	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
ES1.26	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.

3.1.7.1 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 packed cell volume (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)[65]	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)[66]	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)[67]	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)[68]	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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Meremikwu 2000[65] Level I *Good*	2 trials (Bojang 1997, Holzer 1993)[66-67] 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 I^2 = 0%
LEVEL II EVIDENCE									
Olupot-Olupot 2014[68] 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 = 0.15[c] p = 0.12[d]
					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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

d. p-value reported by study authors using Fisher's Exact test.

Secondary outcomes[p]

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, TAGVHD, 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.

[p] 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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Olupot-Olupot 2014[68] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.1.7.2 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.

3.1.8 Neonatal and paediatric patients requiring surgery

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

Recommendation – surgical (RBC transfusion)	
R1 (Grade C)	In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a, b, c] [a] See PP6 for guidance on a restrictive transfusion strategy. [b] Higher Hb thresholds are appropriate in very low birth weight and preterm neonates. [c] See PP2,PP3 and Appendix F 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: • age-specific Hb reference ranges • volume of transfusion and rate of administration • patient monitoring during and after transfusion • transfusion technique (e.g. use of syringe pumps) • recognition and reporting of adverse events.
PP6	In haemodynamically stable paediatric patients (excluding neonates), evidence from other patient groups and CRG consensus[a] suggests that, with a: • Hb concentration <70 g/L, RBC transfusion is often appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Hb concentration of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. • Hb concentration >90 g/L, RBC transfusion is often unnecessary and may be inappropriate. [a] See PP3 in *Patient Blood Management Guidelines: Module 4 – Critical Care*.[15]
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 G (*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*.[16]
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.

3.1.8.1 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)[69] 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)[70] 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)[71] 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)[72]	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)[70]	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)[71]	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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Kneyber 2013[72] 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 = 0.15[c] p = 0.163[d]
						Subgroup analysis: patients with normal physiology post-surgery.			
					In PICU mortality	0/66 (0%)	0/205 (0%)	Not estimable	NA
Nacoti 2012[70] 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 2013[71] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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).

3.1.8.2 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 patients undergoing 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)[73]	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)[74]	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)[75] *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)[76] *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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Wilkinson 2014[73] Level I/II *Good*	1 trial (Cholette 2011)[74] 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 I^2 = NA
	1 trial (Willems 2010)[76] 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 I^2 = NA
Rouette 2010[75] 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 2010[76] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 paediatric logistic organ dysfunction (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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Rouette 2010[75] 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 = 0.91[c]
					age ≥1 year	3/46 (6.5%)	5/50 (10.0%)	RR 0.65 [0.17, 2.58][c]	*No significant difference* p = 0.54[c]
					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 2010[76] 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

Study Level of evidence[a] *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 Heterogeneity[b]**
					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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[q]

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, TAGVHD 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.

[q] 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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Willems 2010[76] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.1.9 Critically ill neonatal and paediatric patients

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

Recommendation – critically ill (RBC transfusion)	
R1 (Grade C)	In paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.[a, b, c] [a] See PP6 for guidance on a restrictive transfusion strategy. [b] Higher Hb thresholds are appropriate in very low birth weight and preterm neonates. [c] See PP2, PP3 and Appendix F for guidance for preterm neonates.
Practice points – critically ill (RBC transfusion)	
PP12	In neonatal and paediatric patients with critical bleeding requiring massive transfusion, use a critical bleeding protocol.[a] A template protocol is provided within the module.[b] [a] The use of the word 'protocol' is not strictly prescriptive. [b] The template given in Appendix K (*Critical bleeding protocol*) is intended for local adaptation.
CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; 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.

3.1.9.1 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)[77] 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)[78] 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)[79] 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 2014[77]	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 2014[78]	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 2014[79]	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 2007[69]	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).[r] 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.

[r] Multivariate analysis using logistic regression adjusted for GCD score, age category, gender and ISS.

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 versus 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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Acker 2014[77] 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 < 0.0001[c]
						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 2014[78] 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 2014[79] 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	Mortality	13/56 (23.2%)	3/16 (18.8%) / 1/9 (11.1%)	NR	*No significant difference*

Study Level of evidence[a] *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 Heterogeneity[b]
				dose 1 versus 2 versus >3 RBC transfusions					p = 0.84
Kneyber 2007[69] 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 versus 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 versus no RBC transfusion	0/12 (0%)	6/228 (2.6%)	RR 1.36 [0.08, 22.77][c]	
					3 RBC transfusions versus no RBC transfusion	1/5 (20%)	6/228 (2.6%)	RR 7.60 [1.11, 51.98][c]	
					4 RBC transfusions versus no RBC transfusion	1/4 (25%)	6/228 (2.6%)	RR 9.50 [1.46, 61.76][c]	
					> 4 RBC transfusions versus no RBC	5/7 (71.4%)	6/228 (2.6%)	RR 27.14 [10.84,	

Study Level of evidence[a] *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 Heterogeneity[b]
					transfusion			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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

Secondary outcomes[s]

Transfusion-related serious adverse events (TACO, TRALI, other[t]*)*

One Level III–2 study (Hassan 2014) reported transfusion-related SAEs (TACO, TRALI, haemolytic transfusion reactions, transfusion transmitted infections, TAGVHD, 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.

[s] 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.

[t] Other includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, and anaphylactic reactions.

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 evidence[a]** ***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** **Heterogeneity[b]**
LEVEL III EVIDENCE									
Hassan 2014[79] 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
					Haemolysis[d]	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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

d. Not specified if this was transfusion-related.

3.1.9.2 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)[80]	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)[81]	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)[82] 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 MODS[a] 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 evidence[a] 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 Heterogeneity[b]
LEVEL II EVIDENCE									
Lacroix 2007[82] 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 = 0.87[d]
						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

Study Level of evidence[a] 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 Heterogeneity[b]
Desjardins 2012[81] Level I/II *Good*	1 trial (Lacroix 2007)[82] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Carson 2012[80] Level I/II *Good*	1 trial (Lacroix 2007)[82] 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 2012[81] Level I/II *Good*	1 trial (Lacroix 2007)[82] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Secondary outcomes[u]

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, TAGVHD, 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%).

u 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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Lacroix 2007[82] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.2 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 chronic kidney disease, ESA therapy to achieve a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient.[a, b, c] [a] See R4 in *Patient Blood Management Guidelines: Module 3 – Medical.*[14] [b] The KDIGO guidelines[83] recommend a Hb target of 110–120 g/L for paediatric patients and state that individualisation of ESA therapy is reasonable because some patients may have improvements in quality of life at higher Hb concentration. [c] The NICE guidelines[84] 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 chronic kidney disease, ESA therapy to achieve a Hb target of >130 g/L is not recommended because of increased morbidity; therefore, it is sensible to apply this limit to paediatric patients.[a] [a] See R6 in *Patient Blood Management Guidelines: Module 3 – Medical*.[14]
PP20	ESA use is less effective in patients with chronic kidney disease 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.
PP23	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*.[15]

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 iron deficiency anaemia, preoperative iron therapy is recommended.[a] [a] See R4 in *Patient Blood Management Guidelines: Module 2 – Perioperative*.[16]
Practice point – oral and/or parenteral iron	
PP13	Preterm and low birth weight infants should receive iron supplementation as necessary to achieve the recommended nutrient intake. However, routine supplementation in excess of the recommended nutrient intake, to reduce transfusion incidence, is not supported.
PP14	Infants and children should receive sufficient dietary iron to achieve the adequate intake or recommended daily intake. If the adequate intake or recommended daily intake cannot be met by dietary means, iron supplementation is advised.
PP15	*Infants and children in populations at high risk[a] 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 Sections 3.6 and 4.5 in Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics*.
PP16	Infants and children with iron deficiency should be treated with iron supplements and dietary modifications.
PP24	In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiency[a] 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.
PP25	To implement PP24, 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 recommended nutrient intake.

Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell

Recommendation – sickle cell disease (hydroxyurea)	
R4 (Grade B)	In paediatric patients with sickle cell disease, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.[a, b] [a] Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke. [b] See R1 and PP21.
Practice point – sickle cell disease (hydroxyurea)	
PP22	In paediatric patients over 9 months of age with sickle cell disease, hydroxyurea should be offered to reduce vaso-occlusive pain crises and acute chest syndromes.
PP, practice point; R, recommendation	

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 chronic kidney disease
- effect of hydroxyurea on stroke prevention (clinical and subclinical) in paediatric patients with sickle cell disease.[a]

a. The Phase III TWiTCH trial did not meet our inclusion criteria as it was a non-inferiorty trial comparing RBC transfusion to hydroxyurea in paediatric patients with sickle cell disease. The trial 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.

3.2.1 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.

3.2.2 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.

3.2.3 Preterm and low birth weight infants

3.2.3.1 ESAs (with or without iron)

Evidence statements – preterm and low birth weight infants (ESAs with or without iron)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.1	In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion incidence. (See evidence matrix D2.A in Volume 2 of the technical report.)	√√√	√	√√	√√	√√√
ES2.2	In preterm infants with RhHDFN, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain. (See evidence matrix D2.B in Volume 2 of the technical report.)	√	NA	√√	√√	√
ES2.3	In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion volume. (See evidence matrix D2.C in Volume 2 of the technical report.)	√√√	√	√√	√√√	√√√
ES2.4	In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES2.5	In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on ROP is uncertain. (See evidence matrix D2.D in Volume 2 of the technical report.)	√	√√	NA	√√	√√
ES2.6	In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on BPD is uncertain. (See evidence matrix D2.E in Volume 2 of the technical report.)	√	√√√	NA	√√	√√
ES2.7	In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on NEC is uncertain. (See evidence matrix D2.F in Volume 2 of the technical report.)	√	√√√	NA	√√	√√
ES2.8	In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on mortality is uncertain. (See evidence matrix D2.G in Volume 2 of the technical report.)	√	√√√	NA	√√	√√

Evidence statements – preterm and low birth weight infants (ESAs with or without iron)	**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
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 with or without iron)	
R3 (Grade C)	In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised.
ESA, erythropoiesis stimulating agent; R, recommendation	

Background

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 outcomes[a]
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 outcomes[a]
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).[v] 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.**

[v] 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]

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	Level II	Preterm infants (≥25 and	rHuEPO (3000 IU/kg, iv	Mortality

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
(2008)[100]	*Low risk of bias*	<32 weeks gestational age) N=45	3–6, 12–18 and 36–42 hours after birth) versus placebo (iv saline) *Use of iron not mentioned *Transfusion guidelines were not provided	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 (9 mg/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	rHuEPO (250 IU/kg, iv or sc tiw) from day 3 of life for 9 weeks versus	Transfusion incidence Mortality

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		N=219	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	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	rHuEPO (200 IU/kg/day, iv qd) for 14 days versus placebo (iv) *All infants received iron	Transfusion incidence and volume Mortality ROP

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		N=28	dextran (1 mg/kg/day) in TPN solution *Transfusion guidelines were in place	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)	rHuEPO (200 IU/kg sc tiw) for 4 weeks versus control (isotonic saline)	Transfusion incidence

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		N=60	*All infants received oral iron (3 mg/kg/day) *Transfusion guidelines were in place	
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	Level II	Preterm infants (>28 and	rHuEPO (500 IU/kg/day,	Transfusion incidence

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
(2008)[121]	*Poor*	<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	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	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	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	Transfusion incidence Mortality Laboratory measures (change in Hb values)

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		N= 29	mg/day if serum concentration fell below 16 µmol/L *Transfusions guidelines were in place	
Bierer (2009)[94]	Level II *Low risk of bias*	Infants with a disease requiring major surgery[a] *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	Transfusion incidence Mortality

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
			in place *Data from rHuEPO groups combined for analysis	
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 10 mg/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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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*	Preterm infants (<31 weeks gestational age) with VLBW	rHuEPO (300 IU/kg/day, iv e3d) versus rHuEPO (300 IU/kg/day, iv e3d) +	Mortality ROP

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
	of bias	(<1300 g) aged >7 days N=38	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	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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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),[w] and in 28 of the 30 RCTs included in Aher (2014),[x] 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.

[w] Not used or not clear in four RCTs (Chang 1998, Fauchere 2008, He 2008, Yasmeen 2012).
[x] Not used or not clear in two RCTs (Akisu 2001, Shannon 2001).

Level II evidence

The literature search and hand-searching process identified four additional Level II studies[150-153] 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 (I^2=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 (I^2=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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 I^2 = 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 I^2 = 0%
					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*	*Subgroup analysis: dosing*			
				High-dose rHuEPO (>500 IU/kg/week) + high or low-dose iron		*335/629 (55.8%)*	*417/599 (69.9%)*	*RR 0.79 [0.73, 0.85]*	*Favours early rHuEPO + iron* p < *0.00001* Substantial heterogeneity I^2 = 81%

Study Level of evidence[a] *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 Heterogeneity[b]
				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 2014[87] Level I *Good*	20 trials[c] (Akisu 2001, Atasay 2002, Bader 1996, Bechensteen 1993, Corona 1998, Donato 1996, Emmerson 1993, Javier Manchon	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,	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			

Study Level of evidence[a] *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 Heterogeneity[b]
	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		UK, USA		*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 I^2 = *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 I^2 = *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 I^2 = *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 I^2 = *0%*
						Subgroup analysis: dosing			
				High-dose rHuEPO (>500 IU/kg/week) + high or low-dose iron	14 trials[c] (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 I^2 = 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 I^2 = *79%*

Study Level of evidence[a] *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 Heterogeneity[b]
				High-dose rHuEPO (>500 IU/kg/week) + low-dose iron (≤5 mg/kg/day)	*8 trials[c] (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 I^2 = *58%*
				Low-dose rHuEPO (≤500 IU/kg/week) + high or low-dose iron	*7 trials[c] (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 I^2 = *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 I^2 = *0%*
				Low-dose rHuEPO (≤500 IU/kg/week) + low-dose iron (≤5 mg/kg/day)	*4 trials[c] (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 I^2 = *76%*
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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
Kremenopoulo	N=85	Preterm infants	Greece	rHuEPO + oral iron	Transfusion				

Study Level of evidence[a] *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 Heterogeneity[b]
s 1997[152] Level II *Poor*		(≤31 weeks gestation) with VLBW (≤1500 g)		versus oral iron *Group A (rHuEPO750) initiation of rHuEPO 3–7 days after birth *Group B (rHuEPO600) initiation of rHuEPO >3 weeks after birth	incidence *Group A	16/24 (66.67%)	23/26 (88.46%)	RR 0.75 [0.55, 1.03][d]	*No significant difference* p = 0.08[d]
					*Group B	4/20 (20%)	13/15 (87%)	RR 0.23 [0.09, 0.57][d]	*Favours late rHuEPO + iron* p = 0.001[d]
						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 complications[e]	14/14 (100%)	14/14 (100%)	RR 1.00 [0.88, 1.14][d]	No significant difference p = 1.00[d]
Ohls 2004[f113] 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 2001[g91] 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 = 0.03[d]
Rocha 2001[h147] 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 *Group 1 *Group 2	1/15 (6.7%) 3/14 (21.4%)	5/13 (38.5%)	NR	*Favours late rHuEPO + iron* p = 0.043[i]
BRONCHOPULMONARY DYSPLASIA									
Garcia 2002[i88] 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 = 0.03[d]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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).

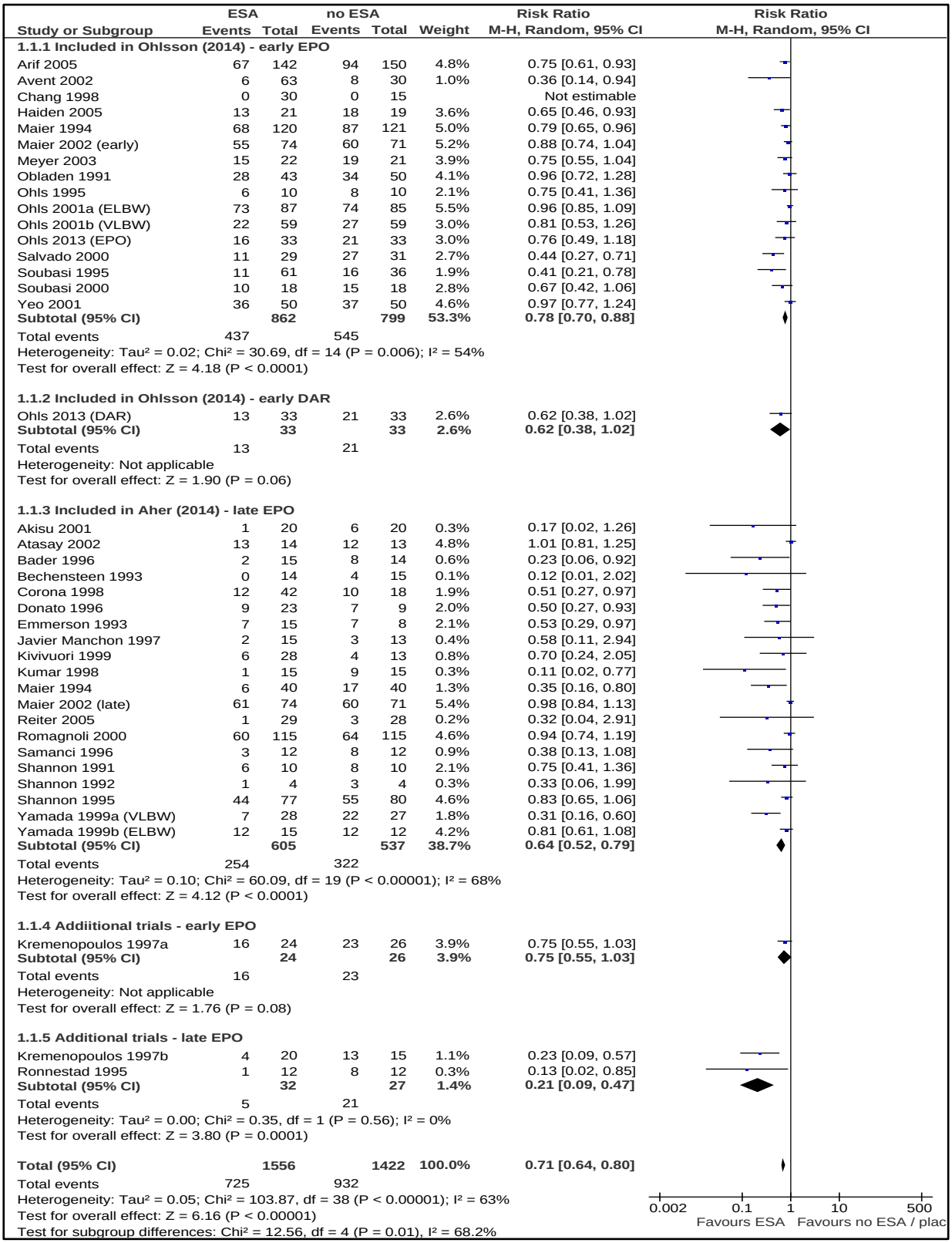
g. Vamvakas et al (2001) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher et al (2014) or Ohlsson et al (2014) are presented here.

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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I *Good*	13 trials[c] (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 I^2 = 64%
Aher 2014[87] Level I *Good*	11 trials[d] (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 = 0.0075[e] Substantial heterogeneity I^2 = 94%

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I/II *Good*	1 trials[c] (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 2008[121] 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 1997[152] Level II	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–	Mean number of RBC transfusions per infant *Group A (n=50)	NR	NR	NR	NR

Study Level of evidence[a] *Quality* *Poor*	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention versus comparator 7 days after birth *Group B (EPO600) initiation of rHuEPO >3 weeks after birth	Outcome	Results ESAs ± iron Mean ± SD Median (range)	Placebo ± iron Mean ± SD Median (range)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					*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 = 0.0003[f]
						Secondary analysis (Group A only): complications (mechanical ventilation, sepsis)			
					Infants without complications	0.2 ± 0.4	1 ± 0.7	MD –0.80 [–1.27, –0.33][f]	Favours early rHuEPO + iron p = 0.0008[f]
					Infants with complications[g]	5 ± 2.5	4.9 ± 2.4	MD 0.10 [–1.72, 1.92][f]	No significant difference p = 0.91[f]
Aher 2014[87] 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 2001[h 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
						Subgroup analysis: weight			
					Infants 1000–1300g (N=36)	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 2001[i 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 = 0.091[j]
Jim 2000[151] 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

Study Level of evidence[a] *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 Heterogeneity[b]
BRONCHOPULMONARY DYSPLASIA									
Garcia 2002[k 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 < 0.00001[f]
RH HAEMOLYTIC DISEASE OF THE FETUS AND NEWBORN									
Ovali 1996[153] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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).

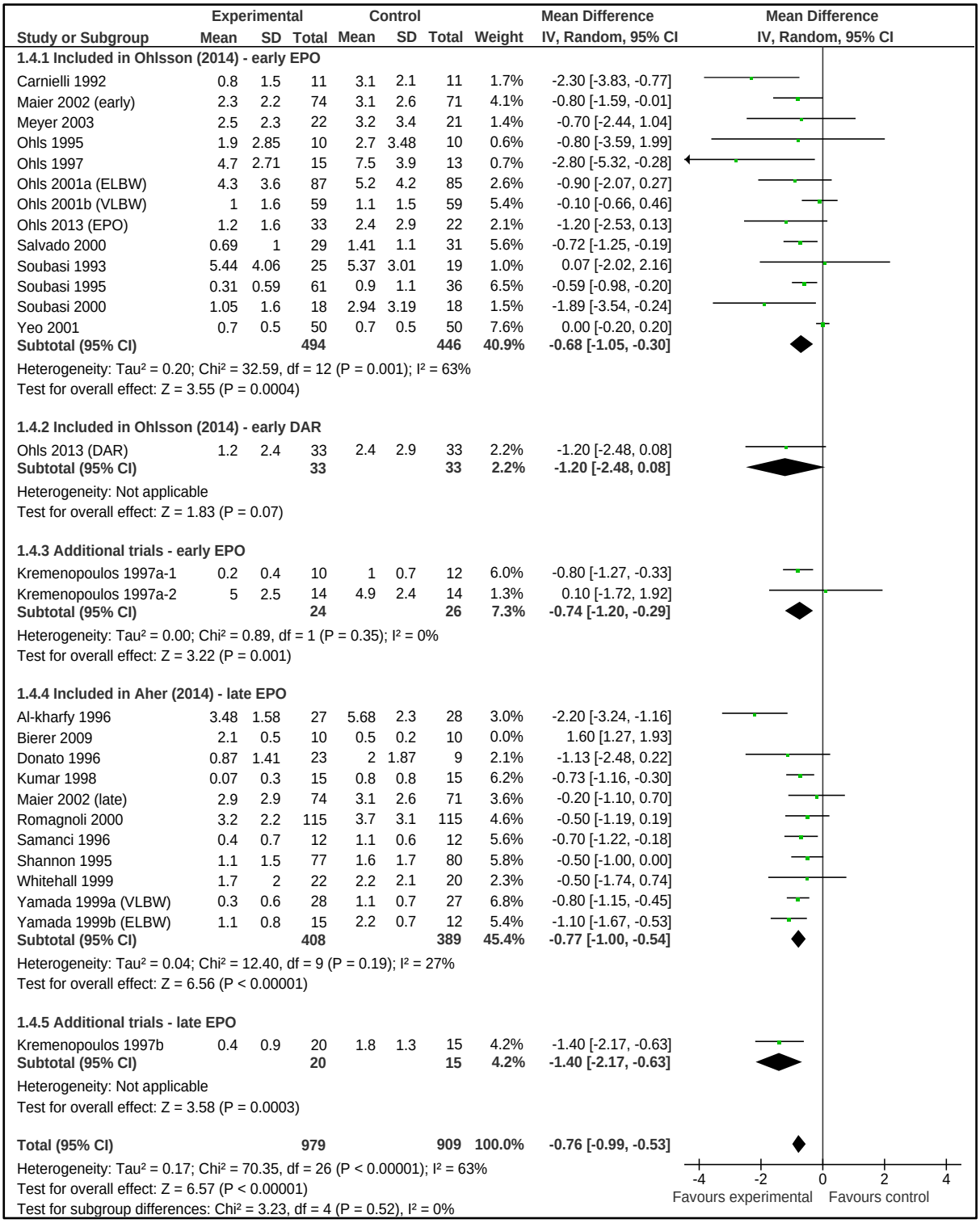
h. Vamvakas et al (2001) meta-analysed eight studies; however, only results of studies not identified or included in the meta-analysis by Aher et al (2014) or Ohlsson et al (2014) are presented here.

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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 I^2 = 63%
Aher 2014[87] Level I *Good*	5 trials[c] (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 I^2 = 92%
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I/II *Good*	1 trial[d] (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 = 0.009[e]
				Early rHuEPO (n=20) versus placebo (n=21)		20.1 [95% CI 6.2, 34.2]		MD 24.3 [NR]	*Favours early rHuEPO* p = 0.028[e]
	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 < 0.04[e,i]

Study Level of evidence[a] *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 Heterogeneity[b]
					*between 7 days of life and up to discharge	35.8 ± NR	94.2 ± NR	MD 58.4 [NR]	*Favours early rHuEPO + iron* p < 0.04[e]
	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 = 0.04[f]
	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 = 0.038[e]
	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 2014[87] 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 < 0.01[e]
Kotto-Kome 2004[89] 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

Study Level of evidence[a] *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 Heterogeneity[b]
Vamvakas 2001[91] 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)	NR	NR	MD 65.1 ± 10.9 (SE)	*Favours late rHuEPO + iron* p < 0.05
					*Infants <1000g (N=32)	NR	NR	MD 42.6 ± 7.9 (SE)	*Favours late rHuEPO + iron* p < 0.05
Khatami 2008[121] 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 2001[g 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) *Group 1 *Group 2	 4.6 ± NR 9.6 ± NR	 17.6 ± NR	 MD 13.0 [NR] MD 8.0 [NR]	*No significant difference* p = 0.156[h]
Juul 2003[149] 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 = 0.67[f]
						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 = 0.73[f]
						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

Study Level of evidence[a] *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 Heterogeneity[b]
Jim 2000[151] 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 1997[132] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2 = 83%).

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

e. p-value according the trial authors.

