Patient Blood Management Guidelines: Module 6

Neonatal and Paediatrics

Technical report

Volume 2
Appendixes

Note

This volume presents the appendixes (Appendix A to Appendix F) to a systematic literature review on neonatal and paediatric patient blood management. Volume 1 presents the main body of evidence. These two volumes cover all research questions developed for this topic.

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Appendix A Literature searches

This appendix documents the literature search results to a systematic literature review on neonatal and paediatric patient blood management. The initial search was conducted on 20-21 February 2014 (Cochrane) and 11–12 March 2014 (EMBASE) for all questions. The searches for each question were again run on 2 September 2014 (Question 2), 21 October 2014 (Question 1 and Question 3), and 29 October (Question 4, Cochrane) or 4–5 November 2014 (Question 4, EMBASE).

A1 Literature search – Question 1

Table A1.1 EMBASE.com search for Level I, Level II, and Level III studies conducted 11 March, 2014 and 21 October, 2014

#	Query	Search Results	
		11 Mar 2014	21 Oct 2014
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	220,200	241,608
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,788,303	2,913,937
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6,717,562	6,962,603
#4	'blood transfusion'/exp OR (blood NEAR/4 transfus*):de,ab,ti OR 'erythrocyte transfusion':de,ab,ti OR 'erythrocyte transfusions':de,ab,ti OR (('red blood cell' OR 'rbc' OR 'red cell') NEAR/1 transfusion*):de,ab,ti OR (('red blood cell' OR 'rbc') NEAR/1 exchange*):de,ab,ti OR (('red cell' OR 'red cells') NEAR/3 exchange*):de,ab,ti	144,335	151,998
#5	'restrictive transfusion trigger':de,ab,ti OR (restrictive NEAR/3 transfus*):de,ab,ti OR (low NEAR/3 transfusion*):de,ab,ti	1,055	1,203
#6	liberal:de,ab,ti AND transfus*:de,ab,ti OR (high NEAR/3 transfusion*):de,ab,ti	1,190	1,393
#7	'hemoglobin blood level'/exp OR (transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*)):de,ab,ti OR ('hemoglobin'/exp OR haemoglobin:de,ab,ti OR hemoglobin:de,ab,ti AND (level*:de,ab,ti OR threshold*:de,ab,ti OR concentration*:de,ab,ti OR content:de,ab,ti)) OR 'blood	182,790	196,254

#	Query	Search Results	
		11 Mar 2014	21 Oct 2014
	hemoglobin':de,ab,ti OR 'blood haemoglobin':de,ab,ti OR 'plasma hemoglobin':de,ab,ti OR 'plasma haemoglobin':de,ab,ti OR 'serum hemoglobin':de,ab,ti OR 'serum haemoglobin':de,ab,ti OR 'hematocrit'/exp OR 'hct':de,ab,ti OR 'haematocrit':de,ab,ti OR 'hemocrit':de,ab,ti		
#8	#4 OR #5 OR #6 OR #7	309,705	329,362
#9	'prematurity'/exp OR 'newborn'/exp OR 'infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR preterm:de,ab,ti OR premature:de,ab,ti OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti OR paediatric*:de,ab,ti OR pediatric*:de,ab,ti OR kid:de,ab,ti OR kids:de,ab,ti OR child*:de,ab,ti OR 'pre adolescent':de,ab,ti OR adolescen*:de,ab,ti OR teenager*:de,ab,ti OR juvenile*:de,ab,ti OR youth*:de,ab,ti OR (young NEAR/3 (person* OR people)):de,ab,ti	3,437,995	3,549,900
#10	#1 AND #8 AND #9 - AND [humans]/lim - AND [humans]/lim AND [English]/lim - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	764 - 619	828 - NA - NA - 664
#11	#2 AND #8 AND #9 - AND [humans]/lim - AND [humans]/lim AND [English]/lim - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	10,808 - 8,164	11,436 - NA - NA - 8,587
#12	#3 AND #8 AND #9 - AND [humans]/lim - AND [humans]/lim AND [English]/lim - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	36,222 - 28,280	38,315 - NA - NA - 29,831
#13	#10 OR #11 OR #12	38,391	40,625

NA, not applied

Table A1.2 Cochrane library search: conducted 20 February, 2014 and 21 October 2014

#	Query	Results	
		20 Feb 2014	21 Oct 2014
#1	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	493	499
#2	MeSH descriptor: [Blood Transfusion] explode all trees	3266	3280
#3	blood near/3 transfusion	6010	6105
#4	"erythrocyte transfusion" or "erythrocyte transfusions"	681	709
#5	("red blood cell" or rbc) near/1 transfusion*	535	547
#6	"red cell" near/1 transfusion*	247	250
#7	"normocyte transfusion" or "normocyte transfusions"	0	0
#8	("red blood cell" or rbc) near/1 exchange	2	2
#9	("red cell" or "red cells") near/3 exchange	6	6
#10	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)	6684	6792
#11	(restrictive and transfus*)	117	126
#12	(restrictive or low) near/3 transfusion*	328	339
#13	(#11 or #12)	377	392
#14	(liberal and transfus*)	91	95
#15	(liberal or high) near/3 transfusion*	251	259
#16	(#14 or #15)	279	288
#17	"transfusion threshold" or "transfusion thresholds"	68	72
#18	transfusion near/1 trigger*	76	78
#19	"transfusion strategy" or "transfusion strategies"	83	85
#20	"transfusion policy" or "transfusion policies"	35	39
#21	"transfusion practice" or "transfusion practices"	73	74
#22	"transfusion protocol" or "transfusion protocols"	72	74
#23	transfusion near/1 guideline*	49	49
#24	"hemoglobin threshold" or "hemoglobin trigger"	10	11
#25	"hematocrit threshold" or "hematocrit trigger"	3	3
#26	"haemoglobin threshold" or "haemoglobin trigger"	9	10
#27	"haematocrit threshold" or "haematocrit trigger"	3	3
#28	"hb threshold" or "hb trigger"	13	14
#29	"hct threshold" or "hct trigger"	0	0
#30	"hemoglobin thresholds" or "hemoglobin triggers"	8	8
#31	"hematocrit thresholds" or "hematocrit triggers"	1	1
#32	"haemoglobin thresholds" or "haemoglobin triggers"	6	6
#33	"haematocrit thresholds" or "haematocrit triggers"	2	2
#34	"hb thresholds" or "hb triggers"	2	2
#35	"hct thresholds" or "hct triggers"	0	0
#36	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35)	351	360
#37	(#10 or #13 or #16 or #36)	6821	6931

#	Query	Results	
		20 Feb 2014	21 Oct 2014
#38	MeSH descriptor: [Infant, Premature] explode all trees	2753	2765
#39	MeSH descriptor: [Infant, Newborn] explode all trees	13156	13200
#40	MeSH descriptor: [Infant] explode all trees	13173	13221
#41	MeSH descriptor: [Child, Preschool] explode all trees	33	42
#42	MeSH descriptor: [Child] explode all trees	85	116
#43	MeSH descriptor: [Adolescent] explode all trees	76288	76619
#44	MeSH descriptor: [Pediatrics] explode all trees	534	539
#45	(premature or prematurity)	10762	10947
#46	(newborn* or neonat* or infant*)	44569	45311
#47	baby or babies	4155	4217
#48	preschool or 'pre school' or pre-school	32683	33082
#49	(child* or kid or kids)	91371	92789
#50	paediatric* or pediatric*	38508	39298
#51	adolescen* or youth* or teenager* or juvenile*	95395	96523
#52	young near/3 (person* or people)	1542	1577
#53	(#38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52)	176812	179454
#54	(#37 and #53) Limit to: - Cochrane reviews - Other reviews - Technology assessments - Economic evaluations - Trials TOTAL added to Level I database after removal of duplicate citations: TOTAL added to Level II database after removal of duplicate citations:	1971 - 457 - 68 - 7 - 92 - NR 624 0	1998 - 464 - 71 - 8 - 95 - 1387 638 805

NA, not applied

A2 Literature search – Question 2

Table A2.1 EMBASE.com search for Level I, Level II, and Level III studies conducted 11 March, 2014 and 2 September, 2014

#	Query	Results	
		11 Mar 2014	2 Sept 2014
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	220,200	237,985
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,788,303	2,893,537
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6,717,562	6,925,417
#4	'erythropoietin'/exp OR 'recombinant erythropoietin'/exp OR erthropoietin OR erythropoietin OR 'erythropoiesis stimulating' OR 'erythropoietic factor' OR hematopoietin OR hemopoietin OR haematopoietin OR haemopoietin OR epog?n OR epoietin OR epoxitin OR darbepoetin OR eprex OR erantin OR erypo OR espo OR exprex OR globuren OR hemax OR marogen OR neorecormon OR procrit OR recormon OR recormone OR rhuepo OR 'rhu epo' OR 'r hu epo'	47,560	49,093
#5	'iron'/exp OR iron OR ferrous NEXT/1 (sulfate OR fumarate) OR 'heme iron polypeptide' OR 'cosmofer' OR 'dexferrum' OR 'imferon' OR 'infed' OR '9004 66 4':rn OR '7720 78 7':rn	259,312	226,216
#6	'hydroxyurea'/exp OR 'hydroxy urea' OR 'hydrea' OR 'hydroxycarbamide' OR 'hydroxy carbamide' OR 'oxyurea' OR '8029-68-3':rn OR '127 07 1':rn	19,937	20,342
#7	#4 OR #5 OR #6	316,318	285,540
#8	'prematurity'/exp OR 'newborn'/exp OR 'infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR preterm:de,ab,ti OR premature:de,ab,ti OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti OR paediatric*:de,ab,ti OR pediatric*:de,ab,ti OR kid:de,ab,ti OR kids:de,ab,ti OR child*:de,ab,ti OR 'pre adolescent':de,ab,ti OR adolescen*:de,ab,ti OR teenager*:de,ab,ti OR juvenile*:de,ab,ti OR youth*:de,ab,ti OR (young NEAR/3 (person* OR people)):de,ab,ti	3,437,995	3,531,789
#9	#1 AND #7 AND #8 - AND [humans]/lim - AND [humans]/lim AND [English]/lim	642 - 521	600 - 484

#	Query	Results	
		11 Mar 2014	2 Sept 2014
	- AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)		
#10	#2 AND #7 AND #8 - AND [humans]/lim - AND [humans]/lim AND [English]/lim - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	7,203 - 5,265	6,669 - 4,880
#11	#3 AND #7 AND #8	19,614	NA
#12	#9 OR #10 OR #11	21,611	NA

NA, Not Applied

Table A2.2 Cochrane library search: conducted 20 February, 2014 and 2 September 2014

#	Query	Results	
		Feb 2014	Sept 2 2014
#1	MeSH descriptor: [Erythropoietin] explode all trees	1473	1479
#2	MeSH descriptor: [Iron] explode all trees	1655	1658
#3	(erthropoietin or "erythropoiesis stimulating factor")	4	4
#4	"erythropoietic NEAR/1 factor"	0	0
#5	(hematopoietin or hemopoietin)	2	2
#6	(haematopoietin or haemopoietin)	1	1
#7	(dynepo or epoch or epoconn or epoetin or epog?n)	1050	1061
#8	(epoietin or epoxitin or eprex or erantin or erypo)	86	88
#9	(espo or exprex or globuren or hemax or marogen)	41	41
#10	(neorecormon or procrit or recormon or recormone)	67	67
#11	(rHuEPO or "rHu EPO" or "r Hu EPO")	409	410
#12	iron or ferrous next/1 (sulfate or fumarate) or 'heme iron polypeptide' or 'cosmofer' or 'dexferrum' or 'imferon' or 'infed'	4925	4983
#13	MeSH descriptor: [Hydroxyurea] explode all trees	323	323
#14	hydroxyurea or 'hydroxy urea' or hydroxycarbamide or 'hydroxy carbamide'	716	720
#15	hydrea or oxyurea	5	5
#16	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)	7427	7504
#17	MeSH descriptor: [Infant, Premature] explode all trees	2753	2761
#18	MeSH descriptor: [Infant, Newborn] explode all trees	13156	13194
#19	MeSH descriptor: [Infant] explode all trees	13173	13214
#20	MeSH descriptor: [Child, Preschool] explode all trees	33	41
#21	MeSH descriptor: [Child] explode all trees	85	111
#22	MeSH descriptor: [Adolescent] explode all trees	76288	76554
#23	MeSH descriptor: [Pediatrics] explode all trees	534	537
#24	(premature or prematurity)	10762	10884
#25	(newborn* or neonat* or infant*)	44569	44973
#26	baby or babies	4155	4199
#27	preschool or 'pre school' or pre-school	32683	32992
#28	(child* or kid or kids)	91371	92419
#29	paediatric* or pediatric*	38508	38966
#30	adolescen* or youth* or teenager* or juvenile*	95395	96267
#31	young near/3 (person* or people)	1542	1566
#32	(#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31)	176812	178663
#33	#16 and #32 Limit to: - Cochrane reviews	2841 - 360	2876 - 360

	- Other reviews	- 63	- 66
	- Technology assessments	- 5	- 5
	- Economic evaluations	- 40	- 40
	- Trials (searched November 2014)	- NA	- 2451
	TOTAL added to Level I database:	468	471
	TOTAL added to Level II database:	NA	2451

NA, not applied

A3 Literature search – Question 3

Table A3.1 EMBASE.com search for Level I, Level II, and Level III studies conducted 11 March, 2014 and 21 October, 2014

#	Query	Results	
		11 Mar 2014	21 Oct 2014
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	220,200	241,608
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,788,303	2,913,937
#3	'clinical study'/exp OR 'case control study'/exp OR 'family study'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR ('prospective study'/exp NOT 'randomized controlled trials'/exp) OR 'cohort analysis'/exp OR cohort NEXT/1 (study OR studies) OR 'case control' NEXT/1 (study OR studies) OR 'follow up' NEXT/1 (study OR studies) OR observational NEXT/1 (study OR studies) OR epidemiologic* NEXT/1 (study OR studies) OR 'cross sectional' NEXT/1 (study OR studies)	6,717,562	6,962,603
#4	'blood component'/exp OR blood NEXT/1 component* OR blood NEXT/1 product* OR transfusion NEXT/1 product* OR blood NEXT/1 constituent*	46,345	23,235
#5	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'fresh frozen plasma' OR ffp	116,821	126,014
#6	'cryoprecipitate'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate'	3,695	3,919
#7	'fibrinogen'/exp OR fibrinogen OR 'factor 1' OR 'factor i'	179,778	175,711
#8	#4 OR #5 OR #6 OR #7	330,159	315,710
#9	'transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR 'blood retransfusion' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfusion OR 'transfusion blood' OR 'transfusion therapy'	308,479	322,046
#10	#8 AND #9	52,863	34,047
#11	'plasma transfusion'/exp OR 'plasma transfusion' OR 'plasma infusion' OR 'serum transfusion'	3,253	3,445
#12	'thrombocyte transfusion'/exp OR ('thrombocyte'/exp AND ('blood transfusion'/exp OR 'transfusion'/exp)) OR 'platelet' NEAR/1 'transfusion' OR 'platelet' NEAR/1 'transfusions' OR 'transfusion' NEAR/3 'platelet' OR 'transfusion' NEAR/3 'platelets' OR 'thrombocyte transfusion' OR 'thrombocytic transfusion'	19,616	20,882
#13	#10 OR #11 OR #12	58,277	49,062
#14	'prematurity'/exp OR 'newborn'/exp OR 'infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR preterm:de,ab,ti OR	3,437,995	3,549,900

#	Query	Results	
		11 Mar 2014	21 Oct 2014
	premature:de,ab,ti OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti OR paediatric*:de,ab,ti OR pediatric*:de,ab,ti OR kid:de,ab,ti OR kids:de,ab,ti OR child*:de,ab,ti OR 'pre adolescent':de,ab,ti OR adolescen*:de,ab,ti OR teenager*:de,ab,ti OR juvenile*:de,ab,ti OR youth*:de,ab,ti OR (young NEAR/3 (person* OR people)):de,ab,ti		
#15	#1 AND #13 AND #14 - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	205 - 156	153 - 105
#16	#2 AND #13 AND #14 - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	2,061 - 1,558	1,561 - 1,147
#17	#3 AND #13 AND #14 - AND [humans]/lim AND [English]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim)	7,717 - 6,051	5,910 - 4,511
#18	#15 OR #16 OR #17	8,099	NA

NA, Not Applied

Table A3.2 Cochrane library search: conducted 21 February 20, 2014 and 21 October 2014

#	Query	Results	
		21 Feb 2014	21 Oct 2014
#1	MeSH descriptor: [Blood Component Transfusion] explode all trees	863	870
#2	MeSH descriptor: [Blood Transfusion] explode all trees	3266	3280
#3	*transfus*	9478	9618
#4	"blood exchange" or "blood infusion"	69	69
#5	"blood replacement"	73	73
#6	hemotherapy or hematherapy or hematotherapy	67	68
#7	haemotherapy or haematherapy or haematotherapy	8	8
#8	(#1 or #2 or #3 or #4 or #5 or #6 or #7)	9585	9893
#9	"blood component" or "blood components"	544	548
#10	"blood product" or "blood products"	884	898
#11	"transfusion product" or "transfusion products"	14	14
#12	"blood constituent" or "blood constituents"	22	22
#13	(#9 or #10 or #11 or #12)	1373	1389
#14	(#8 and #13)	895	909
#15	MeSH descriptor: [Plasma] explode all trees	548	556
#16	"fresh frozen plasma" or FFP	530	538
#17	#15 or #16	966	982
#18	#8 and #17	439	462
#19	"plasma transfusion"	74	76
#20	"plasma infusion" or "serum transfusion"	20	21
#21	(#18 or #19 or #20)	481	506
#22	cryoprecipitate or "cryo precipitate"	102	105
#23	(#22 and #8)	68	73
#24	fibrinogen or "factor 1" or "factor I"	5855	5935
#25	(#8 and #24)	434	446
#26	MeSH descriptor: [Platelet Transfusion] explode all trees	267	267
#27	MeSH descriptor: [Blood Platelets] explode all trees	1656	1658
#28	(#8 and #27)	163	163
#29	platelet* near/3 transfusion*	755	762
#30	"thrombocyte transfusion" or "thrombocytic transfusion"	77	83
#31	(#26 or #28 or #29 or #30)	849	860
#32	(#14 or #21 or #23 or #25 or #31)	2072	2122
#33	MeSH descriptor: [Infant, Premature] explode all trees	2753	2765
#34	MeSH descriptor: [Infant, Newborn] explode all trees	13156	13200
#35	MeSH descriptor: [Infant] explode all trees	13173	13221
#36	MeSH descriptor: [Child, Preschool] explode all trees	33	42
#37	MeSH descriptor: [Child] explode all trees	85	116

#	Query	Results	
		21 Feb 2014	21 Oct 2014
#38	MeSH descriptor: [Adolescent] explode all trees	76288	76619
#39	MeSH descriptor: [Pediatrics] explode all trees	534	539
#40	(premature or prematurity)	10762	10947
#41	(newborn* or neonat* or infant*)	44569	45312
#42	baby or babies	4155	4218
#43	preschool or 'pre school' or pre-school	32683	33082
#44	(child* or kid or kids)	91371	92790
#45	paediatric* or pediatric*	38508	39298
#46	adolescen* or youth* or teenager* or juvenile*	95395	96523
#47	young near/3 (person* or people)	1542	1577
#48	(#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47)	176812	179455
#49	#32 and #48	582	596
	Limit to:		
	- Cochrane reviews	- 173	- 190
	- Other reviews	- 13	- 15
	- Technology assessments	- 1	- 1
	- Economic evaluations	- 32	- 33
	- Trials	- NA	- 212
	TOTAL added to Level I database:	219	239
	TOTAL added to Level II database:	0	212

A4 Literature search – Question 4

The literature search for this question was divided into two searches. The first included all interventions included in the PICO except thermoregulation and antifibrinolytics and the second included these two interventions only. The searches were separated because thermoregulation and antifibrinolytics were included in *Module 2 – Perioperative* and *Module 4 – Critical care* and studies involving these interventions were previously screened for inclusion/exclusion up to the literature search dates in those modules. Different publication date limits were therefore applied to the searches.

Table A4.1 EMBASE.com search for Level I and Level II studies conducted 11 March, 2014 and 5 November, 2014: all included interventions except thermoregulation and antifibrinolytics

#	Query	Results	
		11 Mar 2014	5 Nov 2014
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	220,200	243,174
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,788,303	2,923,666
#3	placenta* NEAR/3 transfus* OR transfus* NEAR/3 'umbilical cord' OR clamp* NEAR/3 cord AND umbilical OR ((delay OR delayed OR delaying OR defer OR deferred OR deferring) NEAR/3 cord AND (clamp OR clamping OR milk OR milking OR strip OR stripping)) OR dcc:de,ab,ti OR (delay OR delayed OR delaying OR defer OR deferred OR deferring AND ('cord clamping' OR 'cord milking' OR 'cord stripping'))	3,753	3,943
#4	'immunoglobulin'/exp OR 'immunoglobulin g'/exp OR immunoglobulin:de,ab,ti OR 'ig':de,ab,ti OR 'igg' OR 'ivig':de,ab,ti OR 'iv ig':de,ab,ti OR 'iv igg':de,ab,ti	544,507	567,541
#5	'newborn hemolytic disease'/exp OR 'hemolytic anemia'/exp OR 'abo hemolytic disease'/exp OR 'erythroblastosis fetalis'/exp OR (hemolytic OR haemolytic) NEAR/2 disease OR (hemolytic OR haemolytic) NEAR/2 jaundice OR (hemolytic OR haemolytic) NEAR/2 (anemia* OR anaemia*) OR 'hdn' OR 'hdfn' OR incompatibility NEAR/1 (abo OR rh OR rhesus) OR 'erythroblastosis fetalis'	102,398	105,587
#6	#4 AND #5	8,492	8,861
#7	#3 OR #6	12,240	12,799
#8	'prematurity'/exp OR 'newborn'/exp OR 'infant'/exp OR preterm:de,ab,ti OR premature:de,ab,ti OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti	1,230,169	1,268,235
#9	#1 AND #7 AND #8	77	88
#10	#2 AND #7 AND #8	460	494

#11	'induced hypotension'/exp OR 'induced hypotension':de,ab,ti OR 'controlled hypotension'/exp OR 'controlled hypotension':de,ab,ti OR 'hypotensive anesthesia':de,ab,ti OR 'hypotensive anaesthesia':de,ab,ti OR 'hypotensive epidural anesthesia':de,ab,ti OR 'hypotensive epidural anaesthesia':de,ab,ti OR 'iatrogenic hypotension'/exp OR 'iatrogenic hypotension':de,ab,ti	102,978	107,492
#12	'hemodilution'/exp OR 'haemodilution'/exp OR 'blood dilution'/exp OR hemodilution:de,ab,ti OR 'haemodilution':de,ab,ti OR haemodilution:de,ab,ti OR 'blood dilution':de,ab,ti	8,635	8,822
#13	'blood salvage'/exp OR 'blood salvage':de,ab,ti OR 'salvage therapy'/exp OR 'salvage therapy':de,ab,ti OR 'cell salvage':de,ab,ti OR 'erythrocyte salvage':de,ab,ti OR cell NEXT/1 saver* OR 'c.a.t.s. plus' OR 'continuous autotransfusion system' OR 'continuous auto-transfusion system'	21,649	23,067
#14	'teg':de,ab,ti OR 'sonoclot':de,ab,ti OR 'rotem':de,ab,ti OR 'roteg':de,ab,ti OR 'thromboelastograph':de,ab,ti OR 'thromboelastography':de,ab,ti OR 'thromboelastograpy':de,ab,ti OR 'thrombelastography':de,ab,ti	6,502	NA[a]
#14	'teg':de,ab,ti OR 'sonoclot':de,ab,ti OR 'rotem':de,ab,ti OR 'roteg':de,ab,ti OR 'thromboelastograph':de,ab,ti OR 'thromboelastography':de,ab,ti OR 'thromboelastograpy':de,ab,ti OR 'thrombelastography':de,ab,ti OR 'thromboelastom':de,ab,ti OR 'thromboelastometry':de,ab,ti OR 'thrombelastometry':de,ab,ti OR 'activated clotting time':de,ab,ti OR 'activated clotting times':de,ab,ti OR 'activated clot time':de,ab,ti OR 'activate clot times':de,ab,ti OR 'activate clotting time':de,ab,ti OR 'activate clotting times':de,ab,ti OR 'multiplate':de,ab,ti OR 'multiplates':de,ab,ti	NA[a]	9,290
#15	recombinant AND blood AND clotting AND factor AND 7a OR (blood AND clotting AND factor AND 7a AND recombinant AND 'protein'/exp) OR 'recombinant fviia':de OR 'recombinant activated factor vii':tn,ab,ti OR ('recombinant' NEXT/3 'viia'):tn,ab,ti OR ('recombinant' NEXT/3 'fviia'):tn,ab,ti OR 'recombinant f viia':tn,ab,ti OR rfviia:tn,ab,ti OR 'r fviia':tn,ab,ti OR 'r f viia':tn,ab,ti OR rf7a:tn,ab,ti OR 'eptacog alfa':tn,ab,ti OR niastase:tn,ab,ti OR 'novo seven':tn,ab,ti OR novoseven:tn,ab,ti OR 'nn 1731':de,tn,ab,ti OR nn1731:tn,ab,ti	6,659	6,852
#16	'cardiopulmonary bypass'/exp OR mini* NEAR/3 ('cardiopulmonary' OR 'bypass' OR 'cpb' OR 'extracorporeal' OR 'extra corporeal') OR reduc* NEAR/3 ('cardiopulmonary' OR 'bypass' OR 'cpb' OR 'extracorporeal' OR 'extra corporeal') OR small* NEAR/3 ('cardiopulmonary' OR 'bypass' OR 'cpb' OR 'extracorporeal' OR 'extra corporeal') OR mecc:de,ab,ti OR 'miniaturised bypass system' OR 'miniaturized bypass system' OR 'low primer bypass system'	33,663	36,636
#17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	175,662	186,928
#18	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period'	22,200,803	6,529,500
#19	'newborn'/exp OR 'infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti OR paediatric*:de,ab,ti OR pediatric*:de,ab,ti OR kid:de,ab,ti OR kids:de,ab,ti OR child*:de,ab,ti OR 'pre adolescent':de,ab,ti OR adolescen*:de,ab,ti OR teenager*:de,ab,ti OR juvenile*:de,ab,ti OR	3,361,838	3,478,754

	youth*:de,ab,ti OR (young NEAR/3 (person* OR people)):de,ab,ti		
#20	#17 AND #18 AND #19	24,276	17,895
#21	#1 AND #20	604	399
#22	#2 AND #20	6,157	4,507
#23	'intensive care'/exp OR intensive NEAR/5 (care OR therap* OR treatment* OR recovery) OR icu OR critical* NEAR/5 (ill* OR care OR patient* OR condition*) OR 'critically ill patient'/exp OR 'high dependency unit' OR itu OR hdu OR major NEAR/5 trauma	752,115	795,708
#24	#14 AND #19 AND #23	136	232
#25	#15 AND #19 AND #23	258	269
#26	#24 OR #25	377	480
#27	#1 AND #26	11	15
#28	#2 AND #26	98	132
#29	#9 OR #21 OR #27	680	487
#30	#10 OR #22 OR #28	6,607	5,010
#31	#29 OR #30	6,781	5,146
#32	#31 AND [1985-2014]/py	NA	5,063
#33	#29 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim	576	406
#34	#30 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim	5,314	4,029

NA, Not Applied

a. Search #14 was slightly modified for the search run on 5 November 2014 to include additional terms (in **bold**) associated with viscoelastometric point of care testing.

Table A4.2 EMBASE.com search for Level I and Level II studies conducted 5 November, 2014 for thermoregulation and antifibrinolytics

#	Query	Results Nov 5 2014[a]
#1	'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*))	243,174
#2	'comparative study'/exp OR 'comparative study' OR 'clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR placebo* OR random* OR rct OR 'single blind' OR 'single blinded' OR 'double blind' OR 'double blinded' OR 'treble blind' OR 'treble blinded' OR 'triple blind' OR 'triple blinded' OR 'prospective study'/exp OR 'prospective study'	2,923,666
#3	'body temperature'/exp OR normothermia:de,ab,ti OR 'thermoregulation'/exp OR 'thermoregulation':de,ab,ti OR 'warming'/exp OR 'warming':de,ab,ti OR 'hypothermia'/exp OR 'hypothermia':de,ab,ti	136,531
#4	'antifibrinolytic agent'/exp OR 'antifibrinolytic agent':de,ab,ti OR antifibrinolytic*:de,ab,ti OR 'anti fibrinolytic':de,ab,ti OR 'anti fibrinolytics':de,ab,ti OR antiplasmin*:de,ab,ti OR 'anti plasmin':de,ab,ti OR 'anti plasmins':de,ab,ti OR antifibrinolysin*:de,ab,ti OR 'anti fibrinolysin':de,ab,ti OR 'anti fibrinolysins':de,ab,ti OR 'fibrinolysis inhibitor'/exp OR 'fibrinolysis inhibitor':de,ab,ti OR 'fibrinolysis inhibitors':de,ab,ti OR 'plasmin inhibitor'/exp OR 'plasmin inhibitor':de,ab,ti OR 'plamin inhibitors':de,ab,ti OR 'tranexamic acid'/exp OR 'tranexamic acid':de,ab,ti OR 'cyklokapron'/exp OR 'cyklokapron':de,ab,ti OR 'aminocaproic acid'/exp OR 'aminocaproic acid':de,ab,ti OR 'eaca'/exp OR 'eaca':de,ab,ti OR 'amicar'/exp OR 'amicar':de,ab,ti AND '1197 18 8':rn OR '701 54 2':rn OR '1319 82 0':rn OR '60 32 2':rn OR 'aprotinin'/exp OR 'aprotinin' OR 'trasylol'/exp OR 'trasylol.'	21,963
#5	#3 OR #4	158,084
#6	'surgery' OR 'surgery'/exp OR surgery OR surger* OR surgical* OR transplant* OR reconstruct* OR procedur* OR operat* OR preoperat* OR intraoperat* OR perioperat* OR peroperat* OR postoperat* OR 'peroperative period'/exp OR 'peroperative period' OR 'postoperative period'/exp OR 'postoperative period' OR 'preoperative period'/exp OR 'preoperative period'	6,529,500
#7	'newborn'/exp OR 'infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatrics'/exp OR infant*:de,ab,ti OR baby:de,ab,ti OR babies:de,ab,ti OR neonat*:de,ab,ti OR newborn*:de,ab,ti OR paediatric*:de,ab,ti OR pediatric*:de,ab,ti OR kid:de,ab,ti OR kids:de,ab,ti OR child*:de,ab,ti OR 'pre adolescent':de,ab,ti OR adolescen*:de,ab,ti OR teenager*:de,ab,ti OR juvenile*:de,ab,ti OR youth*:de,ab,ti OR (young NEAR/3 (person* OR people)):de,ab,ti	3,478,754
#8	#5 AND #6 AND #7	7,630
#9	#1 AND #8	148
#10	#2 AND #8	1,764
#11	#9 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim	120
#12	#10 AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [erratum]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim	1,334

a. the literature search conducted on 11 March 2014 for these two interventions was discarded because the Boolean operator AND was erroneously used instead of OR at step #5. This was corrected in the November 2014 search.

Table A4.3 Cochrane library search: conducted 12 March, 2014 and 4 November 2014

#	Query	Results	
		12 Mar 2014	4 Nov 2014
#1	placenta* near/3 transfus*	42	49
#2	'umbilical cord' near/3 transfus*	10	11
#3	delay or delayed or delaying or defer or deferred or deferring	25,158	25,995
#4	cord and (clamp or clamping or milk or milking or strip or stripping)	502	530
#5	#3 and #4	153	162
#6	(#1 or #2 or #5)	182	197
#7	MeSH descriptor: [Immunoglobulins] explode all trees	14,712	14,900
#8	MeSH descriptor: [Immunoglobulin G] explode all trees	3,079	3,096
#9	immunoglobulin or Ig or IgG or IVIG or 'iv Ig' or 'iv IgG'	9,973	10,324
#10	(#7 or #8 or #9)	19,143	19,654
#11	MeSH descriptor: [Erythroblastosis, Fetal] explode all trees	72	72
#12	(hemolytic or haemolytic) near/3 (jaundice* or disease* or anemia* or anaemia*)	345	352
#13	incompatibility near/3 (abo or rh or rhesus)	66	67
#14	(#11 or #12 or #13)	413	421
#15	#10 and #14	121	122
#16	(#6 or #15)	303	319
#17	MeSH descriptor: [Infant, Premature] explode all trees	2,753	2,775
#18	MeSH descriptor: [Infant, Newborn] explode all trees	13,156	13,238
#19	MeSH descriptor: [Infant] explode all trees	13,173	13,261
#20	premature or prematurity	10,762	11,202
#21	newborn* or neonat* or infant*	44,569	45,975
#22	baby or babies	4,155	4,320
#23	#17 or #18 or #19 or #20 or #21 or #22	49,321	50,908
#24	#16 and #23	233	247
#25	MeSH descriptor: [Hypotension] explode all trees and with qualifier(s): [Prevention & control - PC]	326	327
#26	'induced hypotension' or 'controlled hypotension' or 'iatrogenic hypotension'	7,037	7,339
#27	#25 or #26	7,037	7,339
#28	MeSH descriptor: [Hemodilution] explode all trees	370	370
#29	(acute and (normovolemic or normovolaemic))	181	185
#30	(acute and ("normo volemic" or "normo volaemic"))	0	0
#31	(acute near/2 ("normovolemic hemodilution" or "normovolemic haemodilution"))	126	129
#32	(acute near/2 ("normovolaemic hemodilution" or "normovolaemic haemodilution"))	53	53
#33	(acute near/2 ("normo volemic hemodilution" or "normo volemic haemodilution"))	0	0

#	Query	Results	
		12 Mar 2014	4 Nov 2014
#34	(acute near/2 ("normo volaemic hemodilution" or "normo volaemic haemodilution"))	0	0
#35	(#28 or #29 or #30 or #31 or #32 or #33 or #34)	450	454
#36	MeSH descriptor: [Salvage Therapy] explode all trees	485	488
#37	"blood salvage" or "salvage therapy" or "cell salvage" or "erythrocyte salvage" or "cell saver" or "Cell savers" or "C.A.T.S. plus" or "continuous autotransfusion system" or "continuous auto-transfusion system"	1,017	1,055
#38	#36 or #37	1,017	1,055
#39	MeSH descriptor: [Thrombelastography] explode all trees	172	173
#40	sonoclot	15	16
#41	rotem	48	58
#42	roteg	6	8
#43	(#39 or #40 or #41 or #42)	220	536
#44	MeSH descriptor: [Factor VIIa] explode all trees	195	198
#45	MeSH descriptor: [Recombinant Proteins] explode all trees	7,492	7,534
#46	#44 and #45	134	135
#47	"recombinant activated factor VII"	114	117
#48	"recombinant *2 VIIa" or "Recombinant *2 FVIIa"	103	111
#49	"recombinant F VIIa" or rFVIIa or "r FVIIa" or "r F VIIa" or rf7a	179	186
#50	"eptacog alfa" or niastase or "Novo Seven" or Novoseven	79	82
#51	"nn 1731" or nn1731	5	6
#52	"blood clotting factor viia" or "coagulation factor viia"	9	10
#53	Activated near/2 ("Factor VII" or "FVII")	210	218
#54	Activated near/2 ("Factor 7" or "F7")	3	3
#55	acset	1	1
#56	#52 or #53 or #54 or #55	220	229
#57	recombinant	12,695	13,006
#58	#56 and #57	157	165
#59	#46 or #47 or #48 or #49 or #50 or #51 or #58	287	302
#60	MeSH descriptor: [Cardiopulmonary Bypass] explode all trees	2,405	2,410
#61	mini* near/3 (cardiopulmonary or bypass or cpb)	107	112
#62	reduc* near/3 (cardiopulmonary or bypass or cpb)	394	409
#63	small* near/3 (cardiopulmonary or bypass or cpb)	32	34
#64	'low primer bypass'	1	1
#65	#60 or #61 or #62 or #63 or #64	2,724	2,747
#66	#27 or #35 or #38 or #43 or #59 or #65	11,431	12,033
#67	MeSH descriptor: [Infant, Newborn] explode all trees	13,156	13,238
#68	MeSH descriptor: [Infant] explode all trees	13,173	13,261
#69	MeSH descriptor: [Child, Preschool] explode all trees	33	46

#	Query	Results	
		12 Mar 2014	4 Nov 2014
#70	MeSH descriptor: [Child] explode all trees	85	125
#71	MeSH descriptor: [Adolescent] explode all trees	76,288	76,712
#72	MeSH descriptor: [Pediatrics] explode all trees	534	544
#73	(newborn* or neonat* or infant*)	44,569	45,975
#74	baby or babies	4,155	4,320
#75	preschool or 'pre school' or pre-school	32,683	33,345
#76	child* or kid or kids	91,371	94,316
#77	paediatric* or pediatric*	38,508	40,121
#78	adolescen* or youth* or teenager* or juvenile*	95,395	97,223
#79	young near/3 (person* or people)	1,542	1,650
#80	#67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79	173,717	178,685
#81	#66 and #80	2,439	2,535
#82	#24 or #81 Limit to: - Cochrane reviews - Other reviews - Technology assessments - Economic evaluations - Trials TOTAL added to Level I database: TOTAL added to Level II database:	2,657 - 664 - 71 - 2 - 30 - NA 767 0	2,764 - 695 - 75 - 2 - 31 - 1,956 803 1,956

Table A4.4 Cochrane library search: conducted 29 October, 2014

#	Query	Results 29 Oct, 2014
#1	MeSH descriptor: [Infant, Newborn] explode all trees	13,200
#2	MeSH descriptor: [Infant] explode all trees	13,221
#3	MeSH descriptor: [Child, Preschool] explode all trees	42
#4	MeSH descriptor: [Child] explode all trees	116
#5	MeSH descriptor: [Adolescent] explode all trees	76,619
#6	MeSH descriptor: [Pediatrics] explode all trees	539
#7	(newborn* or neonat* or infant*)	45,315
#8	baby or babies	4,219
#9	preschool or 'pre school' or pre-school	33,085
#10	child* or kid or kids	92,801
#11	paediatric* or pediatric*	39,300
#12	adolescen* or youth* or teenager* or juvenile*	96,525
#13	young near/3 (person* or people)	1,577
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	176,333
#15	MeSH descriptor: [Hypothermia] explode all trees and with qualifier(s):[Prevention & control - PC]	203
#16	(hypothermia near/20 prevent*)	514
#17	#15 or #16	514
#18	MeSH descriptor: [Antifibrinolytic Agents] explode all trees	455
#19	MeSH descriptor: [Tranexamic Acid] explode all trees	412
#20	(antifibrinolytic* or “anti fibrinolytic” or “anti fibrinolytics”)	710
#21	(antiplasmin* or “anti plasmin” or “anti plasmins”)	292
#22	(antifibrinolysin* or “anti fibrinolysin” or “anti fibrinolysins”)	6
#23	“fibrinolysis inhibitor” or “fibrinolysis inhibitors”	46
#24	“plasmin inhibitor” or “plasmin inhibitors”	68
#25	“tranexamic acid” or Cyklokapron	839
#26	“aminocaproic acid” or eaca or Amicar	215
#27	(#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)	1,511
#28	#17 or #27	2,023
#29	#14 and #28 Limit to: - Cochrane reviews - Other reviews - Technology assessments - Economic evaluations - Trials TOTAL added to Level I database: TOTAL added to Level II database:	432 - 83 - 18 - 1 - 6 - 319 108 319

Appendix B Excluded studies

This appendix documents studies that met the inclusion criteria determined by PICO criteria, but were later excluded. These studies, and their reasons for exclusion, are listed below.

B1 Studies excluded from Question 1

Level I evidence

Superseded

Hirst C, and Wang WC. (2009) Blood transfusion for preventing stroke in people with sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **4**.

Hirst C, and Wang WC. (2002) Blood transfusion for preventing stroke in people with sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **1**: CD003146.

Article not available in English

Bassler D, Bialkowski A, Weitz M, et al. (2009) An overview of different red blood cell transfusion strategies for preterm infants. *Padiatrische Praxis*, **73**: 633-643.

Wrong publication type

Butler C, Tay J, Doree C, et al. (2014) Restrictive versus liberal red blood cell transfusion strategies for patients with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. *Cochrane Database of Systematic Reviews*, Issue **9**: CD011305. [protocol]

Crespi J, Braga-Josefina AP, Figueiredo MS et al. (2013) Interventions for preventing silent cerebral infarcts in people with sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **8**: CD010718. [protocol]

No usable data

Alhashimi D, Fedorowicz Z, Alhashimi F, and Dastgiri S. (2010) Blood transfusions for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **1**: CD007843. [no studies identified]

Cho G, and Hambleton IR. (2014) Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **1**: CD008360. [no studies identified]

Kavanagh PL, Sprinz PG, Vinci SR, et al. (2011) Management of children with sickle cell disease: A comprehensive review of the literature. *Pediatrics*, **128** (6): E1552-E1574.

Reilly JT, McMullin MF, Beer PA, et al. (2012) Guideline for the diagnosis and management of myelofibrosis. *British Journal of Haematology*, **158** (4): 453-471.

Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. (2014) Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. *JAMA*, **312** (10): 1033-1048.

Duplicate data

Carson JL, Grossman BJ, Kleinman S, et al. (2012) Red blood cell transfusion: A Clinical practice guidelines from the AABB. *Annals of Internal Medicine*, **157** (1): 49-58.

Curley GF, Shehata N, Mazer CD, Hare GMT, and Friedrich JO. (2014) Transfusion triggers for guiding RBC transfusion for cardiovascular surgery: A systematic review and meta-analysis. *Critical Care Medicine.*

Riordan JM, Fitzgerald J, Smith OP, et al. (2007) Summary of the National Blood Users Group guideline for the transfusion of blood components of preterm infants. *Irish Medical Journal*, **100** (6).

Level II evidence

Wrong publication type

Adams RJ, McKie VC, Brambilla D, et al. (1997) Stroke Prevention in Sickle Cell Anaemia (STOP). *Controlled Clinical Trials*, **19** (1): 110-129. [design paper]

Casella JF, King AA, Barton B, et al. (2010) Design of the silent cerebral infarct transfusion (SIT) trial. *Pediatric Hematology and Oncology*, **27** (2): 69-89. [design paper]

Cholette J. (2014) A prospective, randomized, controlled clinical trial comparing two transfusion strategies in pediatric patients undergoing cavopulmonary connection. Available online: https://clinicaltrials.gov/show/NCT00350220 . [study completed but results not published]

Franz AR, Maier FR, Thome UH, et al. (2012) The 'effects of transfusion thresholds on neurocognitive outcome of extremely low birth-weight infants (ETTNO)' study: Background, aims, and study protocol. *Neonatology*, **101** (4): 301-305. [study ongoing but not recruiting participants]

Kirpalani H, Bell E, D'Angio, C et al. (2012) Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to a Restrictive Strategy? Available online: https://clinicaltrials.gov/ct2/show/NCT01702805. [study currently recruiting participants]

No usable data

Haberkern CM, Neumayr LD, Orringer EP et al. (1997) Cholecystectomy in sickle cell anemia patients: perioperative outcome of 364 cases from the National Preoperative Transfusion Study. Preoperative Transfusion in Sickle Cell Disease Study Group. *Blood*, **89**: 1533-1542.

McCoy TE, Conrad AL, Richman LC, Lindgren D, Nopoulos PG and Bell EF. (2011) Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion. *Child Neuropsychology,* **17** (4): 347-367.

Level III evidence

Article not available in English

Tayman C, Tonbul A, Uras N et al. (2011) Evaluation of risk factors for necrotizing enterocolitis in preterm infants. *Guncel Pediatri*, **9** (1): 7-13.

No usable data

Al-Marzooq R (2010) Prognostic indicators of developmental outcome in preterm infants. *Bahrain Medical Bulletin* **32** (4).

Baer VL, Lambert DK, Henry E, Snow GL, Christensen RD. (2011) Red blood cell transfusion of preterm neonates with a Grade 1 intraventricular haemorrhage is associated with extension to a Grade 3 or 4 hemorrhage. *Transfusion*, **51**:1933-1939.

Baxi AC, Josephson CD, Iannucci GJ and Mahle WT. (2014) Necrotizing enterocolitis in infants with congenital heart disease: The role of red blood cell transfusions. *Pediatric Cardiology*, **35** (6): 1024-1029.

Sample size ≤ 100

Akkoyun I, Oto S, Yilmaz G, Gurakan B, Tarcan A, Anuk D, Akgun S, Akova YA (2006) Risk Factors in the Development of Mild and Severe Retinopathy of Prematurity. *Journal of AAPOS* **10,** 449-453.

Blau J, Calo JM, Dozor D, Sutton M, Alpan G, and La Gamma EF. (2011) Transfusion-related acute gut injury: Necrotizing enterocolitis in very low birth weight neonates after packed red blood cell transfusion. *J Pediatr,* **158** (3):403-9.

Collard KJ, Godeck S, Holley JE, Quinn MW (2004) Pulmonary antioxidant concentrations and oxidative damage in ventilated premature babies. *Archives of Disease in Childhood: Fetal and Neonatal Edition* **89,** F412-F416.

Dani C, Reali MF, Bertini G, Martelli E, Pezzati M, Rubaltelli FF (2001) The role of blood transfusions and iron intake on retinopathy of prematurity. *Early Human Development* **62**, 57-63.

Howard-Quijano K, Schwarzenberger JC, Scovotti JC, Alejos A, Ngo J, Gornbein J, and Mahajan A. (2013) Increased red blood cell transfusions are associated with worsening outcomes in pediatric heart transplant patients. *Anesth Analg,* **116** (6):1295-308.

Ikeda H, Kuriyama S (2004) Risk Factors for Retinopathy of Prematurity Requiring Photocoagulation. *Japanese Journal of Ophthalmology* **48,** 68-71.

Lee MT, Piomelli S, Granger S et al. (2006) Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood*, **108**: 847-852.

Martin FG, Saenz De Pipaon M, Perez Rodriguez J, and Jimenez JQ. (2013) Risk factors for the development of necrotizing enterocolitis: A case-control study. *J Neonatal-Perinat Med,* **6** (4):311-8.

Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari HK (1996) Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. *The National medical journal of India* **9**, 211-214

Nair PMC, Ganesh A, Mitra S, Ganguly SS (2003) Retinopathy of prematurity in VLBW and extreme LBW babies. *Indian Journal of Pediatrics* **70,** 303-306.

Palmcrantz J, Hardcastle TC, Naidoo SR, Muckart DJ, Ahlm K, and Eriksson A. (2012) Pelvic fractures at a new level 1 trauma centre: who dies from pelvic trauma? The Inkosi Albert Luthuli Central Hospital experience. *Orthop Surg,* **4** (4):216-21.

Pieracci FM, Witt J, Moore EE et al. (2012) Early death and late morbidity after blood transfusion of injured children: a pilot study. *Journal of Pediatric Surgery*, **47**:1587-91.

Quinn CT, Johnson VL, Kim HY, Trachtenberg F, Vogiatzi MG, Kwiatkowski JL, Neufeld EJ, Fung E, Oliveri N, Kirby M, and Giardina PJ. (2011) Renal dysfunction in patients with thalassaemia. *Br J Haematol,* **153** (1):111-7.

Rekha S, Battu RR (1996) Retinopathy of prematurity: incidence and risk factors. *Indian Pediatrics* **33**, 999-1003

Silvers KM, Gibson AT, Russell JM, Powers HJ (1998) Antioxidant activity, packed cell transfusions, and outcome in premature infants. *Archives of Disease in Childhood: Fetal and Neonatal Edition* **78**, F214-F219.

Valieva OA, Strandjord TP, Mayock DE, Juul SE (2009) Effects of Transfusions in Extremely Low Birth Weight Infants: A Retrospective Study. *Journal of Pediatrics* **155,** 331-337.

Von Lindern JS, Khodabux CM, Hack KEA, van Haastert IC, Koopman-Esseboom C, van Zwieten PHT, Brand A, and Walther FJ. (2011) Long-term outcome in relationship to neonatal transfusion volume in extremely premature infants: A comparative cohort study. *BMC Pediatr,* **11**: 48.

Studies awaiting assessment (secondary outcomes only)

Al-Essa M, Azad RV, Rashwan N (1999) Rate of and risk factors associated with retinopathy of prematurity: A prospective study from Kuwait. *Medical Principles and Practice* **8,** 115-118.

Bayat-Mokhtari M, Pishva N, Attarzadeh A, Hosseini H, Pourarian S (2010) Incidence and risk factors of retinopathy of prematurity among preterm infants in Shiraz/Iran. *Iranian Journal of Pediatrics* **20,** 303-307.

Demirel N, Bas AY, Zenciroglu A (2009) Bronchopulmonary dysplasia in very low birth weight infants. *Indian Journal of Pediatrics* **76,** 695-698.

Dutta S, Narang S, Narang A, Dogra M, Gupta A (2004) Risk factors of threshold retinopathy of prematurity. *Indian Pediatrics* **41,** 665-671.

Ebrahim M, Ahmad RS, Mohammad M (2010) Incidence and risk factors of retinopathy of prematurity in Babol, North of Iran. *Ophthalmic Epidemiology* **17,** 166-170.

Fortes Filho JB, Eckert GU, Procianoy L, Barros CK, and Procianoy RS (2009). Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil. *Eye* **23**,25-30.

Fortes Filho JB, Eckert GU, Valiatti FB, Dos Santos PGB, Da Costa MC, Procianoy RS (2010) The influence of gestational age on the dynamic behavior of other risk factors associated with retinopathy of prematurity (ROP). *Graefe's Archive for Clinical and Experimental Ophthalmology* **248,** 893-900.

Hesse L, Eberl W, Schlaud M, Poets CF (1997) Blood transfusion: Iron load and retinopathy of prematurity. *European Journal of Pediatrics* **156,** 465-470.

Lad EM, Hernandez-Boussard T, Morton JM, Moshfeghi DM (2009) Incidence of Retinopathy of Prematurity in the United States: 1997 through 2005. *American Journal of Ophthalmology* **148,** 451-458.

Not applicable

Boo NY (1997) A national study of risk factors associated with mortality in very low birthweight infants in the Malaysian neonatal intensive care units. *Journal of Paediatrics and Child Health* **33,** 18-25.

B2 Studies excluded from Question 2

Level I evidence

Superseded

Ojukwu JU, Okebe JU, Yahav D, and Paul M. (2009) Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. *Cochrane Database of Systematic Reviews*, Issue **3**, CD006589.

Article not available in English

Cembranel F, Dallazen C, and Gonzalez-Chica DA. (2013) Effectiveness of ferrous sulfate supplementation in the prevention of anemia in children: a systematic literature review and meta-analysis (provisional abstract). *Database of Abstracts of Reviews of Effects*, **29** (9): 1731-1751.

Wrong publication type

Aronson N, Piper M, Redding FC et al. (2001) Uses of epoetin for anemia in oncology. *Database of Abstracts of Reviews of Effects*. [structured abstract]

Ojukwu JU, and Okebe JU. (2007) Routine iron supplementation for preventing or treating iron-deficiency anaemia in children in malaria-endemic areas. *Cochrane Database of Systematic Reviews*, Issue **3**: CD006589. [protocol]

Quirt I, Bramwell V, Charette M, and Oliver T. (2003) The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy. *Database of Abstracts of Reviews of Effects*. [structured abstract]

Zeng X, and Wu T. (2007) Iron supplementation for iron deficiency anemia in children. *Cochrane Database of Systematic Reviews*, Issue **2**: CD006465. [protocol]

No usable data

Adefita I, and Okomo U. (2009) Iron supplementation for reducing morbidity and mortality in children with HIV. *Cochrane Database of Systematic Reviews*, Issue **1**: CD006736.

Albaramki J, Hodson EM, Craig JC, and Webster AC. (2012) Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database of Systematic Reviews*, Issue **1**: CD007857.

Bohlius J, Schmidlin K, Brillant C et al. (2009) Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet*, **373**: 1532-1542.

Cody JD, Daly C, Campbell MK et al. (2005) Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. *Cochrane Database of Systematic Reviews*, Issue **3**: CD003266.

De-Regil LM, Jefferds ME, Sylvetsky AC, and Dowswell T. (2011) Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database of Systematic Reviews*, Issue **12**: CD009085.

Friel JK, Andrews WL, Hall MS, Rodway MS, Keith M, McCloy UC, Matthew JD, Long DR (1995) Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition. *Journal of parenteral.and enteral nutrition* **19**, 114-118.

Jones AP, Davies SC, and Olujohungbe A. (2001) Hydroxyurea for sickle cell disease. *Cochrane Database of Systematic Reviews*, Issue **2**: CD002202.

Kassem-Moussa H, Muwakkit S, and Mikati M. (2005) Management of acute stroke in the pediatric age group. *Practical Neurology,* **5** (5): 268-277.

Kavanagh PL, Sprinz PG, Vinci SR, et al. (2011) Management of children with sickle cell disease: A comprehensive review of the literature. *Pediatrics*, **128** (6): E1552-E1574.

Long H, Yi JM, Hu PL et al. (2012) Benefits of Iron supplementation for low birth weight infants: A systematic review. BMC Pediatrics, 12

Low M, Farrell A, Biggs BA, and Pasricha SR. (2013) Effects of daily iron supplementation in primary-school-aged children: Systematic review and meta-analysis of randomized controlled trials. *CMAJ*, **185** (17): E791-E802.

Marec-Berard P, Chastagner P, Kassab-Chahmi D et al. (2009) 2007 Standards, Options, and Recommendations: Use of erythropoiesis- stimulating agents (ESA: Epoetin alfa, epoetin beta, and darbepoetin) for the management of anemia in children with cancer. *Pediatric Blood and Cancer*, **53** (1): 7-12.

Mills RJ, and Davies MW. (2012) Enteral iron supplementation in preterm and low birth weight infants. *Cochrane Database of Systematic Reviews*, Issue **3**: CD005095.

National Kidney Foundation. (2002) K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis*, **39**: S1-S266.

Palmer SC, Saglimbene V, Craig JC et al. (2014) Darbepoetin for the anaemia of chronic kidney disease. *Cochrane Database of Systematic Reviews,* Issue **3**: CD009297.

Redding Flamm C, Aronson N, Bohn R et al. (2001) Use of epoetin for anemia in chronic renal failure. *Agency for Healthcare Research and Quality,* **201**.

Strouse JJ, Lanzkron S, Beach MC et al. (2008) Hydroxyurea for sickle cell disease: A systematic review for efficacy and toxicity in children. *Pediatrics*, **122** (6): 1332-1342.

Duplicate data

Glaspy J, Crawford J, Vansteenkiste J et al. (2010) Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *British Journal of Cancer*, **102**: 301-315.

Iannoti LL, Tielsch JM, Black MM, and Black RE. (2006) Iron supplementation in early childhood: Health benefits and risks. *American Journal of Clinical Nutrition*, **84** (6): 1261-1276.

Ojukwu JU, Okebe JU, Yahav D, and Paul M. (2010) Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas: Cochrane systematic review. *International Journal of Epidemiology*, **39** (1): 32-35.

Level II evidence

No usable data

Fujiu T, Maruyama K, Koizumi T. (2004) Oral iron supplementation in preterm infants treated with erythropoietin. *Pediatrics International*, **46** (6):635-639.

Warwood TL, Lambert DK, Henry E, and Christensen RD. (2011) Very low birth weight infants qualifying for a 'late' erythrocyte transfusion: Does giving darbepoetin along with the transfusion counteract the transfusion's erythropoietic suppression? *Journal of Perinatology*, **31** (S1): S17-S21.

Duplicate data

Akisu M, Tuzun S, Arslanoglu S, Yalaz M, and Kultursay N. (2001) Effect of recombinant human erythropoietin administration on lipid peroxidation and antioxidant enzyme(s) activities in preterm infants. *Acta Med Okayama,* **55** (6):357-62.

Al-Kharfy T, Smyth JA, Wadsworth L, Krystal G, Fitzgerald C, Davis J, and Milner R. (1996) Erythropoietin therapy in neonates at risk of having bronchopulmonary dysplasia and requiring multiple transfusions. *J Pediatr,* **129** (1):89-96.

Arif B, and Ferhan K. (2005) Recombinant human erythropoietin therapy in low-birthweight preterm infants: A prospective controlled study. *Pediatr Int,* **47** (1):67-71.

Atasay B, Gunlemez A, Akar N, and Arsan S. (2002) Does early erythropoietin therapy decrease transfusions in anemia of prematurity? *Indian J Pediatr,* **69** (5):389-91.

Avent M, Cory BJ, Galpin J, Ballot DE, Cooper PA, Sherman G, and Davies VA. (2002) A comparison of high versus low dose recombinant human erythropoietin versus blood transfusion in the management of anaemia of prematurity in a developing country. *J Trop Pediatr,* **48** (4):227-33.

Bader D, Blondheim O, Jonas R, Admoni O, Abend-Winger M, Reich D, Lanir A, Tamir A, Eldar I, and Attias D. (1996) Decreased ferritin levels, despite iron supplementation, during erythropoietin therapy in anaemia of prematurity. *Acta Paediatr Int J Paediatr,* **85** (4):496-501.

Baxter LM, Vreman HJ, Ball B, and Stevenson DK. (1995) Recombinant human erythropoietin (r-HuEPO) increases total bilirubin production in premature infants. *Clinical Pediatrics*, **34** (4): 213-216.

Bierer R, Peceny MC, Hartenberger CH, and Ohls RK. (2006) Erythropoietin concentrations and neurodevelopmental outcome in preterm infants. *Pediatrics,* **118** (3):e635-e640.

Buyukpamukcu M, Varan A, Kutluk T, and Akyudie C. (2002) Is epoetin alfa a treatment option for chemotherapy-related anemia in children? *Med Pediatr Oncol,* **39** (4):455-8.

Carnielli VP, Da Riol R, and Montini G. (1998) Iron supplementation enhances response to high doses of recombinant human erythropoietin in preterm infants. *Arch Dis Child Fetal Neonatal Ed,* **79** (1):F44-F48.

Chang L, Liu W, Liao C, and Zhao X. (1998) Preventive effect of different dosage of recombinant human erythropoietin on anemia of premature infants. *J Tongji Med Univ,* **18** (4):239-42.

Chen JY, Wu TS, and Chanlai SP. (1995) Recombinant human erythropoietin in the treatment of anemia of prematurity. *Am J Perinatol,* **12** (5):314-8.

Csaki C, Ferencz T, Schuler D, and Borsi JD. (1998) Recombinant human erythropoietin in the prevention of chemotherapy- induced anaemia in children with malignant solid tumours. *Eur J Cancer,* **34** (3):364-7.

Fauchere JC, Dame C, Vonthein R, Koller B, Arri S, Wolf M, and Bucher HU. (2008) An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. *Pediatrics,* **122** (2):375-82.

Griffiths G, Lall R, Chatfield S, et al. (1997) Randomised controlled double blind study of role of recombinant erythropoietin in the prevention of chronic lung disease. *Archives of Disease in Childhood*, **76** (S3): F190-F192

Juul SE. (2003) Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. *Journal of Pediatrics*, **143** (3): 321-326.

Kivivuori SM, Virtanen M, Raivio KO, Viinikka L, and Siimes MA. (1999) Oral iron is sufficient for erythropoietin treatment of very low birth- weight infants. *Eur J Pediatr,* **158** (2):147-51.

Kumar P, Shankaran S, and Krishnan RG. (1998) Recombinant human erythropoietin therapy for treatment of anemia of prematurity in very low birth weight infants: a randomized, double-blind, placebo-controlled trial. *J Perinatol*, **18** (3):173-7.

Maier RF, Obladen M, Muller-Hansen I, et al. (2002) Early treatment with erythropoietin (beta) ameliorates anemia and reduces transfusion requirements in infants with birth weights below 1000 g. *J Pediatr,* **141** (1):8-15.

Meister B, Maurer H, Simma B, et al. (1997) The effect of recombinant human erythropoietin on circulating hematopoietic progenitor cells in anemic premature infants. *Stem Cells*, **15** (5): 359-363.

Meyer MP, Sharma E, and Carsons M. (2003) Recombinant erythropoietin and blood transfusion in selected preterm infants. *Arch Dis Child Fetal Neonatal Ed*, **88** (1):F41-F45.

Ohls RK, Christensen RD, Kamath-Rayne BD, et al. (2013) A randomized, masked, placebo-controlled study of darbepoetin alfa in preterm infants. *Pediatrics,* **132** (1):e119-e127.

Ohls RK, Ehrenkranz RA, Wright LL, et al. (2001) Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: A multicenter, randomized, controlled trial. *Pediatrics*, **108** (4):934-42.

Ohls RK, Osborne KA, and Christensen RD. (1995) Efficacy and cost analysis of treating very low birth weight infants with erythropoietin during their first two weeks of life: A randomized, placebo-controlled trial. *J Pediatr,* **126** (3):421-6.

Ohls RK, Harcum J, Schibler KR, and Christensen RD. (1997) The effect of erythropoietin on the transfusion requirements of preterm infants weighing 750 grams of less: A randomized, double-blind, placebo- controlled study. *J Pediatr,* **131** (5):661-5.

Pollak A, Hayde M, Hayn M, et al. (2001) Effect of intravenous iron supplementation on erythropoiesis in erythropoietin-treated premature infants. *Pediatrics,* **107** (1):78-85.

Porter JC, Leahey A, Polise K, Bunin G, and Manno CS. (1996) Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: A randomized, double-blind, placebo-controlled trial. *J Pediatr,* **129** (5):656-60.

Razzouk BI, Hord JD, Hockenberry M, Hinds PS, Feusner J, Williams D, and Rackoff WR. (2006) Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy*. J Clin Oncol,* **24** (22):3583-9.

Reiter PD, Rosenberg AA, Valuck R, and Novak K. (2005) Effect of short-term erythropoietin therapy in anemic premature infants. *J Perinatol,* **25** (2):125-9.

Rendo P, Freigeiro D, Barboni G, Donato H, Drelichman G, and Gonzalez F. (2001) A multicenter, randomized, double-blind trial with Recombinant Human Erythropoietin (rHuEPO) in anemic HIV-infected children treated with antiretrovirals. *Int J Pediatr Hematol Oncol,* **7** (3):235-9.

Romagnoli C, Zecca E, Gallini F, Girlando P, and Zuppa AA. (2000) Do recombinant human erythropoietin and iron supplementation increase the risk of retinopathy of prematurity? *Eur J Pediatr,* **159** (8):627-8.

Ronnestad A, Moe PJ, and Breivik N. (1995) Enhancement of erythropoiesis by erythropoietin, bovine protein and energy fortified mother's milk during anaemia of prematurity. *Acta Paediatr Int J Paediatr,* **84** (7):809-11.

Samanci N, Ovali F, and Dagoglu T. (1996) Effects of recombinant human erythropoietin in infants with very low birth weights. *J Int Med Res,* **24** (2):190-8.

Shannon KM, Keith III JF, Mentzer WC, et al. (1995) Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. *Pediatrics,* **95** (1):1-10.

Soubasi V, Kremenopoulos G, Diamanti E et al. (1995) Follow-up of very low birth weight infants after erythropoietin treatment to prevent anemia of prematurity. *J Pediatr,* **127** (2):291-7.

Varan A, Buyukpamukcu M, Kutluk T, and Akyuz C (1999) Recombinant human erythropoietin treatment for chemotherapy-related anemia in children. *Pediatrics,* **103** (2):E16.

Whitehall JS, Patole SK, and Campbell P. (1999) Recombinant human erythropoietin in anemia of prematurity. *Indian Pediatr,* **36** (1):17-27.

Yasmeen BHN, Chowdhury MAKA, Hoque MM, Hossain MM, Jahan R, and Akhtar S. (2012) Effect of short term recombinant human erythropoietin (rHuEPO) therapy in the prevention of anemia of prematurity (AOP) in very low birth weight (VLBW) neonates. *Bangladesh Med Res Counc Bull,* **38** (3):119-23.

Yeo CL, Choo S, and Ho LY (2001) Effect of recombinant human erythropoietin on transfusion needs in preterm infants. *J Paediatr Child Health,* **37** (4):352-8.

B3 Studies excluded from Question 3

Level I evidence

Wrong publication type

Coppola A, Di-Minno-Matteo-Nicola-Dario, and Windyga J. (2012) Treatment for preventing bleeding in people with congenital bleeding disorders undergoing surgery. *Cochrane Database of Systematic Reviews*, Issue **7**: CD009961. [protocol]

Mills JF and Woodgate PG. (2001) Exchange transfusion for neonatal jaundice. *Cochrane Database of Systematic Reviews*, Issue **2**: CD003060. [protocol]

Wood EM, Stanworth S, Doree C, Hyde C, Silvani CM, Montedori A, and Abraha I. (2009) Fresh frozen plasma for cardiovascular surgery. *Cochrane Database of Systematic Reviews*, Issue **1**: CD007614. [protocol]

No usable data

Duguid J, O'Shaughnessy DF, Atterbury C, Maggs PB, Murphy M, Thomas D, Yates S, and Williamson LM. (2004) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology,* **126**:11-28.

George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, and Warrier I. (1996) Idiopathic thrombocytopaenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. *Blood,* **88**:3-40.

Karam O, Tucci M, Combescure C, Lacroix J, and Rimensberger PC. (2013) Plasma transfusion strategies for critically ill patients. *Cochrane Database of Systematic Reviews,* Issue **12**: CD010654.

Kelsey P, Murphy MF, Brown M, Carrington P, Hall G, Jeffrey RR, Machin S, Taylor C, Thomas D, Boulton F, Bruce M, Cohen H, Duguid J, Knowles SM, Murphy MF, Poole G, and Williamson LM. (2003) Guidelines for the use of platelet transfusions. *British Journal of Haematology,* **122**:10-23.

Lunde J., Stensballe J., Wikkelso A., Johansen M., and Afshari A. (2014) Fibrinogen concentrate for bleeding - a systematic review. *The Acta Anaesthesiologica Scandinavica Foundation*, **58:**1061-1074.

Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, Goldstein M, Hume H, McCullough JJ, McIntyre RE, Powell BL, Rainey JM, Rowley SD, Rebulla P, Troner MB, and Wagnon AH. (2001) Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *Journal of Clinical Oncology,* **19**:1519-1538.

Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, and Murphy MF. (2004) Is fresh frozen plasma clinically effective: a systematic review of randomized controlled trials (Provisional abstract). *British Journal of Haematology,* **126**:139-152.

Wikkelso A, Lunde J, Johansen M, Stensballe J, Wetterslev J, Moller AM, Afshjari A. (2013) Fibrinogen concentrate in bleeding patients. *Cochrane Database of Systematic Reviews*, Issue **8**: CD008864.

Williams MD, Chalmers EA, and Gibson BES. (2002) The investigation and management of neonatal haemostasis and thrombosis. *British Journal of Haematology,* **119**:295-309.

Yang, L. Stanworth, S. Hopewell S., Doree C., and Murphy M. (2012) Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials (CME). *Transfusion* **52** (8):1673-1686.

Zimmerman JL. (2004) Use of blood products in sepsis: An evidence-based review. *Critical Care Medicine* **32**:S542-S547.

Level II evidence

Wrong publication type

Curley A, Venkatesh V, Stanworth S, et al. (2014) Platelets for neonatal transfusion - Study 2: A randomised controlled trial to compare two different platelet count thresholds for prophylactic platelet transfusion to preterm neonates. *Neonatology*, **106** (2): 102-106. [protocol]

No usable data

Kaufman RM, Assmann SF, Triulzi DJ et al. (2014) Transfusion-related events in the Platelet Dose study. *Transfusion*, doi: 10.1111/trf.12791. [combined data reported for both adults and children]

Level III evidence

Sample size ≤ 100

Balestracci A, Martin SM, Toledo I, et al. (2013) Impact of platelet transfusions in children with post-diarrheal haemolytic uremic syndrome. *Pediatr Nephrol*, **28**: 919-925.

Jan M, Ahmad SM, Charoo B et al. (2000) Neonatal polycythemia comparison of partial exchange transfusion with plasma versus normal saline. *JK Practitioner*, **7** (3): 195-196.

Kabra SK, Jain Y, Madhulika X, et al. (1998) Role of platelet transfusion in Dengue Hemorrhagic Fever. *Indian Pediatrics*, **35**: 452-455.

Paananen P, Arola MO, Pelliniemi TT et al. (2009) Evaluation of the effects of different transfusion trigger levels during the treatment of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*, **31**: 745-749.

No usable data

Baer VL, Lambert DK, Henry E, and Christensen RD. (2009) Severe thrombocytopaenia in the NICU. *Pediatrics,* **124**: e1095-e1100.

Baer VL, Lambert DK, Henry E, Snow GL, Christensen RD. (2011) Red blood cell transfusion of preterm neonates with a Grade 1 intraventricular haemorrhage is associated with extension to a Grade 3 or 4 hemorrhage. *Transfusion*, **51**:1933-1939.

Lieberman L, Bercovitz RS, Sholapur NS, Heddle NM, Stanworth SJ and Arnold DM. (2014) Platelet transfusions for critically ill patients with thrombocytopaenia. *Blood*, **123** (8): 1146-1151.

McRoberts RJ, Beard D, and Walsh TS. (2007) A study of blood product use in patients with major trauma in Scotland: analysis of a major trauma database. *Emerg Med J*, **24**: 325-329.

Insufficient adjustment for confounders

Jeschke MG, Chinkes DL, Finnerty CC, Przkora R, Pereira CT and Herndon DN. (2007) Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Pediatric Critical Care,* **35** (2): 579-583.

Motta M, del Vecchio A, Perrone B, Ghirardello S and Radicioni M. (2014) Fresh frozen plasma use in the NICU: a prospective, observational, multicentred study. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, **99** (4): F303-F308.

B4 Studies excluded from Question 4

Level I evidence

Superseded

Alcock GS, Liley H. (2002) Immunoglobulin infufusion for isoimmune haemolytic jaundice in neonates. *Cochrane Database of Systematic Reviews*, Issue **3**: CD003313.

Article not available in English

Li MJ, Chen CH, Wu Q, Shi W, Yang Q, and Li MN. (2010) Intravenous immunoglobulin G for hemolytic disease of the newborn: a systematic review (Provisional abstract). *Chinese Journal of Evidence Based Medicine*, **10**:1199-1204.

Li ZH, Wang J, and Chen C. (2010) Meta analysis of the effect of immunoglobulin infusion on neonatal isoimmune hemolytic disease caused by blood group incompatibility (Provisional abstract). *Chinese Journal of Pediatrics,* **48**:656-660.