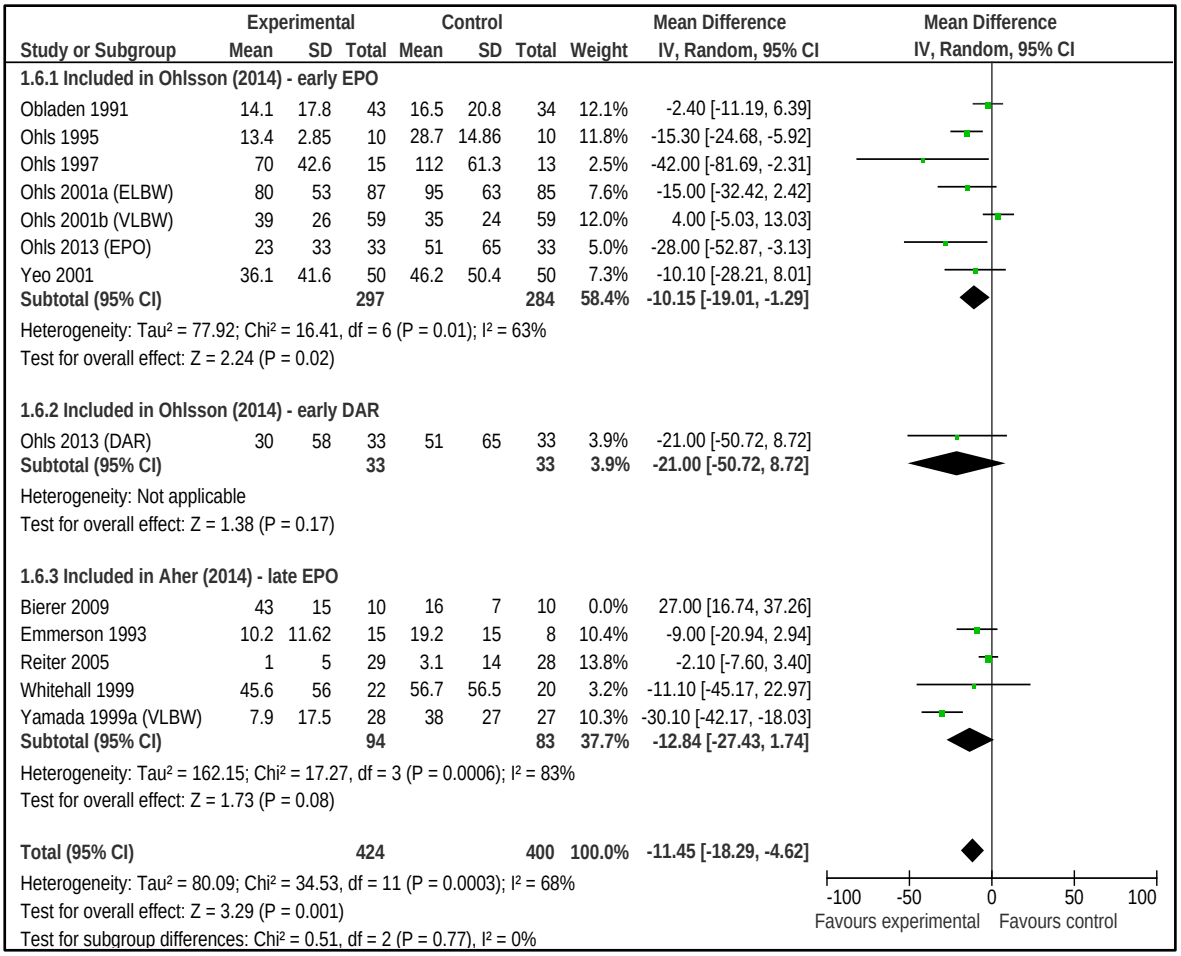
f. Calculated post-hoc using RevMan 5.1.2.

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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=0%).

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Xu 2014[92] Level I *Good*	11 studies[c] 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 I^2 = 82.9%
	5 RCTs[c] (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 I^2 = 55.4%
	4 RCTs[c] (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		high-dose rHuEPO or DAR (>500units/kg/week)	*Subgroup analysis: dosing*			
						456/996 (45.8%)	170/674 (25.2%)	OR 1.74 [0.84, 3.61]	*No significant difference* p = 0.14[d] Substantial heterogeneity I^2 = 87.7%
	2 RCTs[c] (Ohls 2013, Shannon 1995)[114; 139; 143]		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 = 0.50[d]

Study Level of evidence[a] *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 Heterogeneity[b]
	N=222								No significant heterogeneity I^2 = 0%
						Subgroup analysis: timing of administration			
	1 RCT[c] (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 = 0.13[d] Substantial heterogeneity I^2 = 90.5%
	2 RCTs[c] (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 = 0.40[d] Substantial heterogeneity I^2 = 86.1%
	9 studies[c] 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 I^2 = 63.8%
					Severe ROP (stage 3–4)	*Sensitivity analysis: RCTs only*			
	4 RCTs[c] (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 I^2 = 18.3%
						Subgroup analysis: dosing			
	4 RCTs[c] (Ohls 2013, Ohls 2001, Fauchere 2008, Romagnoli		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 = 0.52[d]

Study Level of evidence[a] *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 Heterogeneity[b]
	2000) [100; 112; 114; 139] 2 cohort studies (Figueras-Aloy 2010, Suk 2008)[156; 159] N=1607								Substantial heterogeneity I^2 = 75.6%
	1 RCT[c] (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 RCT[c] (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 = 0.74[d] Substantial heterogeneity I^2 = 86.8%
	1 RCT[c] (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 = 0.44[d] Substantial heterogeneity I^2 = 71.0%
Ohlsson 2014[90] Level I *Good*	8 trials[e] (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 I^2 = 0%
	7 trials[e] (Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Ohls 2001 (group a), Ohls 2001 (group b), Ohls 2013)[100-101; 105-106; 112; 114]		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 I^2 = 0%

Study Level of evidence[a] *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 Heterogeneity[b]
	N=801								
	10 trials[e] (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 I^2 = 0%
								RD 0.03 [0.00, 0.06],	p = 0.03 Moderate heterogeneity I^2 = 50% NNTH 33 [17–∞]
Aher 2014[87] Level I *Good*	3 trials[f] (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 I^2 = 83%
	3 trials[f] (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 I^2 = 18%
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

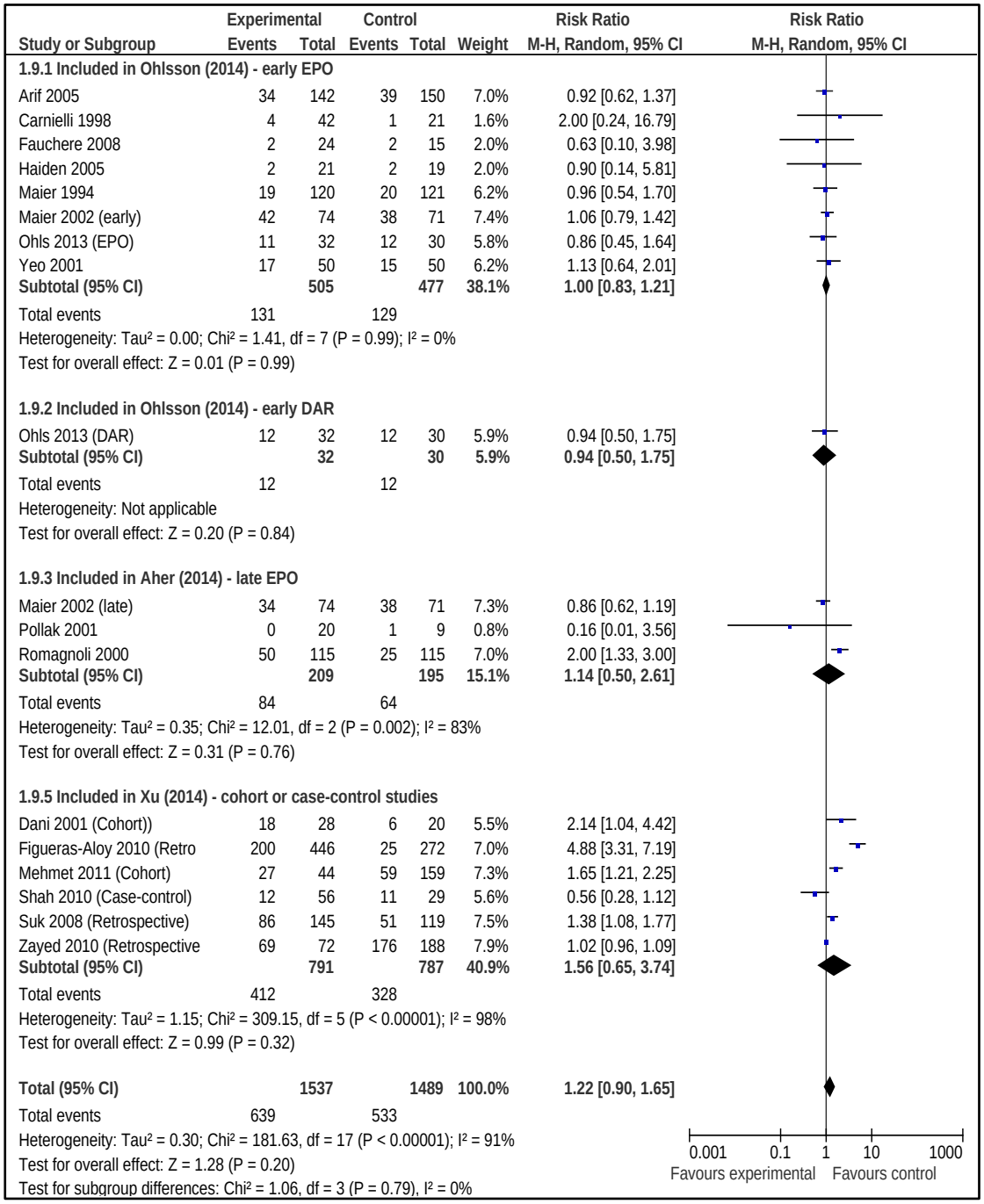


Figure 3.2.5 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – ROP (all stages or stage not reported – RCTs only)

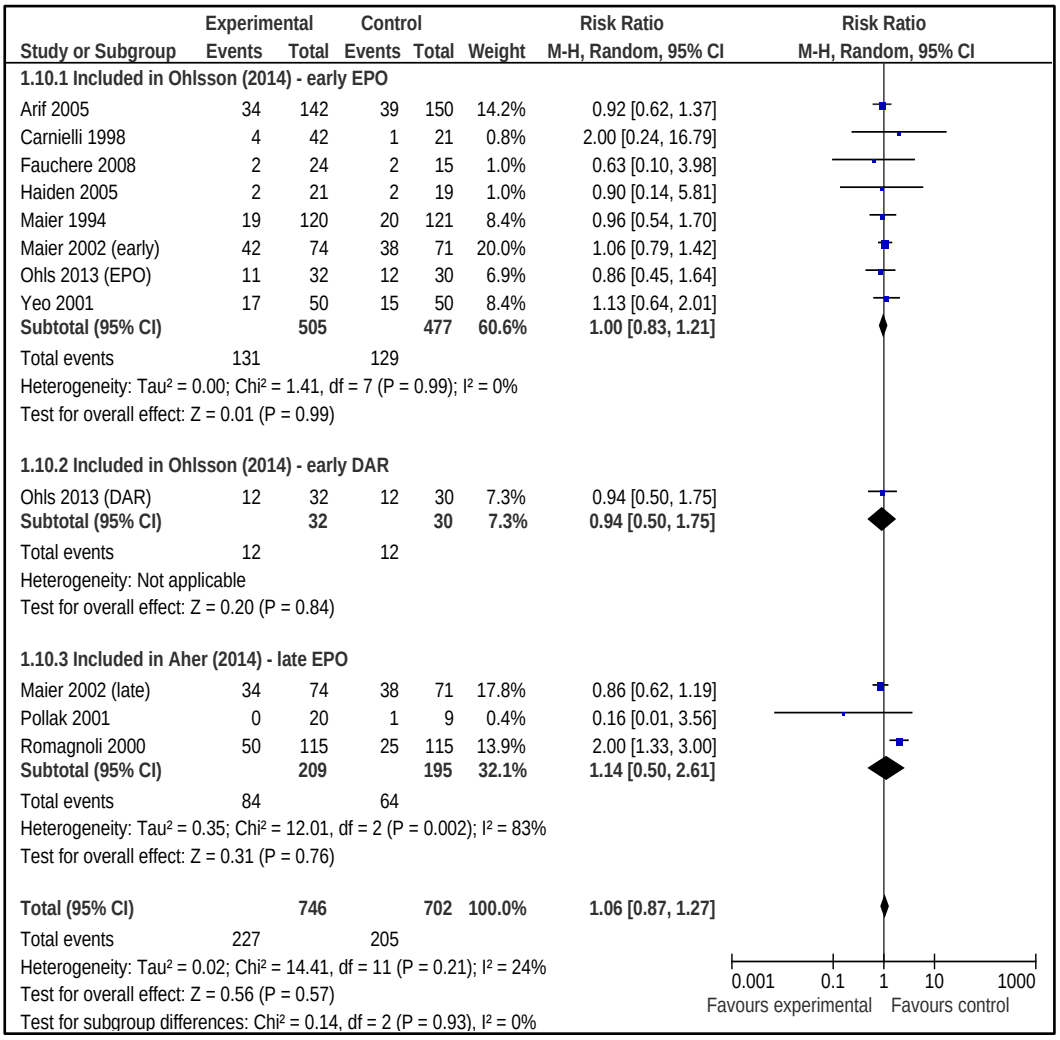


Figure 3.2.6 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – severe ROP (stage 3–4)

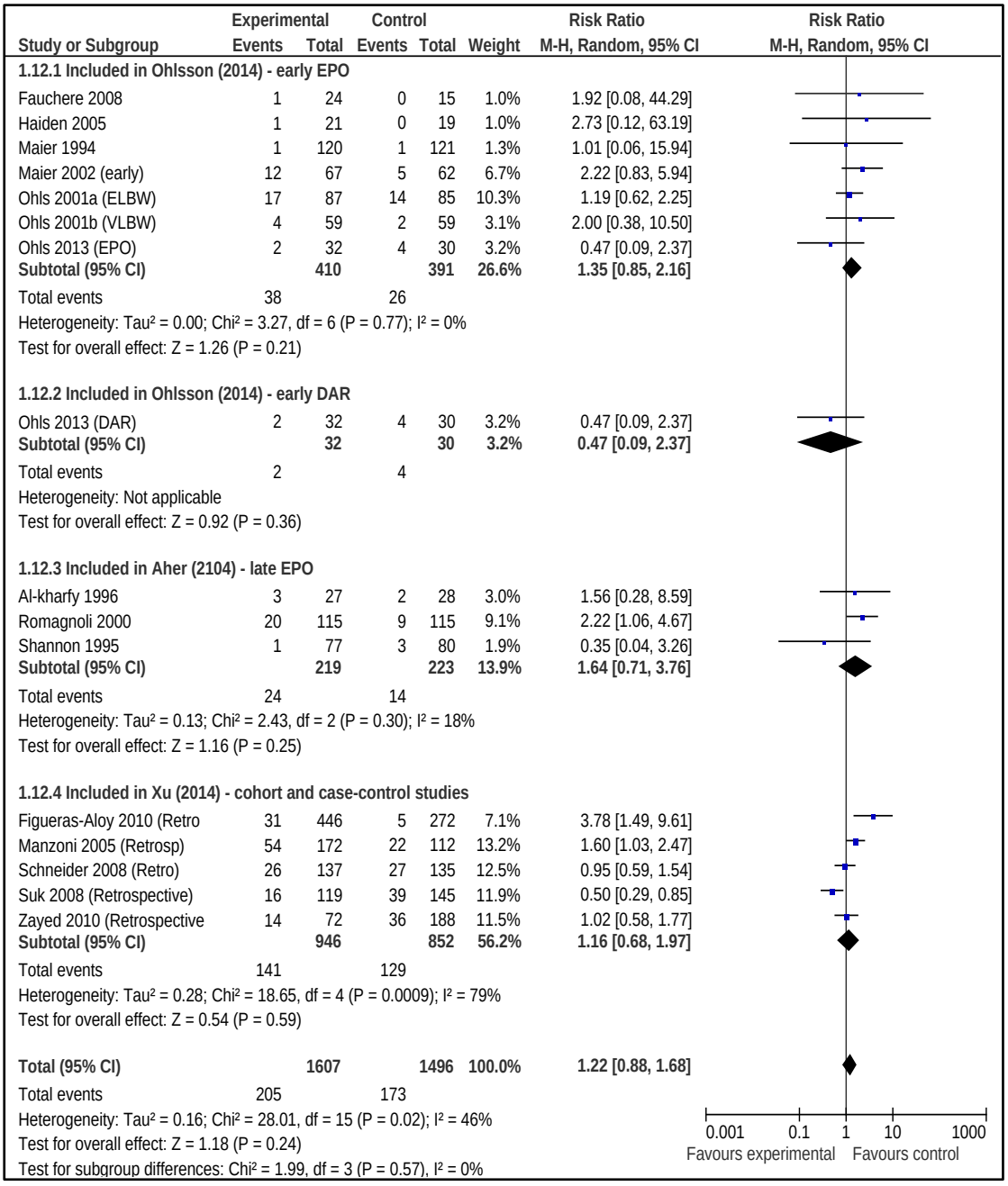
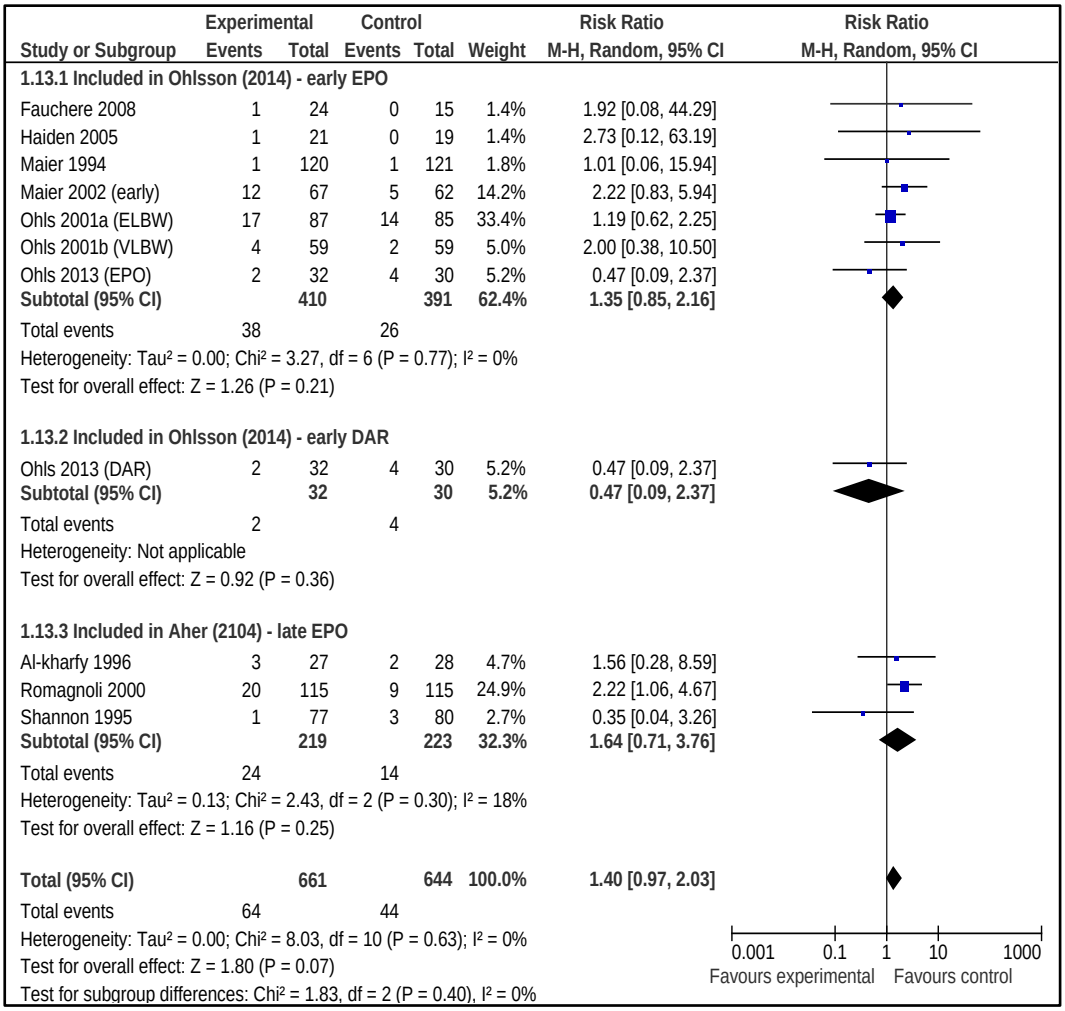


Figure 3.2.7 Meta-analysis of ESAs versus no ESAs (with or without iron) in preterm infants with anaemia of prematurity – severe ROP (stage 3–4 – RCTs only)



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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=0%) for this outcome.

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I *Good*	5 trials[c] (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 I^2 = 0%
	5 trials[d] (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 I^2 = 0%
Aher 2014[87] Level I *Good*	2 trials[e] (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 = 0.051[f] Substantial heterogeneity I^2 = 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 I^2 = 56%

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

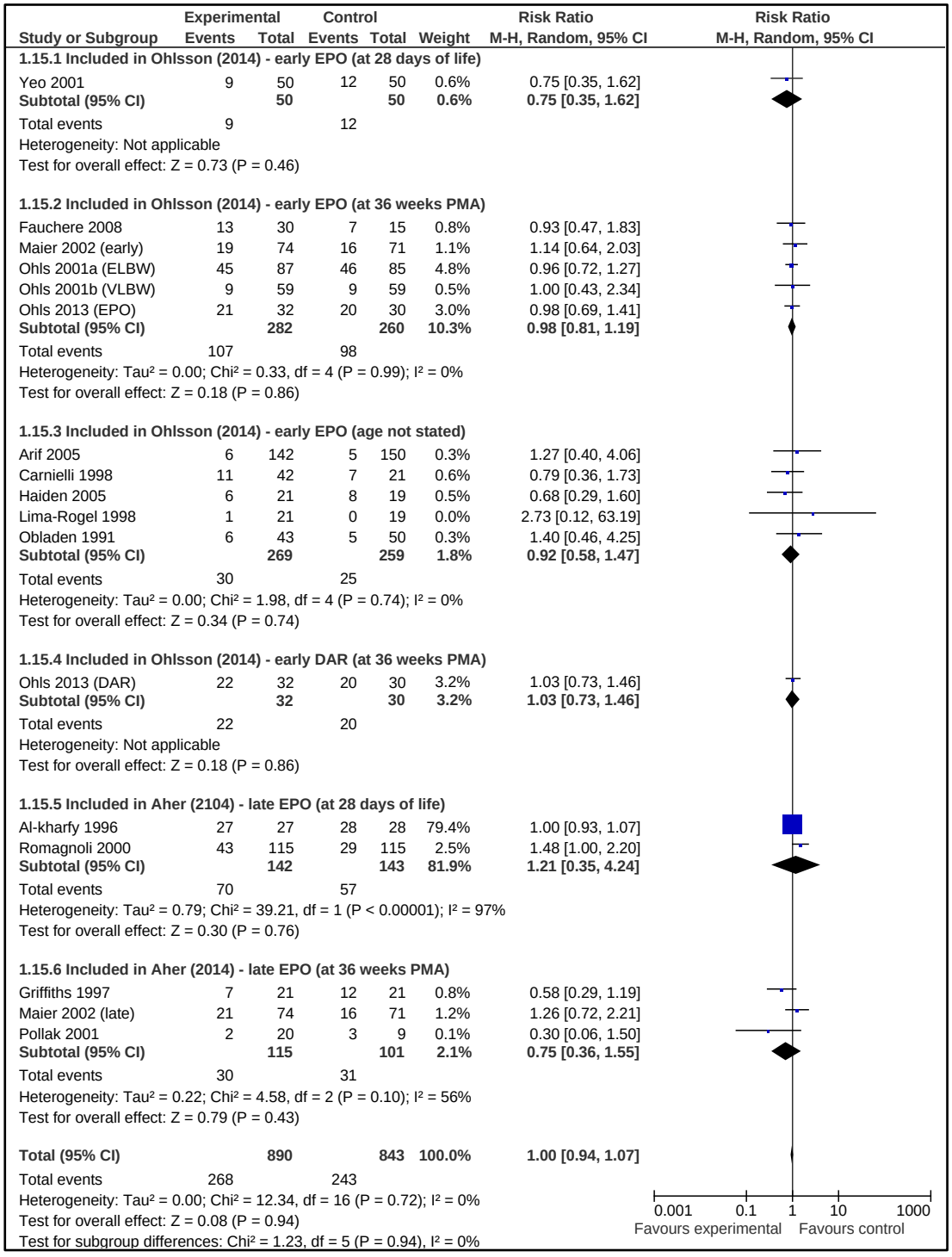
c. Analysis includes one trial (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned).

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 (I^2=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 (I^2=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 (I^2=0%) for this outcome.

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I *Good*	11 trials[c] (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 I^2 = 0%
Aher 2014[87] Level I *Good*	6 trials[d] (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 I^2 = 0%
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 I^2 = 0%
FEEDING INTOLERANCE									
El-Ganzoury 2014[e 150]	N=50	Preterm infants (≤33 weeks	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 = 0.29[f]

Study Level of evidence[a] *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 Heterogeneity[b]
Level II *Fair*	N=40	gestation)		Oral rHuEPO + G-CSF versus G-CSF		0/20 (0%)	0/20 (0%)	Not estimable	*Not applicable* p = 0.165[g]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

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

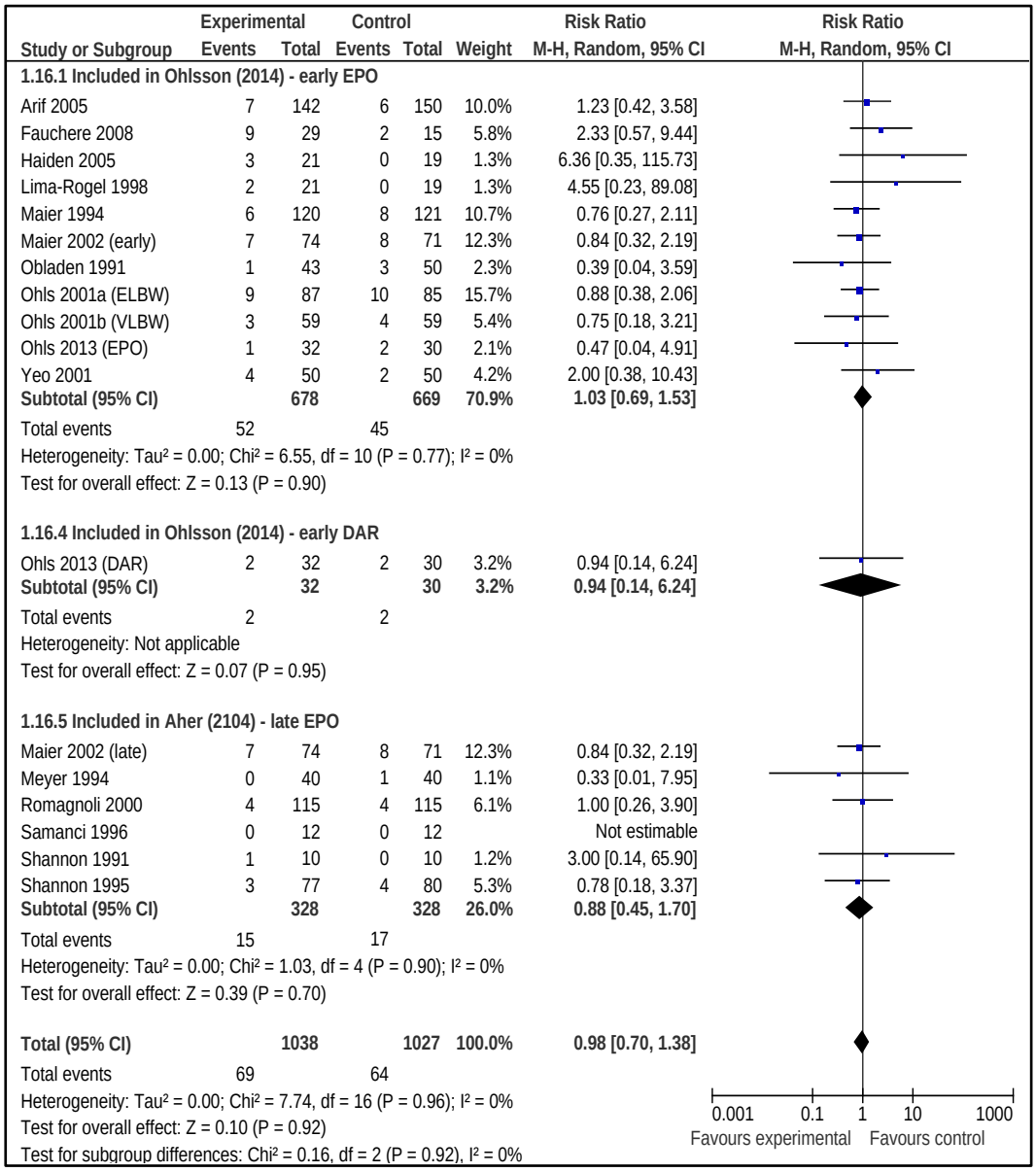
d. Analysis includes one study (Romagnoli 2000) that compared rHuEPO + iron with no rHuEPO (no iron in control group).

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 (I^2=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 (I^2=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 (I^2=0%) for this outcome.

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

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I *Good*	16 trials[c] (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 I^2 = 0%
Aher 2014[87] 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 I^2 = 0%

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] 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 2014[d 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 = 1.0[e] p = 0.92[f]
	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 = 0.56[e]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

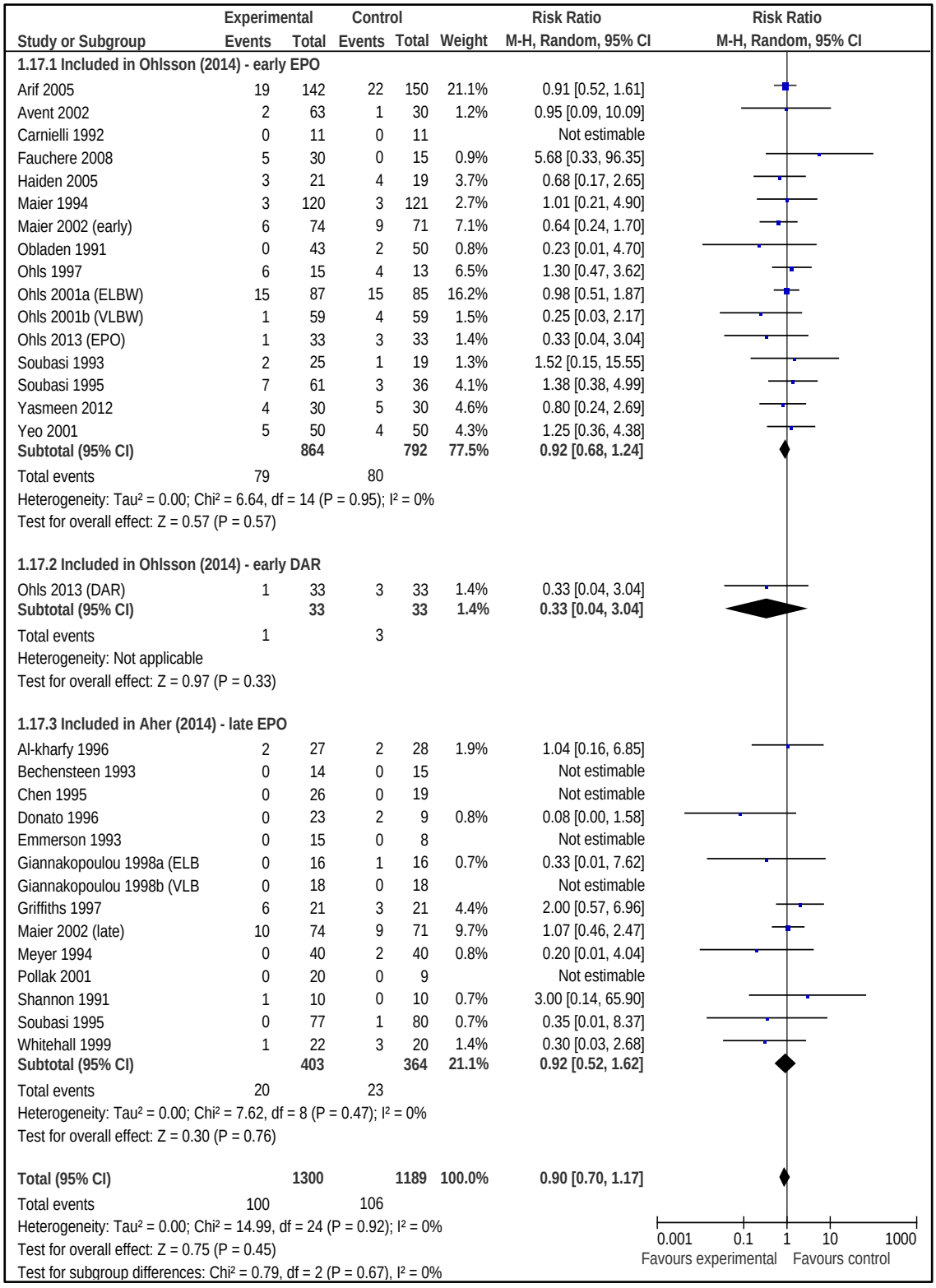
c. Analysis includes one study (Carnielli 1992) that compared rHuEPO + iron to placebo (no iron in control group) and one study (Fauchere 2008) that compared rHuEPO to no rHuEPO (use of iron not mentioned).

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[25]

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.

[25] 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.

Table 3.2.11 Preterm infants: Results for ESAs versus no ESAs (with or without iron) – Functional / performance status (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 ESA + iron n/N (%) Mean ± SD	Iron only n/N (%) Mean ± SD	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Ohlsson 2014[90] Level I/II *Good*	1 trial[c] (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 = 0.65[d]
					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 trial[e] (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 trial[f] (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

Study Level of evidence[a] *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 Heterogeneity[b]
	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 months[f]	97 ± 8	88 ± 12	MD 9.0 [3.33, 14.67]	*Favours DAR + iron* p = 0.0019
Newton 1999[163] 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 assessment[h]	1/20 (5%)	0/20 (0%)	RR 3.00 [0.13, 69.52][d]	*No significant difference* p = 0.49[d]
					Any 'abnormal' neurologic impairment at last assessment[h]	1/20 (5%)	0/20 (0%)	RR 3.00 [0.13, 69.52][d]	*No significant difference* p = 0.49[d]
					Any cognitive development impairment assessed as 'borderline' at last assessment[h]	5/20 (25%)	5/20 (25%)	RR 1.00 [0.34, 2.93][d]	*No significant difference* p = 1.0[d]
					Any cognitive development impairment assessed as 'deficient' at last assessment[h]	2/20 (10%)	0/20 (0%)	RR 5.00 [0.26, 98.00][d]	*No significant difference* p = 0.29[d]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIA OF PREMATURITY									
Jim 2000[151] 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 < 0.05[e]
					Hct (%) after week 5	34.1 ± NR	26.6 ± NR	NR	*Favours late rHuEPO + iron* p < 0.05[e]
					Serum ferritin (ng/mL)	NR ± NR	NR ± NR	NR	*Favours iron only* p < 0.05[e]
Kremenopoulos 1997[152] 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 = 0.38[e]
						Secondary analysis (Group A only): complications (mechanical ventilation, sepsis)			
					infants without complications	100 ± 9 (n=10)	87 ± 12 (n=12)	MD 13.00 [4.21, 21.79][d]	Favours early rHuEPO + iron p < 0.05[e]
					infants with complications	111 ± 16 (n=14)	92 ± 21 (n=14)	MD 19.00 [5.17, 32.83][d]	Favours early rHuEPO + iron p < 0.05[e]
					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 < 0.01[e]
						Secondary analysis (Group A only): complications (mechanical ventilation, sepsis)			
					infants without complications	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	NR	NR	NR	NR

Study Level of evidence[a] *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 Heterogeneity[b]**
					end of treatment *Group A *Group B	237 ± 184	267 ± 185	MD –30.00 [144.35, 84.35][d]	*No significant difference* p = 0.61[d]
						Secondary analysis (Group A only): complications (mechanical ventilation, sepsis)			
					infants without complications	193 ± 161	313 ± 139	MD –120.00 [–247.05, 7.05][d]	*No significant difference* p = 0.06[d]
					infants with complications	334 ± 165	470 ± 250	MD –136.00 [–292.91, 20.91][d]	*No significant difference* p = 0.09[d]
FEEDING INTOLERANCE									
El-Ganzoury 2014[c 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 = 0.09[d] p = 0.27[e]
	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 1995[153] 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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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.

3.2.3.2 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**
ES2.9	In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on transfusion volume or incidence is uncertain. (See evidence matrix D2.H in Volume 2 of the technical report.)	√√	√	NA	√√	√
ES2.10	In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on ROP, BPD and NEC is uncertain. (See evidence matrix D2.I in Volume 2 of the technical report.)	√√	√√√	NA	√√	√
ES2.11	In preterm infants with very low birth weight (<1500 g), the effect of oral iron supplementation compared with no oral iron supplementation on mortality is uncertain. (See evidence matrix D2.J in Volume 2 of the technical report.)	√√	√√√	NA	√√	√
BPD, bronchopulmonary disease; ES, evidence statement; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity √√√=A; √√=B; √=C; X=D; NA, not applicable						

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 recommended nutrient intake. However, routine supplementation in excess of the recommended nutrient intake, to reduce transfusion incidence, is not supported.
PP, practice point	

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 2012[165]) 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[26] 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.

[26] 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.

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 2013[167]	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 2009[168]	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 2004[169]	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 2000[170]	Level II *Poor*	Preterm infants with VLBW (≤1300 g) who reached at least 100 mL/kg/day of oral feeds ITT = 204 PP = 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

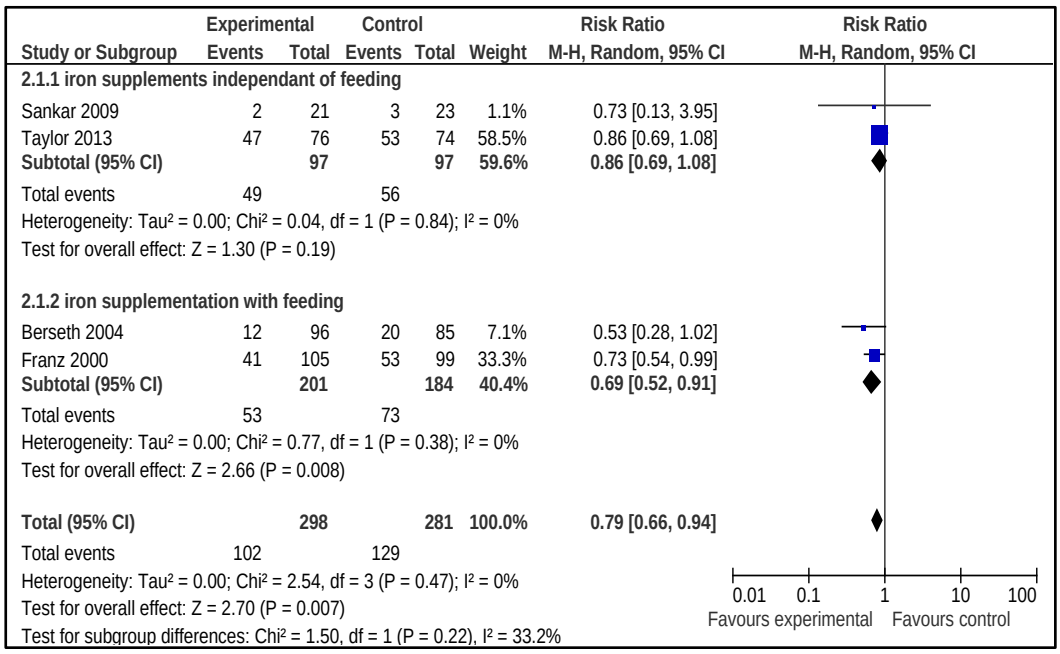


Table 3.2.14 Preterm infants: Results for oral and/or parenteral iron versus no iron – Transfusion incidence or volume

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Taylor 2013[167] 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 = 0.21[c]
					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 2009[168] 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 = 0.72[c] p = 0.63[d]
Berseth 2004[169] 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 = 0.94[c]
					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 = 0.06[c] p = 0.014[d]
Franz 2000[170] Level II *Poor*	ITT = 204 PP = 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 = 0.04[c] p = 0.068[d]
					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 = 0.023[e]

Study Level of evidence[a] *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 Heterogeneity[b]
					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 = 0.0014[e]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Taylor 2013[167] 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 2009[168] 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 = 0.72[c] p = 0.57[d]
					Chronic lung disease	1/21 (4.8%)	1/23 (4.3%)	RR 1.10 [0.07, 16.43][c]	*No significant difference* p = 0.95[c] p = 0.88[d]
					NEC	1/21 (4.8%)	0/21 (%)	RR 3.00 [0.13, 69.70][c]	*No significant difference* p = 0.49
Berseth 2004[169] 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 = 0.93[c]

Study Level of evidence[a] *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 Heterogeneity[b]
					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

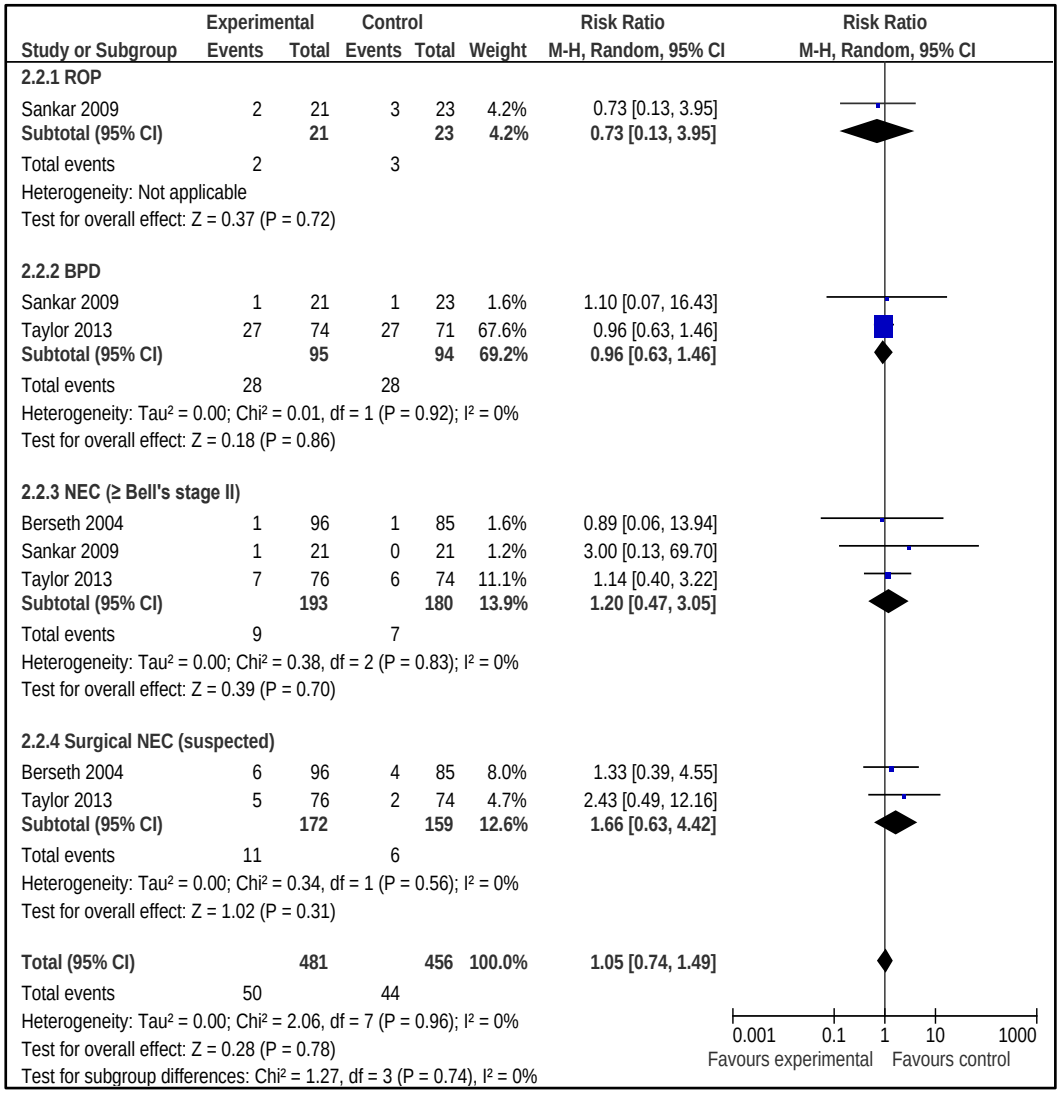
a. Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Taylor 2013[167] 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 = 0.98[c]
Franz 2000[170] 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 = 0.95[c]

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

Secondary outcomes[27]

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.

[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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Taylor 2013[167] 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 2009[168] 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 2004[169] 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 2000[170] 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	Ferritin at day 61 (mean)	87.8 ± NR (n=65)	74.2 ± NR (n=60)	NR	*No significant difference* p = 0.98[c]
					Ferritin at day 61 (median, min-max)	45 (9–478)	51 (9–682)		

Study Level of evidence[a] *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 Heterogeneity[b]
				oral feeds were tolerated	Hct (L/L) at day 61 (mean)	0.291 ± NR (n=67)	0.295 ± NR (n=63)	NR	*No significant difference* p = 0.77[c]
					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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Not clear which value (mean / median) the p-value refers.

3.2.4 Infants, children and adolescents at risk of anaemia

3.2.4.1 ESAs (with or without iron)

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

Summary of evidence

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.

3.2.4.2 Oral and/or parenteral iron

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

Practice points – infants, children and adolescents (oral and/or parenteral iron)	
PP14	Infants and children should receive sufficient dietary iron to achieve the adequate intake or recommended daily intake. If the adequate intake or recommended daily intake cannot be met by dietary means, iron supplementation is advised.
PP15	Infants and children in populations at high risk[a] 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 Sections 3.6 and 4.5 in *Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics.*
PP16	Infants and children with iron deficiency should be treated with iron supplements and dietary modifications.
PP, practice point	

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)

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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	Oral iron (15 mg)	Laboratory measures

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		months N=205	versus placebo for 3 months	(Hb, anaemia)
Northrop-Clewes (1996)[195]	Level II	Infants and children aged <2 years N=191	Oral iron (15 mg) 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)

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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 (I^2=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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
CHILDREN <2.5 YEARS									
Pasricha 2013[171] Level I *Good*	2 trials[c] (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 I^2 = 0%
CHILDREN <18 YEARS									
Okebe 2011[172] 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; 207-222] 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 I^2 = 0%
						Subgroup analysis: malaria endemicity			
					*13 trials conducted in hyper- or holo-endemic settings N=4846	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 I^2 = 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 I^2 = 0%

Study Level of evidence[a] *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 Heterogeneity[b]
	4 trials (Shah 2002, Greisen 1986, Hall 2002, Sazawal 2006)[197; 223-225] 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 I^2 = 0%
						Subgroup analysis: malaria endemicity			
					*3 trials conducted in hyper- or holo-endemic settings N=17,898	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 I^2 = 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 2006[d] [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
						Subgroup analysis: age			

Study Level of evidence[a] *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 Heterogeneity[b]**
					1–5 months	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

Study Level of evidence[a] *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 Heterogeneity[b]
					Uncertain/missing	21/8128 2.28	26/8411 2.66	HR 0.86	No significant difference p = NR
Sazawal 2006[e] [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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 here.

e. Sazawal et al (2006) was a four-arm trial comparing i) iron + folic acid ii) iron + folic acid + zinc iii) placebo iv) zinc. All children received vitamin A. Only the iron + folic acid group results compared with placebo are reported here.

Secondary outcomes[28]

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 (I^2=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.

[28] 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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
CHILDREN <2.5 YEARS									
Pasricha 2013[171] Level I *Good*	6 trials[c] (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 I^2 = 66%
						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 endemicity[e]. Two analyses approached statistical significance for subgroup difference and are reported below.			
						Subgroup analysis: baseline iron status			
					Iron deficient children 3 trials (Akman 2004, Idradinata 1993, Walter 1989) N=281	NR	NR	MD 5.90 [1.81, 10.00]	*Favours iron* p = 0.005 Moderate heterogeneity I^2 = 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 I^2 = 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 I^2 = 66%
					≤12.5 mg	*Subgroup analysis: dose*			

Study Level of evidence[a] *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 Heterogeneity[b]
					3 trials (NR) N=790	NR	NR	MD 1.49 [–0.95, 3.94]	*No significant difference* p = 0.23 Substantial heterogeneity I^2 = 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 – 60 mg 2 trials (NR) N=63	NR	NR	MD –1.84 [–7.70, 4.01]	*No significant difference* p = 0.54 No significant heterogeneity I^2 = 16%
	6 trials[c] (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 I^2 = 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 endemicity[e]. No subgroup differences approached statistical significance.			

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 I^2 <25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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; I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 evidence[a] 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 Heterogeneity[b]
LEVEL I EVIDENCE									
CHILDREN <2.5 YEARS									
Pasricha 2013[171] 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 I^2 = 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 I^2 = 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 I^2 = 99%
					Mixed / not reported 20 trials N=4616	NR	NR	MD 5.81 [3.96, 7.66]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 88%
					≤12.5 mg 16 trials (NR) N=3889	*Subgroup analysis: dose*			*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 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 I^2 = 98%

Study Level of evidence[a] 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 Heterogeneity[b]
					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 I^2 = 48%
	24 trials[d] (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 I^2 = 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).			

Study Level of evidence[a] 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 Heterogeneity[b]
CHILDREN <18 YEARS									
Okebe 2011[172] 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; 207-212; 214-215; 217; 219; 222; 226-242] 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 I^2 = 95%
					Anaemic 11 trials N=2692	*Subgroup analysis: baseline anaemia* NR	NR	MD 1.59 [0.93, 2.26]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 98%
					Non-anaemic 29 trials N=5852	NR	NR	MD 0.64 [0.48, 0.80]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 86%
					Hypo- or meso-endemic 34 trials N=4335	*Subgroup analysis: by location* NR	NR	MD 0.85 [0.54, 1.16]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 96%
					Hyper- or holo-endemic 17 trials N=4209	NR	NR	MD 0.90 [0.59, 1.21]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 86%

Study Level of evidence[a] 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 Heterogeneity[b]
	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; 211; 217-218; 227-229; 236-238; 240; 243-246] N=4205			Oral iron versus placebo / no treatment	Hb, mean change from baseline, end of treatment	NR	NR	MD 0.61 [0.41, 0.80]	*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 88%
						Subgroup analysis: by location			*Favours iron* p < 0.00001 Substantial heterogeneity I^2 = 78%
					Hypo- or meso-endemic 12 trials N=2595	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 I^2 = 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 I^2 = 88%
						Subgroup analysis: baseline anaemia			*Favours iron + folic acid* p = 0.0074 Substantial heterogeneity I^2 = 89%
					Anaemic 4 trials (Gopaldas 1983, Sarma 1977, Seshadri 1982b, Seshadri 1984b) N=273	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 I^2 = 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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].

3.2.5 Neonatal and paediatric patients with cancer

3.2.5.1 ESAs (with or without iron)

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

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.[29]

[29] This reason for exclusion was reported in superseded AHRQ report (Seidenfeld, 2006).

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/stages[a]) 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 treatment[b]	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 quality*[a]	Population N	Comparison	Outcomes
Razzouk (2006)[258]	Level II *High*	Paediatric cancer patients with anaemia[b] receiving myelosuppressive chemotherapy for non-myeloid malignancies[c] N=224	rHuEPO (600 U/kg per week) for 16 weeks versus placebo *dose adjustments allowed and iron supplementation given as needed[d] *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 groups[e]	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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
TRANSFUSION INCIDENCE									
Grant 2013[253] 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, USA[c]	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 = 0.04[d]
						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 = 0.009[d]
					ALL patients	26/40 (65.0%)	22/35 (62.9%)	RR 1.03 [0.73, 1.45][d]	No significant difference p = 0.85[d]
	1 RCT (Porter 1996)[263] N=20	*children receiving chemotherapy for sarcoma	Single centre, USA[c]	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 = 0.46[d]
Mystakidou 2007[255] 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, USA[C]	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, Hungary[c]	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 = 0.78[c]

Study Level of evidence[a] *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 Heterogeneity[b]
	1 RCT (Varan 1999)[260] N=34	*Children receiving chemotherapy for solid tumours at risk for anaemia	Single centre, Turkey[c]	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 1996[263] 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 = 0.03[d]
TRANSFUSION VOLUME									
Feusner 2002[257] Level I/II *Poor*	1 RCT (Porter 1996)[263] N=20	Paediatric cancer patients *children receiving chemotherapy for sarcoma	Single centre, USA[c]	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 = 0.01[e]
					Median volume of RBC transfused (mL/kg)	23 (0–118)	80 (18–226)	Difference in medians 57 [NR]	*Favours rHuEPO* p = 0.02[e]
	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 = 0.06[d] p = 0.11[e]
					low risk ALL patients (n=NR)	*Subgroup analysis* 16.8 ± 12.7	69.5 ± 36.1	NR	Favours rHuEPO p = 0.02
					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 = 0.12[d] p = 0.39[e]
Porter 1996[263] 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.