Wrong publication type

Badeaux J and Hawley D. (2013) Effectiveness of intravenous Tranexamic Acid (TXA) administration in managing perioperative blood loss in patients undergoing spine surgery: A systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports*, **11**:123-131. [protocol]

Coppola A, Di Minno MND, and Windyga J. (2012) Treatment for preventing bleeding in people with congenital bleeding disorders undergoing surgery. *Cochrane Database of Systematic Reviews*, Issue **7**: CD009961. [protocol]

Fabes J, Barker G, Simons G, Curry N, Brunskill SJ, Doree C, Lin Y, McKechnie S, and Stanworth S. (2013) Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews*, Issue **7**: CD010649. [protocol]

Lefevre F, and Ratko TA. (2006) Special report: recombinant activated factor VII for uncontrolled bleeding in non-hemophiliac patients. *Health Technology Assessment Database*, **21** (10). [abstract only]

Malhotra A and Veldman A. (2011) Recombinant activated Factor VII for prevention and treatment of intraventricular haemorrhage in neonates. *Cochrane Database of Systematic Reviews*, Issue **3**: CD009032. [protocol]

No usable data

Curry N, Hopewell S, Doree C, Hyde C, Brohi K, and Stanworth S. (2011) The acute management of trauma hemorrhage: A systematic review of randomized controlled trials. *Critical Care,* **15**.

Faughnan ME, Palda VA, Garcia-Tsao G, et al. (2011) International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *Journal of Medical Genetics,* **48**:73-87.

Franchini M, Manzato F, Salvagno GL, and Lippi G. (2007) Potential role of recombinant activated factor VII for the treatment of severe bleeding associated with disseminated intravascular coagulation: a systematic review. *Blood Coagulation and Fibrinolysis*, **18**:589-593.

Haas T, Gorlinger K, Grassetto A et al. (2014) Thromboelastometry for Guiding Bleeding Management of the Critically Ill Patient: A Systematic Review of the Literature. *Minerva Anestesiol.*

Marti-Carvajal AJ, Sola I and Marti-Carvajal PI. (2012) Antifibrinolytic amino acids for upper gastrointestinal bleeding in patients with acute or chronic liver disease. *Cochrane Database of Systematic Reviews,* Issue **9**: CD006007. [no studies identified]

Mathew P. (2004) The use of rFVIIa in non-haemophilia bleeding conditions in paediatrics. A systematic review. *Thrombosis and Haemostasis,* **92**:738-746.

Okonta KE, Edwin F, Falase B. (2012) Is recombinant activated factor VII effective in the treatment of excessive bleeding after paediatric cardiac surgery? *Interactive Cardiovascular and Thoracic Surgery*, **15**(4): 690-695.

Prutsky G, Domecq JP, Salazar CA, and Accinelli R. (2012) Antifibrinolytic therapy to reduce haemoptysis from any cause. *Cochrane Database of Systematic Reviews,* Issue **4**: CD008711.

Roberts I, Shakur H, Ker K, and Coats T. (2012) Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database of Systematic Reviews,* Issue **12**: CD004896.

Spahn DR, Bouillon B, Cerny V et al. (2010) Management of bleeding and coagulopathy following major trauma: An updated European guideline. *Critical Care,* **14**.

von Heymann C, Jonas S, Spies C, Wernecke KD, Ziemer S, Janssen D, and Koscielny J. (2008) Recombinant activated factor VIIa for the treatment of bleeding in major abdominal surgery including vascular and urological surgery: a review and meta-analysis of published data. *Critical Care,* **12**:R14.

Wardrop D, Estcourt LJ, Brunskill SJ, Doree C, Trivella M, Stanworth S, and Murphy MF. (2013) Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. *Cochrane Database of Systematic Reviews,* Issue **7**: CD009733.

Warren O, Mandal K, Hadjianastassiou V, Knowlton L, Panesar S, John K, Darzi A, and Athanasiou T. (2007) Recombinant activated factor VII in cardiac surgery: a systematic review. *Annals of Thoracic Surgery*, **83**:707-714.

Warren OJ, Rogers PLB, Watret AL, De Wit KL, Darzi AW, Gill R, and Athanasiou T. (2009) Defining the role of recombinant activated factor VII in pediatric cardiac surgery: Where should we go from here? *Pediatric Critical Care Medicine,* **10**:572-582.

Duplicate data

Badeaux J, Hawley D. (2014) Effectiveness of intravenous tranexamic acid administration in managing perioperative blood loss in patients undergoing spine surgery: a systematic review. JBI Database of Systematic Reviews & Implementation Reports, **12**(7):284-314.

Basta MN, Stricker PA, Taylor JA. (2012) A systematic review of the use of antifibrinolytic agents in pediatric surgery and implications for craniofacial use. Pediatr Surg Int, **28**(11):1059-1069.

Hsia CC, Chin Y, I, and McAlister VC. (2008) Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. *Annals of Surgery,* **248**:61-68.

Rabe H, Reynolds G, and Diaz-Rossello J. (2008) A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonatology,* **93**:138-144.

Level II evidence

Article not available in English

Atici A, Satar M, and ebakan M. (1996) [Intravenous immunoglobulin therapy for neonatal hyperbilirubinemia due to ABO or Rh incompatibility]. *Çocuk Sağliği ve Hastaliklari*, **39**:623-630.

Bernardis RC, Silva MP, Gozzani JL, Pagnocca ML, and Mathias LA. (2009) [Use of forced-air to prevent intraoperative hypothermia]. *Revista da Associação Médica Brasileira,* **55**:421-426.

Feng YP, Rao YX, Yin SX, Shen TH, and Wei MF. (1997) [Isoflurane for controlled hypotension in ligation of pediatric patent ductus arteriosus]. *Chinese Journal of Anesthesiology,* **17**:56-57.

Ferreira CA, de Andrade Vicente WV, et al. (2010) Assessment of aprotinin in the reduction of inflammatory systemic response in children undergoing surgery with cardiopulmonary bypass. *Brazilian Journal of Cardiovascular Surgery,* **25**:85-98.

Farhadi R, Naderi M, Rahmani Z, Ghaffari V, and Khalilian A. (2012) Effect of "ZIPKIF" plastic bag on prevention of hypothermia in preterm infants: a randomized controlled trial. *Journal of Mazandaran University of Medical Sciences,* **22**:18-24.

Heesen M, Dietrich GV, Cornelius A, Wirth R, Lorisch M, Bachmann MB, and Hempelmann G. (1995) [Does controlled hypotension with nitroprusside affect platelet function?]. Der Anaesthesist 44:695-699.

Jiao HN, Ren F, Cai HW, and Guo QL. (2009) [Effect of controlled hypotension with different drugs combined with acute hypervolemic hemodilution on bleeding volume and gastrointestinal perfusion in nasal endoscopic surgery]. *Nan fang yi ke da xue xue bao [Journal of Southern Medical University]* **29**:1163-1165.

Not able to be retrieved

Hanna MG, Refaie A, Gouda N, and Obaya G. (2010) Reduction of peri-operative bleeding in craniofacial surgeries in pediatrics. Comparison between recombinant factor VII and tranexamic acid. *Egyptian Journal of Anaesthesia*, **26**:53-61.

Wrong publication type

Andonova A, Gavrilova N, Kotzeva S, and Jekova N. (2008) Efficacy and safety of acute normovolemic hemodilution in pediatric abdominal and orthopedic surgery. *Transfusion Alternatives in Transfusion Medicine*, **10**:37. [abstract only]

Cholette J, Powers K, Alfieris G, Angona R, Henrichs K, and Blumberg N. (2011) Cell saver for volume replacement in children following cardiopulmonary bypass reduces the number of RBC and blood product transfusions and donor exposures. *Critical Care Medicine,* **39**:7. [abstract only]

Elimian A, Goodman J, Escobedo M, Nightingale L, Knudtson E, and Williams M. (2013) A randomized controlled trial of immediate versus delayed cord clamping in the preterm neonate. *American Journal of Obstetrics and Gynecology,* **208**:S22. [abstract only]

Hanson M, Morris P, Kilburn C, Lennox R, Szabo F, Bull A, Harn SA, Williams D, Thomas S, Kearns K, Kirby A, Koops MJ, and Burke K. (2012) Effect of delayed cord clamping on the haemoglobin levels of term newborn aboriginal infants from remote aboriginal communities: A pilot randomised controlled trial. *Journal of Paediatrics and Child Health,* **48**:140. [abstract only]

Hematyar M and Zareian M. (2011) The effects of intravenous immunoglobulin(IVIG) in hemolytic jaundice of the newborn due to ABO and Rh isoimmunization. *Acta paediatrica,* **100**:13-83. [abstract only]

Miqdad AM, Abdelbasit OB, Shaheed MM, Zain SM, Abomelha AM, and Arcala OA. (2003) Intravenous immunoglobulin therapy for hyperbilirubinaemia ABO hemolytic disease. *Pediatric Research,* **53**:27. [abstract only]

Ray MJ and Marsh NA. (1997) Aprotinin reduces blood loss after cardiopulmonary bypass by direct inhibition of plasmin. *Thrombosis and Haemostasis,* **78**:1021-1026. [abstract only]

Santos. (2010) High-Dose Intravenous Immunoglobulin Therapy for Hyperbilirubinemia Due Rh Hemolytic Disease: A Randomized Clinical Trial. *Pediatric Academic Society* http://www.abstracts2view.com/pas/. [abstract only]

Strauss RG and Mock DM. (2007) A randomized clinical trial comparing immediate vs delayed clamping of the umbilical cord in preterm infants. *Transfusion,* **47 Suppl**: 21A. [abstract only]

Ongoing trials

Josephsen J, Vlastos E, Potter S, and Al HM. (2014) Milking the umbilical cord in extreme preterm infants (NCT01666847). *American Journal of Obstetrics and Gynecology,* **210**:S403-S404.

Duplicate data

Albirmawy OA, Saafan ME, Shehata EM, Basuni AS, Eldaba AA. (2013) Topical application of tranexamic acid after adenoidectomy: A double-blind, prospective, randomized, controlled study. *Int J Pediatr Otorhinolaryngol,* **77**:1139-1142.

Alpay F, Sarici SU, Okutan V, Erdem G, Ozcan O, and Gokcay E. (1999) High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. *Acta Paediatrica, International Journal of Paediatrics,* **88**:216-219.

Bulutcu FS, Ozbek U, Polat B, Yalcin Y, Karaci AR, and Bayindir O. (2005) Which may be effective to reduce blood loss after cardiac operations in cyanotic children: Tranexamic acid, aprotinin or a combination? *Paediatric Anaesthesia,* **15**:41-46.

Chauhan S, Bisoi A, Modi R, Gharde P, and Rajesh MR. (2003) Tranexamic acid in paediatric cardiac surgery. *Indian Journal of Medical Research,* **118**:86-89.

Chauhan S, Bisoi A, Kumar N, Mittal D, Kale S, Kiran U, and Venugopal P. (2004) Dose comparison of tranexamic acid in pediatric cardiac surgery. *Asian cardiovascular & thoracic annals,* **12**:121-124.

Chauhan S, Das SN, Bisoi A, Kale S, and Kiran U. (2004) Comparison of Epsilon Aminocaproic Acid and Tranexamic Acid in Pediatric Cardiac Surgery. *Journal of Cardiothoracic and Vascular Anesthesia,* **18**:141-143.

Chauhan S, Kumar BA, Rao BH, Rao MS, Dubey B, Saxena N, and Venugopal P. (2000) Efficacy of aprotinin, epsilon aminocaproic acid, or combination in cyanotic heart disease. *Annals of Thoracic Surgery,* **70**:1308-1312.

Ceriani-Cernadas JM, Carroli G, Pellegrini L, et al. (2006) The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. *Pediatrics,* **117**:e779-e786.

Dadure C, Sauter M, Bringuier S, Bigorre M, Raux O, ROchette A, Canaud N, Capdevila X. (2011) Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniosynostosis surgery: a randomized double-blind study. *Anesthesiology*, **144**:856-861.

Dagoglu T, Ovali F, Samanci N, and Bengisu E. (1995) High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. *Journal of International Medical Research,* **23**:264-271.

Davies MJ, Allen A, Kort H, Weerasena NA, Rocco D, Paul CL, Hunt BJ, and Elliott MJ. (1997) Prospective, randomized, double-blind study of high-dose aprotinin in pediatric cardiac operations. *Annals of Thoracic Surgery,* **63**:497-503.

Ekert H, Brizard C, Eyers R, Cochrane A, and Henning R. (2006) Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions. *Blood Coagulation and Fibrinolysis,* **17**:389-395.

Elalfy MS, Elbarbary NS, and Abaza HW. (2011) Early intravenous immunoglobin (two-dose regimen) in the management of severe Rh hemolytic disease of newborn-a prospective randomized controlled trial. *European Journal of Pediatrics,* **170**:461-467.

Garcia MG, Cordero G, Mucino P, Salinas V, Fernandez LA, and Christensen RD. (2004) Intravenous immunoglobulin (IVIG) administration as a treatment for Rh hemolytic jaundice in Mexico City. *Pediatric Research,* **55**:65.

Goobie SM, Meier PM, Pereira LM, McGowan FX et al. (2011) Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial. *Anesthesiology,* **114**:862-871.

Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T, Takahashi S, and Harada K. (2008) Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: A randomised controlled trial. *Archives of Disease in Childhood: Fetal and Neonatal Edition,* **93**:F14-F19.

Ibrahim HM, Krouskop RW, Lewis DF, and Dhanireddy R. (2000) Placental transfusion: umbilical cord clamping and preterm infants. Journal of perinatology. *Official journal of the California Perinatal Association,* **20**:351-354.

March MI, Hacker MR, Parson AW, Modest AM, and De Veciana M. (2013) The effects of umbilical cord milking in extremely preterm infants: A randomized controlled trial. *Journal of Perinatology,* **33**:763-767.

Maugans TA, Martin D, Taylor J, Salisbury S, and Istaphanous G. (2011) Comparative analysis of tranexamic acid use in minimally invasive versus open craniosynostosis procedures. *Journal of Craniofacial Surgery*, **22**:1772-1778.

McDonnell M and Henderson-Smart DJ. (1997) Delayed umbilical cord clamping in preterm infants: A feasibility study. *Journal of Paediatrics and Child Health,* **33**:308-310.

Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, and Oh W. (2006) Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: A randomized, controlled trial. *Pediatrics,* **117**:1235-1242.

Miqdad AM, Abdelbasit OB, Shaheed MM, Seidahmed MZ, Abomelha AM, and Arcala OP. (2004) Intravenous immunoglobulin G (IVIG) therapy for significant hyperbilirubinemia in ABO hemolytic disease of the newborn. *Journal of Maternal-Fetal and Neonatal Medicine,* **16**:163-166.

Mossinger H, Dietrich W, Braun SL, Jochum M, Meisner H, and Richter JA. (2003) High-dose aprotinin reduces activation of hemostasis, allogeneic blood requirement, and duration of postoperative ventilation in pediatric cardiac surgery. *Annals of Thoracic Surgery,* **75**:430-437.

Nasseri F, Mamouri GA, and Babaei H. (2006) Intravenous immunoglobulin in ABO and Rh hemolytic diseases of newborn. *Saudi Medical Journal,* **27**:1827-1830.

Oh W, Fanaroff AA, Carlo WA, Donovan EF, McDonald SA, and Poole WK. (2011) Effects of delayed cord clamping in very-low-birth-weight infants. *Journal of Perinatology,* **31**:S68-S71.

Rabe H, Wacker A, Hulskamp G, Hornig-Franz I, Schulze-Everding A, Harms E, Cirkel U, Louwen F, Witteler R, and Schneider HPG. (2000) A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. *European Journal of Pediatrics,* **159**:775-777.

Rao BH, Saxena N, Chauhan S, Bisoi AK, and Venugopal P. (2000) Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. *Indian Journal of Medical Research,* **111**:57-61.

Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, and Burrows FA. (1997) The efficacy of tranexamic acid versus placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. *Anesthesia and Analgesia,* **84**:990-996.

Shimizu K, Toda Y, Iwasaki T, Takeuchi M, Morimatsu H, Egi M, Suemori T, Suzuki S, Morita K, Sano S. (2011) Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial. *Joural of Anesthesia,* **25**:823-830.

Smits-Wintjens VEHJ, Walther FJ, Rath MEA, Lindenburg ITM, Te Pas AB, Kramer CM, Oepkes D, Brand A, and Lopriore E. (2011) Intravenous immunoglobulin in neonates with rhesus hemolytic disease: A randomized controlled trial. *Pediatrics,* **127**:680-686.

Strauss RG, Mock DM, Johnson KJ, Cress GA, Burmeister LF, Zimmerman MB, Bell EF, and Rijhsinghani A. (2008) A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: Short-term clinical and laboratory endpoints. *Transfusion,* **48**:658-665.

Ultee CA, Deure J, Swart J, Lasham C, and Baar AL. (2008) Delayed cord clamping in preterm infants delivered at 34 36 weeks' gestation: a randomised controlled trial. Archives of Disease in Childhood. *Fetal and Neonatal Edition,* **93**:F20-F23.

Van Rheenen P, de Moor L, Eschbach S, de Grooth H, and Brabin B. (2007) Delayed cord clamping and haemoglobin levels in infancy: A randomised controlled trial in term babies. *Tropical Medicine and International Health*, **12**:603-616.

Voto LS, Sexer H, Ferreiro G, Tavosnanska J, Orti J, Mathet ER, Margulies M, and Margulies M. (1995) Neonatal administration of high-dose intravenous immunoglobulin in rhesus hemolytic disease. *Journal of Perinatal Medicine,* **23**:443-451.

Williams GD, Ramamoorthy C, Pentcheva K, Boltz MG, Kamra K, and Reddy VM. (2008) A randomized, controlled trial of aprotinin in neonates undergoing open-heart surgery. *Paediatric Anaesthesia,* **18**:812-819.

Zonis Z, Secar M, Reichert C, Sett S, and Allen C. (1996) The effect of preoperative tranexamic acid on blood loss after cardiac operations in children. *Journal of Thoracic and Cardiovascular Surgery,* **111**:982-987.

Appendix C Literature screening results

C1 Search results – Question 1

Question 1 – Level I studies (March 2014)	Number of citations
Number of citations identified	1243
Citations excluded after title/abstract review:	
Published prior to 1995	15
Duplicate citation	82
Superseded	2
Wrong population	365
Wrong intervention	716
Wrong comparator	11
Wrong outcome	4
Wrong publication type	8
Wrong study type (Level II)	2
Wrong study type (Level III)	2
Wrong study type (Level IV or below)	2
Number of studies added from other databases or hand searching	3
Number of studies included for full text review	37
Studies excluded after full text review:	
Not available in English	1
Wrong population	3
Wrong intervention	3
Wrong outcome	1
Wrong publication type	8
Wrong study type (Level III)	3
Wrong study type (Level IV or below)	2
No usable data	4
Duplicate data	2
Number of eligible reviews	10

GQ1 – Level I studies (October 2014)	Number of citations
Number of citations identified	1301
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	1207
Wrong population	17
Wrong intervention	70
Wrong outcome	2
Wrong publication type	1
Wrong study type (Level IV or below)	1
Number of studies included for full text review	3
Studies excluded after full text review:	
Wrong publication type	1
No usable data	1
Duplicate data	1
Number of eligible reviews	0

Question 1 – Level II studies (March 2014)	Number of citations
Number of citations identified	8164
Citations excluded after title/abstract review:	
Published prior to 1995	975
Duplicate citation	32
Non-human study	8
Wrong population	1262
Wrong intervention	5511
Wrong comparator	64
Wrong outcome	34
Wrong publication type	100
Wrong study type (Level I)	18
Wrong study type (Level III)	44
Wrong study type (Level IV or below)	65
Number of studies added from other databases or hand searching	0
Number of studies included for full text review	51
Studies excluded after full text review:	
Wrong population	8
Wrong intervention	2
Wrong comparator	2
Wrong outcome	8
Wrong publication type	7
Wrong study type (Level I)	1
Wrong study type (Level III)	2
Wrong study type (Level IV or below)	7
No usable data	1
Number of eligible studies	13

Question 1 – Level II studies (October 2014)	Number of citations
Number of citations identified	9392
Citations excluded after title/abstract review:	
Published prior to 1995	756
Duplicate citation / previously identified in March 2014 search	7740
Wrong population	120
Wrong intervention	691
Wrong comparator	17
Wrong outcome	25
Wrong publication type	19
Wrong study type (Level I)	1
Wrong study type (Level III)	3
Wrong study type (Level IV or below)	6
Number of studies added from other databases or hand searching	1
Number of studies included for full text review	15
Studies excluded after full text review:	
Wrong outcome	2
Wrong publication type	9
Wrong study type (Level III)	1
No usable data	1
Number of eligible studies	2

Question 1 – Level III studies (March 2014)	Number of citations
Number of citations identified	28,280
Citations excluded after title/abstract review[a]:	
Duplicate citation	86
Published prior to 1995	3901
Non-human study	4
Wrong population	3084
Wrong intervention[b]	10,900
Wrong comparator	60
Wrong outcome	143
Wrong publication type	46
Wrong study type (Level I)	13
Wrong study type (Level II)	13
Wrong study type (Level III-3)	21
Wrong study type (Level IV or below)	301
Case reports[c]	2634
Sample size ≤100	21
Withdrawn	1
Superseded	10
Not screened	6913
Number of studies added from other databases or hand searching[d]	2
Number of studies included for full text review	131
Studies excluded after full text review:	
Not available in English	1
Wrong population	17
Wrong intervention	5
Wrong comparator	9
Wrong outcome	28
Wrong publication type	5
Wrong study type (Level I)	1
Wrong study type (Level II)	3
Wrong study type (Level III-3)	2
Wrong study type (Level IV or below)	8
Sample size ≤100	16
Insufficient adjustment for confounders	1
No usable data	3
Study already included in Level I study	2
Number of eligible studies	30

a. For this question, all studies published between 2011 and the literature search dates were screened. The Level III database was then selectively screened for primary outcomes not addressed in Level I or Level II evidence.
b. The only included intervention was RBC (allogenic) transfusion compared with no RBC transfusion (or alternative dose) (see Volume 1, Appendix 1). Wrong intervention included exchange transfusions, intrauterine transfusions, restrictive vs liberal strategies, prognostic and aetiological studies.
c. Studies identified as case reports were not screened according to *a priori* criteria.
d. 2 systematic reviews of Level III studies were classed as Level III studies and considered with the Level III evidence.

Question 1 – Level III studies (October 2014)	Number of citations
Number of citations identified	29,831
Citations excluded after title/abstract review:	
Published prior to 2011[a]	28,191
Duplicate citation / previously identified in March 2014 search	85
Non-human study	1
Wrong population	219
Wrong intervention	1224
Wrong comparator	5
Wrong outcome	47
Wrong publication type	6
Wrong study type (Level I)	2
Wrong study type (Level II)	3
Wrong study type (Level IV or below)	27
Number of studies included for full text review	21
Studies excluded after full text review:	
Wrong population	3
Wrong intervention	5
Wrong comparator	1
Wrong outcome	7
Sample size ≤100	1
No usable data	1
Number of eligible studies	3

a. Studies published prior to 2011 were assumed to be previously screened/included in March database.

C2 Search results – Question 2

Question 2 – Level I studies – March 2014	Number of citations
Number of citations identified	989
Citations excluded after title/abstract review:	
Published prior to 1995	11
Duplicate citation	70
Superseded	5
Wrong population	184
Wrong intervention	584
Wrong comparator	4
Wrong outcome	21
Wrong publication type	31
Wrong study type (Level II)	2
Wrong study type (Level III)	1
Number of studies added from other databases or hand searching	3
Number of studies included for full text review	79
Studies excluded after full text review:	
Superseded	1
Not available in English	1
Wrong population	3
Wrong intervention	2
Wrong comparator	2
Wrong outcome	3
Wrong outcome (secondary only)	18
Wrong publication type	15
Wrong study type (Level I-4)	1
Wrong study type (Level III)	1
No usable data	15
Duplicate data	3
Number of eligible reviews	14

GQ2 Level I studies – September 2014	Number of citations
Number of citations identified	1092
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	928
Wrong population	32
Wrong intervention	87
Wrong comparator	6
Wrong outcome	19
Wrong publication type	12
Wrong study type (Level II)	2
Wrong study type (Level III)	2
Number of studies included for full text review	4
Studies excluded after full text review:	
Wrong population	1
Wrong publication type	1
No usable data	1
Number of eligible reviews	1

Question 2 – Level II studies (EMBASE and Cochrane) – March 2014	Number of citations
Number of citations identified	5265
Citations excluded after title/abstract review:	
Published prior to 1995	632
Duplicate citation	10
Non-human study	5
Wrong population	554
Wrong intervention	3237
Wrong comparator	136
Wrong outcome	153
Wrong outcome (secondary only)	116
Wrong publication type	172
Wrong study type (Level I)	67
Wrong study type (Level III)	37
Wrong study type (Level IV or below)	13
Number of studies included for full text review	133
Studies excluded after full text review:	
Wrong population	11
Wrong comparator	20
Wrong outcomes	6
Wrong outcomes (secondary only)	15
Wrong publication type	12
Wrong study type (Level I)	5
Wrong study type (Level III)	1
Wrong study type (Level IV or below)	1
No usable data	2
Duplicate data	39
Number of eligible studies	21

Question 2 – Level II studies (EMBASE) – September 2014	Number of citations
Number of citations identified	4880
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	4720
Wrong population	38
Wrong intervention	95
Wrong comparator	7
Wrong outcome	10
Wrong publication type	5
Wrong study type (Level I)	2
Wrong study type (Level III)	1
Wrong study type (Level IV or below)	1
Number of studies included for full text review	1
Studies excluded after full text review:	0
Number of eligible studies	1

Question 2 – Level II studies (Cochrane Trials) – November 2014	Number of citations
Number of citations identified	2451
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March or September 2014 search	476
Published prior to 1995	465
Not available in English	1
Non-human study	5
Wrong population	381
Wrong intervention	737
Wrong comparator	69
Wrong outcome	195
Wrong publication type	34
Wrong study type (Level I)	1
Wrong study type (Level III)	5
Wrong study type (Level IV or below)	2
Number of studies included for full text review	80
Studies excluded after full text review:	
Already identified by included Level I study	40
Not available in English	7
Wrong population	15
Wrong intervention	1
Wrong publication type	11
Wrong study type (Level III)	5
No usable data	1
Number of eligible studies	0

C3 Search results – Question 3

Question 3 – Level I studies – March 2014	Number of citations
Number of citations identified	375
Citations excluded after title/abstract review:	
Published prior to 1995	6
Duplicate citation	20
Superseded	1
Wrong population	65
Wrong intervention	244
Wrong comparator	1
Wrong outcome	1
Wrong publication type	10
Wrong study type (Level IV or below)	1
Number of studies added from other databases or hand searching	2
Number of studies included for full text review	28
Studies excluded after full text review:	
Wrong population	5
Wrong intervention	3
Wrong comparator	0
Wrong outcome	2
Wrong publication type	5
Wrong study type (Level III)	1
No usable data	10
Number of eligible reviews	2

Question 3 – Level I studies – October 2014	Number of citations
Number of citations identified	344
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	314
Superseded	2
Wrong population	7
Wrong intervention	12
Wrong outcome	2
Wrong study type (Level II)	1
Number of studies included for full text review	6
Studies excluded after full text review:	
Wrong population	2
Wrong intervention	2
Wrong study type (Level II)	1
No usable data	1
Number of eligible reviews	0

Question 3 – Level II studies – March 2014	Number of citations
Number of citations identified	1558
Citations excluded after title/abstract review:	
Published prior to 1995	174
Duplicate citation	6
Superseded	8
Wrong population	163
Wrong intervention	1048
Wrong comparator	29
Wrong outcome	10
Wrong publication type	47
Wrong study type (Level I)	6
Wrong study type (Level III)	25
Wrong study type (Level IV or below)	16
Number of studies added from other databases or hand searching	2
Number of studies included for full text review	28
Studies excluded after full text review:	
Wrong population	6
Wrong intervention	3
Wrong comparator	4
Wrong outcome	2
Wrong publication type	1
Wrong study type (Level I-Clinical Practice Guideline)	3
Wrong study type (Level III)	4
Number of eligible studies	5

Question 3 – Level II studies – October 2014	Number of citations
Number of citations identified	1359
Citations excluded after title/abstract review:	
Published prior to 1995	71
Duplicate citation / previously identified in March 2014 search	1112
Not available in English	3
Wrong population	15
Wrong intervention	123
Wrong comparator	10
Wrong outcome	2
Wrong publication type	4
Wrong study type (not interventional)	1
Wrong study type (Level III)	1
Number of studies included for full text review	17
Studies excluded after full text review:	
Wrong population	3
Wrong intervention	4
Wrong comparator	3
Wrong publication type	1
Wrong study type (Level I)	1
Wrong study type (Level III)	3
No usable data	1
Number of eligible studies	1

Question 3 – Level III studies – March 2014	Number of citations
Number of citations identified	6051
Citations excluded after title/abstract review:	
Published prior to 1995	675
Duplicate citation	13
Superseded	4
Non-human study	4
Wrong population	578
Wrong intervention	3767
Wrong comparator	199
Wrong outcome	44
Wrong publication type	51
Wrong study type (Level I)	6
Wrong study type (Level II)	4
Wrong study type (Level III-3)	13
Wrong study type (Level IV or below)	400
Sample size ≤100	120
Number of studies included for full text review	173
Studies excluded after full text review:	
Wrong population	43
Wrong intervention	37
Wrong comparator	32
Wrong outcome	3
Wrong publication type	11
Wrong study type (Level I)	1
Wrong study type (Level II)	2
Wrong study type (Level III-3)	8
Wrong study type (Level IV or below)	20
Sample size n≤100	5
No usable data	3
Insufficient adjustment for confounders	1
Number of eligible studies	7

Question 3 – Level III studies – October 2014	Number of citations
Number of citations identified	4511
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	4276
Wrong population	12
Wrong intervention	160
Wrong comparator	22
Wrong outcome	2
Wrong publication type	1
Wrong study type (Level IV or below)	5
Number of studies included for full text review	33
Studies excluded after full text review:	
Wrong population	3
Wrong intervention	10
Wrong comparator	6
Wrong outcome	4
Wrong study type (Level I)	1
Wrong study type (Level IV or below)	7
No usable data	1
Insufficient adjustment for confounders	1
Number of eligible studies	0

C4 Search results – Question 4

SQ1 Level I studies (March 2014)	Number of citations
Number of citations identified	1343
Citations excluded after title/abstract review:	
Published prior to 1995	10
Duplicate citation	64
Superseded	18
Wrong population	294
Wrong intervention	870
Wrong comparator	6
Wrong outcome	9
Wrong publication type	23
Wrong study type (Level II)	1
Wrong study type (Level III or below)	2
Number of studies added from other databases or hand searching	2
Number of studies included for full text review	48
Studies excluded after full text review:	
Not available in English	2
Superseded	1
Wrong population	10
Wrong intervention	4
Wrong comparator	2
Wrong outcomes	1
Wrong publication type	8
No usable data	8
Duplicate data	2
Number of eligible reviews	10

SQ1 Level I studies (November 2014)	Number of citations
Number of citations identified	1209
Citations excluded after title/abstract review:	
Duplicate citation / previously identified in March 2014 search	1074
Wrong population	43
Wrong intervention	75
Wrong comparator	1
Wrong outcome	1
Wrong publication type	9
Number of studies added from other databases or hand searching	5
Number of studies included for full text review	11
Studies excluded after full text review:	
Duplicate	2
Wrong population	2
Wrong publication type	5
No usable data	1
Number of eligible reviews	1

SQ1 Level I studies, second search (November 2014) [a]	Number of citations
Number of citations identified	228
Citations excluded after title/abstract review:	
Published prior to 2009 [b]	74
Duplicate citation	10
Wrong population	37
Wrong intervention	76
Wrong outcome	1
Wrong publication type	14
Wrong study type (Level II)	1
Wrong study type (Level III)	1
No usable data	1
Number of studies included for full text review	13
Studies excluded after full text review:	
Wrong population	2
Wrong outcomes	1
No usable data	4
Duplicate data	2
Number of eligible reviews	4

a. Second search included interventions of thermoregulation and antifibrinolytics (see Table A4.1)
b. Studies of thermoregulation and antifibrinolytics published until 2009 were captured in *Module 2 – Perioperative* and *Module 4 – Critical Care*. These databases were selectively screened using keyword searches for neonates, infants, children, or adolescents.

SQ1 Level II studies (March 2014)	Number of citations
Number of citations identified	5314
Citations excluded after title/abstract review:	
Published prior to 1995	375
Duplicate citation	4
Non-human study	5
Wrong population	677
Wrong intervention	3861
Wrong comparator	133
Wrong outcome	72
Wrong publication type	65
Wrong study type (Level I)	18
Wrong study type (Level III)	24
Wrong study type (Level IV or below)	7
Number of studies added from other databases or hand searching	1
Number of studies included for full text review	74
Studies excluded after full text review:	
Wrong population	20
Wrong intervention	1
Wrong outcomes	1
Wrong publication type	2
Wrong study type (Level III)	8
Duplicate data (study included in Level I study)	27
Number of eligible studies	15

SQ1 Level II studies (November 2014)	Number of citations
Number of citations identified	5985
Citations excluded after title/abstract review:	
Published prior to 1995	324
Duplicate citation / previously identified in March 2014 search	4379
Superseded	2
Not available in English	1
Non-human study	1
Wrong population	360
Wrong intervention	791
Wrong comparator	15
Wrong outcome	39
Wrong publication type	13
Wrong study type (Level I)	7
Wrong study type (Level III)	4
Wrong study type (Level IV or below)	1
Number of studies included for full text review	48
Studies excluded after full text review:	
Duplicate citation (identified in March)	1
Not available in English	4
Wrong population	12
Wrong intervention	2
Wrong comparator	2
Wrong outcomes	7
Wrong publication type	11
Wrong study type (Level III)	1
Duplicate data (study included in Level I study)	5
Number of eligible studies	3

SQ1 Level II studies, second search (November 2014) [a]	Number of citations
Number of citations identified	1653
Citations excluded after title/abstract review:	
Published prior to 2009 [b]	981
Duplicate citation	59
Wrong population	112
Wrong intervention	391
Wrong comparator	16
Wrong outcome	29
Wrong publication type	25
Wrong study type (Level I)	9
Wrong study type (Level III)	11
Number of studies added from other databases or hand searching	2
Number of studies included for full text review	22
Studies excluded after full text review:	
Duplicate citation (identified in March)	1
Not available in English	3
Wrong population	5
Wrong comparator	1
Wrong publication type	2
Duplicate data (study included in Level I study)	5
Number of eligible studies	5

a. Second search included interventions of thermoregulation and antifibrinolytics (see Table A4.1)
b. Studies of thermoregulation and antifibrinolytics published prior to 2009 were reviewed in *Module 2 – Perioperative* and *Module 4 – Critical Care*. These databases were selectively screened using keyword searches for neonates, infants, children, or adolescents.

Appendix D Evidence matrixes

Evidence matrixes are presented below for each intervention, subpopulation and outcome identified within each question of this module.

Where no evidence was found for a particular intervention, subpopulation or outcome, no evidence statement form has been presented. In the systematic review (**Volume 1**) the corresponding evidence statements are described as 'unknown'. These evidence statements are included in the main body of the guideline.

Where applicable, the complete set of evidence statement forms is followed by a separate form that contains any recommendations which were formulated from the evidence base.

Recommendations were not made where the effect of the intervention was unknown or uncertain or where the underpinning evidence would have led to a Grade D recommendation. Instead, consensus-based practice points were made (see **Section 2.5.2, Volume 1**).

D1 Evidence matrixes – Question 1

Preterm and low birth weight infants

RBC transfusion vs no transfusion

Key question(s): In preterm infants, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.3 Evidence matrix ref: D1.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (dos Santos 2011).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The risk of in hospital mortality was significantly increased with RBC transfusion before the 28th day of life (RR 1.49; 95%CI 1.17, 1.78; p=0.001). This analysis was a multivariate Cox regression which adjusted for gestational age, 1– and 5–minute Apgar scores, SNAPPE II score, IVH, early– and late–onset clinical sepsis, and NEC.	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?)*		
Subjects were VLBW preterm infants aged between 23.0 and 36.9 weeks gestation.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from 8 hospitals in Brazil.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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)*

Whilst an association between RBC transfusion and hospital mortality rates was evident, several others factors assessed by dos Santos remained significantly associated with mortality. Causality has not been established.

One additional Level III study (Boo 1997) was identified and excluded by the systematic review authors. 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 deemed to be of historical interest only.

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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.1 In very low birth weight infants (<1500 g), the effect of RBC transfusion compared with no transfusion on mortality is uncertain (C, NA, C, A, C).

Key question(s): In preterm infants, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on severe morbidity (NEC)?		Evidence table no: 3.1.4 Evidence matrix ref: D1.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I/III studies (Mohamed 2012 [good quality], Kirpalani 2012 [poor quality]) that identified 13 Level III studies (Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Wan-Huen 2011, Harsono 2011, Stritzke 2011, Blau 2011, Holder 2009, Mally 2006, Valieva 2009, Josephson 2010, McGrady 1987). Two additional Level III studies were identified in our literature search (Demirel 2012, Elabaid 2013). Four Level III studies were fair quality (Demirel 2012, Elabaid 2013, Singh 2011, Wan-Huen 2013), and two were poor quality (Paul 2011, Stritzke 2013). Quality could not be assessed for the remaining Level III 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')*		
Both reviews found that RBC transfusion was significantly associated with NEC. In Mohamed 2012, the association was still significant after adjustment for confounders. The Level III studies reported varying results. Harsono 2011 favoured RBC transfusion, Elabaid 2013 favoured RBC transfusion for late-onset NEC (after 28 days) in ELBW infants, and the remaining Level III studies either favoured no transfusion or reported no significant difference.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Mohamed 2012 reported a significant association between RBC and NEC in 3,863 preterm infants after adjusting for confounders (OR 2.01; 95%CI 1.61, 2.50; $P < 0.0001$; I^2=91%). One trial (Harsono 2011) contributed all the heterogeneity. Kirpalani 2012 also reported a significant association between RBC transfusion and NEC but the meta-analysis was unadjusted and had a very high risk of bias due to incomplete reporting of outcome data and a lack of clearly identified preclinical NEC before transfusion. One Level III study (Elabaid 2013) of 3060 V/ELBW preterm infants provided support for RBC transfusion in infants ≤750 g, ($P < 0.01$), and infants 750–1000 g ($P < 0.01$), but not infants 1001–1500 g.	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?)*		
Almost all studies were in preterm or LBW infants. Subjects in four studies were VLBW (Demirel 2012, Paul 2011, Wan-Huen 2013, Elabaid 2013), with Elabaid 2013 also including ELBW infants. Kirpalani 2012 included neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the US (Elabaid 2013, Paul 2011, Singh 2011, Wan-Huen 2013), 26 NICUs in Canada (Stritze 2013), and Turkey (Demirel 2012). The remaining studies	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

were not assessed individually, and the review authors did not report the study location(s).	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Heterogeneity was very high in all analyses, ranging from 58–91% in Mohamed 2012, and 92–98% in Kirpalani 2012.

Timing of administration of transfusion not adequately addressed: some studies included only infants with NEC within 48–hour period of exposure, and other studies included all NEC cases, regardless of timing of transfusion. Lack of clearly identified preclinical NEC before transfusion in Kirpalani 2012. Analyses in Kirpalani 2012 recalculated post-hoc using RevMan 5.1.2 after removal of studies with incomplete data (cohorts: Blau 2011, Mally 2006; case-control: McGrady 1987).

The meta-analyses conducted by Kirpalani (2012) were updated with the unadjusted data identified in this review. Cohort and case-control 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 (cohort studies: RR 1.55; 95% CI 0.94, 2.54; and case-control studies: RR 1.43; 95% CI 0.88, 2.34).

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	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
2.	Consistency	D	Evidence is inconsistent
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.3 In preterm infants, the effect of RBC transfusion compared with no transfusion on NEC is uncertain (C, D, D, B, C).

Key question(s): In preterm infants, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on severe morbidity (ROP)?		Evidence table no: 3.1.5 Evidence matrix ref: D1.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes four Level III studies of fair quality (Feghhi 2012, Fortes Filho 2013, Hakeem 2012, Li 2013) and two Level III studies of poor quality (Kabatas 2013, Weintraub 2011).	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')*		
Three studies (Hakeem 2012, Kabatas 2013, Weintraub 2011) found a significant association between RBC transfusion and ROP/severe ROP after adjusting for confounders. The remaining studies found no significant difference in ROP between groups, two after adjustment of confounders (Feghhi 2012, Li 2013) and one prior to assessing confounders (Fortes Filho 2013). (note Hakeem assessed more than 1 RBC transfusion)	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The three studies that found a significant association between RBC transfusion and ROP/severe ROP after adjusting for confounders reported OR's of 1.9–2.5. Three studies (Feghhi 2012, Fortes Filho 2013, Li 2013) found no significant difference between groups after adjusting for confounders.	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?)*		
All studies were in preterm or LBW infants. Four studies included VLBW infants (Li 2013, Weintraub 2011, Hakeem 2012, Kabatas 2013) and one included ELBW infants (Fortes Filho 2013). Unstable infants were eligible in Hakeem 2012 and Kabatas 2013.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from Iran (Feghhi 2012), Brazil (Fortes Filho 2013), Egypt (Hakeem 2012), Turkey (Kabatas 2013) and Taiwan (Li 2013). Weintraub 2011 did not report the study location(s).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

*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 Appendix B).

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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.4 In preterm infants, the effect of RBC transfusion compared with no transfusion on ROP is uncertain (D, C, D, B, C).

Key question(s): In preterm infants, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on severe morbidity (brain injury on ultrasound)?		Evidence table no: 3.1.6 Evidence matrix ref: D1.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (Baer 2011).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study found a significant association between RBC transfusion and severe IVH (grade 3 or 4) which remained significant in a multiple logistic regression analysis which adjusted for 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; 95%CI 1.54, 3.33).	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?)*		
Subjects were VLBW preterm neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.5 In very low birth weight infants (<1500 g), the effect of RBC transfusion compared with no transfusion on IVH is uncertain (C, NA, C, A, C).

Restrictive RBC transfusion versus liberal RBC transfusion

Key question(s): In preterm infants, what is the effect of a restrictive RBC transfusion strategy on mortality?		Evidence table no: 3.1.9 Evidence matrix ref: D1.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes three Level I studies of good quality (Ibrahim 2014, Whyte 2011, Venkatesh 2012) that identified seven Level II studies (Bell 2005, Blank 1984, Brooks 1999, Chen 2009, Connelly 1999, Kirpalani 2006, Mukhopadhyay 2004) and one long term follow-up studies (Whyte 2009). Kirpalani 2006 was good quality; Whyte 2009, Bell 2005 and Brooks 1999 were fair quality; and Chen 2009 was poor quality. Connelly 1999 was an unpublished trial and Mukhopadhyay 2004 was an abstract only. Note: Whyte 2009 was a follow-up of Kirpalani 2006.	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')*		
All studies found no statistically significant difference in mortality between restrictive RBC transfusion and liberal RBC transfusion.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No study found a statistically significant difference in mortality between restrictive RBC transfusion and liberal RBC transfusion. Studies were also underpowered to detect for meaningful differences in mortality.	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?)*		
Five studies included VLBW infants <1500 g (Chen 2009, Brooks 1999, Connelly 1999, Blank 1984, Bell 2005); two studies included ELBW infants <1000 g (Whyte 2009, Kirpalani 2006); and one study examined term or preterm neonates <28 days corrected age (Mukhopadhyay 2004).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kirpalani 2006 / Whyte 2009 was a multicentre trial in Australia, Canada and the USA. Other subjects were from the USA (Brooks 1999, Bell 2005, Blank 1984), Canada (Connelly 1999) and Taiwan (Chen 2009). Mukhopadhyay 2004 did not report the study location(s).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

In the Bell 2005 trial, six infants in the liberal transfusion group (12%), and five infants in the restrictive transfusion group (10%) did not receive a transfusion. Two transfusions in the liberal group and 17 transfusions in the restrictive group did not meet the study criteria for transfusion. In seven cases, infants in the liberal group met the study criteria for a transfusion but were not transfused. This did not occur in the restrictive group.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	No difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (B, A, NA, B, B).

Key question(s): In preterm infants, what is the effect of a restrictive RBC transfusion strategy on a composite of mortality and severe morbidity?		Evidence table no: 3.1.10 Evidence matrix ref: D1.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Whyte 2011, Bassler 2008) which identified five Level II studies (Kirpalani 2006, Chen 2009, Connelly 1999, Bell 2005, Whyte 2009). No additional Level II studies were identified. Kirpalani 2006 was good quality; Bell 2005 and Whyte 2009 were fair quality; and Chen 2009 as poor quality. Connelly 1999 was an unpublished trial. Note: Whyte 2009 was a follow-up of Kirpalani 2006.	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')*		
Whyte 2009 found a significant association between restrictive RBC transfusion and a composite of mortality and severe morbidity (mental developmental index [MDI] <85) in a post-hoc analysis, 18–21 months post transfusion. No other study reported statistical significance.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Whyte (2011) found no significant difference for the outcomes of severe mortality and morbidity before discharge or severe brain injury. A significant association between restrictive RBC transfusion and a composite of mortality and severe morbidity (MDI<85) reported in a post-hoc analysis only, 18–21 months post-transfusion: RR 1.21 (95%CI: 1.01, 1.44; p=0.034).	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?)*		
Three studies included VLBW preterm infants <1500 g (Chen 2009, Connelly 1999, Bell 2005); and one study and its follow-up study included ELBW preterm infants <1000 g (Kirpalani 2006, Whyte 2009).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kirpalani 2006 / Whyte 2009 was a multicentre trial in Australia, Canada and the USA. Other subjects were from the USA (Bell 2005), Canada (Connelly 1999) and Taiwan (Chen 2009).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Oxygen saturation targets were not standardised and current practice trends towards a higher range of oxygen saturation than employed in these studies. An ongoing trial by Kirpalani et al (TOP trial) will address this issue. In the Bell 2005 trial, six infants in the liberal transfusion group (12%), and five infants in the restrictive transfusion group (10%) did not receive a transfusion. Two transfusions in the liberal group and 17 transfusions in the restrictive group did not meet the study criteria for transfusion. In seven cases, infants in the liberal group met the study criteria for a transfusion but were not transfused. This did not occur in the restrictive group.
Note: the results that demonstrated better outcomes were based on a post-hoc analysis so bias may have been introduced.

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	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
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.7 In very low birth weight infants (<1500 g), the effect of a restrictive RBC transfusion compared with a liberal RBC transfusion on a composite outcome of mortality and severe morbidity is uncertain (B, B, D, B, C).

Key question(s): In preterm infants, what is the effect of a restrictive RBC transfusion strategy on severe morbidity (BPD, ROP, NEC)?		Evidence table no: 3.1.11, 3.1.12, 3.1.13 Evidence matrix ref: D1.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes four Level I studies of good quality (Ibrahim 2014, Whyte 2011, Venkatesh 2012, Bassler 2008) which identified five Level II studies (Bell 2005, Brooks 1999, Chen 2009, Connelly 1999, Kirpalani 2006,). No additional Level II studies were identified. Kirpalani 2006 was good quality; Brooks 1999 and Bell 2005 were fair quality; and Chen 2009 was poor quality. Connelly 1999 was an unpublished trial.	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')*		
All five studies examined BPD and ROP, and three studies (Kirpalani 2006, Chen 2009, Brooks 1999) examined NEC. No study reported statistical significance.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No study reported a significant difference in BPD, ROP or NEC between restrictive RBC transfusion and liberal RBC transfusion.	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?)*		
Three studies included VLBW preterm infants <1500 g (Chen 2009, Brooks 1999, Connelly 1999, Bell 2005); and one study included ELBW preterm infants <1000 g (Kirpalani 2006).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kirpalani 2006 was a multicentre trial in Australia, Canada and the USA. Other subjects were from the USA (Brooks 1999, Bell 2005), Canada (Connelly 1999) and Taiwan (Chen 2009).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Oxygen saturation targets were not standardised and current practice trends towards a higher range of oxygen saturation than employed in these studies. In the Bell 2005 trial, six infants in the liberal transfusion group (12%), and five infants in the restrictive transfusion group (10%) did not receive a transfusion. Two transfusions in the liberal group and 17 transfusions in the restrictive group did not meet the study criteria for transfusion. In seven cases, infants in the liberal group met the study criteria for a transfusion but were not transfused. This did not occur in the restrictive group.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	No difference
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, A, NA, B, B).

Key question(s): In preterm infants, what is the effect of a restrictive RBC transfusion strategy on severe morbidity (brain injury, IVH, PVL)?		Evidence table no: 3.1.14 Evidence matrix ref: D1.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Ibrahim 2014, Whyte 2011) which identified four Level II studies (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999). No additional Level II studies were identified. Kirpalani 2006 was good quality, Bell 2005 was fair quality, and Chen 2009 was poor quality. Connelly 1999 was an unpublished trial.	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')*		
Ibrahim 2014 meta-analysed three trials (Kirpalani 2006, Bell 2005 and Chen 2009) and found a borderline association between restrictive RBC transfusion and brain injury. Whyte 2011 meta-analysed the same studies plus Connelly 1999 and found no significant difference. Two studies examined IVH and/or PVL (Bell 2005, Chen 2009). Bell 2005 found that restrictive RBC transfusion was significantly associated with a composite of IVH (grade 4) and PVL. Chen 2009 reported no significant difference in IVH between groups.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
A meta-analysis of three studies found a borderline association between restrictive RBC transfusion and brain injury (Ibrahim 2014): RR 1.21 (95%CI: 1.00, 1.46; p=0.05) Bell 2005 found a significant association between restrictive RBC transfusion and a composite of IVH (grade 4) and PVL: RD 0.12 (95%CI: 0.03, 0.22; p=0.012).	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?)*		
Three studies included VLBW preterm infants <1500 g (Chen 2009, Connelly 1999, Bell 2005); and one study included ELBW preterm infants <1000 g (Kirpalani 2006).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Kirpalani 2006 was a multicentre trial in Australia, Canada and the USA. Other subjects were from the USA (Bell 2005), Canada (Connelly 1999) and Taiwan (Chen 2009).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Clinical impact could not be determined as oxygen saturation targets were not standardised and current practice trends towards a higher range of oxygen saturation than employed in these studies.
Ongoing trial by Kirpalani et al (TOP trial) and Franz et al (ETTNO) may address this issue.
In the Bell 2005 trial, six infants in the liberal transfusion group (12%), and five infants in the restrictive transfusion group (10%) did not receive a transfusion. Two transfusions in the liberal group and 17 transfusions in the restrictive group did not meet the study criteria for transfusion. In seven cases, infants in the liberal group met the study criteria for a transfusion but were not transfused. This did not occur in the restrictive group.

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	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
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence directly applicable to target population with some caveats

EVIDENCE STATEMENT

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 (B, B, NA, B, B).

IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia

Key question(s): In preterm infants, what is the effect of a restrictive RBC transfusion strategy on neurodevelopmental disability?		Evidence table no: 3.1.15 Evidence matrix ref: D1.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Whyte 2011, Venkatesh 2012) which identified the same fair quality Level II study (Whyte 2009). Note: Whyte 2009 was a follow-up of Kirpalani 2006	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Whyte 2009 found no significant difference in cognitive delay >2SDs below age norm, cerebral palsy, or severe visual, hearing or neurosensory impairment at 18–21 months post-transfusion. In a post-hoc analysis of cognitive delay >1 SD below age norm which adjusted for birth weight and study site, a significant difference was found in favour of liberal transfusion (p=0.016).	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?)*		
Whyte 2009 included ELBW preterm infants <1000 g followed up 18–21 months post transfusion.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Whyte 2009 included subjects from Australia, Canada and the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Oxygen saturation targets were not standardised and current practice trends towards a higher range of oxygen saturation than employed in these studies. An ongoing trial by Kirpalani et al (TOP trial) will address this issue.
The study by McCoy (2011) was a post-hoc long term follow-up trial (8–13 years) of infants enrolled in the study reported by Bell (2005). Attrition rates were high (approx. 50%). The CRG agreed to not consider this evidence as there was clear high risk of bias.

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.10 In very low birth weight infants (<1500 g), liberal RBC transfusion may reduce cognitive delays compared with restrictive RBC transfusion (B, NA, C, B, B)
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 (B, NA, C, B, B)

Neonatal and paediatric patients with sickle cell disease

RBC transfusion versus no transfusion

Key question(s): In neonatal and paediatric patients with sickle cell disease, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.19 Evidence matrix ref: D1.J
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Wang 2013) which identified two Level II studies of good quality (Adams 1998 [SOP], Adams 2005 [STOP 2]). One additional Level II study was identified in our literature search (DeBaun 2014 [fair quality]).	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')*		
All studies found no significant difference in mortality between RBC transfusion and no transfusion.	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)*		
No study found a significant difference in mortality between RBC transfusion and no transfusion, but the studies were not sufficiently powered to detect a significant difference in this outcome	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?)*		
Both STOP trials examined children aged 2 to 16 years with sickle cell disease and a high risk of stroke based on transcranial Doppler (TCD) screening. Debaun 2014 included children aged 5–15 years with sickle cell anaemia and at least one infarct-like lesion on MRI screening.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the USA, Canada, France and the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Both STOP trials were stopped early by the Data Safety and Monitoring Board due to the high rate of stroke in the no transfusion / halted transfusion groups.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	Underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, A, NA, B, B).

Key question(s): In neonatal and paediatric patients with sickle cell disease, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on stroke?		Evidence table no: 3.1.20 Evidence matrix ref: D1.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Cherry 2012, Wang 2013), which identified two Level II studies of good quality (Adams 1998 [STOP], Adams 2005 [STOP 2]). Two additional Level II studies were identified in our literature search (Debaun 2014 [fair quality], Pegelow 2001 [poor quality]). Pegelow 2001 was a follow-up of Adams 1998.	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')*		
All studies found a significant and independent association between no transfusion / halted transfusion and stroke (cerebral infarction or intracerebral haematoma). In sub-analyses, a significant association was found for cerebral infarction, but not intracerebral haematoma (Adams 1998). A significant association was also found between halted transfusion and a composite of stroke and reversion to an abnormal TCD (Adams 2005).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
All studies found a significant and independent association between no transfusion or halted transfusion and stroke. Adams 1998 / Pegelow 2001 - risk of stroke 92% lower in transfusion group (p=<0.001) - risk of cerebral infarction 91% lower in transfusion group (p=0.002) - stroke at 36 months: OR 0.08 (95%CI 0.01, 0.63; p=0.02) Adams 2005 - stroke or reversion to abnormal TCD: *P* < 0.001 - reversion to abnormal TCD: OR 0.02 (95%CI 0.00, 0.43; p=0.01) Debaun 2014 - recurrence of infarct or haemorrhage: OR 0.31 (95% CI 0.10, 0.93; p=0.04)	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?)*		
Subjects in the STOP trials were children aged 2–16 years with sickle cell disease and a high risk of stroke based on TCD screening. Debaun 2014 included children aged 5–15 years with sickle cell anaemia and at least one infarct-like lesion on MRI screening.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the USA, Canada, France and the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Both STOP trials were stopped early by the Data Safety and Monitoring Board due to the high rate of stroke in the no transfusion / halted transfusion groups.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	A	Very large
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 thalassaemia 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 (B, A, A, A, B).

[a] as assessed by transcranial Doppler ultrasonography[1] and MRI[2]

[1] Adams (1998)
[2.] DeBaun (2014),

Neonatal and paediatric patients with cancer

RBC transfusion versus no transfusion

Key question(s): In neonatal and paediatric patients with anaemia associated with cancer, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.23 Evidence matrix ref: D1.L
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of poor quality (Jaime-Perez 2011). The study had three arms comparing transfusion of >5 units RBC to 1–5 units RBC to no transfusion.	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Jaime-Perez 2011 was a retrospective cohort study which found increasing mortality with increasing transfusion. The authors reported a significant association between transfusion of ≥5 units RBCs and mortality in a multivariate Cox regression: HR 4.453 (95%CI 1.64, 12.09; p=0.003).	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?)*		
Subjects were children <15 years with acute lymphoblastic leukaemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from Mexico.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Different blood product used/ not available in Australia. Product was leukoreduced but not leukodepleted or irradiated.

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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	D	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.21 In paediatric patients with anaemia associated with cancer, the effect of RBC transfusion compared with no transfusion on mortality is uncertain (D, NA, NA, B, D).
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).

Neonatal and paediatric patients with severe anaemia associated with malaria

RBC transfusion versus no transfusion

Key question(s): In neonatal and paediatric patients with severe anaemia associated with malaria, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?			Evidence table no: 3.1.26 Evidence matrix ref: D1.M
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level I study of good quality (Meremikwu 2000) that included two Level II studies of poor quality (Bojang 1997, Holzer 1993). One additional Level II study was identified in the literature search (Olupot-Olupot 2014 [good quality]) that compared low dose RBC transfusion (10 mL/kg) to high dose RBC transfusion (15 mL/kg).	A	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	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	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	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')*			
All studies found no significant difference in mortality between RBC transfusion and no transfusion. Only one study comparing transfusion volume	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No significant difference was found for mortality.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	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?)*			
All studies were in children with severe anaemia. All children in Bojang 1997 and Holzer 1993, and 59% of children in Olupot-Olupot 2014 had confirmed malaria parasitaemia.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
All studies were conducted in Africa (Bojang 1997 [Gambia], Holzer 1993 [Tanzania], Olupot-Olupot 2014 [Uganda]).	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare 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	Rating	Description
1. Evidence base	B	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
2. Consistency	A	NA	All studies consistent / Not applicable
3. Clinical impact	NA	NA	No difference
4. Generalisability	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	D	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

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 (B, A, NA, C, D).

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 (B, NA, NA, C, D).

Neonatal and paediatric patients undergoing surgery

RBC transfusion versus no transfusion

Key question(s): In neonatal and paediatric patients undergoing cardiac surgery, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.29 Evidence matrix ref: D1.N
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of good quality (Kneyber 2013), and one Level III study of fair quality (Redlin 2013). Kneyber 2013 assessed RBC transfusion within 48 hours of admission to PICU Redlin 2013 compared intraoperative transfusion to postoperative transfusion to no transfusion.	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')*		
Kneyber 2013 found no significant difference in mortality between RBC transfusion and no transfusion within 48 hours of cardiac surgery after adjusting for confounders Redlin 2013 showed a significant difference in in hospital mortality between treatment arms, with highest mortality in the intraoperative transfusion group and lowest mortality in the no transfusion group but no adjustments for confounders made.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Redlin 2013: there was a significant difference in in hospital mortality between treatment arms which favoured no transfusion (p=0.04) The authors reported that the mortality rate was too low for detailed/adjusted statistical analyses.	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?)*		
Redlin 2013 included paediatric cardiac surgery patients weighing <16kg Kneyber 2013 included paediatric/neonatal patients (< 18 years) admitted to PICU post-surgery	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from Germany (Redlin 2013) and The Netherlands (Kneyber 2013).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

No adjustment for confounders in the Redlin (2013) study, difficult to make judgement of consistency/clinical impact.

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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, NA, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing liver transplant, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.29 Evidence matrix ref: D1.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (Nacoti 2012). Nacoti 2012 compared three doses of RBC transfusion: high (≥3 units) versus medium (2 units) versus low (≤1 unit).	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')*		
Nacoti 2012 showed a significant difference between the three treatment arms but in a propensity score adjusted analysis, only high transfusion (≥3 units RBC) was statistically associated with mortality at 12 months.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Nacoti 2012: in propensity score adjusted analyses, transfusion of ≥3 units RBC was significantly associated with mortality at 12 months (p=0.048). There was no association between transfusion of 2 units RBC and mortality.	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?)*		
Nacoti 2012 included paediatric liver transplant patients <18 years.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from Italy (Nacoti 2012).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.29 In paediatric patients who have received a liver transplant, the effect of RBC transfusion compared with no transfusion on mortality is uncertain (C, NA, NA, B, C).

Restrictive RBC transfusion versus liberal RBC transfusion

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of a restrictive RBC transfusion strategy on mortality?		Evidence table no: 3.1.32 Evidence matrix ref: D1.P
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Wilkinson 2014) that included two Level II studies (Willems 2010 [good quality], Cholette 2001 [poor quality]), and an additional Level II study (Rouette 2010 [good quality]). Note: patients from Willems 2010 and Rouette 2010 were subgroups from the TRIPICU study (Lacroix 2007).	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')*		
All studies found no significant difference in mortality between restrictive and liberal RBC transfusion but were not sufficiently powered for this outcome.	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)*		
No study found a significant difference in mortality between restrictive and liberal RBC transfusion.	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?)*		
Two studies included paediatric cardiac surgery patients (Willems 2010, Cholette 2011), and one study examined paediatric/neonatal general surgery patients (Rouette 2010).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the USA, Canada, Belgium and the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Willems 2010 and Rouette 2010 performed subgroup analyses and were not powered to show statistically significant differences. A significant proportion of patients in the restrictive transfusion groups did not receive a transfusion. Cholette 2001 had a much higher liberal transfusion threshold (13g/dL) than what is used in current practice in Australia.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	Underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES1.31 In neonatal and paediatric patients undergoing surgery, the effect of restrictive RBC transfusion compared with liberal RBC transfusion on mortality is uncertain (B, A, NA, A, B).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of a restrictive RBC transfusion strategy on new or progressive MODS?		Evidence table no: 3.1.33 Evidence matrix ref: D1.Q
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level II studies of good quality (Willems 2010, Rouette 2010). Note: patients from both studies were subgroups from the TRIPICU study (Lacroix 2007).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No study found a significant difference between restrictive and liberal RBC transfusion, and new or progressive MODS. Willems 2010 reported a trend toward more organ dysfunction in patients aged ≥365 days receiving restrictive RBC transfusions, but the sample size was too small to permit any conclusions.	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?)*		
Both studies examined a subgroup of patients from the TRIPICU study. Patients in Willems 2010 were paediatric cardiac surgery patients, and patients in Rouette 2010 were paediatric/neonatal general surgery patients. Patients were aged 3 days to 14 years.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the US, Canada, Belgium and the UK.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		
Willems 2010 and Rouette 2010 performed subgroup analyses and were not powered to show statistically significant differences. A significant proportion of patients in the restrictive transfusion groups did not receive a transfusion.		

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, NA, NA, A, B).

Critically ill neonatal and paediatric patients

RBC transfusion versus no transfusion

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of RBC transfusion versus no transfusion (or alternate dose) on mortality?		Evidence table no: 3.1.36 Evidence matrix ref: D1.R
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level III study of good quality (Kneyber 2007), two Level III studies of fair quality (Acker 2014, Hassan 2014) and one Level III study of poor quality (Fremgen 2014).	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')*		
Two studies (Acker 2014, Fremgen 2014) reported no significant difference in mortality between RBC transfusion and no transfusion after adjusting for confounders. Hassan 2014 reported a significant association between mortality and RBC transfusion after adjusting for injury severity score (*P* < 0.001). Kneyber (2007) reported a significant, independent association between RBC transfusion and mortality	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
After adjusting for confounders Ackers (2014) reported no significant association with mortality (Hb <10 g/dL OR 1.37 (0.622, 3.050]; Hb<9 g/dL OR 1.240 [0.506, 3.039]; Hb<8 g/dL OR 1.072 [0.324, 3.544]). Fremgen (2014) reported unadjusted data showing RR of mortality to be 18.75 [1.06, 331.04, *P* = 0.05]. Using logistic regression and adjusting for confounders Hassan (2014) and Kneyber (2007) 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) and (OR 9.95; 95% CI 1.28, 77.16; p=0.028).	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?)*		
Fremgen 2014 assessed paediatric patients with abdominal trauma resulting in liver laceration. One study assessed paediatric patients with trauma (Hassan 2014). Acker (2014) included patients aged ≤18 years with traumatic brain injury and Kneyber (2007) assessed a mixed population of critically ill neonatal and paediatric patients (excluding cardiothoracic and preterms).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Three studies were conducted in the USA (Acker 2014, Fremgen 2014, Hassan 2014). One study conducted in The Netherlands (Kneyber 2007)	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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)*

One other study identified but excluded (study N<100). Pieracci (2012) assessed mortality in children with serious injuries in the USA. Transfused children were matched 1:1 with control for age, ISS and year of admissions. Thirteen children died, all of whom received at least one RBC transfusion (13/43; 30.2%) compared with four children in the matched control group (4/42; 0.9%).This was a statistically significant difference in favour of children who did not receive a transfusion (RR 3.17; 95% CI 1.13, 8.95; *P* = 0.03)). Using a multivariable logistic regression, Pieracci (2012) adjusted for nadir haemoglobin levels, and reported there was no significant association between RBC transfusions and mortality (details not provided).

A meta-analysis of the four included studies was judged to be inappropriate, due to inconsistency between the studies and the presence of confounders.

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	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
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES1.33 In critically ill neonatal and paediatric patients, the effect of RBC transfusion compared with no transfusion on mortality is uncertain (C, B, D, B, C).

Restrictive RBC transfusion versus liberal RBC transfusion

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of a restrictive RBC transfusion strategy on new or progressive MODS?		Evidence table no: 3.1.40 Evidence matrix ref: D1.S
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Desjardins 2012), and one good quality Level II study (Lacroix 2007). No additional Level II studies were identified.	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')*		
NA	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)*		
No significant difference was found between restrictive and liberal RBC transfusion and new or progressive MODS. Other outcomes with no significant difference included number of dysfunctional organs, average daily PELOD score, and change in PELOD score.	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?)*		
Subjects were stable, critically ill children aged 3 days to 14 years (mean 38 months) with Hb < 9.5 g/dL.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study included subjects from 19 PICUs in four countries (3x Belgium, 10x Canada, 3x UK, 3x US).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Lacroix 2007 was a noninferiority study. A significant proportion of patients in the restrictive transfusion groups did not receive a transfusion 174 (54%) compared with 7 (2%) in the liberal transfusion group ($P < 0.001$).

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, NA, NA, A, B).

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of a restrictive RBC transfusion strategy on mortality?		Evidence table no: 3.1.41 Evidence matrix ref: D1.T
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Carson 2012, Desjardins 2012) that identified the same good quality Level II study (Lacroix 2007). No additional Level II studies were identified.	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference in mortality was found between restrictive and liberal RBC transfusion.	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?)*		
Subjects were stable, critically ill children aged 3 days to 14 years (mean 38 months) with Hb levels < 9.5 g/dL.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study included subjects from 19x PICUs in four countries (3x Belgium, 10x Canada, 3x UK, 3x US).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Lacroix 2007 was a noninferiority study. A significant proportion of patients in the restrictive transfusion groups did not receive a transfusion 174 (54%) compared with 7 (2%) in the liberal transfusion group ($P < 0.001$).

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, NA, NA, A, B).

Recommendations – Question 1

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* 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.*	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D1.E, D1.F, D1.G, D1.H, D1.I, D1.P, D1.Q, D1.S, D1.T
Indicate any dissenting opinions None		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
Smaller population of patients after cardiac surgery (evidence underpowered). No evidence that it was beneficial. The study is a non-inferiority trial. Based on the absence of benefit for a liberal transfusion strategy (in paediatric and adult critically ill patients), and concerns about the potential adverse events associated with transfusion, the CRG suggests a restrictive strategy for paediatric patients other than very low birth weight neonates. Lower exposure to RBC transfusion and conservation of blood products has been considered when making this recommendation.		
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? Probably no. Most PICUs using restrictive protocol.		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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	RELEVANT ESF(S)
In children and adolescents with sickle cell disease who have been assessed to be at high risk of stroke,[a] a programme of prophylactic RBC transfusions should be used in order to reduce stroke occurrence.[b] [a] *Assessed by transcranial Doppler ultrasonography[1] and MRI.[2]* [b] *See PP11 for methods of assessment.* [1] *Adams (1998)* [2] *DeBaun (2014),*	GRADE A	D1.K

Indicate any dissenting opinions
None

UNRESOLVED ISSUES
If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.

Further research is ongoing. The Phase III TWiTCH trial is 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 yet available.

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
Some centres unable reliably assess risk of stroke	NO
Are there any resource implications associated with implementing this recommendation?	YES
There is a need for access to both transcranial Doppler and MRI. R2 is likely to change current practice; however, the resource implications of the additional MRI and TCD screening for SCD are expected to be low, given the size of the relevant population and the small number of scans required.	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
Care can remain in the way it is currently organised	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
Lack of access to centres of excellence specialising in sickle cell disease	NO

D2 Evidence matrixes – Question 2

Preterm and low birth weight infants

ESAs (with or without iron)

Key question: In preterm infants, what is the effect of ESAs (with or without iron) on transfusion incidence?		Evidence table no: 3.2.4 Evidence matrix ref: D2.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Aher 2014, Ohlsson 2014) that assessed early rHuEPO (16 trials) and late rHuEPO (20 trials) in preterm infants. Five additional Level II studies of fair or poor quality were identified (Kremenopoulos 1997, Ohls 1993, Ohls 2004, Rocha 2001, Ronnestad 1995). One Level II study assessed Darbepoetin (Ohls 2013); Ohls 2004 was a follow-up of Ohls 2001a, 18–22 months later.	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')*		
Both reviews found that patients who received rHuEPO + iron required significantly fewer RBC transfusions than patients who received iron only. Significance held for most doses of early rHuEPO/iron in Ohlsson 2012, and all doses of late rHuEPO/iron in Aher 2014. The Darbepoetin study (Ohls 2013) favoured DAR + iron but did not reach statistical significance (p=0.058).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The two largest meta-analyses favoured rHuEPO + iron for one or more transfusions and mean number per infant: *Ohlsson 2012 (early rHuEPO): RR 0.79; 95%CI 0.73, 0.85 and MD –0.27; 95% CI –0.42, –0.12 *Aher 2014 (late rHuEPO): RR 0.71; 95%CI 0.64, 0.79; and MD –0.22; 95% CI –0.38, –0.06	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?)*		
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in a variety of countries including Australia, Europe, England,	A	Evidence directly applicable to Australian healthcare context

USA, Canada, New Zealand, Central/South America, South Africa, China, and Japan.	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Lots of small studies with differing transfusion thresholds and practices in included studies probably contribute to high heterogeneity, resulting in genuine uncertainty in consistency. There is need for a large study with set transfusion thresholds.
A combined meta-analysis of early and late was conducted:
*a significantly reduced risk of transfusion in preterm infants treated with ESAs compared with no ESAs or placebo (725/1556 vs 932/1422; RR 0.71; 95% CI 0.64, 0.80). Heterogeneity was substantial (I^2=63%).
*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%).

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	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.1 In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion incidence (A, C, B, B, A).

Key question: In preterm infants with RhHDFN, what is the effect of ESAs (with or without iron) on transfusion incidence?		Evidence table no: 3.2.5 Evidence matrix ref: D2.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of fair quality (Ovali 1995)	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 significant difference in the mean number of RBC transfusions (MD 2.4) favouring ESA treatment (no SD provided) was reported.	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 <u>unknown</u> 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?)*		
The study was in preterm infants with Rh haemolytic disease of the fetus and newborn	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in a single NICU in Turkey.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.2 In preterm infants with RhHDFN, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain (C, NA, B, B, C).