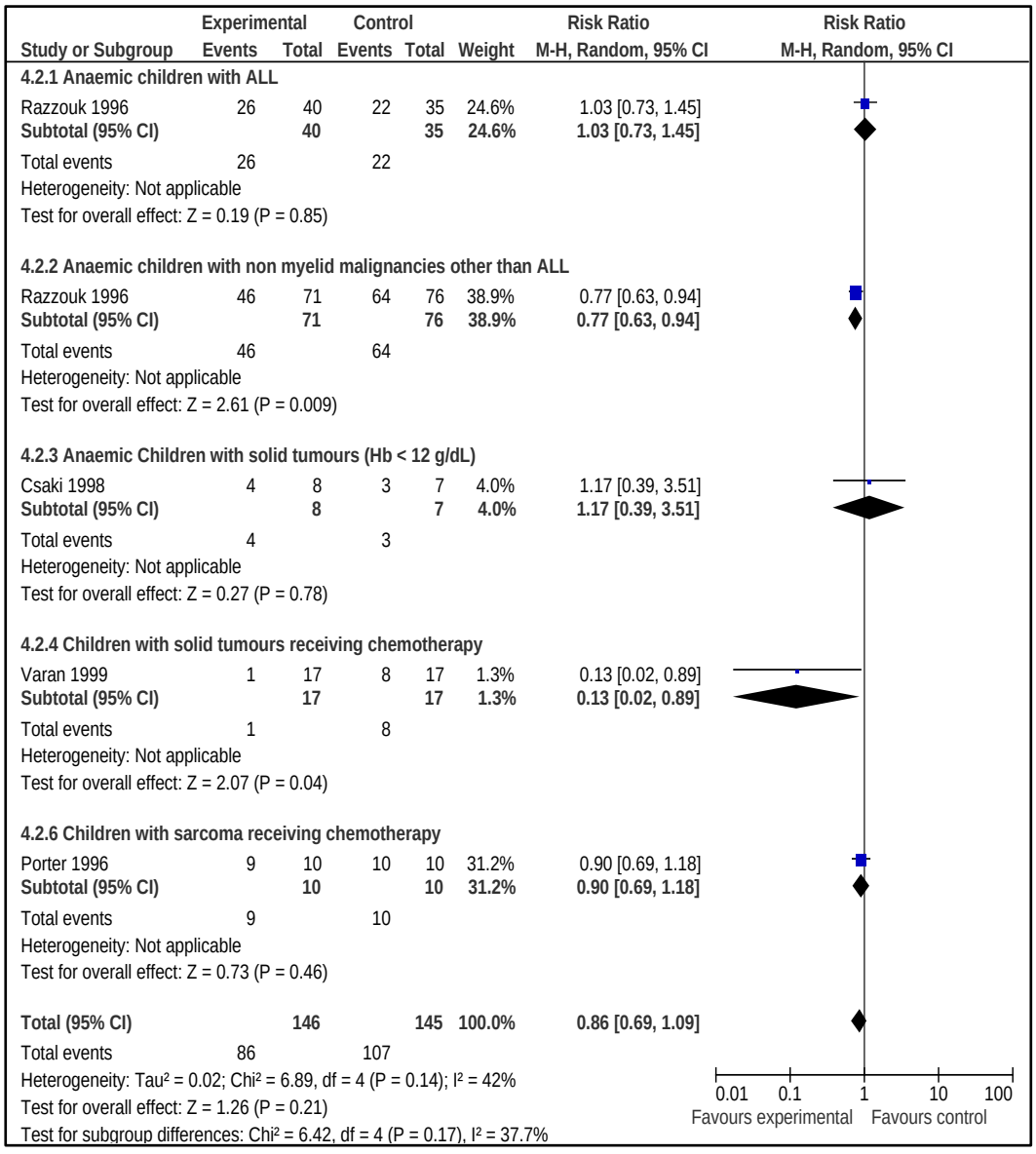
b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

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

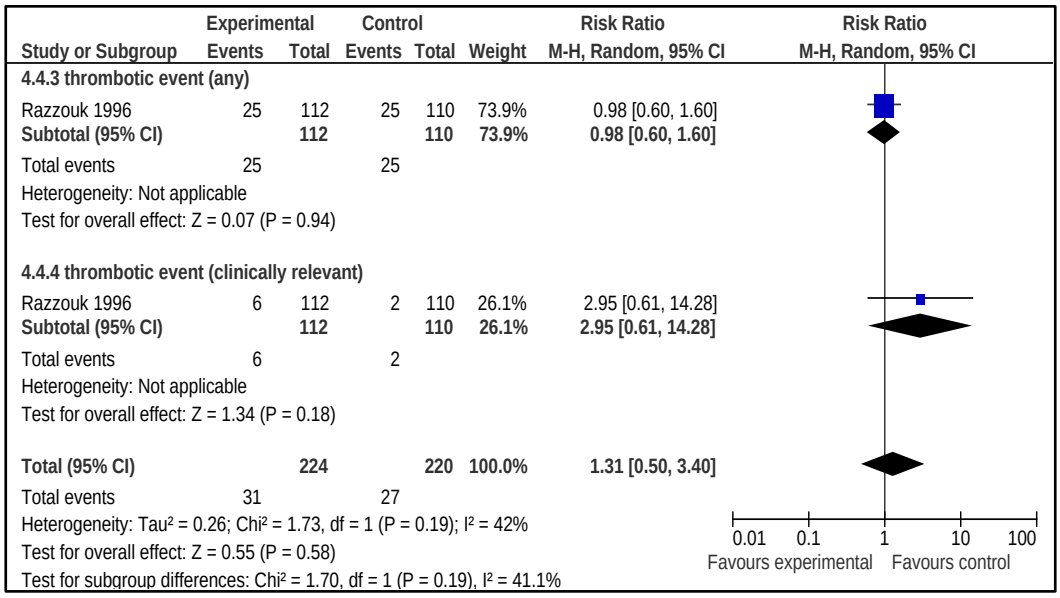


Table 3.2.26 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Thromboembolic events

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Grant 2013[253] 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, USA[c]	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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2=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

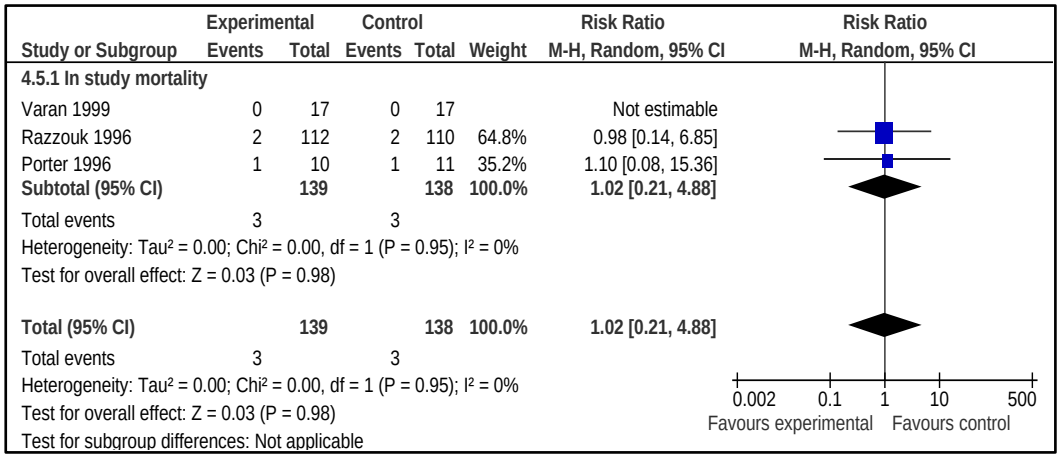


Table 3.2.27 Paediatric patients with cancer: Results for ESAs versus no ESAs (± iron) – Mortality

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Grant 2013[253] 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, USA[c]	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 = 0.99[d]
	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 < *0.0001*[d]
Ross 2006[256] 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, USA[c]	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, Turkey[c]	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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Not reported in systematic review; retrieved from Level II study.

d. Calculated post-hoc using RevMan 5.1.2.

Secondary outcomes[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 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).

[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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Tonia 2012[254] 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, USA[c]	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 2007[255] 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, USA[c]	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
						Subgroup analysis: age			
					children aged 5–7 years	NR (92%)	NR (41%)	NR	Favours rHuEPO p = NR
	1 RCT (Varan 1999)[260] N=34	*Children receiving chemotherapy for solid tumours at risk for anaemia	Single centre, Turkey[c]	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, Hungary[c]	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 2002[257]	1 RCT (Ragni 1998)[262]	Paediatric cancer patients	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

Study Level of evidence[a] *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 Heterogeneity[b]
Level I/II *Poor*	N=82* *number of chemotherapy courses	*children receiving chemotherapy for a variety of tumour types			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 = 0.01[d]
					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 = 0.48[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Grant 2013[253] 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 = 0.80[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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.

3.2.5.2 Oral and/or parenteral iron

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

Summary of evidence

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.

3.2.6 Neonatal and paediatric patients with kidney disease

3.2.6.1 ESAs (with or without iron)

Evidence statements – kidney disease (ESA with or without iron)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.26	In neonatal patients with kidney disease, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown.	NA	NA	NA	NA	NA
ES2.27	In paediatric patients with CKD, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is unknown.	NA	NA	NA	NA	NA
ES2.28	In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion incidence is uncertain. (See evidence matrix D2.P in Volume 2 of the technical report.)	X	NA	NA	√√	√√
ES2.29	In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion volume is unknown.	NA	NA	NA	NA	NA
ES2.30	In neonatal and paediatric patients with kidney disease, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES2.31	In neonatal and paediatric patients with kidney disease, the effect of ESA therapy (with or without iron) on mortality is unknown.	NA	NA	NA	NA	NA

CKD, chronic kidney disease; ES, evidence statement; ESA, erythropoiesis stimulating agent
√√√=A; √√=B; √=C; X=D; NA, not applicable

Practice points – kidney disease (erythropoiesis stimulating agents with or without iron)	
PP18	In paediatric patients with chronic kidney disease, ESA therapy to achieve a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient.[a, b, c] [a] See R4 in *Patient Blood Management Guidelines: Module 3 – Medical.*[14] [b] The KDIGO guidelines[83] recommend a Hb target of 110–120 g/L for paediatric patients and state that individualisation of ESA therapy is reasonable because some patients may have improvements in quality of life at higher Hb concentration. [c] The NICE guidelines[84] 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 chronic kidney disease, ESA therapy to achieve a Hb target of >130 g/L is not recommended because of increased morbidity; therefore, it is sensible to apply this limit to paediatric patients.[a] [a] See R6 in *Patient Blood Management Guidelines: Module 3 – Medical.*[14]
PP20	ESA use is less effective in patients with chronic kidney disease 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.

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 2009[265]	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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
HAEMOLYTIC UREMIC SYNDROME									
Pape 2009[265] 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 = 0.13[c]
					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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[31]

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.

[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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
HAEMOLYTIC UREMIC SYNDROME									
Pape 2009[265] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.2.6.2 Oral and/or parenteral iron

Evidence statements – kidney disease (oral and/or parenteral iron)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.32	In neonatal and paediatric patients with kidney disease, the effect of iron compared with no iron on transfusion incidence or volume is unknown.	NA	NA	NA	NA	NA
ES2.33	In neonatal and paediatric patients with kidney disease, the effect of iron compared with no iron on mortality is unknown.	NA	NA	NA	NA	NA
ES2.34	In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on transfusion incidence is uncertain. (See evidence matrix D2.Q in Volume 2 of the technical report.)	X	NA	NA	√√	√
ES2.35	In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES2.36	In paediatric patients with CKD receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on mortality is unknown.	NA	NA	NA	NA	NA
CKD, chronic kidney disease; ES, evidence statement; rHuEPO, recombinant human 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 2004[266]	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/week[a]) 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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
CHRONIC KIDNEY DISEASE									
Warady 2004[266]	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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[32]

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).

[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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
CHRONIC KIDNEY DISEASE									
Warady 2004[266]	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 = 0.98[c]
					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 = 0.89[c]
					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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.2.7 Neonatal and paediatric patients with malaria

3.2.7.1 ESA (with or without iron)

Evidence statements – malaria (ESAs with or without iron)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.37	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
ES2.38	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
ES2.39	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						

3.2.7.2 Oral and/or parenteral iron

Evidence statements – malaria (oral and/or parenteral iron)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.40	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	√√	√
ES2.41	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 quality*[a]	Population N	Comparison	Outcomes
Gara 2010[267]	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 1996[268]	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 1996[269]	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 incidence[b] Mortality Laboratory measures (Hb, anaemia)
Van Hensbroek 1995[270]	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 evidence[a] 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 Heterogeneity[b]
LEVEL II EVIDENCE									
Van den Hombergh 1996[269] 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 = 1.00[c]
					Transfusion later than day one or two	2/50	2/50	RR 1.00 [0.15, 6.82][c]	No significant difference p = 1.00[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2=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

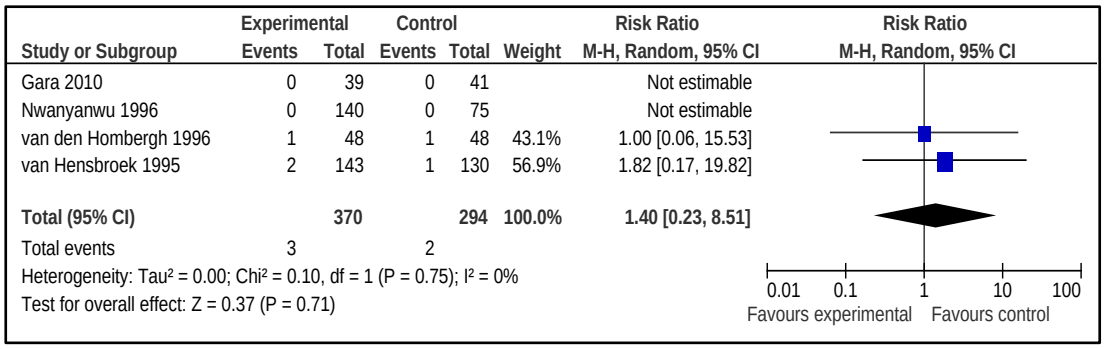


Table 3.2.38 Neonatal and paediatric patients with anaemia associated with malaria: Results for oral and/or parenteral iron versus no iron – Mortality

Study Level of evidence[a] 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 Heterogeneity[b]
LEVEL I EVIDENCE									
Okebe 2011[172] 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 I^2 = 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Secondary outcomes[33]

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.

[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.

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 evidence[a] 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 Heterogeneity[b]
LEVEL I EVIDENCE									
Okebe 2011[172] 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]	*Borderline favours iron* p = 0.058 No significant heterogeneity I^2 = 0.0%
LEVEL II EVIDENCE									
Okebe 2011[172] 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 = 0.03[d]
Van den Hombergh 1996[269] 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	9.4 ± 1.1	9.6 ± 2.1	MD –0.20 [–1.24, 0.84][d]	p = 0.71[d]
					at week 4	9.7 ± 1.5	9.9 ± 1.5	MD –0.20 [–1.13, 0.73][d]	p = 0.67[d]
					at week 8	8.6 ± 2.8	8.4 ± 1.8	MD –0.20 [–1.26, 1.66][d]	p = 0.79[d]
					at week 12	10.1 ± 1.5	9.4 ± 2.1	MD 0.70 [–0.43, 1.83][d]	p = 0.23[d]
						children who did not receive blood transfusion at baseline (N=56)[c]			
					at week 2	8.1 ± 1.4	8.1 ± 1.4	MD 0.00 [–0.73, 0.73][d]	p = 1.00[d]
					at week 4	8.9 ± 1.2	8.7 ± 1.8	MD 0.20 [–0.60, 1.00][d]	p = 0.62[d]
					at week 8	9.0 ± 1.8	8.1 ± 1.9	MD 0.90 [–0.07, 1.87][d]	p = 0.07[d]
					at week 12	9.2 ± 1.5	9.0 ± 1.5	MD 0.20 [–0.59, 0.99][d]	p = 0.62[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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.

3.2.8 Neonatal and paediatric patients with HIV or AIDS

3.2.8.1 ESAs (with or without iron)

Evidence statements – HIV (ESAs with or without iron)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.42	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
ES2.43	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
ES2.44	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						

3.2.8.2 Oral and/or parenteral iron

Evidence statements – HIV (oral and/or parenteral iron)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.45	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
ES2.46	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 2011[271]	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 B_{12} 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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIC CHILDREN WITH HIV									
Marti-Carvajal 2011[271] 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 = 0.94[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.
c. Calculated post-hoc using RevMan 5.1.2.

Secondary outcomes[34]

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**).

[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.

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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
ANAEMIC CHILDREN WITH HIV									
Rendo 2001[d] [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 < 0.05[c]
					Hct (%)	36.0 ± NR	31.7 ± NR	MD –4.3 [NR]	*Favours rHuEPO* p < 0.05[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. p-value reported by trial authors.

d. Data extracted from abstract only.

3.2.9 Neonatal and paediatric patients with sickle cell disease

3.2.9.1 Hydroxyurea

Evidence statements – sickle cell disease (hydroxyurea)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.47	In neonatal patients with sickle cell disease, the effect of hydroxyurea on transfusion incidence or volume is unknown.	NA	NA	NA	NA	NA
ES2.48	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.)	√√	√√√	√√	√√√	√√
ES2.49	In neonatal patients with sickle cell disease, the effect of hydroxyurea on stroke is unknown.	NA	NA	NA	NA	NA
ES2.50	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 with sickle cell disease, hydroxyurea should not be given for the primary purpose of reducing transfusion incidence.[a, b] [a] Although hydroxyurea reduces transfusion incidence, it may not be the optimal treatment for prevention of stroke. [b] See R1 and PP21.
Practice point – sickle cell disease (hydroxyurea)	
PP22	In paediatric patients over 9 months of age with sickle cell disease, hydroxyurea should be offeredto reduce vaso-occlusive pain crises and acute chest syndromes.
PP, practice point; R, recommendation	

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 2008[275]) 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 2012[276], Wang 2011[277]) 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)[276] 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)[277] 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)[278] 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)[276]	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)[277]	Level II *Good*	Infants (aged 9–18 months) with sickle cell anaemia (HbSS) or Hb Sβ^{0}thalassemia 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

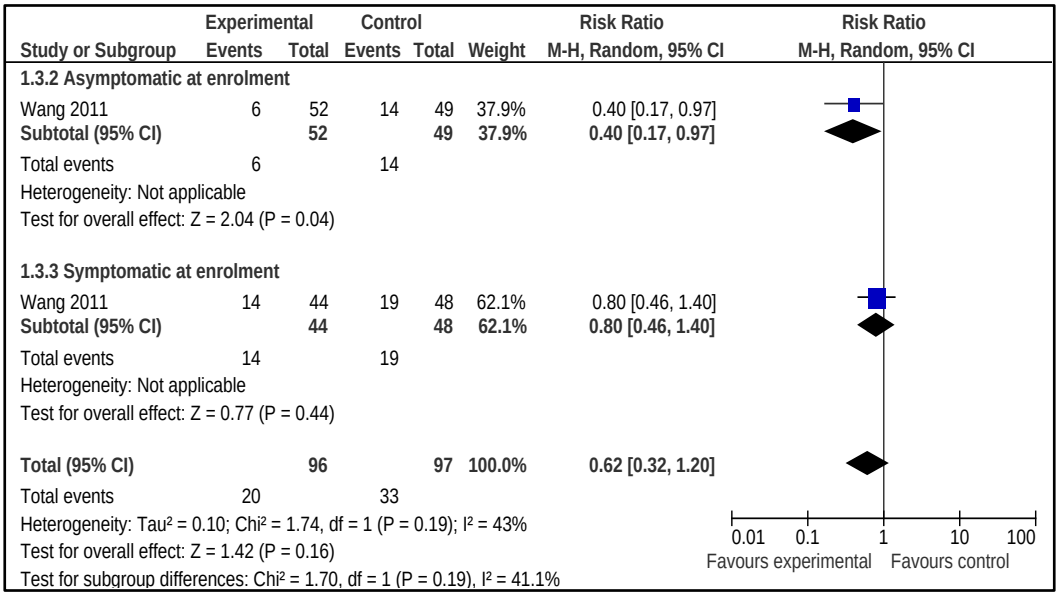


Table 3.2.45 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Transfusion volume or incidence

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Jain 2012[276] 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 2011[277] (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 = 0.04[c] p = 0.03[e]
					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 = 0.27[c]
						Subgroup analysis: cohort of infants from the BABY HUG trial who were asymptomatic at enrolment reported in Thornburg 2012 (N=101)			
					Number of children who received a transfusion	6/52 (11.5%)	14/49 (28.6%)	HR 2.7 [1.0, 6.9][c]	*Favours hydroxyurea* p = 0.04
					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 = 0.38[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Wang 2011[277] (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 = 0.50[c] p = 0.31[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[35]

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).

[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.

Table 3.2.47 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Functional/performance status (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			
						Hydroxyurea Mean ± SD	No hydroxyurea Mean ± SD	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
Wang 2011[277] (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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Jain 2012[276] 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 2011[277] (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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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

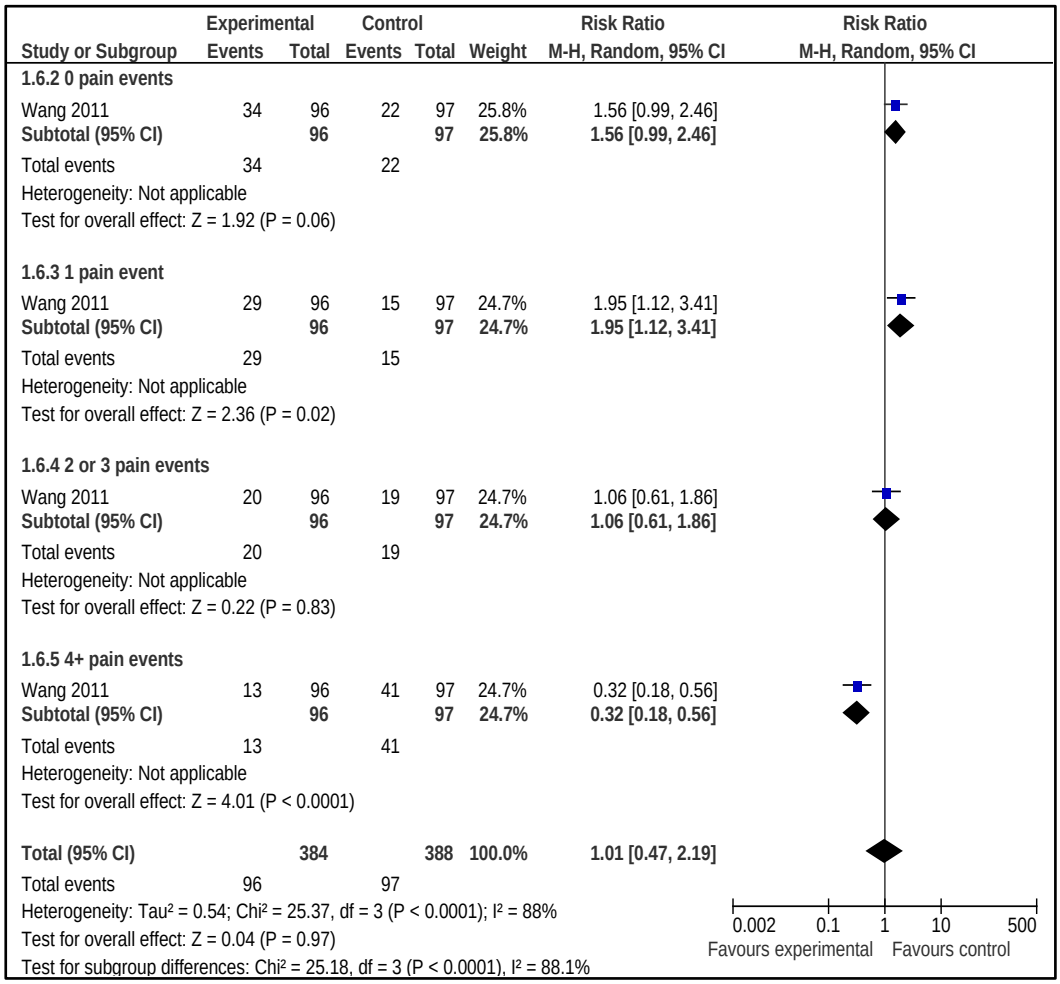


Table 3.2.49 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Chronic pain (secondary outcome)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Wang 2011[277] (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 = 0.002[d]
					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 = 0.004[d]
					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 = 0.002[d]
					Subjects with 0 pain events	34/96 (35%)	22/97 (23%)	RR 1.56 [0.99, 2.46][e]	*No significant difference* p = 0.06[e]
					Subjects with 1 pain event	29/96 (30%)	15/97 (15%)	RR 1.95 [1.12, 3.41][e]	*Favours placebo* p = 0.02[e]
					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 = 0.83[e]
					Subjects with 4+ pain events	13/96 (14%)	41/97 (42%)	RR 0.32 [0.18, 0.56] [e]	*Favours hydroxyurea* p < 0.0001[e]
					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 = 0.17[e] p = 0.23[d]

Study Level of evidence[a] *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 Heterogeneity[b]
						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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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

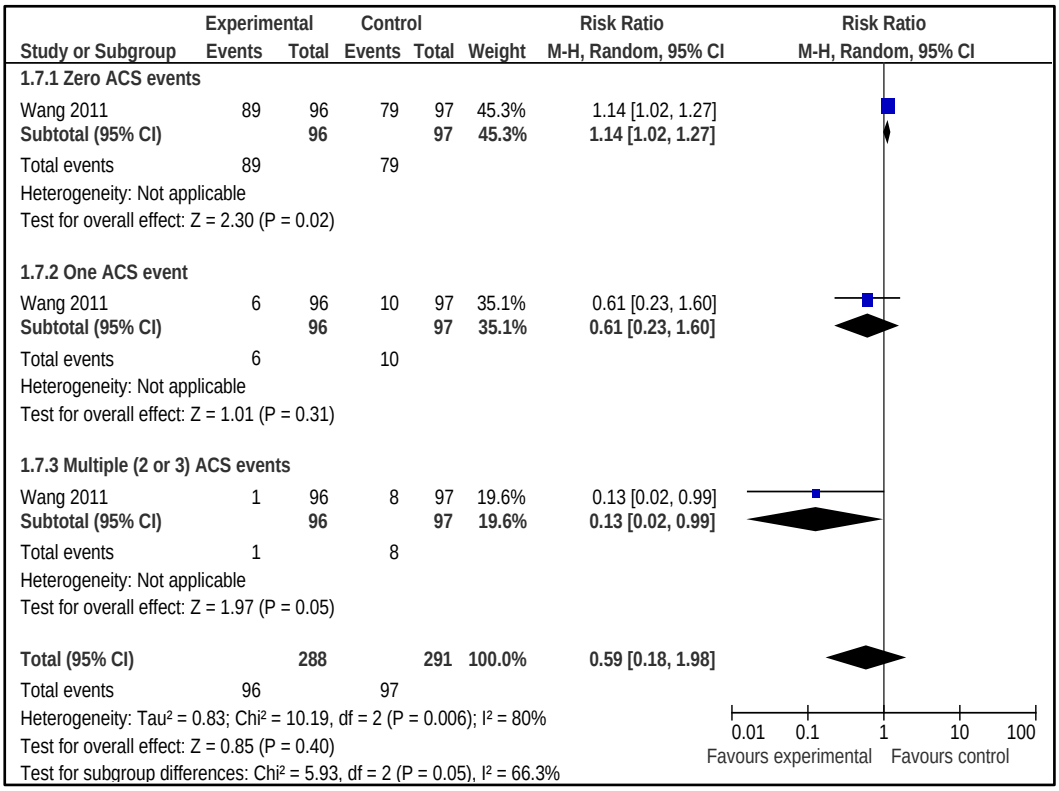


Table 3.2.50 Paediatric patients with sickle cell disease: Results for hydroxyurea versus no hydroxyurea – Vaso-occlusive events (secondary outcome)

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Jain 2012[276] 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 < 0.001[d]
Wang 2011[277] (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 = 0.02[d]
					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 0.36[C]	*Favours hydroxyurea* p = 0.02[d]
					Subjects with 0 ACS events	89/96 (93%)	79/97 (82%)	RR 1.14 [1.02, 1.27][e]	*Favours placebo* p = 0.02[e]
					Subjects with 1 event of ACS	6/96 (6%)	10/97 (10%)	RR 0.61 [0.23, 1.60][e]	*No significant difference* p = 0.31[e]
					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 = 0.05[e]
						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 = 0.17[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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.

3.2.10 Neonatal and paediatric patients requiring surgery

3.2.10.1 ESAs (with or without iron)

Evidence statements – surgical (ESAs with or without iron)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.51	In neonatal patients requiring surgery, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is uncertain. (See evidence matrix D2.W in Volume 2 of the technical report.)	X	NA	√	√√	√
ES2.52	In paediatric patients requiring surgery, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain. (See evidence matrix D2.W in Volume 2 of the technical report.)	X	NA	√	√√	√
ES2.53	In paediatric patients requiring surgery, the effect of ESA therapy (with or without iron) on transfusion volume is unknown.	NA	NA	NA	NA	NA
ES2.54	In neonatal patients requiring cardiac surgery, the effect of ESA therapy compared with no ESA therapy on thromboembolic events is uncertain. (See evidence matrix D2.X in Volume 2 of the technical report.)	√√	NA	NA	√	√
ES2.55	In neonatal patients requiring noncardiac surgery, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES2.56	In paediatric patients requiring surgery, the effect of ESA therapy (with or without iron) on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES2.57	In neonatal patients requiring cardiac surgery, the effect of ESA therapy compared with no ESA therapy on mortality is uncertain. (See evidence matrix D2.Y in Volume 2 of the technical report.)	√√	NA	NA	√	√
ES2.58	In neonatal patients requiring noncardiac surgery, the effect of ESA therapy (with or without iron) on mortality is unknown.	NA	NA	NA	NA	NA
ES2.59	In paediatric patients requiring 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 with or without iron)	
PP23	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 2013, Bierer 2009, 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 surgery[b] *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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Bierer 2009[94] 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 < 0.00001[c] p = 0.07[d]
					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 < 0.00001[c]
					Volume transfused during study (mL/kg)	17 ± 4	4 ± 4	MD 13.00 [9.49, 16.51] [c]	*Favours placebo* p < 0.00001[c]
					Volume transfused during hospitalisation (mL/kg)	43 ± 15	16 ± 7	MD 27.00 [16.74, 37.26][c]	*Favours placebo* p < 0.00001[c]
Fearon 2002[280] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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

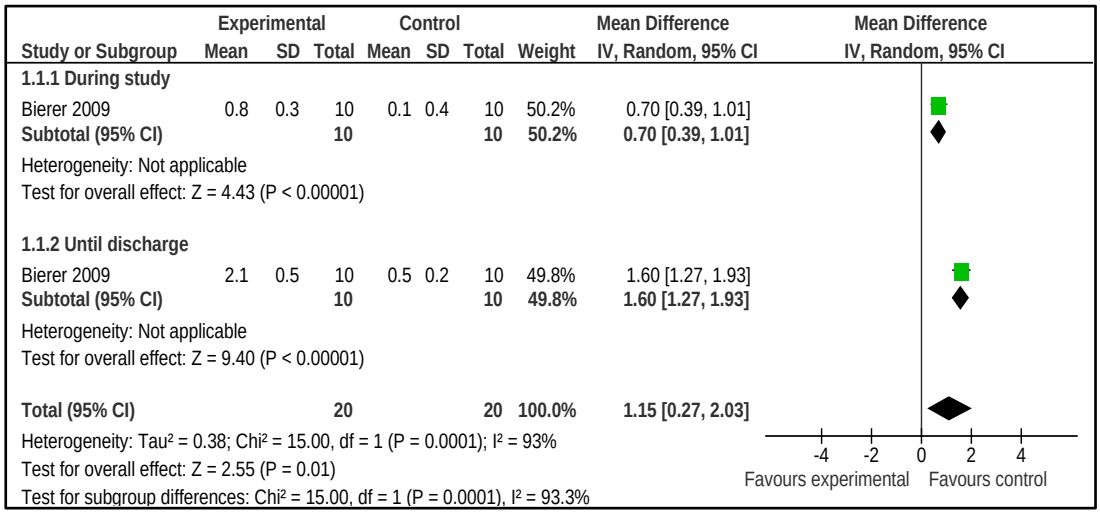


Figure 3.2.21 ESAs versus no ESAs in neonates requiring major surgery – transfusion volume (mL/kg)

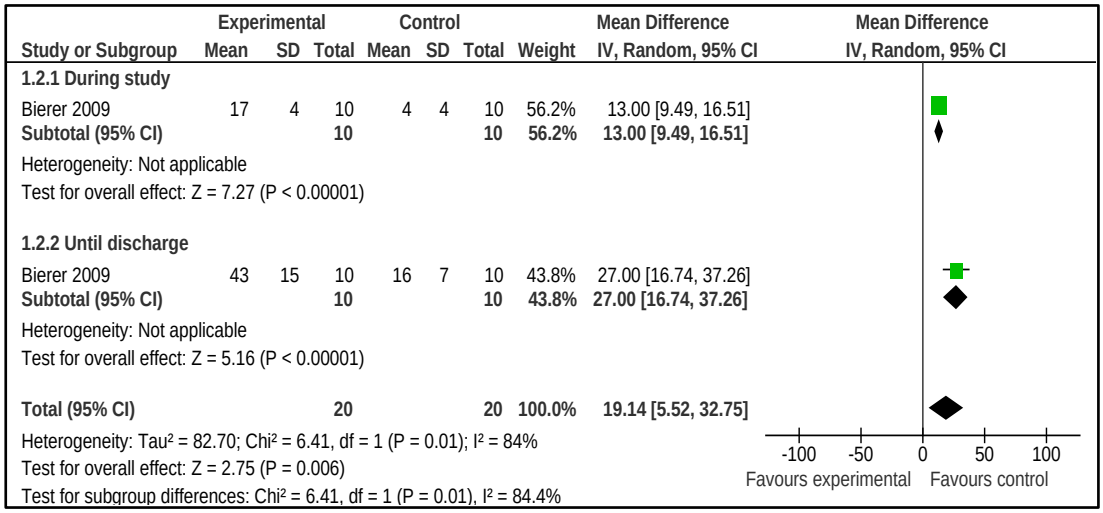
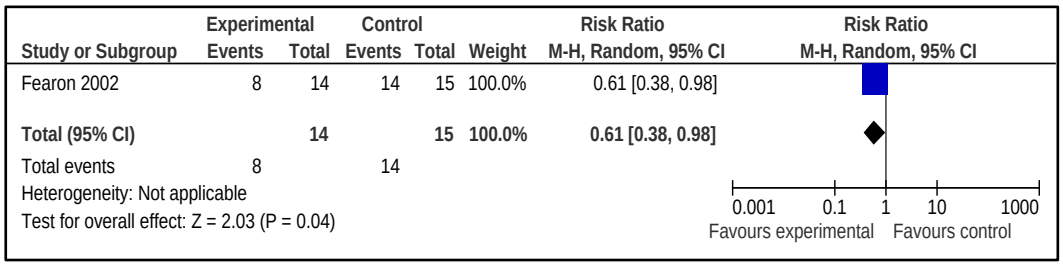


Figure 3.2.22 ESA with iron versus iron alone in infants aged <8 years scheduled for primary cranial vault remodelling – transfusion incidence



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

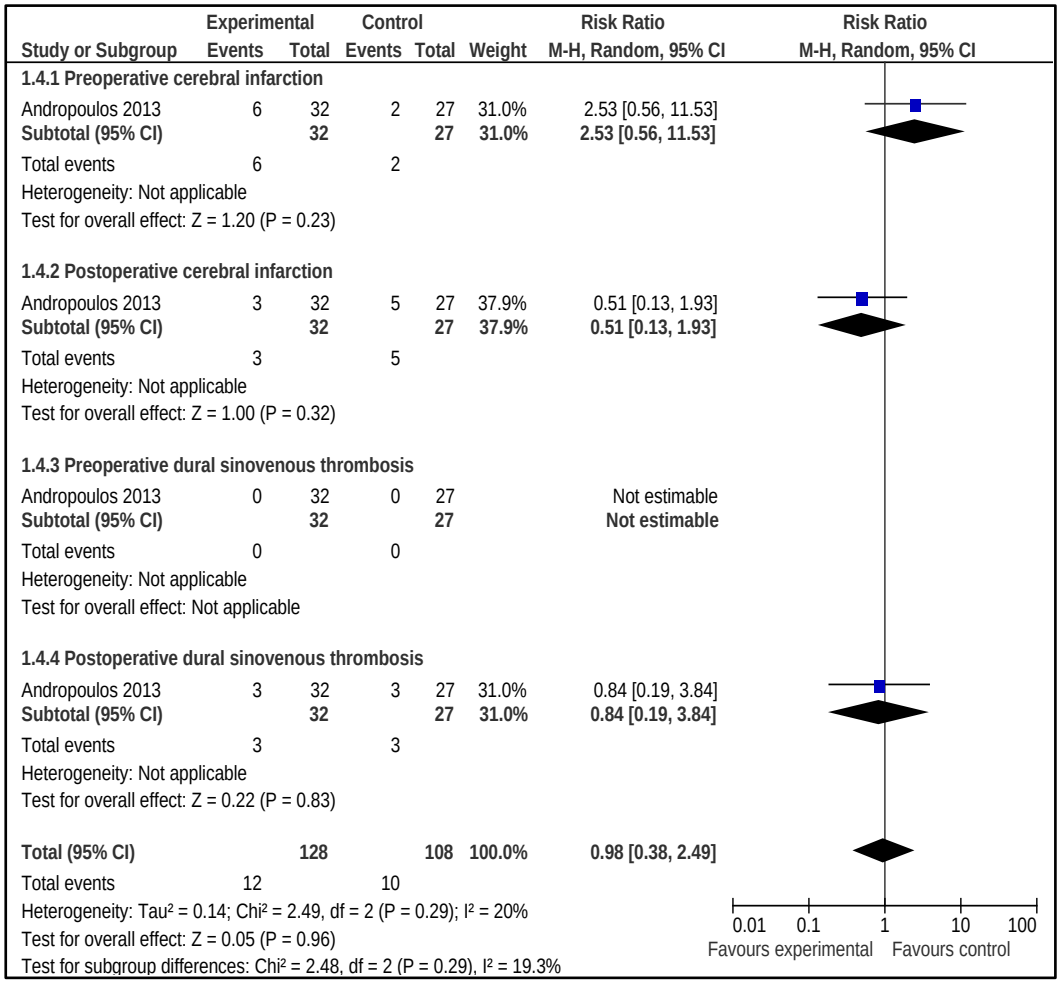


Table 3.2.53 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Thromboembolic events

Study Level of evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Andropoulos 2013[279] 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	4/32 (12.5%)	2/27 (7.4%)	RR 1.69 [0.33, 8.51]c	p = 0.53c
					Moderate	1/32 (3.1%)	0/27 (0%)	RR 2.55 [0.11, 60.04]c	p = 0.56c
					Severe	1/32 (3.1%)	0/27 (0%)	RR 2.55 [0.11, 60.04]c	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	3/32 (9.4%)	5/27 (18.5%)	RR 0.51 [0.13, 1.93]c	p = 0.32c
					Moderate	0/32 (0%)	0/27 (0%)	Not estimable	p = NA
					Severe	0/32 (0%)	0/27 (0%)	Not estimable	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	2/32 (6.3%)	2/27 (7.4%)	RR 0.84 [0.13, 5.60]c	p = 0.86c
					Moderate	1/32 (3.1%)	1/27 (3.7%)	RR 0.84 [0.06, 12.86]c	p = 0.90c
					Severe	0/32 (0%)	0/27 (0%)	Not estimable	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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Andropoulos 2013[279] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

Secondary outcomes[36]

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.

[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.

Table 3.2.55 Neonatal and paediatric patients requiring surgery: Results for ESAs versus no ESAs – Functional / performance status (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 ESAs Mean ± SD Median (IQR)	No ESAs Mean ± SD Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
Andropoulos 2013[279] 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-emotional[d]	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

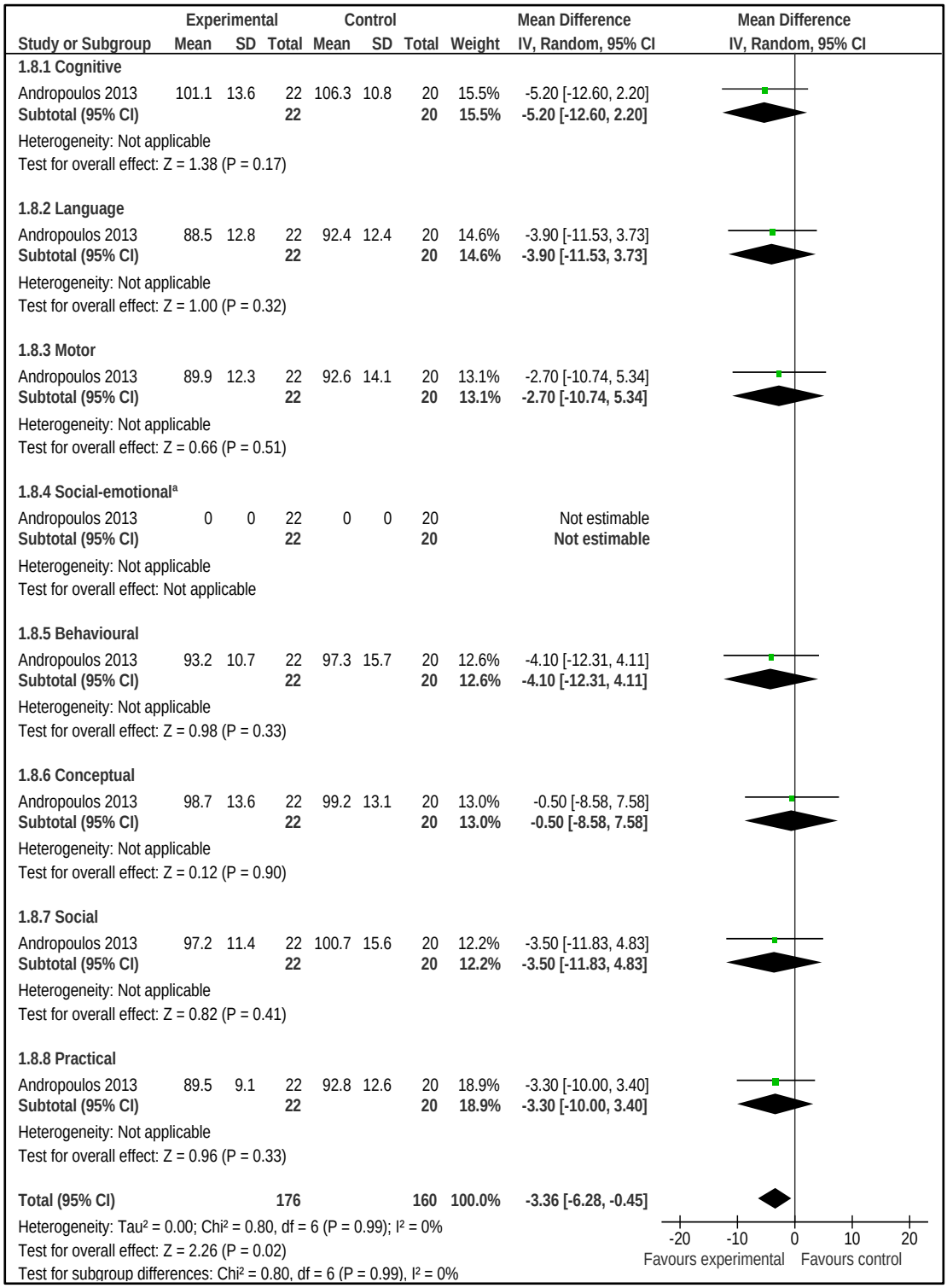
a. Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

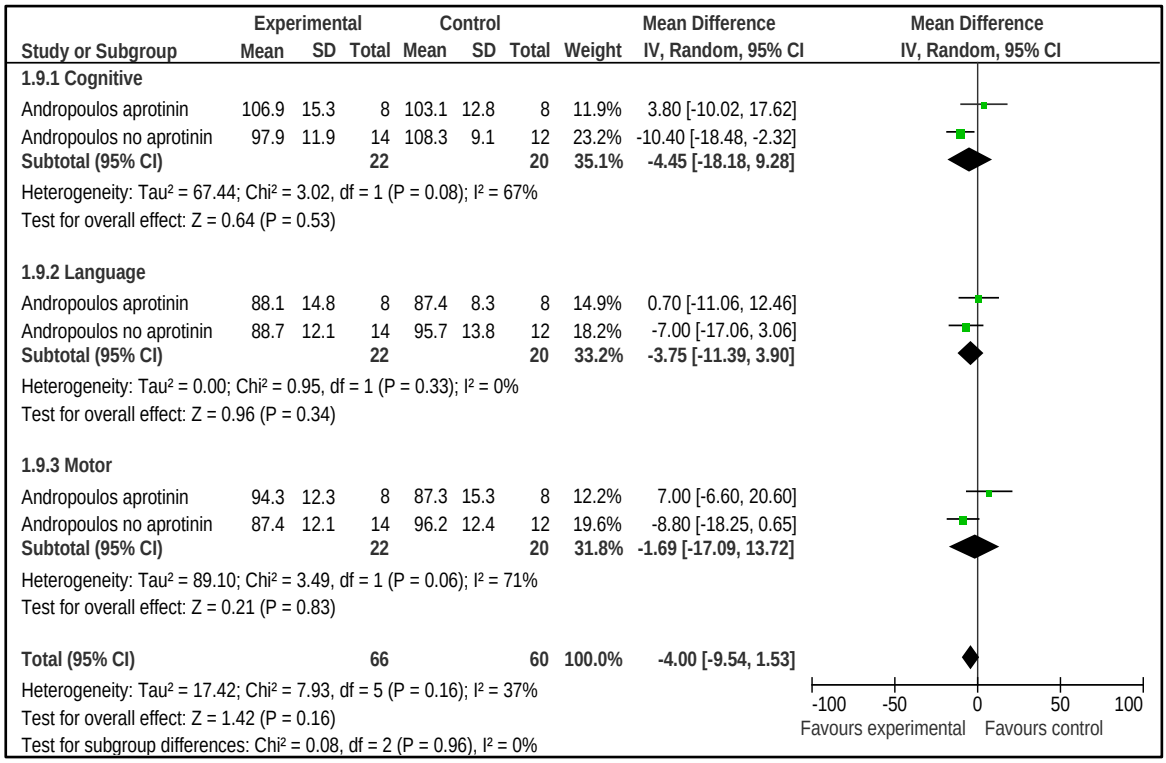
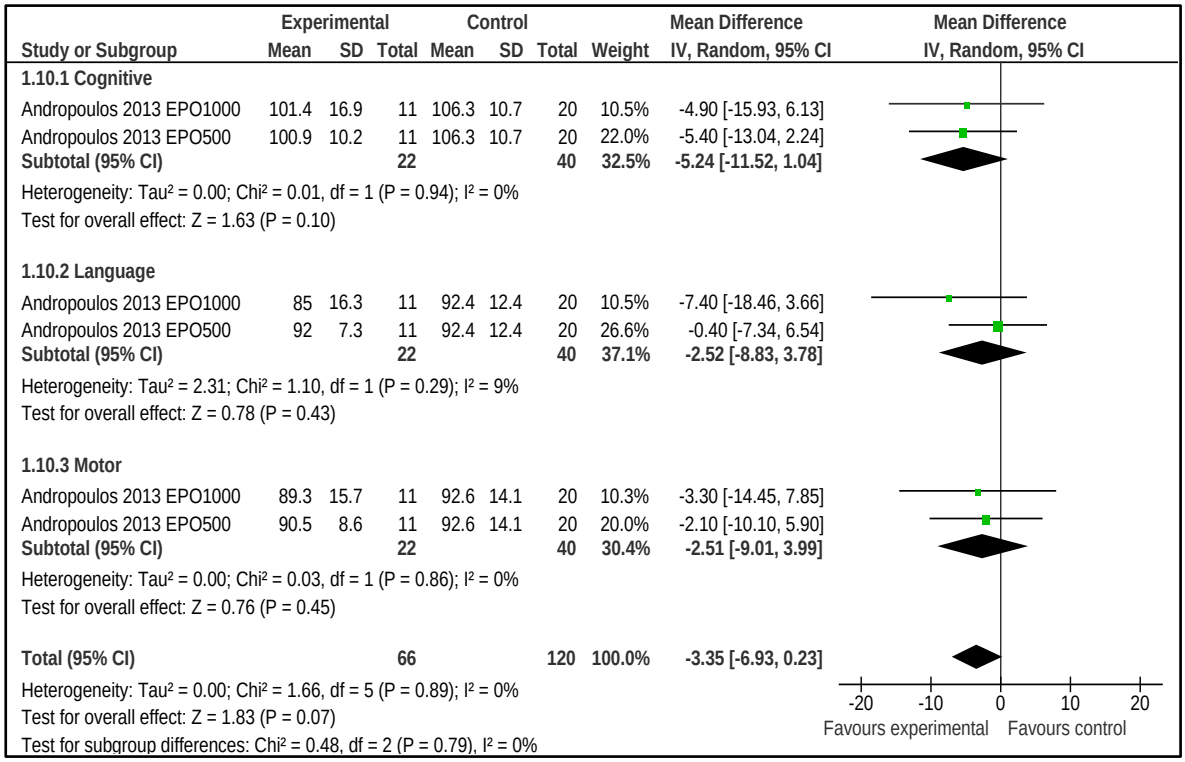


Figure 3.2.26 ESAs versus no ESAs in neonates requiring cardiac surgery – Bayley III scores at 12-months follow-up (subgroup analysis by rHuEPO dose)



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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Fearon 2002[280] 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)	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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.2.10.2 Oral and/or parenteral iron

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

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.*[16]
Practice points – surgical (oral and/or parenteral iron)	
PP24	In neonatal and paediatric surgical patients in whom substantial blood loss is anticipated, preoperative anaemia and iron deficiency[a] 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.
PP25	To implement PP24, 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.
PP, practice point; R, recommendation; RBC, red blood cell	

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.

3.2.11 Critically ill neonatal and paediatric patients

3.2.11.1 ESAs (with or without iron)

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

Practice point – critically ill (erythropoiesis stimulating agents with or without iron)	
PP26	In critically ill paediatric patients with anaemia, ESAs should not be *routinely* used.[a] [a] This point is based on the lack of effect of ESAs on mortality in critically ill adult patients. See R2 in *Patient Blood Management Guidelines: Module 4 – Critical Care.*[15]
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 (Chicella 2006[281], Jacob 2003[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 (I^2=0%).

Table 3.2.58 Critically ill paediatric patients: Results for ESAs versus no ESAs – 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 ESAs n/N (%) Mean ± SD	No ESAs n/N (%) Mean ± SD	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
Chicella 2006[281] 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 2003[282] 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 = 0.76[c]
					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 = 0.10[c]
					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 > 0.05[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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

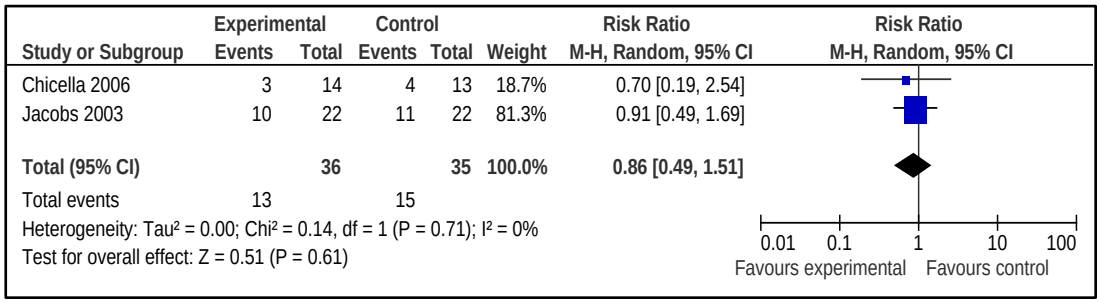
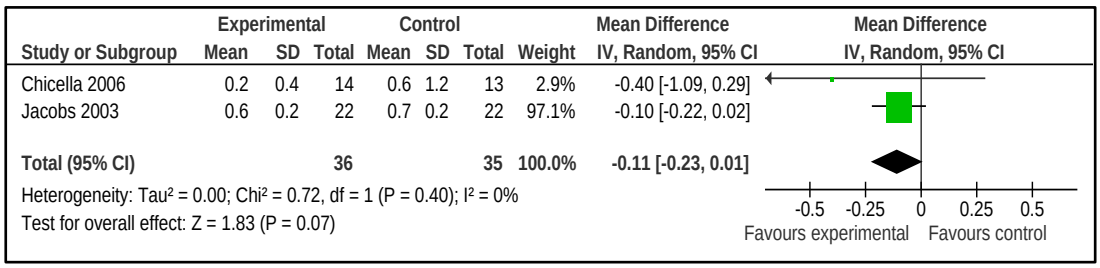


Figure 3.2.28 Meta-analysis: ESAs versus no ESAs in critically ill paediatric patients – mean number of transfusions



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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Jacobs 2003[282] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

Secondary outcomes[37]

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.

[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.

Table 3.2.60 Critically ill paediatric patients: Results for ESAs versus no ESAs – Laboratory measures (Hb, Hct, ferritin) (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 ESAs n/N (%) Mean ± SD	No ESAs n/N (%) Mean ± SD	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
Chicella 2006[281] 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 2003[282] 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 < 0.00001[c]
					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 = 0.45[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.2.11.2 Oral and/or parenteral iron

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

Practice point – critically ill (oral and/or parenteral iron)	
PP27	Critically ill paediatric patients should receive iron supplementation as necessary to achieve the 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 in critically ill neonatal and/or paediatric patients.