ESAs, erythropoietin stimulating agents; RhHDFN, Rh haemolytic disease of the fetus and newborn

Key question: In preterm infants, what is the effect of ESAs (with or without iron) on transfusion volume?		Evidence table no: 3.2.6 Evidence matrix ref: D2.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Aher 2014, Ohlsson 2014) that assessed early rHuEPO (11 trials) and late rHuEPO (6 trials) in preterm infants. Five of the included trials did not provide sufficient or suitable data for inclusion in a meta-analysis. Seven additional Level II studies of variable quality were identified (Soubasi 1993, Giannakopoulou 1998, Khatami 2008, Rocha 2005, Juul 2003, Jim 2000, Griffiths 1997). Note: One study assessed Darbepoetin (Ohls 2013).	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')*		
Ohlsson 2012 (early rHuEPO): patients who received rHuEPO + iron received significantly less blood than patients who received iron only. Aher 2014 (late rHuEPO): no significant difference in total RBC volume transfused per infant. Most other Level II studies provided support for rHuEPO. The darbepoetin study (Ohls 2013) found no significant difference between groups but the study was small and the direction of effect favoured DAR.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
One large meta-analysis favoured rHuEPO + iron: *Ohlsson 2012 (early rHuEPO): MD –6.82; 95%CI –11.52, –2.11; p=0.0045 and the other found no significant difference: *Aher 2014 (late rHuEPO): MD –1.61; 95%CI –5.78, 2.57; p=0.45	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?)*		
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in a variety of countries including Australia, Europe, England, USA, Canada, New Zealand, Central/South America, South Africa, China, and Japan.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

A combined meta-analysis of early and late was conducted:
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.

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	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

ES2.3 In preterm infants with low birth weight (<2500 g), ESA therapy (with or without iron) may reduce transfusion volume (A, C, B, A, A).

Key question(s): In preterm infants, what is the effect of ESAs (with or without iron) on ROP?			Evidence table no: 3.2.7 Evidence matrix ref: D2.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes three Level I studies of good quality (Aher 2014, Ohlsson 2014, Xu 2014) that assessed early rHuEPO (10 trials) and late rHuEPO (5 trials) in preterm infants. Xu 2014 included an additional eight observational studies. RCTs were of variable quality and were generally small. One Level II study assessed DAR (Ohls 2013).	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')*			
For ROP (all stages), no Level I study found a significant difference between treatment groups, regardless of whether ESAs were administered early or late. For severe ROP (stage 3–4), only Ohlsson 2014 found a significant difference which favoured rHuEPO + iron when early and late studies were combined (post-hoc analysis). Xu 2014 and Aher 2014 reported no significant difference.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Studies were unlikely to be powered to detect for statistically significant differences in ROP which was a secondary outcome.	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?)*			
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Studies were in Europe (Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Romagnoli 2000, Carnielli 1998, Pollak 2001), the USA (Ohls 2001a, Ohls 2001b, Ohls 2013), Canada (Shannon 1995, Al-Kharfy 1996), Turkey (Arif 2005), Singapore (Yeo 2001) and Japan (Fujiu 2004).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.5 In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on ROP is uncertain (C, B, NA, B, B).

Key question(s): In preterm infants, what is the effect of ESAs (with or without iron) on BPD?		Evidence table no: 3.2.8 Evidence matrix ref: D2.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Aher 2014, Ohlsson 2014) that assessed early rHuEPO (11 trials) and late rHuEPO (5 trials) in preterm infants. Included RCTs were of variable quality and were generally small. One Level II study assessed DAR (Ohls 2013).	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')*		
All studies found no significant difference in BPD for ESAs + iron vs iron alone.	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)*		
There was no significant difference in BPD for ESAs + iron vs iron alone.	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?)*		
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in Europe (Fauchere 2008, Haiden 2005, Maier 2002, Romagnoli 2000, Carnielli 1998, Pollak 2001, Obladen 1991), the USA (Ohls 2001a, Ohls 2001b, Ohls 2013), Canada (Al-Kharfy 1996), England (Griffiths 1997), Turkey (Arif 2005), Mexico (Lima-Rogel 1998), and Singapore (Yeo 2001).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		
BPD was not a primary outcome of any study. Studies were likely underpowered to detect for statistically significant differences.		

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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.6 In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on BPD is uncertain (C, A, NA, B, B).

Key question(s): In preterm infants, what is the effect of ESAs (with or without iron) on NEC?		Evidence table no: 3.2.9 Evidence matrix ref: D2.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Aher 2014, Ohlsson 2014) that assessed early rHuEPO (11 trials) and late rHuEPO (6 trials) in preterm infants. Included RCTs were of variable quality and were generally small. One additional Level II study was identified (El-Ganzoury 2014 [fair quality]). One Level II study assessed DAR (Ohls 2013).	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')*		
All studies found no significant difference in NEC for ESAs + iron vs iron alone.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was no significant difference in NEC for ESAs + iron vs iron alone.	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?)*		
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in Europe (Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Obalden 1991, Romagnoli 2000), the USA (Ohls 2001a, Ohls 2001b, Ohls 2013), Canada (Shannon 1991, Shannon 1995), Turkey (Arif 2005, Samanci 1996), Egypt (El-Ganzoury), New Zealand (Meyer 1994), Singapore (Yeo 2001) and Mexico (Lima-Rogel 1998).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

NEC was not a primary outcome of any study. Studies were likely underpowered to detect for statistically significant differences.

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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.7 In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on NEC is uncertain (C, A, NA, B, B).

Key question(s): In preterm infants, what is the effect of ESAs (with or without iron) on Mortality?			Evidence table no: 3.2.10 Evidence matrix ref: D2.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes two Level I studies of good quality (Aher 2014, Ohlsson 2014) that assessed early rHuEPO (16 trials) and late rHuEPO (13 trials) in preterm infants. Included RCTs were of variable quality and were generally small. One additional Level II study was identified (El-Ganzoury 2014 [fair quality]). One Level II study assessing DAR (Ohls 2013).	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')*			
In meta-analyses of early and late rHuEPO, no significant difference in all-cause mortality was found between ESAs (with or without iron) and iron only.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
No significant difference in mortality was found between ESAs (with or without iron) and iron only.	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?)*			
All studies were in preterm (<37 weeks gestational age) and/or LBW (<2500 g) neonates.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Studies were in Europe (Carnielli 1992, Fauchere 2008, Haiden 2005, Maier 1994, Maier 2002, Obladen 1991, Bechensteen 1993, Giannakoloulou 1998a, Giannakopoulou 1998b, Pollak 2001, Soubasi 1993, Soubasi 1995), the USA (Ohls 1997, Ohls 2001a, Ohls 2001b, Ohls 2013), Canada (Al-Kharfy 2005, Shannon 1991, Shannon 1995), the UK (Emmerson 1993, Griffiths 1997), Australia (Whitehall 1999), New Zealand (Meyer 1994), South Africa (Avent 2002), Bangladesh (Yasmeen 2012), Turkey (Arif 2005), Egypt (El-Ganzoury 2014), Singapore (Yeo 2001), China (Chen 1995), Japan (Fujiu 2004) and Argentina (Donato 1996).	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare 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)*

Mortality was not a primary outcome of any study. Studies were likely underpowered to detect for statistically significant differences.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.8 In preterm infants with low birth weight (<2500 g), the effect of ESA therapy (with or without iron) on mortality is uncertain (C, A, NA, B, B).

Oral and/or parenteral iron

Key question: In preterm infants, what is the effect of iron therapy (oral and/or parenteral) on transfusion volume or incidence?		Evidence table no: 3.2.14 Evidence matrix ref: D2.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Taylor 2013) and three Level II studies of fair or poor quality (Sankar 2009, Berseth 2004, Franz 2000).	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')*		
Two studies (Taylor 2013, Sankar 2009) reported no significant treatment effect. Two studies (Berseth 2004, Franz 2000) reported an effect in favour of iron therapy. Berseth 2004 found that significantly fewer infants who received iron therapy were transfused from days 15–28 of life, although there was no significant difference from days 0–14. Franz 2000 favoured iron therapy for number and volume of transfusions received from days 14–68 of life.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Transfusion volume or incidence was not a primary outcome of any study, and thus studies were likely underpowered to detect for statistically significant differences.	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?)*		
Subjects included VLBW (<1500 g) preterm infants who had reached 100–120 mL/kg/day of feedings before 32 weeks postmenstrual age.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in the USA, India and Germany.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		
This is compared with enteral intakes of iron consistent with Recommended Nutrient Intakes as defined by the American Academy of Paediatrics (AAP)		

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	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
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (B, C, NA, B, C).

Key question(s): In preterm infants, what is the effect of iron therapy (oral and/or parenteral) on ROP, BPD and NEC?		Evidence table no: 3.2.15 Evidence matrix ref: D2.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Taylor 2013) and two Level II studies of fair or poor quality (Sankar 2009, Berseth 2004).	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')*		
All studies found no significant difference in ROP, BPD or NEC between iron therapy and no iron therapy.	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)*		
No significant differences observed. Studies were also unlikely to be powered to detect for statistically significant differences.	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?)*		
Subjects were VLBW (<1500 g) preterm infants who had reached 100–120 mL/kg/day of feedings before 32 weeks postmenstrual age.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in the USA and India.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (B, A, NA, B, C).

Key question(s): In preterm infants, what is the effect of iron therapy (oral and/or parenteral) on mortality?		Evidence table no: 3.2.16 Evidence matrix ref: D2.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Taylor 2013) and one Level II study of poor quality (Franz 2000).	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')*		
Both studies found no significant differences in all-cause mortality.	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)*		
No significant differences were observed. Studies were also underpowered to detect for statistically significant differences.	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?)*		
Subjects were VLBW (<1500 g) preterm infants who had reached 100–120 mL/kg/day of feedings before 32 weeks postmenstrual age.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in the USA and Germany.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (B, A, NA, B, C).

Infants, children and adolescents at risk of anaemia

Oral and/or parenteral iron

Key question: In neonatal and paediatric patients at risk of anaemia, what is the effect of iron therapy (oral and/or parenteral) on mortality?		Evidence table no: 3.2.20 Evidence matrix ref: D2.K
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies of good quality (Pasricha 2013, Okebe 2011). Pasricha 2013 included two Level II studies and Okebe 2011 included 22 Level II 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')*		
Both studies found no significant difference in mortality between iron therapy and no iron therapy.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference was observed.	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?)*		
Children in two studies were aged <2 years and children in 22 studies were aged <18 years. All children were at high risk for anaemia and malnutrition.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in Nepal, Tanzania and malaria-endemic areas. Study sites were mainly poor rural settings.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.16 In infants and children at risk of anaemia, oral iron supplementation has no effect on mortality (A, A, NA, C, C).

Neonatal and paediatric patients with cancer

ESAs (with or without iron)

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of ESAs (with or without iron) on transfusion incidence		Evidence table no: 3.2.25 Evidence matrix ref: D2.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies (Grant 2013 [good], Mystakidou 2007 [poor]) that identified four Level II studies of variable quality (Razzouk 2006, Porter 1996, Csaki 1998, Varan 1999). Razzouk 2006 was the largest study (multicentre) and was good quality. The other studies were small (n<50). Porter 1996 was good quality, Varan 1999 was fair quality, and Csaki 1998 was a pilot study.	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')*		
Overall, Razzouk 2006 and Varan 1999 favoured rHuEPO for RBC transfusion incidence. In a subgroup analysis by Razzouk 2006, significance only held for patients with non-myeloid malignancies and not for children with ALL. Porter 1996 and Csaki 1998 found no significant difference in transfusion incidence but both studies had 20 or fewer subjects.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Razzouk 2006 (overall): favours rHuEPO (RR 0.84; 95%CI 0.71, 0.99; p=0.04) Varan 1999: favours rHuEPO (RR 0.13; 95%CI 0.02, 0.89; p=0.008)	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?)*		
Subjects were paediatric patients aged 6 months to 18 years receiving chemotherapy with anaemia or at risk for anaemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Two studies were in the USA (Razzouk 2006, Porter 1996), one was in Turkey (Varan 1999) and one was in Hungary (Csaki 1998).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.18 In paediatric patients receiving chemotherapy, ESA therapy (with or without iron) may reduce transfusion incidence (B, B, C, B, C).

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of ESAs (with or without iron) on transfusion volume		Evidence table no: 3.2.25 Evidence matrix ref: D2.M
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of poor quality (Feusner 2002) that identified two Level II studies (Porter 1996, Bennetts 1995). Porter 1996 was a small study of good quality, and Bennetts 1995 was an abstract only.	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')*		
Porter 1996 favoured rHuEPO for RBC transfusion volume (p=0.02) and median number of units transfused (p=0.01) in children with sarcoma. Bennetts 1995 reported significance in a subgroup of 'low risk' ALL patients (p=0.02) but not overall.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Although both studies reported significance in favour of rHuEPO for transfusion volume, studies were too small to permit firm conclusions.	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?)*		
Subjects were paediatric patients aged 6 months to 18 years receiving chemotherapy with anaemia or at risk for anaemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Porter 1996 was in the USA. Bennetts 1995 did not report the study location(s).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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
6.	Evidence base	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
7.	Consistency	B	Most studies consistent and inconsistency can be explained
8.	Clinical impact	C	Moderate
9.	Generalisability	B	Evidence directly generalisable to target population with some caveats
10.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.19 In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on transfusion volume is uncertain (C, B, C, B, C).

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of ESAs (with or without iron) on thromboembolic events?		Evidence table no: 3.2.26 Evidence matrix ref: D2.N
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Grant 2013) that identified one Level II study of good quality (Razzouk 2006).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Razzouk 2006 did not report any significant differences in thromboembolic events (RR 2.95, 95% CI 0.61, 14.28, p=0.18). The study was also unlikely to be powered to detect for statistically significant differences in this outcome.	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?)*		
Subjects were paediatric patients with solid tumours and/or haematological malignancies undergoing chemotherapy.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in multiple centres in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.21 In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on thromboembolic events is uncertain (B, NA, NA, B, C).

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of ESAs (with or without iron) on mortality?		Evidence table no: 3.2.27 Evidence matrix ref: D2.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies (Grant 2013 [good], Ross 2006 [fair]) that identified four Level II studies (Razzouk 2006 [good], Wagner 2004 [fair], Varan 1999 [fair], Porter 1996 [good]). Three studies reported mortality and one study (Wagner 2004) reported progression-free survival. Wagner 2004 compared rHuEPO + granulocyte colony stimulating factors (G–CSFs) to G–CSFs alone.	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')*		
Three studies reported no significant difference in mortality (Razzouk 2006, Porter 1996, Varan 1999). Wagner 2004 reported an effect favouring rHuEPO + G–CSFs for 5–yr survival, but the study was too small (n=38) to detect statistically significant differences).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference / studies underpowered.	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?)*		
Subjects were paediatric patients aged 6 months to 18 years receiving chemotherapy with anaemia or at risk for anaemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were in the USA or Turkey. Wagner 2004 did not report the study location(s).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.23 In paediatric patients receiving chemotherapy, the effect of ESA therapy (with or without iron) on mortality is uncertain (B, B, NA, B, C).

Neonatal and paediatric patients with kidney disease

ESAs (with or without iron)

Key question: In neonatal and paediatric patients with haemolytic uremic syndrome, what is the effect of ESAs on transfusion volume or incidence?		Evidence table no: 3.2.31 Evidence matrix ref: D2.P
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Pape 2009).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Study had 10 participants and was underpowered to detect for statistically significant differences.	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?)*		
Subjects were children aged 1–6 years with EHEC-positive HUS, or likely EHEC infection and bloody diarrhoea.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study was conducted in a single centre, Germany.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.28 In paediatric patients with haemolytic uremic syndrome, the effect of ESA therapy on transfusion incidence is uncertain (D, NA, NA, B, B).

Oral and/or parenteral iron

Key question: In neonatal and paediatric patients with chronic kidney disease, what is the effect of IV iron compared with oral iron on transfusion volume or incidence?		Evidence table no: 3.2.34 Evidence matrix ref: D2.Q
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Warady 2004).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No transfusion events were recorded in either treatment group.	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?)*		
Subjects were paediatric patients with end stage renal disease receiving haemodialysis.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study was conducted in paediatric nephology centres in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.34 In paediatric patients with chronic kidney disease receiving maintenance rHuEPO therapy, the effect of IV iron compared with oral iron on transfusion incidence is uncertain (D, NA, NA, B, C).

Neonatal and paediatric patients with malaria

Oral and/or parenteral iron

Key question: In neonatal and paediatric patients with malaria, what is the effect of iron therapy (oral and/or parenteral) on transfusion volume or incidence?		Evidence table no: 3.2.37 Evidence matrix ref: D2.R
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Van den Hombergh 1996).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference between treatment groups reported for transfusion incidence.	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?)*		
Subjects were children <30 months with severe malaria-associated anaemia (Hb ≤ 5 g/dL)	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Study was conducted in a single hospital in Tanzania	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, NA, NA, B, C).

Key question: In neonatal and paediatric patients with malaria-associated anaemia, what is the effect of iron therapy (oral and/or parenteral) on mortality?		Evidence table no: 3.2.38 Evidence matrix ref: D2.S
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Okebe 2011) that included 4 trials (Gara 2010, Nwanyanwu 1996, van den Hombergh 1996, van Hensbroek 1995).	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')*		
No difference between treatment groups reported for mortality (RD 0.00, 95%CI –0.01, 0.02, p=0.74). No significant heterogeneity (I^2=0%).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No differences / study underpowered.	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?)*		
Subjects were children <30 months with clinical malaria	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Nigeria, Malawi, Tanzania, and Gambia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	D	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

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 (A, A, NA, C, D).

Neonatal and paediatric patients with HIV or AIDS

ESAs (with or without iron)

Key question: In neonatal and paediatric patients with HIV or AIDS, what is the effect of ESAs (with or without iron) on mortality?		Evidence table no: 3.2.42 Evidence matrix ref: D2.T
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Marti-Carvajal 2011) that included one trial of poor quality (Rendo 2001).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference reported / study underpowered and had a high risk of reporting bias.	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?)*		
Subjects were anaemic children with HIV or AIDS receiving antiretroviral therapy	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies was conducted in Argentina	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, NA, C, C).

Neonatal and paediatric patients with sickle cell disease

Hydroxyurea

Key question(s): In neonatal and paediatric patients with sickle cell disease, what is the effect of hydroxyurea on transfusion volume or incidence?		Evidence table no: 3.2.45 Evidence matrix ref: D2.U
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Wang 2011) and one Level II study of fair quality (Jain 2012).	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')*		
Both studies favoured hydroxyurea for transfusion volume and incidence. Wang 2011 reported that the number of children who received 2+ transfusions was not significantly difference between groups, as were transfusions associated with acute chest syndrome.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both studies favoured hydroxyurea: - Transfusion incidence (Wang 2011): 20.8% vs 34.0%, HR 0.55, 95% CI 0.32, 0.96; p=0.03 - Mean no. transfusions per patient per year (Jain 2012): 0.13 ± 0.43 vs 1.98 ± 0.82, MD –1.85, 95% CI –2.18, –1.52, *P* < 0.001	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?)*		
Both Level II studies examined paediatric patients with sickle cell disease. Subjects in Jain 2012 were children aged 5–18 years with severe sickle cell anaemia, and subjects in Wang 2011 were infants aged 9–18 months with sickle cell anaemia or sickle beta thalassemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA (Wang 2011) and India (Jain 2012).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Management of sickle cell disease in USA is considered comparable with Australia.
Transfusion volume or incidence was not the primary outcome of either study.

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	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
2. Consistency	A	All studies consistent
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.48 In paediatric patients with sickle cell disease, hydroxyurea decreases the incidence of transfusions (B, A, B, A, B).

Key question(s): In neonatal and paediatric patients with sickle cell disease, what is the effect of hydroxyurea on stroke			Evidence table no: 3.2.46 Evidence matrix ref: D2.V
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study of good quality (Wang 2011).	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')*			
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Wang 2011 reported no difference in stroke: 0% vs 1.0%, RR 0.31, 95%CI 0.01, 8.17, p=0.50. Stroke was not a primary outcome of this study.	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?)*			
Subjects were infants aged 9–18 months with sickle cell anaemia or sickle beta thalassemia of all clinical severities.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES2.50 In paediatric patients with sickle cell disease, the effect of hydroxyurea on stroke is uncertain (B, NA, NA, A, B).

Neonatal and paediatric patients requiring surgery

ESAs (with or without iron)

Key question: In neonatal and paediatric patients requiring surgery, what is the effect of ESAs (with or without iron) on transfusion incidence or volume?			Evidence table no: 3.2.52 Evidence matrix ref: D2.W
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes two Level II studies of poor quality with low to moderate risk of bias Bierer 2009 – neonates Fearon 2002 – infants and children.	A	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	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	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	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')*			
Not applicable (neonate/paediatric population considered separately)	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Bierer 2009 favoured placebo for mean number of transfusion per infant during the study period ($P < 0.00001$) (see note) and during hospitalisation ($P < 0.00001$), and volume of blood transfused during the study ($P < 0.00001$) and during hospitalisation ($P < 0.00001$). Fearon 2002 favoured rHuEPO + iron for transfusion incidence (p=0.03).	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	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?)*			
Subjects were neonates aged <28 days requiring major surgery (Bierer 2009) or infants and children aged <8 years scheduled for cranial vault remodelling (Fearon 2002).	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Both studies were in the USA.	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	D	Evidence not applicable to Australian healthcare 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)*

Reported as non-significant (*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

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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.51 In neonatal patients requiring surgery, the effect of ESA therapy (with or without iron) on transfusion incidence or volume is uncertain (D, NA, C, B, C).
ES2.52 In paediatric patients requiring surgery, the effect of ESA therapy (with or without iron) on transfusion incidence is uncertain (D, NA, C, B, C).

Key question(s): In neonatal and paediatric patients requiring surgery, what is the effect of ESAs (with or without iron) on thromboembolic events		Evidence table no: 3.2.53 Evidence matrix ref: D2.X
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Andropoulos 2013).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Andropoulos 2013 did not report any significant differences in thromboembolic events including pre– and post–operative cerebral infarction, or pre– and post–operative dural sinovenous thrombosis (DSVT).	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?)*		
Subjects were neonates scheduled for cardiac surgery with hypothermic CPB for greater than 60 minutes.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.54 In neonatal patients requiring cardiac surgery, the effect of ESA therapy compared with no ESA therapy on thromboembolic events is uncertain (B, NA, NA, C, C).

Key question(s): In neonatal and paediatric patients requiring surgery, what is the effect of ESAs (with or without iron) on mortality?		Evidence table no: 3.2.54 Evidence matrix ref: D2.Y
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Andropoulos 2013).	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')*		
NA	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)*		
Andropoulos 2013 reported no significant difference in mortality (p=0.83) but was underpowered for this outcome.	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?)*		
Subjects were neonates scheduled for cardiac surgery with hypothermic CPB for greater than 60 minutes.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.57 In neonatal patients requiring cardiac surgery, the effect of ESA therapy compared with no ESA therapy on mortality is uncertain (B, NA, NA, C, C).

Critically ill neonatal and paediatric patients

ESAs (with or without iron)

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of ESAs (with or without iron) on transfusion volume or incidence		Evidence table no: 3.2.58 Evidence matrix ref: D2.Z
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of fair quality (Jacobs 2003) and one Level II study of poor quality (Chicella 2006).	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')*		
Neither study found a significant difference in transfusion volume or incidence.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both studies reported no significant difference in transfusion volume or incidence.	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?)*		
Subjects were critically ill children ≤18 years with Hct ≤30% (Chicella 2006) and critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure and anaemia (Jacobs 2003)	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were from two PICUs in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, A, NA, B, C).

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of ESAs (with or without iron) on mortality?			Evidence table no: 3.2.59 Evidence matrix ref: D2.AA
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Includes one Level II study of fair quality (Jacobs 2003).	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')*			
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
The study reported no mortality but was underpowered.	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?)*			
Subjects were critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure and anaemia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Subjects were from a single PICU in the USA.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES2.65 In critically ill paediatric patients with acute respiratory failure, the effect of ESA therapy plus iron compared with iron only on mortality is uncertain (C, NA, NA, B, C).

Recommendations – Question 2

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* In preterm infants with low birth weight (<2500 g), the *routine* use of ESAs is not advised.	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D2.A, D2.C, D2.D, D2.E, D2.F, D2.G
Indicate any dissenting opinions None		
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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	RELEVANT ESF(S)
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, this may not be the optimal treatment for prevention of stroke* [b] *See R1 and PP21.*	Grade B	D1.K D2.U, D2.V, D2.V

Indicate any dissenting opinions

None

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.

Further research is ongoing. The Phase III TWiTCH trial is a non-inferiority 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 yet available.

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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	GRADE OF RECOMMENDATION	RELEVANT ESF(S)
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.*	Grade C	See *Patient Blood Management Guidelines: Module 2 – Perioperative* Technical report volume 2a Appendix D6 p.280–283.
Indicate any dissenting opinions None.		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
This Recommendation is based on the evidence reviewed in the *Patient Blood Management Guidelines: Module 2 – Perioperative*. Please refer to the Technical report volume 1a Question 6 p. 162–206 and volume 2a Appendix D6 p.280–311.		
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

D3 Evidence matrixes – Question 3

Preterm infants

Fresh frozen plasma

Key question(s): In preterm infants, what is the effect of FFP compared with no FFP on mortality?		Evidence table no: 3.3.3 Evidence matrix ref: D3.A
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Osborn 2004) that identified three Level II studies (Beverley 1985, Gottuso 1976, NNNI 1996a) that reported the outcome of mortality. The studies were not blinded and were of fair quality. One additional Level II study (NNNI 1996b) of fair quality that reported 2 year follow-up data.	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')*		
All studies found no significant association between FFP transfusion and mortality.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No study found a significant association between FFP transfusion and mortality.	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?)*		
All studies examined VLBW (< 1500 g) or very preterm infants born ≤ 32 weeks gestation. All infants were ≤ 72 hours old when administered FFP. Infants in NNNI 1996b were followed up two years.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the UK (NNNI 1996a, NNNI 1996b). Study location(s) were not reported for the remaining studies. Study older than 20 years and clinical practice has changed.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence not applicable to Australian healthcare context

EVIDENCE STATEMENT

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 (C, A, NA, A, C).

Key question(s): In preterm infants, what is the effect of FFP compared with no FFP on bleeding events?		Evidence table no: 3.3.4 Evidence matrix ref: D3.B
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Osborn 2004) that identified three Level II studies (Beverley 1985, Ekblad 1991, NNNI 1996a) that reported bleeding events. The studies were not blinded and were of fair or unclear quality	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')*		
All Level II studies found no significant association between FFP transfusion and any grade of peri/intraventricular haemorrhage (P/IVH), IVH or severe IVH.	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)*		
Osborn (2004) meta-analysed two Level II studies (Beverley 1985, Ekblad 1991) and found no significant difference in P/IVH of any grade (RR 0.58; 95%CI 0.30, 1.11; p=0.099). There were also no significant differences observed for IVH (any grade) or severe IVH in the Level II studies.	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?)*		
All studies examined VLBW (<1500 g) or very preterm infants born ≤ 32 weeks gestation.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the UK (NNNI 1996a) study older than 20 years and clinical practice has changed. Study location(s) were not reported for the remaining studies.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)* When considering the evidence the clinicians acknowledged evidence was older than 20 years and importantly clinical practice has changed since then.		

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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Slight/Restricted Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, B, NA, A, C).

Platelet transfusion

Key question(s): In preterm infants, what is the effect of platelet transfusion compared with no platelet transfusion on mortality?		Evidence table no: 3.3.6 Evidence matrix ref: D3.C
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III studies of good quality (Baer 2007) and two Level III studies of poor quality (Bonifacio 2007, Christensen 2006).	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')*		
Two studies (Baer 2007, Bonifacio 2007) found a significant association between platelet transfusion and mortality in neonates with thrombocytopenia. One study (Christensen 2006) found that platelet transfusion was associated with mortality in ELBW infants who were thrombocytopenic, but that no significant difference was observed once thrombocytopenia had resolved.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Baer 2007 conducted a logistic regression in neonates with thrombocytopenia who received up to 10 platelet transfusions and found a significant association between platelet transfusion and mortality (OR 1.45; 95%CI NR; *P* = NR). Bonifacio 2007 found a significant association between platelet transfusion and mortality in very preterm infants ≤32 weeks gestation (2.66; 95%CI 1.05, 6.70; *P* = 0.04). Christensen 2006 found a significant association between platelet transfusion and mortality in thrombocytopenic patients (*P* = 0.02) but not infants whose thrombocytopenia had resolved (*P* = 0.60).	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?)*		
All studies included infants or neonates with thrombocytopenia. Infants in Bonifacio 2007 were very preterm (≤32 weeks gestation), and infants in Christensen 2006 were ELBW (<1000 g).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
All studies included subjects from the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Baer 2007 conducted a sensitivity analysis combining the risk of additional platelet transfusions and unmeasured variables on mortality there was a statistically significant adverse effect of additional platelet transfusions on mortality, beyond the effect of the observed variable (Baer 2007).

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	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
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, B, D, B, C).

Key question(s): In preterm infants, what is the effect of platelet transfusion compared with no platelet transfusion on bleeding events?		Evidence table no: 3.3.8 Evidence matrix ref: D3.D
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of good quality (Baer 2007) and one Level III study of poor quality (Bonifacio 2007).	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')*		
Both studies found a significant association between platelet transfusion and IVH in preterm infants with thrombocytopenia. Baer 2007 examined severe IVH (grade 3–4) and Bonifacio 2007 examined IVH of any grade. In a subgroup analysis of number of platelet transfusions, Baer 2007 found that platelet transfusion was associated with severe IVH regardless of whether infants received 1 or >10 transfusions. Bonifacio 2007 conducted a subgroup analysis based on gestational age and found no significant difference in IVH within each subgroup, although the overall result favoured no platelet transfusion.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Severe IVH in neonates with thrombocytopenia (Baer 2007): - RR 5.04 (95%CI, 3.59, 7.07; *P* < 0.00001) - Subgroup analyses by number of transfusions all significant IVH (any grade) in very preterm infants with thrombocytopenia (Bonifacio 2007): - RR 1.94 (95%CI 1.02, 3.69; p=0.04) - Subgroup analyses by gestational age non-significant	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?)*		
Both studies examined infants or neonates with thrombocytopenia. Infants in Bonifacio 2007 were very preterm (≤ 32 weeks gestation).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Both studies included subjects from USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, A, D, B, C).

Key question(s): In preterm infants, what is the effect of platelet transfusion compared with a different platelet transfusion protocol on mortality?		Evidence table no: 3.3.7 Evidence matrix ref: D3.E
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (von Lindern 2012) that compared a restrictive platelet transfusion strategy (when active haemorrhage and platelet count <50 x109 /L) protocol with a liberal platelet transfusion strategy (predefined platelet count threshold).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant association was found between restrictive platelet transfusion (when active haemorrhage and platelet count < 50 $x10^9$ /L) and liberal platelet transfusion (predefined platelet count threshold) and mortality (RR 1.05, 95%CI 0.60, 1.82).	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?)*		
Subjects were very preterm infants (<32 weeks gestational age) with or without thrombocytopenia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from 2x NICUs, The Netherlands.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (C, NA, NA, A, B).

Key question(s): In preterm infants, what is the effect of platelet transfusion compared with different platelet transfusion protocol on bleeding events?		Evidence table no: 3.3.9 Evidence matrix ref: D3.F
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
One Level III of fair quality (von Lindern 2012) that examined restrictive platelet transfusion (when active haemorrhage and platelet count < 50 x10^9 /L) compared with liberal platelet transfusion (predefined platelet count threshold).	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')*		
There was no significant difference in IVH (any grade) between groups. There was also no significant difference for major haemorrhage other than IVH. According to the analysis by IVH grade, restrictive platelet transfusion was significantly associated with IVH grade 1 and liberal platelet transfusion was significantly associated with IVH grade 2. There was no significant difference between groups for severe IVH (grade 3–4).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
IVH, all grades (von Lindern 2012): no significant difference (p=0.31) Major haemorrhage other than IVH (von Lindern 2012): no significant difference (p=0.72) Thrombocytopenic patients: IVH (grade 1): favours liberal transfusion (RR 1.94; 95%CI 1.09, 3.46, p=0.02) IVH (grade 2): favours restrictive transfusion (RR 0.19; 95%CI 0.04, 0.87; p=0.02) IVH (grade 3 or 4): no significant difference (p=0.38)	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?)*		
The subjects were <32 weeks gestation with or without thrombocytopenia.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were enrolled from The Netherlands (von Lindern 2012).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Cranial ultrasounds were interpreted by the individual ICUs. This may account for the observed differences between IVH (grade 1) and IVH (grade 2).

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	Not applicable/no difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (C, NA, NA, B, B).

Neonatal and paediatric patients with cancer

Platelet transfusion

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of platelet transfusion compared with a different platelet transfusion protocol on mortality?		Evidence table no: 3.3.11 Evidence matrix ref: D3.G
1. Evidence base (*number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Estcourt 2012) that identified one Level II study (Murphy 1982) with an overall unclear or high risk of bias. Murphy 1982 examined therapeutic platelet transfusion (administered only in the presence of bleeding) compared with prophylactic platelet transfusion (administered to maintain platelet count above 20x10^9/L).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Murphy 1982 found no significant difference in mortality (all-cause) or due to bleeding between therapeutic and prophylactic platelet transfusion.	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?)*		
Subjects were children hospitalised with previously untreated acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were enrolled from a single centre in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, NA, B, C).

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of platelet transfusion compared with a different platelet transfusion strategy on bleeding events?			Evidence table no: 3.3.12 Evidence matrix ref: D3.H
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*			
Includes one Level I study of good quality (Estcourt 2012) that identified one Level II studies (Murphy 1982) with overall unclear to high risk of bias. Murphy 1982 examined therapeutic platelet transfusion (administered only in the presence of bleeding) compared with prophylactic platelet transfusion (administered to maintain platelet count above 20x10^9/L).	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')*			
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
1+ significant bleeding events: no significant difference (p=0.10) - Sub-analysis of children with ALL: borderline favours prophylactic (p=0.05) - Sub-analysis of children with AML: no significant difference (p=0.85 The subgroup analyses were underpowered to detect for statistically significant differences.	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?)*			
Murphy 1982 included children with previously untreated acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Study was conducted in the USA.	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, NA, B, C).

Key question(s): In neonatal and paediatric patients with cancer, what is the effect of platelet transfusion compared with a different platelet transfusion protocol on transfusion volume or incidence?		Evidence table no: 3.3.13 Evidence matrix ref: D3.I
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Estcourt 2012) that identified one Level II study (Murphy 1982) with an unclear to high risk of bias.	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Murphy 1982 found no significant difference in the mean number of platelet transfusions per course of chemotherapy between patients who received a therapeutic platelet transfusion and those who received a prophylactic platelet transfusion.	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?)*		
Subjects were children hospitalised with previously untreated acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from a single centre in the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, NA, B, C).

Neonatal and paediatric patients undergoing surgery

Fresh frozen plasma

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of FFP compared with no FFP on mortality?		Evidence table no: 3.3.16 Evidence matrix ref: D3.J
1. Evidence base (*number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (Nacoti 2012).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study found a significant difference in cumulative patient survival at one year between postoperative FFP transfusion (≥1 unit) and no postoperative FFP transfusion favouring no transfusion (p = 0.022). The effect did not remain significant when analysed using a multivariate Cox regression model. Cumulative patient survival at one year was significantly associated with FFP usage during surgery (p=0.001). This effect was dose-related and remained significant when analysed using a multivariate Cox regression model (HR 3.35, 95%CI 1.20, 9.36, p=0.021) (≥3 units FFP). However in a propensity score adjusted analysis of possible confounders, this result was no longer significant (p=0.068). No significant difference was found for intraoperative transfusion of 2 units of FFP and patient survival.	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?)*		
Subjects were paediatric liver transplant patients aged <18 years from deceased brain-dead donors. Combined organ transplantations were excluded.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.28 In paediatric liver transplant patients, any association between FFP transfusion and mortality is uncertain (C, NA, D, A, B).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of FFP compared with no FFP on bleeding events?		Evidence table no: 3.3.17 Evidence matrix ref: D3.K
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Three Level II studies were identified in the literature search (Lee 2013, Oliver 2003, McCall 2004). Two Level II studies were rated as fair quality (Lee 2013, McCall 2004), and one as poor quality (Oliver 2003).	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')*		
Most studies found no significant association between FFP and no FFP for post-operative blood loss. One study (Oliver 2003) found a significant association between no FFP transfusion and 24–hour post-operative blood loss in complex surgery patients and cyanotic patients (results estimated from graph). One study examined bleeding after heparin reversal and found no significant difference between groups (Lee 2013).	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No difference was found for FFP compared with no FFP in two studies. The remaining study wasn't powered to detect for statistically significant differences in subgroups.	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?)*		
All studies examined patients undergoing cardiac surgery. Two studies were in infants <10 kg (McCall 2004, Oliver 2003), and one study included infants and children aged <12 months to 16 years (Lee 2013). Oliver 2003 stratified patients as either simple or complex surgery grade, and cyanotic or acyanotic.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
One study included subjects from Korea (Lee 2013), two studies included subjects from the US (Oliver 2003, McCall 2004)	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	No difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES3.31 In neonatal and paediatric patients undergoing cardiac surgery, the use of an FFP-based pump priming fluid compared with an albumin-based fluid does not reduce postoperative blood loss (C, B, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of FFP compared with no FFP on transfusion volume or incidence?		Evidence table no: 3.3.18 Evidence matrix ref: D3.L
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes two Level II studies of fair quality (Lee 2013, McCall 2004) and one of poor quality (Oliver 2003).	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')*		
All studies examined post-operative transfusion requirements, with two studies also examining intraoperative transfusion requirements (Lee 2013, Oliver 2003). One study examined donor exposures per patient (McCall 2004). - Intra-op: Lee 2013 found a significant association between FFP transfusion and increased RBC and total transfusion requirements in infants. FFP transfusion was associated with lower intraoperative FFP requirements in infants and children. - Post-op: two studies found no significant difference in transfusion requirements between groups (Lee 2013, McCall 2004) - Intra– and post-op: Oliver 2003 found a significant association between FFP transfusion and increased total units of blood transfused. However when the intervention FFP was excluded, the result was no longer significant. - Donor exposures per patient: McCall 2004 found a significant association between no FFP transfusion and increased exposures to cryoprecipitate.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Intra-op (infants): - Additional RBC into CPB circuit, favours control (p=0.002) - RBC requirements after heparin reversal, favours control (p=0.047) - FFP requirements after heparin reversal, favours FFP (p=0.042) - Total transfusion requirements, favours control (p=0.001) Intra-op (children): - FFP requirements after heparin reversal, favours FFP (p=0.002) Donor exposures per patient to cryoprecipitate: favours FFP (*P* < 0.001)	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?)*		
All studies examined patients undergoing cardiac surgery. Two studies were in infants <10kg (McCall 2004, Oliver 2003), and one study included infants and children aged <12 months to 16 years (Lee 2013).	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		

Subjects were from the US (Oliver 2003, McCall 2004) and Korea (Lee 2013).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (C, B, NA, A, C).

Platelets

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of platelet transfusion compared with no platelet transfusion protocol on mortality?		Evidence table no: 3.3.20 Evidence matrix ref: D3.M
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (Nacoti 2012).	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')*		
NA	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)*		
The authors found no significance difference in patient survival at 1 year and intra/postoperative platelet transfusion compared to no intra/postoperative platelet transfusion (p=0.342 and p=0.237). The authors found no significance difference in patient survival at 1 year and the volume of preoperative platelet transfusion (p=0.929). The authors compared high preoperative platelet transfusion (≥181x1000/cc) to medium (91–180x1000/cc) to low preoperative platelet transfusion (≤90x1000/cc).	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?)*		
Subjects were paediatric liver transplant patients aged <18 years from deceased brain-dead donors. Combined organ transplantations were excluded.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.48 In paediatric liver transplant patients, the effect of platelet transfusion compared with no platelet transfusion on mortality is uncertain (D, NA, NA, A, B).

Fibrinogen concentrate

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of fibrinogen concentrate compared with no fibrinogen concentrate on mortality?		Evidence table no: 3.3.23 Evidence matrix ref: D3.N
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of fair quality (Nacoti 2012).	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')*		
NA	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)*		
The authors found no significant difference in patient survival at 1 year and higher preoperative fibrinogen transfusion (≥221mg/dL) compared with medium (141–220mg/dL) compared with low preoperative fibrinogen transfusion (≤140mg/dL) (p=0.308).	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?)*		
Subjects were paediatric liver transplant patients aged <18 years from deceased brain-dead donors. Combined organ transplantations were excluded.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Italy.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (C, NA, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of fibrinogen concentrate compared with cryoprecipitate on mortality?		Evidence table no: 3.3.24 Evidence matrix ref: D3.O
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Galas 2014).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study was not powered to detect between group differences.	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?)*		
Subjects were children < 7 years receiving CPB surgery and plasma fibrinogen concentration < 1 g/L	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Brazil.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES3.65 In paediatric patients with acute acquired hypofibrinogenaemia after cardiopulmonary bypass weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on mortality is uncertain (B, NA, NA, A, C).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of fibrinogen concentrate compared with cryoprecipitate on bleeding events?		Evidence table no: 3.3.25 Evidence matrix ref: D3.P
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Galas 2014).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The authors reported no significant difference (P = 0.672) on mean blood volume loss up to 48–hours post-surgery	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?)*		
Subjects were children < 7 years receiving CPB surgery and plasma fibrinogen concentration < 1 g/L	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Brazil.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES3.66 In paediatric patients with acute acquired hypofibrinogenaemia after cardiopulmonary bypass weaning, the effect of fibrinogen concentrate compared with cryoprecipitate on bleeding events is uncertain (B, NA, NA, A, C).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of fibrinogen concentrate compared with cryoprecipitate on transfusion incidence?		Evidence table no: 3.3.26 Evidence matrix ref: D3.Q
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Galas 2014).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The authors reported a significant difference (RR 0.86; 95% CI 0.72, 1.02) favouring fibrinogen concentrate for total postoperative transfusion needs (including RBC, platelets, FFP, fibrinogen) but not for the individual products	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?)*		
Subjects were children < 7 years receiving CPB surgery and plasma fibrinogen concentration < 1 g/L	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Patients were from one hospital in Brazil.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*		

Noted that the selected patients in this study have much higher complication rates and length of hospital stay than would be seen in Australian practice.

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/restricted
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES3.69 In paediatric patients with acute acquired hypofibrinogenaemia after cardiopulmonary bypass weaning, fibrinogen concentrate compared with cryoprecipitate may reduce transfusion incidence (B, NA, D, A, C).

Critically ill neonatal and paediatric patients

Fresh frozen plasma

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of FFP compared with no FFP on mortality?		Evidence table no: 3.3.29 Evidence matrix ref: D3.R
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes two Level III studies of good quality (Church 2009, Karam 2013).	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')*		
Church 2009 found a significant association between FFP transfusion and in PICU mortality, which remained significant in a multivariate analysis which adjusted for organ system dysfunction, Pao2/FIo2 and disseminated intravascular coagulation (OR 1.08 95%CI 1.00, 1.18; p=0.04). However, in a second multivariate analysis which adjusted for PRISM III score, the result was no longer significant (OR 1.08, 95%CI 0.98, 1.19; p=0.09). Karam 2013 found a significant association between FFP transfusion and 28–day mortality (OR 10.6, 95%CI 4.9, 23.1; *P* < 0.0001]; however, after adjusting for potential confounders, this was no longer significant (AR 2.2, 95%CI 0.5, 8.6)	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both studies found a significant association between FFP transfusion and mortality; however the effect was not significant when adjusted for potential confounders.	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?)*		
Both studies included paediatric intensive care patients aged <18 years. Subjects in Church 2009 had acute lung injury and were aged from 36 weeks corrected age to 18 years.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from the USA (Church 2009) and Canada (Karam 2013).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	C	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES3.76 In critically ill neonatal and paediatric patients, the effect of FFP compared with no FFP on mortality is uncertain (C, B, D, B, B).

Platelets

Key question(s): In critically ill neonatal and paediatric patients, what is the effect of platelet transfusion compared with no platelet transfusion on mortality?		Evidence table no: 3.3.31 Evidence matrix ref: D3.S
1. Evidence base *(number of studies, Level of evidence and risk of bias in the included studies)*		
Includes one Level III study of good quality (Church 2009).	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')*		
NA	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)*		
The study found a significant association between platelet transfusion and in PICU mortality ($P < 0.005$); however, when this was adjusted for organ system dysfunction, Pao2/FIo2 and disseminated intravascular coagulation in a multivariate analysis, the result was no longer significant (p=0.26).	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?)*		
Subjects were paediatric intensive care patients aged 36 weeks corrected age to 18 years with acute lung injury.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Subjects were from two PICUs in the US.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES3.92 In critically ill neonatal and paediatric patients, the effect of platelet transfusion compared with no platelet transfusion on mortality is uncertain (C, NA, NA, B, C).

Recommendations – Question 3

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* In neonatal and paediatric patients undergoing cardiac surgery, the *routine* use of an FFP-based pump prime solution is not recommended, because it offers no advantages over an albumin-based solution in relation to postoperative blood loss, or perioperative transfusion requirements.	GRADE OF RECOMMENDATION C	RELEVANT ESF(S) D3.K, D3.L
Indicate any dissenting opinions None		
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

D4 Evidence matrixes – Question 4

Preterm and term infants

Placental transfusion

Key question(s): In preterm and term infants, what is the effect of placental transfusion on transfusion volume or transfusion incidence?		Evidence table no: 3.4.3 Evidence matrix ref: D4.A
1. Evidence base (*number of studies, level of evidence and risk of bias in the included studies)*		
Includes four Level I studies (Backes 2014 [good quality], Rabe 2012 [good quality], Mathew 2011 [fair quality], Ghavam 2013 [poor quality]) which identified 12 Level II studies (Aladangady 2006, Hosono 2008, Ibrahim 2000, Kinmond 1993, March 2011, March 2013, McDonnell 1997, Mercer 2006, Strauss 2008, Kugelman 2007, Rabe 2000, Oh 2002). Two additional Level II studies of fair quality were identified in the literature search (Katheria 2014, Alan 2014).	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')*		
All reviews and Katheria 2014 found that infants who received placental transfusion required significantly fewer transfusions or a significantly lower volume of blood. Alan 2014 found that in VLBW very preterm infants <32 weeks gestation, there was no significant difference in RBC transfusion incidence.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
25% risk reduction in transfusion incidence.	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?)*		
All subjects were preterm infants. Backes 2014, Katheria 2014 and Alan 2014 included VLBW (<1500 g) or very preterm infants <32 weeks gestation. Ghavam 2013 included ELBW (<1000 g) preterm neonates <30 weeks gestation	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA, UK, Europe, Japan, Israel, Turkey and Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Many of the included studies had some risk of selection bias. The Chair noted that it is almost impossible for this intervention to be blinded and this has also led to some bias. Members agreed that a larger study on preterms is required to be more confident about the end-points. Members also agreed that there is evidence for healthy near-terms and term infants on cord clamping with regards to haematological outcomes, but it is lacking in the preterm population. This was noted in the evidence gaps.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	B	Substantial
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.1 In preterm infants, placental transfusion compared with no placental transfusion may reduce transfusion volume and incidence (C, A, B, B, B).

Key question(s): In preterm and term infants, what is the effect of placental transfusion on mortality?		Evidence table no: 3.4.4 Evidence matrix ref: D4.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes four Level I studies (Backes 2014 [good quality], Rabe 2012 [good quality], McDonald 2013 [good quality], Mathew 2011 [fair quality]) which identified 16 Level II studies (Hosono 2008, Kinmond 1993, March 2013, McDonnell 1997, Mercer 2003, Mercer 2006, Oh 2002, Baenziger 2007, Cernadas 2006, van Rheenen 2007, Strauss 2008, Ultee 2008, Hofmeyr 1988, Hofmeyr 1993, Kugelman 2007, Rabe 2000). Mathew 2011 did not report which Level II studies were included. Two additional Level II studies of fair quality were identified in the literature search (Katheria 2014, Alan 2014).	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')*		
One study (Backes 2014) found a significant difference in mortality before discharge which favoured placental transfusion. Subjects were very preterm infants <32 weeks gestation. All other studies reported no significant difference.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Underpowered.	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?)*		
McDonald 2013 included term infants >37 weeks gestation; all other studies included preterms. Backes 2014, Katheria 2014 and Alan 2014 included VLBW (<1500 g) or very preterm infants <32 weeks gestation.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA, Central & South America, UK, Europe, South Africa, Africa, Japan, Israel, Turkey and Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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)*

Many of the included studies had some risk of selection bias. The Chair noted that it is almost impossible for this intervention to be blinded and this has also led to some bias. Members agreed that a larger study on preterms is required to be more confident about the end-points. Members also agreed that there is evidence for healthy near-terms and term infants on cord clamping with regards to haematological outcomes, but it is lacking in the preterm population. This was noted in the evidence gaps.
Members agreed to include both 'term' and 'preterm' infants to the mortality evidence statement but the evidence base, consistency and clinical impact were downgraded.

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	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
2.	Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3.	Clinical impact	NA	Underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.2 In preterm and term infants, the effect of placental transfusion compared with no placental transfusion on mortality is uncertain (C, C, NA, B, B).

IVIg for haemolytic disease

Key question(s): In preterm and term infants, what is the effect of IVIg on exchange transfusion incidence?		Evidence table no: 3.4.8 Evidence matrix ref: D4.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Louis 2014) that identified 11 Level II studies (Alpay 1999, Dagoglu 1995, Rubo 1992, Elalfy 2011, Nasseri 2006, Pishva 2000, Garcia 2004, Santos 2013*, Smits-Wintjens 2011*, Huang 2006, Miqdad 2004). *Studies with a low risk of bias.	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')*		
Overall, there were significantly more infants in the control group (phototherapy only) who required exchange transfusion compared with infants who received IVIg plus phototherapy. However in a sensitivity analysis of studies with a low risk of bias, the result was no longer significant.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Studies with a low risk of bias were underpowered due to small sample size.	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?)*		
Subjects were term or preterm neonates with isoimmune haemolytic disease secondary to ABO or Rh incompatibility.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Turkey (Alpay 1999, Dagoglu 1995), Egypt (Elalfy 2011), Iran (Nasseri 2006, Pishva 2000), Saudi Arabia (Miqdad 2004), Mexico (Garcia 2004), Brazil (Santos 2013), China (Huang 2006), Germany (Rubo 1992) and The Netherlands (Smits-Wintjens 2011).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

The majority of studies had a high risk of bias due to lack of blinding and no rigorous decision criteria on when to give an exchange transfusion. The Level II studies demonstrating a high risk of bias were excluded from the analysis when considering the available evidence. Three studies (Garcia 2004, Santos 2013, Smit-Wintjens 2011) were identified as having a low risk of bias but were underpowered to detect significant between group differences.

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	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
2.	Consistency	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	NA	Underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.3 In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on exchange transfusion incidence is uncertain (B, B, NA, A, C).

Key question(s): In preterm and term infants, what is the effect of IVIg on mortality?		Evidence table no: 3.4.9 Evidence matrix ref: D4.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Louis 2014) which identified 12 Level II studies (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).	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')*		
There were no fatalities in any study.	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 <u>unknown</u> 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?)*		
Subjects were term or preterm neonates with isoimmune haemolytic disease secondary to ABO or Rh incompatibility.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Turkey (Alpay 1999, Dagoglu 1995), Egypt (Elalfy 2011), Iran (Nasseri 2006, Pishva 2000), Saudi Arabia (Miqdad 2004), Mexico (Garcia 2004), Brazil (Santos 2013), Argentina (Voto 1995), China (Huang 2006), Germany (Rubo 1992) and The Netherlands (Smits-Wintjens 2011).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.4 In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on mortality is uncertain (B, A, NA, A, C).

Neonatal and paediatric patients undergoing surgery

Prevention of hypothermia

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of the prevention of hypothermia on mortality?		Evidence table no: 3.4.11 Evidence matrix ref: D4.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Caputo 2011).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported no mortality.	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?)*		
Subjects were paediatric patients (median age 6.5 years) undergoing cardiac surgery with CPB.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single hospital in England.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

When considering the evidence for prevention of hypothermia in paediatric patients, the CRG noted that the evidence is strong (Grade A) in the adult population (see R12 in *Module 2 – Perioperative*) and agreed to consider this evidence when drafting recommendations for the paediatric population.

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, NA, NA, A, B).

ES4.6 In paediatric patients undergoing non-cardiac surgery, the effect of preventing hypothermia compared with no prevention of hypothermia on mortality is unknown (NA, NA, NA, NA, NA).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of prevention of hypothermia on transfusion volume and incidence?		Evidence table no: 3.4.12 Evidence matrix ref: D4.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of good quality (Caputo 2011).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study found no significant difference in RBC, platelet or FFP transfusion volume or incidence.	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?)*		
Subjects were paediatric patients (median age 6.5 years) undergoing cardiac surgery with CPB.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single hospital in England.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

When considering the evidence for prevention of hypothermia in paediatric patients, the CRG noted that the evidence is strong (Grade A) in the adult population (see R12 in *Module 2 – Perioperative*) and agreed to consider this evidence when drafting recommendations for the paediatric population.

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	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
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

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 (B, NA, NA, A, B).

ES4.8 In paediatric patients undergoing non-cardiac surgery, the effect of preventing hypothermia compared with no prevention of hypothermia on transfusion volume or incidence is unknown (NA, NA, NA, NA, NA).

Deliberate/controlled induced hypotension

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of deliberate/controlled induced hypotension on transfusion volume and incidence?		Evidence table no: 3.4.14 Evidence matrix ref: D4.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Precious 1996).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No patients required transfusion.	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?)*		
Subjects were adolescent patients aged 13 to 15 years undergoing osteotomy or genioplasty.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single hospital in Canada.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	NA	Not applicable (one study only)
3.	Clinical impact	NA	No difference / underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.10 In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on transfusion incidence is uncertain (D, NA, NA, B, B).

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).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of deliberate/controlled induced hypotension on bleeding events?		Evidence table no: 3.4.15 Evidence matrix ref: D4.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Precious 1996).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study found a statistically significant difference in estimated blood loss ($P < 0.002$) and surgical field rating ($P < 0.001$) which favoured induced hypotension.	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?)*		
Subjects were adolescent patients aged 13 to 15 years undergoing osteotomy or genioplasty.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted at a single hospital in Canada.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.12 In paediatric patients undergoing surgery, the effect of deliberate induced hypotension compared with no deliberate induced hypotension on bleeding events is uncertain (D, NA, C, B, B).

Acute normovolemic haemodilution (ANH)

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of ANH on transfusion volume and incidence?		Evidence table no: 3.4.17 Evidence matrix ref: D4.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes three Level II studies (Friesen 2006 [fair quality], Hans 2000 [poor quality], Lisander 1996 [poor quality]). Lisander 1996 was a pilot study.	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')*		
No study found a significant difference in transfusion volume or incidence.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
As above.	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?)*		
Subjects in Friesen 2006 were infants undergoing non-complex open heart surgery with CPB; subjects in Hans 2000 were infants undergoing surgical repair for scaphocephaly or pachycephaly; and subjects in Lisander 1996 were paediatric patients (mean age 14.5 months) undergoing scoliosis surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Belgium, Sweden and the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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)*

The studies were small; therefore, the effect on transfusion volume and incidence is uncertain.

Studies in adults were also considered (see R14 and PP12 in *Patient Blood Management Module 2 – Perioperative*). CRG discussed applicability of the adult evidence to older children undergoing spinal surgery.

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	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
2.	Consistency	A	All studies consistent
3.	Clinical impact	NA	No difference
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.14 In paediatric patients undergoing surgery, the effect of ANH compared with no ANH on transfusion volume and incidence is uncertain (C, A, NA, B, B).

Intraoperative cell salvage

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of intraoperative cell salvage on mortality?		Evidence table no: 3.4.19 Evidence matrix ref: D4.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level II studies (Cholette 2013 [good quality], Ye 2013 [poor quality]). Cholette 2013 was a pilot study.	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')*		
Both studies found no significant difference in mortality.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Studies were not powered to detect for differences in mortality.	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?)*		
Subjects in both studies were paediatric patients scheduled for cardiac surgery with CPB. Cholette 2013 included children weighing ≤20kg, and Ye 2013 included children aged 6 days to 13 years and weighing 2 to 36kg who were undergoing open heart surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA (Cholette 2013) and China (Ye 2013).	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (B, A, NA, A, C).

ES4.16 In paediatric patients undergoing non-cardiac surgery, the effect of intraoperative cell salvage compared with no cell salvage on mortality is unknown (NA, NA, NA, NA, NA).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of intraoperative cell salvage on transfusion volume and incidence?			Evidence table no: 3.4.20 Evidence matrix ref: D4.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	Cardiac	Non-cardiac	
Cardiac surgery Includes two Level II studies (Cholette 2013 [good quality], Ye 2013 [poor quality]). Cholette 2013 was a pilot study. Non-cardiac surgery Includes one Level II pilot study of scoliosis surgery (Lisander 1996 [poor quality]).	A	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	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	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	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')*			
Cardiac surgery Both studies favoured cell salvage for transfusion volume. Children who received cell salvaged blood required significantly less postoperative RBCs at 24 and 48hrs post-surgery, but at 7 days the difference was no longer significant. A significant difference was also observed for platelets, FFP and cryoprecipitate transfused 48hrs post-surgery. Non-cardiac surgery: NA (one study only)	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	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)*			
Cardiac surgery Cholette 2013 favoured cell salvage for RBC transfusion volume at 24hrs (p=0.001) and 48hrs (p=0.003), but not at 7 days post-surgery (p=0.07). Cell salvage was also favoured for transfusion of platelets (p=0.03), FFP (p=0.02) and cryoprecipitate (p=0.04) at 48hrs post-surgery. The study was adequately powered. Ye 2013 favoured cell salvage for perioperative allogeneic RBC transfusion volume and incidence. Non-cardiac surgery Lisander 1996 found no significant difference in transfusion volume.	A	A	Very large
	B	B	Substantial
	C	C	Moderate
	D	D	Slight/Restricted
	NA	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?)*			
Cardiac surgery Subjects in Cholette 2013 & Ye 2013 were paediatric patients scheduled for cardiac	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats

surgery with CPB. Cholette 2013 included children weighing ≤20kg, and Ye 2013 included children aged 6 days to 13 years and weighing 2 to 36kg who were undergoing open heart surgery. Non-cardiac surgery Subjects were paediatric patients (mean age 14.5 years) undergoing scoliosis surgery.	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	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 healthcare context in terms of health services/delivery of care and cultural factors?)*

Cardiac surgery Studies were conducted in the USA (Cholette 2013) and China (Ye 2013). Non-cardiac surgery Lisander 1996 was conducted in Sweden.	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats
	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare 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)*

The CRG considered the evidence in adults (see R15 and PP13 in *Patient Blood Management Module 2 – Perioperative*)

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
		Cardiac	Non-cardiac	
1.	Evidence base	C	D	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias (C) Level IV studies or Level I to III studies/SRs with a high risk of bias (D)
2.	Consistency	B	NA	Most studies consistent and inconsistency can be explained (B) Not applicable (one study only) (NA)
3.	Clinical impact	C	NA	Moderate (C) Not applicable/no difference/underpowered (NA)
4.	Generalisability	A	C	Evidence directly generalisable to target population (A) Evidence not directly generalisable to the target population but could be sensibly applied (C)
5.	Applicability	C	B	Evidence probably applicable to Australian healthcare context with some caveats (C) Evidence applicable to Australian healthcare context with few caveats (B)

EVIDENCE STATEMENT

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 (C, B, C, A, C).

ES4.18 In paediatric patients undergoing non-cardiac surgery, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on transfusion volume and incidence is uncertain (D, NA, NA, C, B)

Antifibrinolytics

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of antifibrinolytics on mortality?		Evidence table no: 3.4.24 Evidence matrix ref: D4.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Cardiac surgery Five Level II studies (Coniff 1998 [poor], Ferreira 2010 [poor], Sarupria 2013 [fair], Singh 2001 [fair], Vacharaksa 2002 [fair]) provided evidence for mortality. Scoliosis surgery One Level I study (Tzortzopoulos 2008 [good]) that identified six Level II studies (Cole 2002 [fair], Cole 2003 [good], Khoshhal 2003 [good], Neilipovitz 2001 [fair], Sethna 2005 [fair], Florentino 2004 [good]). Craniofacial surgery Two Level II studies (Ahmed 2014 [fair quality], D'Errico 2003 [good quality]. Note: Cole 2002 was an abstract only.	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')*		
Cardiac surgery No study reported a significant different in mortality. Scoliosis surgery No deaths were reported in six trials (N=163) Craniofacial surgery No deaths were reported	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)*		
No study found a significant different in mortality. The studies were not powered to detect between group differences for this outcome.	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?)*		
Tzortzopoulos 2008 included paediatric patients aged <18 years scheduled for scoliosis surgery. Subjects in five studies (Coniff 1998, Ferreira 2010, Sarupria 2013, Singh 2001, Vacharaska 2002) were paediatric patients scheduled for cardiac surgery (four	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

with CPB), and subjects in two studies (Ahmed 2014, D'Errico 2003) were paediatric patients scheduled for major reconstructive craniofacial surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA, Canada, Brazil, India and Thailand.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.22 In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on mortality is uncertain (B, A, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing cardiac surgery, what is the effect of antifibrinolytics on transfusion volume and incidence?	Evidence table no: 3.4.25 Evidence matrix ref: D4.M

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Includes three Level I studies (Arnold 2006 [good quality], Faraoni 2012 [good quality], Schouten 2009 [good quality]) which identified 16 Level II studies (Boldt 1993a, Boldt 1994, Bulutcu 2005, Chauhan 2000, Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Davies 1997, D'Errico 1996, Herynkopf 1994, Miller 1998, Mossinger 2003, Rao 2000, Reid 1997, Seghaye 1996, Shimizu 2011). Six additional Level II studies were identified in the literature search. Three were fair quality (Sarupria 2013, Singh 2001, Vacharaska 2002) and three were poor quality (Coniff 1998, Ferreira 2010, Flaujac 2007).	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')*

Arnold 2006: favoured aprotinin for transfusion incidence but not volume. Faraoni 2012: favoured TXA for postoperative RBC, PLT and FFP transfusion volume and incidence, but in a sensitivity analysis excluding studies with potential bias, only RBC transfusion remained significant. Schouten 2009: favoured antifibrinolytics for plasma transfusion volume. Patients with tetralogy of Fallot: favoured aprotinin and EACA (low dose) for transfusion volume and incidence; Cyanotic patients with a right-to-left shunt: no significant difference in postop transfusion volume.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Arnold 2006: favoured aprotinin for transfusion incidence (*P* = NR); remained significant in several sensitivity and sub-analyses. Faraoni 2012: favoured TXA for postoperative transfusion volume and incidence (RBC *P* < 0.00001; platelets *P* < 0.0001; FFP *P* < 0.00001). Schouten 2009: favoured aprotinin TXA and EACA for RBC and plasma transfusion volume (*P* = NR).	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?)*

Subjects were infants and children undergoing cardiac surgery, mostly with CPB. Sarupria 2013 and Singh 2001 included patients with tetralogy of Fallot. Patients in Vacharaska 2002 had cyanotic CHD and a right-to-left shunt.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*

Studies were conducted in the USA, Turkey, India, Brazil, Thailand and France.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

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. While the included studies have not been formally retracted, care should be taken in the interpretation of this analysis.

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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.23 In paediatric patients undergoing cardiac surgery, antifibrinolytics compared with no antifibrinolytics reduce transfusion volume and incidence (B, B, C, B, C).

Key question(s): In neonatal and paediatric patients undergoing surgery for scoliosis, what is the effect of antifibrinolytics on transfusion volume and incidence?			Evidence table no: 3.4.26 Evidence matrix ref: D4.N
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	Volume	Incidence	
Includes two Level I studies (Schouten 2009 [good quality], Tzortzopoulou 2008 [good quality]) which identified 5 Level II studies (Cole 2003 [good], Florentino 2004 [good], Khoshhal 2003 [good], Neilipovitz 2001 [fair], Sethna 2005 [fair]). One additional Level II study (Thompson 2005 [poor quality]) was identified in the literature search.	A	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	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	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	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')*			
Tzortzopoulou 2008 reported significance favouring antifibrinolytics for total blood transfused but not transfusion incidence. Thompson 2005 reported significance favouring EACA for units of autologous blood transfused but not allogeneic transfusion incidence.	A	A	All studies consistent
	B	B	Most studies consistent and inconsistency can be explained
	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	Evidence is inconsistent
	NA	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
Tzortzopoulou 2008 reported no difference in transfusion incidence ($P = 0.28$) but found significant differences favouring antifibrinolytics ($P < 0.00001$), aprotinin ($P = 0.0015$) and TXA ($P = 0.0081$) for total blood transfused.	A	A	Very large
	B	B	Substantial
	C	C	Moderate (transfusion volume)
	D	D	Slight/Restricted
	NA	NA	Not applicable/no difference/underpowered (transfusion incidence)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*			
Subjects were paediatric patients undergoing surgery for scoliosis.	A	A	Evidence directly generalisable to target population
	B	B	Evidence directly generalisable to target population with some caveats
	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	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 healthcare context in terms of health services/delivery of care and cultural factors?)*			
Studies were conducted in Canada and the USA.	A	A	Evidence directly applicable to Australian healthcare context
	B	B	Evidence applicable to Australian healthcare context with few caveats

	C	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	D	Evidence not applicable to Australian healthcare 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
	Volume	Incidence	
1. Evidence base	B	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
2. Consistency	B	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	NA	(C) Moderate (NA) Underpowered
4. Generalisability	A	A	Evidence directly generalisable to target population
5. Applicability	B	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.24 In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume (B, B, C, A, B).

ES4.25 In paediatric patients undergoing surgery for scoliosis, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain (B, B, NA, A, B)

Key question(s): In neonatal and paediatric patients undergoing craniofacial surgery, what is the effect of antifibrinolytics on transfusion volume and incidence?		Evidence table no: 3.4.27 Evidence matrix ref: D4.O
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Song 2013 [fair quality]) which identified 2 Level II studies (Dadure 2011, Goobie 2011). Two additional Level II studies (Ahmed 2014 [fair quality], D'Errico 2003 [good quality]) were identified in the literature search.	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')*		
Song 2013 found a significant difference in RBC transfusion volume which favoured TXA. Ahmed 2014 reported no significant difference in postoperative RBC and/or PLT transfusion incidence but did for intraoperative RBC transfusion volume, favouring aprotinin. There was no significant difference in FFP transfusion incidence or volume.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Song 2013 favoured TXA for RBC transfusion volume (p=0.0004). Ahmed 2014 and D'Errico 2003 favoured aprotinin for intra– or post-operative RBC transfusion volume by weight (p=0.05).	A	Very large
	B	Substantial
	C	Moderate (volume)
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered (incidence)
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*		
Song 2013 included children undergoing craniosynostosis surgery, and subjects in Ahmed 2014 and D'Errico 2003 were paediatric patients scheduled for major reconstructive craniofacial surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA and France.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C / NA	Moderate / No difference/Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.26 In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics may reduce transfusion volume (B, B, C, B, B).

ES4.27 In paediatric patients undergoing craniofacial surgery, the effect of antifibrinolytics compared with no antifibrinolytics on transfusion incidence is uncertain (B, B, NA, B, B)

Key question(s): In neonatal and paediatric patients undergoing ENT surgery, what is the effect of antifibrinolytics on transfusion volume and incidence?		Evidence table no: 3.4.28 Evidence matrix ref: D4.P
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Ker 2013 [good quality]) which identified one Level II study (Albirmawy 2013).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Ker 2013 (Albirmawy 2013) reported no significant difference in transfusion incidence. Note: TXA was administered topically.	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?)*		
Subjects were children undergoing primary isolated adenoidectomy.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Egypt.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.28 In paediatric patients undergoing primary adenoidectomy, the effect of topical tranexamic acid compared with no tranexamic acid on transfusion incidence is uncertain (B, NA, NA, A, C).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of antifibrinolytics on thromboembolic events?		Evidence table no: 3.4.29 Evidence matrix ref: D4.Q
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Tzortzopoulos 2008) which identified one Level II study (Cole 2003 [good]), and an additional four Level II studies (Ahmed 2014 [fair quality], Flaujac 2007 [poor quality], Thompson [poor quality], Vacharaska 2002 [fair quality].	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')*		
All studies found no significant difference in postoperative DVT, thrombotic events or complications.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
One study (Cole 2003) reported thromboembolic events: three incidences of postoperative DVT occurred in the control group compared with no events in the antifibrinolytic group (not significant).	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?)*		
Subjects in Cole 2003 and Thompson 2005 were paediatric patients undergoing scoliosis surgery; subjects in Ahmed 2014 were paediatric patients undergoing major reconstructive craniofacial surgery; subjects in Flaujac 2007 were infants aged 4 days to 36 months undergoing primary corrective cardiac surgery with CPB; and subjects in Vacharaska 2002 were paediatric patients aged ≤14 years with cyanotic CHD and a right-to-left shunt undergoing open heart surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA, France and Thailand.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.29 In paediatric patients undergoing surgery, the effect of antifibrinolytics compared with no antifibrinolytics on thromboembolic events is uncertain (B, A, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing cardiac surgery, what is the effect of antifibrinolytics on bleeding events?		Evidence table no: 3.4.30 Evidence matrix ref: D4.R
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes two Level I studies (Arnold 2006 [good quality], Faraoni 2012 [good quality]) which identified 18 Level II studies (Boldt 1993a, Boldt 1993b, Boldt 1994, Bulutcu 2005, Chauhan 2000, Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Davies 1997, D'Errico 1996, Dietrich 1993, Gomar 1995, Levin 2000, Miller 1998, Mossinger 2003, Reid 1997, Shimizu 2011, Zonis 1996). An additional five Level II studies were identified in the literature search. Four were fair quality (Aggarwal 2012, Sarupria 2013, Singh 2001, Vacharaska 2002) and one was poor quality (Ferreira 2010).	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')*		
Arnold 2006 (aprotinin): no significant difference in chest tube drainage. Faraoni 2012 (TXA): no significant difference in 24 hr postop blood loss, but in sensitivity analyses excluding studies with potential bias, TXA favoured. Tetralogy of Fallot patients: favoured antifibrinolytics, low dose when available. Cyanotic patients with right-to-left shunt: no significant difference in postop bleeding / blood loss.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Arnold 2006: no significant difference in chest tube drainage (*P* = NR). Faraoni 2012: no significant difference in postop blood loss (*P* = 0.11); sensitivity analyses excluding Chauhan studies favoured TXA (*P* = NR); subgroup analysis of acyanotic patients no significant difference (*P* = 0.47). Tetralogy of Fallot patients: favoured antifibrinolytics or low dose EACA in three arm study; Cyanotic patients: no significant difference in postop blood loss.	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?)*		
Subjects were paediatric cardiac surgery patients. Patients in Aggarwal 2012, Sarupria 2013 and Singh 2001 had tetralogy of Fallot. Patients in Vacharaska 2002 had cyanotic CHD and a right-to-left shunt.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA, Canada, Turkey, India, Brazil and Thailand.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats

	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Analysis includes studies 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.