3.3 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 or fibrinogen concentrate	
R6 (Grade C)	In neonatal and paediatric patients undergoing cardiac surgery, the *routine* use of an FFP-based pump prime solution is not recommended, because it offers no advantages over an albumin-based solution in relation to postoperative blood loss, or perioperative transfusion requirements.
Practice points – FFP, cryoprecipitate or fibrinogen concentrate	
PP29	In neonatal and paediatric patients, the decision to transfuse FFP, cryoprecipitate or fibrinogen concentrate should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders.
PP30	For guidance on the use of FFP in specific patient groups, refer to:[a] • *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011)[283] • *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*[16] • *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) • *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]
Expert opinion points – FFP, cryoprecipitate or fibrinogen concentrate	
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 situations (e.g. when critical bleeding is occurring or anticipated).[a] [a] The template given in Appendix K (*Critical bleeding protocol*) is intended for local

	adaptation.
EOP4	In general, neonatal and paediatric patients with an INR ≤2 can undergo invasive procedures without any serious bleeding; however, higher INRs may be tolerated.[a] [a] See PP17 *Patient Blood Management Guidelines: Module 2 – Perioperative.*[16]
EOP5	Specialist guidelines or haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with severe thrombocytopenia or coagulopathy.
EOP, expert opinion point; FFP, fresh frozen plasma; INR, international normalised ratio; POC, point of care; PP, practice point; R, recommendation	

Practice point – platelets	
PP28	In neonatal and paediatric patients, the decision to transfuse platelets should take into account the potential risks and benefits. The decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition. Factors that may influence the decision include active bleeding, medications affecting platelet function and coagulation status, and congenital and acquired bleeding disorders.
PP31	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 10^9/L in the absence of risk factors, and at <20 x 10^9/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]
Expert opinion point – platelets	
EOP3	In general, neonatal and paediatric patients with a platelet count ≥ 50 × 10^9/L can undergo invasive procedures without any serious bleeding; however, lower platelet counts may be tolerated.[a] [a] See PP17 *Patient Blood Management Guidelines: Module 2 – Perioperative.*[16]
EOP, expert opinion point; 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 or fibrinogen concentrate in the management of coagulopathy with or without bleeding
- the appropriate dose of cryoprecipitate, FFP or fibrinogen concentrate in the management of coagulopathy with or without bleeding
- the appropriate transfusion thresholds for platelet transfusion in the management of

thrombocytopenic patients with or without bleeding
- the appropriate dose of platelets in the management of thrombocytopenic patients with or without bleeding
- the appropriate roles of factor concentrates in reducing RBC transfusion in the management of coagulopathy with or without bleeding.

3.3.1 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, craniofacial 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. Primary triggers 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.

3.3.2 Methods

The systematic review examined the evidence for FFP, cryoprecipitate, fibrinogen concentrate, and/or 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 or 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.

3.3.3 Preterm and low birth weight infants

3.3.3.1 Fresh frozen plasma

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

Summary of evidence

Level I evidence

The systematic review and hand-searching process identified one Level I study (Osborn 2004)[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 1985[287]; Ekblad 1992[288]; Gottuso 1976[289]; NNNI 1996a[290]) and one 2-year follow-up report (NNNI 1996b[291]) 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) trial[290] 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=515[a]	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=515[a]	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 (I^2=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 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 2004[286] Level I *Good*	3 trials (Beverley 1985,[287] Gottuso 1976,[289] NNNI 1996a[290]) 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 I^2 = 0%
LEVEL II EVIDENCE									
NNNI 1996a[290] 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 = 0.98[d]
					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 = 0.80[d]
						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 = 0.90[d]
					due to IVH	15/257 (5.8%)	8/258 (3.1%)	RR 1.88 [0.81, 4.36][d]	*No significant difference* p = 0.14[d]
					due to NEC	5/257 (1.9%)	7/258 (2.7%)	RR 0.72 [0.23, 2.23][d]	*No significant difference* p = 0.57[d]
					due to other reasons	2/257 (0.8%)	4/258 (1.6%)	RR 0.50 [0.09, 2.72][d]	*No significant difference* p = 0.42[d]
NNNI 1996b[291] Level II *Fair* *2-year follow-up of NNNI 1996a[290]	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 = 0.90[d]
					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 = 0.73[d]
					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 = 0.40[d]
						Subgroup analysis: Cause-specific mortality (age 1–23 months)			

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]
					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 = 0.56[d]
					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 = 0.21[d]
					due to infection	2/257 (0.8%)	2/258 (0.8%)	RR 1.00 [0.14, 7.07][d]	*No significant difference* p = 1.00[d]
					due to other reasons	1/257 (0.4%)	2/258 (0.8%)	RR 0.50 [0.05, 5.50][d]	*No significant difference* p = 0.57[d]

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 (I^2=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 2004[286] Level I *Good*	2 trials (Beverley 1985,[287] Ekblad 1991[288]) 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 I^2 = 33%
LEVEL II EVIDENCE									
Osborn 2004[286] Level I/II *Good*	1 trial (Beverley 1985[287]) 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 1996a[290] 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 = 0.45[d]
					Subependymal only	31/147 (21.1%)	26/161 (16.1%)	RR 1.31 [0.82, 2.09][d]	*No significant difference* p = 0.27[d]
					Severe IVH	13/147 (8.8%)	16/161 (9.9%)	RR 0.89 [0.44, 1.79][d]	*No significant difference* p = 0.74[d]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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.

3.3.3.2 Platelet transfusion

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

Evidence statements – preterm and low birth weight infants (platelet transfusion using a different platelet transfusion strategy)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.14	In preterm infants (<32 weeks), the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on mortality is uncertain. (See evidence matrix D3.E in Volume 2 of the technical report.)	√	NA	NA	√√√	√√
ES3.15	In preterm (<32 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on bleeding events is uncertain. (See evidence matrix D3.F in Volume 2 of the technical report.)	√	NA	NA	√√	√√
ES3.16	In preterm (<37 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.17	In preterm (<37 weeks) infants, the effect of a restrictive platelet transfusion strategy compared with a liberal platelet transfusion strategy on RBC transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; FFP, fresh frozen plasma; 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 ≤150 x 10^9/L) and controls as those without thrombocytopenia. Of the 94 included cases, 12 were defined as having mild thrombocytopenia (100–150 x 10^9/L), 34 with moderate (50–100 x 10^9/L), and 48 with severe (<50 x 10^9/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 x 10^9/L) and examined the effect of restrictive platelet transfusion strategy (transfused when active haemorrhage and platelet count <50 x 10^9/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 x 10^9/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 x 10^9/L) N=679	Restrictive platelet transfusion[a] versus liberal platelet transfusion[b]	Mortality Bleeding events

ELBW, extremely low birth weight

a. Transfused when active haemorrhage and platelet count <50 x 10^9/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 2007[292] 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 2007[293] Level III–2	N=164	Preterm infants (≤ 32 weeks gestational age)	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 = 0.04[c]

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]
Poor		with thrombocytopenia				*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 2006[294] 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 = 0.02[c]
						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 = 0.05[c]
					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 = 0.007[c]
					Mortality during thrombocytopenia	26/129 (20%)	6/79 (7.6%)	RR 2.65 [1.14, 6.16]	*Favours no platelet transfusion* p = 0.02[c]
						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 = 0.04[c]
					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 = 0.02[c]
					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 = 0.60[c]
						Subgroup analysis: number of platelet transfusions			

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]
					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 = 0.90[c]
					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 = 0.20[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 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 2012[295] 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 x 10^9/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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2007[292] 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 2007[293] 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 = 0.04[c]
						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 = 0.57[c]
					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 = 0.66[c]

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 2012[295] 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 x 10^9/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 = 0.72[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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 thrombocytopenia 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 thrombocytopenic patients in the restrictive transfusion unit were administered significantly fewer platelets compared with those patients in the liberal transfusion unit.

3.3.4 Neonatal and paediatric patients with cancer

3.3.4.1 Platelet transfusion

Evidence statements – cancer (platelet transfusion)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.18	In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on mortality is unknown.	NA	NA	NA	NA	NA
ES3.19	In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on bleeding events is unknown.	NA	NA	NA	NA	NA
ES3.20	In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.21	In paediatric patients with cancer, the effect of platelet transfusion compared with no platelet transfusion on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES3.22	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on mortality is uncertain. (See evidence matrix D3.G in Volume 2 of the technical report.)	X	NA	NA	√√	√
ES3.23	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on significant bleeding events is uncertain. (See evidence matrix D3.H in Volume 2 of the technical report.)	X	NA	NA	√√	√
ES3.24	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.25	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on the incidence of platelet transfusions is uncertain. (See evidence matrix D3.I in Volume 2 of the technical report.)	X	NA	NA	√√	√

Evidence statements – cancer (platelet transfusion)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.26	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on the incidence of RBC transfusions is unknown.	NA	NA	NA	NA	NA
ES3.27	In paediatric patients with acute leukaemia, the effect of a prophylactic platelet transfusion strategy compared with platelet transfusion in response to bleeding on transfusion volume is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

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 x 10^9/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 regimens in paediatric patients with AML or 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 2012[296] 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 x 10^9/L)	Mortality (all causes)	7/21 (33.3%)	12/35 (34.3%)	RR 0.97 [0.46, 2.08]	*No significant difference* p = 0.94[c]
					Mortality (from bleeding)	2/21 (9.5%)	1/35 (2.9%)	RR 3.33 [0.32, 34.56]	*No significant difference* p = 0.31[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 regimens 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 x 10^9/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 2012[296] 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 x 10^9/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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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 regimens 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 2012[296] 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 x 10^9/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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.3.5 Neonatal and paediatric patients undergoing surgery

3.3.5.1 Fresh frozen plasma

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

Evidence statements – surgical (fresh frozen plasma)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.38	In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.39	In neonatal and paediatric patients undergoing surgery, the effect of a restrictive versus liberal FFP transfusion strategy on transfusion volume and incidence is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; FFP, fresh frozen plasma √√√=A; √√=B; √=C; X=D; NA, not applicable						

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 200 mL 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)[70]	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 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 (%) Mean ± SD	Low /no FFP n/N (%) Mean ± SD	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL III EVIDENCE									
FFP versus no FFP									
Nacoti 2012[70] 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 year[c]	10/51 (20.3%)	17/192 (8.7%)	RR 2.21 [1.08, 4.54][d]	*Favours no FFP* p = 0.03[d] p = 0.022[e]
						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 2012[70] 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 year[c]	15/63 (24.2%)	5/60 (8.7%) / 7/120 (6%)	NR	*Favours low FFP* p = 0.001[e]
						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 2013[298] 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 2004[299] 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 = 1.0[c]
					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 = 1.0[c]
Oliver 2003[300] 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 = 0.152[e]
						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, TAGVHD, 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; 95% CI –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 2013[298] 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 FFP* 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

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]
					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

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]
					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 2004[299] 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 = 0.05[c] p = 0.06[d]
					RBC	1.8 ± 0.4	2.1 ± 0.3	MD–0.30 [–0.61, 0.01][c]	*No significant difference* p = 0.06[c] p = 0.09[d]
					platelets	0.9 ± 0.7	1.0 ± 0.7	MD –0.10 [–0.71, 0.51][c]	*No significant difference* p = 0.75[c] p = 0.8[d]
					cryoprecipitate	0.4 ± 0.8	2.0 ± 0.9	MD –1.60 [–2.35, –0.85][c]	*Favours FFP* p < 0.0001[c] p < 0.001[d]
					FFP	1.0 ± 0.0	0.3 ± 0.5	MD 0.70 [0.39, 1.01][c]	*Favours no FFP* p < 0.0001[c] p < 0.001[d]
					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 = 1.00[c]
					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

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]
Oliver 2003[300] 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 = 0.10[c] p = 0.035[d]
					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 = 0.44[c] p > 0.10[d]
					RBC	2.6 ± 0.7	2.5 ± 0.6	MD 0.10 [–0.24, 0.44][c]	*No significant difference* p = 0.57[c], p > 0.10[d]
					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 < 0.0001[c] p = <0.001[d]
					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 = 0.06[c] p = 0.038[d]
					Platelet concentrate	2.1 ± 1.7	1.3 ± 1.6	MD 0.80 [–0.06, 1.66][c]	*No significant difference* p = 0.07[c] p = 0.069[d]
					Cryoprecipitate	0.1 ± 0.8	0.1 ± 0.4	MD 0.00 [–0.33, 0.33][c]	*No significant difference* p = 1.00[c] p > 0.10[d]

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[38]

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).

[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.

3.3.5.2 Cryoprecipitate

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

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**).

3.3.5.3 Platelets

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

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)[70]	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 evidence[a] *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 Heterogeneity[b]
LEVEL III EVIDENCE									
Platelet transfusion versus no platelet transfusion									
Nacoti 2012[70] 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 year[c]	2/11 (18.2%)	25/232 (10.9%)	RR 1.69 [0.46, 6.24][d]	*No significant difference* p = 0.342[e]
				Postoperative platelets (≥ 1 unit) versus no platelets *within 48 hours after liver transplant	Mortality at 1 year[c]	3/15 (20.6%)	24/228 (10.6%)	RR 1.90 [0.64, 5.60][d]	*No significant difference* p = 0.237[e]
						*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 2012[70] Level III Fair	N=243	Paediatric liver transplant patients aged <18 years	Single hospital, Italy	Preoperative platelets (high-dose, ≥181 x 1000/cc) versus medium dose (91–180 x 1000/cc) versus low-dose (≤90 x 1000/cc)	Mortality at 1 year[c]	9/79 (11.9%)	9/82 (11.5%)	7/76 (9.8%)	NR	No significant difference p = 0.929[e]

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 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 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, TAGVHD, 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.

3.3.5.4 Fibrinogen concentrate

Evidence statements – surgical (fibrinogen concentrate)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.58	In paediatric liver transplant patients, the effect of a higher volume of preoperative fibrinogen concentrate compared with a lower volume of preoperative fibrinogen concentrate on mortality is uncertain. (See evidence matrix D3.N in Volume 2 of the technical report.)	√	NA	NA	√√	√
ES3.59	In paediatric patients undergoing surgery other than liver transplant, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown.	NA	NA	NA	NA	NA
ES3.60	In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality is unknown.	NA	NA	NA	NA	NA
ES3.61	In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on bleeding events is unknown.	NA	NA	NA	NA	NA
ES3.62	In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.63	In neonatal and paediatric patients undergoing surgery, the effect of fibrinogen concentrate compared with no fibrinogen concentrate on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES3.64	In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on mortality is unknown.	NA	NA	NA	NA	NA
ES3.65	In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on mortality is uncertain. (See evidence matrix D3.O in Volume 2 of the technical report.)	√√	NA	NA	√√√	√
ES3.66	In paediatric patients with acute acquired hypofibrinogenaemia after CPB weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on bleeding events is uncertain. (See evidence matrix D3.P in Volume 2 of the technical report.)	√√	NA	NA	√√√	√
ES3.67	In neonatal patients undergoing surgery, the effect of fibrinogen concentrate compared with an alternative fibrinogen-containing product on bleeding events is unknown.	NA	NA	NA	NA	NA

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

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; RCT, randomised controlled trial

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)[70]	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. **Table 3.3.24** 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 evidence[a]** ***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** **Heterogeneity[b]**
LEVEL III EVIDENCE										
Fibrinogen versus a different fibrinogen volume										
Nacoti 2012[70] 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 year[c]	12/82 (15.1%)	9/80 (11.6%)	5/79 (6.6%)	NR (univariate analysis)	*No significant difference* p = 0.308[d]
						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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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 evidence[a] *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 Heterogeneity[b]
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 = 0.06[c] p = 0.046[d]
					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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

d. p-value reported by trial authors.

Secondary outcomes[39]

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.

[39] 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.

Table 3.3.27 Neonatal and paediatric patients requiring cardiac surgery: Results for fibrinogen concentrate compared with cryoprecipitate – thromboembolic 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			
						Fibrinogen concentrate n/N (%)	Cryoprecipitate n/N (%)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
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 (60 mg/kg) versus cryoprecipitate (10 mL/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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.3.5.5 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**
ES3.72	In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on mortality is unknown.	NA	NA	NA	NA	NA
ES3.73	In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on bleeding events is unknown.	NA	NA	NA	NA	NA
ES3.74	In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.75	In neonatal and paediatric patients undergoing surgery, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; FFP, fresh frozen plasma √√√=A; √√=B; √=C; X=D; NA, not applicable						

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.

3.3.6 Critically ill neonatal and paediatric patients

3.3.6.1 Fresh frozen plasma

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

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 2009[302], Karam 2013[303]) 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 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 III EVIDENCE									
Church 2009[302] 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, PaO_2/FIO_2 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 2013[303] 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 < 0.0001[c]
						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; FP, 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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.

3.3.6.2 Cryoprecipitate

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

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.

3.3.6.3 Platelets

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

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 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									
Church 2009[302] 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, Pao_2/FIo_2 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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, TAGVHD, 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.

3.3.6.4 Fibrinogen concentrate

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

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**).

3.3.6.5 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**
ES3.108	In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on mortality is unknown.	NA	NA	NA	NA	NA
ES3.109	In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on bleeding events is unknown.	NA	NA	NA	NA	NA
ES3.110	In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion-related serious adverse events is unknown.	NA	NA	NA	NA	NA
ES3.111	In critically ill neonatal and paediatric patients, the effect of a combination of FFP, cryoprecipitate, platelet transfusion or fibrinogen concentrate compared with a different combination on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; FFP, fresh frozen plasma √√√=A; √√=B; √=C; X=D; NA, not applicable						

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.

3.4 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

3.4.1 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) viscoelastic point of care (POC) testing compared with no viscoelastic 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) viscoelastic POC testing compared with no viscoelastic 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.

3.4.2 Preterm and term infants

3.4.2.1 Placental transfusion

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

Practice points – preterm and term infants (placental transfusion)	
PP32	In preterm infants, deferring cord clamping for between 30 seconds and 3 minutes may reduce transfusion volume and incidence, and incidence of intraventricular haemorrhage. However, the effect of this practice on other outcomes (death, major morbidity and neurodevelopmental outcomes) is uncertain or unknown, particularly in extremely preterm infants (e.g. <28 weeks) and in those who require active resuscitation.
PP33	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]
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*	Term[a] 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 studies[a, 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	RCT	Preterm infants (aged	DCC (delay time 20 s)	Transfusion incidence

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
(2000)[c317]	*modified Jadad score 10/10*	between 24–29 weeks gestation) with VLBW (501–1250 g) N=32 *vaginal birth only	(n=16) versus ICC (n=16)	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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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 (I^2=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 (I^2=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 evidence[a] *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 Heterogeneity[b]
LEVEL I EVIDENCE									
Backes 2014[305] Level I *Good*	6 trials (Hosono 2008,[316] Ibrahim 2000,[317] Kinmond 1993,[318] March 2013,[320] McDonnell 1997,[321] Mercer 2006[323]) 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 I^2 = 0%
	6 trials (Gokmen 2011,[313] Hosono 2008[c],[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 I^2 = 64%
Ghavam 2013[306] Level I *Poor*	5 trials (Hosono 2008,[316] Ibrahim 2000,[317] Kugelman 2007,[319] March 2011,[331] Rabe 2000[326]) 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 I^2 = NR
Mathew 2011[307] Level I *Fair*	6 trials (NR[d]) 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 I^2 = NR
	4 trials (NR[d]) N=144				Mean no. of transfusions administered	NR	NR	MD –0.92 (–1.78, –0.05)	*Favours placental transfusion* p = NR

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 (%) Mean ± SD (n) Median (range)	No placental transfusion n/N (%) Mean ± SD (n) Median (range)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
									Heterogeneity NR I^2 = NR
Rabe 2012[308] Level I *Good*	7 trials (Hosono 2008,[316] Kinmond 1993[e],[318] Kugelman 2007,[319] McDonnell 1997,[321] Mercer 2006,[323] Rabe 2000,[326] Strauss 2008[327]) 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 I^2 = 0%
	5 trials (Hosono 2008,[316] Kinmond 1993,[318] Mercer 2006,[323] Oh 2002,[324] Rabe 2000[326]) 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 I^2 = 0%
LEVEL II EVIDENCE									
Alan 2014[309] 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	3 (0–7)	3 (0–8)	NR	*No significant difference*

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 (%) Mean ± SD (n) Median (range)	No placental transfusion n/N (%) Mean ± SD (n) Median (range)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					NICU stay				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 2014[310] 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 = 1.00[f]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 versus 7/13) whereas Backes (2014) is assumed to report data retrieved from the authors and which included all patients (5/17 versus 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

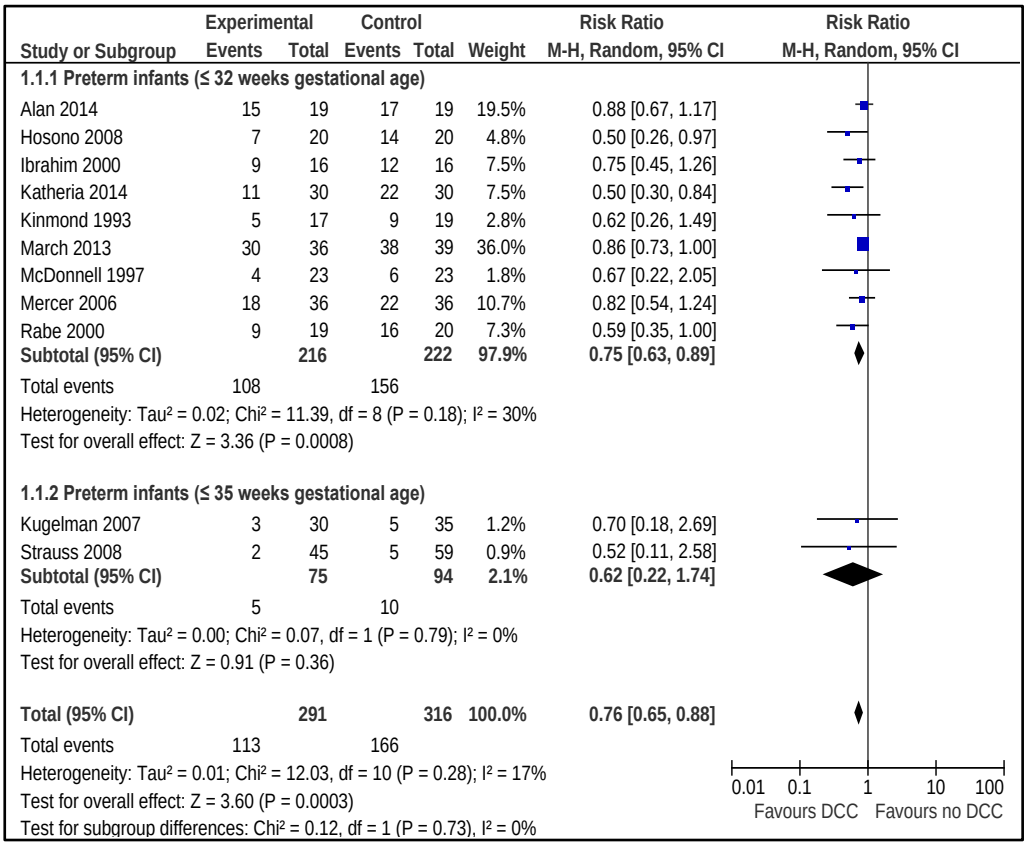
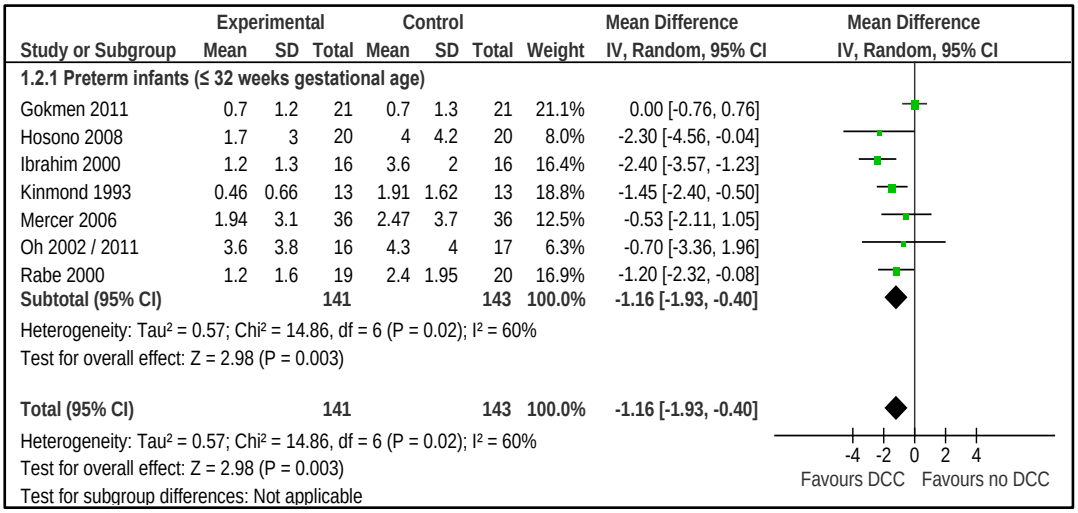


Figure 3.4.2 Meta-analysis: placental transfusion versus control in preterm infants by gestational age at birth – mean number of transfusions per infant



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).

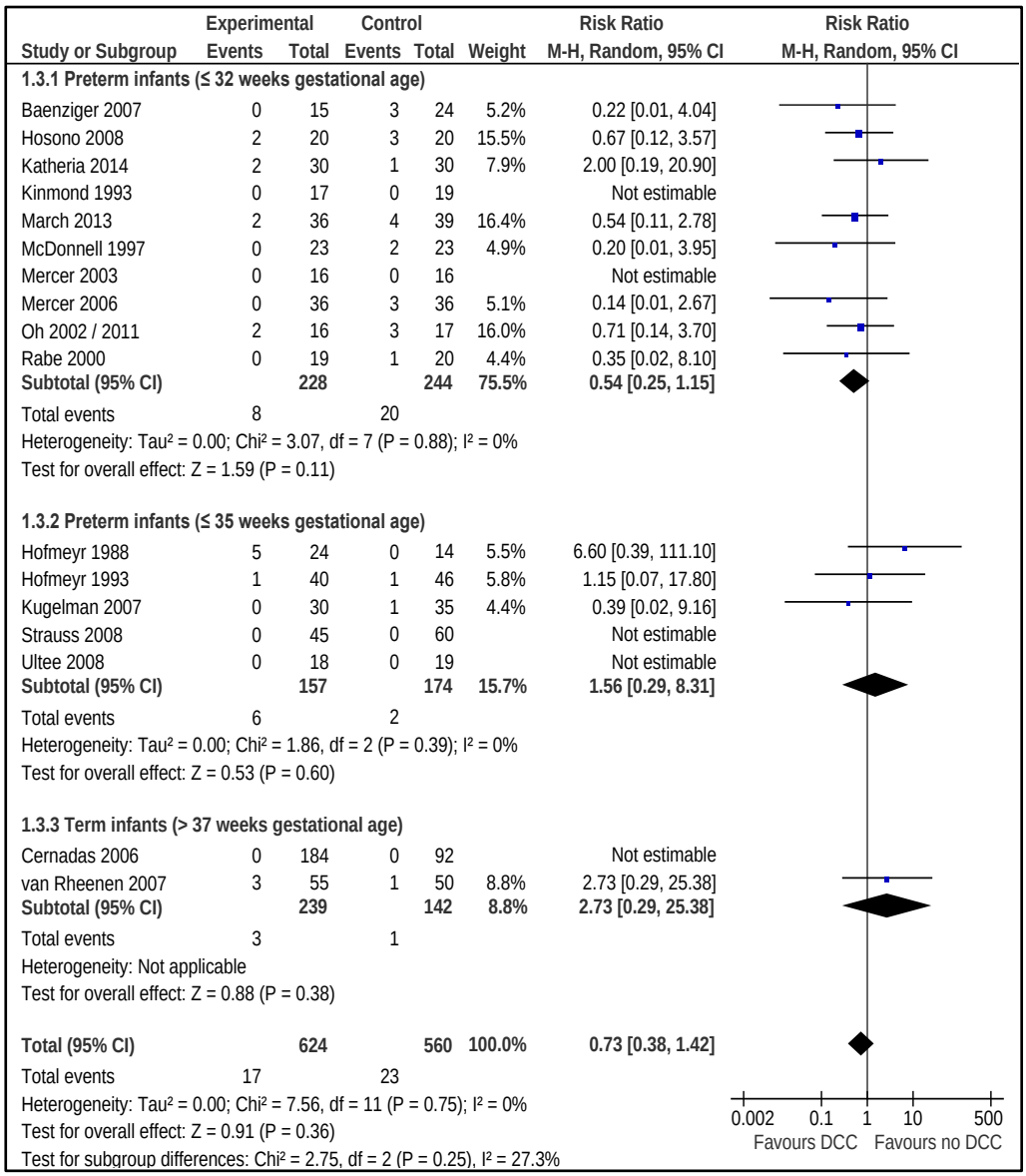
Two additional RCTs provided evidence for mortality; however neither study was sufficiently powered to detect a statistically significant difference between groups for this outcome.