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	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
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	Underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.30 In paediatric patients undergoing cardiac surgery, the effect of antifibrinolytics compared with no antifibrinolytics on postoperative blood loss is uncertain (C, C, NA, B, C).

Key question(s): In neonatal and paediatric patients undergoing surgery for scoliosis, what is the effect of antifibrinolytics on bleeding events?		Evidence table no: 3.4.31 Evidence matrix ref: D4.S
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Tzortzopoulou 2008 [good quality]) which identified 5 Level II studies (Cole 2003 [good], Khoshhal 2003 [good], Neilipovitz 2001 [fair], Sethna 2005 [fair], Florentino 2004 [good]). Two additional Level II studies were identified in the literature search (Thompson 2005 [poor quality], Verma 2014 [good quality]).	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')*		
Tzortzopoulou 2008: favoured antifibrinolytics for total blood loss. This remained significant in sub-analyses of aprotinin, TXA and EACA. Thompson 2005: favoured EACA for peri– and post– but not intraoperative blood loss. Verma 2014: favoured antifibrinolytics (TXA or EACA) for total blood loss. In subgroup analyses results favoured TXA for total blood loss, drain volume and intraoperative blood loss with MA*P* <75 mmHg for TX but for EACA, only intraoperative blood loss was significant.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Tzortzopoulou 2008: favoured antifibrinolytics for total blood loss (*P* < 0.00001), aprotinin (*P* = 0.0014), TXA (*P* = 0.0042) and EACA (*P* = 0.015). Thompson 2005: favoured EACA for perioperative blood loss (*P* = 0.03), postop drainage (*P* < 0.05) but not intraoperative blood loss (*P* = NR) Verma 2014: favoured antifibrinolytics (TXA or EACA) for total blood loss (*P* = 0.019)	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?)*		
Subjects were scoliosis surgery patients. Patients in Thompson 2005 and Verma 2014 were adolescents with idiopathic scoliosis.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in Canada and the USA.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.31 In paediatric patients undergoing surgery for scoliosis, antifibrinolytics compared with no antifibrinolytics reduce blood loss (B, B, C, A, B).

Key question(s): In neonatal and paediatric patients undergoing craniofacial surgery, what is the effect of antifibrinolytics on bleeding events?		Evidence table no: 3.4.32 Evidence matrix ref: D4.T
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Song 2013 [fair quality]) which identified two Level II studies (Dadure 2011, Goobie 2011). Two additional Level II studies were identified in the literature search (Ahmed 2014 [fair quality], D'Errico 2003 [good quality]).	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')*		
Song 2013 favoured TXA for perioperative blood loss. Ahmed 2014 (aprotinin) and D'Errico 2003 (aprotinin) reported no significant differences in drain output, total intraoperative or postoperative bleeding, or estimated blood loss.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Song 2013: favoured TXA for perioperative blood loss (P = 0.0006). Ahmed 2014 (aprotinin): no significant difference in drain output. D'Errico 2003 (aprotinin): no significant difference in estimated blood loss.	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?)*		
Song 2013: children undergoing craniosynostosis surgery. Ahmed 2014 & D'Errico 2003: infants and children undergoing major reconstructive craniofacial surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the USA and France.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	A	All studies consistent
3. Clinical impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

EVIDENCE STATEMENT

ES4.32 In paediatric patients undergoing craniofacial surgery, antifibrinolytics compared with no antifibrinolytics reduce perioperative blood loss (B, A, C, B, C)

Key question(s): In neonatal and paediatric patients undergoing ENT surgery, what is the effect of antifibrinolytics on bleeding events?		Evidence table no: 3.4.33 Evidence matrix ref: D4.U
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Ker 2013 [good quality]) which identified 1 Level II study (Albirmawy 2013). Two additional Level II studies were identified in the literature search (Brum 2012 [good quality], Eldaba 2013 [fair quality]).	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')*		
Ker 2013 favoured topical TXA for perioperative blood loss. Eldaba 2013 favoured TXA for bleeding volume and moderate intraoperative bleeding, but no significant difference for mild or severe intraoperative bleeding. Brum 2012 (TXA) reported no significant differences in drain total intraoperative or postop bleeding.	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Ker 2013 (Albirmawy 2013): favoured topical TXA for blood loss (*P* = NR). Brum 2012 (TXA): no significant difference in intraoperative or postoperative bleeding. Eldaba 2013: favoured TXA for bleeding volume (*P* < 0.0001), and moderate intraoperative bleeding (p=0.0006 at 15mins; *P* < 0.0001 at 30mins)	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?)*		
Ker 2013 (Albirmawy 2013): children undergoing primary isolated adenoidectomy Brum 2012: children scheduled for adenotonsillectomy Eldaba 2013: children with chronic rhinosinusitis undergoing endoscopic sinus surgery.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
Studies were conducted in the Egypt and Brazil.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

ES4.33 In paediatric patients undergoing ENT surgery, antifibrinolytics compared with no antifibrinolytics may reduce perioperative blood loss (B, B, D, B, C).

Recombinant activated factor VII

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of rFVIIa on mortality?		Evidence table no: 3.4.35 Evidence matrix ref: D4.V
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Simpson 212) which included one Level II study (Ekert 2006).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There were no fatalities.	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?)*		
Subjects were infants aged <1 year with congenital heart disease scheduled for surgery with CPB.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

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 (B, NA, NA, A, A).

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).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of rFVIIa on transfusion volume and incidence?		Evidence table no: 3.4.36 Evidence matrix ref: D4.W
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Simpson 212) which included one Level II study (Ekert 2006).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
No significant difference in transfusion incidence	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?)*		
Subjects were infants aged <1 year with congenital heart disease scheduled for surgery with CPB.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable
5. Applicability	A	Evidence applicable to Australian healthcare context

EVIDENCE STATEMENT

ES4.36 In infants aged <1 year requiring cardiac surgery with cardiopulmonary bypass, the effect of prophylactic rFVIIa compared with no rFVIIa on transfusion incidence is uncertain (B, NA, NA, A, A).

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).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of rFVIIa on thromboembolic events?		Evidence table no: 3.4.37 Evidence matrix ref: D4.X
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study of good quality (Simpson 212) which included one Level II study (Ekert 2006).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported no thrombotic or embolic events in either group.	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?)*		
Subjects were infants aged <1 year with congenital heart disease scheduled for surgery with CPB.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Australia.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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)*

Note: the study excluded infants at baseline with known thrombotic disorders, preoperative coagulopathy or prior treatment with rFVIIa or antifibrinolytics, which may explain why no thromboembolic events were observed.

The CRG also considered R22 and PP20 in *Patient Blood Management Module 2 – Perioperative* when making recommendations and practice points. Concerns remain about its safety profile, particularly in relation to thrombotic events.

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	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
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context

EVIDENCE STATEMENT

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 (B, NA, NA, A, A).

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).

Miniaturised cardiopulmonary bypass systems

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of miniaturised CPB systems on mortality?		Evidence table no: 3.4.39 Evidence matrix ref: D4.Y
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Mozol 2008).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study reported no mortality.	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?)*		
Subjects were paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Poland.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats

	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	NA	No difference / underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, NA, A, C).

ES4.42 In paediatric patients aged >1 year undergoing cardiac surgery with cardiopulmonary bypass, the effect of a miniaturised CPB system compared with a standard-sized system on mortality is unknown (NA, NA, NA, NA, NA).

Key question(s): In neonatal and paediatric patients undergoing surgery, what is the effect of miniaturised CPB systems on transfusion volume and incidence?		Evidence table no: 3.4.40 Evidence matrix ref: D4.Z
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study of poor quality (Mozol 2008).	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')*		
NA	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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The study found a statistically significant difference in perioperative RBC transfusion volume (p=0.001), plasma transfusion volume (p=0.01) and total blood products transfused (p=0.0007) which favoured a miniaturised CBP system. No significant difference was observed for albumin transfused.	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?)*		
Subjects were paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support.	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 healthcare context in terms of health services/delivery of care and cultural factors?)*		
The study was conducted in Poland.	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian healthcare context with some caveats

EVIDENCE STATEMENT

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 (D, NA, C, A, C).

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).

Recommendations – Question 4

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* In neonates with haemolytic disease of the fetus and newborn, the *routine* use of IVIg is not recommended.	GRADE OF RECOMMENDATION GRADE B	RELEVANT ESF(S) D4.C, D4. E
Indicate any dissenting opinions NONE		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
The effect on incidence of exchange transfusion and mortality is uncertain. High quality trials with low to moderate risk of bias did not show evidence of benefit.		

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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* In paediatric patients undergoing surgery, measures to prevent hypothermia should be used.[a] [a] *See R12 in Patient Blood Management Guidelines: Module 2 – Perioperative.*	GRADE OF RECOMMENDATION GRADE B	RELEVANT ESF(S) D4.E, D4.F

Indicate any dissenting opinions

NONE. Members acknowledged that the evidence for prevention of hypothermia in the adult population is strong (Grade A) and agreed to extrapolate this for the paediatric population when drafting recommendations. See *Patient Blood Management Guidelines: Module 2 – Perioperative Technical report volume 2b* – Intervention 6 pp241–269.

UNRESOLVED ISSUES

If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.

Evidence is based on the adult literature. Generalisability has been downgraded, but the adult data can be sensibility applied.

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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* 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.*	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D4.L, D4.M, D4.Q, D4.R
Indicate any dissenting opinions NONE. Members acknowledged that the evidence for antifibrinolytics in the adult population is moderate to strong and agreed to extrapolate this for the paediatric population when drafting recommendations. See *Patient Blood Management Guidelines: Module 2 – Perioperative Technical report volume 2b* – Intervention 8 pp307–442.		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
TXA is approved for in this context in Australia. Aprotinin is licensed in Australia but it's used in this context is considered off-label. EACA is not licensed for use in Australia. Concerns about the safety of antifibrinolytics in paediatric patients remain unresolved.		

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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* 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.*	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D4.L, D4.N, D4.Q, D4.S
Indicate any dissenting opinions NONE. Members acknowledged that the evidence for antifibrinolytics in the adult population is moderate to strong and agreed to extrapolate this for the paediatric population when drafting recommendations. See *Patient Blood Management Guidelines: Module 2 – Perioperative Technical report volume 2b* – Intervention 8 pp307–442.		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
TXA is approved for in this context in Australia. Aprotinin is licensed in Australia but it's used in this context is considered off-label. EACA is not licensed for use in Australia. Concerns about the safety of antifibrinolytics in paediatric patients remain unresolved.		
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? Use of antifibrinolytics in scoliosis surgery could increase, but significant cost differences not anticipated.	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	

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* 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.*	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D4.L, D4.O, D4.Q, D4.T
Indicate any dissenting opinions NONE. Members acknowledged that the evidence for antifibrinolytics in the adult population is moderate to strong and agreed to extrapolate this for the paediatric population when drafting recommendations. See *Patient Blood Management Guidelines: Module 2 – Perioperative Technical report volume 2b* – Intervention 8 pp307–442.		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.* TXA is approved for in this context in Australia. Aprotinin is licensed in Australia but it's used in this context is considered off-label. EACA is not licensed for use in Australia. Concerns about the safety of antifibrinolytics in paediatric patients remain unresolved.		

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? Use of antifibrinolytics in this context could increase, but significant cost differences not anticipated.	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

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.* In paediatric patients undergoing cardiac surgery with cardiopulmonary bypass, the *routine* use of rFVIIa is not recommended.	GRADE OF RECOMMENDATION GRADE C	RELEVANT ESF(S) D4.V, D4.W, D4.X
Indicate any dissenting opinions None. Members acknowledged that the evidence for rFVIIa (prophylaxis or treatment) in the adult population is moderate and agreed to consider this for the paediatric population when drafting recommendations.		
UNRESOLVED ISSUES *If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.*		
Concerns about the safety profile of rFVIIa, particularly in relation to thrombotic events, remain unresolved. See *Patient Blood Management Guidelines: Module 2 – Perioperative Technical report volume 2a* – Question 7 pp312–323.		
IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*		
Will this recommendation result in changes in usual care?	YES	
	NO	
Are there any resource implications associated with implementing this recommendation?	YES	
	NO	
Will the implementation of this recommendation require changes in the way care is currently organised?	YES	
	NO	
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES	
	NO	

Appendix E Quality analyses

One aspect of the 'strength of the evidence' domain in the NHMRC Dimensions of Evidence is study quality. The full quality checklist is based on the quality assessment questions that are included in the NHMRC toolkit – *How to use the evidence: assessment and application of scientific evidence* (NHMRC, 2000). 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.

Each eligible study was assessed against each quality criterion as Y (yes), N (no), NR (not reported) or NA (not applicable). Where applicable, clarification of the criteria or justification for a downgrading of study quality, were provided as comments. Based on the checklist of quality criteria, studies were ultimately graded as good, fair or poor.

As not all quality assessment criteria are applicable to all study types, separate checklists have been applied for systematic reviews, RCTs and cohort studies.

E1 Quality analysis – Question 1

Level I evidence

Study type:				Systematic review	
Citation:				Bassler D, Weitz M, Bialkowski A, Poets CF (2008) Restrictive Versus Liberal Red Blood Cell Transfusion Strategies for Preterm Infants: A Systematic Review of Randomized Controlled Trials. Current Pediatric Reviews, 4: 143-50.	
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:				The review authors planned to perform meta-analyses using a random effects model but pooling of data wasn't possible due to significant methodological and clinical heterogeneity in regards to study design, patient characteristics, transfusion strategies, and reported outcomes.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: The review authors rated the overall quality of both included RCTs as adequate (fair).	

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.

Study type:				Systematic review	
Citation:				Carson JL, Carless PA & Hebert PC (2012) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review). Cochrane Database of Systematic Reviews, Issue 4 CD002042.	
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:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: 19 studies were included, of which one was in a paediatric population (Lacroix 2007). This was an RCT of with an overall low risk of bias, with unclear risk attributed to random sequence generation (no information) and blinding (clinical staff and parents of patients aware of allocation, but statisticians and safety committee members were not).	

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.

Study type:				Systematic review	
Citation:				Cherry MG, Greenhalgh J, Osipenko L et al. (2012) The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technology Assessment, 16(43): 1-129.	
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:				The review authors planned to pool data in the included RCTs using a standard meta-analytic approach, but considered the populations to be too heterogeneous.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: The review authors rated the overall quality of both included RCTs as adequate (fair). No quality assessment was performed for the included cohort study.	

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.

Study type:				Systematic review	
Citation:				Desjardins P, Turgeon AF, Tremblay M, Lauzier F, Zarychanski R, Boutin A, Moore L, McIntyre LA, English SW, Rigamonti A Lacroix J, Fergusson DA. (2012) Hemoglobin levels and transfusion in neurocritically ill patients: a systematic review of comparative studies. Critical Care 16:R54	
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:				Search terms were reported in an additional file and were able to be retrieved.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Six studies were included (3 RCTs and 3 retrospective cohort studies), of which one RCT (Lacroix 2007) was in the paediatric population. Subjects in this study had various neurocritical conditions and was judged by review authors as having a low risk of bias, despite lack of blinding. This was deemed acceptable due to the nature of the intervention.	

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.

Study type:				Systematic review of RCTs	
Citation:				Ibrahim M, Ho Kah Ying S, Cheo Lian Y (2014) Restrictive versus liberal red blood cell transfusion thresholds in very low birth weight infants: A systematic review and meta-analysis. Journal of Paediatrics and Child Health, 50: 122-30.	
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:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Three RCTs were included and were rated by the review authors as having sufficient (fair) methodological quality. All studies performed randomisation and had allocation concealment. No studies reported blinding of the caregiver or principle investigator; however, this was reported for the patients, outcome assessors and data analysts. Intention-to-treat analysis was conducted in all studies.	

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.

Study type:				Systematic review of cohort and case-control studies	
Citation:				Kirpalani H, Zupancic JAF (2012) Do Transfusions Cause Necrotizing Enterocolitis? The Complementary Role of Randomized Trials and Observational Studies. Seminars in Perinatology, 36: 269-76.	
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:				Results from the current review were compared with pooled data from three RCTs as reported in a Cochrane review by Whyte (2011). Inclusion criteria were clearly reported but exclusion criteria were not.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: 6 cohort and 4 case-control studies. The review authors rated all six cohort studies as having an overall low risk of bias, but with a medium risk of bias on confidence the outcome of interest did not exist at study start. The case-control studies were all rated as having an overall low risk of bias. Still, the major potential for bias in all studies was in clear identification of absence of preclinical NEC before transfusion. Study validity concerns were also raised for case-control studies regarding assessment of outcome and blinding for retrospective chart reviews, leading to possible over-diagnosis of NEC.	

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.

Study type:				Systematic review	
Citation:				Meremikwu MM, Smith HJ (2010) Blood transfusion for treating malarial anaemia (Review). Cochrane Database of Systematic Reviews, Issue 4 CD001475.	
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:				No specific exclusion criteria were initially noted for the review; however, studies were then excluded on the basis of geographical location (outside malarious zones). “Very severe” cases of malarial anaemia were excluded from both RCTs.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Two RCTs were included; both rated by review authors as having an unclear risk of bias. For both studies, adequacy of allocation concealment could not be determined and investigators were not blinded to treatment allocation. Neither study was analysed according to the intention-to-treat principle.	

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.

Study type:				Systematic review of observational studies.	
Citation:				Mohamed A, Shah PS (2012) Transfusion Associated Necrotizing Enterocolitis: A Meta-analysis of Observational Data. Paediatrics, 129: 529-40.	
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:					
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Twelve studies were included (11 case controls, 1 retrospective cohort study). The review authors rated four studies as having a moderate risk of bias (score 6 out of 10), and eight studies with a low risk of bias (score 8 out of 10). The majority of bias stemmed from selection of control subjects, and lack of adjustment for confounders. There was some dissimilarity in patient baseline characteristics.	

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.

Study type:				Systematic review	
Citation:				Venkatesh V, Khan R, Curley A, Hopewell S, Doree C, Stanworth S. (2012) The safety and efficacy of red cell transfusions in neonates: a systematic review of randomized controlled trials. British Journal of Haematology, 158: 370-85.	
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:				Meta-analysis could only be performed for a small number of trials due to clinical diversity, the small number of studies in sub-categories, and lack of data on clinical outcomes in many trials.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: 27 RCTs were included, of which seven were relevant to this overview (Kirpalani 2006, Chen 2009, Bell 2005, Brooks 1999, Meyer 1993, Mukhopadhyay 2004, Wong 2005). The review authors stated that the overall quality of reporting was poor, with only three studies having good methodological practices in all areas examined (including Bell 2005 and Kirpalani 2006). Blinding varied across studies with 18 studies reporting no blinding, and nine studies reporting blinding of participants and/or trial personnel.	

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.

Study type:				Systematic review	
Citation:				Wang WC and Dwan K (2013) Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. Cochrane Database Systematic Reviews, Issue 11 CD003146.	
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:				Adequate search strategies and inclusion criteria. No specific exclusion criteria noted. Some baseline demographics included. Although the authors intended to include persons of all ages with sickle cell disease, the included studies were all in children. The literature search also identified three ongoing trials.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Adams 1998 (STOP) and Adams 2005 (STOP 2). Both studies used adequate randomisation methods but neither concealed patient allocations. STOP did not blind subjects or investigators. STOP 2 did not provide information on blinding. An intention-to-treat analysis was utilised in STOP 1, but was not reported in STOP 2. In STOP 2, the reasons for patient withdrawals were not provided. Inclusion criteria were reported in both trials. No meta-analysis was performed due to heterogeneity between patient populations (all patients in STOP 2 had been treated with chronic transfusion for a minimum of 30 months).	

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.

Study type:				Systematic review	
Citation:				Whyte, R. and Kirpalani, H. (2011) Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database Syst Rev (11) CD000512-	
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:				Quasi-randomised trials were included. While the haemoglobin thresholds for restrictive transfusion were similar among the included studies, this was not the case for liberal transfusion thresholds. Note: The review authors reported adding several outcomes after the review was conducted. These were directly relevant to the outcomes being targeted.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Bell 2005, Blank 1984, Chen 2009, Connelly 1999, PINT 2006. Most trials had a low risk of allocation bias but none attempted to blind participants. The authors noted that the risk of measurement or judgement bias was minimal given the nature of outcomes.	

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.

Study type:				Systematic review	
Citation:				Wilkinson, Kirstin L., Brunskill, Susan J., Doree, Carolyn, Trivella, Marialena, Gill, Ravi, and Murphy, Michael F. (2014) Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease. Cochrane Database Syst.Rev.	
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:				Due to the diverse patient populations included in the individual studies, no meta-analyses were conducted and thus, a test for heterogeneity was not required.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Eleven RCTs were included. Two (Cholette 2011; Willems 2010) were relevant to this review. Cholette 2011 had an unclear risk of bias relating to random sequence generation (insufficient information), allocation concealment (not reported), and blinding of outcome assessment (not reported). The review authors also noted a high risk of performance bias due to staff and patient families being aware of transfusion assignment. Other domains were assessed as low risk. Willems 2010 was assessed as having a low risk of bias, with the exception of blinding (performance bias) where clinicians and carers were aware of treatment allocation.	

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.

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Adams RJ, Brambilla D. (2005) Discontinuing Prophylactic Transfusions Used to Prevent Stroke in Sickle Cell Disease. The New England Journal of Medicine, 353: 2769-78.	
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:				Patients were stratified according to absence/presence of ischaemic lesions. Standardised TCD and MRI/MRA protocols were interpreted blindly, and primary endpoint (stroke) was assessed blind to treatment assignment. Subjects could not be blinded to treatment group due to the nature of the intervention. Some loss to follow-up was reported, but it was unclear whether this was included in the analysis. Note: the design paper which included study methodology was published separately.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Adams RJ, McKie VC, Hsu L et al. (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. The New England Journal of Medicine, 339(1): 5-11.	
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:				Subjects could not be blinded to treatment group due to the nature of the intervention but investigators and outcome assessors were blind to treatment assignment. Loss to follow-up was reported. Patient characteristics were similar between treatment groups with the exception of baseline haemoglobin and haematocrit values being lower in the transfusion group. This trial is also known as the STOP trial. Due to the high rate of stroke in the standard care (no transfusion) group, and the significant effect of transfusion found at the second interim analysis, the data safety and monitoring board recommended that the trial be stopped 16 months prematurely. Note: the design paper which included study methodology was published separately.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Bell EF, Strauss RG, Widness JA et al. (2005) Randomized Trial of Liberal Versus Restrictive Guidelines for Red Blood Cell Transfusion in Preterm Infants. Pediatrics, 115(6): 1685-91.	
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:				Methods of randomisation and allocation concealment were reported. Blinding was not reported. It is assumed that the trial was not blinded due to differences in procedures between groups. Loss to follow-up was reported. Patient baseline characteristics were similar between groups, although males were more predominant in the restrictive transfusion group (61% vs 41%, p=0.049). Some protocol violations occurred.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Brooks SE, Marcus DM, Gillis D et al. (1999) The Effect of Blood Transfusion Protocol on Retinopathy of Prematurity: A Prospective, Randomized Study. Pediatrics, 104(3): 514-518.	
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:				Examiners were masked to treatment assignment. No mention of whether subjects were; however being premature infants, this would be unlikely to introduce bias or effect outcome variables. Patient characteristics were similar at baseline and during the study period. Loss to follow-up was reported (16 infants in the restrictive group and 18 infants in the liberal group completed the full 6-week study period (p=0.77).	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Chen H, Tseng H, Lu C et al. (2009) Effect of Blood Transfusions on the Outcome of Very Low Body Weight Preterm Infants under Two Different Transfusion Criteria. Pediatric Neonatology, 50(3): 110-116.	
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:				Blinding was not reported, and it is assumed that the trial was not blinded due to differences in procedures between groups. Three cases were excluded from analysis (2 restrictive / 1 liberal). The power analysis of 80% required 17 infants in each group in order to detect differences in number of transfusions; however, only 16 infants completed the full duration of the liberal study arm.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Cholette JM, Rubenstein JS, Alfieris GM et al. (2011) Children with single-ventricle physiology do not benefit from higher haemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trail of a restrictive versus liberal red-cell transfusion strategy. Pediatric Critical Care Medicine, 12(1): 39-45.	
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:				Method of randomisation not reported but blocking was used to ensure equal numbers of subjects having BDG or Fontan procedures within groups. The cardiac surgeon, anaesthesiologist, perfusionist, operating room staff and data safety monitor were blinded to study assignment; but clinical staff and patient families were not. No subjects dropped out of the study and none were lost to follow-up. One subject from each group was unable to have surgery and was therefore excluded from analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Debaun MR, Gordon M, Mckinstry RC, Noetzel MJ, White DA, Sarnaik SA. (2014) Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. New Engl J Med 2014; 371(8):699-710.	
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:				Participants were randomised by a statistical data coordinating centre with the use of a permuted block design and stratified by site, age and sex. No attempt at allocation concealment is reported. The study was a single blinded trial. Baseline patient characteristics and demographics were similar except for reticulocyte count (P = 0.002). Loss to follow-up was documented. It is not reported if outcome was assessed blind to treatment allocation. This was a multicentre study but results are only provided collectively, rather than by site. No subgroup analyses were reported.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Kirpalani H, Whyte RK, Andersen C et al. (2006) The Premature Infants In Need of Transfusion (PINT) Study: A randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. Journal of Pediatrics 149: 301-7.	
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:				Randomisation was reported and achieved via computer-generated sequencing. No attempt was made to blind clinicians or caregivers as concealment of haemoglobin levels were considered unethical and impractical. Morbidity outcomes were assessed blind to treatment allocation. There was no reported loss to follow and primary outcome data was available for all 451 infants.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Lacroix J, Hebert PC, Hutchison JS et al. (2007) Transfusion Strategies for Patients in Pediatric Intensive Care Units. The New England Journal of Medicine, 356(16): 1609-19.	
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:				Clinical staff and parents were aware of the treatment assignment, but the statistician and members of the data and safety monitoring committee were not. Loss to follow-up (2%) was reported in 11 patients due to protocol violation (missing data (n=3) and invalidated data (n=8)); however, the authors report this was low enough to prevent any bias attributable to sample size slippage. Site specific data was only reported for primary outcomes.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial (follow-up study)	
Citation:				McCoy TE, Conrad AL, Richman LC et al. (2011) Neurocognitive profiles of preterm infants randomly assigned to lower or higher haematocrit thresholds for transfusion. Child Neuropsychology, 17(4): 347-67.	
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:				This is a follow-up study of the RCT by Bell (2005). Authors referred readers to the original RCT for information on study design, including methods regarding randomisation and allocation concealment. Almost 50% lost to follow-up. Post-hoc analyses were conducted to determine whether children who participated in the current study were less sick than children who did not participate, and whether differences existed between treatment groups. No statistically significant differences were observed. In the current study, males and females were unevenly distributed between treatment groups (restrictive group: 19 boys, 4 girls; liberal group: 12 boys, 21 girls). This was discussed with authors noting the potential interaction between sex and brain development. Subjects were aware of their treatment group, the intervention having occurred 8-15 years prior. Outcome assessors were blind to treatment group.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Olupot-Olupot , P, Engoru C, Thompson J, Nteziyaremye J, Chebet M, Ssenyondo T. (2014) Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anemia. BMC Med 2014; 12(1).	
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:				Randomisation was stratified by clinical centre with the treatment allocation kept in consecutively numbered, sealed, opaque envelopes. The randomisation list and envelopes were not available to investigators. It is not reported if subjects were blinded to treatment allocation. Most baseline characteristics between the two groups were similar but there were a few moderate differences. Loss to follow up was reported (11 did not attend the 28-day follow-up but survival status was confirmed for 10 of these children and the remaining child died four days after hospital discharge). The Endpoint Review Committee consisting of independent clinicians assessed whether fatal and non-fatal events were related to transfusion. It is not stated whether all outcomes were assessed in this manner (blinded to treatment allocation). The results are presented collectively, rather than by site. No subgroup analyses were reported.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial (follow-up study)	
Citation:				Pegelow CH, Wang W, Granger S et al. (2001) Silent Infarcts in Children With Sickle Cell Anemia and Abnormal Cerebral Artery Velocity. Archives of Neurology, 58: 2017-21.	
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:				Study referred to the STOP trial (Adams 1998) for details of subjects. Blinding wasn't reported, but assumed not blinded due to differences in procedures between groups. Baseline characteristics were provided for MRI findings prior to randomisation. Patients that had a silent infarct at baseline were significantly older than those who had no abnormalities (p=0.003). However, analyses were unaffected when age was included as a variable. Intention-to-treat analysis was not used since the question being addressed was secondary to those in the STOP trials. Data was difficult to interpret.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Rouette, J., Trottier, H., Ducruet, T., Beaunoyer, M., Lacroix, J., and Tucci, M. (2010) Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: A randomized clinical trial. Ann.Surg. 251 (3) 421-427.	
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:				Details of randomisation and allocation concealment were not reported in the current paper – readers were referred to the primary study (Lacroix 2007) for more detailed information regarding methodology. Blinding of subjects and clinical staff was not feasible due to the visible nature of the intervention; however, the statistician and members of the data and safety monitoring committee were unaware of group assignments. There was no loss to follow-up. Site specific results are only given for the primary outcome.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Whyte, R. K., Kirpalani, H., Asztalos, E. V., Andersen, C., Blajchman, M., Heddle, N., Lacorte, M., Robertson, C. M. T., Clarke, M. C., Vincer, M. J., Doyle, L. W., and Roberts, R. S. (2009) Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 123 (1) 207-213.	
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:				Details of randomisation and allocation concealment were not reported in the current study – readers referred to the primary study (Kirpalani 2006 [PINT]) for more detailed information. Blinding of intervention not possible due to treatment effects being visible in Hb levels. However the authors report that evaluators to follow-up were blinded to treatment allocation.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Willems, A., Harrington, K., Lacroix, J., Biarent, D., Joffe, A. R., Wensley, D., Ducruet, T., Hebert, P. C., and Tucci, M. (2010) Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis. Crit.Care Med. 38 (2) 649-656.	
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:				Readers were referred to the primary study (Lacroix 2007) for details of randomisation and allocation concealment. The authors noted potential for site-related bias due to only those centres whose cardiac surgeons and intensivists who were willing to accept a lower Hb threshold included their patients in the study.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Level III evidence

Study type:				Cohort study	
Citation:				Acker SN, Partrick DA, Ross JT, Nadlonek NA, Bronsert M, Bensard DD. Blood component transfusion increases the risk of death in children with traumatic brain injury. J Trauma Acute Care Surg 2014; 76(4):1082-8.	
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:				Demographic were provided for the 'transfusion' and 'no transfusion' groups. There were significant differences between the groups, such as age, ISS (Injury Severity Score) and GCS (Glasgow Coma Scale). However, it should be noted that this 'transfusion' group includes participants who received RBC, fresh frozen plasma, platelets or cryoprecipitate. Demographic information is not provided to compare the 'RBC transfusion' and 'no RBC transfusion' groups. It is not reported if all eligible participants agreed to take part in the study. Patients with missing predictor variables were excluded. No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. Demographic characteristics are controlled for in the multivariate model, which included GCS score, age category, gender and ISS. It is not reported if outcome assessment was blinded to exposure status.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Baer VL, Lambert DK, Henry E, Snow GL, Butler A, Christensen RD (2011) Among very-low-birth-weight neonates is red blood cell transfusion an independent risk factor for subsequently developing a severe intraventricular haemorrhage? Transfusion, 51: 1170-8.	
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:				Exclusion criteria not reported. The study retrospectively reviewed electronic data to include participants. Only participants with repeat ultrasounds were included, but no comparison with those who did not meet this inclusion criterion was made. Not clear if all potential confounders included.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Chiravuri SD, Riegger LQ, Christensen R, Butler RR, Malviya S, Tait AR, Voepel-Lewis T (2011) Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study. Pediatric Anesthesia, 21: 880-6.	
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:				Patients were enrolled retrospectively from hospital databases. Eight patients died intraoperatively or immediately postoperatively and were therefore unable to have laboratory measures taken. These patients were excluded from analysis. Research assistants blinded to the purpose of the study recorded all data.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Retrospective cohort study	
Citation:				Demirel G, Celik IH, Aksoy HT, Erdeve O, Oguz SS, Uras N & Dilmen U (2012) Transfusion-associated necrotising enterocolitis in very low birth weight premature infants. Transfusion Medicine, 22: 332-7.	
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:				Retrospective design, therefore loss to follow-up not possible.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				dos Santos AMN, Guinsburg R, de Almedia MFB et al (2011) Red Blood Cell Transfusions are Independently Associated with Intra-Hospital Mortality in Very Low Birth Weight Preterm Infants. The Journal of Pediatrics, 159(3): 371-6.	
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:				Outcome was mortality. Retrospective nature of study meant that loss to follow-up not possible. A limitation was that patients in the transfused group were sicker than those who were not transfused.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				Elabaid MT, Harsono M, Talati AJ, Dhanireddy R (2013) Effect of birth weight on the association between necrotising enterocolitis and red blood cell transfusions in ≤1500 g infants. BMJ Open, 3: 1-7.	
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:				Final analysed numbers were less than 3060 as some non-NEC cases were lost due to incomplete data in the multivariable analyses (n=13). The authors note the limitations of the retrospective nature of the study and the potential for overlapping clinical signs of NEC and anaemia. Limited clinical data may have been available i.e. anaemia tests, steroid use, fresh versus stored blood transfusions, total feeds and breastfeeding that may influence NEC.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Cross-sectional case-control study	
Citation:				Feghhi M, Altayeb SMH, Haghi F et al (2012) Incidence of Retinopathy of Prematurity and Risk Factors in the South-Western Region of Iran. Middle East African Journal of Ophthalmology, 19(1): 101-6.	
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:				Limitations of the study were poor patient follow-up, lack of comprehensive records, and the high mortality rate in infants under 1000 g and 28 weeks gestational age (possibly due to the inadequate nursery and healthcare system for premature infants), that resulted in a low rate of cases in these populations. The authors also advised that the recommended age for initial ophthalmic examination is 4 weeks postnatal age or 31 weeks postmenstrual age, but that they examined infants at 6 weeks after birth, which may have led to a higher than expected incidence of ROP. The ROP group underwent statistically longer periods of oxygen therapy compared with the non-ROP group (p=0.001), which should be considered when interpreting results.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Prospective cohort study	
Citation:				Fortes Filho JB, Fortes BGB, Tartarella MB, Procianoy RS (2013) Incidence and Main Risk Factors for Severe Retinopathy of Prematurity in Infants Weighing Less Than 1000 Grams in Brazil. Journal of Tropical Pediatrics, 59(6): 502-6.	
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:				Patients who died during hospitalisation before the first ophthalmological examination were excluded from analysis. There was no loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Cohort study	
Citation:				Fremgen HE, Bratton SL, Metzger RR, Barnhart DC. 2014. Pediatric liver lacerations and intensive care: Evaluation of ICU triage strategies. Pediatr Crit Care Med 2014; 15(4):e183-e191.	
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:				Patient demographics, such as age, gender and weight, are only compared between the group admitted to the ICU and the group admitted to the inpatient ward. Similar demographics comparing the transfused and non-transfused groups within the ICU are not presented in the article but there was a significant difference in ISS (Injury Severity Score) and GCS (Glasgow Coma Scale) between these groups. It is not reported if all eligible participants agreed to take part in the study. Two patients died prior to admission and were excluded from the analysis. No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. The study does not adequately control for potential confounders in the data analysis. It is not reported if outcome assessment was blinded to exposure status.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Prospective cohort study	
Citation:				Hakeem Abdel A, Mohamed CG, Othman MF (2012) Retinopathy of Prematurity: A Study of Incidence and Risk Factors in NICU of Al-Minya University Hospital in Egypt. Journal of Clinical Neonatology, 1(2): 76-81.	
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:				Neonates who died before the first ophthalmological examination (n=24), or with congenital anomalies (n=26) were excluded. There was no loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Cohort study	
Citation:				Hassan NE, DeCou JM, Reischman D, Nickoles TA, Gleason E, Ropele DL. 2014. RBC transfusions in children requiring intensive care admission after traumatic injury. Pediatr Crit Care Med.	
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:				The two groups were comparable with regard to age, sex, race and mechanism of injury. However, patients receiving RBC transfusions had significantly greater ISS (Injury Severity Score), PICU length of stay, hospital length of stay and mortality. It is not reported if all eligible participants agreed to take part in the study. Massive transfusion and burn patients were excluded and patients who received "blood products" were separated from those receiving "RBC transfusions". No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. Multivariate logistic regression analysis was used to test multiple risk factors, such as age, ISS (Injury Severity Score), GCS (Glasgow Coma Scale). It is not reported if outcome assessment was blinded to exposure status.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective longitudinal study	
Citation:				Jaime-Perez JC, Colunga-Pedraza PR, Gomez-Almaguer D (2011) Is the Number of Blood Products Transfused Associated With Lower Survival in Children With Acute Lymphoblastic Leukemia? Pediatric Blood Cancer, 57: 217-23.	
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:				Outcome was mortality/survival. Retrospective design, therefore loss to follow-up not possible. Outliers (≥2SD) were excluded from analysis for relapse (outcome). Median overall and event-free survival were not reached because death (n=20, 18.5%) or relapse (n=32, 29.6%) of ≥50% of the group did not occur.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Prospective cohort study	
Citation:				Kabatas EU, Beken S, Aydin B, Dilli D, Zenciroglu A, Okumus N (2013) The Risk Factors for Retinopathy of Prematurity and Need for Laser Photocoagulation: A Single Center Experience. GMJ, 24: 108-12.	
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:				All fundus examinations were performed by the same ophthalmologist (first author). Loss to follow-up was not explicitly stated, although it appeared all infants were included in the final analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Retrospective cohort study	
Citation:				Kneyber MCJ, Grotenhuis F, Berger RFM et al (2013) Transfusion of Leukocyte-Depleted RBCs Is Independently Associated With Increased Morbidity After Pediatric Cardiac Surgery, Paediatric Critical Care Medicine, 14(3): 298-305.	
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:				Outcome of interest was mortality. Data for final analyses were available for all 335 patients who were eligible. Non-survivors and patients who were not ventilated were censored for statistical analysis.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Retrospective cohort study	
Citation:				Kneyber MCJ, Hersi MI, Twisk JR, Markhorst DG, Plotz FB. (2007) Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med, 33: 1414-1422.	
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:					
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Retrospective cohort study	
Citation:				Li ML, Hsu SM, Chang YS et al (2013) Retinopathy of prematurity in southern Taiwan: A 10-year tertiary medical center study. Journal of the Formosan Medical Association, 112: 445-53.	
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:				Patients were enrolled in the neonatal period. Study was a retrospective review of medical records. Infants were excluded who failed to survive longer than 28 days for the first ROP screening, who did not live for 6 months postnatally to complete ROP screening, and who had congenital diseases such as chromosomal anomaly. Fundus examinations were conducted by three of the authors. Blinding to outcome assessment was not reported, and potential for bias should be considered. Retrospective nature of study meant loss to follow-up not possible.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				Nacoti M, Cassaniga S, Lorusso F et al (2012) The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. Pediatric Transplantation, 16: 357-66.	
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:				Outcomes were mortality and graft survival. Seven hepato-biliary surgeons performed all the liver transplants with two involved in each procedure. Fifteen anaesthesiologists were involved throughout the study period. Transfusion policy was based on clinical assessment. Missing data were <2%. 39 patients stopped follow-up within one year.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				Paul DA, Mackley A, Novitsky A, Zhao Y, Brooks A, Locke RG (2011) Increased Odds of Necrotizing Enterocolitis After Transfusion of Red Blood Cells in Premature Infants. Pediatrics, 127(4): 635-41.	
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:				The study was retrospective. The authors note that as a limitation that subtle signs of NEC may have been evident before 48 hours but did not manifest until after this period. NEC may also have been evident but not diagnosed prior to transfusion. 2311 infants were enrolled in the study, but only 2310 were included in the final analyses. Not reported why one patient excluded.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Retrospective cohort study	
Citation:				Redlin M, Kukucka M, Boettcher W et al (2013) Blood transfusion determines postoperative morbidity in pediatric cardiac surgery applying a comprehensive blood-sparing approach. The Journal of Thoracic and Cardiovascular Surgery, 146(3): 537-42.	
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:				Outcomes were length of mechanical ventilation and ICU stay, and mortality. Patients were enrolled by retrospective chart review; loss to follow up not possible. Patients were recruited from another study by Redlin et al (2012). More detailed methodology described in original paper. In hospital mortality was too low for detailed statistical analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Singh R, Visintainer PF, Frantz ID et al (2011) Association of necrotizing enterocolitis with anemia and packed red blood cell transfusions in preterm infants.	
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:				Retrospective review of charts to enrol infants. The authors state case charts were reviewed to confirm diagnosis of NEC but do not state by whom and whether reviewers were aware of NEC diagnosis during case ascertainment.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Stritzke AI, Smyth J, Synnes A, Lee SK, Shah PS (2013) Transfusion-associated necrotising enterocolitis in neonates. Arch Dis Child Fetal Neonatal Ed, 98: F10-F14	
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:				Retrospective chart review. Some of the main potential confounders were identified but were not controlled for in the analysis: data were not collected for feeding practices, including volume and type of feed, which varied between centres. Data about the blood, the donors and the exact indications and the degree of urgency of the need for transfusion may have varied widely between centres and were also not available. The threshold for transfusion also varied between centres, and the practice of holding feeds during transfusion varied both between and within centres. Storage of RBC ranged from 1-42 days, which could significantly impact outcomes.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Wan-Huen P, Bateman D, Shapiro DM, Parravicini E (2013) Packed red blood cell transfusion is an independent risk factor for necrotizing enterocolitis in premature infants. Journal of Perinatology, 33: 786-90.	
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:				Study was retrospective and subjects were enrolled via medical records. The authors verified the accuracy of all critical data elements using several sources to address the limitation of a case-control study design. The authors noted a limitation was the details of feeding exposure during the transfusion epoch itself (including volume, type and tolerance) were not documented and might have had a role in modifying susceptibility to NEC.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective case-control study	
Citation:				Weintraub Z, Carmi N, Elouti H, Rumelt S (2011) The association between stage 3 of higher retinopathy of prematurity and other disorders of prematurity. Canadian Journal of Ophthalmology, 46: 419-24.	
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:				Retrospective review of charts to enrol consecutive infants. Exclusion criteria not reported. Not clear if all potential confounders taken into account.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

E2 Quality analysis – Question 2

Level I evidence

ESAs (with or without iron)

Study type:				Systematic review	
Citation:				Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD004868. DOI: 10.1002/14651858.CD004868.pub4.	
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:				Randomised and quasi-randomised trials were included. Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Akisu 2001 (low/unclear risk of bias), Atasay 2002 (unclear risk of bias), Samanci 1996 (low risk of bias), Al-Kharfy 1996 (low risk of bias), Bader 1996 (low/unclear risk of bias), Bechensteen 1993 (low/unclear risk of bias), Bierer 2009 (low risk of bias), Kumar 1998 (low/unclear risk of bias), Reiter 2005 (low/unclear risk of bias), Shannon 1991 (low/unclear risk of bias), Shannon 1992 (low/unclear risk of bias), Shannon 1995 (low risk of bias), Chen 1995 (low/unclear risk of bias), Corona 1998 (low/unclear risk of bias), Romagnoli 2000 (low/unclear risk of bias), Donato 1996 (low/unclear risk of bias), Emerson 1993 (low/unclear risk of bias), Griffiths 1997 (low risk of bias), Giannakopoulou 1998a (low/unclear risk of bias), Giannakopoulou 1998b (low/unclear risk of bias), Javier Manchon 1997 (low/unclear risk of bias), Kivivuori 1999 (high/unclear risk of bias), Maier 2002 (low risk	

	of bias), Meyer 1994 (low risk of bias), Pollak 2001 (low/unclear risk of bias), Whitehall 1999 (low risk of bias), Yamada 1999a (low/unclear risk of bias) and Yamada 1999b (low/unclear risk of bias).	

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.

Study type:				Systematic review	
Citation:				Feusner J and Hastings C (2002) Recombinant Human Erythropoietin in Pediatric Oncology: A Review. Med Pediatr Oncol 2002;39:463–468	
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:				Four randomised controlled clinical trials and four open, Phase I/II single-institution trials were included. However, only data from the RCTs has been included in this review. Appropriate search strategies used but exclusion criteria were not clearly defined. Study selection and data extraction was not applied by two researchers. Study quality was not assessed. The authors note much variability evident in the included studies, hence, a meta-analysis was not conducted and tests for heterogeneity were not applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Bennetts (1995), Porter (1996), Ragni (1998). Study quality not assessed.	

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.

Study type:				Systematic review	
Citation:				Garcia Maria G., Hutson Alan D., Christensen Robert D. (2002) Effect of Recombinant Erythropoietin on ''Late'' Transfusions in the Neonatal Intensive Care Unit: A Meta-Analysis. Journal of Perinatology 2002; 22:108 – 111	
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:				Appropriate search strategies applied and inclusion/exclusion criteria were clearly defined. Only randomised studies utilising a double-masked design were selected. The quality of the included studies was not reported. The method of randomisation or blinding was not assessed for any of the included studies. Characteristics of the individual studies are reported but not baseline demographic and clinical characteristics of the patients enrolled in these trials. 8 RCTs were included in the meta-analysis. A dose–response curve, modelling the probability of a transfusion as a function of weekly rHuEPO dose was generated.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Shannon (1991), Shannon (1992), Emmerson (1993), Ohls (1993), Meyer (1994), Shannon (1995), Samanci (1996), Kumar (1998). Study quality not assessed.	

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.

Study type:				Systematic review	
Citation:				Grant MD, Piper M, Bohlius J, Tonia T, Robert N, Vats V, Bonnell C, Ziegler KM, Aronson N. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Comparative Effectiveness Review No. 113. AHRQ Publication No. 13-EHC077-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2013.	
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:				Appropriate search strategies used to search multiple databases. Grey literature and scientific information packs were obtained but it is not stated if hand searching was carried out. Inclusion/exclusion criteria detailed. Meta-analyses and randomised controlled trials were included. A separate search for comparative observational studies was conducted for evidence on adverse events; however, no observational studies were found that met the specified inclusion criteria. A modified version of The Cochrane Collaboration's tool for assessing risk of bias was used to assess RCT quality. Although a meta-analysis was conducted, it included various populations, including adults. Hence, the results were not applicable to this review.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Porter 1996 (low quality), Razzouk 2006 (high quality) and Wagner 2004 (low quality).	

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.

Study type:				Systematic review	
Citation:				Kotto-Kome, A. C., Garcia, M. G., Calhoun, D. A., and Christensen, R. D. (2004) Effect of beginning recombinant erythropoietin treatment within the first week of life, among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: A meta-analysis. J.Perinatol. 24 (1) 24-29	
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:				Appropriate search strategies used and inclusion/exclusion criteria detailed. Only randomised studies utilising a double-masked design were selected; studies that were not randomised or blinded were excluded. The quality of the included studies was not reported and the method of randomisation or blinding was not assessed for any of the included studies. Characteristics of the individual studies are reported but not baseline demographic and clinical characteristics of the patients enrolled in these trials. Data was pooled selectively, depending on the level of heterogeneity present in the data. Parameters that produced significant heterogeneity, individual study data was presented.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Obladen 1991, Emmerson 1993, Soubasi 1993, Maier 1994, Soubasi 1995, Ohls 1995, Lauterbach 1995, Ohls 1997, Lima 1998, Donato 2000, Ohls 2001, Maier 2002. The quality of the included studies was not reported (as described above).	

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.

Study type:				Systematic review	
Citation:				Marti-Carvajal, A. J., Sola, I., Pena-Marti, G. E., and Comunian-Carrasco, G. (2011) Treatment for anemia in people with AIDS. Cochrane Database Syst Rev (10) CD004776-	
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:				Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. For this review, only one RCT was relevant but other studies were pooled where appropriate and tests for heterogeneity applied. As only one study was considered, a discussion of heterogeneity was not applicable.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Rendo 2001 (unclear risk of bias)	

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.

Study type:				Systematic review	
Citation:				Mystakidou, K., Potamianou, A., and Tsilika, E. (2007) Erythropoietic growth factors for children with cancer: A systematic review of the literature. Curr.Med.Res.Opin. 23 (11) 2841-2847	
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:				The authors only searched Medline, explaining that since an identified Cochrane review (2006) had searched several databases, these detailed searches were not repeated. They did hand search the reference list of this Cochrane review and other previously published literature reviews. RCTs, case-control studies and an open-label uncontrolled study were included. However, only the 5 RCTs are relevant to this review. The quality of the included studies is not reported. The authors briefly mention that studies involving rHuEPO in paediatric cancer patients are "often small and rarely randomised" but no further details are provided. A meta-analysis was not conducted; hence, tests for heterogeneity are not applicable.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Csaki 1998, Porter 1996, Razzouk 2006, Varan 1999, Wagner 2004 (quality of included studies not reported).	

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.

Study type:				Systematic review	
Citation:				Ohlsson, A. and Aher, S. M. (2012) Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 9 CD004863-	
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:				Randomised and quasi-randomised trials were included. Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied. May have been more appropriate to report random effects.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Al-Kharfy 1996 (low risk of bias), Arif 2005 (low/unclear risk of bias), Avent 2002 (low/unclear risk of bias), Carnielli 1992 (low/unclear risk of bias), Carnielli 1998 (low/unclear risk of bias), Chang 1998 (low/unclear risk of bias), Fauchére 2008 (low risk of bias), Haiden 2005 (low/unclear risk of bias), He 2008 (unclear risk of bias),Lima-Rogel 1998 (low/unclear risk of bias), Maier 1994 (low/unclear risk of bias), Maier 2002 (low risk of bias), Meyer 2003 (low risk of bias), Obladen 1991 (low/unclear risk of bias), Ohls 1995 (low/unclear risk of bias), Ohls 1997 (low risk of bias), Ohls 2001A (low risk of bias), Ohls 2001B (low risk of bias), Ohls 2013 (low risk of bias), Romagnoli 2000 (low/unclear risk of bias), Salvado 2000 (low risk of bias), Shannon 1995 (low risk of bias), Soubasi 1993 (low risk of bias), Soubasi 1995 (low/unclear risk of bias), Soubasi 2000 (low/unclear risk of bias), Yasmeen 2012 (unclear risk of bias), Yeo 2001 (low/unclear risk of bias).	

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.

Study type:				Systematic review	
Citation:				Ross, S. D., Allen, I. E., Henry, D. H., Seaman, C., Sercus, B., and Goodnough, L. T. (2006) Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature (Structured abstract). Clin.Ther. 28 801-831	
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:				Appropriate search strategies used, search terms provided and inclusion/exclusion criteria detailed. Randomised and non-randomised studies were included. Study quality was assessed using the Jadad method. However, scores were presented collectively per treatment comparison, rather than by individual study. Meta-analyses were conducted for several outcomes, with the Cochran Q test specified for quantifying heterogeneity. Although the results of this test are not presented, the authors state that several covariates were examined using meta-regression analyses. Detailed results of these investigations are not presented.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: Porter 1996, Varan 1999. Study quality assessed but not reported by individual study.	

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.

Study type:				Systematic review	
Citation:				Tonia, Thomy, Mettler, Annette, Robert, Nadège, Schwarzer, Guido, Seidenfeld, Jerome, Weingart, Olaf, Hyde, Chris, Engert, Andreas, and Bohlius, Julia (2012) Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst.Rev.	
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:				Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Razzouk, 2006 (low risk of bias).	

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.

Study type:				Systematic review	
Citation:				Vamvakas, E. C. and Strauss, R. G. (2001) Meta-analysis of controlled clinical trials studying the efficacy of EPO in reducing blood transfusions in the anemia of prematurity. Transfusion 41 (3) 406-415	
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:				One data base searched and search terms were not reported. 20 of the 21 included studies used random allocation. However, the remaining study compared three sequentially enrolled groups receiving various doses of rHuEPO with a concurrent control group. Quality assessments clear and pre-determined. It was not appropriate to pool all available data into a single meta-analysis, rather outcomes were selectively combined. Studies were pooled if the variation in results was sufficiently modest to be attributed to chance. Twelve variables were suitable for meta-analysis. A test for heterogeneity was not applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: Obladen 1991 (Jadad score (JS) 3), Shannon 1991 (JS 4), Ohls 1991 (JS 3), Shannon 1992 (JS 4), Carnielli 1992 (JS 3), Emmerson 1993 (JS 4), Bechensteen 1993 (JS 3), Maier 1994 (JS 5), Meyer 1994 (JS 5), Ronnestad 1994 (JS 4), Shannon 1995 (JS 5), Ohls 1995 (JS 4), Bader 1996 (JS 2), Al-Kharfy 1996 (JS 5), Samanci 1996 (JS 5), Ohls 1997 (JS 4), Kumar 1998 (JS 4), Giannakopoulou 1998 (JS 2).	

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.

Study type:				Systematic review	
Citation:				Xu XJ, Huang HY, Chen HL (2014) Erythropoietin and retinopathy of prematurity: a meta-analysis. European Journal of Pediatrics.	
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:				The authors reported manual searching of references. Evaluation for inclusion, data extraction and qualitative assessment was carried out by two independent reviewers, with disagreements resolved by discussion between the two. Quality of RCTs was assessed according to the Jadad scale. In the absence of significant heterogeneity, studies were pooled using a fixed-effect model. If heterogeneity was observed, a random effects model was used. Publication bias was assessed by visual inspection of a funnel plot, the Egger's regression test and Begg's adjusted rank correlation test. Sensitivity analysis was performed for included RCTs.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Five RCTs rated 4/5 on the Jadad scale, one RCT rated 3/5.	

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.

Oral and/or parenteral iron

Study type:				Systematic review	
Citation:				Okebe, J. U., Yahav, D., Shbita, R., and Paul, M. (2011) Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev (10) CD006589-	
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:				Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Adam 1997 (unclear risk of bias), Aggarwal 2005 (low/unclear risk of bias), Aguayo 2000 (low/unclear risk of bias), Angeles 1993 (unclear risk of bias), Ayoya 2009 (high risk of bias), Bacqui 2003 (low/unclear risk of bias), Berger 1997 (unclear risk of bias), Berger 2000 (high/unclear risk of bias), Berger 2006 (low/unclear risk of bias), Bhatia 1993 (unclear risk of bias), Charoenlarp 1973 (unclear risk of bias), Chwang 1988 (unclear risk of bias), de Silva 2003 (unclear risk of bias), Desai 2003 (high risk of bias), Devaki 2007 (unclear risk of bias), Dossa 2001a (high/unclear risk of bias), Dossa 2001b (low risk of bias), Fahmida 2007 (low risk of bias), Gebresellassie 1996 (high risk of bias), Gopaldas 1983 (unclear risk of bias), Greisen 1986 (low risk of bias), Hall 2002 (high/unclear risk of bias), Harvey 1989 (low/unclear risk of bias), Hettiarachchi 2008 (low/unclear risk of bias), Irdjradinata 1993 (low/unclear risk of bias), Kapur 2003 (unclear risk of bias), Kashyap 1987 (unclear risk of bias), Kianfar 1999 (unclear risk of bias), Latham 1990 (high/unclear risk of bias), Lawless 1994 (unclear risk of bias), Lind 2004 (low risk of bias), Massaga 2003 (low risk of bias), Mebrahtu 2004 (low risk of bias), Mejia 1988 (low/unclear risk of bias), Menendez 1997 (low risk of bias), Mwanri 2000 (low/unclear risk of bias), Nagpal 2004 (low/unclear risk of bias), Olsen 2006 (low risk of bias), Palupi 1997 (unclear risk of bias), Powers 1983 (unclear risk of bias), Richard 2006 (high risk of bias),	

	Rosado 1997 (unclear risk of bias), Roschnik 2004 (low/unclear risk of bias), Sarma 1977 (high/unclear risk of bias), Sazawal 2006a (low/unclear risk of bias), Sazawal 2006b (low risk of bias), Seshadri 1982 (low/unclear risk of bias), Seshadri 1984a (unclear risk of bias), Seshadri 1984b (unclear risk of bias), Shah 2002 (low risk of bias), Smith 1989 (high risk of bias), Smuts 2005 (low/unclear risk of bias), Soemantri 1989 (unclear risk of bias), Soewondo 1989 (unclear risk of bias), Verhoef 2002 (low risk of bias), Wasantwisut 2006 (low risk of bias), Zlotkin 2003 (low risk of bias).	

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.

Study type:				Systematic review	
Citation:				Pasricha, S., Shet, A., Sachdev, H. P. S., and Shet, A. S. (2009) Risks of routine iron and folic acid supplementation for young children. Indian Pediatr. 46 (10) 857-866	
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:				Appropriate search strategies used and search terms provided. WHO and Indian Government documents were searched but it is not specified if this was done systematically or by hand searching. Inclusion and exclusion criteria were not detailed. The characteristics of studies are reported but not baseline demographic and clinical characteristics. The quality of the included studies was not assessed. A meta-analysis was not conducted; hence tests for heterogeneity are not applicable.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Sazawal 2006, Tielsch 2006. Study quality not assessed.	

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.

Hydroxyurea

Study type:				Systematic review	
Citation:				Mulaku, M., Opiyo, N., Karumbi, J., Kitonyi, G., Thoithi, G., and English, M. (2013) Evidence review of hydroxyurea for the prevention of sickle cell complications in low-income countries. Arch.Dis.Child. 98 (11) 908-914	
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:				Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Systematic reviews, RCTs and observational studies were included. Only 2 RCTs were relevant to this review. Although the RCTs were described, baseline demographic and clinical characteristics were not reported for patients in the individual studies. The authors note that heterogeneity was present (due to the different study designs, e.g. RCTs vs observational studies and outcome measures). As such, pooling the data was considered inappropriate so a meta-analysis was not conducted.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: Wang 2011, Ware 2012.	

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.

Level II evidence

ESAs (with or without iron)

Study type:				Randomised controlled trial	
Citation:				Andropoulos DB, Brady K, Easley RB et al (2013) Erythropoietin neuroprotection in neonatal cardiac surgery: A phase I/II safety and efficacy trial. The Journal of Thoracic and Cardiovascular Surgery, 146(1): 124-31.	
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:				Baseline characteristics were similar between treatment arms except for OR midazolam dose, which was significantly higher in the placebo group (P = 0.044). Randomisation was performed by computer-generated random number assignment to rHuEPO or placebo. Blinding of groups was maintained until the final patient had undergone 12–month Bayley III assessment.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Bechensteen AG, Haga P, Halvorsen S et al (1993) Erythropoietin, protein, and iron supplementation and the prevention of anaemia of prematurity. Archives of Disease in Childhood, 69: 19-23.	
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:				Infants were randomised separately at each centre to the intervention or control group. Randomisation was performed by pre-numbered sealed envelopes. The analyses of all main variables were repeated in a subgroup analysis which eliminated data from the excluded infant and from the infants with initial haemoglobin concentrations above 150 g/l or below 90 g/l. Results were very close to those obtained for the complete data set. Statistical power required 15 infants per group, but there were only 14 infants in the intervention group.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Bierer R, Roohi M, Peceny C, Ohls RK. Erythropoietin increases reticulocyte counts and maintains hematocrit in neonates requiring surgery. J Pediatr Surg 2009; 44(8):1540-5.	
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:				Participants were randomised using a random number list and stratified by weight (≥1500 g and <1500 g). No attempt at allocation concealment was reported. The study was conducted in a "double-masked fashion". Baseline patient characteristics and demographics were similar between the groups, but the author note that infants in the rHuEPO group with sicker than those in the placebo group due to the nature of their illness. Loss to follow-up was not reported but the authors note that data for all enrolled infants is reported so it is assumed all infants completed the study. It is not reported if outcome assessment was blinded to treatment allocation but all outcomes were objective. No subgroup analyses were reported.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Chicella MF, Krueger KP (2006) Prospective Randomized Double-Blind Placebo Controlled Trial of Recombinant Human Erythropoietin Administration to Reduce Blood Transfusions in Anemic Pediatric Intensive Care Patients. J Pediatr Pharmacol Ther, 11: 101-106.	
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:				PICU attending physicians were blinded to the patient's treatment arm. The study aimed to enrol 100 patients; however due to difficulty enrolling patients, the study was stopped prematurely. Analyses were underpowered due to the small sample sizes. There was no loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				El-Ganzoury M ; Awad H ; El-Farrash, R; El-Gammasy, T; Ismail, E; Mohamed, H and Suliman S. (2014) Enteral Granulocyte-Colony stimulating factor and Erythropoietin early in life improves feeding tolerance in preterm infants: A randomised controlled trial. The Journal of Pediatrics	
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:				Allocation was via a predetermined schedule generated from random numbers in a 1:1 manner based on a computer-generated randomisation sequence maintained within the investigational drug pharmacy. Allocation concealment was achieved with the use of opaque sequentially numbered sealed envelopes. The study was double-blinded, but not stated whether outcome assessors were blind to treatment allocation. There was no loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Fearon JA, Weinthal J (2002) The Use of Recombinant Erythropoietin in the Reduction of Blood Transfusion Rates in Craniosynostosis Repair in Infants and Children. Plastic and Reconstructive Surgery, 109(7): 2190-6.	
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:				Study was single blinded. There was no loss to follow-up, although two patients were excluded prior to study commencement due to infection and diagnosis of alpha-thalassemia respectively.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Griffiths G, Lall R, Chatfield S et al (1997) Randomized controlled double blind study of role of recombinant erythropoietin in the prevention of chronic lung disease. Archives of Disease in Childhood, 76: F190-2.	
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:				The two groups were broadly similar at baseline, although the placebo group may have had more severe respiratory illness, as suggested by the higher proportion of infants in intermittent positive pressure ventilation. No subgroup analyses were reported, although stratified randomisation was used to account for participating centres, gestational age and multiple births. A sensitivity analysis was carried out to assess the impact of deaths, by setting the duration of respiratory support for all infants who died to the maximum recorded.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Jacobs BR, Lyons K, Brilli RJ (2003) Erythropoietin therapy in children with bronchiolitis and anemia. Pediatric Critical Care Medicine, 4(1): 44-8.	
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:				Upon entry into the study, patients were randomised using a random numbers table technique. Physicians and nurses were blinded to patient treatment group. The hospital pharmacists were unblinded and responsible for assigning patients to a treatment group according to the randomisation schedule. The study was stopped early after the interim analysis revealed no difference between the groups in terms of the primary outcome variable (percentage of children requiring a blood transfusion).	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Jim, W. T., Chen, L. T., Huang, F. Y., and Shu, C. H. (2000) The early use of recombinant human erythropoietin in anemia of prematurity. Clin.Neonatol. 7 (2) 12-16	
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:				Infants were randomly assigned to two groups but the method of randomisation is not reported. Similarly, no method of allocation concealment is discussed. The authors do not report whether the study participants or investigators were blinded, nor if outcome was assessed blind to treatment allocation. Baseline characteristics and demographics were similar between treatment groups. No loss to follow-up is reported in the study so it is assumed all participants are included in the final analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Juul SE (2003) Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. The Journal of Pediatrics, 143(3): 321-6.	
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:				Blinding was reported, but details were not provided on who was blinded. Infants in the rHuEPO group ranged from 2 to 8 weeks postnatal age at study entry, with a median of 4 weeks, whereas infants in the placebo group ranged from 1 to 7.4 weeks postnatal age, with a median of 2 weeks. Blood transfusion requirements were presented as overall results, and stratified according to infant birth weight.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Khatami SF, Mamouri G, Torkaman M (2008) Effects of Early Human Recombinant Erythropoietin Therapy on the Transfusion in Healthy Preterm Infants. Indian Journal of Pediatrics, 75(12): 1227-30.	
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:				Patients were randomised by means of numbered, sealed envelopes. Loss to follow-up not reported but it appeared all 40 infants completed the study.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Kremenopoulos, G., Soubasi, V., Tsantali, C., Diamanti, E., and Tsakiris, D. (1997) The best timing of recombinant human erythropoietin administration in anemia of prematurity: A randomized controlled study. Int.J.Pediatr.Hematol.Oncol. 4 (4) 373-383	
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:				Infants were allocated to Group A or B based on consecutive admission to the nursery. The authors report randomly assigning infants to either the intervention or control arm within each group, but the method of randomisation is not reported. Similarly, no method of allocation concealment is discussed in the article. The authors do not report whether the study participants or investigators were blinded, nor if outcome assessment was blind to treatment allocation. Baseline characteristics and demographics were similar between treatment groups except for birth weight, which was higher in the control neonates without complications than the corresponding rHuEPO group. No loss to follow-up is reported in the study so it is assumed all participants are included in the final analysis. A subgroup analysis compared the neonates in Group A without complications and those with complications.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Meister Bernhard, Heiner Maurer, Simma Burkard, Kern Hannelore, Ulmer Hanno, Anton Hittmair, Franz-Martin Fink (1997) The Effect of Recombinant Human Erythropoietin on Circulating Hematopoietic Progenitor Cells in Anemic Premature Infants. STEM CELLS 1997;15:359-363	
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:				Infants were randomly assigned to the intervention or control group using a computerised random numbers generator. Blinding was not reported. One patient (control group) was withdrawn from the study because of development of intraventricular haemorrhage grade IV on study day 6.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial (follow-up of Ohls 2001)	
Citation:				Ohls Robin K., Ehrenkranz Richard A., Das Abhik, Dusick Anna M., Yolton Kimberly, Romano Elaine, Delaney-Black Virginia, Papile Lu-Ann, Simon Neal P., Steichen Jean J. and Lee Kimberly G., for the National Institute of Child Health and Human Development Neonatal Research Network (2004) Neurodevelopmental Outcome and Growth at 18 to 22 Months' Corrected Age in Extremely Low Birth Weight Infants Treated With Early Erythropoietin and Iron. Pediatrics 2004;114;1287	
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:				Fair	
Quality rating: [Good/Fair/Poor]				A follow-up at 18-22 months of ELBW infants enrolled in Ohls 2001. Method of randomisation not reported here, but in original trial it was stated that randomisation was stratified by centre and for trial by birth weight (401–750, 751-1000 g) using a permuted block method. All caregivers and investigators (except the research nurses) were masked to the treatment assignment (as reported in Ohls 2001). Outcomes were assessed by certified examiners masked to treatment group. Only 70% of study survivors were evaluated at 18 to 22 months' corrected age. Follow-up investigators generally sought to assess at least 80% of the potential study population to ensure that findings are generalisable, not affected by acquisition bias, and not prone to type I or II errors.	

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.

Study type:				Randomised controlled trial	
Citation:				Ovali Fahri, Samanci Nedim and Dağoğlu Türkan (1995) Management of Late Anemia in Rhesus Hemolytic Disease: Use of Recombinant Human Erythropoietin (A Pilot Study) Pediatric Research (1996) 39, 831–834; doi:10.1203/00006450-199605000-00015	
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:				The study is reported as a double blind, placebo-controlled randomised pilot study. The drugs were prepared in sets of small vials and numbered randomly from 1 to 20. Only the pharmacist was aware of the content of the vials, the investigators and the administrators were blinded. The number of intrauterine and exchange transfusions and demographic data were similar in both groups at baseline.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Pape L, Ahlenstiel T, Kreuzer M et al (2009). Early erythropoietin reduced the need for red blood cell transfusion in childhood haemolytic uremic syndrome – a randomised prospective pilot trial. Pediatric Nephrology, 24: 1061-4.	
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:				Although loss to follow-up not explicitly reported, all children appeared to be included in the final analysis. **In text: "…the early administration of rHuEPO can reduce the number of RBC transfusions, even in a subgroup of children with a relatively higher rate of renal failure, as demonstrated by the longer time of dialysis in the rHuEPO group than in the control group." Randomisation was conducted using a local sealed envelope technique and took place directly after admission. There were no protocol violations.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Porter JC, Leahey A, Polise K, Bunin G, Manno CS (1996) Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: A randomized, double-blind, placebo-controlled trial. The Journal of Pediatrics, 129(5): 656-60.	
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:				Patients were randomised using a computer-generated list of random numbers. Single-dose vials of rHuEPO and placebo were labelled identically. At the end of the 16 week study period, the patient's treatment assignment was revealed to both the patient and the investigator. Four patients were lost to follow-up; reasons were provided.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Warady, B. A., Kausz, A., Lerner, G., Brewer, E. D., Chadha, V., Brugnara, C., Dahl, N. V., and Watkins, S. L. (2004) Iron therapy in the pediatric hemodialysis population. Pediatr.Nephrol. 19 (6) 655-661	
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:				Patients were randomised using a random numbers table but no method of allocation concealment was described. It is not reported whether subjects and investigators were blinded to treatment arm. Baseline characteristics were similar between the groups. Loss to follow-up was not reported but it is assumed that all patients completed the study. Participants were recruited from the dialysis units of five paediatric nephrology centres. However, results are only reported collectively, rather than by recruitment site so it is not known if results were comparable.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Oral and/or parenteral iron

Study type:				Randomised controlled trial	
Citation:				Berseth, C. L., Van Aerde, J. E., Gross, S., Stolz, S. I., Harris, C. L., and Hansen, J. W. (2004) Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier. Pediatrics 114 (6) e699-e706	
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:				Infants were stratified by gender and birth weight (≤1000 or >1000 g) before being randomised. A randomisation schedule was used to maintain a balance between each stratification level but no further detail was provided on the method of randomisation, nor was any attempt at allocation concealment reported. The study was double blind and baseline characteristics were similar between treatment groups. The study was conducted across multiple sites but the results are presented collectively, rather than by study location, so it is not possible to determine if the results were comparable for all sites. A subgroup analysis of infants who met more stringent criteria is presented for the outcomes of growth and energy intake only.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Franz, A. R., Mihatsch, W. A., Sander, S., Kron, M., and Pohlandt, F. (2000) Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. Pediatrics 106 (4 I) 700-706	
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:				Infants were assigned to 1 of 2 strata, depending on the need for blood transfusions within the first 7 days of life (stratum 1: no blood transfusion, stratum 2: ≥ 1 transfusion within the first 7 days of life). At day 7 of life, infants were randomised in blocks of 10 within each stratum to the treatment groups. However, the method of randomisation is not reported. Similarly, no attempt at allocation concealment is reported in the study. The participants were not blinded but laboratory staff were unaware of treatment allocation. Baseline characteristics were similar across a number of variables including gestational age, birth weight and markers of nutritional iron status. However, there was a trend towards more infants with chronic lung disease and severe retinopathy of prematurity in the late iron group. Loss to follow-up was reported and appropriately accounted for in the analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Fujiu T, Maruyama K, Koizumi T (2004) Oral iron supplementation in preterm infants treated with erythropoietin. Pediatrics International, 46: 635-9.	
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:				One patient died before follow-up but was still included in the final analysis (ITT).	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Taylor TA and Kennedy K A. Randomized Trial of Iron Supplementation versus Routine Iron Intake in VLBW Infants. (2013). Pediatrics 2013;131;e433; originally published online January 21, 2013; DOI: 10.1542/peds.2012-1822	
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:				The authors conclude that iron supplementation, in addition to routine iron intake, did not significantly increase the 36-week Hct or the decrease number of transfusions. Infants were assigned to 1 of 2 strata according to gestational age (GA) by dates of birth (<27 weeks GA and ≥27 weeks GA). Once infants reached 120 mL/kg per day of feedings, they were randomly allocated (computer-generated randomisation table with variable block size) by the research pharmacy to intervention (multivitamin with iron) or control group (multivitamin without iron) in a 1:1 ratio. The enrolling investigators were masked to the allocation sequence; the study investigators, clinicians, and parents were masked to group assignment until the study data collection was complete. It is possible that bedside nurses who administered the medication could have identified differences in the appearance or smell of the preparations with and without iron, but there were no known episodes of unmasking of physicians or nurse practitioners. Multiple births were randomly assigned separately. A sample size of 75 per group was calculated to achieve 80% power to detect a difference in Hct of 2% between groups.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Tielsch, J. M., Khatry, S. K., Stoltzfus, R. J., Katz, J., Leclerq, S. C., Adhikari, R., Mullany, L. C., Shresta, S., and Black, R. E. (2006) Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: Community-based, cluster-randomised, placebo-controlled trial. Lancet 367 (9505) 144-152	
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:				Children were randomised by sector, stratified by geographic area and in blocks of four. To prevent the investigators from determining treatment allocation, a data file was given to an independent systems analyst who replaced the individual identifiers with a new, random set of identification numbers, filed the linked information in a secure location and replaced all treatment codes with the actual treatment received. Baseline characteristics were similar between the groups. Loss to follow-up was reported and appropriately accounted for the in the analysis. A subgroup analysis was conducted using a subset of participants from the trial who were younger than 24 months of age.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Sankar, M. J., Saxena, R., Mani, K., Agarwal, R., Deorari, A. K., and Paul, V. K. (2009) Early iron supplementation in very low birth weight infants – A randomized controlled trial. ACTA PAEDIATR.INT.J.PAEDIATR. 98 (6) 953-958	
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:				Randomisation and allocation concealment strategies were detailed and adequate. The investigators were not blinded. However, the laboratory staff who estimated serum ferritin and other parameters were masked to treatment groups. The authors do not specify whether this was the case for all outcome variables. Baseline characteristics were similar between the groups except for the incidence of late-onset sepsis, which was higher in the control group. Loss to follow-up is reported and accounted for in the analysis. There were no subgroup analyses reported.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Sazawal, S., Black, R. E., Ramsan, M., Chwaya, H. M., Stoltzfus, R. J., Dutta, A., Dhingra, U., Kabole, I., Deb, S., Othman, M. K., and Kabole, F. M. (2006) Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: Community-based, randomised, placebo-controlled trial. Lancet 367 (9505) 133-143	
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:				Children were randomised to one of four groups using a permuted block allocation sequence, with a block length of 16. Strips of supplements were labelled with 16 letter codes, which were hidden in the batch number of each strip of tablets before each child was assigned a code. Baseline characteristics were similar between the groups. Loss to follow-up was reported and appropriately accounted for in the analysis. There were limitations regarding the classification of cause-specific effects, as noted by the authors. Lumbar puncture, coma scoring, blood cultures or blood gas analytics were not available in the hospitals on the island and as such, it is possible that misclassifications occurred regarding meningitis, septicaemia with acidosis and cerebral malaria. However, alternate methods of diagnosis are detailed in the trial for these conditions. A subgroup analysis was conducted using a subset of the participants from the trial stratified by baseline anaemia, iron status and anthropometry.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				van den Hombergh J, Dalderop E, Smit Y. (1996) Does Iron Therapy Benefit Children with Severe Malaria-associated Anaemia? A Clinical Trial with 12 Weeks Supplementation of Oral Iron in Young Children from the Turiani Division, Tanzania. Journal of Tropical Pediatrics, 42: 220-7.	
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:				Simple randomisation was used to allocate children to the iron or control group. The diagnosing physician was not blinded to treatment group. At baseline, 20 children from each group (40%) had received a blood transfusion. Subgroup analyses were performed accounting for this variable. Follow-up was reported to be 100%; however between 5 and 8 children were not included in the analyses at 2, 4, 8 and 12 weeks. Reasons for these exclusions were not reported.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Hydroxyurea

Study type:				Randomised controlled trial	
Citation:				Jain Dipty L., Vijaya Sarathi, Saumil Desai, Manoj Bhatnagar, and Abhijit Lodha. Low fixed-dose Hydroxyurea in severely affected Indian children with sickle cell disease. (2012). Hemoglobin, 2012; 36(4): 323–332 Copyright © Informa Healthcare USA, Inc. ISSN: 0363-0269 print/1532-432X online DOI: 10.3109/03630269.2012.697948	
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:				Subjects were randomised using randomisation tables. Trial was double-blinded; the laboratory technician and the clinician who assessed patients were not aware of the treatment arm. The study had sufficient statistical power (90%) to detect a mean difference in the primary outcome of 1.9 per patient per year with a SD of 0.5, assuming an alpha error or 0.05.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Wang WC, RE Ware, ST Miller, RV Iyer, JF Casella, CP Minniti, SRana, CD Thornburg, ZR Rogers, RV Kalpatthi, JC Barredo, RC Brown, SA Sarnaik, TH Howard, LW Wynn, A Kutlar, FD Armstrong, BA Files, JC Goldsmith, MA Waclawiw, X Huang, BW Thompson, for the BABY HUG investigators (2011) Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 2011; 377: 1663–72		
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:				The authors conclude that on the basis of the safety and efficacy data from this trial, hydroxycarbamide can now be considered for all very young children with sickle-cell anaemia. The study required a sample size of 100 patients per group to provide greater than 95% power. Participants, caregivers, and medical coordinating centre staff were masked to treatment allocation. Analysis was by intention-to-treat.	
Quality rating: [Good/Fair/Poor]				Good	

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.

E3 Quality analyses – Question 3

Level I evidence

Study type:				Systematic review	
Citation:				Estcourt L, Stanworth S, Doree C et al. (2012) Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation (Review). Cochrane Database of Systematic Reviews, Issue 5 CD004269.	
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:				Baseline demographics and details of patients recruited were detailed in some of the Characteristics of Studies monographs.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: 13 studies were included of which one was relevant to this overview (Murphy 1982). The review authors rated this study as having an unclear risk of bias (fair quality) according to the Cochrane Risk of bias assessment.	

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.

Study type:				Systematic review	
Citation:				Osborn, D. A. and Evans, N. (2004) Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database Syst Rev (2) CD002055-	
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]:				Appropriate search strategies and inclusion criteria applied in an unbiased way. No statistically significant heterogeneity was found in any of the analyses.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Beverley 1985, Ekblad 1991, Gottuso 1976, NNNI 1996. Three studies (Beverley 1985; Gottuso 1976; NNNI 1996) reported adequate randomisation and allocation concealment. Ekblad 1991 did not report method of randomisation and allocation concealment was unclear. No study reported blinding; however, given the nature of the interventions it is probable that caregivers unblinded. Beverley 1985 and NNNI 1996 blinded outcome measurement. No losses to follow-up were reported by Gottuso 1976 and NNNI 1996. Beverley 1985 reported seven (12.5%) losses and Ekblad 1991 reported on data of 38/40 in one paper and 35/40 in another.	

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.

Level II evidence

Study type:				Randomised controlled trial	
Citation:				F Galas, J. de Almeida, J. Fukushima, J Vincent, E. Osawa, S Zeferino, L. Camara, V Guimaraes, M Jatene and L. Hajjar. 2014. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: A randomized pilot trial. The Journal of Thoracic and Cardiovascular Surgery c Volume 148, Number 4.	
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]:				No patients were lost to follow-up or withdrew from the study. There were no between group differences in baseline demographics and intraoperative characteristics. Patients were randomly assigned in a 1:1 ratio. Opaque envelopes arranged using a random number table were prepared by the chief statistician and opened sequentially to determine the patient's treatment group. The research coordinator enrolled the participants and obtained informed consent. Outcome assessors and patients were unaware of group assignments but not all personnel were blinded due to feasibility.	

Quality rating: [Good/Fair/Poor]	Good

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.

Study type:				Randomised controlled trial	
Citation:				Lee, J. W., Yoo, Y. C., Park, H. K., Bang, S. O., Lee, K. Y., and Bai, S. J. (2013) Fresh frozen plasma in pump priming for congenital heart surgery: Evaluation of effects on postoperative coagulation profiles using a fibrinogen assay and rotational thromboelastometry. Yonsei Med.J. 54 (3) 752-762.	
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:				Sealed envelopes were used as a method of randomisation and allocation concealment. The patient cohort was divided by age, with infants and children analysed separately for all outcomes. The perfusionists involved in the trial were not blinded but anaesthesiologists, ICU staff and surgeons were all blinded to treatment assignment. Patient characteristics were similar between treatment groups for both infants and children.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				McCall MM, Blackwell MM, Smyre JT et al. (2004) Fresh Frozen Plasma in the Pediatric Pump Prime: A Prospective, Randomized Trial. Ann Thorac Surg 77: 983-7.	
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]:				Patients were randomised the day before surgery using sealed envelopes. Blinding was not reported for clinicians, investigators or outcome assessors. Patient characteristics were similar between groups although 3 patients (30%) were cyanotic in the FFP group compared with 2 patients (20%) in the no FFP group. Loss to follow-up not reported although the analysis was described for 20 patients as per recruited.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				The Northern Neonatal Nursing Initiative (NNNI) Trial Group (1996a) A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. European Journal of Pediatrics, 155(7): 580-8.	
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:				Randomisation reported via a telephone call to a central randomisation service. Allocation concealment not reported and treating clinicians not blinded to treatment. Outcome assessors were usually unaware of (but not formally "blind" to) the baby's original trial allocation. Patient characteristics were similar between groups. Protocol violations adequately reported. All randomised babies included in the analysis but selective reporting for some outcomes also included.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				The Northern Neonatal Nursing Initiative (NNNI) Trial Group (1996b) Randomized trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Lancet, 348: 229-32.	
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:				Follow-up of NNNI 1996a at 2 years. There was no loss to follow-up. In the follow-up study an independent neurodevelopmental assessment was performed by one paediatrician who reviewed all children prior to hospital records and reports being abstracted. The paediatrician was blinded to treatment group allocation of the children. There were two children living overseas, who were assessed by a local clinician.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Oliver WC, Beynen FM, Nuttall GA et al. (2003) Blood Loss in Infants and Children for Open Heart Operations: Albumin 5% Versus Fresh-Frozen Plasma in the Prime. Ann Thorac Surg 75:1506-12.	
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:				Method of randomisation was not reported. All personnel associated with the perioperative care of patients (except perfusionists) were blinded to treatment group. Patient characteristic were similar between groups. No loss to follow-up was noted, although analysis was conducted on the same number of patients recruited.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Level III evidence

Study type:				Retrospective cohort study	
Citation:				Baer VL, Lambert DK, Henry E et al. (2007) Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopaenic neonates in a multihospital healthcare system. Journal of Perinatology, 27: 790-796.	
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]:				There was no difference in gender or ethnicity between the groups but participants who received platelet transfusions had lower birth weights and gestational age than those who did not received platelet transfusions. The authors report that there was no correlation between birth weight and the number of transfusions given. The study was retrospective and included all eligible patient data in the analysis. There were uniform guidelines for administering platelet transfusions across all the participating NICUs however some patients who met the criteria did not receive platelet transfusions, with no apparent explanation. The authors conducted 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.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Case-control study	
Citation:				Bonifacio L, Petrova A, Nanjundaswamy S and Mehta R. (2007) Thrombocytopenia related neonatal outcome in preterms. Indian Journal of Pediatrics, 74(3): 269-74.	
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]:				There were 114 available cases and 80 controls, but 28 infants (18 cases, 10 controls) were excluded as per the exclusion criteria. A comparison was made between those participants who had thrombocytopenia (cases) and those who did not (controls) to establish the similarity between the groups at baseline. A comparison of those who received platelets compared with no platelet transfusion was also made, with the authors noting that infants who received platelet transfusions were significantly more likely to be < 28 weeks gestational age and have lower birth weights than those who did not received platelet transfusions; and that the transfusion rate was higher among infants between 28–32 weeks gestational age with more severe thrombocytopenia. The authors collected data for potential confounding variables from maternal and neonatal medical charts. It is not stated whether or not these were adjusted for in the analyses. For data extraction, the authors utilised clinical notes as well as results of the instrumental and laboratory tests.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Retrospective cohort study	
Citation:				Christensen RD, Henry E, Wiedmeier SE et al. (2006) Thrombocytopenia among extremely low birth weight neonates: data from a multihospital healthcare system. Journal of Perinatology, 26: 384-353.	
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]:				A retrospective cohort study of 284 ELBW preterm infants from multiple NICUs in the USA. Data were collected from electronic medical records, case mix, pharmacy, and laboratory systems. Trained clinical personnel entered additional data, with data managed by authorised data analysts. In addition, the medical records of 208 neonates with thrombocytopenia were reviewed by the authors to determine reasons for ordering each platelet transfusion. There were 76 infants without thrombocytopenia; one received a platelet transfusion. Usable data was only reported for thrombocytopenic patients.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Retrospective analysis of a prospective cohort study	
Citation:				Church GD, Matthay MA, Liu K, Milet M & Flori HR (2009) Blood product transfusions and clinical outcomes in pediatric patients with acute lung injury. Pediatric Critical Care Medicine, 10(3): 297-302.	
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]:				Only transfusions that occurred within the first 72 hours after diagnosis of acute lung injury were included in the analysis to decrease the impact of patient dropout secondary to death or discharge. Exclusions from analysis were reported, and it is assumed there was no loss to follow-up. Primary outcome was mortality.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Prospective cohort study	
Citation:				Karam O, Lacroix J, Robitaille N, Rimensberger PC & Tucci M (2013) Association between plasma transfusions and clinical outcome in critically ill children: a prospective observational study. The International Journal of Transfusion Medicine, 104: 342-9.	
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]:				No patients were excluded from analysis (except those who were initially excluded for not meeting inclusion criteria)	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				Nacoti M, Cassaniga S, Lorusso F et al (2012) The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. Pediatric Transplantation, 16: 357-66.	
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]:				Outcomes were mortality and graft survival. Seven hepato-biliary surgeons performed all the liver transplants with two involved in each procedure. Fifteen anaesthesiologists were involved throughout the study period. Transfusion policy was based on clinical assessment, therefore subject to bias. Missing data were <2%. 39 patients stopped follow-up within one year.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Retrospective cohort study	
Citation:				von Lindern JS, Hulzebos CV, Bos AF, Brand A, Walther FJ & Lopriore E (2012) Thrombocytopaenia and intraventricular haemorrhage in very premature infants: a tale of two cities. Arch Dis Child Fetal Neonatal Ed, 97: F348-F352.	
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]:				There were 689 infants eligible for inclusion. Ten infants died shortly after birth, before a cranial ultrasound or other tests (e.g., platelet counts) could be performed, and were therefore not included in the analysis. No cranial ultrasound scans were performed in 18 other infants (reasons not reported). Patients were also excluded from final analysis if their platelet count was unknown (n=8). There were no significant differences in patient demographic and clinical characteristics between the two units but among those with thrombocytopenia the incidence of NEC was higher in the restrictive transfusion unit (10%) compared with those in the liberal transfusion unit (4%). Blinding of outcome assessment is unclear (each NICU read their own scans). Due to the potential for differences in interpretation of cranial ultrasounds between centres, it would have been preferable for an independent reviewer to evaluate the ultrasound scans. There were two protocol violations in the restrictive transfusion group and one in the liberal transfusion group.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

E4 Quality analyses – Question 4

Level I evidence

Study type:				Systematic review	
Citation:				Arnold D M, Fergusson D A, Chan A K, Cook R J, Fraser G A, Lim W, Blajchman M A, Cook D J. (2006) Avoiding transfusions in children undergoing cardiac surgery: a meta-analysis of randomized trials of aprotinin. Anesthesia and Analgesia; 102(3): 731-737.	
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:				Screening and data extraction was performed by two independent reviewers. Methodological quality was determined by two independent reviewers blinded to the details of the studies, using the Jadad quality assessment scale. Areas assessed included adequacy of allocation concealment and the use of an objective, predefined transfusion protocol. Meta-analyses were conducted but the authors reported that heterogeneity was high for the outcomes volume of blood transfused and volume of chest tube drainage.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Jadad score 3/5 (Mossinger 2003; Davies 1997; D'Errico 1996; Herynkopf 1994); Jadad score 0-1/5 (other 8 RCTs). The authors reported that the methodological quality of most included studies were poor, mainly due to inadequate description of the methods (e.g. attrition, allocation concealment, the use of an objective transfusion protocol) or potential bias in the funding sources.	

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.

Study type:				Systematic review	
Citation:				Backes CH, Rivera BK, Haque U, Bridge JA et al. (2014) Placental transfusion strategies in very preterm neonates: a systematic review and meta-analysis. Obstetrics and Gynecology, 124(1): 47–56.	
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:				Appropriate search strategies, with search terms reported in the supplementary material. Two authors independently assessed the eligibility of identified studies and extracted data using standardised forms. Trial authors were contacted for additional data when necessary. Any discrepancies were resolved via a third author, with the final decision agreed by consensus. The methodological quality of each study was independently assessed using a modified version of the Jadad scale. Trials rated ≥10 were considered high quality. There were no disagreements between reviewers regarding trial quality. Characteristics of individual studies were reported in the supplementary material but baseline demographics and characteristics of individual patients were not provided.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Jadad score 10 (high quality) (Kinmond 1993, McDonnell 1997, Ibrahim 2000, Mercer 2003, Mercer 2006, Hosono 2008, Sommers 2012, March 2013). Jadad score 9 (did not justify sample size) (Baezinger 2007, Gokmen 2011). Jadad score 8 (inclusion/exclusion criteria and withdrawals not clearly stated) (Oh 2011). Oh 2002 was an abstract only and did not have enough detail to receive a quality rating.	

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.

Study type:				Systematic review	
Citation:				Faraoni D, Willems A, Melot C, De Hert S, Van der Linden P. (2012) Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. 42(5):781-6. doi: 10.1093/ejcts/ezs127. Epub 2012 Apr 24.	
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:				• The authors reported that the SR was performed in accordance with the Quality of Reporting of Meta-analyses (QUORUM) consensus. Screening and data extraction were performed by two authors.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: The methodological quality of included studies was assessed by study design, method of randomisation, blinding, transfusion policy and reporting of primary and secondary outcomes. Each study was assigned a level of recommendation and grade; however the range of possible grades and what these meant were not described. Meta-analyses were performed using both fixed and random effects models.	

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.

Study type:				Systematic review	
Citation:				Ghavam S, Batra D, Mercer J, Kugelman A et al. (2013) Effects of placental transfusion in extremely low birthweight infants: meta-analysis of long– and short-term outcomes. Transfusion, 54: 1192–8.	
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:				RCTs and quasi-randomised trials were eligible for inclusion. Two independent investigators performed the literature search. Additional information was requested from authors if necessary. Data were obtained for all neonates <30 weeks and <1000 g from authors in which studies included a mixed cohort of neonates. Two observers extracted data. Individual study results were also not provided, with only pooled data presented. Several meta-analyses were conducted but a test for heterogeneity was not applied.	
Quality rating: [Good/Fair/Poor]				Systematic review: Poor	
				Included studies: Hosono 2008, Hosono 2009, Ibrahim 2000, Kugelman 2007, March 2011, Mercer 2006, Mercer 2010, Oh 2011, Rabe 2000 and Windrim 2011. Details of included and excluded studies were reported in supplementary materials. However the quality of the included studies was not reported.	

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.

Study type:				Systematic review	
Citation:				Ker K, Beecher D, Roberts I (2013). Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database of Systematic Reviews, Issue 7. Art No.: CD010562.	
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:				Appropriate search strategies and inclusion/exclusion criteria detailed. The quality of included studies was assessed using the Cochrane Risk of Bias tool. The characteristics, patient demographics and results of the individual studies were presented. Although 29 studies are included in the review only one was in a paediatric population (Albirmawy 2013).	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Albirmawy (2013): low risk of bias to random sequence generation, a low/unclear risk of bias to blinding (participants, investigators and outcome assessors) and incomplete outcome data; and an unclear risk of bias to allocation concealment and selective reporting.	

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.

Study type:				Systematic review	
Citation:				Louis D, More K, Oberoi S, Shah PS. Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: An updated systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2014.	
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:				The search strategy was appropriate, with three databases searched and search terms reported in appendices. Inclusion/exclusion criteria were detailed. The authors intended to include RCTs and quasi-randomised trials but only RCTs were identified. The quality of studies was assessed using the Cochrane Risk of Bias tool, with the overall risk of bias presented in the main article for each included study and more detail available in appendices. The characteristics and patient demographics of individual studies were reported in appendices. Two meta-analyses were conducted for the primary outcome (need for exchange transfusion); one using studies with a low risk of bias and one using studies with a high risk of bias.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Low risk of bias (Santos 2013, Smits-Wintjens 2011, Garcia 2004); high risk of bias (Elalfy 2011, Nasseri 2006, Huang 2006, Miqdad 2004, Pishva 2000, Alpay 1999, Dagaglu 1995, Voto 1995, Rubo 1992).	

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.

Study type:				Systematic review	
Citation:				Mathew JL. (2011) Timing of umbilical cord clamping in term and preterm deliveries and infant and maternal outcomes: a systematic review of randomized controlled trials. Indian Pediatrics, 48: 123–9.	
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:				Appropriate search strategy used and search terms reported. Inclusion/exclusion criteria detailed. Only RCTs included. The quality of studies was assessed using the Cochrane Risk of Bias Tool and reported in the supplementary material (Web Table 1). The outcomes for the individual studies were reported but not the results for each trial, with only pooled data presented. Although several meta-analyses were conducted, a test for heterogeneity was not applied. However, the authors briefly discuss potential heterogeneity, in relation to procedural differences between the trials, and suggest caution when interpreting results.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: The authors rated seven of the preterm studies as having a low risk of bias based on criteria in the Cochrane Risk of Bias tool (Kugelman 2007, Kugelman 2009, Mercer 2003, Mercer 2006, Mercer 2010, Strauss 2008, Strauss 2007). The remainder had moderate or high risk of bias.	

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.

Study type:				Systematic review	
Citation:				McDonald SJ, Middleton P, Dowswell T, Morris PS. (2013) Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database of Systematic Reviews, Issue 7: CD004074.	
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:				Appropriate search strategies and inclusion/exclusion criteria detailed. Only RCTs were included in this review, quasi-randomised studies were excluded. At least two review authors independently assessed the full text of potential studies for inclusion. Data extraction was performed separately and double-checked for discrepancies. There was thorough discussion about the appropriateness of all studies for inclusion. Individual investigators were contacted if clarification was required before inclusion. Risk of bias was assessed using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Both studies attempted to blind the collection of at least some outcome data. Attrition was relatively low in Cernadas 2006. Van Rheenen 2007 had high attrition.	

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.

Study type:				Systematic review	
Citation:				Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. (2012) Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews, Issue 8: CD003248.	
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:				Appropriate search strategies and inclusion/exclusion criteria. RCTs and cluster RCTs were included. Two authors independently assessed all potential studies for inclusion and performed data extraction. Any disagreement was resolved through discussion or with the consult of a third author. Where trial information was unclear, authors of the original trials were contacted for further details. Two authors independently assessed risk of bias for each study using the Cochrane Handbook for Systematic Reviews. Any disagreement was resolved through discussion or by involving a third assessor. Several subgroup analyses were conducted which investigated the impact of specific interventions (eg. cord milking) and study quality (eg. allocation concealment).	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: methods of randomisation and allocation concealment were poorly described for most studies, with only three studies providing clear information (Mercer 2006, Strauss 2008, Oh 2002). Ultee 2008 was judged as having a high risk of bias for allocation concealment. Blinding was not possible due to the nature of the intervention. Blinding of outcome assessment was judged to have an unclear or high risk of bias across all studies. Most outcome data across studies was collected soon after birth so follow-up was not generally a problem. Three studies (Baezinger 2007, Strauss 2008, Ultee 2008) had a high risk of bias in this area due to	

	post-randomisation exclusions leading to results which were difficult to interpret. No clear instances of outcome reporting bias.

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.

Study type:				Systematic review	
Citation:				Schouten ES, van de Pol AC, Schouten ANJ, Turner NM et al. (2009) The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery a meta-analysis. Pediatric Critical Care Medicine, 10(2): 182-190.	
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:				Appropriate search strategies, with inclusion/exclusion criteria reported. Methodological quality of included studies judged independently by two reviewers, with discrepancies resolved by discussion. Quality was judged in terms of allocation, blinding, and follow-up, whereby each criterion was assigned a score of two, one, or zero points. A combined score for allocation, blinding, and follow-up greater than four was considered good. Several meta-analyses were conducted and a test for heterogeneity applied. Studies that were too heterogeneous were not included in the meta-analyses.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: The methodological quality of cardiac studies was generally poor, with only 8/23 studies scoring more than 4 points. Three studies provided an adequate description of allocation concealment, seven studies were double-blinded, and 10 studies reported a follow-up of ≥80%. All patients were randomly allocated except for the large-dose aprotinin arm in the Miller study, and this arm was excluded from analysis. All the scoliosis studies were good quality with a score of four points or more. They adequately described allocation concealment and had a follow-up of at least 80%.	

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.

Study type:				Systematic review	
Citation:				Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. (2012) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database of Systematic Reviews, Issue 3 CD005011.	
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:				Two authors screened all titles and abstracts of papers identified in the literature search. Two authors independently assessed papers at full text, with any discrepancies noted. Data extraction was performed by two authors using standardised forms, with any disagreement resolved through consensus. Quality of included studies was assessed based on criteria from the Cochrane Handbook for Systematic Reviews of Interventions (v 5.0.1). Domains assessed included random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors; reporting of outcome data and other potential threats to validity.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: There were two RCT is paediatric surgery patients (Ekert 2006, Hanna 2010). Ekert 2006 received a low risk of bias for blinding and reporting of outcome data, and an unclear risk of bias for random sequence generation, allocation concealment and selective reporting. Hanna 2010 received an unclear risk of bias in all domains but did not meet our inclusion criteria (not cardiac surgery).	

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.

Study type:				Systematic review	
Citation:				Song G, Yang P, Zhu S, Luo E et al. (2013) Tranexamic acid reducing blood transfusion in children undergoing craniosynostosis surgery. J Cradiofac Surg, 24: 299–303.	
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:				Only controlled trials were included but they could be retrospective, prospective, randomised or non-randomised with a placebo/no treatment group. To be included, studies had to contain sufficient raw data for weighed mean difference with 95% confidence intervals. Data were extracted independently by two reviewers with disagreement resolved by consensus. Methodological quality was assessed using the Jadad composite scale. High quality trials scored >2/5. Characteristics of individual studies were reported but not baseline demographics and characteristics of individual patients.	
Quality rating: [Good/Fair/Poor]				Systematic review: Fair	
				Included studies: The two RCTs (Dadure 2011, Goobie 2011) provided detailed descriptions of the randomisation method (computer-generated), and scored 5/5 points. The main study limitations pertained to justification of sample size, allocation concealment and double blinding. Quality of the retrospective study (Maugans 2011) was not assessed.	

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.

Study type:				Systematic review	
Citation:				Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006883. DOI: 10.1002/14651858.CD006883.pub2.	
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:				The authors reported that data was extracted from each study by two independent reviewers with disagreements resolved through a third author. Trial authors were contacted for additional information on the method of randomisation, allocation concealment, period of outcome evaluation and measures of dispersion. Quality of the studies were assessed on the basis of method of randomisation, method of allocation concealment, blinding of the study, completeness of follow-up and the use of ITT analysis. They rated the studies using a scale of A to D, with D being the lowest quality.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: The authors reported that three studies had low risk of bias (Cole 2003; Florentino 2004; Khoshhal 2003); and three had moderate risk of bias (Cole 2002;Neilipovitz 2001; Sethna 2005).	

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.

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Aggarwal V, Kapoor PM, Choudhury M, Kiran U, Chowdhury U (2012) Utility of sonoclot analysis and tranexamic acid in tetralogy of Fallot patients undergoing intracardiac repair. Annals of Cardiac Anaesthesia, 15(1): 26–31.	
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:				Children were randomised using the random table method. Of the 94 children randomised, 80 completed the study. Of the 14 children excluded, three were receiving aspirin in the preceding 2 weeks, one had renal dysfunction and five in each group underwent intracardiac repair without pulmonary valvotomy and patch repair. Baseline characteristics were similar between groups.	

Quality rating: [Good/Fair/Poor]	Fair

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.

Study type:				Randomised controlled trial	
Citation:				Ahmed Z, Stricker L, Rozzelle A, Zestos M. (2014) Aprotinin and transfusion requirements in pediatric craniofacial surgery. Pediatric Anesthesia, 24: 141–5.	
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:				Method of randomisation not reported. Drug and placebo were prepared and labelled in double blind fashion by an anaesthesiologist not involved in the clinical care of the patients. Baseline characteristics were similar between the groups. All randomised patients were included in final analyses.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Alan S, Arsan S, Okulu E et al. (2014) Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born ≤1500 g: a prospective, randomized, controlled trial. J Pediatr Hematol Oncol, 36(8): e493-e498.	
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:				There were 48 infants randomised. Two infants were excluded from each group due to inappropriate milking technique in the UCM group, and major bleeding or death in the control group. After analysis on the first day, three infants from each group were lost to follow-up due to death or major bleeding. There were 19 infants per group in subsequent analyses. Patients were randomised using sequentially numbered sealed non-transparent envelopes. In case of twin pregnancies, the first one was randomised and the second one was automatically assigned to the opposite arm without randomisation. Umbilical cord milking was performed by one of the investigators (SA) who also took part in most of the deliveries. The intervention was unmasked for the attending neonatal and obstetric teams in the delivery room.	
Quality rating:				Fair	

[Good/Fair/Poor]	

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.

Study type:				Randomised controlled trial	
Citation:				Brum MR, Miura MS, de Castro SF, Machado GM et al. (2012) Tranexamic acid in adenostonsillectomy in children: a double-blind randomized clinical trial. International Journal of Pediatric Otorhinolaryngology, 76: 1401–5.	
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:				Randomised blocks were used to keep a balanced number of patients in each group. Participants within blocks were given increasing numbers which identified a sealed opaque envelope containing treatment assignment. Each surgeon received a randomised block of four patients. At the time of surgery, the team contacted the hospital pharmacy and provided the patient's information and name of the surgeon. The pharmacist in charge opened the corresponding envelope containing the treatment assignment. Blinding of the surgeon, main investigator and patient/family were maintained until after study completion. An ITT analysis was performed as well as a per-protocol analysis where participants who did not receive the intervention or discontinued the intervention were excluded. There was no difference in sex or age between the groups but weight in the TXA group was significantly less than the placebo group. One patient in the TXA group was lost to follow-up. Linear regression including weight, age and treatment showed no significant difference in bleeding between groups.	

Quality rating: [Good/Fair/Poor]	Good

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.

Study type:				Randomised controlled trial	
Citation:				Caputo M, Patel N, Angelini GD, de Siena P et al. (2011) Effect of normothermic cardiopulmonary bypass on renal injury in pediatric cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg, 142: 1114–21.	
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:				Random treatment allocations were generated by computer in advance using block randomisation with varying block sizes. Allocation details were concealed in sequentially numbered, opaque sealed envelopes. Randomisation was revealed to the surgeon after the start of the operation. Urinary markers were measured in duplicate and in a blinded fashion. Patients were managed in the ICU by intensivists and cardiologists blinded to randomisation. Baseline characteristics were similar between the groups. Loss to follow-up not reported, but infants were analysed by ITT. The study sample size was set at 29 patients per group based on previous experience in similar studies, for 80% power at a 5% significance level (two-tailed). There were only 28 patients in the normothermic group.	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Cholette JM, Powers KS, Alfieris GM, Angona R et al. (2013) Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomised, clinical trial. Pediatr Crit Care Med, 14(2): 137–47.	
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:				Block randomisation was used. Subjects were stratified by weight (≤10 kg or >10 kg) and risk-adjusted congenital heart surgery (RACHS-1) score (1-3 = less severe; 4-6 = more severe). The cardiac surgeon was blinded to study group but differences in packaging and labelling of blood products prevented blinding of percussionists, anaesthesiologist, the attending physician and PICU personnel. Knowledge of the treatment groups may have influenced the decision to transfuse RBCs. Baseline characteristics were similar between the groups. Of the 110 infants randomised, 106 participated (three patients had surgery performed off CPB and one patient had surgery postponed). Of the 53 patients in the cell saver group, 50 had cell saver blood collected and 49 had cell saver blood transfused. Subgroup analysis was performed with subjects divided according to low or high RACHS scores. There was no loss to follow-up and no protocol violations.	

Quality rating: [Good/Fair/Poor]	Good

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.

Study type:				Randomised controlled trial	
Citation:				Coniff RF. (1998) The Bayer 022 Compassionate-Use Pediatric Study. Ann Thorac Surg, 65: S31–4.	
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:				The randomisation method and blinding was not reported. Patients were stratified by primary or repeat sternotomy (there were 43 primary and 73 repeat sternotomies). There were only three patients aged ≤1 year randomised to high dose aprotinin which may have distorted results. The authors reported that the sample size was too small to permit formal statistical analysis of outcome data. Also, due to this being a compassionate use study, the authors did not do hands-on monitoring of the trial and reported that data may not be quite as clean as data from a more formal trial. Baseline characteristics and demographics were not reported. Loss to follow-up was not reported but it appeared that all randomised infants were included in analyses.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				D'Errico CC, Munro HM, Buchman SR, Wagner D, Muraszko KM. (2003) Efficacy of aprotinin in children undergoing craniofacial surgery. J Neurosurg, 99:287-290.	
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:				Patients were assigned to a treatment group based on a computer-generated list of random numbers. The same surgical team performed all operations and all were blinded to treatment allocation. Study drugs were prepared by the pharmacy and administered in a double blind fashion. Only the pharmacist who kept a record of the patient's identification number and the randomisation list could identify which study drug was used in case of an emergency. Baseline patient characteristics were similar between groups except for median age (higher in aprotinin group) and lowest Hct level (higher in aprotinin group). Loss to follow-up not explicitly reported, but assumed all patients remained in the study.	

Quality rating: [Good/Fair/Poor]	Good

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.

Study type:				Randomised controlled trial	
Citation:				Eldaba AA, Amr YM, Albirmawy OA. Effects of tranexamic acid during endoscopic sinsus surgery in children. Saudi J Anaesth 2013;7:229-33.	
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:				Randomisation was performed using a computer based random number generator in permuted blocks of varying sizes. Treatment allocations were entered in sealed envelopes that were not opened until consent was obtained. Anaesthesiologists, operating personnel, chief nurse and study staff were blinded to treatment groups. All surgical procedures were conducted by the same surgical team using the same technique. The surgical team was blinded to the study protocol. Baseline characteristics were similar between the groups. Loss to follow-up is not reported but it is assumed all participants were included in the final analysis. No subgroup analyses were reported.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Ferreira CA, Vicente WV, Evora PRB, Rodrigues AJ et al. (2009) Does aprotinin preserve platelets in children with acyanogenic congenital heart disease undergone surgery with cardiopulmonary bypass? Rev Bras Cir Cardiovasc, 24(3): 373–81.	
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:				The method of randomisation was not reported. The study was unblinded. Transfusion of RBC was according to the PICU protocol (details not provided). Baseline characteristics were similar between the groups. Loss to follow-up not reported.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Flaujac C, Pouard P, Boutouyrie P, Emmerich J et al. (2007) Platelet dysfunction after normothermic cardiopulmonary bypass in children: Effect of high-dose aprotinin. Thromb Haemost, 98: 385–91.	
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:				Method of randomisation not described. There were nine newborns aged ≤1 month and 11 infants aged 2-36 months. All patients weighed <15kg and none had a history of major heart surgery. Groups were similar at baseline. Surgeons were unaware of treatment allocation. Loss to follow-up not reported; however it appeared all randomised infants were included in analyses.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Friesen RH, Perryman KM, Weigers KR, Mitchell MB, Friesen RM. (2006) A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants. Pediatric Anesthesia, 16: 429-435.	
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:				Patients were randomised using sealed envelopes opened prior to induction of anaesthesia. How randomisation sequence was generated not stated. Blinding not reported, but assumed patients blinded due to timing of envelopes being opened. Blinding of surgeons and anaesthesiologists would not have been possible due to nature of intervention. No loss to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Hans P, Collin V, Bonhomme V, et al. (2000) Evaluation of acute normovolemic hemodilution for surgical repair of craniosynostosis. Journal of Neurosurgical Anesthesiology, 12(1): 33-6.	
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:				• The method of randomisation and blinding were not reported. All patients were operated by the same surgeon and managed by the same anaesthetist. There were no significant differences between groups at baseline.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Katheria AC, Leone TA, Woelkers D, Garey DM et al. (2014) The effects of umbilical cord milking on hemodynamic and neonatal outcomes in premature neonates. The Journal of Pediatrics, 164: 1045–50.	
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:				Infants were randomised using opaque sealed envelopes immediately before delivery, with stratification by gestational age (23 to <29 or 29 to <32 weeks). Obstetricians and the neonatology team were aware of allocated groups before delivery. Assessment of the primary outcome was blinded. After randomisation, three infants from the UCM group and two infants from the ICC group were excluded due to predefined criteria. Baseline characteristics were similar between the groups. Loss to follow-up was not reported, although it appeared no more infants were excluded from final analyses. A subgroup analysis was conducted based on gestational age.	

Quality rating: [Good/Fair/Poor]	Fair

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.

Study type:				Randomised controlled trial	
Citation:				Lisander B, Jonsson R, and Nordwall A. (1996) Combination of Blood-Saving Methods Decreases Homologous Blood Requirements in Scoliosis Surgery. Anaesth Intens Care, 24: 555-8.	
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:				The method of randomisation and blinding were not reported. Patient baseline characteristics between groups were similar except for the number of segments fused during surgery which were significantly lower in the control group compared to the others ($P < 0.05$). All randomised patients were included in analyses.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Mozol K, Haponiuk I, Byszewski A, Maruszewski B (2008) Cost-effectiveness of mini-circuit cardiopulmonary bypass in newborns and infants undergoing open heart surgery. Kardiologia Polska, 66: 9.	
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:				The method of randomisation and whether blinding was used were not reported. The anaesthetic technique and postoperative management were carried out according to the same protocols. Baseline characteristics were similar between the groups. Loss to follow-up was not reported and it was unclear whether all infants were included in final analyses.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Precious DS, Splinter W, Bosco D. (1996) Induced hypotensive anaesthesia for adolescent orthognathic surgery patients. J Oral Maxillofac Surg, 54: 680–3.	
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:				The method of randomisation was not described. Patients were stratified and blocked according to their proposed surgery. The surgeon was unaware of treatment assignment, and was the one to estimate intraoperative blood loss (based on surgical experience). The anaesthetist also estimated blood loss via accurate tabulation of the volume of fluid within the suction containers minus the amount of irrigation fluids used throughout the procedure. The weight of blood in the sponges was measured and figured into the total estimate. Baseline characteristics were similar between the groups.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Sarupria A, Makhija N, Lakshmy R, Kiran U. (2013) Comparison of difference doses of e-aminoproic acid in children for tetralogy of Fallot sugery: clinical efficacy and safety. Journal of cardiothoracic and vascular anesthesia, 27(1): 23–9.	
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:				Children were randomised via a computer-generated randomisation list. Baseline characteristics were similar between groups except for platelet count, which was significantly higher in groups 2 and 3 (p=0.002). Anaesthesiologists were not blind to treatment allocation, but physicians involved in re-exploration were unaware of treatment allocation. Anaesthetic and surgical management were standardised in all groups, with operations all performed by the same team. A sample size of 40 children per group was calculated to have 80% power to show a difference with a p-value of 0.05.	

Quality rating: [Good/Fair/Poor]	Fair

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.

Study type:				Randomised controlled trial	
Citation:				Singh R, Vellaichamy M, Gowda N, Kumar V et al. (2001) Aprotinin for open cardiac surgery in cyanotic heart disease. Asian Cardiovascular and Thoracic Annals, 9(2): 101–4.	
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:				Patients were randomised using computer-generated random numbers. Standard anaesthetic and surgical techniques were followed in all patients. Patients received aprotinin in a blinded fashion where the principle investigator was unaware of treatment allocation. Baseline characteristics were similar between the groups. Loss to follow-up not reported, although it appeared that all randomised patients were included in analyses.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Thompson GH, Florentino-Pineda I, Poe-Kochert C. (2005) The role of Amicar in decreasing perioperative blood loss in idiopathic scoliosis. Spine, 30(17S):S94-S99.	
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:				The pharmacy allocated patients to Amicar or control using random numbers. Baseline characteristics were reported to be similar between groups; however, individual patient characteristics were not presented. The anaesthesiologist and surgeon were blind to treatment group until study completion. Not reported whether outcome assessors were blind to treatment group. Transfusion was given when Hb<7g/dL. Methods of statistical analysis not reported.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Study type:				Randomised controlled trial	
Citation:				Vacharaksa K, Prakanrattana U, Suksompong S and Chumpathong S. (2002) Tranexamic acid as a means of reducing the need for blood and blood component therapy in children undergoing open heart surgery for congenital cyanotic heart disease. J Med Assoc Thai, 85(S3): S904-S909.	
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:				The method of randomisation was not reported. There were 67 children enrolled, but five were excluded from the placebo group due to reoperation (n=3) and pleural effusion as a result of CHF (n=2) within 24hrs post-surgery. All TXA and placebo solutions were prepared in a blind manner by an individual not involved in the study. Although the study was described as being double-blinded, it was not reported who administered the intervention solution, or whether the surgeons/anaesthesiologists and/or outcome assessors were blind to treatment assignment. Baseline characteristics were similar between the groups.	
Quality rating: [Good/Fair/Poor]				Fair	

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.

Study type:				Randomised controlled trial	
Citation:				Verma K, Errico T, Diefenbach C, Hoelscher C, Peters A, Dryer J, et al. The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: A prospective randomized trial. J Bone Jt Surg Am Vol 2014;96(10):e80.	
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:				Patients were randomised using a computer-generated random assignment. Allocation assignments were blinded from all persons except the pharmacist and remained unchanged for the duration of the study. Unblinding from the study was allowed at any time for medical necessity. Allocation assignments favoured the saline solution group over the treatment groups when the allocation assignments were revealed. Baseline characteristics were similar between groups except for estimated blood volume, which was larger in the saline group. There was no loss to follow-up and all patients were included in the final analysis. Within each group patients were stratified according to mean arterial pressure (MAP) and a subgroup analysis was conducted among patients with low MAP (< 75mmHg).	
Quality rating: [Good/Fair/Poor]				Good	

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.

Study type:				Randomised controlled trial	
Citation:				Ye L, Lin R, Fan Y, Yang L et al. (2013) Effects of circuit residual volume salvage reinfusion on the postoperative clinical outcome for pediatric patients undergoing cardiac surgery. Pediatr Cardiol, 34: 1088–93.	
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:				The method of randomisation and blinding were not reported. There were significantly more patients in the intervention group due to there only being one blood cell saver machine in the hospital during the early stages of research. Another cell saver machine was purchased later which lead to an increased number of patients receiving this treatment. Baseline characteristics between groups were similar. No patients dropped out during the study and it appeared all randomised patients were included in analyses.	
Quality rating: [Good/Fair/Poor]				Poor	

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.

Appendix F Evidence summaries

F1 Evidence summaries – Question 1

Level I evidence

STUDY DETAILS: SR/MA				
Citation				
Bassler D, Weitz M, Bialkowski A, Poets CF (2008) Restrictive Versus Liberal Red Blood Cell Transfusion Strategies for Preterm Infants: A Systematic Review of Randomized Controlled Trials. Current Pediatric Reviews, 4: 143-50.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs and quasi-RCTs	I	Single centre, NR (Bell 2005, Brooks 1999) Multicentre, Canada/USA/Aus (Kirpalani 2006)		
Intervention	Comparator			
Restrictive RBC transfusion	Liberal RBC transfusion			
Population characteristics				
Preterm (<37 weeks gestation) or low birth weight (<2500 g) infants				
Length of follow-up	Outcomes measured			
As reported in included studies	Any clinical outcome			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Seven RCTs were identified of which three reported outcomes relevant to this overview (Bell 2005, Brooks 1999, Kirpalani 2006). All were in VLBW or ELBW infants. Two trials had adequate randomisation (Bell 2005, Kirpalani 2006). Allocation concealment was present in Kirpalani (2006) and was likely present in Bell (2005). ROP examiners were masked to treatment allocation in two studies (Brooks 1999, Kirpalani 2006), as were radiologists (Bell 2006) and investigators (Kirpalani 2006) who interpreted ultrasounds. Follow-up was accounted for in all three studies. The review authors planned to perform meta-analyses using a random effects model but pooling of data wasn't possible due to significant methodological and clinical heterogeneity in regards to study design, patient characteristics, transfusion strategies, and reported outcomes.				
RESULTS:				
Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
BPD (oxygen dependence at 28 days) 2 trials (Bell 2005, Brooks 1999) N=148	33/72 (45.8%)	40/76 (52.6%)	NR	NR

BPD (oxygen dependence at 36 weeks) 2 trials (Bell 2005, Kirpalani 2006) N=458	116/233 (49.8%)	121/225 (53.8%)	NR	NR
ROP (all) 2 trials (Bell 2005, Brooks 1999) N=150	42/73 (57.5%)	46/77 (59.7%)	NR	NR
ROP (≥stage 3) 3 trials (Bell 2005, Brooks 1999, Kirpalani 2005) N=497	40/253 (15.8%)	38/244 (15.6%)	NR	NR
ROP requiring laser treatment 2 trials (Bell 2005, Brooks 1999; N=134)	6/65 (9.2%)	4/69 (5.8%)	NR	NR
Brain injury 1 trial (Kirpalani 2006) N=363	30/188 (16.0%)	22/175 (12.6%)	NR	NR
IVH (grade 3 or 4) 1 trial (Bell 2005) N=100	5/49 (10.2%)	8/51 (15.7%)	NR	NR
PVL 1 trial (Bell 2005) N=100	4/49 (8.2%)	0/51 (0%)	NR	NR
IVH (grade 4) or PVL 1 trial (Bell 2005) N=100	6/49 (12.2%)	0/51 (0%)	NR	NR
NEC 2 trials (Brooks 1999, Kirpalani 2006) N=501	25/247 (10.1%)	19/254 (7.5%)	NR	NR
Death before discharge 2 trials (Bell 2005, Kirpalani 2006) N=551	49/272 (18.0%)*	42/279 (15.1%)*	NR	NR
Death before discharge or severe ROP, BPD or brain injury 1 trial (Kirpalani 2006) N=451	165/223 (74.0%)*	159/228 (69.7%)*	NR	NR
Sepsis 1 trial (Kirpalani 2006) N=451	96/223 (43.0%)	93/228 (40.8%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				

Evidence directly generalisable to low birth weight preterm infants <2500 g. (Level A)
Applicability
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)
Comments
The review authors concluded that clinical and methodological heterogeneity between studies prevents firm conclusions based on the totality of available evidence. According to the results of the largest RCT, maintaining higher haemoglobin levels in ELBW infants seems to confer little clinical benefit. *Numbers adjusted to fix error / typo of treatment group sizes (sizes switched for two outcomes).

BPD, bronchopulmonary dysplasia; CI, confidence interval; ITT, intention-to-treat; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PP, per-protocol; PVL, periventricular leukomalacia; RCT, randomised controlled trial; ROP, retinopathy of prematurity; SD, standard deviation

STUDY DETAILS: SR/MA		
Citation		
Carson JL, Carless PA & Hebert PC (2012) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (Review). Cochrane Database of Systematic Reviews, Issue 4 CD002042.		
Affiliation/Source of funds		
Internal: None. External: NSW Ministerial Advisory Committee on Quality in Health Care, Australia; NSW Health Department, Australia.		
Study design	Level of evidence	Location/setting
Systematic review of controlled trials	I	NR for paediatric trial (Lacroix 2007)
Intervention	Comparator	
Red blood cell transfusion (allogeneic or autologous) at a 'trigger' haemoglobin (Hb) or haematocrit (Hct) threshold.	Red blood cell transfusion (allogeneic or autologous) at a higher Hb or Hct threshold, or transfusion in accordance with current practices	
Population characteristics		
Surgical or medical patients of any age. Neonates were excluded.		
Length of follow-up	Outcomes measured	
120 days.	Primary: proportion of patients "at risk" who were transfused. Secondary: amount of blood transfused, mortality, morbidity (non-fatal myocardial infarction, cardiac events, pulmonary oedema, cerebral vascular accident, thromboembolism, renal failure, infection, haemorrhage, mental confusion), haematocrit level, length of hospital stay.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: 19 studies were included, of which one was in a paediatric population (Lacroix 2007). This was an RCT in stable critically ill children with Hb <9.5 g/dL (anaemic). The authors reported that overall Lacroix 2007 had a low risk of bias, with unclear risk attributed to random sequence generation (no information) and blinding (clinical staff and parents of patients aware of allocation, but statisticians and safety committee members were not).		

RESULTS

Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
30-day mortality 1 trial (N=637)	14/320 (4.4%)	14/317 (4.4%)	RR 0.99 [0.48, 2.04]	No significant difference *P* = NR Heterogeneity=NA
ICU mortality 1 trial (N=637)	11/320 (3.4%)	8/317 (2.5%)	RR 1.36 [0.56, 3.34]	No significant difference *P* = NR Heterogeneity=NA
Renal failure 1 trial (N=637)	2/320 (0.6%)	0/317 (0%)	RR 4.95 [0.24, 102.77]	No significant difference *P* = NR Heterogeneity=NA
Pulmonary oedema 1 trial (N=637)	0/320 (0%)	5/317 (1.6%)	RR 0.09 [0.01, 1.62]	No significant difference *P* = NR Heterogeneity=NA

Pneumonia 1 trial (N=637)	11/320 (3.4%)	10/317 (3.2%)	RR 1.09 [0.47, 2.53]	No significant difference *P* = NR Heterogeneity=NA
Infection 1 trial (N=637)	65/320 (20.3%)	79/317 (24.9%)	RR 0.82 [0.61, 1.09]	No significant difference *P* = NR Heterogeneity=NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill children with anaemia. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)				
Comments				
The authors made no conclusions specific to the paediatric population.				

CI, confidence interval; ICU, intensive care unit; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: SR/MA		
Citation		
Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y, Marsh K, Dickson R, Rees DC. (2012) The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technology Assessment, 16(43): 1-129.		
Affiliation/Source of funds		
Funding received form the National Institute for Health Research Health Technology Assessment programme.		
Study design	Level of evidence	Location/setting
Systematic review of RCTs and cohort studies.	I/III	RCTs: multicentre, USA (Adams 1998); multicentre, USA and Canada (Adams 2005).
Intervention	Comparator	
Blood transfusion, hydroxycarbamide or bone marrow transplantation.	Standard care (no intervention).	
Population characteristics		
Children <16 years with sickle cell disease, identified using TCD ultrasonography, as being at high risk of stroke.		
Length of follow-up	Outcomes measured	
As reported in included studies.	Stroke; major complications e.g. disability from stroke, iron overload, associated morbidity; frequency and duration of hospitalisation; quality of life; major adverse event e.g. alloimmunisation, bloodstream infection, transfusion of wrong components.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Two RCTs were identified for blood transfusion vs standard care (Adams 1998 [STOP], Adams, 2005 [STOP 2]). The review authors rated the overall quality of these trials as adequate. Method of randomisation was reported in a separate design paper. Baseline characteristics were partially comparable in STOP and comparable in STOP 2. Blinding was used where possible/ethical. Both studies reported outcome assessors as blinded to treatment allocation. An intention-to-treat analysis was reported in STOP 1 but not STOP 2. Dropouts were accounted for.		
RESULTS:		

Outcome No. trials (No. patients)	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
Transfusion vs no transfusion (Adams 1998, STOP 1)				
Stroke (all) (N=130)	1/63 (1.6%)	11/67 (16.4%)	92% risk reduction in transfusion group.	Favours transfusion $P < 0.001$
Stroke (cerebral infarction) (N=130)	1/63 (1.6%)	10/67 (14.9%)	NR	NR
Stroke (intracerebral haematoma) (N=130)	0/63 (0.0%)	1/67 (1.5%)	NR	NR
Alloimmunisation to RBC (N=130)	10/63 (15.9%)	0/67 (0%)	NR	NR
Transfusion reaction (N=130)	12/63 (19.0%)	0/67 (0%)	NR	NR

Outcome No. trials (No. patients)	Transfusion n/N (%) Mean ± SD (N)	No transfusion n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
Continued transfusion vs halted transfusion (Adams 2005, STOP 2)				
Stroke (N=79)	0/38 (0%)	2/41 (4.9%)	NR	NR
Reversion to abnormal TCD (N=79)	0/38 (0%)	14/41 (34.1%)	NR	NR
Stroke or reversion to abnormal TCD (N=79)	0/38 (0%)	16/41 (39.0%)	NR	Favours transfusion *P* < 0.001
Alloimmunisation to RBC (N=79)	1/38 (2.6%)	0/41 (0%)	NR	NR
Transfusion reaction (N=79)	7/38 (18.4%)	0/41 (0%)	NR	NR
Serious transfusion reaction (N=79)	1/38 (2.6%)	0/41 (0%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children with sickle cell disease and at high risk of stroke.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)				
Comments				
Both STOP studies were halted early due to safety concerns and risks associated with the control arm. The review authors concluded that the use of TCD ultrasonography to identify children at high risk of stroke, and treating these children with prophylactic blood transfusions, appears to be both clinically effective and cost-effective compared with TCD ultrasonography only (no transfusion). Clinically, more research is needed to assess the effects and optimal duration of long-term blood transfusion in primary stroke prevention.				

CI, confidence interval; RCT, randomised controlled trial; SD, standard deviation; TCD, transcranial Doppler

STUDY DETAILS: SR/MA				
Citation				
Desjardins P, Turgeon AF, Tremblay M, Lauzier F, Zarychanski R, Boutin A, Moore L, McIntyre LA, English SW, Rigamonti A Lacroix J, Fergusson DA. (2012) Hemoglobin levels and transfusion in neurocritically ill patients: a systematic review of comparative studies. Critical Care 16:R54				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs and non-randomised comparative studies.	Level I	Belgium/Canada/UK/USA (Lacroix 2007)		
Intervention	Comparator			
Haemoglobin thresholds or targets at one level RBC transfusion protocol	Haemoglobin thresholds or targets at another level RBC transfusion alternate protocol			
Population characteristics				
Neurocritically ill patients admitted to Intensive Care Unit (ICU). Exclusion criteria: sickle cell anaemia and scoliosis surgery patients, neonates (< 28 days old).				
Length of follow-up	Outcomes measured			
28 days (Lacroix 2007)	Primary: all-cause mortality Secondary: neurological status, ICU length of stay, hospital length of stay, duration of mechanical ventilation, surrogate measures of brain oxygen delivery, complications, serious adverse events.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Six studies were included, of which one RCT (Lacroix 2007) was in the paediatric population. Subjects in this study were children with neurocritical conditions (traumatic brain injury, intracranial haemorrhage, brain tumour, neurosurgery, cerebral oedema, and other space-occupying injuries). Lacroix 2007 was judged by review authors as having a low risk of bias, despite lack of blinding which was accepted due to the nature of the intervention. Lacroix 2007 examined the effect of restrictive RBC transfusion (when Hb≤7g/dL) compared with liberal RBC transfusion (when Hb≤9.5 g/dL).				
RESULTS				
Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Mortality 1 study (Lacroix 2007) N=66	2/30 (6.7%)	1/36 (2.8%)	OR 2.50 [0.22, 29.01]	No significant difference *P* = NR Heterogeneity=NA
New or worsening MODS (multiple organ dysfunction) 1 study (Lacroix 2007) N=66	16.6%	8.3%	NR	No significant difference *P* = 0.45 Heterogeneity=NA
Infection 1 study (Lacroix 2007) N=66	10/30 (33.3%)	14/36 (38.9%)	NR	*P* = NR Heterogeneity=NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill paediatric patients with neurocritical conditions. (Level A)				

Applicability
Evidence applicable to Australian healthcare context with few caveats. (Level B)
Comments
The authors made no conclusions specific to the paediatric population. Overall, they concluded that there was insufficient evidence to confirm or refute a difference in effect between lower– and higher Hb thresholds in neurocritically ill patients.

CI, confidence interval; Hb, haemoglobin; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: SR/MA		
Citation		
Ibrahim M, Ho Kah Ying S, Cheo Lian Y (2014) Restrictive versus liberal red blood cell transfusion thresholds in very low birth weight infants: A systematic review and meta-analysis. Journal of Paediatrics and Child Health, 50: 122-30.		
Affiliation/Source of funds		
None reported.		
Study design	Level of evidence	Location/setting
Systematic review of RCTs	I	Australia, USA, Canada (Kirpalani 2006), USA (Bell 2005), Taiwan (Chen 2009).
Intervention	Comparator	
Restrictive red blood cell transfusion.	Liberal red blood cell transfusion.	
Population characteristics		
Very low birth weight (VLBW) infants (<1500 g).		
Length of follow-up	Outcomes measured	
NR	Primary: mortality Secondary: number of RBC transfusions, donor exposure rate, brain injury (diagnosed via cranial ultrasonography), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) or necrotising enterocolitis (NEC)	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Three RCTs were included (Kirpalani 2006, Bell 2005, Chen 2009) which were rated by review authors as having sufficient methodological quality. All studies performed randomisation and had allocation concealment. No studies reported blinding of the caregiver or principle investigator; however, this was reported for the patients, outcome assessors and data analysts. ITT analyses were conducted in all studies.		
RESULTS		

Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
Mortality 3 trials (N=590)	53/292 (18.2%)	44/298 (14.8%)	RR 1.23 [0.86, 1.76]	No significant difference *P* = 0.26 Heterogeneity=0%
Brain injury 3 trials (N=491)	118/238 (49.6%)	105/253 (41.5%)	RR 1.21 [1.00, 1.46]	Borderline favours liberal RBC transfusion *P* = 0.05 Heterogeneity=0%
ROP ≥stage 3 3 trials (N=496)	35/241 (14.5%)	37/255 (14.5%)	RR 1.04 [0.68, 1.58]	No significant difference *P* = 0.87 Heterogeneity=0%
BPD 3 trials (N=491)	119/237 (50.2%)	126/254 (49.6%)	RR 1.03 [0.86, 1.22]	No significant difference *P* = 0.77 Heterogeneity=0%
NEC 3 trials (N=590)	21/292 (7.2%)	13/298 (4.4%)	RR 1.62 [0.83, 3.13]	No significant difference *P* = 0.16 Heterogeneity=0%
EXTERNAL VALIDITY				

Generalisability
Evidence directly generalisable to VLBW infants (<1500 g).
Applicability
Evidence applicable to the Australian healthcare context with few caveats.
Comments
The review authors concluded that in VLBW infants, a restrictive transfusion threshold does not appear to effect ROP, BPD, NEC or mortality outcomes. This suggests its utilisation will not increase the risk of death or major short-term morbidities. Authors noted that larger trials are required to explore the effects of restrictive RBC transfusion thresholds on long-term neurodevelopmental outcomes.

BPD, bronchopulmonary disease; CI, confidence interval; ITT, intention-to-treat; NEC, necrotising enterocolitis; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; SD, standard deviation; VLBW, very low birth weight.

STUDY DETAILS: SR/MA				
Citation				
Kirpalani H, Zupancic JAF (2012) Do Transfusions Cause Necrotizing Enterocolitis? The Complementary Role of Randomized Trials and Observational Studies. Seminars in Perinatology, 36: 269-76.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence	Location/setting		
Systematic review of cohort and case-control studies.	I/III	NR		
Intervention	Comparator			
Packed red blood cell (RBC) transfusion.	No transfusion.			
Population characteristics				
Newborns who developed necrotising enterocolitis (NEC)				
Length of follow-up	Outcomes measured			
NR	NEC			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: 10 studies were included; 6 cohort (Blau 2011, Christensen 2009, Holder 2009, Mally 2006, Paul 2011, Valieva 2009) and 4 case-control (El-Dib 2011, Josephson 2010, McGrady 1987, Singh 2011). Results were compared with the pooled data of three RCTs reported in a Cochrane Review by Whyte (2011). Of the cohort studies, the review authors rated all six as having a medium risk of bias. The case-control studies were rated as having a lower risk of bias. The authors stated that the major concern for bias in all studies was in clear identification of absence of preclinical NEC before transfusion. Study validity concerns were also raised regarding outcome assessment and blinding for retrospective chart reviews, leading to possible over-diagnosis of NEC. Two studies in the meta-analysis of cohort studies, and one study in the meta-analyses of case-control studies, did not report the total number of participants for intervention and control groups, only the number of events. Pooled results include incomplete data and overestimate the incidence of NEC. Heterogeneity was also very high for both meta-analyses, so results should be interpreted with a high level with caution.				
RESULTS:				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity (I^2)
RBC transfusion vs no transfusion				
NEC 6 cohort studies (Blau 2011, Christensen 2009, Holder 2009, Mally 2006, Paul 2011, Valieva 2009; N=22,155)	150/2940 (5.1%)	182/19215 (0.9%)	OR 7.48 [5.87, 9.53]	Favours no transfusion *P* < 0.00001 Heterogeneity=98%
NEC 4 case-control studies (El-Dib 2011, Josephson 2010, McGrady 1987, Singh 2011; N=567)	129/186 (69.4%)	129/381 (33.9%)	OR 2.19 [1.52, 3.17]	Favours no transfusion *P* < 0.0001 Heterogeneity=92%
Restrictive RBC transfusion vs liberal RBC transfusion (from Whyte 2011)				
NEC 3 RCTs (N=590)	21/292 (7.2%)	13/298 (4.4%)	RR 1.67 [0.82, 3.38]	No significant difference *P* = 0.15 Heterogeneity=0%
EXTERNAL VALIDITY				

Generalisability
Evidence directly generalisable to newborns. No information was provided on individual patient characteristics within the included studies.
Applicability
Evidence may or may not be applicable to Australian healthcare context (study locations not reported).
Comments
The authors noted that their point estimates differed from those observed by Mohammed (2012) but were of a similar direction and magnitude.

CI, confidence interval; RCT, randomised controlled trial; SD, standard deviation;

STUDY DETAILS: SR/MA				
Citation				
Meremikwu MM, Smith HJ (2010) Blood transfusion for treating malarial anaemia (Review). Cochrane Database of Systematic Reviews, Issue 4 CD001475.				
Affiliation/Source of funds				
Internal: University of Calabar, Nigeria. External: Department for International Development, UK; European Commission, Belgium; Liverpool School of Tropical Medicine, UK.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs and quasi-RCTs.	I	Gambia (Bojang 1997), Tanzania (Holzer 1993).		
Intervention	Comparator			
Blood transfusion.	Conservative management (no transfusion).			
Population characteristics				
Children or adults with severe anaemia (haematocrit <20%) and confirmed malaria parasitaemia. Studies outside of malarious areas were excluded.				
Length of follow-up	Outcomes measured			
2 months.	Primary: death within 2 months. Secondary: severe adverse events, duration of hospital stay, re-admissions, respiratory distress in 1st week, need for additional transfusion, increase in haematocrit, HIV and Hepatitis B status.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Two RCTs were included; both were in paediatric populations (Bojang 1997, Holzer 1993). Study quality was assessed using the standard methods of the Cochrane Infectious Diseases Group. The review authors rated both studies as having an unclear risk of bias. Allocation concealment was unclear and investigators were not blind to treatment allocation. Neither study was analysed according to the intention-to-treat principle. Note: "very severe" cases of malarial anaemia were reported as being excluded from both RCTs; although the included cases were still much more severe than anaemias seen in Australia.				
RESULTS				
Outcome No. trials (No. patients)	Blood transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)
Death 2 studies (N=230)	1/118 (0.8%)	3/112 (2.7%)	RR 0.41 [0.06, 2.70]	No significant difference *P* = 0.35 Heterogeneity=0.0%
Severe adverse events 2 studies (N=230)	8/118 (6.8%)	0/112 (0%)	RR 8.60 [1.11, 66.42]	Favours no transfusion *P* = 0.039 Heterogeneity=0.0%
Respiratory distress events 1 study (N=114)	0/58 (0%)	11/56 (19.6%)	RR 0.04 [0.00, 0.70]	Favours transfusion *P* = 0.027 Heterogeneity=NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with severe anaemia (Hct <20%) and confirmed malaria parasitaemia.				
Applicability				

Evidence not applicable to Australian healthcare context. Studies conducted in least developed countries (Level D).
Comments
The review authors concluded that for children living in malarious areas with severe anaemia and no respiratory distress, there is insufficient reliable information to determine whether blood transfusion is beneficial. Note: Holzer 1993 was published prior to 1995 and the control group in Bojang 1997 received iron.

CI, confidence interval; Hct, haematocrit; HIV, human immunodeficiency virus; NA, not applicable; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: SR/MA				
Citation				
Mohamed A, Shah PS (2012) Transfusion Associated Necrotizing Enterocolitis: A Meta-analysis of Observational Data. Paediatrics, 129: 529-40.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence	Location/setting		
Systematic review of cohort and case-control studies.	I/III	NR		
Intervention	Comparator			
Packed red blood cell (RBC) transfusion.	No transfusion.			
Population characteristics				
Neonates.				
Length of follow-up	Outcomes measured			
48 hours.	Primary: Development of necrotising enterocolitis (NEC) within 48hrs of transfusion.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Twelve studies were included (11 case controls, 1 retrospective cohort study). The review authors rated the quality of four studies 6/10 which correlated to a moderate risk of bias, and eight studies 8/10 which correlated to a low risk of bias. There was some dissimilarity in patient baseline characteristics. The review authors reported adjusted analyses but did not state which confounders were controlled for.				
RESULTS				
Outcome No. trials (No. patients)	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity (I^2)
NEC (unadjusted estimate) 5 trials (Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Wan-Huen 2011; N=916)	NR	NR	OR 3.91 [2.97, 5.14]	Favours no transfusion *P* < 0.00001 Heterogeneity=58%
NEC (adjusted estimate) 4 trials (Harsono 2011, Paul 2011, Stritzke 2011, Wan-Huen 2011; N=3863)	NR	NR	OR 2.01 [1.61, 2.50]	Favours no transfusion *P* < 0.00001 Heterogeneity=91%
NEC (adjusted estimate) 3 trials (Paul 2011, Stritzke 2011, Wan-Huen 2011; N=NR)	NR	NR	OR 2.48 [1.97, 3.12]	Favours no transfusion *P* = NR Heterogeneity=0%
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to neonates.				
Applicability				
Evidence may or may not be applicable to Australian healthcare context (study location not reported).				
Comments				

Seven studies (Perciaccante 2008, Christensen 2009, El-Dib 2011, Paul 2011, Singh 2011, Stritzke 2011, Wan-Huen 2011) reported an association between transfusions and NEC. One study (Mally 2006) reported no association between transfusion and NEC within or after 48 hours. One study (Harsono 2011) reported divergent results, with a protective effect of RBC transfusion observed. When this was removed from the adjusted meta-analysis, heterogeneity was reduced to 0%.

CI, confidence interval; NEC, necrotising enterocolitis; RBC, red blood cell; SD, standard deviation;

STUDY DETAILS: SR/MA		
Citation		
Venkatesh V, Khan R, Curley A, Hopewell S, Doree C, Stanworth S. (2012) The safety and efficacy of red cell transfusions in neonates: a systematic review of randomized controlled trials. British Journal of Haematology, 158: 370-85.		
Affiliation/Source of funds		
None reported.		
Study design	Level of evidence	Location/setting
Systematic review of RCTs and quasi-RCTs.	I	NR
Intervention	Comparator	
RBC transfusion. RBC transfusion at one threshold. RBC transfusion at one dose. RBC transfusion of one type/product (e.g. storage medium, leucodepletion).	No transfusion. RBC transfusion at another threshold. RBC transfusion at another dose. RBC transfusion of another type/product (e.g. storage medium, leucodepletion).	
Population characteristics		
Neonates (term or preterm) less than 28 days corrected postnatal age.		
Length of follow-up	Outcomes measured	
NR	Primary: mortality, neurodevelopmental outcome at 2 years corrected age, respiratory morbidities e.g. chronic lung disease Secondary: duration of ventilation and oxygen therapy (days), time to discharge, co-morbidities, retinopathy of prematurity (ROP), intraventricular haemorrhage, necrotising enterocolitis (NEC), periventricular leukomalacia (PVL), total transfusions requirements, changes in Hb concentration/haematocrit, adverse effects.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: 27 RCTs were included, of which five were relevant to this overview (Kirpalani 2006, Chen 2009, Bell 2005, Brooks 1999, Mukhopadhyay 2004). All examined restrictive RBC transfusion compared with liberal RBC transfusion. The review authors stated that the overall quality of reporting was poor, with only two studies having good methodological practices in all areas examined (Bell 2005, Kirpalani 2006).		
RESULTS:		

Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity (I^2)
Restrictive RBC transfusion vs liberal RBC transfusion				
Mortality 4 trials (Kirpalani 2006, Chen 2009, Bell 2005 and Brooks 1999; N=636)	51/313 (16.3%)	43/323 (13.3%)	RR 1.22 [0.84, 1.75]	No significant difference *P* = 0.30 Heterogeneity=0%
Mortality 1 trial (Mukhopadhyay 2004, N=38)	NR/20	NR/18	RR 3.5 [0.62, 1.18]	No significant difference *P* = NR Heterogeneity=NA
Chronic lung disease 4 trials (Kirpalani 2006, Chen 2009, Bell 2005 and Brooks 1999; N=544)	135/263 (51.3%)	147/281 (52.3%)	RR 0.99 [0.84, 1.15]	No significant difference *P* = 0.86 Heterogeneity=4%
Neurodevelopmental disability				

Any neurosensory impairment (18-21 months follow-up) 1 trial (Kirpalani 2006; N=328)	46/160 (28.8%)	37/168 (22.0%)	OR 1.62 [0.95, 2.76]	No significant difference *P* = NR Heterogeneity=NA
Cerebral Palsy (18-21 months follow-up) 1 trial (Kirpalani 2006; N=335)	11/163 (6.7%)	9/172 (5.2%)	OR 1.32 [0.53, 3.27]	No significant difference *P* = NR Heterogeneity=NA
Cognitive delay (18-21 months follow-up) 1 trial (Kirpalani 2006; N=321)	38/156 (24.4%)	29/165 (17.6%)	OR 1.74 [0.98, 3.11]	No significant difference *P* = NR Heterogeneity=NA
Severe visual impairment (18-21 months follow-up) 1 trial (Kirpalani 2006; N=334)	2/161 (1.2%)	1/173 (1.7%)	OR 2.16 [0.19, 24.09]	No significant difference *P* = NR Heterogeneity=NA
Severe hearing impairment (18-21 months follow-up) 1 trial (Kirpalani 2006; N=334)	4/161 (2.5%)	3/173 (1.7%)	OR 1.45 [0.32, 6.58]	No significant difference *P* = NR Heterogeneity=NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to neonates less than 28 days corrected age.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study locations not reported.				
Comments				
Meta-analyses could only be performed for a small number of trials due to clinical diversity, the small number of studies in sub-categories, and lack of data on clinical outcomes in many trials. Note: Mukhopadhyay 2004 was an abstract only, therefore not identified in our literature search.				