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[nn] 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 (I^2=0%).

Figure 3.4.3 Meta-analysis: placental transfusion versus control in preterm and term infants by gestational age at birth – mortality



[nn] Alan (2014)[309] was not included in the meta-analysis as a composite outcome was reported.

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 2014[305] Level I *Good*	8 trials (Baenziger 2007,[311] Hosono 2008,[316] Kinmond 1993[318], March 2013,[320] McDonnell 1997,[321] Mercer 2003,[322] Mercer 2006,[323] Oh 2002[324]) 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 2011[307] 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 I^2 = NR
McDonald 2013[304] Level I *Good*	2 trials (Cernadas 2006,[312] van Rheenen 2007[329]) 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 I^2 = 0%
Rabe 2012[308] 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	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 I^2 = 0%

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]
	2008,[327] Ultee 2008[328]) N=668								
	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 2008[328]) 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 I^2 = 0%
	1 trial (Hosono 2008[316]) 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
	2 trials (Oh 2002,[324] Mercer 2006[323]) N=105		USA		Studies with low risk of bias	*Sensitivity analysis: risk of bias for allocation concealment*			
						2/52 (3.8%)	6/53 (11.3%)	RR 0.40 (0.10, 1.59)	*No significant difference* p = 0.19 No significant heterogeneity I^2 = 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 2008[328]) 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 I^2 = 0%
LEVEL II EVIDENCE									
Alan 2014[309] Level II	N=48	Preterm infants (≤32 weeks gestation) with	Single NICU, Turkey	Placental transfusion (cord milking) versus no	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 = 0.29[c]

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]
Fair		VLBW (≤1500 g)		placental transfusion (ICC)	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 2014[310] 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 = 0.56[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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[oo]

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.[pp]

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

[oo] 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.

[pp] Note: The systematic review by Rabe (2012) included Oh (2002) in a meta-analysis for IVH (all grades) only.

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 2014[305] Level I *Good*	9 trials[c] (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 2011[325]) 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 I^2 = 0%
	6 trials[d] (Hosono 2008,[316] March 2013,[320] McDonnell 1997,[321] Mercer 2003,[322] Mercer 2006,[323] Oh 2002[324]) 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 I^2 = 0%
Ghavam 2013[306] Level I *Poor*	6 trials (Ibrahim 2000,[317] Kugelman 2007,[319] Mercer 2006,[323] Oh 2011,[325] Rabe 2000,[326] Windrim 2011[330]) 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 I^2 = NR
Mathew 2011[307] 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 I^2 = NR

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]
Rabe 2012[308] 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 2008[327]) 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 I^2 = 0%
	6 trials (Hofmeyr 1988,[314] Hofmeyr 1993,[315] Hosono 2008,[316] Mercer 2003,[322] Mercer 2006,[323] Rabe 2000[326]) 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 I^2 = 0%
						Subgroup analysis: intervention			
	5 trials (Mercer 2003,[322] Rabe 2000,[326] Hofmeyr 1988,[314] Mercer 2006,[323] Hofmeyr 1993[315]) 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 I^2 = 0%
	1 trial (Hosono 2008[316]) 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 2006[323]) 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 2000[326])		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 I^2 = 0%

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]
	N=233								
LEVEL II EVIDENCE									
Alan 2014[309] 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 = 0.19[e]
Katheria 2014[310] 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 = 0.40[e]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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)

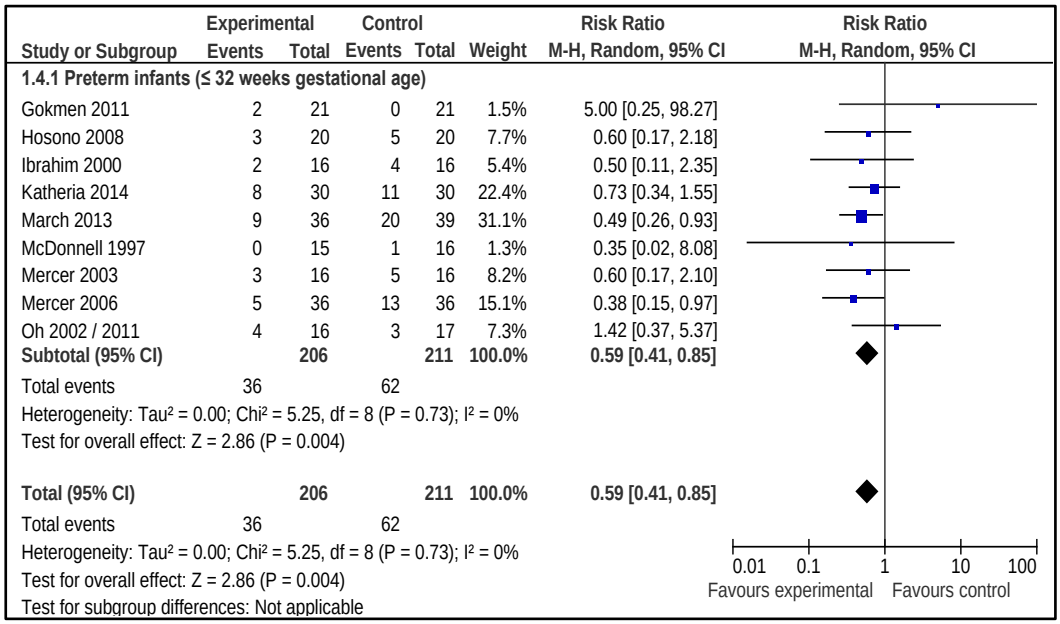
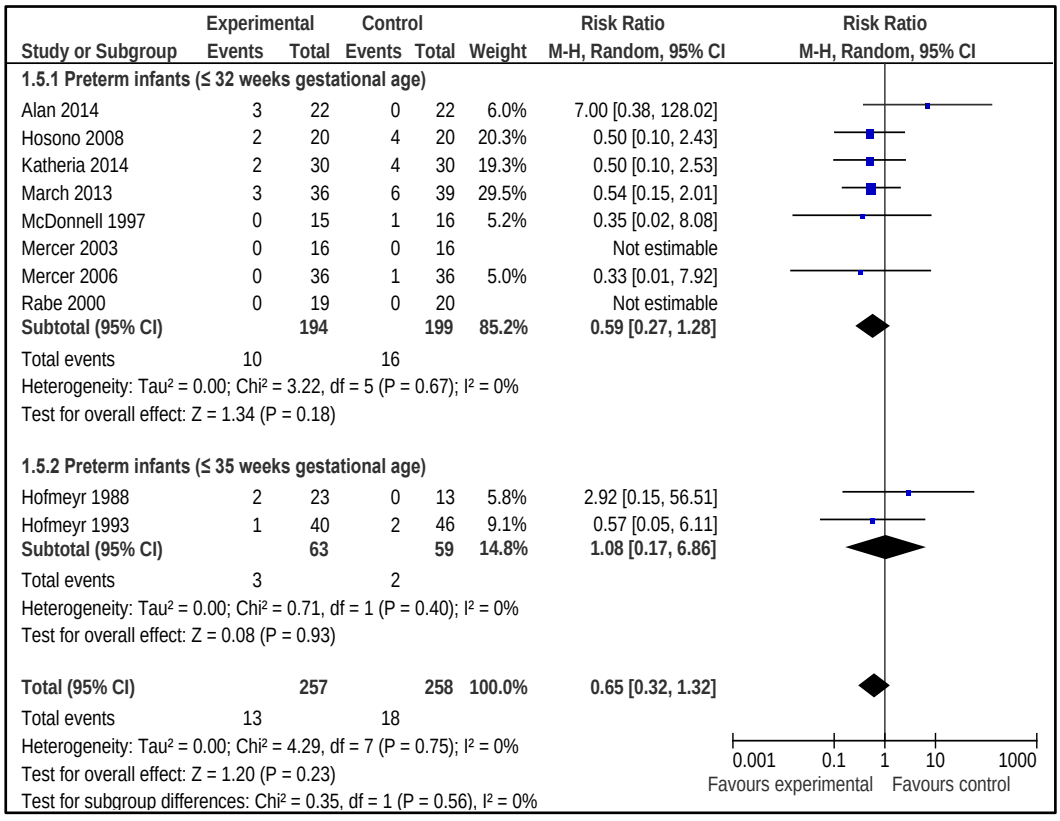


Figure 3.4.5 Meta-analysis of placental transfusion versus control in preterm infants by gestational age at birth – severe IVH (grades 3 and 4)



3.4.2.2 IVIg for haemolytic disease

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

Recommendation – preterm and term infants (IVIg for haemolytic disease)	
R7 (Grade B)	In neonates with haemolytic disease of the fetus and newborn, the *routine* use of IVIg is not recommended.
Practice point – preterm and term infants (IVIg for haemolytic disease)	
PP34	Neonates at risk of haemolytic disease of the fetus and newborn should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy.
Expert opinion point – preterm and term infants (IVIg for haemolytic disease)	
EOP6	In maternity patients with a fetus affected by haemolytic disease of the fetus and newborn who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered.
EOP, expert opinion point; IVIg, intravenous immunoglobulin; 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 haemolytic disease of the fetus and newborn.

Background

Haemolytic disease of the fetus and newborn (HDFN) is characterised by a breakdown of RBCs by maternal antibodies. During pregnancy, some of the mother's antibodies are transported across the placenta and enter the fetal circulation. 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 2014 [a]				
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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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=34[c] *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	IVIg (0.8 g/kg/day) for 3 days (n=20) versus no IVIg (n=20) *all infants received	Exchange transfusion incidence[d] Mortality

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
		test N=40 *neonates who received prenatal therapy (maternal IVIg or IUT) were excluded	conventional phototherapy	

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 (I^2=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

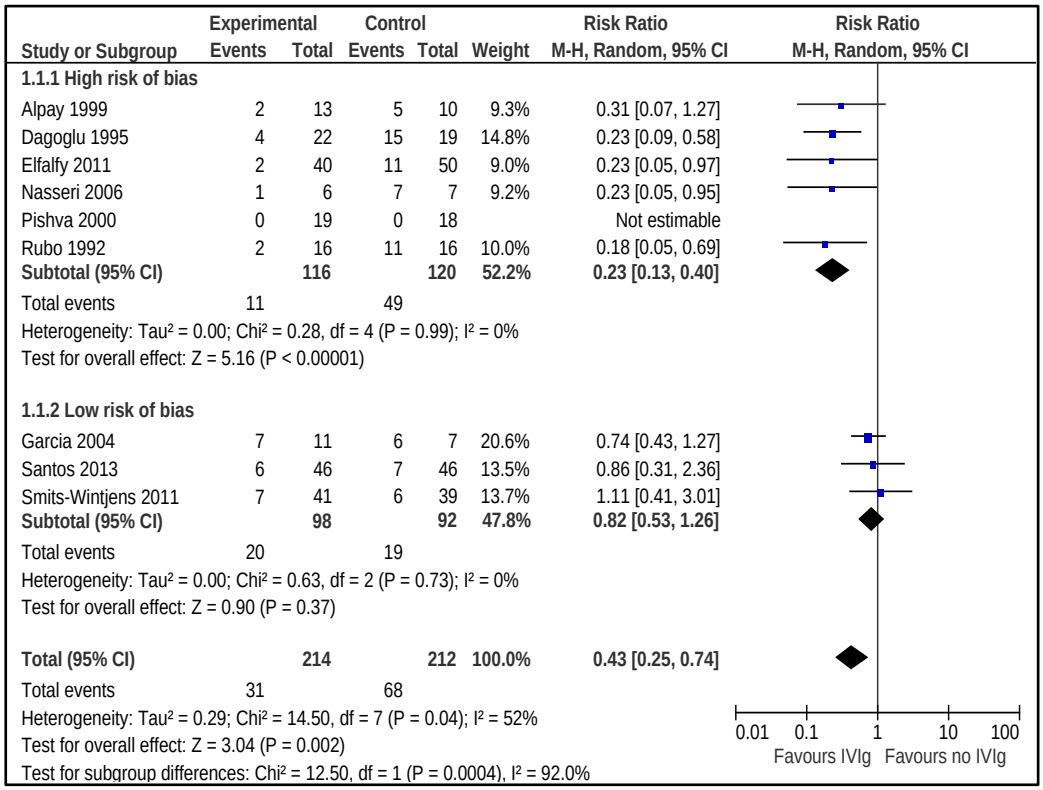


Figure 3.4.7 Meta-analysis: IVIg for haemolytic disease due to Rh isoimmunisation (prophylactic only) in preterm and term infants – exchange transfusion incidence

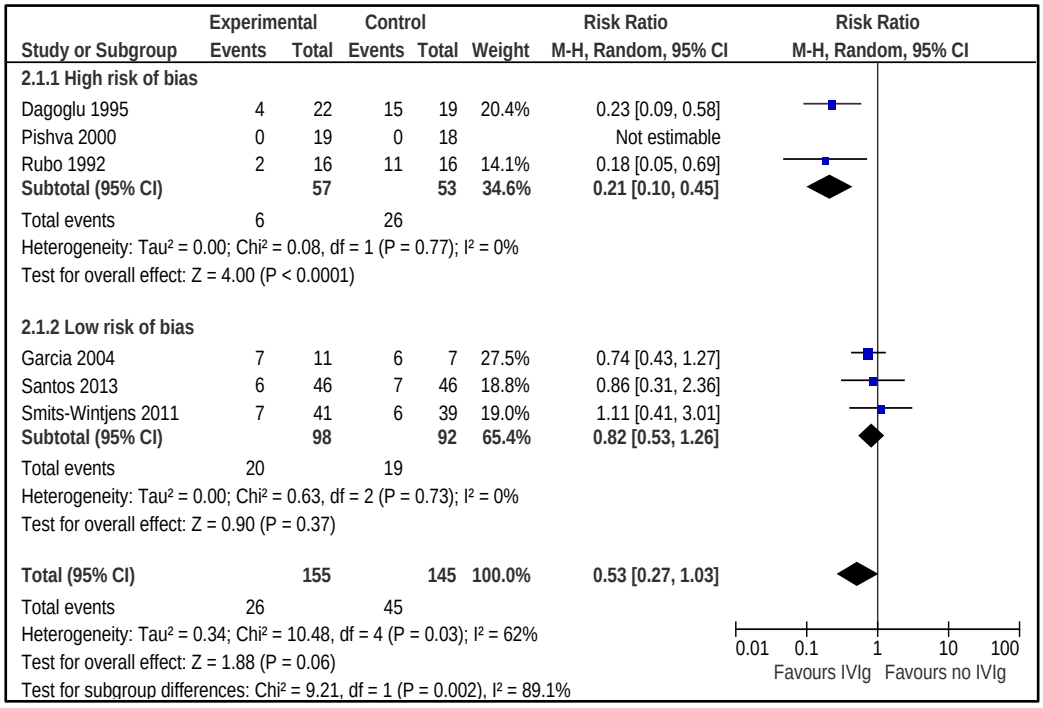


Figure 3.4.8 Meta-analysis: IVIg for haemolytic disease due to ABO isoimmunisation in preterm and term infants – exchange transfusion incidence

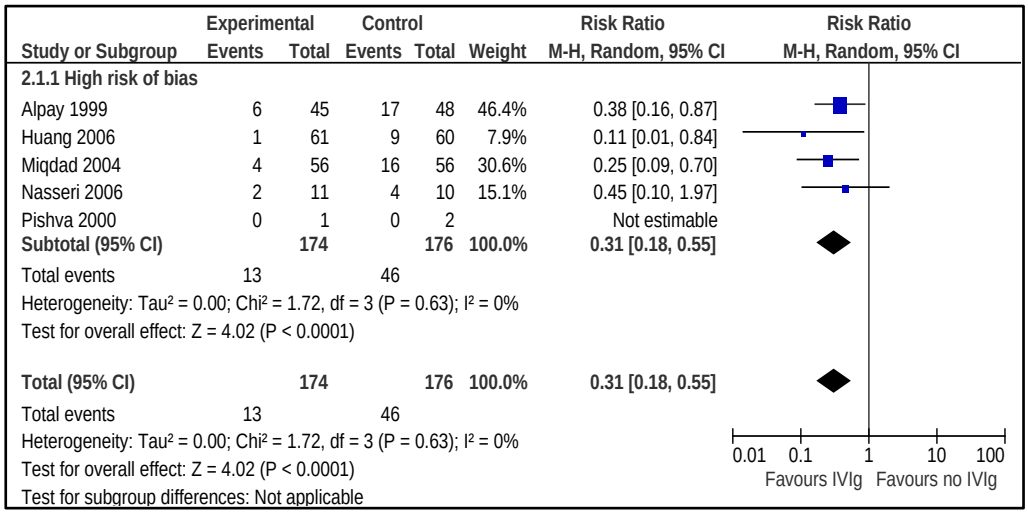


Table 3.4.8 Preterm and term infants: Results for IVIg versus no IVIg – exchange transfusion incidence

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 2014[333] 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 2011[344]) 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 = 0.002[c] Significant heterogeneity I^2 = 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 I^2 = 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 I^2 = 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 I^2 = 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 < 0.0001[c] No significant heterogeneity I^2 = 0%
						Subgroup analysis: gestational age at birth			

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]
					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 I^2 = 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 I^2 = 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 I^2 = 92%
	5 trials (Alpay 1999,[334] Huang 2006,[338] Miqdad 2004,[339] Nasseri 2006,[340] Pishva 2000[341]) 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 I^2 = 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 I^2 = 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2014[333] 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 2000[341], Rubo 1992,[342] Santos 2013,[343] Smits-Wintjens 2011,[344] Voto 1995[345]) 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 I^2 = 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.4.3 Neonatal and paediatric patients undergoing surgery

3.4.3.1 Prevention of hypothermia

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

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.*[16]
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 2011[346]	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 2011[346] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2011[346] 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 = 0.81[c]
					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 = 0.60[c]
					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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.4.3.2 Deliberate/controlled induced hypotension

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

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 1996[347] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 1996[347] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.4.3.3 Acute normovolaemic haemodilution

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

Practice points – surgical (acute normovolemic haemodilution)	
PP35	In paediatric patients, acute normovolemic haemodilution has not been shown to reduce transfusion or improve clinical outcomes. However, if acute normovolemic haemodilution is used, it requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.
PP, practice point	

Evidence gaps and areas for future research
• Further research is needed on the role of acute normovolemic haemodilution 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 = 0.63[c]
					RBC transfusion post CPB	3/16 (18.8%)	3/16 (18.8%)	RR 1.00 [0.24, 4.23][c]	*No significant difference* p = 1.00[c]
					FFP transfusion incidence	1/16 (6.3%)	3/16 (18.8%)	RR 0.33 [0.04, 2.87][c]	*No significant difference* p = 0.32[c]
					Platelet transfusion incidence	0/16 (0.0%)	3/16 (18.8%)	RR 0.14 [0.01, 2.56][c]	*No significant difference* p = 0.19[c]
					FFP or platelet transfusion incidence	1/16 (6.2%)	5/16 (31%)	RR 0.20 [0.03, 1.53][c]	*No significant difference* p = 0.12[c]
					Cryoprecipitate transfusion incidence	0/16 (0.0%)	0/16 (0.0%)	Not estimable	*No significant difference* p = NA
Hans 2000[349] 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 = 0.63[c]
					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 = 0.17[c]
Lisander 1996[350] 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 = 0.56[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.4.3.4 Intraoperative cell salvage

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

Practice points – surgical (intraoperative cell salvage)	
PP36	In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, intraoperative cell salvage may be considered. If intraoperative cell salvage is used, it requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.
PP, practice point	

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 RBCs 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 2013[351] 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 2013[352] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2013[351] 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 1996[350] 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 2013[352] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.4.3.5 Viscoelastic point-of-care testing

Evidence statements – neonatal and paediatric patients undergoing surgery (viscoelastic point-of-care testing)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.19	In paediatric patients undergoing surgery, the effect of viscoelastic POC testing compared with no viscoelastic POC testing on mortality is unknown.	NA	NA	NA	NA	NA
ES4.20	In paediatric patients undergoing surgery, the effect of viscoelastic POC testing compared with no viscoelastic POC testing on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES4.21	In paediatric patients undergoing surgery, the effect of viscoelastic POC testing compared with no viscoelastic 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						

Practice points – surgical (viscoelastic point-of-care testing)	
PP37	In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, viscoelastic point-of-care testing may be considered.
POC, point of care; PP, practice point	

Evidence gaps and areas for future research
Further research is needed on: • the role of viscoelastic point-of-care testing in paediatric patients undergoing other types of surgery in which substantial blood loss is anticipated • the role of viscoelastic point-of-care testing in neonates and infants.

Background

Viscoelastic 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 viscoelastic POC testing compared with no viscoelastic 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 viscoelastic POC testing compared with no viscoelastic POC testing in neonatal and paediatric patients undergoing surgery.[qq]

[qq] One small RCT[353] 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 results reported by Nakayma (2015) will be included in the technical report when the module is reviewed and updated.

3.4.3.6 Antifibrinolytics (aprotinin, tranexamic acid or epsilon-aminocaproic acid)

Evidence statements – neonatal and paediatric patients undergoing surgery (antifibrinolytics)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.22	In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on mortality is uncertain. (See evidence matrix D4.L in Volume 2 of the technical report.)	√√	√√√	NA	√√	√
ES4.23	In paediatric patients undergoing cardiac surgery, antifibrinolytics compared with no antifibrinolytics reduce transfusion volume and incidence. (See evidence matrix D4.M in Volume 2 of the technical report.)	√√	√√	√	√√	√
ES4.24	In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume. (See evidence matrix D4.N in Volume 2 of the technical report.)	√√	√√	√	√√√	√√
ES4.25	In paediatric patients undergoing surgery for scoliosis, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain. (See evidence matrix D4.N in Volume 2 of the technical report.)	√√	√√	NA	√√√	√√
ES4.26	In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume. (See evidence matrix D4.O in Volume 2 of the technical report.)	√√	√√	√	√√	√√
ES4.27	In paediatric patients undergoing craniofacial surgery, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain. (See evidence matrix D4.O in Volume 2 of the technical report.)	√√	√√	NA	√√	√√
ES4.28	In paediatric patients undergoing primary adenoidectomy, the effect of topical 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	√√√	√
ES4.29	In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on thromboembolic events is uncertain. (See evidence matrix D4.Q in Volume 2 of the technical report.)	√√	√√√	NA	√√	√

Evidence statements – neonatal and paediatric patients undergoing surgery (antifibrinolytics)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.30	In paediatric patients undergoing cardiac surgery, the effect of antifibrinolytics compared with no antifibrinolytics on postoperative blood loss in uncertain. (See evidence matrix D4.R in Volume 2 of the technical report.)	√	√	NA	√√	√
ES4.31	In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics may reduce blood loss. (See evidence matrix D4.S in Volume 2 of the technical report.)	√√	√√	√	√√√	√√
ES4.32	In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics reduce perioperative blood loss. (See evidence matrix D4.T in Volume 2 of the technical report.)	√√	√√√	√	√√	√
ES4.33	In paediatric patients undergoing ENT surgery, antifibrinolytics compared with no antifibrinolytics may reduce perioperative blood loss. (See evidence matrix D4.U in Volume 2 of the technical report.)	√√	√√	X	√√	√
ENT, ear nose throat; ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendation – surgical (antifibrinolytics)	
R9 (Grade C)	In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, the use of antifibrinolytics is suggested.[a, b, c] [a] Although there is evidence of a reduction in transfusion, there is insufficient evidence to determine the risk of thromboembolic complications. [b] Tranexamic acid in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. Epsilon-aminocaproic acid is not licensed for use in Australia. [c] See Appendix J (*Tranexamic acid dosing guidance*) for further information.
R10 (Grade C)	In paediatric patients undergoing surgery for scoliosis in whom substantial blood loss is anticipated, the use of antifibrinolytics may be considered.[a, b] [a] Tranexamic acid in this context is approved in Australia. The use of aprotinin in this context is considered off label in Australia. Epsilon-aminocaproic acid is not licensed for use in Australia. [b] See Appendix J (*Tranexamic acid dosing guidance*) for further information.
R11 (Grade C)	In paediatric patients undergoing craniofacial surgery in whom substantial blood loss is anticipated, the use of antifibrinolytics may be considered.[a, b] [a] Tranexamic acid in this context is approved in Australia. The use of aprotinin in this

	context is considered off label in Australia. Epsilon-aminocaproic acid is not licensed for use in Australia. [b] See Appendix J (*Tranexamic acid dosing guidance*) for further information.

Practice points – surgical (antifibrinolytics)	
PP38	In acutely bleeding critically ill paediatric trauma patients, tranexamic acid should be administered within 3 hours of injury.[a, b] [a] See R3 in *Patient Blood Management Guidelines: Module 4 – Critical Care.*[15] [b] See Appendix J (*Tranexamic acid dosing guidance*) for further information.
PP39	In paediatric trauma patients aged under 12 years, a tranexamic acid dose of 15 mg/kg (maximum 1000 mg) infused intravenously over 10 minutes, followed by 2 mg/kg/hour (maximum 125 mg/hour) until bleeding is controlled or for up to 8 hours is suggested.[a, b] [a] See the template given in Appendix K (*Critical bleeding protocol*), which is intended for local adaptation.[354] [b] See Appendix J (*Tranexamic acid dosing guidance*) for further information.
PP, practice point; R, recommendation	

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) may 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 trial[355] 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*[16]).