CI, confidence interval; Hb, haemoglobin; RCT, randomised controlled trial; SD, standard deviation;

STUDY DETAILS: SR/MA		
Citation		
Wang WC and Dwan K (2013) Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. Cochrane Database Systematic Reviews, Issue 11 CD003146		
Affiliation/Source of funds		
Internal: None reported. External: Department of Health, Research and Development, UK. Winifred Wang was a principal investigator on all included trials.		
Study design	Level of evidence	Location/setting
Systematic review of randomised controlled trials	Level I	USA (Adams 1998 [STOP]), USA/Canada (Adams 2005 [STOP 2])
Intervention	Comparator	
Chronic blood transfusion	Standard care (other transfusion regimen) Hydroxyurea No treatment	
Population characteristics		
Persons with sickle cell disease (HbSS, SC, Sß$^{+}$, Sß^{0} proven by electrophoresis, with family studies or DNA tests as appropriate) of all ages, whether or not they have a history of prior stroke or transient ischaemic attack.		
Length of follow-up	Outcomes measured	
NR	Primary: death from any cause, incidence of stroke (by clinical signs and symptoms, MRI scan, CT scan or autopsy), transfusion-related complications (including alloimmunisation, infection from blood product, procedural complications, transfusion reactions, reduced immunocompetency, iron overload). Secondary: incidence of transient ischaemic attacks or silent infarction, measures of neurological impairment and neuropsychiatric performance, incidence of other sickle cell complications (e.g. pain crises, acute chest syndrome, splenic sequestration), quality of life, inpatient stay, immobility and disability, measures of organ damage (e.g. renal, liver and lung function tests), haemoglobin level and HbS percentage.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Three RCTs were included, of which two were relevant to this overview (Adams 1998 [STOP], Adams 2005 [STOP 2]). Blinding of participants and clinicians was not feasible in either study due to the nature of interventions. In both trials, outcome assessors were blind to subjects' treatment allocation. This included experts who adjudicated suspected strokes in STOP 2. An intention-to-treat analysis was utilised in STOP 1, but was not reported in STOP 2. In STOP 2, the reasons for patient withdrawals were not provided. No meta-analysis was performed due to heterogeneity between patient populations (all patients in STOP 2 had been treated with chronic transfusion for a minimum of 30 months).		
RESULTS		

Outcome No. trials (No. patients)	Blood transfusion n/N (%)	Standard care n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Mortality 1 trial (N=130) 1 trial (N=79)	 0/63 (0%) 1/38 (2.63%)	 0/67 (0%) 0/41 (0%)	 0.0 [0.0, 0.0] 3.32 [0.13, 84.01]	NA
Clinical stroke 1 trial (N=130) 1 trial (N=79)	 1/63 (1.59%) 0/38 (0%)	 11/67 (16.42%) 2/41 (4.88%)	 0.08 [0.01, 0.66] 0.21 [0.01, 4.41]	NA

Other neurological events: new silent infarcts 1 trial (N=127)	1/56 (1.79%)	11/71 (15.49%)	0.10 [0.01, 0.79]	NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with sickle cell disease at high risk of stroke and/or who had received regular blood transfusions for at least 30 months.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Included study origin/sites are Level B (Canada) and Level C (USA).				
Comments				
Although the authors intended to include persons of all ages with sickle cell disease, the studies identified were all in children. The literature search also identified three ongoing trials.				

CI, confidence interval; NA, not applicable; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: SR/MA				
Citation				
Whyte, R. and Kirpalani, H. (2011) Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database of Systematic Reviews, Issue 11 CD000512.				
Affiliation/Source of funds				
The authors have no conflicts of interest to declare.				
Study design	Level of evidence	Location/setting		
Systematic review of randomised and quasi-randomised clinical trials.	Level I	USA (Bell 2005, Blank 1984), Canada (Connelly 1999), Taiwan (Chen 2009), and Australia/Canada/USA (Kirpalani 2006 [PINT]).		
Intervention		Comparator		
Restrictive transfusion at a low haemoglobin/haematocrit level No transfusion until clinical signs of anaemia		Liberal transfusion at a high haemoglobin/haematocrit level Transfusion at a set level of haemoglobin or haematocrit		
Population characteristics				
Very low birth weight infants (birth weight less than or equal to 1500 g, or infants less than 32 weeks gestational age) admitted to neonatal intensive care, at less than one week of age.				
Length of follow-up	Outcomes measured			
N/A	Primary: death (before discharge from initial hospitalisation or before a defined follow-up period), a composite of death or severe adverse outcomes: death or severe morbidity e.g. retinopathy of prematurity, severe adverse ultrasound findings, bronchopulmonary dysplasia (BPD); death or severe adverse neurosensory outcome e.g. cerebral palsy, developmental delay, blindness, deafness. Secondary: severe morbidity, moderate morbidity, haemoglobin or haematocrit level at discharge, number of transfusions and donor exposures per infant, measures of cost-effectiveness of blood transfusion, postnatal acquisition of viral infection, weight gain, incidence of apnoea of prematurity. Added after the review: persistent patency of the ductus arteriosus, necrotising enterocolitis (NEC), moderate to severe adverse neurosensory outcomes at 18 months follow-up.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Five RCT studies were included (Bell 2005, Blank 1984, Connelly 1999, Chen 2009, Kirpalani 2006). Four studies examined restrictive transfusion vs liberal transfusion, and one study (Blank 1984) examined no transfusion until clinical symptoms vs transfusion at a set Hb or Hct level. All studies had a high or unclear risk of performance or detection bias due to lack of blinding and selective reporting. Allocation concealment was reported as low risk for all studies. Bell 2005 was at high risk of bias for incomplete outcome data. Infant deaths were reported in individual studies and excluded from analyses – the review authors note they have been reintroduced into their own analyses. Connelly 1999 was closed early due to poor recruitment and compliance, resulting in a lack of power and ability to detect differences in outcomes. The review authors note that the risk of measurement or judgement bias is minimal given the nature of the outcomes. Appropriate search strategies were used. While the haemoglobin thresholds for restrictive transfusion were similar among the included studies, this was not the case for liberal transfusion thresholds.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Control n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity (I^2)
Restrictive RBC transfusion vs liberal RBC transfusion				
Mortality				

Prior to first hospital discharge 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=614)	53/305 (17.38%)	44/309 (14.24%)	RR 1.23 [0.86, 1.76]	No significant difference *P* = 0.26 Heterogeneity=0%
By 18-21 months follow-up 1 trial (Kirpalani 2006; N=421)	48/208 (23.08%)	45/213 (21.13%)	RR 1.09 [0.76, 1.56]	No significant difference *P* = 0.63 Heterogeneity=NA
Composite of mortality and severe morbidity				
Death or severe morbidity prior to first hospital discharge 3 trials (Kirpalani 2006, Bell 2005, Chen 2009; N=511)	180/255 (70.59%)	167/256 (65.23%)	RR 1.07 [0.96, 1.20]	No significant difference *P* = 0.22 Heterogeneity=0%
Death or severe morbidity with MDI <70 by 18-21 months follow-up 1 trial (Kirpalani 2006; N=421)	94/208 (45.19%)	82/213 (38.50%)	RR 1.17 [0.94, 1.47]	No significant difference *P* = 0.16 Heterogeneity=NA
Death or severe morbidity with MDI <85 by 18-21 months follow-up 1 trial (Kirpalani 2006; N=421)	125/208 (60.10%)	106/213 (49.77%)	RR 1.21 [1.01, 1.44]	Favours liberal transfusion *P* = 0.034 Heterogeneity=NA
Death or severe brain injury by first hospital discharge 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=614)	87/305 (28.52%)	79/309 (25.57%)	RR 1.12 [0.81, 1.55]	No significant difference *P* = 0.48 Heterogeneity=6%
Severe morbidity				
Brain injury on ultrasound in survivors 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=517)	34/252 (13.49%)	35/265 (13.21%)	RR 1.07 [0.50, 2.27]	No significant difference *P* = 0.86 Heterogeneity=30%
BPD (oxygen dependence at 28 days) 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=544)	198/266 (74.44%)	207/278 (74.46%)	RR 0.99 [0.92, 1.06]	No significant difference *P* = 0.78 Heterogeneity=0%

BPD (oxygen dependence at 36 weeks gestation) 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=524)	125/254 (49.21%)	133/270 (49.26%)	RR 1.03 [0.87, 1.21]	No significant difference *P* = 0.75 Heterogeneity=0%
NEC 3 trials (Kirpalani 2006, Bell 2005, Chen 2009; N=590)*	21/292 (7.19%)	13/298 (4.36%)	RR 1.62 [0.83, 3.13]	No significant difference *P* = 0.16 Heterogeneity=0%
ROP (all cases) 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=517)	134/252 (53.17%)	146/265 (55.09%)	RR 0.98 [0.84, 1.14]	No significant difference *P* = 0.81 Heterogeneity=0%
ROP (grade 1 or 2) 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=517)	99/252 (39.29%)	109/265 (41.13%)	RR 0.96 [0.78, 1.18]	No significant difference *P* = 0.67 Heterogeneity=0%
ROP (≥ grade 3) 4 trials (Kirpalani 2006, Bell 2005, Chen 2009, Connelly 1999; N=517)	35/252 (13.89%)	37/265 (13.96%)	RR 1.04 [0.68, 1.58]	No significant difference *P* = 0.87 Heterogeneity=0%
Neurodevelopmental disability				
Cognitive delay MDI <70 (unadjusted) 1 trial (Kirpalani 2006; N=321)	38/156 (24.36%)	38/156 (24.36%)	RR 1.39 [0.90, 2.13]	No significant difference *P* = NR
Cognitive delay MDI <70 (adjusted for gestational age and study site) 1 trial (Kirpalani 2006; N=321)			OR 1.74 [0.98, 3.11]	No significant difference *P* = NR
Cognitive delay MDI <85 (unadjusted) 1 trial (Kirpalani 2006; N=321)	70/156 (44.87%)	56/165 (33.94%)	RR 1.32 [1.00, 1.74]	Borderline favours liberal transfusion *P* = NR
Cognitive delay MDI <85 (adjusted for gestational age and study site) 1 trial (Kirpalani 2006; N=321)			OR 1.81 [1.1, 1.8]	Favours liberal transfusion *P* = NR
Cerebral palsy 1 trial (Kirpalani 2006; N=335)	11/163 (6.75%)	9/172 (5.23%)	RR 1.29 [0.55, 3.03]	No significant difference *P* = NR

Severe visual impairment 1 trial (Kirpalani 2006; N=334)	2/16 (1.24%)	1/173 (0.58%)	RR 2.15 [0.20, 23.47]	No significant difference *P* = NR
Severe hearing impairment 1 trial (Kirpalani 2006; N=334)	4/161 (2.48%)	3/173 (1.73%)	RR 1.43 [0.33, 6.30]	No significant difference *P* = NR
Any neurosensory impairment 1 trial (Kirpalani 2006; N=328)	46/160 (28.75%)	37/168 (22.02%)	RR 1.31 [0.90, 1.90]	No significant difference *P* = NR
Transfusion for clinical signs only vs transfusion at haemoglobin threshold				
Mortality (Blank 1984)				
Death prior to discharge 1 trial (N=56)	0/30 (0%)	0/26 (0%)	NA	NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to very low birth weight infants (<1500 g).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study sites/origins are Level A (Australia), Level B (Canada), and Level C (USA, Taiwan).				
Comments				
The review authors concluded that the use of restrictive as compared with liberal haemoglobin thresholds in infants of very low birth weight results in modest reductions in exposure to transfusion and in Hb levels. Restrictive practice does not appear to have a significant impact on death or major morbidity at first hospital discharge or at follow-up. However, given the uncertainties of these conclusions, it would be prudent to avoid haemoglobin levels below the lower limits tested here. Further trials are required to clarify the impact of transfusion practice on long-term outcome. Note: Blank 1984 was identified in our literature search and excluded based on "wrong publication date." Connelly 1999 was an unpublished trial and not identified in our literature search. It was stopped early due to poor enrolment and compliance. *Bell 2005 did not report on NEC in the original paper.				

BPD, bronchopulmonary dysplasia; CI, confidence interval; MA, meta-analysis; NA, not applicable; NEC, necrotising enterocolitis; NR, not reported; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review

STUDY DETAILS: SR/MA		
Citation		
Wilkinson KL, Brunskill SJ, Doree C, Trivella M, Gill R, and Murphy MF (2014) Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease. Cochrane Database of Systematic Reviews, Issue 2 CD009752.		
Affiliation/Source of funds		
Internal: NHS Blood and Transplant, Research and Development, UK. External: None reported.		
Study design	Level of evidence	Location/setting
Systematic review of randomised controlled trials	Level I	USA (Cholette 2011), USA/Canada/Belgium (Willems 2010).
Intervention	Comparator	
Restrictive transfusion (haemoglobin trigger ~7-8g/dL) Higher volume red cell transfusion Leukoreduced red cell transfusion Whole blood transfusion 'New' (not near expiry date) red cell transfusion Standard CPB prime	Liberal transfusion (haemoglobin trigger ~9-10 g/dL) Lower volume red cell transfusion Non-leukoreduced red cell transfusion Packed red cell transfusion 'Old' (near to expiry date) red cell transfusion Non-standard CPB prime	
Population characteristics		
Patients undergoing cardiac surgery for congenital heart disease. The congenital heart disease could be cyanotic or acyanotic. Patients were grouped by age: neonates (newborns up to four weeks old), paediatrics (children four weeks post birth to age 16 years) and adults (over 16 years).		
Length of follow-up	Outcomes measured	
Until hospital discharge (Cholette 2011) 28 days (Willems 2010)	Primary: all-cause mortality (0 to 30 days post-surgery) Secondary: all-cause mortality long-term (30 days to 2 years post-surgery), severe adverse events (cardiac events, acute lung injury, stroke, thromboembolism, renal failure, infection, haemorrhage), haematocrit/haemoglobin concentrations postoperative and at discharge, volume or number of red cell units transfused, volume or number of other blood products transfused (i.e. fresh frozen plasma, platelets or cryoprecipitate), postoperative chest drain output, duration of mechanical ventilation, duration of ICU stay, rehospitalisation rates, biochemistry levels.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Eleven RCTs were included, of which two (Cholette 2011, Willems 2010) were relevant to this overview. Cholette 2011 had an unclear risk of bias relating to random sequence generation (insufficient information), allocation concealment (not reported), and blinding of outcome assessment (not reported). The review authors also noted a high risk of performance bias due to staff and patient families being aware of transfusion assignment. Other domains were assessed as low risk. Willems 2010 was assessed as having a low risk of bias in all domains except blinding (performance bias) where clinicians and carers were aware of treatment allocation. Due to the diverse patient populations included in individual studies, no meta-analyses were conducted.		
RESULTS		

Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity (I^2)
Restrictive RBC transfusion vs liberal RBC transfusion				
Mortality				

All-cause mortality: 30 days post-surgery 1 trial (Willems 2010, N=125)	2/63 (3.17%)	2/62 (3.23%)	RR 0.98 [0.14, 6.77]	N/A
All-cause mortality: at two years 1 trial (Cholette 2011, N=60)	0/30 (0%)	1/30 (3.33%)	RR 0.33 [0.01, 7.87]	N/A
Transfusion related SAEs				
Acute lung injury 1 trial (Willems 2010, N=125)	38/63 (60.32%)	39/62 (62.90%)	RR 0.96 [0.73, 1.26]	N/A
Infection 1 trial (Willems 2010, N=125)	13/63 (20.63%)	18/62 (29.03%)	RR 0.71 [0.38, 1.32]	N/A
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with congenital heart disease undergoing or post cardiac surgery.				
Applicability				
Evidence applicable to Australian healthcare context with some caveats. Included study origins were Canada/Belgium (Level B) and USA (Level C).				
Comments				
The review authors concluded that due to the small number of small and heterogeneous trials, there is insufficient evidence to assess the impact of red cell transfusion in patients with congenital heart disease undergoing cardiac surgery. It is possible that the presence or absence of cyanosis impacts on outcomes, which would necessitate different clinical management of the two groups.				

CI, confidence interval; CPB, cardiopulmonary bypass; ICU, intensive care unit; MA, meta-analysis; NA, not applicable; RCT, randomised controlled trial; RR, risk ratio; SAE, serious adverse event; SR, systematic review

Level II evidence

STUDY DETAILS: RCT				
Citation				
Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. The New England Journal of Medicine, 339(1): 5-11.				
Affiliation/Source of funds				
Supported by Cooperative Agreements with the National Heart, Lung and Blood Institute.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, USA	
Intervention	Comparator			
Blood transfusion.	Standard care (no transfusion).			
Population characteristics				
130 children (60 boys, 70 girls) aged 2 to 16 years diagnosed with sickle cell anaemia or sickle beta thalassemia, and with a high risk of stroke. Exclusion criteria: history of stroke, indication or contraindication to long-term transfusion, receiving treatments that affect risk of stroke, HIV infection, previously treated for seizures, pregnant, serum ferritin >500 ng/mL.				
Length of follow-up	Outcomes measured			
42 months (study halted after 26 months).	Primary: stroke (cerebral infarction or intracranial haemorrhage) Secondary: mortality, adverse reactions.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: An RCT of 130 children with sickle cell disease and a high risk of stroke, to examine the effect of RBC transfusion compared with standard care on stroke. Standardised TCD and MRI/MRA protocols were interpreted blindly, and primary endpoint (stroke) was assessed blind to treatment assignment. Subjects could not be blind to treatment group due to the nature of the intervention. The sample size was sufficient to detect 70% reduction in the primary endpoint at 90% power. Loss to follow-up was reported (one patient). Patient characteristics were similar between treatment groups with the exception of baseline haemoglobin and haematocrit values being lower in the transfusion group.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	63		67	
Efficacy analysis (ITT)	63		67	
Efficacy analysis (PP)	NA		NA	
Safety analysis	63		67	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Stroke (cerebral infarction or intracerebral hematoma)	1/63 (1.6%)	11/67 (16.4%)	Risk of stroke 92% lower in transfusion group.	Favours transfusion $P < 0.001$
Cerebral infarction	1/63 (1.6%)	10/67 (14.9%)	Risk of stroke 91% lower in transfusion group.	Favours transfusion $P = 0.002$
Intracerebral hematoma	0/63 (0%)	1/67 (1.5%)	NR	NR
Mortality	0/63 (0%)	0/67 (0%)	NR	No significant difference P = NA

Alloimmunisation	10/63 (15.9%)	0/67 (0%)	NR	NR
Mild reactions to blood products	12/63 (19.0%)	0/67 (0%)	NR	NR
Hepatitis C	0/63 (0%)	0/67 (0%)	NR	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
The results are generalisable to children with sickle cell anaemia or sickle beta thalassemia.				
Applicability				
The results are somewhat applicable to the Australian setting.				
Comments				
This trial is also known as the STOP trial. Due to the high rate of stroke in the standard care (no transfusion) group, and the significant effect of transfusion found at the second interim analysis, the data safety and monitoring board recommended that the trial be stopped 16 months prematurely. The authors concluded that RBC transfusion greatly reduces the risk of a first stroke in children with sickle cell anaemia who have abnormal results on transcranial Doppler ultrasonography. Note: the design paper which included study methodology was published separately.				

CI, confidence interval; ITT, intent to treat; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; TCD, transcranial Doppler

STUDY DETAILS: RCT				
Citation				
Adams RJ, Brambilla D. (2005) Discontinuing Prophylactic Transfusions Used to Prevent Stroke in Sickle Cell Disease. The New England Journal of Medicine, 353: 2769-78.				
Affiliation/Source of funds				
Grants from the National Heart, Lung, and Blood Institute. No conflicts of interest relevant to the article were reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre, USA and Canada.	
Intervention		Comparator		
Continued blood transfusion.		No continued blood transfusion (transfusion halted).		
Population characteristics				
79 children with sickle cell disease aged 2-16 years who had a high risk of stroke based on transcranial Doppler screening, who had been receiving chronic RBC transfusions. Exclusion criteria: severe stenotic lesions on cerebral magnetic resonance angiography.				
Length of follow-up		Outcomes measured		
48 months (trial halted after 4th interim analysis due to safety concerns).		Primary: stroke, reversion to a result on Doppler examination indicative of a high risk of stroke (within 6 months of intervention). Secondary: laboratory values (6-months post intervention), adverse reactions.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: An RCT comparing continued blood transfusion to halted blood transfusion in children with sickle cell disease at high risk of stroke. Patients were stratified according to absence/presence of ischaemic lesions. Standardised TCD and MRI/MRA protocols were interpreted blindly, and primary endpoint (stroke) was assessed blind to treatment assignment. Subjects could not be blind toed to treatment group due to the nature of the intervention. There were no significant differences in baseline characteristics between groups. Of 38 patients in the continued transfusion group, 32 were still receiving transfusions at the end of the study (5 stopped treatment and 1 died of complications of acute chest syndrome). Of 41 patients in the control group, 9 recommenced transfusion or started hydroxyurea treatment (patients designated as crossover and data censored) and 16 were being followed without treatment or end point events at study end.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	38		41	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Transfusion continued n/N (%) Mean ± SD (N)	Transfusion halted n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance *P*-value
Stroke	0/38 (0%)	2/41 (4.9%)	NR	NR
Reversion to high risk Doppler result	0/38 (0%)	14/41 (34.1%)	NR	NR
Stroke or reversion to high risk Doppler result	0/38 (0%)	16/41 (39.0%)	NR	Favours continued transfusion $P < 0.001$

Mortality as a result of acute chest syndrome	1/38 (2.6%)	0/41 (0%)	NR	NR
Transfusion reaction	7/38 (18.4%)	NA	NA	NA
Serious transfusion reaction	1/38 (2.6%)	NA	NA	NA
Alloimmunisation	1/38 (2.6%)	NA	NA	NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children with sickle cell disease at high risk of stroke.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study sites Canada (Level B) and USA (Level C)				
Comments				
This is an extension of the STOP trial (Adams 1998), also known as STOP 2. Some patients participated in the original trial and others were recruited. The trial was halted prematurely on the advice of the data safety and monitoring committee because of safety concern at the fourth interim analysis. The authors concluded that discontinuation of transfusion for the prevention of stroke in children with sickle cell disease results in a high rate of reversion to abnormal blood flow velocities on Doppler studies and stroke. Note: the design paper which included study methodology was published separately.				

CI, confidence interval; ITT, intent to treat; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; TCD, transcranial Doppler

STUDY DETAILS: RCT				
Citation				
Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, Cress GA, Johnson KJ, Kromer IJ, Zimmerman MB. (2005) Randomized Trial of Liberal Versus Restrictive Guidelines for Red Blood Cell Transfusion in Preterm Infants. Pediatrics, 115(6): 1685-91.				
Affiliation/Source of funds				
Grants were received from the National Institute of Health, USA. No conflicts of interest were declared.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, USA.	
Intervention		Comparator		
Restrictive RBC transfusion (Hct threshold varied according to respiratory status).		Liberal RBC transfusion (Hct threshold varied according to respiratory status).		
Population characteristics				
100 preterm infants with birth weights 500-1300 g. Exclusion criteria: alloimmune haemolytic disease, congenital heart disease, major birth defects requiring surgery, chromosomal abnormality.				
Length of follow-up	Outcomes measured			
NR	No. of RBC transfusions, no. of RBC donor exposures, survival to discharge, occurrence of patent ductus arteriosus, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), duration of assisted ventilation, duration of supplemental oxygen therapy, no. and frequency of apnoea episodes ≥20 seconds, time to regain birth weight and to double birth weight, length of hospital stay.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 103 preterm infants with VLBW, to examine the effect liberal compared with restrictive RBC transfusion on mortality and severe morbidity. Methods of randomisation and allocation concealment were reported. Blinding was not reported, and it is assumed that the trial was not blinded due to differences in procedures between groups. Loss to follow-up was reported due to death (2 infants in the liberal group and 1 infant in the restrictive group)*. Patient baseline characteristics were similar between groups, although males were more predominant in the restrictive transfusion group (61% vs 41%, p=0.049). Some protocol violations occurred. Note: six infants in the liberal transfusion group (12%), and five infants in the restrictive transfusion group (10%) did not receive a transfusion. Two transfusions in the liberal group and 17 transfusions in the restrictive group did not meet the study criteria for transfusion. In seven cases, infants in the liberal group met the study criteria for a transfusion but were not transfused. This did not occur in the restrictive group.				
RESULTS				
Population analysed	Restrictive transfusion		Liberal transfusion	
Randomised	50		53	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	49		51	
Safety analysis	NR		NR	
Outcome	Restrictive n/N (%)	Liberal n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality*	2/49 (4.1%)	1/51 (2.0%)	NR	No significant difference *P* = 0.614
PVL (brain injury)	4/49 (8.2%)	0/51 (0%)	NR	No significant difference *P* = 0.115

IVH (any grade)	14/49 (28.6%)	17/51 (33.3%)	NR	No significant difference *P* = 0.669
IVH (grade 3 or 4)	5/49 (10.2%)	8/51 (15.7%)	NR	No significant difference *P* = 0.555
IVH (grade 4)	4/49 (8.2%)	0/51 (0%)	NR	No significant difference *P* = 0.054
IVH (grade 4) or PVL	6/49 (12.2%)	0/51 (0%)	NR	Favours liberal transfusion *P* = 0.012
ROP (total)	22/49 (44.9%)	27/51 (52.9%)	NR	No significant difference *P* = 0.520
ROP ≥ stage 3	2/49 (4.1%)	2/51 (3.9%)	NR	No significant difference *P* = 1.0
BPD, oxygen dependence at 28d	17/48 (35.4%)	19/50 (38.0%)	NR	No significant difference *P* = 0.836
BPD, oxygen dependence at 36wk	13/45 (28.9%)	20/50 (40.0%)	NR	No significant difference *P* = 0.287
Sepsis	0/49 (0%)	0/51 (0%)	NR	No significant difference *P* = NR
Transfusion reaction	0/49 (0%)	0/51 (0%)	NR	No significant difference *P* =NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors noted some concern regarding the difference between adverse neurological events between liberal and restrictive transfusion groups, although cite no causal relationship. The authors concluded that although both transfusion programs were well tolerated, the finding of more frequent major adverse neurologic events in the restrictive RBC transfusion group suggests that this practice may be harmful to preterm infants. *published analysis excluded 3 infants who died within 48 hours of randomisation; these infants were added to the analysis (ITT) in published meta-analyses by Whyte (2011) and Ibrahim (2014).				

BPD, bronchopulmonary dysplasia; CI, confidence interval; Hct, haematocrit; ITT, intent to treat; IVH, intraventricular haemorrhage; NR, not reported; PP, per-protocol; PVL, periventricular leukomalacia; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; VLBW, very low birth weight

STUDY DETAILS: RCT				
Citation				
Brooks SE, Marcus DM, Gillis D, Pirie E, Johnson MH, Bhatia J. (1999) The Effect of Blood Transfusion Protocol on Retinopathy of Prematurity: A Prospective, Randomized Study. Pediatrics, 104(3): 514-518.				
Affiliation/Source of funds				
A grant was received from the Knights Templar Eye Foundation, Inc.				
Study design	Level of evidence		Location/setting	
RCT	Level II		NICU unit, single hospital, USA.	
Intervention	Comparator			
RBC transfusions from age 29-71 days with the goal to maintain haematocrit ratio between 20 and 30% (restrictive).	RBC transfusions from age 29-71 days with the goal to maintain haematocrit ratio ≥40% (liberal).			
Population characteristics				
50 infants with birth weights ≤1250 g. Exclusion criteria: lethal congenital anomalies, cyanotic heart disease, coagulopathy, major ocular abnormalities bilaterally, too medically unstable according to the attending neonatologist.				
Length of follow-up	Outcomes measured			
6 weeks.	Primary: retinopathy of prematurity (ROP). Secondary: mortality, necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), mean Hct, mean Hb, mean number of RBC transfusions.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 50 preterm infants with VLBW, to examine the effect of restrictive compared with liberal RBC transfusion on ROP and other severe morbidities. Examiners were masked to treatment assignment. Patient characteristics were similar at baseline and during the study period. Loss to follow-up was reported (16 infants in the restrictive group and 18 infants in the liberal group completed the full 6-week study period (p=0.77).				
RESULTS				
Population analysed	Restrictive RBC transfusion		Liberal RBC transfusion	
Randomised	24		26	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Restrictive n/N (%)	Liberal n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality	0/24 (0%)	0/26 (0%)	NR	No difference between groups *P* = NA
ROP (total)*	20/24 (83.3%)*	19/26 (73.0%)	NR	No significant difference *P* = 0.38
ROP (birth weight ≤750 g) N=11	6/6 (100%)	3/5 (60.0%)	NR	No significant difference *P* = 0.18
ROP (birth weight 751-1000 g) N=24	9/11 (81.8%)	10/13 (76.9%)	NR	No significant difference *P* = 1.00

ROP (birth weight 1001-1250 g) N=15	4/7 (57.1%)	6/8 (75.0%)	NR	No significant difference *P* = 0.61
NEC	6/24 (25.0%)	7/26 (26.9%)	NR	No significant difference *P* = 0.88
BPD	16/24 (66.7%)	21/26 (80.8%)	NR	No significant difference *P* = 0.26
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
No differences in morbidity or mortality were noted between the groups. The authors concluded that a transfusion policy aimed at limiting the amount of blood given to premature infants during the neonatal period does not impart a significantly different risk for ROP or other associated conditions, than does a policy in which transfusions are given more liberally. * As reported in text (in table 19/24 patients in the restrictive group developed ROP).				

BPD, bronchopulmonary dysplasia; CI, confidence interval; Hb, haemoglobin; ITT, intent to treat; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; VLBW, very low birth weight

STUDY DETAILS: RCT				
Citation				
Chen H, Tseng H, Lu C, Yang SN, Chen H, Yang RC. (2009) Effect of Blood Transfusions on the Outcome of Very Low Body Weight Preterm Infants under Two Different Transfusion Criteria. Pediatric Neonatology, 50(3): 110-116.				
Affiliation/Source of funds				
A grant was received from the Premature Baby Foundation of Taiwan.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single NICU, Taiwan.	
Intervention	Comparator			
Restrictive RBC transfusion - Infants with assisted ventilation: >33% Hct - Infants with nasal CPAP support: >30% Hct - Infants breathing spontaneously: >22% Hct	Liberal RBC transfusion - Infants with assisted ventilation: >45% Hct - Infants with nasal CPAP support: >40% Hct - Infants breathing spontaneously: >30% Hct			
Population characteristics				
36 very low birth weight (VLBW, ≤1500 g) preterm infants. Exclusion criteria: major birth defects or chromosomal abnormality.				
Length of follow-up	Outcomes measured			
30 days.	Mortality, intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), patent ductus arteriosus, sepsis, oxygen dependence at 28 days and at 36 weeks postconceptional age, days on ventilator, apnoea and bradycardia, time to regain and double birth weight, length of hospital stay.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 36 preterm infants with VLBW, to examine the effect of restrictive compared with liberal RBC transfusion on mortality and severe morbidity. Blinding was not reported, and it is assumed that the trial was not blinded due to differences in procedures between groups. Patient baseline characteristics were similar between groups. Three cases were excluded from analysis (2 restrictive, 1 liberal). Seventeen infants per treatment arm were required to detect statistically significant differences in number of transfusions between groups (80% power); however, only 16 infants completed the full duration of the liberal study arm.				
RESULTS				
Population analysed	Restrictive RBC transfusion		Liberal RBC transfusion	
Randomised	19		17	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Restrictive n/N (%)	Liberal n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality	2/19 (10.5%)	1/17 (5.9%)	NR	No significant difference *P* = 0.337
IVH (all)	5/17 (29.4%)	4/16 (25.0%)	NR	No significant difference *P* = 0.776
IVH (grade 3 or 4)	1/17 (5.9%)	2/16 (12.5%)	NR	No significant difference *P* = 0.509
ROP (all)	4/17 (23.5%)	4/16 (25.0%)	NR	No significant difference *P* = 0.922

ROP (≥ stage 3)	0/17 (0%)	2/16 (12.5%)	NR	No significant difference *P* =0.133
NEC	1/17 (5.9%)	0/16 (0%)	NR	No significant difference *P* = 0.325
Oxygen dependence at 28 days	9/17 (52.9%)	5/16 (31.3%)	NR	No significant difference *P* = 0.208
Oxygen dependence at 36 weeks	5/17 (29.4%)	3/16 (18.8%)	NR	No significant difference *P* =0.475
Sepsis	9/17 (52.9%)	11/16 (68.8%)	NR	No significant difference *P* = 0.353
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with birth weights ≤1500 g.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site Taiwan (Level C).				
Comments				
The authors concluded that both transfusion thresholds had similar clinical outcomes, although liberal transfusion resulted in a greater amount of blood transfused and a low reticulocyte count at 30 days of age. The authors suggest restrictive criteria for minimizing the overall amount of transfusion to less than 30 mL may be a better way of preventing chronic lung disease (indicated by oxygen dependence at 28 days) in VLBW infants.				

CI, confidence interval; CPAP, continuous positive airway pressure; ITT, intent to treat; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity; VLBW, very low birth weight

STUDY DETAILS: RCT				
Citation				
Cholette JM, Rubenstein JS, Alfieris GM, Power KS, Eaton M, Lerner NB. (2011) Children with single-ventricle physiology do not benefit from higher haemoglobin levels post cavopulmonary connection: Results of a prospective, randomized, controlled trail of a restrictive versus liberal red-cell transfusion strategy. Pediatric Critical Care Medicine, 12(1): 39-45.				
Affiliation/Source of funds				
Support in part was received from the University of Rochester Strong Children's Research Center Research and Development Award. The authors reported no conflict of interest.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single centre, USA	
Intervention	Comparator			
Restrictive RBC transfusion (Hb <9.0 g/dL plus clinical symptoms of anaemia)	Liberal RBC transfusion (Hb <13.0 g/dL regardless of clinical symptoms)			
Population characteristics				
62 children (mean age ~30 months) scheduled for elective partial or total cavopulmonary connection (Bi-directional Glenn (BDG) or Fontan procedure). Exclusion criteria: no consent.				
Length of follow-up	Outcomes measured			
48 hours.	Primary: peak and mean arterial lactate post cavopulmonary connection. Secondary: surrogate measures of oxygen delivery, clinical outcomes including mortality.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 62 children undergoing cardiac surgery, to examine the effect of restrictive compared with liberal RBC transfusion on arterial lactate, oxygen delivery and clinical outcomes. Method of randomisation not reported; however, blocking (size 8) was used to ensure equal numbers of subjects having BDG or Fontan procedures within groups. Allocation concealment not reported. The cardiac surgeon, anaesthesiologist, perfusionist, operating room staff and data safety monitor were blinded to study assignment; but clinical staff and patient families were not. No subjects dropped out of the study and none were lost to follow-up, however, one subject from each group was unable to have surgery and was therefore excluded from analysis. There was 100% compliance to protocol procedures. The study was not powered to assess for clinical outcome differences including mortality. Note: the liberal threshold is much higher than what would be used for current practice in Australia.				
RESULTS				
Population analysed	Restrictive RBC transfusion		Liberal RBC transfusion	
Randomised	31		31	
Efficacy analysis (ITT)	30		30	
Efficacy analysis (PP)	NA		NA	
Safety analysis	30		30	
Outcome	Restrictive n/N (%)	Liberal n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality	0/30 (0%)	1/30 (3.3%)	NR	Z = -0.01
EXTERNAL VALIDITY				
Generalisability				
Evidence generalisable to paediatric patients scheduled for cardiac surgery.				

Applicability
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).
Comments
The authors concluded that children with single-ventricle physiology do not benefit from a liberal transfusion strategy after cavopulmonary connection. A restrictive RBC transfusion strategy decreases the number of transfusions, donor exposures, and potential risks in these children. Subgroup analysis was completed of BDG and Fontan subjects and although not powered to test for statistical differences, revealed similar results between groups. The authors noted that if the sample size had been larger, differences between groups may have reached significance.

BDG, bi-directional Glenn; CI, confidence interval; Hb, haemoglobin; ITT, intent to treat; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial

STUDY DETAILS: RCT		
Citation		
DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA (2014). Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. New Engl J Med 2014; 371(8):699-710.		
Affiliation/Source of funds		
Supported by grants from the National Institute of Neurological Disorders and Stroke (5U01NS042804, 3U01NS042804 [American Recovery Reinvestment ACT supplementary grant] to Dr. DeBaun); the Institute of Clinical and Translational Sciences, National Center for Research Resources, and the National Center for Advancing Translational Sciences, Clinical and Translational Research; NIH Roadmap for Medical Research (UL1TR000448, to Washington University; UL1TR001079, to Johns Hopkins University; and UL1TR000003, to the Children's Hospital of Philadelphia); and Research and Development in the National Health Service, United Kingdom. Dr. McKinstry reports receiving honoraria and lecture fees from Siemens Healthcare and consulting fees from Guerbet; Dr. Woods, receiving fees for serving on a data and safety monitoring board from Mast Therapeutics and grant support from ClinDatrix and Novartis; Dr. Kwiatkowski, receiving fees for serving on an advisory board from Shire Pharmaceuticals, consulting fees from Shire Pharmaceuticals and Sideris Pharmaceuticals, and grant support from Resonance Health; Dr. Heiny, receiving lecture fees from Novartis; Dr. Redding-Lallinger, receiving grant support from Eli Lilly and Mast Therapeutics; and Dr. Casella, receiving honoraria, travel support, and consulting fees through his institution from Mast Therapeutics and being an inventor and a named party on a patent and licensing agreement for an assay panel of brain biomarkers for the detection of brain injury (PCT US2011/056338), licensed to ImmunArray with pending royalties only. No other potential conflict of interest relevant to this article was reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Multi-centre, USA, Canada, France and United Kingdom

Intervention	Comparator
Regular blood transfusion – transfusion approximately monthly to maintain a target haemoglobin concentration greater than 9.0 g/dL and a target haemoglobin S concentration of 30% or less of total haemoglobin (transfusion group) *Site investigators were advised to initiate chelation therapy for patients who had ferritin levels greater than 1500 ng/mL for 2 or more consecutive months.	Standard care – no treatment for silent infarcts, including no hydroxyurea therapy (observation group)
Population characteristics	
Paediatric patients aged 5-15 years with a confirmed diagnosis of haemoglobin SS or haemoglobin Sß^0 and at least one infarct-like lesion on the screening MRI scan. An infarct-like lesion was defined as an MRI signal abnormality that was at least 3 mm in one dimension and that was visible in two planes on fluid-attenuated inversion recovery (FLAIR) T_2-weighted images, as determined by agreement of two of the three study neuroradiologists. Exclusion criteria: history of focal neurologic deficit associated with an infarct on brain MRI, a seizure disorder, treatment with hydroxyurea in the previous 3 months, a history of regular transfusion therapy or imaging or non-imaging transcranial Doppler measurement that was above the study-defined thresholds.	
Length of follow-up	Outcomes measured
Up to 44 months	Primary: recurrence of infarct or haemorrhage as determined by neuroimaging, clinical evidence of permanent neurologic injury or both (primary end point). A transient ischaemic attack (TIA) was included in secondary analyses of neurologic outcomes, mortality, transfusion reactions. Secondary: changes in cognition (IQ scores using Wechsler Preschool and Primary Scale of Intelligence III), Behaviour Rating Inventory of Executive Function (BREIF) scores
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	

Rating: Fair

Description: Participants were randomised by a statistical data coordinating centre with the use of a permuted block design and stratified by site, age and sex. No attempt at allocation concealment is reported. The study was a single blinded trial. Baseline patient characteristics and demographics were similar except for reticulocyte count (*P* = 0.002). Loss to follow-up was documented but it is not reported if outcome was assessed blind to treatment allocation. This was a multicentre study but results are only provided collectively, rather than by site. No subgroup analyses were reported.

RESULTS

Population analysed	Intervention		Comparator	
Randomised	99		97	
Efficacy analysis (ITT)	99		97	
Efficacy analysis (PP)	90		106	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Blood transfusion vs standard care				
Mortality	0	0	NR	NA
Recurrence of infarct or haemorrhage as determined by neuroimaging, clinical evidence of permanent neurologic injury or both	6/99 (6.1%)	14/97 (14.4%)	OR 0.31 [0.10, 0.93]	Favours blood transfusions *P* = 0.04
Incidence of infarct recurrence	2.0/100 person-years at risk	4.8/100 person-years at risk	RR 0.41 [0.12, 0.99]	Favours blood transfusions *P* = 0.04
TIA	0/99 (0%)	3/97 (3.1%)	NR	*P* = NR
Incidence 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 blood transfusions *P* = 0.02
Transfusion reactions	15/90 (16.7%) *9 participants had one reaction, 6 had two reactions and 1 had four reactions	1/106 (0.95%)	NR	*P* = NR
Transfusion reaction (allergic)	13/25 (52.0%)			
Transfusion reaction (febrile non-haemolytic)	8/25 (32.0%)			

EXTERNAL VALIDITY

Generalisability

The study is generalisable to paediatric patients with sickle cell anaemia.

Applicability

Evidence applicable to Australian health-care context with few caveats. The study was conducted in Canada, France, United Kingdom (Level B) and the USA (Level C).

Comments
The authors noted that more than 15% of patients (15/99) assigned to the transfusion group never received effective therapy; 9 participants declined transfusion therapy following treatment allocation and 6 crossed over to the observation group at a median of 34 days.

ITT, intention-to-treat; MRI, magnetic resonance imaging; NR, not reported; OR, odds ratio; PP, per-protocol; SD, standard deviation; RCT, randomised controlled trial; RR, risk ratio; TIA, transient ischaemic attack

STUDY DETAILS: RCT				
Citation				
Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman A, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS, Tech M.. (2006) The Premature Infants In Need of Transfusion (PINT) Study: A randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. Journal of Pediatrics 149: 301-7.				
Affiliation/Source of funds				
The study was supported by the Canadian Institutes Health Research (FR No.41549, 2000-2004).				
Study design	Level of evidence		Location/setting	
RCT	Level II		10 NICUs in Canada, the US and Australia (2x USA, 6x Canada, 2x Australia).	
Intervention	Comparator			
Restrictive RBC transfusion (Hb ≤68-115 g/L depending on age and level of respiratory support)	Liberal RBC transfusion (Hb ≤77-135 g/L depending on age and level of respiratory support)			
Population characteristics				
451 infants weighing <1000 g birth weight (ELBW), gestational age <31 weeks and <48 hours old. Exclusion criteria: infants with cyanotic heart disease, congenital anaemia, acute shock, transfusion after 6 hours of age, family history of anaemia and haemolytic disease, or where the attending physician anticipated using erythropoietin.				
Length of follow-up	Outcomes measured			
12 weeks.	Primary: composite of death before discharge home or survival with severe morbidity (ROP, BPD or brain injury) Secondary: Hb level, no. of RBC transfusions, no. of donor exposures, rate of growth, supplemental oxygen, ventilation, apnoea, NEC, bowel perforation, serum ferritin changes, sepsis.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A multicentre RCT of 451 ELBW preterm infants, to examine the effect of restrictive compared with liberal RBC transfusion on a composite of mortality and severe morbidity. Randomisation was achieved via computer-generated sequencing. No attempt was made to blind clinicians or caregivers as concealment of Hb levels was considered unethical and impractical. Morbidity outcomes were assessed blind to treatment allocation. There were no significant differences in baseline characteristics between groups. There was no reported loss to follow and primary outcome data was available for all 451 infants.				
RESULTS				
Population analysed	Restrictive transfusion		Liberal transfusion	
Randomised	223		228	
Efficacy analysis (ITT)	223		228	
Efficacy analysis (PP)	NA		NA	
Safety analysis	NR		NR	
Outcome	Restrictive n/N (%)	Liberal n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Composite of death, severe ROP, BPD and brain injury	165/223 (74.0%)	159/228 (69.7%)	OR 1.30 [0.83, 2.02]	No significant difference *P* = 0.25
Death	48/223 (21.5%)	40/228 (17.5%)	OR 1.38 [0.84, 2.27]	No significant difference *P* = 0.21

Survival with severe ROP (≥grade 3)	33/175 (18.9%)	33/188 (17.6%)	OR 1.27 [0.71, 2.26]	No significant difference *P* = 0.42
Survival with BPD	101/175 (57.7%)	103/188 (54.8%)	OR 1.18 [0.76, 1.85]	No significant difference *P*-value = 0.46
Survival with brain injury	22/175 (12.6%)	30/188 (16.0%)	OR 0.86 [0.53, 1.39]	No significant difference *P* = 0.53
NEC	NR (8.5%)	NR (5.3%)	Mean difference 3.3% [-1.8, 7.8]	No significant difference *P* = 0.20
Sepsis	NR (43%)	NR (41%)	Mean difference 1.8% [-7.7, 11.3]	No significant difference *P* = 0.70
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW preterm infants.				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. Study sites/origins were Australia (Level A), Canada (Level B) and USA (Level C). Specific sites and patient numbers per site were not reported.				
Comments				
The authors concluded that maintaining higher Hb levels in ELBW infants results in more infants receiving transfusions but confers little evidence of benefit. They state that transfusion thresholds in ELBW infants can be moved downwards by at least 10 g/L without increased risk of death or neonatal morbidity. Note: All centres used iron supplementation according to treatment guidelines.				

BPD, bronchopulmonary dysplasia; CI, confidence interval; ELBW, extremely low birth weight; Hb, haemoglobin; ITT, intent to treat; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; ROP, retinopathy of prematurity

STUDY DETAILS: RCT				
Citation				
Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K, Peters MJ. (2007) Transfusion Strategies for Patients in Pediatric Intensive Care Units. The New England Journal of Medicine, 356(16): 1609-19.				
Affiliation/Source of funds				
Supported by grants (84300 and 130770) from the Canadian Institutes of Health Research and by grants (3348 and 3568) from the Fonds de la Recherche en Sante du Quebec. Drs. Lacroix and Hebert report receiving consulting fees and grant support from Johnson & Johnson; Dr. Hebert also reports receiving consulting fees and unrestricted funds from Novo Nordisk and Amgen serving as a Career Scientist of the Ontario Ministry of Health (1994-2004), and receiving unrestricted training funds from Canadian Blood Services; Dr. Hume reports being employed by the Canadian Blood Services; and Dr. Peters reports receiving consulting fees from Baxter, Xoma, and Eli Lilly. No other potential conflicts of interest relevant to this article were reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		19 PICUs in four countries (3x Belgium, 10x Canada, 3x UK and 3x US).	
Intervention	Comparator			
Restrictive RBC transfusion (7g/dL).	Liberal RBC transfusion (9.5 g/dL).			
Population characteristics				
637 stable, critically ill children between 3 days and 14 years of age with Hb ≤9.5 g/dL within the first 7 days after admission into PICU. Exclusion criteria: patients expected in stay <24hrs in PICU, acute blood loss, weight <3kg, cardiovascular problems, haemolytic anaemia, enrolled in another study, or no approval from physician.				
Length of follow-up	Outcomes measured			
28 days.	Primary: concurrent dysfunction to 2+ organ systems (MODS), progression of MODS as evidenced by worsening of 1+ organ dysfunctions. Secondary: change in Paediatric Logistic Organ Dysfunction (PELOD) score, mortality, sepsis, transfusion reaction, nosocomial respiratory infection, catheter-related infection, adverse events, length of stay in hospital and PICU.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: An RCT in 19 PICUs in four countries comparing restrictive RBC transfusion to liberal RBC transfusion in stable, critically ill children. Randomisation method, allocation concealment and blinding were reported. Clinical staff and parents were aware of the treatment assignment, but the statistician and members of the data and safety monitoring committee were not. A per-protocol analysis was performed for the primary outcome – 99% of patients met the 80% adherence criterion. This differed only slightly from the intention-to-treat analysis. An interim analysis was conducted when 50% of participants had been enrolled. Loss to follow-up (2%) was reported in 11 patients due to missing data (n=3) and invalid data (n=8); however, the authors report this was low enough to prevent any bias attributable to sample size slippage. Site specific data was only reported for primary outcomes.				
RESULTS				
Population analysed	Restrictive transfusion		Liberal transfusion	
Randomised	327		321	
Efficacy analysis (ITT)	320		317	
Efficacy analysis (PP)	319		307	
Safety analysis	NR		NR	
Outcome	Restrictive n/N (%) Mean ± SD (n)	Liberal n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value

New or progressive MODS	38/320 (12%)	39/317 (12%)	RR 0.4 [-4.6, 5.5]	No significant difference *P* = NI
No. of dysfunctional organs	1.6 ± 1.4 (320)	1.5 ± 1.2 (317)	Difference in means -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)	Difference in means -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)	Difference in means -0.8 [-1.7, 0.1]	No significant difference *P* = 0.13
Mortality in PICU	11/320 (3%)	8/317 (3%)	RR -0.9 [-3.6, 1.7]	No significant difference *P* = 0.50
Mortality in 28 days (all-cause)	14/320 (4%)	14/317 (4%)	RR 0 [-3.2, 3.2]	No significant difference *P* = 0.98
Nosocomial infection	65/320 (20%)	79/317 (25%)	RR 4.6 [-1.9, 11.1]	No significant difference *P* = 0.16
Transfusion reaction	3/320 (1%)	6/317 (2%)	RR 1.0 [-0.9, 2.8]	No significant difference *P* = 0.34
1+ adverse events	97/320 (30%)	90/317 (28%)	RR -1.92 [-9.0, 5.2]	No significant difference *P* = 0.59
1+ serious adverse events	19/320 (5.9%)	19/317 (6.0%)	NR	No significant difference *P* = 0.98
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to stable, critically ill paediatric patients.				
Applicability				
Evidence applicable to the Australian healthcare context with some caveats. Studies were performed in predominantly Level B countries (Belgium (n=132), Canada (n=408) and UK (n=49)).				
Comments				
The authors note that the low mortality rate in children (4%) would not allow them to design a study with sufficient power to detect a meaningful change in death rates as has been done in adult studies. As such, a composite outcome of death and development of MODS was used. The authors concluded that in stable, critically ill children, a haemoglobin threshold of 7g/dL for RBC transfusion can decrease transfusion requirements without increasing adverse outcomes. Recommendations were made for a restrictive transfusion strategy in paediatric patients whose condition is stable in the ICU. This recommendation is not applicable to adult or other paediatric populations.				

CI, confidence interval; Hb, haemoglobin; ITT, intent to treat; MODS, multiple organ dysfunctions; NR, not reported; PELOD, paediatric logistic organ dysfunction; PICU, paediatric intensive care unit; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
McCoy TE, Conrad AL, Richman LC, Lindgren SD, Nopoulos PC, Bell EF (2011) Neurocognitive profiles of preterm infants randomly assigned to lower or higher haematocrit thresholds for transfusion. Child Neuropsychology, 17(4): 347-67.				
Affiliation/Source of funds				
A grant was received from the National Centre for Research Resources, National Institute of Health, USA.				
Study design	Level of evidence		Location/setting	
RCT (follow-up)	Level II		USA	
Intervention	Comparator			
Liberal RBC transfusion at birth.	Restrictive RBC transfusion at birth.			
Population characteristics				
56 children aged 8 to 15 years (31 boys, 25 girls) who were born preterm with a birth weight 500-1300 g. Exclusion criteria: significant hearing loss, history of epilepsy, brain tumour or head injury resulting in unconsciousness/concussion.				
Length of follow-up	Outcomes measured			
NA	Cognitive and achievement measures: general ability index (GAI), verbal comprehension index (VCI), perceptual reasoning index (PRI), processing speed index (PSI), wide range achievement test, including reading ability (WRAT-III). Language, visual-spatial/motor, and memory measures: controlled oral word association (COWA), rapid automatized naming (RAN), judgement of line (JOL), grooved pegboard (GPB), Bender visual-motor gestalt test (Bender-II), visual memory, verbal memory.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A follow-up study of the Bell RCT (2005) in preterm low birth weight infants who received either restrictive or liberal RBC transfusion, to assess neurocognitive profiles 8-15 years later. Methods regarding randomisation and allocation concealment were not reported in the current study; however, the authors referred readers to the original RCT for this information. There were 100 preterm infants in the original study. Post-hoc analyses were conducted to determine whether children who participated in the current study were less sick than children who did not participate, and whether differences existed between treatment groups. No statistically significant differences were observed. Of the children who participated in the current study, males and females were unevenly distributed between treatment groups (restrictive group: 19 boys, 4 girls; liberal group: 12 boys, 21 girls). This was discussed with authors noting the potential interaction between sex and brain development. Subjects were aware of their treatment group, the intervention having occurred 8-15 years prior. Outcomes were assessed blind to treatment group.				
RESULTS				
Population analysed	Liberal RBC transfusion		Restrictive RBC transfusion	
Randomised	33		23	
Efficacy analysis (ITT)	33		23	
Efficacy analysis (PP)	33		23	
Safety analysis	NA		NA	
Outcome	Liberal Mean ± SD (N)	Restrictive Mean ± SD (N)	Risk estimate (95% CI)	Significance *P*-value
Cognitive and achievement measures				
GAI	93.21 ± 20.7 (33)	103.61 ± 15.7 (23)	Effect size 0.267	No significant difference *P* = 0.047
VCI	93.85 ± 26.0 (33)	104.78 ± 15.7 (23)	Effect size 0.238	No significant difference *P* = 0.078

PRI	91.67 ± 18.1 (33)	99.70 ± 15.5 (23)	Effect size 0.229	No significant difference *P* = 0.089
PSI	88.82 ± 14.4 (33)	95.5 ± 14.8 (23)	Effect size 0.225	No significant difference *P* = 0.096
WRAT-III	93.94 ± 15.0	105.83 ± 10.2 (23)	Effect size 0.410	Favours restrictive transfusion *P* = 0.002
Language, visual spatial/motor and memory measures				
COWA	-1.30 ± 1.24 (33)	-0.31 ± 1.10 (23)	Effect size 0.386	Favours restrictive transfusion *P* = 0.003
RAN	0.08 ± 1.70 (33)	0.59 ± 1.02 (23)	Effect size 0.189	No significant difference *P* = 0.167
JOL	-1.06 ± 1.54 (33)	-0.81 ± 1.23 (23)	Effect size 0.091	No significant difference *P* = 0.593
GBP	-0.75 ± 2.00 (33)	-0.24 ± 0.97 (23)	Effect size 0.152	No significant difference *P* = 0.152
Bender-II	0.12 ± 1.19 (33)	0.75 ± 0.90 (23)	Effect size 0.279	No significant difference *P* = 0.037
Visual memory	-3.05 ± 1.75 (33)	-1.95 ± 1.38 (23)	Effect size 0.324	Favours restrictive transfusion *P* = 0.015
Verbal memory	-1.41 ± 1.42 (33)	-0.92 ± 0.96 (23)	Effect size 0.192	No significant difference *P* = 0.157
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children who had received blood transfusion at birth for prematurity and low birth weight.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C)				
Comments				
The authors stated the results provide evidence that liberal RBC transfusion can have a significant negative impact on neurocognitive functioning and academic achievement above and beyond the impact that is associated with preterm status alone. They concluded that children in the liberal transfusion group performed more poorly than those in the restrictive group on measures of associative verbal fluency, visual memory and reading. These findings highlight possible long-term neurodevelopmental consequences of maintaining higher haematocrit levels. Statistical analyses: 1. Cognitive ability and achievement (GAI, VCI, PRI, PSI, WRAT-III): p-values below <0.01 significant 2. Language functioning (COWA, RAN): p-values <0.025 significant 3. Visual-spatial/motor functioning (JOL, GPB, Bender-II): p-values <0.017 significant 4. Memory (visual and verbal): p-values <0.025 significant				

Bender-II, Bender visual-motor gestalt test; CI, confidence interval; COWA, controlled oral word association; GAI, general ability index; GBP, grooved pegboard; ITT, intent to treat; JOL, judgement of line; NR, not reported; PP, per-protocol; PRI, perceptual reasoning index; PSI, processing speed index; RAN, rapid automatized naming; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; VCI, verbal comprehension index; WRAT-III, wide range achievement test

STUDY DETAILS: RCT				
Citation				
Olupot-Olupot P, Engoru C, Thompson J, Nteziyaremye J, Chebet M, Ssenyondo T. (2014) Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anemia. BMC Med 2014; 12(1).				
Affiliation/Source of funds				
The authors declare they have no conflicts of interest. The study was supported by a grant (G0801439) from the Medical Research Council, United Kingdom (provided through the MRC DFID concordat). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.				
Study design	Level of evidence		Location/setting	
RCT *Phase II trial	Level II		Two centres(Uganda)	
Intervention	Comparator			
20 mL/kg whole blood transfusion (alternatively 10 mL/kg of RBC) (standard of care)	30 mL/kg whole blood transfusion (alternatively 15 mL/kg RBC)			
Population characteristics				
Paediatric patients >60 days and <12 years old, with severe anaemia at admission to the paediatric ward. Children were eligible if they had severe anaemia (haemoglobin <6g/dL) at the time of hospital admission, no previous transfusion during the course of current illness and a guardian or parent willing/able to provide consent. Children with malignancy, surgery, acute trauma or acute severe malnutrition were excluded from the study. Overall 160 children were randomised.				
Length of follow-up	Outcomes measured			
28 days	Primary: correction of severe anaemia (to haemoglobin >6 g/dL) at 24 hours Secondary: meeting criteria for additional transfusion (development of profound anaemia Hb <4 g/dL) or haemoglobin 4-6 g/dL with new markers of severity (impaired consciousness or respiratory distress) from 8 hours post randomisation; serious adverse events including suspected pulmonary oedema, biventricular heart failure and suspected transfusion reaction; mortality through 48 hours and 28 days post-admission and redevelopment of severe anaemia (haemoglobin <6 g/dL).			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Randomisation was stratified by clinical centre with the treatment allocation kept in numbered, sealed, opaque envelopes. The cards were numbered consecutively and opened in numerical order. The randomisation list and envelopes were prepared before the trial by a statistician and the list was not available to investigators. It is not reported if subjects were blinded to treatment allocation. Most baseline characteristics were similar between the two groups but there were a few moderate differences. In total, 11 children did not attend the 28 day follow-up but survival status was confirmed for 10 of these children and the remaining child died four days after hospital discharge. Whether fatal and on-fatal events were related to transfusion or the volume transfused was assessed blind by the Endpoint Review Committee (ERC). This committee consisted of independent clinicians but it is not stated whether all outcomes were assessed in this manner (blinded to treatment allocation). The results are presented collectively, rather than by site. No subgroup analyses were reported.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	82		78	
Efficacy analysis (ITT)	82		78	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
20 mL/kg whole blood transfusion vs 30 mL/kg whole blood transfusion				

Died before 48 hours	4/82 (4.9%)	0/78 (0%)	NR	No significant difference *P* = 0.12
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
Allergic reaction/transfusion reaction	0/82 (0%)	1/78 (1.3%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to paediatric patients aged >60 days to <12 years with severe anaemia.				
Applicability				
Evidence not applicable to Australian health-care context. The study was conducted in Uganda (Level D).				
Comments				
Children received standard treatments recommended by national guidelines, depending on their illness, including parenteral antimalarials, antibiotics and/or antipyretics, anticonvulsants, oxygen (for oxygen saturations <90%) and glucose for hypoglycaemia. All children received a transfusion and the initial volume infused followed the randomisation strategy (within 5 mL/kg) in 80/82 patients in the 20 mL/kg treatment arm and 75/78 patients in the 30 mL/kg treatment arm. All initial transfusions were whole blood rather than packed RBCs (pRBCs). There was only one prescription of pRBC in the whole trial, given as a second transfusion in the 30 mL/kg treatment arm. The authors note this reflects the difficulties local transfusion services have in preparing pRBC and general lack of availability in the areas/populations investigated in this study. The authors also note that the higher mortality in the 20 mL/kg treatment arm was consistent with chance, owing to the small sample size of the trial.				

CI, confidence interval; Hb, haemoglobin; ITT, intention-to-treat; NR, not reported; PP, per-protocol; pRBC, packed red blood cell; RCT, randomised controlled trial; SD, standard deviation; RR, risk ratio

STUDY DETAILS: RCT				
Citation				
Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, Bello J, Zimmerman RA, Adams RJ, Brambilla D. (2001) Silent Infarcts in Children With Sickle Cell Anemia and Abnormal Cerebral Artery Velocity. Archives of Neurology, 58: 2017-21.				
Affiliation/Source of funds				
This study was funded by the National Institutes of Health, USA and the National Heart, Lung and Blood Institute, USA.				
Study design	Level of evidence		Location/setting	
RCT (follow-up)	Level II		USA	
Intervention	Comparator			
Long-term transfusion therapy.	Standard care (no transfusions)			
Population characteristics				
130 children aged 2 to 16 with HbSS or sickle beta zero thalassemia and elevated transcranial Doppler (TCD) ultrasonography velocity.				
Length of follow-up	Outcomes measured			
36 months.	Stroke, new or worse silent lesions.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT comparing long-term transfusion therapy to standard care in children with sickle cell disease and elevated TCD ultrasonography velocity, for the prevention of stroke. Study referred to the STOP trial (Adams 1998) for details of subjects. Blinding wasn't reported, but assumed not blinded due to differences in procedures between groups. Baseline characteristics were provided for MRI findings prior to randomisation. Patients that had a silent infarct at baseline were significantly older than those who had no abnormalities (p=0.003). However, analyses were unaffected when age was included as a variable. Three patients were excluded after randomisation. Intention-to-treat analysis was not used since the question being addressed was secondary to those in the STOP trials. Outcome assessors were unaware of subjects' clinical status or treatment arm. Data was difficult to interpret and p-values were unclear.				
RESULTS				
Population analysed	Long-term transfusion		No transfusion	
Randomised	NR (total 130)		NR (total 130)	
Efficacy analysis (ITT)	NA		NA	
Efficacy analysis (PP)	56		71	
Safety analysis	NA		NA	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Stroke (all patients)	1/56 (1.8%)	13/71 (18.3%) *9 children had silent infarct at baseline	NR	Favours transfusion *P* = unclear
Patients with silent infarcts at baseline who had a stroke N=47	0/18 (0%)	9/29 (31.0%)	NR	Favours transfusion *P* = unclear
New or worse silent lesions (all patients)	1/56 (1.8%)	11/71 (15.5%) *6 children had silent infarct at baseline	NR	Favours transfusion *P* = unclear

Patients with silent infarcts at baseline who developed new or worse silent lesions N=47	0/18 (0%)	6/29 (20.7%)	NR	No significant difference *P* = unclear
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children with sickle cell disease and elevated TCD ultrasonography velocity.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study origin is USA (Level C).				
Comments				
The authors noted that subjects in both groups (no abnormality at baseline or silent infarct at enrolment) were significantly less likely to have a stroke or develop new or worse lesions if they received transfusion therapy. The authors concluded that transfusion therapy lowers the risk of new silent infarct or stroke in children having both abnormal TCD ultrasonographic velocity and silent infarct, although they conclude that predictors for stroke are complex and further study is needed.				

CI, confidence interval; Hb, haemoglobin; HbSS, sickle cell anaemia; ITT, intention-to-treat; MRI, magnetic resonance imaging; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; TCD, transcranial Doppler

STUDY DETAILS: RCT				
Citation				
Rouette, J., Trottier, H., Ducruet, T., Beaunoyer, M., Lacroix, J., and Tucci, M. (2010) Red blood cell transfusion threshold in postsurgical pediatric intensive care patients: A randomized clinical trial. Ann.Surg. 251 (3) 421-427.				
Affiliation/Source of funds				
Supported by the Canadian Institutes of Health Research Grants (84300 and 130770) and Fonds de la Recherche en Sante du Quebec grants (3568 and 13904).				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre (17x PICUs), Belgium, Canada, USA, UK	
Intervention	Comparator			
Restrictive blood transfusion (transfusion threshold 7.0 g/dL) using prestorage leukocyte reduced allogeneic red-cell units	Liberal blood transfusion (transfusion threshold 9.5 g/dL) using prestorage leukocyte reduced allogeneic red-cell units			
Population characteristics				
Subgroup of 124 postoperative general surgery paediatric patients (aged 3 days to 14 years) from the TRIPICU (Transfusion Requirements in Pediatric Intensive Care Units) study (Lacroix 2007). TRIPICU study exclusion criteria specific to this subgroup: non-surgical patients and patients who underwent any form of cardiac surgery.				
Length of follow-up	Outcomes measured			
28 days	Primary outcomes: proportion of patients who developed or had progression of multiple organ dysfunction syndrome (MODS), markers of severity of MODS (the highest number of organ dysfunction per patient and the Pediatric Logistic Organ Dysfunction (PELOD) score) Secondary outcomes: 28 day and hospital all causes mortality, nosocomial infections, duration of mechanical ventilation, paediatric ICU length of stay.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: This study was a general surgery subgroup analysis of the TRIPICU study (Lacroix 2007), representing 19.5% of patients in the original study. The subgroup analysis was planned prior to unblinding of data. Details of randomisation and allocation concealment were not reported in the current paper – readers were referred to the primary study (Lacroix 2007) for detailed information regarding methodology. Blinding of subjects and clinical staff was not feasible due to the visible nature of the intervention; however, the statistician and members of the data and safety monitoring committee were unaware of group assignments. The authors report performing a per-protocol analysis of the primary outcome, which had similar results to the intent to treat analysis. There was no loss to follow-up. Site specific results were only given for the primary outcome. Note: In the restrictive group, 30 patients (50%) did not receive any transfusion, whereas 62 patients (97%) in the liberal group were transfused ($P < 0.01$).				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	60		64	
Efficacy analysis (ITT)	60		64	
Efficacy analysis (PP)	60 (primary outcome only)		64 (primary outcome only)	
Safety analysis	60		64	
Outcome	Restrictive n/N (%) Mean ± SD	Liberal n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value

Mortality				
Number of deaths in PICU	1/60 (1.67%)	0/64 (0%)	NR	NR
Number of deaths 28 days post PICU	0/60 (0%)	1/64 (1.56%)	NR	NR
Overall 28 day mortality	1/60 (1.67%)	1/64 (1.56%)	NR	NR
New or progressive multiple organ dysfunction/failure				
Patients with new or progressive MODS -Total -Age ≤ 28 days -Age 29-364 days -Age ≥ 365 days	 5/60 (8.33%) 1/2 (50.00%) 1/12 (8.33%) 3/46 (6.52%)	 6/64 (9.38%) 0/0 (0%) 1/14 (7.14%) 5/50 (10.00%)	 ARR 1 [-9, 11] - ARR -1 [-22, 20] ARR 3 [-8, 15]	No significant difference *P* = 0.83 NR NR NR
Highest number of organ dysfunctions	1.3 ± 1.2	1.3 ± 1.0	MD 0.0 [-0.4, 0.4]	No significant difference *P* = NR
PELOD score over all PICU stay	4.0 ± 7.1	3.5 ± 3.8	MD -0.5 [-2.5, 1.5]	No significant difference *P* = NR
PELOD score on day 1	5.3 ± 6.3	4.9 ± 5.4	MD -0.4 [-2.5, 0.4]	No significant difference *P* = NR
Highest daily PELOD score after day 1	7.4 ± 9.6	7.6 ± 8.8	MD 0.3 [-3.0, 3.5]	No significant difference *P* = NR
Change in PELOD score	2.1 ± 6.3	2.8 ± 6.7	MD 0.6 [-1.7, 2.9]	No significant difference *P* = NR
Average daily PELOD score	4.0 ± 7.1	3.5 ± 3.8	MD -0.5 [-2.5, 1.5]	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients following general surgery (excluding cardiac surgery).				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. The majority of study sites and patients were located in Level B countries: Canada (4 sites, 65 patients), Belgium (2 sites, 59 patients), UK (2 sites, 7 patients).				
Comments				
The results were very similar to the TRIPICU study in terns if primary and secondary outcomes. The authors noted sample size was too small for definitive statistical results and should only be used to generate hypotheses. The authors concluded that a restrictive strategy for PICU surgical patients is probably safe, and allows a reduction in number of transfusions without changing outcomes.				