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 2012[357]) 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 surgery[a] 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 RCTs[b], 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 score[b] 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 score[b] 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 score[b] 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 100 mg/kg doses versus aprotinin + TXA versus no treatment	Transfusion volume Blood loss
Chauhan (2000)[366]	RCT *Jadad score[b] 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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
Chauhan (2004 a)[368]	RCT *Jadad score[b] 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 score[b] 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/m^2 + 56,000 KIU/m2/hr until skin closure + 240,000 KIU/m^2 prime (BSA <1.16 m^2) OR 250,000 KIU/m^2 + 70,000 KIU/m2/hr until skin closure + 280,000 KIU/m^2 prime (BSA >1.16 m^2) versus placebo	Transfusion volume and incidence Blood loss
D'Errico (1996)[371]	RCT *Jadad score[b] 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/m^2 + 28 mg/m^2 continuous infusion + 120 mg/m^2 prime versus IV aprotinin 240 mg/m^2 + 56 mg/m^2 continuous infusion + 240 mg/m^2 prime versus placebo	Transfusion volume and incidence Blood loss
Dietrich (1993)[372]	RCT *Jadad score[b] 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/m^2 + 50 mg/m^2/hr until end of surgery + 50 mg KIU/m^2 prime versus placebo	Blood loss
Herynkopf (1994)[374]	RCT *Jadad score[b] 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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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 score[b] 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 score[b] 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 score[b] 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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
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 surgery[b]				
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/m^2 followed by 56 mg/m2/hr continuous infusion (max 280 mg/m^2) 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

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
Goobie (2011)[390]	RCT *Jadad composite scale[d] 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/m^2 infusion and in perfusate oxygenator + 56 mg/m^2 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	RCT	Children aged 11–18	IV EACA 100 mg/kg	Transfusion volume

Study ID	Study type *Study quality*	Population N	Comparison	Outcomes
(2005)[381]	*Poor*	years with idiopathic scoliosis scheduled for posterior spinal fusion with segmental spinal instrumentation N=36	before skin incision followed by maintenance infusion 10 mg/kg/hr until skin closure versus no treatment	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 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 I EVIDENCE									
Scoliosis surgery									
Tzortzopoulou 2008[361] Level I *Good*	6 trials (Cole 2002[c,383] Cole 2003,[384] Florentino-Pineda 2004,[385] Khoshhal 2003,[386] Neilipovitz 2001,[387] Sethna 2005[388]) 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 I^2 = NR
LEVEL II EVIDENCE									
Cardiac surgery									
Coniff 1998[d393] 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 = 0.08[e]
					High-dose	1/31 (3.2%)			
					Low-dose	2/33 (6.1%)			
					Pump prime only	1/18 (5.6%)			
Ferreira 2010[394] 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
Saruprria 2013[396] 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 2001[397] Level II *Fair*	N=75	Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot undergoing total	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

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]
		correction with CPB							
Vacharaksa 2002[398] 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 2014[400] 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 2003[401] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 I^2=96% and reasons for heterogeneity were not explored.[rr]

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.

[rr] 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.

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).[ss] However, in a

[ss] 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.

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 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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL I EVIDENCE									
Transfusion volume									
Arnold 2006[c358] Level I *Good*	6 trials[d] (Boldt 1993 a,[404] Chauhan 2000,[366] Davies 1997,[370] D'Errico 1996,[371] Herynkopf 1994,[374] Seghaye 1996[380]) 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 I^2 = 96%
Faraoni 2012[e359] Level I *Fair*	6 trials[f] (Bulutcu 2005,[365] Chauhan 2003,[367] Chauhan 2004 a,[368] Chauhan 2004b,[369] Reid 1997,[379] Shimizu 2011[381]) 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 I^2 = 0%
	4 trials[f] (Chauhan 2003,[367] Chauhan 2004 a,[368] Chauhan 2004b,[369] Shimizu 2011[381]) 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 I^2 = 0%
	5 trials[f] (Bulutcu 2005,[365] Chauhan 2003,[367] Chauhan 2004 a,[368] Chauhan 2004b,[369] Shimizu 2011[381]) 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 I^2 = 0%
						Sensitivity analyses: excluding Chauhan 2004 a due to potential bias			

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					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 I^2 = 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 I^2 = 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 I^2 = 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 I^2 = 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 I^2 = 40%
Schouten 2009[360] Level I *Good*	3 trials (Davies 1997,[370] Chauhan 2000,[366] Bulutcu 2005[365]) 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 I^2 = 0%
	2 trials (Chauhan 2000,[366] Bulutcu 2005[365]) N=228				Plasma transfusion volume	NR	NR	WMD –5 (–8, –2)	*Favours aprotinin* p = NR No significant

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
									heterogeneity I^2 = 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 I^2 = 0%
	3 trials (Chauhan 2000,[366] Chauhan 2004,[368-369] Rao 2000[378]) N=410			EACA versus placebo	Plasma transfusion volume	NR	NR	WMD –3 (–5, –1)	*Favours EACA* p = NR Mild heterogeneity I^2 = 20%
Transfusion incidence									
Arnold 2006[c358] Level I *Good*	6 trials[d] (Mossinger 2003,[377] Miller 1998,[376] Davies 1997,[370] D'Errico 1996,[371] Herynkopf 1994,[374] Boldt 1994[364]) 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 I^2 = 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 I^2 = 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 I^2 = NR
					Patients undergoing primary sternotomy 3 trials (Mossinger 2003, Boldt 1994, Herynkopf 1994)	NR	NR	RR 0.44 [0.26, 0.76]	*Favours aprotinin* p = NR Heterogeneity NR I^2 = NR

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					N=120				
						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 I^2 = 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 1998[g393] 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			
									No significant difference
					High-dose	2.9 ± 8.5 (n=31)	11.3 ± 23.7 (n=34)	MD –8.40 [–16.91, 0.11][h]	p = 0.05[h]
					Low-dose	6.0 ± 5.1 (n=33)	11.3 ± 23.7 (n=34)	MD –5.30 [–13.45, 2.85][h]	p = 0.20[h]
					Pump prime only	9.1 ± 12.6 (n=18)	11.3 ± 23.7 (n=34)	MD –2.20 [–12.07, 7.67][h]	p = 0.66[h]
						Subgroup analyses: patients undergoing redo operations (more prone to bleeding)			
									No significant difference
					High-dose	7.1 ± 10.4 (n=19)	5.2 ± 28.6 (n=22)	MD –8.10 [–20.93, 4.73][h]	p = 0.22[h]
					Low-dose	7.4 ± 5.4 (n=22)	15.2 ± 28.6 (n=22)	MD –7.80 [–19.96, 4.36][h]	p = 0.21[h]
					Pump prime only	11.9 ± 16.3 (n=10)	15.2 ± 28.6 (n=22)	MD –3.30 [–18.95, 12.35][h]	p = 0.68[h]
						Subgroup analysis: age			
					Patients aged ≤1 year				*No significant difference*
					High-dose	7.3 ± 3.2 (n=3)	9.0 ± 6.5 (n=6)	MD –1.70 [–8.04, 4.64][h]	p = 0.60[h]
					Low-dose	5.0 ± 3.1 (n=14)	9.0 ± 6.5 (n=6)	MD –4.00 [–9.45, 1.45][h]	p = 0.15[h]

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					Pump prime only	14.1 ± 17.6 (n=8)	9.0 ± 6.5 (n=6)	MD 5.10 [–8.16, 18.36][h]	p = 0.45[h]
					Patients aged 1–17 years				*No significant difference*
					High-dose	5.0 ± 8.9 (n=28)	11.8 ± 26.0 (n=28)	NR	NR
					Low-dose	6.8 ± 6.1 (n=19)	11.8 ± 26.0 (n=28)	NR	NR
					Pump prime only	5.1 ± 4.5 (n=10)	11.8 ± 26.0 (n=28)	NR	NR
					Donor blood transfused (units)	*Subgroup analysis: patients aged >1 and <17 years*			
					High-dose	2.6 ± 1.8 (n=28)	4.8 ± 6.5 (n=28)	MD –2.20 [–4.70, 0.30][h]	*No significant difference* p = 0.08
					Low-dose	3.7 ± 2.3 (n=19)	4.8 ± 6.5 (n=28)	MD –1.10 [–3.72, 1.52][h]	p = 0.41
					Pump prime only	2.8 ± 2.2 (n=10)	4.8 ± 6.5 (n=28)	MD –2.00 [–4.77, 0.77][h]	p = 0.16
Ferreira 2010[394] 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 = 0.37[h]
					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 = 0.20[c]
Flaujac 2007[395] 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 2013[396] 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)				

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					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 2001[397] Level II *Fair*	N=75	Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot	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

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
		undergoing total correction with CPB			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 2002[398] 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 1998[f393]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 product transfusion incidence	All patients			
					High-dose	NR (93.5%)	NR (85.3%)	NR	NR
					Low-dose	NR (93.9%)	NR (85.3%)	NR	NR
					Pump prime only	NR (88.9%)	NR (85.3%)	NR	NR
						Subgroup analysis: patients undergoing redo operations (more prone to bleeding)			
					High-dose	NR (94.7%)	NR (90.9%)	NR	NR
					Low-dose	NR	NR	NR	NR
					Pump prime only	NR	NR	NR	NR
						Subgroup analysis: age			
					Patients aged ≤1 year High-dose	NR	NR	NR	NR

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					Low-dose	NR (92.9%)	NR	NR	NR
					Pump prime only	NR	NR	NR	NR
					Patients aged >1 and <17 years				
					High-dose	NR (92.9%)	NR (82.1%)	NR	NR
					Low-dose	NR (94.7%)	NR (82.1%)	NR	NR
					Pump prime only	NR (80.0%)	NR (82.1%)	NR	NR
					Patients requiring ≥ 20 units of donor blood *or* blood products	All patients			
					High-dose	NR (3.2%)	NR (11.8%)	NR	NR
					Low-dose	NR (3.0%)	NR (11.8%)	NR	NR
					Pump prime only	NR (5.6%)	NR (11.8%)	NR	NR
						Subgroup analysis: patients undergoing redo operations (more prone to bleeding)			
					High-dose	NR (5.3%)	NR (13.6%)	NR	NR
					Low-dose	NR (4.5%)	NR (13.6%)	NR	NR
					Pump prime only	NR (10.0%)	NR (13.6%)	NR	NR
						Subgroup analysis: age			
					Patients aged ≤1 year				
					High-dose	NR	NR (16.7%)	NR	NR
					Low-dose	NR	NR (16.7%)	NR	NR
					Pump prime only	NR (12.5%)	NR (16.7%)	NR	NR
					Patients aged >1 and <17 years				
					High-dose	NR (3.6%)	NR (10.7%)	NR	NR
					Low-dose	NR (5.3%)	NR (10.7%)		
					Pump prime only	NR	NR (10.7%)		
					Patients requiring ≥ 20 units of donor blood	*Subgroup analysis: patients aged >1 and <17 years*			
					High-dose	NR (14.3%)	NR (28.6%)	NR	NR
					Low-dose	NR (31.6%)	NR (28.6%)	NR	NR

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					Pump prime only	NR (30.0%)	NR (28.6%)	NR	NR
Ferreira 2010[394] 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 = 0.52[h]
					Postoperative platelet concentration transfusion incidence	0/10 (0%)	2/9 (22%)	RR 0.18 [0.01, 3.35][h]	*No significant difference* p = 0.25[h]
					No. of postoperative donor exposures	2/10 (20%)	2/9 (22.2%)	RR 0.90 [0.16, 5.13][h]	*No significant difference* p = 0.91[h]
Flaujac 2007[395] 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 = 0.06[h]
					24 hr postoperative platelet transfusion incidence	3/10 (30%)	6/10 (60%)	NR	*No significant difference* p = 0.21[h]
					24 hr postoperative FFP transfusion incidence	2/10 (20%)	3/10 (30%)	NR	*No significant difference* p = 0.61[h]
					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 2013[396] 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				

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) Median (IQR)	No antifibrinolytics n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
					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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2= 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 2008[361] Level I *Good*	5 trials (Cole 2003,[384] Khoshhal 2003,[386] Neilipovitz 2001,[387] Sethna 2005,[388] Florentino-Pineda 2004[385]) 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 I^2 = 0%
	4 trials (Khoshhal 2003,[386] Neilipovitz 2001,[387] Sethna 2005,[388] Florentino-Pineda 2004[385]) 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 I^2 = 0%
	2 trials (Cole 2003,[384] Khoshhal 2003[386]) 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 I^2 = 0%
	1 trial (Khoshhal 2003[386]) 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 2005[388]) 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 I^2 = 0%
					Transfusion incidence	0	0	Not estimable	*No significant difference* p = NA

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]**
					(allogeneic blood only)				Heterogeneity NR I^2 = NR
					Total blood transfused (mL)	NR	NR	MD –395.14 [–687.55, –102.73]	*Favours TXA* p = 0.0081 No significant heterogeneity I^2 = 0%
	1 trial (Florentino-Pineda 2004[385]) 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 2009[360] Level I *Good*	2 trials (Sethna 2005,[388] Neilipovitz 2001[387]) 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 I^2 = 24%
LEVEL I EVIDENCE									
Thompson 2005[405] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2=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 2013[362] Level I/III *Fair*	3 trials[c] (Dadure 2011,[389] Goobie 2011,[390] Maugans 2011[406]) 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 I^2 = 0%
LEVEL II EVIDENCE									
Ahmed 2014[400] 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 = 0.08 [d]
					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 = 0.20 [d]
					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 = 0.8 [d]
					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 = 0.62 [d]
					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 2003[401]	N=39	Paediatric patients aged 1 month to 12	Single hospital, USA	IV aprotinin versus placebo	Intraoperative blood transfusion volume	32 ± 25 (n=18)	52 ± 34 (n=21)	MD –20.00 [–38.57, –1.43]	*Favours aprotinin* p = 0.04

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 *Good*		years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement			(mL/kg)				
					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 = 0.44 [d]
					FFP transfusion incidence	2/18 (11.1%)	5/21 (23.8)	RR 0.47 [0.10, 2.12][d]	*No significant difference* p = 0.32 [d]
					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

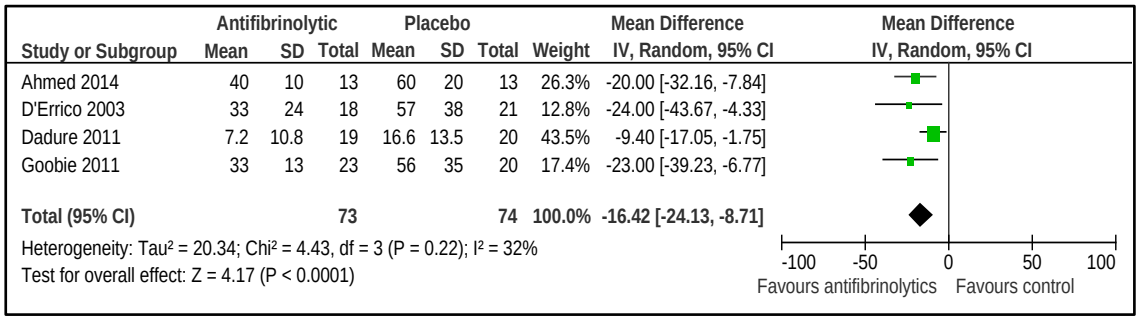
a. Where only one study is available in systematic review, the level of evidence has been downgraded to Level I/II. The quality of the Level II study is based on the quality assessment reported by the systematic review authors.

b. Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet >0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2013[363] Level I/II *Good*	1 trial (Albirmawy 2013[391]) 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 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									
Cardiac surgery									
Flaujac 2007[395] 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 2002[398] 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 2008[361] Level I/II *Good*	1 trial (Cole 2003[384]) 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 = 0.21[c]
Thompson 2005[405] 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 2014[400] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 (I^2=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 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									
Arnold 2006[358] Level I *Good*	11 trials[c] (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 2003[377]) 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 I^2 = 77%
Faraoni 2012[d359] Level I *Fair*	8 trials[e] (Bulutcu 2005,[365] Chauhan 2003,[367] Chauhan 2004 a,[368] Chauhan 2004b,[369] Levin 2000,[375] Reid 1997,[379] Shimizu 2011,[381] Zonis 1996[382]) 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 I^2 = 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 I^2 = 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 I^2 = 0%
						Subgroup analysis of acyanotic patients			
					3 trials (NR) N=298	NR	NR	NR	*No significant difference* p = 0.47 Heterogeneity NR I^2 = NR

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									
Aggarwal 2012[392] 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 = 0.26[e]
Ferreira 2010[394] 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 2013[396] 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 2001[397] Level II *Fair*	N=75	Paediatric cyanotic patients (mean age 3.5 years) with tetralogy of Fallot	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

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]**
		undergoing total correction with CPB			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 2002[398] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2008[361] Level I *Good*	5 trials (Cole 2003,[384] Khoshhal 2003,[386] Neilipovitz 2001,[387] Sethna 2005,[388] Florentino-Pineda 2004[385]) N=163	Paediatric patients aged <18 years undergoing scoliosis surgery	Canada (Khoshhal 2003, Neilipovitz 2001), USA (Cole 2003, Sethna 2005, Florentino-Pineda 2004[385])	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 I^2 = 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 I^2 = 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 I^2 = 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 2005[405] 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 = 0.48[c]
					Postoperative chest tube drainage (mL)	498 ± 179 (n=19)	764 ± 284 (n=17)	MD –266.00 [–423.17, –108.83][c]	*Favours EACA* p = 0.0009[c]
					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 2014[399] Level II	N=125	Patients with adolescent idiopathic scoliosis	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

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]**
Good		undergoing posterior spinal arthrodesis			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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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).

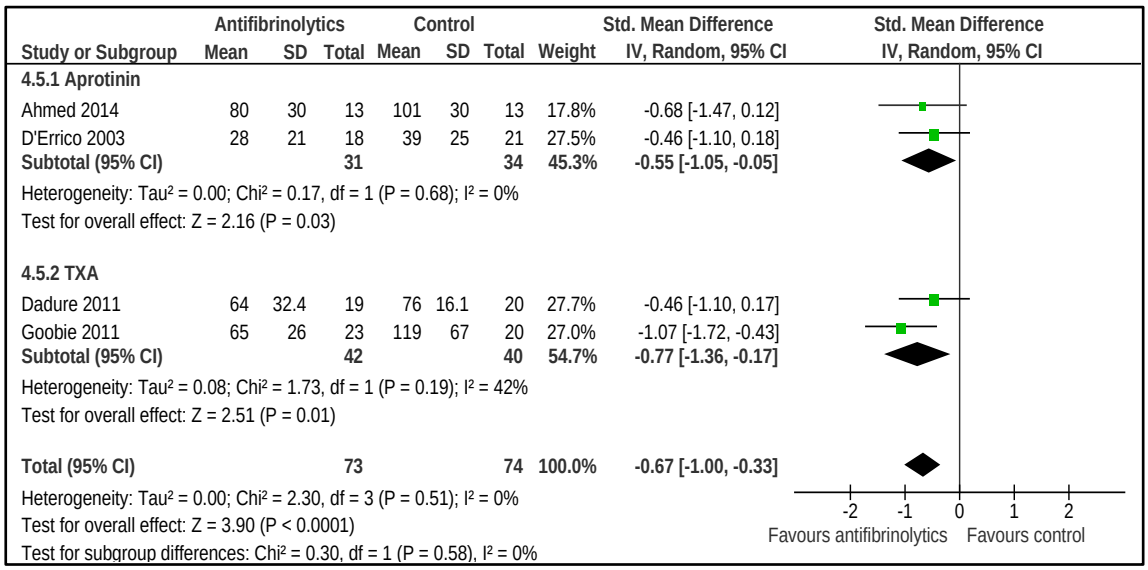
A meta-analysis of all included Level II studies was conducted to assess the effect of antifibrinolytics (TXA or aprotinin) on perioperative blood loss (**Figure 3.4.10**). The analysis showed a significant reduction in the volume of blood loss favouring the use of antifibrinolytics in craniofacial surgery (SMD –0.67, 95% CI –1.00, –0.33). There was no significant heterogeneity for this outcome (I^2=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 2013[362] Level I/III *Fair*	3 studies[c] (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 I^2 = 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 I^2 = 82%
LEVEL II EVIDENCE									
Ahmed 2014[400] 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 = 0.07[e]
D'Errico 2003[401] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2013[363] Level I/II *Good*	1 trial (Albirmawy 2013[391]) 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 2012[402] 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 2013[403] 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	8/50 (16.0%)	24/50 (48.0%)	NR	*Favours TXA*

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]
					bleeding) 15 minutes after beginning surgery				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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

c. Calculated post-hoc using RevMan 5.1.2.

3.4.3.7 Recombinant activated factor VII

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

Recommendation – surgical (recombinant activated factor VII)	
R12 (Grade C)	In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, the *routine* use of rFVIIa is not recommended.

Practice points – surgical (rFVIIa)	
PP40	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*.[16]
CPB, cardiopulmonary bypass; PP, practice point; R, recommendation; rFVIIa, recombinant activated 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.[tt] 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.

[tt] Only studies that assessed the use of rFVIIa in neonatal and paediatric patients undergoing cardiac surgery or receiving ECMO were included.

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 RCTs[a], 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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Simpson 2012[408] Level I *Good*	1 trial (Ekert 2006[409]) 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence[a] *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 Heterogeneity[b]
LEVEL II EVIDENCE									
Simpson 2012[408] Level I/II *Good*	1 trial (Ekert 2006[409]) 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 = 0.56[c]

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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 evidence**[a] ***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** **Heterogeneity**[b]
LEVEL II EVIDENCE									
Simpson 2012[408] Level I *Good*	1 trial (Ekert 2006[409]) 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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.

3.4.3.8 Miniaturised cardiopulmonary bypass systems

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

Evidence gaps and areas for future research
The use of miniaturised cardiopulmonary bypass 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 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 (%)	Standard-sized systems n/N (%)	Risk estimate (95% CI)	*Statistical significance* p-value Heterogeneity[b]
LEVEL II EVIDENCE									
Mozol 2008[410] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >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 2008[410] 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 I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

3.4.4 Critically ill neonatal and paediatric patients

3.4.4.1 Recombinant activated factor VII

Evidence statements – critically ill neonatal and paediatric patients (recombinant activated factor VIIa)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.46	In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on mortality is unknown.	NA	NA	NA	NA	NA
ES4.47	In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES4.48	In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is unknown.	NA	NA	NA	NA	NA
ES4.49	In critically ill paediatric patients, the effect of rFVIIa compared with no rFVIIa on bleeding events is unknown.	NA	NA	NA	NA	NA
ES, evidence statement; rFVIIa, recombinant activated factor 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.

3.4.4.2 Viscoelastic point-of-care testing

Evidence statements – critically ill neonatal and paediatric patients (viscoelastic point-of-care testing)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.50	In critically ill paediatric patients, the effect of viscoelastic POC testing compared with no viscoelastic POC testing on mortality is unknown.	NA	NA	NA	NA	NA
ES4.51	In critically ill paediatric patients, the effect of viscoelastic POC testing compared with no viscoelastic POC testing on transfusion volume or incidence is unknown.	NA	NA	NA	NA	NA
ES4.52	In critically ill paediatric patients, the effect of viscoelastic POC testing compared with no viscoelastic 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

Viscoelastic (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 viscoelastic POC testing compared with no viscoelastic 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 viscoelastic POC testing compared with no viscoelastic POC testing in critically ill neonatal and paediatric patients.

4 Appendixes

4.1 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 versus Comparator = (1) versus (1), (2) versus (2) [Intervention Foreground Question]				
Population[a]	**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 versus non-cyanotic) ▪ Transplantation ▪ Orthopaedic ▪ Burns Critical illness ▪ ECMO/ECLS ▪ Trauma <u>Stratify by:</u> • 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 <u>Primary</u> • Mortality • Composite of mortality & severe morbidity (BPD, ROP, brain injury on ultrasound, etc.) <u>Secondary</u> • Bronchopulmonary dysplasia (BPD) • Necrotising enterocolitis (NEC) • ROP • Neurodevelopmental disability • Transfusion-related SAEs (TACO, TRALI, other[a]) Infant/child/adolescent/Medical/Surgical <u>Primary</u> • Mortality • Stroke – *sickle cell disorder subgroups only* • New or progressive M/ failure – *surgical patient subgroup only* <u>Secondary</u> • Transfusion-related SAEs (TACO, TRALI, other[b]) • Functional/performance status Critical illness <u>Primary</u> • New or progressive multiple organ dysfunction/failure <u>Secondary</u> • Mortality • Transfusion-related SAEs (TACO, TRALI, other[b])	▪ 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 versus liberal studies may also use other terminology (e.g. protocol, algorithm, threshold) **Limits:** ▪ Studies published after 1995[c] ▪ 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]				
Population[a]	**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 versus non-cyanotic) ▪ Transplantation ▪ Orthopaedic ▪ Burns Critical illness ▪ ECMO/ECLS ▪ Trauma <u>Stratify by:</u> • 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 <u>or</u> any active head-to-head (e.g. 1 versus 2, 1 versus 3) 2. No intervention <u>or</u> any active head-to-head (e.g. 1 versus 2, 2 versus 3) 3. Different combination of above 4. No hydroxyurea	<u>Primary</u> • 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* <u>Secondary</u> • 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 versus 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 **<u>Limits</u>:** ▪ Studies published after 1995[c] ▪ 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 versus Comparator* = (1) versus (1), (2) versus (2), etc. [Intervention Foreground Question]				
Population[a]	**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 versus non-cyanotic) ▪ Transplantation ▪ Orthopaedic ▪ Burns ▪ Craniofacial surgery Critical illness ▪ ECMO/ECLS ▪ Trauma <u>Stratify by:</u> • 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*	<u>Primary</u> • Mortality • Bleeding events (major and minor) • Transfusion-related SAEs (TACO, TRALI, other[b]) • Transfusion volume or transfusion incidence <u>Secondary</u> • 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 **<u>Limits</u>:** ▪ studies published after 1995[c] ▪ 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; SR, systematic review; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TTP, thrombotic thrombocytopenic purpura; versus, 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-associated 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 versus comparator* = (1) versus (1), (2) versus (2), (3) versus (3), (2) versus (3) [Intervention Foreground Question]				
Population[a]	**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 versus 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,	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 <u>Primary</u> • Transfusion volume (in transfused patients only) or transfusion incidence – *placental transfusion only* • Exchange transfusion incidence – IVIg for haemolytic disease intervention only • Mortality <u>Secondary</u> • Intracranial/IVH – *placental transfusion intervention only* Infant/child/adolescent Surgical/critical illness <u>Primary</u> • 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. **<u>Limits</u>:** ▪ Limit to studies published after 1995[b] ▪ 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'

	thromboelastography)			▪ 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; SR, systematic review; TXA, tranexamic acid; versus, 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 Preterm, 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.

4.2 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.

4.2.1 Systematic reviews

Study type:				Systematic review	
Citation:					
Y	N	NR	NA	Quality criteria	Error rating[a]
				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
Comments[b]:					
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.

4.2.2 Randomised controlled trials

Study type:				Randomised controlled trial	
Citation:					
Y	N	NR	NA	Quality criteria	Error rating[a]
				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
Comments[b]:					
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.

4.2.3 Cohort studies/ Concurrent control

Study type:				Cohort study	
Citation:					
Y	N	NR	NA	Quality criteria	Error rating[a]
				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
Comments[b]:					
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.

4.2.4 Case–control studies

Study type:				Case–control study	
Citation:					
Y	N	NR	NA	Quality criteria	Error rating[a]
				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
Comments[b]:					
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.

4.3 Appendix 3 Modified NHMRC evidence statement form

4.3.1 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		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

EVIDENCE STATEMENT

Indicate any dissenting opinions

4.3.2 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

4.4 Appendix 4 Consensus process for development of practice points

4.4.1 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.

4.4.2 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.

4.4.3 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.

4.4.4 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.

4.4.5 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.

4.4.6 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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