ARR, absolute risk reduction; CI, confidence interval; Hb, haemoglobin; ITT, intention-to-treat; MD, mean difference; MODS, multiple organ dysfunctions; NR, not reported; PELOD, paediatric logistic organ dysfunction; PICU, paediatric intensive care unit; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Whyte, R. K., Kirpalani, H., Asztalos, E. V., Andersen, C., Blajchman, M., Heddle, N., Lacorte, M., Robertson, C. M. T., Clarke, M. C., Vincer, M. J., Doyle, L. W., and Roberts, R. S. (2009) Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 123 (1) 207-213.				
Affiliation/Source of funds				
This work was supported by the Canadian Institutes for Health Research registration MCT-58455. Dr Kirpalani is currently affiliated with the Division of Neonatology, Children's Hospital Philadelphia, USA				
Study design	Level of evidence		Location/setting	
RCT (follow-up)	Level II		Multicentre (10 NICUs), Australia, Canada, USA	
Intervention		Comparator		
Low (restrictive) transfusion threshold + iron *The thresholds were specified by postnatal age and the need for respiratory support		High (liberal) transfusion threshold + iron *The thresholds were specified by postnatal age and the need for respiratory support		
Population characteristics				
421 extremely low birth weight (ELBW) infants of birth weight <1000 g, gestation age < 31 weeks and < 48 hours old at time of enrolment, followed up 18-21 months later.				
Length of follow-up	Outcomes measured			
18-21 months	Primary outcome: **composite of death or neurodevelopmental impairment** in survivors, where neurodevelopmental impairment was defined as one or more of the following: cerebral palsy, cognitive delay, visual or hearing impairment Secondary outcomes: individual components of the composite primary outcome (**death, neurodevelopmental impairment**), as well as personal and social skills, gross motor function skills, measures of growth and hematologic measures			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Follow-up of Kirpalani 2006 [PINT] which was an RCT in 10 NICUs in three countries. Readers were referred to the original study for details of the methodology e.g. randomisation and allocation concealment. Blinding was not possible due to treatment effects being visible in Hb levels. However the authors reported that outcome assessors were blinded to treatment allocation. There were no significant differences in baseline characteristics between groups. Of the 451 patients enrolled in the original study, primary outcome data was available for 430. Nine patients were subsequently lost to follow-up, so final analysis was possible for 421 (93%) enrolled infants.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	223		228	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	212		219	
Safety analysis	208		213	
Outcome	Restrictive n/N (%) Mean ± SD	Liberal n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality				

Died *these data include 1 patient lost to follow-up known to be alive	48/212 (22.64%)	45/219 (20.55%)	OR 1.18 [0.72, 1.93] *Adjusted for birth weight and centre	No significant difference *P* = 0.52
Composite of mortality and neurodevelopmental disability				
Composite of death and neurodevelopmental impairment	94/208 (45.19%)	82/213 (38.50%)	OR 1.45 [0.94, 2.21] *Adjusted for birth weight and centre	No significant difference *P* = 0.09
Neurodevelopment disability				
Any neurosensory impairment	46/160 (28.75%)	37/168 (22.02%)	OR 1.62 [0.95, 2.76] *Adjusted for birth weight and centre	No significant difference *P* = 0.074
Cerebral palsy	11/163 (6.75%)	9/172 (5.23%)	OR 1.32 [0.53, 3.27] *Adjusted for birth weight	No significant difference *P* = 0.55
Cognitive delay (MDI below 70, i.e. > 2 SDs below age norm)	38/156 (24.36%)	29/165 (17.58%)	OR 1.74 [0.98, 3.11] *Adjusted for birth weight and centre	No significant difference *P* = 0.06
Cognitive delay (MDI > 1 SD below age norm) *post-hoc analysis	70/156 (44.87%)	56/165 (33.94%)	OR 1.81 [1.12, 2.93] *Adjusted	Favours liberal transfusion *P* = 0.016
Severe visual impairment	2/161 (1.24%)	1/173 (0.58%)	OR 2.16 [0.19, 24.09] *Adjusted for birth weight	No significant difference *P* = 0.53
Severe hearing impairment	4/161 (2.48%)	3/173 (1.73%)	OR 1.45 [0.32, 6.58] *Adjusted for birth weight	No significant difference *P* = 0.63
Cognitive function *post-hoc analysis	85.2 ± 18.6	88.7 ± 18.7	Mean difference 4.3 [0.4, 8.2] *Adjusted for birth weight and centre	Favours liberal transfusion *P* = 0.03
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW (<1000 g) infants with some caveats. Authors report generalizability to most ELBW infants treated in NICUs.				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. Study sites/origins were Australia (Level A), Canada (Level B) and USA (Level C). Specific sites and numbers of patients per site were not reported.				
Comments				
Authors concluded that the study provides weak evidence of benefit for a higher Hb threshold based on secondary analysis of cognitive delay. Authors advise caution in interpretation of results. *Two post-hoc analyses were conducted regarding cognitive delay. One analysis was a quantitative comparison of cognitive function and the other utilised a different definition of cognitive delay (both using the MDI).				

CI, confidence interval; ELBW, extremely low birth weight; Hb, haemoglobin; ITT, intention-to-treat; MDI, mental developmental index; NICU, neonatal intensive care unit; OR, odds ratio; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Willems A., Harrington K, Lacroix J, Biarent, D., Joffe, A R., Wensley, D., Ducruet, T., Hebert, P. C., and Tucci, M. (2010) Comparison of two red-cell transfusion strategies after pediatric cardiac surgery: A subgroup analysis. Crit.Care Med. 38 (2) 649-656.		
Affiliation/Source of funds		
This study was supported in part by Grants 84300 and 130770 from the Canadian Institutes of Health Research (CIHR) and Grant 13904 from the Fonds de la Recherche en Sante du Quebec (FRSQ). Drs Lacroix and Hebert have received consulting fees and grant support from Johnson and Johnson; Dr Hebert also received consulting fees and unrestricted funds from Novo Nordisk and Amgen serving as a Career Scientist of the Ontario Ministry of Health (1994-2004) and received unrestricted training funds from Canadian Blood Services. The remaining authors have not disclosed any potential conflicts of interest.		
Study design	Level of evidence	Location/setting
RCT	Level II	Multicentre study (PICUs), Belgium, Canada, USA
Intervention	Comparator	
Restrictive blood transfusion (transfusion threshold 70 g/L) using prestorage leukocyte reduced allogeneic red-cell units	Liberal blood transfusion (transfusion threshold 95 g/L) using prestorage leukocyte reduced allogeneic red-cell units	
Population characteristics		
Paediatric patients post cardiac surgery or catheterisation from the TRIPICU (Transfusion Requirements in Pediatric Intensive Care Units) study (subgroup of 125 patients). TRIPICU study exclusion criteria specific to this subgroup: patients <28 days old and patients with cyanotic heart disease who had a palliation intervention.		
Length of follow-up	Outcomes measured	
28 days	Primary outcomes: proportion of patients who developed or had progression of multiple organ dysfunction syndrome (MODS), markers of severity of MODS (the highest number of organ dysfunction per patient and the Pediatric Logistic Organ Dysfunction (PELOD) score) Secondary outcomes: 28 day and hospital all causes mortality, nosocomial infections, transfusion reactions, other adverse events, duration of mechanical ventilation, paediatric ICU and hospital length of stay, total number of transfusions per patient and the proportion of patients who received no red-cell transfusion.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: This study was a cardiac surgery subgroup analysis of the TRIPICU study (Lacroix 2007) representing 19.6% of patients in the original study. The subgroup analysis was planned before the initiation of the primary study. Details of randomisation and allocation concealment were not reported in the current paper – readers were referred to the primary study (Lacroix 2007) for more detailed information regarding methodology. Authors reported no loss to follow-up and no difference in any co-intervention. The authors noted potential for site-related bias due to only those centres whose cardiac surgeons and intensivists who were willing to accept a lower Hb threshold included their patients in the study. Site specific results were only given for the primary outcome. Note: In the restrictive group, 52 patients (83%) received no transfusion, whereas all patients in the liberal group were transfused ($P < 0.01$).		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	63	62
Efficacy analysis (ITT)	63	62
Efficacy analysis (PP)	Patients who met the 80% adherence criterion (n=115)	

Safety analysis	63		62	
Outcome	Restrictive n/N (%) Mean ± SD	Liberal n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality				
Number of deaths 28 days post randomisation	2/63 (3.17%)	2/62 (3.23%)	RD -0.05 [-6.22, 6.12]	NR
Number of deaths in PICU	2/63 (3.17%)	0/62 (0%)	RD 3.2 [-0.01, 0.08]	NR
New or progressive multiple organ dysfunction/failure				
Patients with new or progressive MODS -Total -Age ≤ 28 days -Age 29-364 days -Age ≥ 365 days	 8/63 (12.70%) 0 (0%) 4/33 (12.12%) 4/30 (13.33%)	 4/62 (6.45%) 0/1 (0%) 4/36 (11.11%) 0/25 (0%)	 ARR 6.2 [-7.6, 10.4] - ARR 1.0 [-14.1, 16.2] ARR 13.3 [1.2, 25.5]	No significant difference *P* = 0.36 NR NR NR*
Highest number of organ dysfunctions	1.4 ± 1.2	1.34 ± 0.96	MD 0.09 [-0.29, 0.47]	No significant difference *P* = NR
PELOD score over all PICU stay	6.6 ± 9.4	5.8 ± 6.4	MD 0.78 [-2.06, 3.62]	No significant difference *P* = NR
Highest daily PELOD score after day 1	7.0 ± 10.6	6.7 ± 7.3	MD 0.27 [-2.96, 3.51]	No significant difference *P* = NR
Change in PELOD score from day 1	2.9 ± 9.9	3.1 ± 6.5	MD -0.18 [-3.13, 2.78]	No significant difference *P* = NR
Average daily PELOD score after day 1	3.9 ± 4.7	3.3 ± 4.3	MD 0.58 [-1.02, 2.17]	No significant difference *P* = NR
Adverse events				
Nosocomial infection	12/63 (19.0%)	12/62 (19.4%)	RD -0.3 [-14.12, 13.5]	No significant difference *P* = NR
1+ adverse events	2/63 (3.2%)	4/62 (6.5%)	RD -3.3 [-10.77, 4.22]	No significant difference *P* = NR
Reaction to red-cell transfusion	0/63 (0%)	1/62 (1.6%)	RD -1.61 [-4.75, 1.52]	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence generalisable to paediatric cardiac surgery patients.				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. The majority of study sites and patients were located in Level B countries: Canada (4 sites, 65 patients), Belgium (2 sites, 59 patients).				
Comments				

*There seemed to be a trend toward more organ dysfunction in patients older than 365 days in the restrictive group, but the number of patients was too small to permit any conclusions.

The authors concluded that a restrictive versus liberal transfusion strategy was not associated with significant difference in new or progressive MODS, but evidence is not definitive. The authors noted that the study lacked power and results should only be used to generate hypothesis.

The authors report performing a per-protocol analysis of the primary outcome excluding 10 patients from the analysis, with a total of 80% of patients meeting the 80% adherence criteria (defined as the proportion of days after randomisation that Hb level was above the transfusion threshold). The results of the PP analysis (absolute RR in liberal group = 5.56%; [5.08, 16.19], (p=0.37)) differed slightly from the ITT analysis (absolute RR = 6.2% [-76, 10.4] (p=0.36).

ARR, absolute risk reduction; CI, confidence interval; Hb, haemoglobin; ITT, intention-to-treat; MD, mean difference; MODS, multiple organ dysfunctions; NR, not reported; PELOD, paediatric logistic organ dysfunction; PICU, paediatric intensive care unit; PP, per-protocol; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation

Level III evidence

STUDY DETAILS: cohort/case-control		
Citation		
Acker SN, Partrick DA, Ross JT, Nadlonek NA, Bronsert M, Bensard DD. (2014) Blood component transfusion increases the risk of death in children with traumatic brain injury. J Trauma Acute Care Surg 76(4):1082-8.		
Affiliation/Source of funds		
The authors declare no conflicts of interest. They are affiliated with the Department of Pediatric Surgery (S.N.A., D.A.P., J.T.R., N.A.N., D.D.B.), Children's Hospital Colorado; and Department of Surgery, Surgical Outcomes and Applied Research (M.B.), University of Colorado School of Medicine, Aurora; and Department of Surgery (D.D.B.), Denver Health and Hospital Authority, Denver, Colorado.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Two urban paediatric trauma centres (USA)
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion	Age, sex, Injury Severity Score, Glasgow Coma Scale, cause of injury	
Population characteristics		
Patients aged ≤18 years who were admitted to the hospital from 2002 to 2011 and survived greater than 24 hours with a diagnosis of traumatic brain injury (TBI). All patients with TBI were included, not just those with isolated head injuries. Patients were identified from the trauma registries based on the diagnosis of TBI. Exclusion criteria: children who underwent a craniotomy, thoracotomy, exploratory laparotomy, or any orthopaedic procedure during their hospitalisation (to eliminate confounding factors related to intraoperative blood loss).		
Length of follow-up	Outcomes measured	
NR (10 year study period. Participants followed to hospital discharge)	Survival to hospital discharge, discharge to rehabilitation facility, dependence on caretakers at the time of follow-up, admission to the ICU and infectious complications including bacteraemia, pneumonia, urinary tract infection and sepsis.	
Method of analysis		
All predictor variables (age, sex, ISS (Injury Severity Score), GCS (Glasgow Coma Scale) score and cause of injury) were converted to categorical variables to facilitate statistical analysis. These categorical variables were compared using Pearson's X^2 test or Fisher's exact test. Univariate analyses were conducted using the X^2 test or Fisher's exact test. Logistic regression was used for multivariate analyses.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Demographic characteristics are provided for the 'transfusion' and 'no transfusion' groups. There are significant differences between the groups, such as age, ISS (Injury Severity Score) and GCS (Glasgow Coma Scale). However, it should be noted that this 'transfusion' group includes participants who received RBC, fresh frozen plasma, platelets or cryoprecipitate. Demographic information is not provided to compare the 'RBC transfusion' and 'no RBC transfusion' groups. It is not reported if all eligible participants agreed to take part in the study. Patients with missing predictor variables were excluded. No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. Demographic characteristics are controlled for in the multivariate model, which included GCS score, age category, gender and ISS. It is not reported if outcome assessment was blinded to exposure status.		
RESULTS		
Population	Intervention (n)	Comparator (n)
Available Nadir Hb <10 g/dL Nadir Hb <9 g/dL Nadir Hb <8 g/dL	 146 126 91	 269 155 58
Analysed	As above	As above

Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Survived to hospital discharge (patients with nadir haemoglobin <10 g/dL)[a]	123/146 (84.2%)	256/269 (95.2%)	OR 1.377 [0.622, 3.050]	No significant difference *P* = 0.4307
Survived to hospital discharge (patients with nadir haemoglobin <9 g/dL)[a]	108/126 (85.7%)	145/155 (93.5%)	OR 1.240 [0.506, 3.039]	No significant difference *P* = 0.6378
Survived to hospital discharge (patients with nadir haemoglobin <8 g/dL)[a]	79/91 (86.8%)	53/58 (91.4%)	OR 1.072 [0.324, 3.544]	No significant difference *P* = 0.9098
Deaths up to hospital discharge (patients with nadir haemoglobin <10 g/dL)	23/146 (15.8%)	13/269 (4.8%)	RR 3.26 [1.70, 6.24][b]	Favours no RBC transfusion *P* = 0.0004
Deaths up to hospital discharge (patients with nadir haemoglobin <9 g/dL)	18/126 (14.3%)	10/155 (6.5%)	RR 2.21 [1.06, 4.62][b]	Favours no RBC transfusion *P* = 0.03
Deaths up to hospital discharge (patients with nadir haemoglobin <8 g/dL)	12/91 (13.2%)	5/58 (8.6%)	RR 1.53 [0.57, 4.12][b]	No significant difference *P* = 0.40
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to paediatric patients with traumatic brain injury.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in the USA (Level C).				
Comments				
The study results show that as haemoglobin nadir decreases, the composite odds associated with transfusion and the complications evaluated in the study (only mortality presented above) also tended to decrease. At a haemoglobin nadir of 7–8 g/dL, the rates of adverse events between the groups began to equalise. This leads the authors to suggest a restrictive transfusion policy, whereby a haemoglobin of 8 g/dL be used as a transfusion trigger among paediatric patients with traumatic brain injury. The authors also note the limitations of the study, discussing the type of evidence generated by a retrospective design and suggesting the study be used as a guideline for future work in the area.				

CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; RR, risk ratio; TBI, traumatic brain injury

a. Multivariate analysis (including GCS score, age category, gender and ISS)

b. Calculated post-hoc

STUDY DETAILS: Case-control study				
Citation				
Baer VL, Lambert DK, Henry E, Snow GL, Butler A, Christensen RD (2011) Among very-low-birth-weight neonates is red blood cell transfusion an independent risk factor for subsequently developing a severe intraventricular haemorrhage? Transfusion, 51: 1170-8.				
Affiliation/Source of funds				
The authors state that they have no conflict of interest.				
Study design	Level of evidence		Location/setting	
Retrospective case-control study.	Level III-2		Three large perinatal centres of Intermountain Healthcare, USA.	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion within 72 hours of birth, use of vasopressors, days of initial ampicillin course, elevation in nucleated RBC count.		Gestational age, birth weight, sex, race, surfactant use, 5-minute Apgar score, maternal use of steroids, endotracheal intubation within 72 hours of birth.		
Population characteristics (including size)				
155 VLBW neonates: 54 cases who developed severe IVH and 101 matched controls matched for gestational age (±2 weeks) and birth weight (±200 g) with no IVH.				
Length of follow-up		Outcomes measured		
1 month. Retrospective period was 5 years.		Primary: severe IVH (grade 3 or 4) one month post-baseline. Secondary: mortality, infection, thrombocytopenia		
Method of analysis				
Stepwise Akaike's Information Criterion logistic regression and a sensitivity analysis were performed to evaluate potential correlations between RBC transfusion and development of a severe IVH. The sensitivity analysis assumes a model where RBC transfusions and unmeasured variables are both predictors of developing a severe IVH. Differences in categorical variables were assessed using the Fisher exact or Chi-squared test. A t-test was used to assess continuous variables. Significance was set at $p < 0.05$.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a retrospective case-control study in VLBW infants including 54 severe IVH cases and 101 matched controls, to assess the risk of RBC transfusion on development of severe IVH within one month. Cases and controls were taken from an electronic database for location sites. Cases and controls were similar, with the authors noting no statistical difference in potential confounding variables (p=0.538). During the first 24 hours after birth, 59% of the cases and 36% of the controls received one or more RBC transfusions ($p < 0.005$). During the first 72 hours, 89% of the cases and 69% of the controls received one or more RBC transfusions ($p = 0.006$). During the period where the head ultrasound was normal, 67% of the cases versus 31% of the controls received one or more RBC transfusions ($p = 0.000$). 18 cases died (33%) compared with 8 controls (8%). Potential for bias was noted as not all cases of severe IVH were studied and the results only included VLBW infants that had a normal head ultrasound prior to the IVH. A further limitation noted by authors was the possibility that RBC transfusions may have been a marker for the severity of illness which may have contributed to developing IVH.				
RESULTS				
Population (N)	1+ RBC transfusion(s)		No RBC transfusion	
Available	NR		NR	
Analysed (N=155)	118		37	
Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Severe IVH	52/118 (44.1%)	2/37 (5.4%)	NR	NR
Logistic regression: development of severe IVH (grade 3 or 4)				
As the number of RBC transfusions in the first week increases by one		RR 2.02 [1.54, 3.33]		NR

EXTERNAL VALIDITY
Generalisability
Evidence directly generalisable to VLBW infants (Level A).
Applicability
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).
Comments
Although RBC transfusions appeared to be an independent risk factor for developing a severe IVH, the authors concluded that RBC transfusion might have no direct involvement in IVH genesis.

CI, confidence interval; Hb, haemoglobin; IVH, interventricular haemorrhage NR, not reported; OR, odds ratio; RBC, red blood cell; RR, risk ratio; VLBW, very low birth weight

STUDY DETAILS: Case-control study		
Citation		
Chiravuri SD, Riegger LQ, Christensen R, Butler RR, Malviya S, Tait AR, Voepel-Lewis T (2011) Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study. Pediatric Anesthesia, 21: 880-6.		
Affiliation/Source of funds		
None reported.		
Study design	Level of evidence	Location/setting
Retrospective case-control study	Level III-2	USA
Risk factor/s assessed		
For kidney failure: age; preoperative diuretics, nephrotoxic antibiotics, mechanical ventilation, milrinone and dobutamine; intraoperative minutes; CPB minutes; multiple cross-clamps; ultrafiltrate; milrinone; epinephrine; and RBC transfusion.		
Population characteristics (including size)		
558 children aged from birth to <18 years who underwent cardiopulmonary bypass (CPB) for repair of congenital heart defects between 1998 and 2006. Cases were identified from the nephrology consult list and were defined as either acute kidney risk or injury (AKI-RI, n=161) or kidney failure (KF, n=89). Controls were obtained from the cardiac perfusion database over the same period, and did not have AKI-RI or KF (n=308). All duplicate patients (who underwent CPB more than once) were excluded, as were children who had chronic renal failure preoperatively or who underwent cardiac transplantation.		
Length of follow-up	Outcomes measured	
Retrospective period was 8 years.	Primary: acute kidney risk or injury (AKI-RI), kidney failure (KF), death. Secondary: cardiac failure, neurological complications or sepsis related to AKI-RI or KF.	
Method of analysis		
Univariate analyses (Student t-tests or chi-square with Fisher's exact tests) were conducted to evaluate the associations between patient, perioperative factors, and renal outcome groups (cases vs controls). Several logistic regression models (backward, stepwise) were developed to examine the relationships between preoperative, intraoperative and pertinent post-operative outcomes and the renal outcome groups. A p-value <0.05 was considered statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: a retrospective case-control study in the US of 558 children who underwent CPB for repair of congenital heart defects, to assess the risk of multiple factors including RBC transfusion on development of acute renal injury/failure. Cases were identified from the nephrology consult list over the study period to generate a large sample of children with potential adverse renal outcomes. The control group was identified using a probability sample (computer-generated, random selection), twice the size of the consultation list, obtained from the cardiac perfusion database over the same period. Research assistants who recorded all data were blinded to the purpose of the study. Eight children who died intraoperatively or in the immediate postoperative period were excluded from analysis, as they had no laboratory values and could not be classified into a renal outcome group. Of those included in the study, 154 patients died (68 in the AKI-RI group [42%], 68 in the KF group [76%] and 18 in the control group [6%]). No data was available as to whether any of these had undergone RBC transfusions.		
RESULTS		

Population	RBC transfusion	No transfusion
Available	NR	NR
Analysed (n=558)	180	378

Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Kidney failure (n=89)	38/180 (21.1%)	51/378 (13.5%)	NR	NR

EXTERNAL VALIDITY

Generalisability
Evidence directly generalisable to paediatric surgical patients with some caveats (Level B).
Applicability
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).
Comments
The authors concluded that there are multiple perioperative risk factors for AKI-RI, failure, and mortality in children undergoing CPB. RBC transfusion was significantly associated with, but not an independent predictor of AKI or kidney failure. RBC transfusion was not independently associated with mortality. Sepsis, cardiac failure and neurological complications were independently associated with mortality. NB: This study was not included in the final evidence review as the CRG determined that acute renal dysfunction was not a reasonable proxy for MODS.

AKI-RI, acute kidney risk of injury; CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; KF, kidney failure; MODS, multiple organ dysfunctions; NR, not reported; RBC, red blood cell

STUDY DETAILS: Cohort study				
Citation				
Demirel G, Celik IH, Aksoy HT, Erdeve O, Oguz SS, Uras N & Dilmen U (2012) Transfusion-associated necrotising enterocolitis in very low birth weight premature infants. Transfusion Medicine, 22: 332-7.				
Affiliation/Source of funds				
The authors reported no conflicts of interest.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study.	Level III-2		Single tertiary NICU, Turkey.	
Risk factor/s assessed	Potential confounding variables measured			
RBC transfusion	Gestational age, birth weight, day of transfusion, antenatal steroid use, RDS, PDA, umbilical catheter usage, ROP, breast fed, haematocrit level before and after transfusion.			
Population characteristics (including size)				
647 VLBW (<1500 g) preterm infants admitted to NICU. Exclusion criteria: congenital anomalies, sepsis at time of transfusion, feeding intolerance before clinical symptoms had manifested.				
Length of follow-up	Outcomes measured			
NR	NEC within 48 hours of RBC transfusion.			
Method of analysis				
Demographic data compared between groups using the Kruskal-Wallis test, followed by a Kruskal-Wallis post-hoc analysis for dichotomous variables. A χ^2 test was used for the comparison of percentages between groups. A p-value <0.05 was considered statistically significant.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a retrospective cohort study of 647 VLBW preterm infants admitted to NICU in Turkey, to assess the risk of RBC transfusion on development of NEC within 48 hours. 700 VLBW infants were admitted to NICU, of which 15 were excluded based on predefined criteria. Files for 38 infants could not be obtained, leaving 647 to be enrolled in the study. Mean gestational age and birth weight were 29 ± 3.1 weeks and 1157 ± 237g respectively. Where NEC was identified, physician notes and all radiographic images were re-evaluated. Blinding of outcome assessors was not possible due to the retrospective nature of the study. The total incidence of NEC was 14.8% (96/647). All patients were on enteral feeds before RBC transfusion. There were no statistically significant differences in weight, breast milk feeding, and positive blood cultures prior to onset of NEC between groups (P > 0.05). There were no differences in demographic or clinical variables in patients who developed NEC within 48hrs of transfusion and those who were transfused but never developed NEC.				
RESULTS				
Population	Transfused		Never transfused	
Available	296		351	
Analysed	296		351	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
NEC within 48hrs	15/296 (5.1%)	NR	NR	NR
NEC after 48hrs	31/296 (10.5%)	NR	NR	NR
NEC (all)	46/296 (15.5%)	50/351 (14.2%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW (<1500 g) preterm infants (Level A).				
Applicability				

Evidence probably applicable to the Australian healthcare context with some caveats. Study site Turkey (Level C).
Comments
The age of NEC onset was later, and the interval between transfusion and NEC was shorter in transfused vs non-transfused patients despite no statistically significant differences in clinical variables between the two groups. The authors concluded that transfusion-associated NEC exists, but that many other factors influence this multi-factorial disease.

CI, confidence interval; Hb, haemoglobin; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; PDA, patent ductus arteriosus; RBC, red blood cell; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; VLBW, very low birth weight

STUDY DETAILS: Cohort study		
Citation		
dos Santos AMN, Guinsburg R, de Almedia MFB et al (2011) Red Blood Cell Transfusions are Independently Associated with Intra-Hospital Mortality in Very Low Birth Weight Preterm Infants. The Journal of Pediatrics, 159(3): 371-6.		
Affiliation/Source of funds		
The authors reported no conflicts of interest.		
Study design	Level of evidence	Location/setting
Cohort study.	Level III-2	8 centres of the Brazilian Network on Neonatal Research.

Risk factor/s assessed	Potential confounding variables measured
RBC transfusion before the 28th day of life.	Gestational age, 1– and 5-minute Apgar score, SNAPPE II, presence of respiratory distress syndrome (RDS), IVH, early– and late-onset clinical sepsis, NEC.

Population characteristics (including size)	
1077 VLBW (<1500 g) preterm infants with a gestational age between 23.0 and 36.9 weeks. Infants with congenital anomalies were excluded (n=149).	
Length of follow-up	Outcomes measured
Until hospital discharge or death.	Mortality

Method of analysis
Comparisons in groups were done with the two-tailed χ^2 test for categorical variables and t-tests for continuous variables. To analyse the hazard of death, univariate and multivariate Cox regression analyses were applied. A p-value of <0.05 was considered statistically significant.
INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Fair Description: a retrospective cohort study of 1077 VLBW preterm infants admitted to 8 centres in Brazil, to assess the risk of RBC transfusion before the 28th day of life on mortality. Mortality rates during hospital stay were higher in infants who underwent transfusion than in those who did not (34.3% vs 20.3%, *P* < 0.001). A limitation of this study was that patients in the transfused group were sicker than those who were not transfused. The authors attempted to control for this selection bias by adjusting for variables related to illness severity (see above). Gestational transfusion guidelines varied for each site. The authors did not note this as a limitation, however varying transfusion protocols could influence transfusion outcomes.
RESULTS

Population	Transfused	Not transfused
Available (n=1077)	574	503
Analysed (n=1077)	574	503

Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality during hospital stay (n=299)	197/574 (34.3%)	102/503 (20.3%)	NR	Favours no transfusion *P* < 0.001
Risk factor	**Death during hospital stay (n=299)**	**Discharged alive (n=778)**	**Risk estimate (95% CI)**	**Significance *P*-value**
1+ transfusion(s) during hospital stay	65.9%	48.5%	NR	Favours no transfusion *P* < 0.001
>2 transfusions during hospital stay (per infant)	26.8%	21.6%	NR	Favours no transfusion *P* = 0.072

1+ transfusion(s) before 14 days of life	56.9%	26.7%	NR	Favours no transfusion *P* < 0.001
1-2 transfusions before 14d (per infant)	41.1%	22.1%	NR	Favours no transfusion *P* < 0.001
>2 transfusions before 14d (per infant)	15.5%	4.6%	NR	Favours no transfusion *P* < 0.001
1+ transfusion(s) before 28 days of life	63.9%	39.8%	NR	Favours no transfusion *P* < 0.001
1+ transfusion(s) after 28 days of life (per infant)	14.4%	33.4%	NR	Favours no transfusion *P* < 0.001
Univariate Cox regression analysis:				
Mortality during hospital stay (N=1077)	1+ RBC transfusion within 28 days of life		1.46 (1.20-1.53)	NR
Mortality during hospital stay (N=1077)	>2 RBC transfusion during hospital stay		0.96 (0.88-1.03)	NR
Mortality after 28 days of life (N=838)	1+ RBC transfusion within 28 days of life		4.17 (1.83-6.91)	NR
Mortality after 28 days of life (N=838)	>2 RBC transfusion during hospital stay		2.63 (1.91-3.30)	NR
Multivariate Cox regression:				
Mortality during hospital stay (N=1077)	Any transfusion before 28 days of life		RR 1.49 [1.17, 1.78]	Significant association *P* = 0.001
Mortality after 28 days of life (N=839)	>2 RBC transfusions		RR 1.89 [1.19, 2.69]	Significant association *P* = 0.01
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW (<1500 g) preterm infants (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site Brazil (Level C).				
Comments				
Whilst an association between RBC transfusion and hospital mortality rates was evident, authors could not determine causality and mortality may be associated with unknown and unmeasured factors. The authors concluded that transfusion was associated with increased death and transfusion guidelines should consider risks and benefits of transfusion. Other factors that remained significantly associated with mortality during hospital stay: gestational age <28 weeks, SNAPPE II >45, RDS, Early-onset sepsis, NEC Other factors that remained significantly associated with mortality after 28 days of life: 5-minute Apgar <7, Late-onset sepsis, NEC				

CI, confidence interval; Hb, haemoglobin; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; 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

STUDY DETAILS: Cohort study		
Citation		
Elabaid MT, Harsono M, Talati AJ, Dhanireddy R (2013) Effect of birth weight on the association between necrotising enterocolitis and red blood cell transfusions in ≤1500 g infants. BMJ Open, 3: 1-7.		
Affiliation/Source of funds		
The authors stated that they received no specific grant from any funding agency in the public, commercial or not-for-profit sectors, and had no competing interests.		
Study design	Level of evidence	Location/setting
Retrospective cohort study.	Level III-2	NICU at The Regional Medical Centre, Memphis, Tennessee, USA.

Risk factor/s assessed	Potential confounding variables measured
Birth weight, RBC transfusion.	Gestational age, gender, race, 5 minute Apgar score, small for gestational age (SGA) status (BW<10% for gestational age), pharmacological treatment of patent ductus arteriosus (PDA), umbilical arterial catheter (UAC) insertion days, ventilator days.
Population characteristics (including size)	
3060 VLBW (<1500 g) preterm infants. Patients who died or who were transferred from the study site by day 7 of life were excluded to decrease the effects from perinatal factors.	
Length of follow-up	Outcomes measured
48hrs, and after 28 days of life. Retrospective period was 16 years.	Primary: NEC ≥stage 2 within 48hrs of transfusion, and after 28 days of life. Secondary: mortality
Method of analysis	
A χ^2 test was used to measure the degree of association between the categorical variables. A Wilcoxon rank-sum test was used to compare the continuous variables between the NEC and non-NEC groups. All tests were two-sided with $P < 0.05$ considered statistically significant. A simple logistic regression model was initially run between NEC and all independent variables of interest including exposure to blood transfusions. When $P < 0.1$, interactions and collinearity among variables were evaluated before progressing with the model. If collinearity was present, the independent variable was divided in groups and quartiles, then association analysed. To address potential variations in the secular rates of NEC over time, the 16-year study duration was divided into two 8-year periods. The time NEC occurred in either period was entered as another variable in the analysis.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	
Rating: Fair Description: a retrospective cohort study of 3060 VLBW infants discharged from a single NICU in the US between January 1996 and December 2011, to assess the risk of birth weight and RBC transfusion on development of NEC. 3,462 VLBW infants were admitted during the study period; 397 infants (including 3 with NEC) were excluded as they died or were transferred out by day 7 of life. 174 infants developed NEC and 2886 did not. To reduce potential bias and dampen a possible positive association between transfusions and NEC, the period of which infants data was included was set at 2 SD's from the average timing of all NEC cases based on postmenstrual age (PMA). The mean PMA for developing NEC was 30.4 ± 2.6 weeks. Using this mean, the upper limit of the NEC period was defined at 35.6 weeks. Five infants were excluded who developed NEC after this period. Each infant received a median 2 transfusions. Transfusions were based on the care team's clinical decisions as there were no written guidelines transfusions thresholds. Default RBC transfusions were O-negative, irradiated, leucocyte-depleted and cytomegalovirus negative. Final analysed numbers were less than 3060 as some non-NEC cases were lost due to incomplete data in the multivariable analyses (n=13). The authors note the limitations of the retrospective nature of the study and the potential for overlapping clinical signs of NEC and anaemia. Limited clinical data may have been available i.e. anaemia tests, steroid use, fresh versus stored blood transfusions, total feeds and breastfeeding that may influence NEC.	
RESULTS		

Population	RBC transfusion	No transfusion
Available	NR	NR

Analysed (n=3060)	1842		1218	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
NEC	116/1842 (6.3%)	58/1218 (4.8%)	NR	NR
Univariate analysis				
Outcome	NEC (n=174)	No NEC (n=2886)	Risk estimate (95% CI)	Significance *P*-value
Exposure to blood transfusion, %	66.7	59.8	RR 1.32 [0.97, 1.80]	No significant difference *P* = 0.073
Number of transfusions, median (IQR)	6 (8)	5 (8)	RR 1.060 [1.039, 1.080]	Patients who developed NEC received significantly more transfusions *P* = 0.017
Clinical characteristics by birth weight group				
Birth weight group	Exposure to transfusion (%)	NEC (%)	Risk estimate (95% CI)	Significance *P*-value
Infants ≤750 g	93.5	7.7	NR	NR
Infants 751-1000 g	84.8	6.8	NR	NR
Infants 1001-1250 g	51.0	5.7	NR	NR
Infants >1250 g	20.5	3.0	NR	NR
Multivariate risk of the (late) onset NEC after day 28 by birth weight group				
Birth weight group	Exposure to transfusion n/N (%)	NEC n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Infants ≤750 g	10/629 (1.6%)	19/629 (3.0%)	RR 0.057 [0.021, 0.15]	Infants ≤750 g were less likely to develop NEC after exposure to a transfusion *P* <0.01
Infants 751-1000 g	8/711 (1.1%)	15/711 (2.1%)	RR 0.17 [0.058, 0.49]	Infants 751-1000 g were less likely to develop NEC after exposure to a transfusion *P* <0.01
Infants 1001-1250 g	6/771 (0.8%)	7/771 (0.9%)	RR 4.32 [0.49, 37]	No significant association *P* = 0.19
Infants >1250 g	0/810 (0%)	1/810 (0.1%)	NA	NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW infants (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				

Exposure to blood transfusions was protective in infants with birth weight ≤1000 g, those who stayed longer on a ventilator, and those who required a longer UAC insertion period. However, exposure to blood transfusions carried a risk for developing NEC in infants 1001-1500 g with less severity of illness markers. These infants had a higher risk of developing NEC after a transfusion exposure. Smaller infants were again less likely to develop NEC after 28 days of life after exposure to a transfusion. The authors concluded that exposure to transfusions does not increase the risk of NEC. Exposures to transfusions was less likely associated with NEC in ≤1000 g infants and remained a risk factor in 1001-1500 g infants, which were likely to have lower transfusions thresholds as they were less ill and probably more anaemic. The authors speculate that anaemia could be the cause of the transfusion-associated NEC. The authors noted that birth weight should be factored in any study evaluating the association between RBC transfusions and NEC.

CI, confidence interval; Hb, haemoglobin; IQR, interquartile range; NA, not applicable; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; PDA, patent ductus arteriosus; RBC, red blood cell; RR, risk ratio; SGA, small for gestational age; UAC, umbilical arterial catheter; VLBW, very low birth weight

STUDY DETAILS: Case-control study				
Citation				
Feghhi M, Altayeb SMH, Haghi F et al (2012) Incidence of Retinopathy of Prematurity and Risk Factors in the South-Western Region of Iran. Middle East African Journal of Ophthalmology, 19(1): 101-6.				
Affiliation/Source of funds				
Support was received from the research deputy of Ahwaz Jundishapur University Medical Sciences. The authors reported no conflicts of interest.				
Study design	Level of evidence	Location/setting		
Cross-sectional case-control	Level III-2	NICUs of all educational hospitals in the Khuzestan province, Iran.		
Risk factor/s assessed				
Gestational age, birth weight, gender, single/twin birth, glaucoma, cataract, strabismus, sepsis, jaundice, duration of oxygen therapy, phototherapy, transfusion.				
Population characteristics (including size)				
576 LBW infants (≤2000 g) and/or preterm infants born <32 weeks gestational age and admitted to NICU. Exclusion criteria: fatal systemic anomaly, unilateral or bilateral retinal or choroidal disease, or media opacity precluding fundus visualisation (e.g. cataract). Infants were also excluded if the neonatologist considered that inclusion would unduly challenge the infant, or if consent was refused.				
Length of follow-up		Outcomes measured		
Examined at 6 weeks after delivery followed by eye examinations every 1-2 weeks until death, discharge or complete retinal vascularisation.		ROP (all stages)		
Method of analysis				
One way analysis of variance (ANOVA) was performed to analyse continuous variables between groups, and the chi-square test was used to compare categorical variables. Multiple logistic analyses were performed. Results considered statistically significant for $P < 0.05$.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a cross-sectional case-control study of 576 LBW/preterm infants admitted to multiple NICUs in Iran, to assess the risk of various factors including transfusion on development of ROP. Of the 183 infants who developed ROP (32%), 137 were <stage 3 (75%), and 46 were ≥stage 3 (25%). Significant demographic and medical differences existed between the ROP and non-ROP groups, with those in the ROP having younger gestational age, lower birth weight and higher incidence of sepsis. The ROP group underwent statistically longer periods of oxygen therapy compared with the non-ROP group (p=0.001), which should be considered when interpreting results. The authors reported no significant association between blood transfusion and ROP after adjusting for confounders. The authors noted limitations of their study were the poor patient follow-up, lack of comprehensive records, and the high mortality rate in infants <1000 g and <28 weeks gestational age (possibly due to the inadequate nursery and healthcare for premature infants) that resulted in a low rate of cases in these populations. The authors also advised that the recommended age for initial ophthalmic examination is 4 weeks postnatal age or 31 weeks postmenstrual age, but that they examined infants at 6 weeks after birth, which may have led to a higher than expected incidence of ROP.				
RESULTS				
Population	Transfusion		No transfusion	
Available (n=576)	40		536	
Analysed (n=576)	40		536	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value

ROP (all cases)	27/40 (67.5%)	156/536 (29.1%)	NR	Favours no transfusion *P* = NR
Multiple Logistic Regression analysis				
Risk factor	OR (95% CI)		Significance *P*-value	
Transfusion	0.43 [0.89, 1.61]		Not significant *P* = NR	
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to LBW preterm infants with some caveats (Level B).				
Applicability				
Evidence not applicable to the Australian healthcare context. Study site Iran (Level D).				
Comments				
The authors concluded that the incidence of ROP in the current study is higher than that in other parts of the world. Awareness and knowledge of ROP and its relative risks need to be reinforced in ophthalmologists and other health practitioners.				

CI, confidence interval; Hb, haemoglobin; LBW, low birth weight; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; ROP, retinopathy of prematurity

STUDY DETAILS: Cohort study				
Citation				
Fortes Filho JB, Fortes BGB, Tartarella MB, Procianoy RS (2013) Incidence and Main Risk Factors for Severe Retinopathy of Prematurity in Infants Weighing Less Than 1000 Grams in Brazil. Journal of Tropical Pediatrics, 59(6): 502-6.				
Affiliation/Source of funds				
The authors declared that they had no financial support or relationships that may pose a conflict of interest.				
Study design	Level of evidence	Location/setting		
Prospective cohort study.	Level III-2	Single NICU at a tertiary university hospital in Southern Brazil.		
Risk factor/s assessed				
Birth weight, gestational age, gender, small for gestational age (SGA), gemelarity, patients' weight at sixth week of life, use of oxygen therapy (mechanical ventilation or nasal CPAP), number of days on mechanical ventilation, use of surfactant or indomethacin, blood transfusions, erythropoietin therapies, sepsis, meningitis, IVH, persistent ductus arteriosus (PDA).				
Population characteristics (including size)				
157 ELBW (≤1000 g) preterm infants admitted to NICU. Patients who died during hospitalisation before the first ophthalmological examination were excluded.				
Length of follow-up	Outcomes measured			
42nd week of PCA.	Severe ROP (≥stage 3) in either eye.			
Method of analysis				
The chi-square test was used to compare no ROP/mild ROP (Stage 1 or 2) patients with severe ROP patients. Student's unpaired t-test was used to compare continuous data. Logistic regression was performed to the variables with significance after univariate analysis. Significance was determined at p <0.05.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a prospective cohort study of 157 ELBW preterm infants admitted to a single NICU in Southern Brazil, to assess various risk factors including blood transfusion on development of severe ROP (≥stage 3). Infants were examined for ROP between fourth and sixth week of life. Patients with incomplete peripheral retinal vascularisation were followed up every 2 weeks until the 42nd week of postconceptual age. 20 infants (13%) developed severe ROP (≥stage 3). Of these, 18 were stage 3 (90%), one was stage 4 (5%) and one was stage 5 (5%). 19 out of 20 infants with severe ROP were treated with diode laser photocoagulation (the other patient missed their appointment and ROP progressed to stage 5 and blindness). Of the remaining infants, 38 (24%) developed mild ROP (stage 1 or 2), and 99 (63%) did not develop ROP. After univariate analysis, the main risk factors for severe ROP were gestational age at birth (P = 0.029), patient's weight at sixth week of life (P < 0.001) and number of days of oxygen therapy under mechanical ventilation (P < 0.001). Need for blood transfusion was not statistically associated with severe ROP (p=0.077). Clinical co-morbidities were more significant among the severe ROP group, who also had more difficulty gaining weight during the study period when compared with the no ROP/mild ROP group. The authors note that the study was carried out over 10 years and practices in NICU had changed significantly over this time.				
RESULTS				
Population	Transfusion		No transfusion	
Available (n=157)	124		33	
Analysed (n=157)	124		33	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Severe ROP (≥stage 3)	19/124 (15.3%)	1/33 (3.0%)	NR	NR
Univariate analysis				

Variable	No ROP/Mild ROP n/N (%)	Severe ROP (%)	Risk estimate (95% CI)	Significance *P*-value
Blood transfusion	105/137 (76.6%)	19/20 (95.0%)	NR	No significant association *P* = 0.077
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW preterm infants (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site Brazil (Level C).				
Comments				
The authors concluded that the incidence of severe ROP needing treatment among ELBW infants at their institution was 12.5%. Laser coagulation was effective to stabilize the natural progression of ROP among 19 treated patients. The authors noted that their results were in agreement with other published studies.				

CI, confidence interval; CPAP, continuous positive airway pressure; ELBW, extremely low birth weight; Hb, haemoglobin; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SGA, small for gestational age

STUDY DETAILS: cohort/case-control				
Citation				
Fremgen HE, Bratton SL, Metzger RR, Barnhart DC. Pediatric liver lacerations and intensive care: Evaluation of ICU triage strategies. Pediatr Crit Care Med 2014; 15(4):e183-e191.				
Affiliation/Source of funds				
This study was supported in part by the Primary Children's Hospital and the Trauma Nursing Program at the University of Utah. Dr. Fremgen is employed by the University of Utah (PICU Fellow). Dr. Bratton served as the sub-board chair with the American Board of Pediatrics, is employed by the University of Utah, and received travel support from the Western Pediatric Trauma Conference 2013. The remaining authors have disclosed that they do not have any potential conflicts of interest.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single paediatric trauma centre (USA)	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion		Age, gender, mechanism of injury, grade of injury, Glasgow Coma Scale, Injury Severity, Score, surgical management		
Population characteristics				
171 infants and children, aged 1 month to 17 years, admitted to a children's hospital from January 2002 to December 2010 after blunt abdominal trauma resulting in a liver laceration. Patients with liver lacerations graded 3 through 6 by scans interpreted by paediatric radiologists (based on American Association for the Surgery of Trauma organ injury scaling) were included.				
Length of follow-up		Outcomes measured		
NR		Mechanical ventilation, PICU length of stay, hospital length of stay, mortality		
Method of analysis				
Data were analysed using summary statistics and compared using non-parametric tests with Bonferroni adjustment for multiple pairwise comparisons. Categorical data were compared using the chi-square test and test for trend.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Patient demographics, such as age, gender and weight, are only compared between the group admitted to the ICU and the group admitted to the inpatient ward. Similar demographics comparing the transfused and non-transfused groups within the ICU are not presented in the article but there was a significant difference in ISS (Injury Severity Score) and GCS (Glasgow Coma Scale) between these groups. It is not reported if all eligible participants agreed to take part in the study. Two patients died prior to admission and were excluded from the analysis. No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. The study does not adequately control for potential confounders in the data analysis. It is not reported if outcome assessment was blinded to exposure status. * Five children admitted to the ICU died; all had severe multisystem trauma.				
RESULTS				
Population	Intervention (n)		Comparator (n)	
Available	43		74	
Analysed	43		74	
Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Death (among ICU patients)	5/43 (11.6%)	0/74 (0%)	RR 18.75 [1.06, 331.04)	No significant difference $P = 0.05$[a]
EXTERNAL VALIDITY				
Generalisability				
Evidence generalisable to paediatric abdominal trauma patients.				

Applicability
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in the USA (Level C).
Comments
Mortality data was presented as a comparison between three groups: transfused prior to admission to ICU, transfused only after admission to ICU and never transfused. For the purposes of this review the two transfusion groups were combined and compared with the non-transfused group using Review Manager. Transfusions in this study were based on receipt of RBC transfusion, rather than prespecified or protocol-driven transfusion criteria. The authors note the limitations of the study due to its retrospective nature and small sample size of patients treated with delayed transfusion.

CI, confidence interval; GCS, Glasgow coma scale; Hb, haemoglobin; ICU, intensive care unit; ISS, injury severity score; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio

a. Although *P* = 0.05 suggests statistical significance, the CIs are extremely wide and there are no adjustment for confounders.

STUDY DETAILS: Cohort study		
Citation		
Abdel Hakeem A, Mohamed CG, Othman MF (2012) Retinopathy of Prematurity: A Study of Incidence and Risk Factors in NICU of Al-Minya University Hospital in Egypt. Journal of Clinical Neonatology, 1(2): 76-81.		
Affiliation/Source of funds		
The authors reported no conflicts of interest.		
Study design	Level of evidence	Location/setting
Prospective cohort study.	Level III-2	NICU of a tertiary referral hospital in Egypt.
Risk factor/s assessed		
Sex, mode of delivery, gestational age, birth weight, respiratory distress syndrome (RDS), sepsis, patent ductus arteriosus (PDA), IVH, hypotension, phototherapy, oxygen therapy, duration of oxygen therapy, mode of oxygen therapy (mechanical ventilation or CPAP), frequency of blood transfusions.		
Population characteristics (including size)		
172 VLBW (≤1500 g) preterm neonates (≤32 weeks gestational age) admitted to NICU between January 2009 and December 2010. Infants >32 weeks gestational age or >1500 g birth weight were included if they were exposed to oxygen therapy for more than 7 days. Infants 32-34 weeks gestational age were also considered if they had a course of instability such as sepsis, asphyxia or ventilation. Neonates who died before the first ophthalmological examination (n=24), or with congenital anomalies (n=26) were excluded.		
Length of follow-up	Outcomes measured	
Each infant was followed until vascularisation of the retina reached zone 3, or until full remission after treatment.	ROP (stage 1-3)	
Method of analysis		
Group comparisons were done by the Chi-squared test or Fisher's exact test for categorical variables. A logistic regression model was performed and the adjusted OR was obtained for the risk factors which had been shown to be significant in the univariate analysis. A p-value <0.05 was considered significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a prospective cohort study of 172 VLBW preterm infants admitted to a single NICU in Egypt to assess various risk factors including frequency of blood transfusions on development of ROP. Ophthalmological examinations were initiated at the fourth week of life and were repeated weekly or biweekly until full vascularisation of the retina reached zone 3 (most peripheral), or until full remission of ROP after treatment. 33 infants developed ROP (19.2%). Of these, 18 were stage 1 (54.5%), nine were stage 2 (27.3%) and six were stage 3 (6%). All patients diagnosed with stage 3 ROP were treated with laser photocoagulation.		

RESULTS					
Population	>1 transfusion		1 transfusion		No transfusion
Available (n=222)	NR		NR		NR
Analysed (n=172)	23		25		124
Outcome	>1 transfusion	1 transfusion	No transfusion	Risk estimate (95% CI)	Significance *P*-value
ROP (all cases)	9/23 (39.1%)	3/25 (12.0%)	21/124 (16.9%)	NR	NR
Group comparisons for categorical variables					
Risk factor	ROP n/N (%)		No ROP n/N	Risk estimate (95% CI)	Significance *P*-value
No transfusion	21/33 (63.6%)		103/139 (74.1%)	NR	NR

1 blood transfusion	3/33 (9.1%)	22/139 (15.8%)	NR	Significant association *P* = 0.03
>1 blood transfusion	9/33 (27.3%)	14/139 (10.1%)	NR	NR
Logistic regression analysis				
Risk factor		Risk estimate (95% CI)		Significance *P*-value
Frequency of blood transfusions		OR 2.483 [1.182, 5.222]		Significant association *P* = 0.016
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				
Applicability				
Evidence not applicable to the Australian healthcare context. Study site Egypt (Level D).				
Comments				
The authors concluded that low gestational age, sepsis, oxygen therapy and frequent blood transfusions were significant independent risk factors for ROP. The most significant risk factors were low gestational age and low birth weight, which has also been shown in previous studies. Laser was effective in treatment and decreasing the progression of ROP. The authors noted limitations of their study were the small number of patients in a single centre which reduced generalisability and applicability to the wider Egyptian population.				

CI, confidence interval; CPAP, continuous positive airway pressure; Hb, haemoglobin; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; RR, risk ratio; VLBW, very low birth weight

STUDY DETAILS: cohort/case-control		
Citation		
Hassan NE, DeCou JM, Reischman D, Nickoles TA, Gleason E, Ropele DL 2014. RBC transfusions in children requiring intensive care admission after traumatic injury. Pediatr Crit Care Med.		
Affiliation/Source of funds		
The authors have disclosed that they do not have any potential conflicts of interest. They are affiliated with the Division of Pediatric Critical Care, Helen DeVos Children's Hospital, Grand Rapids, Michigan, Department of Statistics, Grand Valley State University, Grand Rapids, Michigan, Grand Rapids Medical Education Partners, Grand Rapids, Michigan, Department of Pathology, Spectrum Health, Grand Rapids, Michigan.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Paediatric trauma centre, USA
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion	Age, sex, race, mechanism of injury, Injury Severity Score, Glasgow Coma Scale, CNS trauma	
Population characteristics		
Paediatric trauma patients under the age of 18 years admitted to the hospital (paediatric trauma centre) between June 2007 and July 2010, either directly from the emergency department or transferred from another institution for further management. Burn patients and massive transfusion patients were excluded. Of 389 trauma patients, 107 patients (27.5%) transferred to the PICU were transfused with blood products. Of these transfusions, 81 were packed RBC transfusions and 26 were other blood products.		
Length of follow-up	Outcomes measured	
NR	Primary outcome: PICU length of stay Secondary outcomes: hospital length of stay, prevalence of complications, mechanical ventilations needs, oxygenation indices, fever, mortality, DC-GCS (discharge Glasgow Coma Scale) and home discharge	
Method of analysis		
Numerical data were compared using the Kruskal-Wallis analysis of variance for multiple group comparison. When the Kruskal-Wallis test concluded significant differences between the groups, the Mann-Whitney test was used to perform pairwise tests to compare the groups with a Bonferroni correction for multiple comparisons. Percentages were compared using the chi-square test or Fisher exact test for smaller counts. Multivariate logistic regression analysis was used to test multiple risk factors (ISS, GCS, patient's age, age of blood, volume transfused, and number of transfusions) in relation to multiple outcome variables (need for mechanical ventilation, PICU LOS, complications, infections, home discharge, DC-GCS, and mortality) in the transfused patients.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: The two groups were comparable with regard to age, sex, race and mechanism of injury. However, patients receiving RBC transfusions had significantly greater ISS (Injury Severity Score), PICU length of stay, hospital length of stay and mortality. It is not reported if all eligible participants agreed to take part in the study. Massive transfusion and burn patients were excluded and patients who received "blood products" were separated from those receiving "RBC transfusions". No loss to follow-up is specifically described but it is assumed all remaining patients were included in the final analysis. Multivariate logistic regression analysis was used to test multiple risk factors, such as age, ISS (Injury Severity Score), GCS (Glasgow Coma Scale). It is not reported if outcome assessment was blinded to exposure status.		
RESULTS		
Population	Intervention (n)	Comparator (n)
Available	81	282
Analysed	81	282

Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality (adjusted for Injury Severity Score)	17/81 (21.0%)	5/282 (1.8%)	OR 8.6 [2.6, 28.6]	Favours no transfusion *P* <0.001
TRALI	0/81 (0%)	0/282 (0%)	NA	NA
Haemolysis[a]	0/81 (0%)	0/282 (0%)	NA	NA
Febrile reactions (transfusion related with 3 infusions being discontinued)	9/81 (11.11%)	0/282 (0%)	OR 74.03 [4.26,1286.95]	Favours no transfusion *P* = 0.003
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to paediatric trauma patients.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in the USA (Level C).				
Comments				
The authors highlight the differences between children who received a transfusion and those who did not, noting transfused patients are often much sicker than those who are not transfused. As such, severity of illness becomes a significant confounder in any retrospective study of this nature. Statistical regression modelling was used to control for these differences, with the results suggesting patients who required a transfusion still had a much higher mortality rate after adjustment for potential confounders. The authors also discuss the limitations of the study, stemming from the retrospective design and its inability to establish a causal effect. They comment on the need for large multi-centre studies, as the majority of studies examining the adverse effect of blood transfusions are small, single centre trials.				

CI, confidence interval; CNS, central nervous system; DC-GCS, discharge Glasgow coma scale; GCS, Glasgow coma scale; Hb, haemoglobin; ISS, injury severity score; LOS, length of stay; NA, not applicable; OR, odds ratio; PICU, paediatric intensive care unit; RBC, red blood cell; RR, risk ratio; TRALI, transfusion related acute lung injury

a. Not specified whether this is a haemolytic transfusion reaction or not

STUDY DETAILS: Cohort study		
Citation		
Jaime-Perez JC, Colunga-Pedraza PR, Gomez-Almaguer D (2011) Is the Number of Blood Products Transfused Associated With Lower Survival in Children With Acute Lymphoblastic Leukemia? Pediatric Blood Cancer, 57: 217-23.		
Affiliation/Source of funds		
The authors stated they had no conflicts of interest to declare.		
Study design	Level of evidence	Location/setting
Retrospective longitudinal study	Level III-2	Single hospital, Mexico
Risk factor/s assessed	Potential confounding variables measured	
Transfusion of one or more single units of RBC or whole blood-derived platelet concentrate (PC)* * Blood products were leukoreduced but not irradiated.	Initial Hb level, patient age and age at ALL diagnosis, WBC and platelet count, platelet count.	
Population characteristics (including size)		
108 children <15 years of age fulfilling the clinical and laboratory criteria for diagnosis of acute lymphoblastic leukemia (ALL)		
Length of follow-up	Outcomes measured	
Average: 37.5 months (range: 2 to 103 months)	Overall survival (OS), event-free survival (EFS), relapse	
Method of analysis		
Descriptive analyses were performed. Overall survival and event-free survival were determined with the Kaplan-Meier method. Equality of data distribution was estimated with the log-rank test. Cox proportional hazards models were used for uni– and multivariate analysis. 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. Spearman correlations were calculated for quantitative variables (Hb, WBC, platelets, and blood products transfused). A p-value <0.05 was considered statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: a retrospective longitudinal study of 108 paediatric patients with acute lymphoblastic leukaemia admitted to hospital in Mexico, to assess the risk of number of blood products transfused and overall and event-free survival. Median patient age was 6 years (range 0 to 15 years). Median overall and event-free survival were not reached because death (n=20, 18.5%) or relapse (n=32, 29.6%) of ≥50% of the group did not occur. After multivariate analysis, transfusion >5 RBC remained a significant predictor of death (Hazard Ratio (HR) Adjusted 4.45; 95%CI: 1.64, 12.09; p=0.003). When the total number of blood products transfused, including RBC and PC, was incorporated into the analysis, maximal significance for predicting death was observed after transfusion of >30 blood products (HR 5.07; 95%CI: 1.94, 13.25; p=0.001). Outliers (≥2SD) were excluded from analysis for relapse.		

RESULTS

Population	Transfused >5 RBC	Transfused 1-5 RBC	Not transfused
Available	NR	NR	NR
Analysed (n=108)	24* (22.2%)	72* (66.7%)	12 (11.1%)

Outcome	Transfusion >5 RBC n/N (%)	Transfusion 1-5 RBC n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
OS, 20 months	~85%	~90%	100%	NR	
OS, 40 months	~58%	~81%	100%	NR	
OS, 60 months	~29%	~78%	100%	NR	*P* = 0.001
OS, 80 months	NR	~78%	NR	NR	

OS, 100 months	NR	~78%	NR	NR	
Multivariate Cox regression analysis					
Risk factor		Risk estimate (95% CI)			Significance *P*-value
RBC transfusion		HR 4.453 [1.64, 12.09]			Transfusion of >5 units RBC a significant predictor of mortality *P* = 0.003
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to paediatric patients with acute lymphoblastic leukaemia (Level A).					
Applicability					
Evidence not applicable to the Australian healthcare context (Level D).					
Comments					
The authors concluded that the number of blood products transfused to children with ALL appears to be significantly associated with lower survival rates. This may reflect both the severity of disease, and the TRIM effect, which may decrease immune surveillance capacity and the probability of leukemic clone eradication. * Note; there is a discrepancy between reported number of transfusion in text (n=97) and these totalled (n=96)					

ALL, acute lymphoblastic leukomalacia; CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; NR, not reported; OS, overall survival; PC, platelet concentrate; RBC, red blood cell; TRIM, transfusion-related immunomodulation; WBC, white blood cell

STUDY DETAILS: Cohort study		
Citation		
Kabatas EU, Beken S, Aydin B, Dilli D, Zenciroglu A, Okumus N (2013) The Risk Factors for Retinopathy of Prematurity and Need for Laser Photocoagulation: A Single Center Experience. GMJ, 24: 108-12.		
Affiliation/Source of funds		
The authors declared they had no conflicts of interest.		
Study design	Level of evidence	Location/setting
Prospective cohort study.	Level III-2	NICU at a tertiary hospital in Ankara, Turkey.
Risk factor/s assessed		
Gender, gestational age, birth weight, presence of associated disorders such as respiratory distress syndrome (RDS) with prophylactic or therapeutic use of surfactant, significant patent ductus arteriosus (PDA) with ibuprofen use, indirect hyperbilirubinaemia requiring phototherapy, intracranial haemorrhage (ICH) ≥grade 2, apnoea with prophylactic or therapeutic use of caffeine, hypotension with inotropic support, sepsis, NEC ≥grade 2, chronic lung disease (CLD) with diuretic or steroid use, duration of TPN, anaemia with need for RBC transfusion, oxygen exposure, number of hyperoxia, hypoxia and hypercarbia episodes prior to ROP.		
Population characteristics (including size)		
113 VLBW (<1500 g) preterm infants <32 weeks gestational age, or preterm infants 32-37 weeks gestational age with anaemia, apnoea, RDS, PDA, ICH, NEC, CLD, perinatal asphyxia or sepsis requiring prolonged mechanical ventilation. Patients with severe congenital anomalies were excluded.		
Length of follow-up		Outcomes measured
Follow-up ROP examinations were performed once a fortnight in patients with low risk pre-threshold disease, and at least once a week for high risk patients. Retrospective period: March 2011 – August 2012.		Severe ROP requiring laser photocoagulation (LP), ROP not requiring LP.
Method of analysis		
Kolmogorov-Smirnov test was used to determine the distribution of data. Differences among two groups were analysed by Student's t-test or Mann-Whitney U-test. The chi-square test was used to compare categorical variables. Pearson or Spearman test was used to analyse correlation between variables. The odds ratio (OR) and logistic regression analysis were done with development of ROP as the dependent variable and possible risk factors as independent variables. Multivariate analysis was repeated for need of LP as the dependent variable. The level of significance was set at 5% for all comparisons.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: a prospective cohort study of 113 preterm infants admitted to a single NICU in Turkey to assess various risk factors including RBC transfusion on incidence of ROP. All fundus examinations were performed by the same ophthalmologist (first author) which may be a source of bias. Not reported whether examinations were performed blind to transfusion status. Mean gestational age was 30 weeks (24-36) and mean birth weight was 1412 ± 473g. The first ROP examination was performed at 34 ± 3 weeks of corrected age. There were 53 (47%) infants who developed ROP, 19 (36%) were <1000 g and 25% were in infants aged 32-37 weeks gestation. Fifteen cases were ≥stage 3 ROP (28%) and 18 cases (34%) required LP. Birth weight and gestational age were lower in the ROP group, while rates of associated disorders and transfusion requirements in the first 10 days of life were higher ($P < 0.05$). The authors noted that infants with ROP had prolonged oxygen exposure. Infants requiring LP also had higher total oxygen exposure. The authors also noted that the incidence of ROP was higher among infants having prophylactic or therapeutic caffeine, used for the treatment of apnoea. These confounders should be considered when interpreting results. Loss to follow-up was not explicitly stated, although it appeared all infants were included in analyses.		
RESULTS		
Population	RBC transfusion	No transfusion
Available	NR	NR
Analysed (n=113)	87	26

Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
ROP (all cases)	49/87 (56.3%)	4/26 (15.4%)	NR	NR
Outcome	Transfusion in first 10 days of life n/N (%)	No transfusion in first 10 days of life n/N (%)	Risk estimate (95% CI)	Significance *P*-value
ROP	25/33 (75.8%)	28/80 (35.0%)	NR	NR
Group comparisons for categorical variables				
Risk factor	ROP n/N (%)	No ROP n/N	Risk estimate (95% CI)	Significance *P*-value
No transfusion	4/53 (7.5%)	22/60 (36.7%)	NR	NR
RBC transfusion	49/53 (94.5%)	38/60 (63.3%)	NR	Significant association *P* = 0.001
RBC transfusion in the first 10 days of life	25/53 (47.2%)	8/60 (13.3%)	NR	Significant association *P* = 0.001
Mean number of RBC transfusions (min-max)	4 (0-15)	1 (0-16)	NR	Significant association *P* = 0.04
Risk factor	ROP + LP n/N (%)	ROP + no LP n/N	Risk estimate (95% CI)	Significance *P*-value
No transfusion	8/18 (44.4%)	3/35 (8.6%)	NR	NR
RBC transfusion	10/18 (55.6%)	32/35 (91.4%)	NR	No significant association *P* = 0.20
RBC transfusion in the first 10 days of life	6/18 (33.3%)	19/35 (54.3%)	NR	No significant association *P* = 0.60
Mean number of RBC transfusions (min-max)	3 (0-11)	4 (0-15)	NR	No significant association *P* = 0.80
Multivariate analysis				
Risk factor	ROP n/N (%)	No ROP n/N	Risk estimate (95% CI)	Significance *P*-value
RBC transfusion in the first 10 days of life	NR	NR	OR 1.9 [1.1, 3.3]	RBC transfusion increased the risk for ROP *P* = 0.01
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants with some caveats (Level B).				
Applicability				
Evidence not applicable to the Australian healthcare context. Study site Turkey (Level D).				
Comments				
In multivariate analysis of possible risk factors for ROP including gestational age, having RDS, PDA and sepsis, use of caffeine, need of transfusion in the first 10 days of life, duration of TPN and total oxygen exposure, it was found that the need of transfusion in the first 10 days of life has increased the risk for ROP. The authors concluded that RBC transfusion in early neonatal period may contribute to the development of ROP.				

CI, confidence interval; CLD, chronic lung disease; Hb, haemoglobin; ICH, intracranial haemorrhage; LP, laser photocoagulation; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; TPN, total parenteral nutrition; VLBW, very low birth weight

STUDY DETAILS: Cohort study		
Citation		
Kneyber MCJ, Grotenhuis F, Berger RFM et al (2013) Transfusion of Leukocyte-Depleted RBCs Is Independently Associated With Increased Morbidity After Pediatric Cardiac Surgery, Paediatric Critical Care Medicine, 14(3): 298-305.		
Affiliation/Source of funds		
The authors did not disclose any potential conflicts of interest.		
Study design	Level of evidence	Location/setting
Retrospective cohort study.	Level III-2	Single tertiary PICU, The Netherlands.
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion (leukocyte-depleted) within 48 hours of PICU admission.	PRISM II score, RACHS category, duration of surgery, occurrence of VAP, repair status, RBC transfusion within 48hrs propensity score.	
Population characteristics (including size)		
335 children aged 0 months to 18 years admitted to PICU post-surgery. All children were ventilated. Children admitted to NICU or adult ICU were not considered. Children with chronic anaemia, haemoglobinopathies, or active blood loss prompting surgical reintervention were excluded.		
Length of follow-up	Outcomes measured	
NR	Primary: use and duration of mechanical ventilation. Secondary: use and duration of inotropic support, occurrence of acute kidney injury or VAP during PICU admission, mortality.	
Method of analysis		
In the bivariate analysis, demographical and clinical data were compared for the primary and secondary outcome measures between patients who were transfused within the first 48 hours of PICU admission and those who were not. The Mann-Whitney U-test was used for continuous variables, whereas for categorical variables the chi-square test was used or Fisher's exact test when the expected value of a cell was less than 5. Correlations were assessed calculating the Spearman correlation coefficient. A propensity score was calculated to limit confounding by indication. This score estimated the likelihood for an individual patient to be or not be transfused within the first 48 hours of PICU admission. The propensity score was based upon the type of surgery defined by the RACHS category, Hb <9.6 g/dL during the first 48 hours of PICU admission, cumulative drain production, transfusion with CPB machine blood in the PICU, patient age, and repair status (normal physiology) after surgery. Two bivariate analyses were performed, one with all patients and one including only patients with normal physiology after surgery. The authors calculated a minimum sample size of 270 patients would be needed (with a 1:3 ratio between transfused and non-transfused patients) to detect a statistically significant difference with 80% power and alpha 0.05 for the primary outcome. *P*-values below 0.05 were accepted as statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: a retrospective cohort study of 335 paediatric post-surgery patients, to assess the risk of RBC transfusion within 48 hours of PICU admission on use and duration of mechanical ventilation. The decision to transfuse a patient during PICU stay was at the discretion of the attending physician. Routinely, the quantity per RBC transfusion was 10-15 mL/kg. Cardiovascular drugs used in the PICU included dopamine, dobutamine, milrinone, epinephrine and norepinephrine. Perioperative antimicrobial prophylaxis was used for 24 hours in all patients. Non-survivors and patients who were not ventilated were censored for statistical analysis. Transfused patients were significantly younger (19.4±30.5 days vs 48.0±52.5 days; $P < 0.001$), weighed less (8.6±0.7 kg vs. 16.8±1.0 kg, $p < 0.001$), and had a higher PRISM II score (10.1±0.8 vs. 5.7±0.3; $P < 0.001$) compared with non-transfused patients. Duration of surgery and CPB was also significantly longer among transfused patients. The authors noted a limitation of the study was the decision to transfuse often being made on a subjective basis where no transfusion algorithm was available, leading to confounding by indication (e.g. severely ill patients or those with low Hb were more easily transfused). Observations were adjusted using propensity score analysis, but the propensity score was not externally validated. The authors also noted the retrospective nature of the study as a limitation, as well as the study being conducted at a single centre which could limit generalizability. Causality between outcome and event could not be determined due to the potential for confounding.		

RESULTS				
Population	RBC transfusion		No RBC transfusion	
Available (n=335)	111 (86 within 48 hours and 25 after 48 hours of PICU admission)		224	
Analysed (n=335)	111 (86 within 48 hours and 25 after 48 hours of PICU admission)		224	
Outcome	RBC transfusion within 48hrs n/N (%)	No transfusion within 48hrs n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality during PICU stay (all patients)	2/86 (2.3%)	1/249 (0.4%)	NR	No significant difference *P* = 0.163
Mortality during PICU stay (patients with normal physiology after surgery)	0/66 (0%)	0/205 (0%)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill paediatric post-surgery patients (Level A).				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site The Netherlands (Level B).				
Comments				
The authors concluded that transfusion of leukocyte-depleted RBCs within the first 48 hours of PICU admission after cardiac surgery is independently associated with prolonged duration of mechanical ventilation. There were no significant differences in mortality or acute kidney injury between transfusion and non-transfused patients.				

CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; NA, not applicable; NR, not reported; PICU, paediatric intensive care unit; PRISM, paediatric risk of mortality; RBC, red blood cell; VAP, ventilator assisted pneumonia

STUDY DETAILS: Cohort study		
Citation		
Kneyber MCJ, Hersi MI, Twisk JR, Markhorst DG, Plotz FB. (2007) Red blood cell transfusion in critically ill children is independently associated with increased mortality. Intensive Care Med, 33: 1414-1422.		
Affiliation/Source of funds		
Not reported		
Study design	Level of evidence	Location/setting
Retrospective cohort study.	Level III-2	Single tertiary PICU, The Netherlands.
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion (leukocyte depleted)	Paediatric Index of Mortality (PIM) probability of death, mean TISS-28 score during the first 48 h of PICU admission, post-operative admission, presence of sepsis and/or malignancy, and pre-transfusion haemoglobin concentration.	
Population characteristics (including size)		
295 critically ill children aged 0 to 18 years admitted to PICU between January and December 2003. Exclusion criteria: children with chronic (> 6 weeks) anaemia, haemoglobinopathies, or active blood loss.		
Length of follow-up	Outcomes measured	
1 year retrospective period	Primary: in PICU mortality Secondary: duration of mechanical ventilation, duration of infusion of vasoactive agents, duration of PICU stay	
Method of analysis		
In the univariate analysis demographical and clinical data were compared between patients who were transfused and those who were not. For continuous variables the Mann-Whitney U-test was used, and for categorical variables the $\chi 2$ test or Fisher's exact test. Missing variables were not imputed. The authors applied multiple logistic regression analysis for the primary outcome (mortality), and Cox proportional hazards regression analysis for the secondary outcome measures to the estimate the independent contribution of RBC transfusion to each outcome parameter. To adjust for disease severity upon PICU admission, the authors adjusted for PIM probability of death. To adjust for confounding by indication, the authors adjusted for the mean TISS-28 score during the first 48 h after PICU admission. Finally, the authors adjusted for pre-transfusion Hb concentration, admission postoperatively, and admission diagnosis. Each potential confounding variable was separately entered into the model. To study if RBC transfusion would lead to an excess in mortality, the authors calculated the Standardised Mortality Ratio (SMR) for five probability of death strata calculated from the PIM score. The SMR was calculated by dividing the observed number of deaths by the expected number of deaths per strata. The expected number of deaths was obtained from the Dutch Working Group on Pediatric Intensive Care Evaluation (PICE).		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: a retrospective, single centre observational study of 295 critically ill children aged 0 to 18 years admitted to PICU, to assess whether RBC transfusion is independently associated with increased mortality, irrespective of pre-transfusion Hb and disease severity. The PICU unit did not have a transfusion guideline. The decision to transfuse a patient was made by the attending physician. Routinely, the quantity per erythrocyte transfusion amounts to 10–15 mL/kg. Anaemia was defined as a Hb concentration below 9.6 g/dL. Disease severity upon PICU admission was defined by the Pediatric Index of Mortality (PIM) probability of death. The validated PIM score is composed of variables that are noted during the first hour of PICU admission. For this study the PIM score was retrospectively calculated. Data on all variables necessary for this score were available in all patients.		
RESULTS		
Population	RBC transfusion	No RBC transfusion
Available	67	228

Analysed	67		228	
Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality (unadjusted)	11/67 (16.4%)	6/228 (2.6%)	NR	Favours no RBC transfusion *P* < 0.001
Mortality (logistic regression[a])			OR 9.95 (1.28, 77.16)	Favours no RBC transfusion *P* = 0.028
Mortality (adjusted for PIM probability of death)			OR 5.730 (1.89, 17.31)	Favours no RBC transfusion *P* = 0.002
Mortality (adjusted for TISS-28 during first 48h of PICU stay)			OR 4.699 (1.14, 19.30)	Favours no RBC transfusion *P* = 0.032
Mortality (adjusted for sepsis and/or malignancy)			OR 7.157 (2.49, 20.60)	Favours no RBC transfusion *P* < 0.001
Mortality (adjusted for post-operative admission)			OR 7.065 (2.50, 20.00)	Favours no RBC transfusion *P* < 0.001
Mortality (adjusted for pre-transfusion Hb)			OR 9.309 (2.37, 36.59)	Favours no RBC transfusion *P* = 0.001
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill paediatric patients (Level A).				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site The Netherlands (Level B).				
Comments				
The authors concluded that RBC transfusions in critically ill children are independently associated with increased mortality and prolonged duration of mechanical ventilation, infusion of vaso-active agents and PICU length of stay. [a] Adjusted for PIM probability of death, mean TISS-28, sepsis and/or malignancy, postoperative admission and pre-transfusion Hb.				

CI, confidence interval; Hb, haemoglobin; NR, not reported; OR, odds ratio; PICU, paediatric intensive care unit; PIM, paediatric index of mortality; RBC, red blood cell; SMR, standardised mortality ratio; TISS-28, therapeutic intervention scoring system-28

STUDY DETAILS: Cohort study				
Citation				
Li ML, Hsu SM, Chang YS et al (2013) Retinopathy of prematurity in southern Taiwan: A 10-year tertiary medical center study. Journal of the Formosan Medical Association, 112: 445-53.				
Affiliation/Source of funds				
The authors reported they had no financial support.				
Study design	Level of evidence	Location/setting		
Retrospective cohort study.	Level III-2	National Cheng Kung University Hospital, Taiwan		
Risk factor/s assessed				
Birth weight, gestational age, in– vs out-of– hospital birth, paternal and maternal age, multiple gestations, parity, Apgar scores at 1 and 5 minutes, length of hospital stay, respiratory distress syndrome (RDS), mechanical ventilation, chronic lung disease (CLD), patent ductus arteriosus (PDA), prenatal use of steroids, postnatal surfactant and indomethacin use, sepsis, IVH, upper GI bleeding, blood transfusion, NEC.				
Population characteristics (including size)				
503 VLBW (<1500 g) infants or preterm infants <32 weeks gestational age, admitted between January 2000 and December 2009. Infants were excluded who failed to survive longer than 28 days for the first ROP screening, who did not live for 6 months postnatally to complete ROP screening, and who had congenital diseases such as chromosomal anomaly.				
Length of follow-up		Outcomes measured		
6 months for ROP screening and average follow-up of 2.7 years		ROP		
Method of analysis				
The chi-square test was used to compare categorical data related to clinical outcomes. Student t-test and analysis of variance were used to compare continuous data. Univariate analyses were used to test for the potential risk factors for ROP. If significant at $P < 0.05$, risk factors were included in the stepwise multivariable logistic regression analyses.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a retrospective cohort study of 503 VLBW or preterm infants admitted to a single tertiary hospital in Taiwan, to assess the risk of various factors including blood transfusion on development of ROP. Birth weight ranged from 455 to 1968g and gestational age from 21 to 38 weeks. The first ROP screening was conducted at 31-33 weeks GA for infants born <27weeks, and 4 weeks postnatal age for infants born 27-32 weeks GA. Eye examinations were weekly or biweekly depending on findings of the screening examination. Fundus examinations were conducted by three of the authors. Blinding to outcome assessment was not reported, and potential for bias should be considered. Birth weight and gestational age was significantly lower in the ROP group than the non-ROP group ($P < 0.001$). Among infants with a GA < 32 weeks versus >32 weeks, ROP was diagnosed in 42.6% versus 13.3% respectively. ROP was identified in 190 infants (38%). 59 infants (12%) underwent laser photocoagulation therapy or cryotherapy. The authors note limitations such as the small sample size in comparison to other studies, study data obtained from only a single site which may not reflect the incidence of ROP in southern Taiwan, and the different ages at which refractive status was examined limiting the generalisability and comparative value among groups.				
RESULTS				
Population	RBC transfusion		No transfusion	
Available (n=503)	228		275	
Analysed (n=503)	228		275	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
ROP	110/228 (48.2%)	80/275 (29.1%)	NR	NR
Univariate analysis				
Risk factor	ROP n/N (%)	No ROP n/N	Risk estimate (95% CI)	Significance *P*-value

Blood transfusion, %	58.1	37.6	NR	Significant association *P* < 0.001
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants with some caveats (Level B).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site Taiwan (Level C).				
Comments				
Although univariate analysis showed ROP having a significant association (as in other studies) with lower BW, younger GA, lower Apgar score at 1 and 5 minutes, longer length of hospital stay, RDS, CLD, PDA, administration of surfactant or indomethacin, sepsis, upper GI bleeding, NEC and blood transfusion; multivariate analysis showed only BW as a predictor for ROP (data not reported). The authors concluded that low birth weight is a major risk factor for ROP. Infants with extremely low birth weight had a higher risk of severe ROP. Common ocular sequelae of advanced ROP were myopia and anisometropia.				

BW, body weight; CI, confidence interval; CLD, chronic lung disease; GI, gastrointestinal; Hb, haemoglobin; NEC, necrotising enterocolitis; NR, not reported; PDA, patent ductus arteriosus; RBC, red blood cell; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; VLBW, very low birth weight

STUDY DETAILS: Cohort study		
Citation		
Nacoti M, Cazzaniga S, Lorusso F et al (2012) The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. Pediatric Transplantation, 16: 357-66.		
Affiliation/Source of funds		
The authors stated they had no conflicts of interest to declare.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	General Hospital of Bergamo, Italy.
Risk factor/s assessed	Potential confounding variables measured	
Perioperative transfusion of blood products (RBC and FFP).	Age, sex, weight, height, BMI, indication for transplantation, PELD score, lab tests, PICU's variables.	
Population characteristics (including size)		
243 pediatric liver transplant patients aged <18 years from deceased brain-dead donors. Combined organ transplantations were excluded.		
Length of follow-up	Outcomes measured	
1 year	Primary: patient and graft survival in the first year after transplantation	
Method of analysis		
Kaplan–Meier product-limit estimator was used to compute cumulative survival rates. Univariate analysis with log-rank test was used to assess survival differences among variables categories. For comparison purpose, continuous variables were categorised using their median or tertiles as cut-off points. All variables with a p-value ≤0.1 in the univariate analysis were included in a multivariate analysis to assess which factors influenced patient and graft survival. Cox proportional hazard regression with forward stepwise selection was used to identify main risk factors. Complications in the first year were considered in survival analysis to adjust for postoperative confounders. Effects of identified factors were presented as hazard ratios with 95% confidence interval together with their p-values. Propensity score analysis was used to adjust risk factors for selection biases in the use of blood products. Outcome for propensity score was defined as children with overall blood components transfused above the median value of 700 mL vs. children below this value. Multivariate logistic regression with stepwise selection was used to assess propensity score function. All statistical tests were considered significant for p-values ≤0.05.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a retrospective cohort study of 243 pediatric liver transplant patients aged <18 years at a single hospital in Italy, to assess the risk of perioperative transfusion of RBC and FFP on patient and graft survival in the first year after transplantation. Seven hepatobiliary surgeons performed all the liver transplants with two involved in each procedure. Fifteen anaesthesiologists were involved throughout the study period. Transfusion policy was based on clinical assessment. Due to the nature of the study blinding to outcome was not feasible. Missing data were <2%. Thirty-nine patients stopped follow-up within one year. Twenty-six patients died. One year patient survival was significantly associated with the number of allogenic RBC and FFP units transfused during surgery. Limitations of the study included retrospective nature, inability to distinguish whether survival was related to massive transfusion due to different triggers.		

RESULTS

Population	Transfused >3 RBC units	Transfused 2 RBC units	**Transfused ≤1** RBC unit
Available	NR	NR	NR
Analysed (n=243)	39 (16.0%)	75 (30.9%)	129 (53.1%)

Outcome	Transfusion **≥3** RBC units n/N (%)	Transfusion 2 RBC units n/N (%)	Transfusion **≤1** RBC unit n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Survival, 2 months	~78%	~90%	~97%	NR	NR

Survival, 4 months	~75%	~90%	~94%	NR	NR
Survival, 6 months	~75%	~90%	~92%	NR	NR
Survival, 8 months	~73%	~90%	~95%	NR	NR
Survival, 10 months	~70%	~90%	~95%	NR	NR
Survival, 12 months	69.9%	89.1%	94.3%	NR	Significant difference *P* < 0.001
Standard analysis: RBC transfusion during surgery and patient survival					
		Risk estimate (95% CI)			Significance *P*-value
RBC during surgery, ≤ 1 units		HR 1.847 [0.647, 5.267]			*P* = 0.251
RBC during surgery, ≥ 3 units		HR 3.146 [1.097, 9.022]			*P* = 0.033
Propensity score – adjusted analysis: RBC transfusion during surgery and patient survival					
		Risk estimate (95% CI)			Significance *P*-value
RBC during surgery, 2 units		HR 2.170 [0.747, 6.301]			*P* = 0.154
RBC during surgery, ≥ 3 units		HR 3.010 [1.009, 8.979]			*P* = 0.048
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to paediatric liver transplant patients (Level A).					
Applicability					
Evidence applicable to the Australian healthcare context with few caveats. Study site Italy (Level B).					
Comments					
Although a relationship between number of units transfused and infant survival was observed, the authors noted this may not be considered causal but rather a surrogate marker for sicker patients. Multiple regressions controlling for confounding factors however confirmed the negative and independent impact of blood products transfusion and survival. The authors concluded that most mortality and graft loss occurred in the first few months after transplantation, confirming findings of earlier studies. Decreasing early surgical complications and perioperative transfusion will improve the overall long-term patient and graft survival after pediatric liver transplantation.					

BMI, body mass index; CI, confidence interval; FFP, fresh frozen plasma; Hb, haemoglobin; HR, hazard ratio; NR, not reported; PELD, paediatric end stage liver disease; PICU, paediatric intensive care unit; RBC, red blood cell

STUDY DETAILS: Cohort study		
Citation		
Paul DA, Mackley A, Novitsky A, Zhao Y, Brooks A, Locke RG (2011) Increased Odds of Necrotizing Enterocolitis After Transfusion of Red Blood Cells in Premature Infants. Pediatrics, 127(4): 635-41.		
Affiliation/Source of funds		
The authors stated that they have no relevant financial relationships to disclose.		
Study design	Level of evidence	Location/setting
Retrospective cohort study.	Level III-2	Level 3 NICU at a single hospital in the USA.
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion	Neonatal variables: birth weight, gestational age, inborn status, gender, Apgar score at 1 and 5 minutes, time on ventilator, surfactant use, PDA, PDA ligation, sepsis, postnatal steroid use. Maternal variables: race, multiple gestation, preeclampsia, chorioamnionitis, caesarean delivery, antenatal Mg, indomethacin, steroids or antibiotics.	
Population characteristics (including size)		
2311 VLBW (<1500 g) preterm infants admitted to hospital between July 1993 and June 2007.		
Length of follow-up	Outcomes measured	
Retrospective period was 14 years.	NEC within 48hrs of transfusion.	
Method of analysis		
Statistical analyses included both uni– and multivariable analyses. Univariable analyses included χ^2 for categorical variables and analysis of variance for continuous variables with normal distribution. The Levene test of homogeneity of variances was used to assess data distribution. The Mann-Whitney *U*-test was used for continuous variables that were not normally distributed. Multivariable analyses included logistic regression. Independent variables in the multivariable models included those with a *p*-value of <0.15 on univariable analysis. A *p*-value <0.05 was considered statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: a retrospective cohort study of 2311 VLBW infants admitted to a Level 3 NICU in the US, to assess the risk of RBC transfusion on the development of NEC within 48hrs. Data was obtained from a computerised database and from a review of medical records which were entered into the database by trained reviewers. Diagnosis of NEC and the decision to transfuse RBCs was made at the discretion of the attending medical team. After 1995 transfusion protocols were instituted. The yearly rate of NEC did not change over the study period. Infants in the NEC group had a lower birth weight and gestational age than the no NEC group ($P < 0.01$), and were more likely to be male ($P = 0.03$). The incidence of NEC was 5.3% (122). 59 cases of NEC received a blood transfusion but not in the preceding 48 hours of diagnosis (interval between transfusion and diagnosis was 11.2±11.3 days). The infants who developed NEC within 48 hours of transfusion had lower birth weight and gestational age compared with those who developed NEC and never received a transfusion. In addition, infants who developed NEC within 48 hours of transfusion reached full feeds at a later time and developed NEC at a later age than infants who developed NEC and never received a transfusion. There were no differences in gestational age, birth weight, days to full enteral feeds, or age at diagnosis of NEC between the infants in whom NEC occurred 48 hours after transfusion, and those in whom NEC occurred >48 hours after transfusion. There were no differences in the rate of surgical NEC between the 3 groups. 2311 infants were enrolled in the study, but only 2310 were included in the final analyses. Not reported why one patient excluded. Authors note limitations due to retrospective nature of the study, inability to determine causality of RBC transfusions, and inclusion of cases with Bells stage >2 meant that milder cases were missed that may have influenced the incidence of NEC after transfusion. The authors further note the limitation that subtle signs of NEC may have been evident before 48 hours but did not manifest until after this period. NEC may also have been evident but not diagnosed prior to transfusion.		
RESULTS		

Population	RBC transfusion	No transfusion
Available (n=2311)	NR	NR
Analysed (n=2310)*	1148	1162

Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
NEC (n=122)	98/1148 (8.5%)	24/1162 (2.1%)	NR	NR
NEC within 48hrs (n=63)	33/1148 (2.9%)	30/1162 (2.6%)	NR	NR
NEC requiring surgical intervention (n=35)	30/1148 (2.6%)	5/1162 (0.4%)	NR	NR
NEC within 48hrs requiring surgical intervention (n=16)	11/1148 (1.0%)	5/1162 (0.4%)	NR	NR
Risk factor	NEC Mean ± SD (n)	No NEC Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value
Total RBC transfusions during hospital course	5.6 ± 5.0 (122)	2.7 ± 4.1 (2188)	NR	Significant difference $P < 0.01$
RBC transfusions excluding those after NEC diagnosis	3.1 ± 3.2 (122)	2.7 ± 4.1 (2188)	NR	Significant difference $P < 0.01$

Unadjusted and adjusted analyses			
Risk factor	Unadjusted OR (95% CI)	Multivariable Model #1 [a] OR (95%CI)	Multivariable Model #2 [b] OR (95%CI)
RBC transfusion	8.9 [3.3, 24.8]	9.6 [5.0, 18.2]	11.3 [3.8, 33.3]
RBC transfusion, excluding transfusions after NEC diagnosis	2.9 [1.9, 4.4]	2.3 [1.2, 4.2]	2.1 [1.1, 4.3]

EXTERNAL VALIDITY
Generalisability
Evidence directly generalisable to VLBW infants (<1500 g) (Level A).
Applicability
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).
Comments
The authors concluded that RBC transfusion was associated with increased odds of NEC. The rate of NEC after transfusion was 1.4%. The authors state that they could not determine if RBC transfusions were part of the causal pathway for NEC or were indicative of other factors that may be. * Calculated from Table 3 using any transfusions, excluding those after NEC diagnosis [a] Adjusted for gestational age, gender, antenatal steroids, magnesium sulphate and indomethacin; maternal preeclampsia, and SNAP (Score for Neonatal Acute Physiology) [b] Adjusted for same variables as model #1 plus ventilator days, surfactant, postnatal steroids, PDA and sepsis.

CI, confidence interval; Hb, haemoglobin; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; RBC, red blood cell; SD, standard deviation; VLBW, very low birth weight

STUDY DETAILS: Cohort study		
Citation		
Redlin M, Kukucka M, Boettcher W et al (2013) Blood transfusion determines postoperative morbidity in pediatric cardiac surgery applying a comprehensive blood-sparing approach. The Journal of Thoracic and Cardiovascular Surgery, 146(3): 537-42.		
Affiliation/Source of funds		
The authors stated they have nothing to disclose with regard to commercial support.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Germany
Risk factor/s assessed	Potential confounding variables measured	
Intraoperative and postoperative RBC transfusion	RACHS-1 score, CPB time, body weight, reoperation, DHCA, postoperative cyanosis, Hb CPB, base excess CPB, rSO2 CPB (brain and lower body), preoperative antithrombin III, postoperative fibrinogen and platelets, 48hr blood loss.	
Population characteristics (including size)		
288 pediatric cardiac surgery patients weighing <16 kg		
Length of follow-up	Outcomes measured	
NR	Primary: length of mechanical ventilation and ICU stay Secondary: mortality	
Method of analysis		
Patient characteristics and morbidity data were compared among groups by analysis of variance on ranks; followed by all pairwise multiple comparisons using Dunn's method or the rank sum test, as appropriate. Rates were assessed using the chi-square test. *P*-values from all pairwise multiple comparisons were adjusted according to the sequentially rejective method of Holm. On univariate analysis, the effects of transfusion on length of mechanical ventilation and ICU stay were assessed using Kaplan-Meier curves and log-rank tests. Multivariate analyses were applied to determine whether transfusion vs no transfusion or, within the subgroup of transfused infants, the transfused volume of RBC independently affected the morbidity parameters, length of mechanical ventilation and ICU stay.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: A retrospective study of 288 pediatric cardiac surgery patients from a previous German Study (Redlin 2012*), to assess the risk of intraoperative and postoperative RBC transfusion on length of mechanical ventilation and ICU stay. Median age was 161 days (range 3 days to 4.8 years) and median body weight was 5.8kg (range 1.7 to 15.9kg). RBC were added to the priming solution only when estimated Hb was <7.0 g/dL. The transfusion trigger during CPB was Hb <7.0 g/dL. The decision for postoperative transfusion was determined by the attending physicians. The major finding of this study was that blood transfusion independently worsened the in hospital outcome of paediatric cardiac surgery patients, with those receiving intraoperative blood transfusions presenting with the longest mechanical ventilation and ICU stay. The major limitation of this study was that the multivariate analyses might not have been sufficiently adjusted for group assignment bias. Coagulation disorders leading to increased blood loss and severity of underlying cardiac malformations might have affected both the need for transfusion and post-operative morbidity. The authors attempted to adjust for potential confounding variables (see above). Other limitations included the lack of a universally applicable lower limit for tolerable Hct or Hb levels during CBP, and the lack of long-term outcome data (i.e. psychomotor development of infants). In hospital mortality was too low for detailed statistical analysis.		
RESULTS		

Population	Intraoperative transfusion	Postoperative transfusion	Not transfusion
Available	NR	NR	NR
Analysed (n=288)	149 (51.7%)	68 (23.6%)	71 (24.7%)

Outcome	Intraoperative transfusion n/N (%)	Postoperative transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value

In hospital mortality	9/149 (6.0%)	1/68 (1.5%)	0/71 (0%)	NR	Significant difference *P* = 0.04 (chi-square test)
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to paediatric cardiac surgery patients with few caveats (Level B).					
Applicability					
Evidence applicable to the Australian healthcare context with few caveats. Study site Germany (Level B).					
Comments					
The authors concluded that the incidence and volume of blood transfusion markedly affects postoperative morbidity in pediatric cardiac surgery. * Redlin M, Habazettl H, Boettcher W et al (2012) Effects of a comprehensive blood-sparing approach using body weight adjusted miniaturised cardiopulmonary bypass circuits on transfusion requirements in pediatric cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery, 144: 493-9.					

CI, confidence interval; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; Hb, haemoglobin; Hct, haematocrit; NR, not reported; ICU, intensive care unit; RACHS-1, Risk Adjusted classification for Congenital Heart Surgery-1; RBC, red blood cell; rSO2, regional oxygen saturation

STUDY DETAILS: Case-control study		
Citation		
Singh R, Visintainer PF, Frantz ID et al (2011) Association of necrotizing enterocolitis with anemia and packed red blood cell transfusions in preterm infants. Journal of Perinatology 31:176-82.		
Affiliation/Source of funds		
The study was supported in part by two grants from the National Institute of Child Health and Human Development, and the National Institutes of Health. Additional funding was received from institutional/departmental funds. The authors stated they had no conflicts of interest.		
Study design	Level of evidence	Location/setting
Retrospective case-control study	Level III-2	Two Level III NICUs at Baystate Children's Hospital and Tufts Medical Centre, USA
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion within 24, 48 and 96 hrs of NEC diagnosis for cases. For controls, timing was determined using the day of diagnosis in the index case and then using this chronological age as the reference point.	Maternal: pregnancy-induced hypertension, chorioamnionitis, use of antenatal steroids, premature prolonged rupture of membranes (PPROM), abnormal end-diastolic placental flow. Infant: birth date, gestational age, birth weight, gender, mode of delivery, Apgar scores at 1 and 5 minutes, presence of central lines, hypotension, use of volume expander or vasopressor therapy, PDA, sepsis, breast milk or formula feedings, use of additives e.g. HMF; iron, rHuEPO or antacid therapy, use of postnatal steroids for CLD.	
Population characteristics (including size)		
333 preterm infants (≤32 weeks gestational age) admitted to NICU between January 2000 and December 2008 (111 NEC cases ≥stage 2a, and 222 matched controls with similar gestational age (±1 week) and birth weight). Infants with known chromosomal anomalies, congenital heart disease or spontaneous intestinal perforation were excluded.		
Length of follow-up	Outcomes measured	
96 hours.	Primary: NEC stage 2a or above (early NEC defined as onset within first 21 days of life). Secondary: associated inpatient morbidities including short gut syndrome, cholestasis, chronic lung disease, ROP, IVH, length of stay and death.	
Method of analysis		
Continuous variables were examined with the paired t-tests and categorical variables with McNemar's test. Propensity scores were generated for RBC transfusion and Hct, and used in subsequent analyses as covariates. Multiple conditional logistic regression models were created using the variables that were significant at a p-value <0.05. Separate models were created for NEC and Hct, NEC and RBC transfusions and NEC with four levels of anaemia. Combined models were created to assess Hct and RBC transfusion and any interaction between them. Subgroup analyses were performed for early and late NEC.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a case-control study of 333 infants (111 NEC cases and 222 matched controls) admitted to NICU in the USA, to assess the risk of RBC transfusion within 24, 48 and 96 hours on development of NEC stage 2a or above. The authors state case charts were reviewed to confirm diagnosis of NEC but do not state by whom and whether reviewers were aware of NEC diagnosis during case ascertainment. NEC cases and controls had similar mean gestational age (cases 26.9 ± 2.5 weeks; controls 27.2 ± 2.3 weeks; p=0.21) and birth weight (cases 969 ± 309 g; controls 1023 ± 338 g; p=0.16). Difference in breast milk feeds between groups approached significance (cases 83.8%; controls 74.8%; p=0.06).		
RESULTS		
Population	Received RBC transfusion	Did not received RBC transfusion
Available	NR	NR
Analysed (n=333)		

transfusion within 24 hrs transfusion within 48 hrs transfusion within 96 hrs	51 67 95		282 266 238	
Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
RBC transfusion within 24 hours				
NEC (n=111)	36/51 (70.6%)	75/282 (26.6%)	NR	NR
RBC transfusion within 48 hours				
NEC (n=111)	44/67 (65.7%)	67/266 (25.2%)	NR	NR
RBC transfusion within 96 hours				
NEC (n=111)	49/95 (51.6%)	62/238 (26.1%)	NR	NR
Univariate and multivariate conditional logistic regression models				
Outcome	Unadjusted OR (95% CI)	Significance *P*-value	Adjusted OR (95% CI)	Significance *P*-value
RBC transfusion within 24 hours				
All NEC (n=111)	11.70 [4.55, 30.09]	Significant *P* < 0.001	7.60 [2.19, 26.42]	Significant *P* = 0.001
Early NEC (n=67)	22.13 [5.23, 93.69]	Significant *P* < 0.001	15.49 [2.20, 109.08]	Significant *P* = 0.006
Late NEC (n=44)	4.67 [1.21, 18.05]	Significant *P* = 0.026	2.05 [0.20, 21.29]	Not significant *P* = 0.55
RBC transfusion within 48 hours				
All NEC (n=111)	7.26 [3.62, 14.54]	Significant *P* < 0.001	5.55 [1.98, 15.59]	Significant *P* = 0.001
Early NEC (n=67)	9.55 [3.67, 24.86]	Significant *P* < 0.001	10.22 [1.83, 57.15]	Significant *P* = 0.008
Late NEC (n=44)	4.93 [1.75, 13.89]	Significant *P* = 0.003	6.39 [1.00, 40.83]	Borderline significant *P* = 0.05
RBC transfusion within 96 hours				
All NEC (n=111)	3.63 [2.04, 6.45]	Significant *P* < 0.001	2.13 [0.95, 4.80]	Not significant *P* = 0.07
Early NEC (n=67)	4.14 [1.92, 8.90]	Significant *P* < 0.001	3.03 [0.94, 9.80]	Borderline significant *P* = 0.06
Late NEC (n=44)	3.02 [1.25, 7.30]	Significant *P* = 0.01	1.11 [0.24, 5.11]	Not significant *P* = 0.89
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants (≤ 32 weeks gestational age) (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors concluded that anaemia is associated with increased risk of developing NEC in preterm infants and this risk increases as anaemia worsens. Although the majority of RBC transfusions do not result in NEC, in a subset of at risk preterm infants, RBC transfusions may be associated with increased odds of NEC. This association appears to have a temporal relationship, even after controlling for 'transfusion propensity' within a multivariable model also including Hct and other important clinical factors.				

CI, confidence interval; CLD, chronic lung disease; Hb, haemoglobin; Hct, haematocrit; HMF, human milk fortifier; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PDA, patent ductus arteriosus; PPROM, premature

prolonged rupture of membranes; RBC, red blood cell; rHuEPO, recombinant human erythropoietin; ROP, retinopathy of prematurity; SD, standard deviation; VLBW, very low birth weight

STUDY DETAILS: Case-control study				
Citation				
Stritzke AI, Smyth J, Synnes A, Lee SK, Shah PS (2013) Transfusion-associated necrotising enterocolitis in neonates. Arch Dis Child Fetal Neonatal Ed, 98: F10-F14.				
Affiliation/Source of funds				
The study was supported by a grant from the Canadian Institutes of Health Research, and additional funding by individual hospitals. The authors reported that funding agencies had no role in the design, collection, analyses or interpretation of results. The authors state they have no competing interests.				
Study design	Level of evidence		Location/setting	
Retrospective case-control study.	Level III-2		26 regional tertiary NICUs in the Canadian Neonatal Network.	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion in previous 2 days* (irradiated, cytomegalovirus negative, leukocyte reduced, generally not washed). Usual transfusion volume was 15-20 mL/kg		Birth weight, small for gestational age (SGA), male gender, outborn, 5-min Apgar score, SNAP II score, prenatal steroid use.		
Population characteristics (including size)				
3708 preterm infants admitted between 2003 and 2008 (927 NEC cases and 2781 controls matched by gestational age). Infants with major congenital anomalies involving the gastrointestinal tract were excluded.				
Length of follow-up		Outcomes measured		
2 days.		Primary: NEC stage 2 or 3 Secondary: outcomes of transfusion-associated NEC (TANEC) vs non-transfusion-associated NEC (non-TANEC) including mortality, severe ROP and severe neurological injury.		
Method of analysis				
Infant characteristics were compared between NEC cases and controls using χ^2 tests for categorical variables and t-tests or non-parametric tests for continuous variables, as appropriate. A multiple conditional logistic regression model was used to examine the association between recent exposure to transfusion and NEC after controlling for confounders (see above). Secondary outcomes were compared using multiple logistic regression methods.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: a 1:3 matched case-control study of 927 NEC cases and 2781 age-matched controls in infants admitted to one of 26 NICUs in the Canadian Neonatal Network, to assess the risk of RBC transfusion in the previous two days on development of stage 2 or 3 NEC. Data was collected by trained abstractors at each site until discharge from NICU and entered directly from patient charts into a customised computer program. The threshold for transfusion varied between centres, and the practice of holding feeds during transfusion varied both between and within centres. Storage of RBC ranged from 1-42 days, which could significantly impact outcomes. Birth weight, small for gestational age, outborn status, Apgar and SNAP II scores were significantly lower in the NEC vs non-NEC groups. A large, multicentre trial and the sample heterogeneous improving generalisability. Some of the main potential confounders were identified but were not controlled for in the analysis: data were not collected for feeding practices, including volume and type of feed, which varied between centres. Data about the blood, the donors and the exact indications and the degree of urgency of the need for transfusion may have varied widely between centres and were also not available.				
RESULTS				
Population	Transfused (n)		Not transfused (n)	
Available	NR		NR	
Analysed (N=3708)	357		3351	
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value

NEC (n=927)	144/357 (40.3%)	783/3351 (23.4%)	NR	NR
Risk factors for NEC in cases vs controls				
Variable	Adjusted OR (95% CI)			Significance *P*-value
RBC transfusion in previous 2 days	2.44 [1.87, 3.18]			Significant association *P* < 0.01
Multivariate analysis: outcomes between TANEC and non-TANEC infants				
Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)		Significance *P*-value
Mortality	2.06 [1.40, 3.03]	1.28 [0.82, 2.01]		Significant when unadjusted, but not adjusted *P* = NR
Severe ROP	2.19 [1.45, 3.33]	1.15 [0.71, 1.87]		Significant when unadjusted, but not adjusted *P* = NR
Severe neurological injury	2.47 [1.47, 4.17]	0.83 [0.43, 1.60]		Significant when unadjusted, but not adjusted *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats (Level B).				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site Canada (Level B).				
Comments				
The authors concluded that exposure to transfusion in previous two days was an independent risk factor for NEC. Infants who developed TANEC were younger of lower birth weight and had higher illness severity scores. After controlling for confounders, no significant differences in mortality and morbidities were observed between infants who had TANEC and those with NEC not associated with transfusion. *In cases, previous two days referred to the two days before NEC diagnosis; in controls, it referred to the two calendar days before the median age of NEC diagnosis among cases of the same gestational age.				

CI, confidence interval; Hb, haemoglobin; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; ROP, retinopathy of prematurity; SGA, small for gestational age; SNAP, score for neonatal acute physiology; TANEC, transfusion-associated necrotising enterocolitis

STUDY DETAILS: Case-control study		
Citation		
Wan-Huen P, Bateman D, Shapiro DM, Parravicini E (2013) Packed red blood cell transfusion is an independent risk factor for necrotizing enterocolitis in premature infants. Journal of Perinatology, 33: 786-90.		
Affiliation/Source of funds		
The authors declared no conflict of interest. They reported that no external funding was used to support the collection of data, the analysis or preparation of the manuscript.		
Study design	Level of evidence	Location/setting
Retrospective case-control study	Level III-2	Single NICU, USA.
Risk factor/s assessed	Potential confounding variables measured	
RBC transfusion.	Sex, chronological age, indicators of disease severity, gestational age, feeding status in the prior 48 hours.	
Population characteristics (including size)		
146 VLBW preterm infants admitted to NICU. Cases were infants who developed NEC (n=49) and controls were infants with similar gestational age (±1 week) and birth weight (±100 g) who did not develop NEC (n=97). Infants with congenital malformations were excluded.		
Length of follow-up	Outcomes measured	
48 hours.	NEC within 48 hours of transfusion.	
Method of analysis		
Bivariate analyses were used to compare baseline characteristics of NEC infants and matched controls. A 2x2 contingency table with epoch as the unit of analysis was used to compute the raw OR of NEC vs RBC transfusion. Logistic models were used to test the assumption that the probability of RBC transfusion and that of developing NEC do not differ across epochs. The models regressed the occurrence of NEC and transfusion against the week of life (excluding week 1). They indicated that the odds of developing NEC decreased by 9% per week ($P < 0.001$) and the odds of receiving a transfusion decreased by 20% per week ($P < 0.001$). To compensate for these and other effects, logistic generalised estimating equations were used to estimate the adjusted OR for developing NEC within each epoch with and without antecedent transfusion, controlling for chronological age, enteral feeding status by prior epoch, and the indicators of disease severity (symptomatic PDA, sepsis, urinary tract infection or phlebitis; pressor use, mechanical ventilation, exposure to inspired oxygen >40%). The unequal distribution of risk factors of disease severity between the categories of the exposure of interest (transfusion) represents a potential source of confounding. To compensate, a propensity score was added to the model which represents the conditional probability of being transfused, given the other risk factors. The score was derived as the vector of predicted mean values resulting from the logistic regression of transfusion on risk factors, with epoch as the unit of analysis.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a retrospective case-control study of 146 VLBW preterm infants admitted to NICU in the US, to assess the risk of RBC transfusion on NEC within 48 hours. The definition of NEC was based on clear radiographic evidence of pneumatosis, portal air and/or surgical pathology, consistent with Bell stage II to III disease. The study institution did not have a strict transfusion protocol in place. However, consistent practice was to transfuse 15 mL/kg RBC over 4 hours. Nursing staff had a protocol to obtain vital signs every 15 mins and to evaluate IV patency during transfusion. For each infant, the 6-63 day period was divided into 48 hr epochs, corresponding to 2 calendar days. Each infant had 29 epochs. Infants who died (n=8), were transferred (n=5) or discharged home (n=26) prior to study end had fewer epochs than infants who remained hospitalised for the duration of the study. To estimate the effect of these "missing epochs" on the magnitude of the OR, the authors calculated the additional numbers of non-transfusion related NEC cases and non-NEC-related transfusions these infants would have had, had they remained alive and hospitalised through to study end, using gestational age-, outcome– and epoch-specific NEC and transfusion rates for each infants' absent period. The authors verified the accuracy of all critical data elements using several sources to address the limitation of a case-control study design. The authors noted a limitation was the details of feeding exposure during the transfusion epoch itself (including volume, type and tolerance) were not documented and might have had a role in modifying susceptibility to NEC.		
RESULTS		
Population	RBC transfusion	No RBC transfusion

Available	NR		NR	
Analysed	557		3095	
Outcome	RBC transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
NEC within 48 hours	17/557 (3.1%)	32/3095 (1.0%)	OR 3.01 [1.67, 5.47]	Favours no transfusion $P < 0.001$
NEC within 48 hours (adjusted for "missing epochs")	NR	NR	OR 2.70 [1.51, 4.85]	Favours no transfusion $P < 0.001$
Logistic generalised estimating equation model				
Outcome	Risk estimate (95% CI)			Significance *P*-value
NEC within 48 hours	OR 2.97 [1.46, 6.05]			Favours no transfusion $P < 0.003$
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors concluded that in premature infants, antecedent RBC transfusion appears to be an independent risk factor for developing NEC during the subsequent 48 hours. The relationship cannot be concluded to be the cause and effects. However, these results provide a basis for several paths of future research.				

CI, confidence interval; Hb, haemoglobin; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; SD, standard deviation; VLBW, very low birth weight

STUDY DETAILS: Case-control study				
Citation				
Weintraub Z, Carmi N, Elouti H, Rumelt S (2011) The association between stage 3 or higher retinopathy of prematurity and other disorders of prematurity. Canadian Journal of Ophthalmology, 46: 419-24.				
Affiliation/Source of funds				
The authors reported no proprietary or commercial interest in any materials discussed in this article.				
Study design	Level of evidence	Location/setting		
Retrospective case-control study	Level III-2	NR (authors based in Israel)		
Risk factor/s assessed				
Demographic: gestational age, birth weight, ethnicity, number of foetuses, type of labour, age of ROP setting. Clinical: sepsis, neonatal jaundice, high frequency ventilation and intermittent mandatory ventilation, daily fluid intake, use of corticosteroids, theophylline and surfactants; number of blood transfusions, grade III-IV IVH or bronchopulmonary dysplasia (BPD).				
Population characteristics (including size)				
165 VLBW preterm infants <32 weeks gestational age, born between 1st January 1996 and 31st December 2002 (55 cases of severe ROP and 110 controls without ROP). Exclusion criteria not reported.				
Length of follow-up	Outcomes measured			
NR	Severe ROP (≥stage 3)			
Method of analysis				
Statistical significance was calculated by the Mann-Whitney or Student t-test for continuous covariates and by the chi-square test for categorical covariates. A Fisher exact test was employed for categorical covariates with an expectancy of less than 5. A 2-tailed $P < 0.05$ was considered statistically significant. A logistic regression model was used to correlate multiple parameters.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: a case-control study of 55 VLBW preterm infants with severe ROP and 110 controls with no ROP, to assess the risk of various factors including transfusion on the development of severe ROP. Neonates were evaluated at 3 weeks of age and then at 1-2 week intervals depending on clinical findings, gestational age and birth weight. Of the 55 infants with severe ROP, 47 had stage 3 ROP (85.5%), seven had stage 4 ROP (12.7%) and one had stage 5 ROP (1.8%). All neonates were Caucasian. Birth weight and gestational age was significantly lower in the ROP vs non-ROP groups. The sample size had 80% power to detect 20% difference in the parameters between cases and controls with a type I error of 5%.				
RESULTS				
Population	Transfused	Not transfused		
Available	NR	NR		
Analysed (n=165)	135	30		
Outcome	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
ROP ≥stage 3	54/135 (40.0%)	1/30 (3.3%)	NR	NR
Multiple logistic regression model				
Parameter	B	OR (95% CI)		Significance *P*-value
Transfusion	2.650	14.159 [1.570, 127.7]		Significant $P = 0.018$
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				

Applicability
Evidence may or may not be applicable to the Australian healthcare context (study site not reported).
Comments
The authors concluded that certain disorders and parameters, such as sepsis and blood transfusions, may predict the appearance of severe ROP. Early detection and treatment of sepsis and reduction of blood transfusions may decrease the incidence of severe ROP that requires treatment.

BPD, bronchopulmonary dysplasia; CI, confidence interval; Hb, haemoglobin; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; ROP, retinopathy of prematurity; VLBW, very low birth weight

F2 Evidence summaries – Question 2

Level I evidence

ESAs (with or without iron)

STUDY DETAILS: SR/MA		
Citation		
Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD004868. DOI: 10.1002/14651858.CD004868.pub4.		
Affiliation/Source of funds		
Internal sources: Mount Sinai Hospital, Toronto, Canada. External sources: Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA. Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver. National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C		
Study design	Level of evidence	Location/setting
Systematic review of randomised or quasi-randomised controlled trials	Level I	Turkey (Akisu 2001, Atasay 2002, Samanci 1996) Canada (Al-Kharfy 1996) Israel (Bader 1996) Norway (Bechensteen 1993) USA (Bierer 2009, Juul 2003, Kumar 1998, Reiter 2005, Shannon 1991, Shannon 1992, Shannon 1995) Taiwan (Chen 1995) Italy (Corona 1998, Romagnoli 2000) Argentina (Donato 1996) UK (Emerson 1993, Griffiths 1997) Greece (Giannakopoulou 1998a, Giannakopoulou 1998b) Spain (Javier Manchon 1997) Finland (Kivivuori 1999) Europe (Maier 2002) South Africa (Meyer 1994) Austria (Pollak 2001) Brazil (Rocha 2001) Norway (Ronnestad 1995) Australia (Whitehall 1999) and Japan (Yamada 1999a, Yamada 1999b)
Intervention	Comparator	
Late initiation of rHuEPO (at eight to 28 days of age, using any dose, route, or duration of treatment) + iron	Placebo or no intervention + iron	
Population characteristics		
Preterm (< 37 weeks) and/or low birth weight (< 2500 g) neonates between eight and 28 days of age.		
Length of follow-up	Outcomes measured	
28 days	Primary outcomes: use of one or more red blood cell transfusions Secondary outcomes: the total volume (mL/kg) of blood transfused per infant, number of transfusions per infant, number of donors to whom the infant was exposed, mortality during initial hospital stay (all causes of mortality), retinopathy of prematurity (ROP) (any stage and stage ≥ 3), proven sepsis, necrotising enterocolitis (NEC) (Bell's stage II or more), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD) (supplementary oxygen at 28 days of age or at 36 weeks postmenstrual age (PMA) and compatible X-ray), sudden infant death after discharge, long-term outcomes assessed at any age beyond one year of age by a validated cognitive, motor, language, or behavioural/school/social interaction/adaptation test, neutropenia, hypertension, length of hospital stay (days), any side effects reported in the trials	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Good

Description: Randomised and quasi-randomised trials were included. Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied. 31 RCTs were included in the systematic review. These RCTs were of variable quality and were assessed using the Cochrane risk of bias tool. Not all studies reported proper random sequence generation or allocation concealment and sample sizes were generally small.

RESULTS

Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Late rHuEPO + iron vs placebo/no treatment + iron				
Use of one or more red blood cell transfusions (low or high dose rHuEPO) 20 trials (N=1142)	254/605 (42.0%)	322/537 (60.0%)	RR 0.71 [0.64, 0.79]	Favours late rHuEPO *P* < 0.00001 Substantial heterogeneity *P* < 0.00001 (I^2 =68%)
Use of one or more red blood cell transfusions (high dose rHuEPO, low or high dose iron) 14 studies (N=912)	202/465 (43.4%)	259/447 (57.9%)	RR 0.76 [0.68, 0.86]	Favours late rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.00022 (I^2 =66%)
Use of one or more red blood cell transfusions (high dose rHuEPO, high dose iron) 6 studies (N=318)	72/168 (42.9%)	91/150 (60.7%)	RR 0.74 [0.62, 0.88]	Favours late rHuEPO *P* = 0.00075 Substantial heterogeneity *P* = 0.00026 (I^2 =79%)
Use of one or more red blood cell transfusions (high dose rHuEPO, low dose iron) 8 studies (N=594)	130/297 (43.8%)	168/297 (56.6%)	RR 0.78 [0.67, 0.91]	Favours late rHuEPO *P* = 0.0013 Substantial heterogeneity *P* = 0.02 (I^2 =58%)
Use of one or more red blood cell transfusions (low dose rHuEPO, high or low dose iron) 7 trials (N=239)	52/140 (37.1%)	70/99 (70.7%)	RR 0.53 [0.42, 0.67]	Favours late rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.02 (I^2 =59%)
Use of one or more red blood cell transfusions (low dose rHuEPO, high dose iron) 3 studies (N=77)	15/45 (33.3%)	18/32 (56.3%)	RR 0.50 [0.31, 0.79]	Favours late rHuEPO *P* = 0.0028 No significant heterogeneity *P* = 0.42 (I^2 =0.0%)
Use of one or more red blood cell transfusions (low dose rHuEPO, low dose iron) 4 studies (N=162)	37/95 (38.9%)	52/67 (77.6%)	RR 0.54 [0.41, 0.71]	Favours late rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.01 (I^2 =76%)

Mortality during initial hospital stay (all causes) 14 studies (N=767)	20/403 (5.0%)	23/364 (6.3%)	RR 0.82 [0.49,1.39]	No significant difference *P* = 0.47 No significant heterogeneity *P* = 0.47 (I^2=0.0%)
Retinopathy of prematurity (all stages or stage not reported) 3 studies (N=404)	84/209 (40.2%)	64/195 (32.8%)	RR 1.27 [0.99,1.64]	No significant difference *P* = 0.063 Substantial heterogeneity *P* = 0.002 (I^2 =83%)
Retinopathy of prematurity (all stages or stage not reported) 3 studies (N=404)			RD 0.09 (-0.00 – 0.18)	No significant difference (I^2 =82%)
Retinopathy of prematurity (stage ≥3) 3 studies (N=442)	24/219 (11.0%)	14/223 (6.3%)	RR 1.73 [0.92,3.24]	No significant difference *P* = 0.087 No significant heterogeneity *P* = 0.30 (I^2 =18%)
Retinopathy of prematurity (stage >≥3) 3 studies (N=442)			RD 0.05 (-0.01 – 0.10)	No significant difference (I^2 =79%)
Necrotising Enterocolitis ≥ Bell's stage 2 6 studies (N=656)	15/328 (4.6%)	17/328 (5.2%)	RR 0.88 [0.46, 1.69]	No significant difference *P* = 0.70 No significant heterogeneity *P* = 0.90 (I^2 =0.0%)
Bronchopulmonary dysplasia (supplementary oxygen at 28 days) 2 studies (N=285)	70/142 (49.3%)	57/143 (39.9%)	RR 1.25 [1.00, 1.55]	No significant difference *P* = 0.051 Substantial heterogeneity *P* < 0.00001 (I^2 =97%)
Bronchopulmonary dysplasia (supplementary oxygen at 36 weeks postmenstrual age) 3 studies (N=216)	30/115 (26.1%)	31/101 (30.7%)	RR 0.89 [0.59, 1.35]	No significant difference *P* = 0.57 Substantial heterogeneity *P* = 0.10 (I^2 =56%)
	Mean ± SD	Mean ± SD		
Total volume (mL/kg) of red blood cells transfused per infant 5 studies (N=197)	NR	NR	MD -1.61 [-5.78,2.57]	No significant difference *P* = 0.45 Substantial heterogeneity *P* < 0.00001 (I^2=92%)
Number of red blood cell transfusions per infant 11 studies (N=817)	NR	NR	MD -0.22 [-0.38, -0.06]	Favours late rHuEPO *P* = 0.0075 Substantial heterogeneity *P* < 0.00001 (I^2 =94%)
EXTERNAL VALIDITY				

Generalisability
Evidence is generalisable to preterm (<37 weeks) and/or low birth weight (<2500 g) neonates between 8 and 28 days after birth.
Applicability
Evidence applicable to the Australian healthcare context with few caveats. Studies were conducted in Australia (level A), Canada, Israel, Norway, United Kingdom, Finland, Europe, Austria, Norway, Japan, Italy, Greece, Spain (level B) and Argentina, South Africa and Brazil (level C) .
Comments
The authors conclude the number needed to treat for an additional beneficial outcome (NNTB) to avoid one red blood cell transfusion was low (range 3 to 8, for different combinations of rHuEPO and iron). Late rHuEPO administration results in a reduction in the use of one or more red blood cell transfusions following initiation of therapy. It minimally reduces the number of red blood cell transfusions per infant. It is not associated with reductions in mortality or other neonatal morbidities. The use of late rHuEPO is not associated with any short-term serious side effects except for a possible association with retinopathy of prematurity (ROP) stage 3 or higher.

ITT, intention-to-treat; CI, confidence interval; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; rHuEPO, recombinant human erythropoietin; SD, standard deviation; SR, systematic review.

a. 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%.

STUDY DETAILS: SR/MA				
Citation				
Feusner J and Hastings C (2002) Recombinant Human Erythropoietin in Paediatric Oncology: A Review. Med Pediatr Oncol 2002;39:463–468.				
Affiliation/Source of funds				
The publication of this article was supported by an educational grant from Ortho Biotech.				
Study design	Level of evidence	Location/setting		
Systematic review of randomised or quasi-randomised controlled trials and community-based clinical trials	Level I	Various (individual trial locations not specified)		
Intervention	Comparator			
Epoetin alfa (with or without iron supplementation)	Placebo (with or without iron supplementation)			
Population characteristics				
Paediatric cancer patients with haemoglobin (Hb) levels ranging from 'before anaemia' to <10.5, <10.0, <7.5 g/dL, levels under the third percentile for sex and age or no specific Hb level.				
Length of follow-up	Outcomes measured			
NA	RBC transfusion, platelet transfusion and Hb laboratory measures.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Four randomised controlled clinical trials and four open, phase I/II single-institution trials were included. However, only data from the RCTs has been included in this review. Appropriate search strategies used but exclusion criteria were not clearly defined. Study selection and data extraction was not applied by two researchers. Study quality was not assessed. The authors note that many variabilities were evident in the included studies, hence, a meta-analysis was not conducted and tests for heterogeneity were not applied.				
RESULTS				
Outcome RBC transfusions	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs Placebo				
Iron deficiency 1 trial (N=37) (Bennetts 1995)	5/19 (26.3%)	3/18 (16.7%)	NR	*P* = NR Heterogeneity not applicable
RBC transfusion No. of patients receiving transfusion 1 trial (N=20) (Porter 1996)	9/10 (90%)	10/10 (100%)	NR	*P* = NR Heterogeneity not applicable
Platelet transfusion No. of patients receiving transfusion 1 trial (N=20) (Porter 1996)	3/10 (30%)	9/10 (90%)	NR	*P* = NR Heterogeneity not applicable

RBC transfusion (cc/kg) (Total amount RBC administered) 1 trial (N=37) (Bennetts 1995)	27 ± 18	35 ± 5	NR	No significant difference *P* = 0.11 Heterogeneity not applicable
RBC transfusions (cc/kg) (Per patient amounts of RBC administered) 1 trial (N=37) (Bennetts 1995)	2.21 ± 1.58	3.06 ± 1.69	NR	No significant difference p=0.39 Heterogeneity not applicable
Volume of RBC (cc/kg) Sub-analysis of the low risk ALL (acute lymphocytic leukemia) group 1 trial (N=NR) (Bennetts 1995)	16.8 ± 12.7	69.5 ± 36.1	NR	Favours rHuEPO *P* = 0.02 Heterogeneity not applicable
RBC transfusion No. of units transfused 1 trial (N=20) (Porter 1996)	4.5 median (0-9 range)	13 median (2-22 range)	NR	Favours rHuEPO *P* = 0.01 Heterogeneity not applicable
RBC transfusion Amount (mL/kg) Transfused 1 trial (N=20) (Porter 1996)	23 median (0-118 range)	80 median (18-226 range)	NR	Favours rHuEPO *P* = 0.02 Heterogeneity not applicable
Platelet transfusion No. of units transfused 1 trial (N=20) (Porter 1996)	0 median (0-3 range)	4 median (0-17 range)	NR	Favours rHuEPO *P* = 0.005 Heterogeneity not applicable
Mean haemoglobin nadir (g/dL) 1 trial (N=22 courses of chemotherapy in rHuEPO group, 60 in control group) (Ragni 1998)	10.36 (range 7.7–13.8)	8.7 (range 5.5–13.5)	NR	Favours rHuEPO *P* < 0.05 Heterogeneity not applicable
Haemoglobin decrease to <9 g/dL 1 trial (N=22 courses of chemotherapy in rHuEPO group, 60 in control group) (Ragni 1998)	4 (18.2%) courses of chemotherapy	36 (60%) courses of chemotherapy	NR	*P* = NR Heterogeneity not applicable
Mean time to haemoglobin recovery 1 trial (N=22 courses of chemotherapy in rHuEPO group, 60 in control group) (Ragni 1998)	3.5 days (range 3-5 days)	7.3 days (range 3-23 days)	NR	*P* = NR Heterogeneity not applicable

EXTERNAL VALIDITY
Generalisability
Evidence is generalisable to paediatric oncology patients.
Applicability
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.
Comments
The authors acknowledge that rHuEPO appears to be an effective and safe treatment for anaemia in paediatric cancer patients by increasing Hb levels and decreasing transfusion requirements. However, the authors also acknowledge that these observations are based on limited clinical data (<100 treated children).

ITT, intention-to-treat; CI, confidence interval; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a 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%.

STUDY DETAILS: SR/MA				
Citation				
Maria G. Garcia, Alan D. Hutson, Robert D. Christensen (2002) Effect of Recombinant Erythropoietin on ''Late'' Transfusions in the Neonatal Intensive Care Unit: A Meta-Analysis. Journal of Perinatology 2002; 22:108 – 111 #2002 Nature Publishing Group All rights reserved. 0743-8346/02				
Affiliation/Source of funds				
No competing interests declared. Maria Garcia is affiliated with The National Institute of Perinatology, Mexico City, Mexico; Maria Garcia and Alan Hutson are affiliated with The Department of Pediatrics, Division of Neonatology, and the Division of Biostatistics, Department of Statistics; Maria Garcia and Alan Hutson are affiliated with the University of Florida College of Medicine, Gainesville, FL, USA; and Robert Christensen is affiliated with The Department of Pediatrics, University of South Florida and All Children's Hospital, St. Petersburg, FL, USA.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs	Level I	Various (individual trial locations not specified)		
Intervention	Comparator			
rHuEPO (administered after the first week of life) + iron	Placebo/no treatment + iron			
Population characteristics				
Very low birth weight (1500 g) neonates. Studies were included if rHuEPO and placebo treatments began after the first week of life				
Length of follow-up	Outcomes measured			
NA	Proportion of neonates transfused and number of transfusions per patient (focusing exclusively on the transfusions that were given after the third week, day 22, of life and before hospital discharge)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Appropriate search strategies were applied and inclusion/exclusion criteria were clearly defined. The quality of the included studies was not reported. However the inclusion criterion specifies that only randomised studies utilising a double-masked design were selected. The method of randomisation or blinding was not assessed for any of the included studies. Characteristics of the individual studies are reported but not baseline demographic and clinical characteristics of the patients enrolled in these trials. 8 RCTs were included in the meta-analysis. A dose–response curve, modelling the probability of a transfusion as a function of weekly rHuEPO dose was generated.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO + iron vs placebo + iron				
Transfusion incidence 8 trials* (N=357)	69/183 (37.7%)	111/174 (63.8%)	OR=0.33 (0.21–0.51)	Favours rHuEPO *P* = NR Heterogeneity NR
Transfusion incidence Number needed to treat (NNT) 8 trials* (N=357)	3.8/10 (38%) (500U/kg per week)	6.5/10 (65%) (500U/kg per week)	NR	*P* = NR Heterogeneity NR
Transfusion incidence NNT 8 trials (N=357)	1.7/10 (17%) (1000 U/kg per week)	6.5/10 (65%) (1000 U/kg per week)	NR	*P* = NR Heterogeneity NR

Transfusion incidence NNT 8 trials* (N=357)	0.6/10 (6%) (1500 U/kg per week)	6.5/10 (65%) (1500 U/kg per week)	NR	*P* = NR Heterogeneity NR
Number receiving transfusions 1 trial (N=20) (Shannon 1991)	6/10 (60%)	8/10 (80%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=8) (Shannon 1992)	1/4 (25%)	3/4 (75%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=23) (Emmerson 1993)	7/15 (46.7%)	7/8 (87.5%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=15) (Ohls 1993)	1/10 (10%)	4/5 (80%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=80) (Meyer 1994)	6/40 (15%)	17/40 (42.5%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=157) (Shannon 1995)	44/77 (57.1%)	55/80 (68.8%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=24) (Samanci 1996)	3/12 (25%)	8/12 (66.7%)	NR	*P* = NR Heterogeneity not applicable
Number receiving transfusions 1 trial (N=30) (Kumar 1998)	1/15 (6.7%)	9/15 (60%)	NR	*P* = NR Heterogeneity not applicable
	Mean ± SD	Mean ± SD		
Number of transfusions per patient 1 trial (N=8) (Shannon 1992)	0.5±1.0	2.2±2.0	NR	*P* = NR Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=15) (Ohls 1993)	0.1±0.31	1.8±0.5	NR	*P* = NR Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=80) (Meyer 1994)	1.1±0.4	NR	NR	*P* = NR Heterogeneity not applicable

Number of transfusions per patient 1 trial (N=157) (Shannon 1995)	1.1±1.5	1.6±1.7	NR	*P* = NR Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=24) (Samanci 1996)	0.4±0.7	1.1±0.6	NR	*P* = NR Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=30) (Kumar 1998)	0.07±0.3	0.8±0.8	NR	*P* = NR Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to VLBW with anaemia of prematurity.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations not specified.				
Comments				
The authors note that administering rHuEPO to VLBW neonates can result in a modest reduction in 'late' erythrocyte transfusions, and that this effect is dependent on the dose of rHuEPO used. A dose–response curve, modelling the probability of a transfusion as a function of cumulative weekly rHuEPO dose was generated. * Shannon 1991, Shannon 1992, Emmerson 1993, Ohls 1993, Meyer 1994, Shannon 1995, Samanci 1996, Kumar 1998.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a. 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%.

STUDY DETAILS: SR/MA				
Citation				
Grant MD, Piper M, Bohlius J, Tonia T, Robert N, Vats V, Bonnell C, Ziegler KM, Aronson N. Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update. Comparative Effectiveness Review No. 113. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC077-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.				
Affiliation/Source of funds				
Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under Contract No. 290-2007-10058-I. None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.				
Study design	Level of evidence		Location/setting	
Systematic review	Level I		Various (individual trial locations not specified)	
Intervention		Comparator		
Erythropoietin + chemotherapy and/or radiotherapy and RBC transfusions if necessary *Iron administered as needed		No erythropoietin or placebo + chemotherapy and/or radiotherapy and RBC transfusions if necessary *Iron administered as needed		
Population characteristics				
Paediatric patients diagnosed with malignant disease, using histological/cytological criteria, regardless of type or stage of the disease or previous therapy. Only patients who were anaemic or at risk for anaemia from chemotherapy and/or radiotherapy or the underlying malignant disease were included.				
Length of follow-up		Outcomes measured		
N/A		Haematologic response (proportion of patients with an increase in haemoglobin level of 2g/dL or more), proportion of patients receiving blood transfusions, quality of life (only from studies using a validated instrument), tumour response (only in studies that were prospectively designed to assess tumour response), overall survival, disease-free and progression-free survival, adverse effects (thromboembolic events, hypertension, rash, seizures, rHuEPO antibodies, adverse transfusion events)		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Appropriate search strategies used to search multiple databases. Grey literature and scientific information packs (including unpublished trials) were obtained but it is not stated if hand searching was carried out. Inclusion/exclusion criteria detailed. Meta-analyses and randomised controlled trials were included. A separate search for comparative observational studies was conducted for evidence on adverse events; however, no observational studies were found that met the specified inclusion criteria. A modified version of The Cochrane Collaboration's tool for assessing risk of bias was used to assess RCT quality. Although a meta-analysis was conducted, it included various populations, including adults. Hence, the results were not applicable to this review.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs control				

Haematologic response ≥ 2g/dL (haemoglobin increase at any time after 4 weeks independent of RBC transfusions) 1 trial (N=222) Razzouk 2006	63/111 (56.8%)	39/111 (35.1%)	RR 1.6 [1.2, 2.2]	Favours epoetin *P* = NR Heterogeneity not applicable
Transfusion 1 trial (N= 20) Porter 1996	9/10 (90.0%)	10/10 (100.0%)	RR 0.90 [0.73, 1.11]	No significant difference *P* = NR Heterogeneity not applicable
Transfusion 1 trial (N=222) Razzouk 2006	72/111 (64.9%)	86/111 (77.5%)	RR 0.84 [0.71, 0.99]	Favours epoetin *P* = NR Heterogeneity not applicable
Transfusion 1 trial (N=75) Razzouk 2006 Subgroup analysis-ALL (acute lymphocytic leukemia)	26/40 (65.0%)	22/35 (62.9%)	NR	NR
Thromboembolism (clinically relevant) 1 trial (N=222) Razzouk 2006	6/112 (5.4%)	2/110 (1.8%)	NR	NR
Thromboembolism (any) 1 trial (N=222) Razzouk 2006	25/112 (22.3%)	25/110 (22.7%)	NR	NR
On-study mortality 1 trial (N=222) Razzouk 2006	2/112 (1.8%)	2/110 (1.8%)	NR	NR
Tumour response (complete response + partial response) 1 trial (N=35) Wagner 2004	12/17 (70.6%)	12/18 (66.7%)	RR 0.94 [0.60, 1.48]	No significant difference *P* = NR Heterogeneity not applicable
	Mean ± SD	Mean ± SD		
Three-year PFS (progression-free survival) (%) 1 trial (N=38) Wagner 2004	38.9 ± 11.5 (18)	25.0 ± 8.8 (20)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to paediatric patients with, or at risk of, anaemia who are undergoing cancer treatment.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.				
Comments				

Patients of all ages were included in this review. However, only trials of paediatric cancer patients are presented above. All three of the included paediatric studies administered iron as needed. The authors concluded that ESA use improves haemoglobin levels and helps avoid transfusions. Thromboembolic events and on-study mortality were increased in ESA-treated patients. There was limited and insufficient evidence to determine if a delay in ESA treatment until baseline Hb was less than 10 g/dL resulted in fewer thromboembolic events or on-study mortality. Whether there are subgroups (e.g. paediatric patients) at higher and lower risk of adverse events and mortality is unclear.

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a. 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%.

STUDY DETAILS: SR/MA				
Citation				
Kotto-Kome, A. C., Garcia, M. G., Calhoun, D. A., and Christensen, R. D. (2004) Effect of beginning recombinant erythropoietin treatment within the first week of life, among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: A meta-analysis. J.Perinatol. 24 (1) 24-29				
Affiliation/Source of funds				
R Christensen was supported by grants HL-61798, HL-69990 and HD-42308. D Calhoun supported by HD-01180 and HD-42326 from the National Institutes of Health.				
Study design	Level of evidence		Location/setting	
Systematic review of RCTs	Level I		Europe (Obladen 1991, Maier 1994, Maier 2002), England (Emmerson 1993), Greece (Soubasi 1993, Soubasi 1995), USA (Ohls 1995, Ohls 1997, Ohls 2001), Poland (Lauterbach 1995), Mexico (Lima 1998), Argentina (Donato 2000)	
Intervention		Comparator		
rHuEPO (administered in the first week of life) + iron		Placebo/no treatment + iron		
Population characteristics				
Very low birth weight (<1500 g) neonates. Studies were included if rHuEPO and placebo treatments were begun in the first week of life and excluded if rHuEPO was begun after the first week of life.				
Length of follow-up		Outcomes measured		
NA		Proportion of neonates transfused, mean number of transfusions per patient and mean volume of erythrocyte transfusion.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Appropriate search strategies used and inclusion/exclusion criteria detailed. Only randomised studies utilising a double-masked design were selected, i.e. studies that were not randomised or blinded were excluded. Quality of the included studies was not reported. The method of randomisation or blinding was not assessed for any of the included studies. Characteristics of the individual studies are reported but not baseline demographic and clinical characteristics of the patients enrolled in these trials. Data was pooled selectively, depending on the level of heterogeneity present in the data. For parameters which produced significant heterogeneity, the data was presented by the individual study. The authors reported a Q-test statistic for homogeneity; the criterion of $P < 0.10$ was used to reject the null hypothesis of homogeneity; however, when the number of studies is small, Cochran's Q test has low power. Q > k-1 suggests statistical heterogeneity (k=no. of included trials)				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%) Mean ± SE	Comparator n/N (%) Mean ± SE	Risk estimate (95% CI) MD ± SE	Statistical significance *P*-value Heterogeneity[a] *P*-value (Q-test)
Early rHuEPO + iron vs placebo/no treatment + iron				
Risk of receiving a transfusion (early or late) 12 trials (N=1090) (Obladen 1991, Maier 1994, Maier 2002, Emmerson 1993, Soubasi 1993, Soubasi 1995, Ohls 1995, Ohls 1997, Ohls 2001, Lauterbach 1995, Lima 1998, Donato 2000) *only 10 trials included in the	NR	NR	OR 0.52 [0.34, 0.79]	*Favours rHuEPO* *P* = 0.001 No significant heterogeneity (reported in text as "failed to reject the null hypothesis of homogeneity) *P* = 0.267 (Q=12.27)[b]

table. Not clear which studies were 'not evaluable'				
Risk of receiving an early transfusion 4 trials (N=NR) (Ohls 1995, Lima 1998, Donato 2000, Ohls 2001)	NR	NR	OR 0.54 [0.25, 1.15]	No significant difference *P* = 0.055 No significant heterogeneity (reported in text as "failed to reject the null hypothesis of homogeneity) *P* = 0.267 (Q=3.95)
Risk of receiving a late transfusion 9 trials (N=NR)	NR	NR	OR 0.56 [0.37, 0.83]	Favours rHuEPO *P* = 0.036 No significant heterogeneity (reported in text as "failed to reject the null hypothesis of homogeneity) *P* = 0.289 (Q=10.81)
Number of transfusions per patient and volume of blood transfused 1 trial (2 groups receiving rHuEPO) 12 trials (n=1090)				Homogeneity rejected No summary effect could be estimated Q=70.72 *P* < 0.001
Risk of receiving a late RBC transfusion – Individual trial data				
Obladen 1991 (N=83)	NR	NR	OR 0.85 (0.35–2.07)	*P* = NR Heterogeneity=NA
Emmerson 1993 (N=23)	NR	NR	OR 0.12 (0.01–1.28)	*P* = NR Heterogeneity=NA
Soubasi 1993 (N=16)	NR	NR	OR 0.083 (0.07–1.04)	*P* = NR Heterogeneity=NA
Maier 1994 (N=241)	NR	NR	OR 0.49 (0.29–0.82)	*P* = NR Heterogeneity=NA
Soubasi 1995 (N=75)	NR	NR	OR 0.25 (0.09–0.67)	*P* = NR Heterogeneity=NA
Ohls 1995/7? (N=20)	NR	NR	OR 0.11 (0.01–0.86)	*P* = NR Heterogeneity=NA
Lima 1998 (N=40)	NR	NR	OR 0.18 (0.03–1.01)	*P* = NR Heterogeneity=NA
Donato 2000 (N=114) *appears data from only 1 arm included in the analysis (early vs late)	NR	NR	OR 0.81 (0.39–1.70)	*P* = NR Heterogeneity=NA
Ohls 2001 (N=175) *LBW <1000 g	NR	NR	OR 0.87 (0.47–1.61)	*P* = NR Heterogeneity=NA
Ohls 2001 (N=118)	NR	NR	OR 2.11 (0.50–8.87)	*P* = NR Heterogeneity=NA

*LBW between 1000–1250 g				
Maier 2002 (N=145)	NR	NR	OR 0.49 (0.21–1.15)	*P* = NR Heterogeneity=NA
Number of transfusions per patient – Individual trial data				
1 trial (Soubasi 1993) N=NR *not complicated	NR	NR	MD 0.84±0.37	No significant difference *P* = 0.1081 Heterogeneity=NA
1 trial (Soubasi 1993) N=NR *complicated	NR	NR	MD -0.5±1.64	No significant difference *P* = 0.3042 Heterogeneity=NA
1 trial (Soubasi 1995) N=NR	NR	NR	MD 0.52±0.24	No significant difference *P* = 0.2905 Heterogeneity=NA
1 trial (Soubasi 1995) N=NR	NR	NR	0.67±0.22	No significant difference *P* = 0.1265 Heterogeneity=NA
1 trial (Ohls 1995) N=NR	NR	NR	1.2±0.13	Favours rHuEPO *P* = 0.0000* Heterogeneity=NA
1 trial (Ohls 1997) N=NR	NR	NR	0.1±0.13	Favours rHuEPO *P* = 0.0132* Heterogeneity=NA
1 trial (Donato 2000) N=NR	NR	NR	0.1±0.23	No significant difference *P* = 0.1075 Heterogeneity=NA
1 trial (Ohls 2001) N=NR	NR	NR	0.9±0.60	No significant difference *P* = 0.1913 Heterogeneity=NA
1 trial (Ohls 2001) N=NR	NR	NR	0.1±0.28	No significant difference *P* = 0.1637 Heterogeneity=NA
Total volume of blood transfused per patient (mL) – Individual trial data				
1 trial (Obladen 1991) N=NR	NR	NR	2.40±4.20	Favours rHuEPO *P* = 0.0208 Heterogeneity=NA
1 trial (Emmerson 1993) N=NR	NR	NR	9.4±1.70	No significant difference *P* = 0.1545 Heterogeneity=NA
1 trial (Soubasi 1993) N=NR	NR	NR	20.9±5.00	Favours rHuEPO *P* = 0.0255 Heterogeneity=NA
1 trial (Soubasi 1993) N= NR	NR	NR	1.40±15.11	No significant difference *P* = 0.2596 Heterogeneity=NA
1 trial (Maier 1994) N=NR	NR	NR	13.1±0.84	Favours rHuEPO *P* = 0.0108

				Heterogeneity=NA
1 trial (Soubasi 1995) N=NR	NR	NR	7.3±5.76	No significant difference *P* = 0.2523 Heterogeneity=NA
1 trial (Soubasi 1995) N= NR	NR	NR	13.3±5.11	No significant difference *P* = 0.3368 Heterogeneity=NA
1 trial (Ohls 1995) N= NR	NR	NR	15.3±1.51	Favours rHuEPO *P* = 0.0030 Heterogeneity=NA
1 trial (Lauterbach 1995) N=NR	NR	NR	10.9±13.04	No significant difference *P* = 0.4925 Heterogeneity=NA
1 trial (Lauterbach 1995) N=NR	NR	NR	28.2±10.91	No significant difference *P* = 0.0592 Heterogeneity=NA
1 trial (Ohls 1997) N=NR	NR	NR	0.00±1.90	Favours rHuEPO *P* = 0.0000 Heterogeneity=NA
1 trial (Donato 2000) N=NR	NR	NR	-0.30±6.80	Favours rHuEPO *P* = 0.0463 Heterogeneity=NA
1 trial (Ohls 2001) N=NR	NR	NR	15.0±8.87	No significant difference *P* = 0.3319 Heterogeneity=NA
1 trial (Ohls 2001) N=NR	NR	NR	-4.00±4.60	Favours rHuEPO *P* = 0.0005* Heterogeneity=NA
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to very low birth weight (<1500 g) neonates.				
Applicability				
Evidence applicable to Australian health-care context with few caveats. Studies were conducted in England, Europe, Poland and Greece (Level B), the USA and Argentina (Level C), Mexico (Level D).				
Comments				
This study considered an early transfusion to be one received during the first three weeks of life and a late transfusion to be one received thereafter. For the outcomes of 'number of transfusions received per patient' and 'total volume of blood transfused per patient', high heterogeneity prevented pooling of data (as described above).				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a. 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%. Authors reported a Q-test statistic for homogeneity; the criterion of *P* < 0.10 was used to reject the null hypothesis of homogeneity.

b. Reported as "failed to reject the null hypothesis of homogeneity"; however, when the number of studies is small, Cochran's Q test has low power. Q > k-1 suggests statistical heterogeneity (k=no. of included trials)

STUDY DETAILS: SR/MA				
Citation				
Marti-Carvajal, A. J., Sola, I., Pena-Marti, G. E., and Comunian-Carrasco, G. (2011) Treatment for anemia in people with AIDS. Cochrane Database Syst Rev (10) CD004776-				
Affiliation/Source of funds				
Internal sources: Universidad de Carabobo, Venezuela. Academic. External sources: Centro Cochrane Iberoamericano, Spain. Academic. Cochrane HIV/AIDS Group, USA. Academic.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs	Level I	Argentina (Rendo 2001)		
Intervention	Comparator			
rHuEPO + oral folic acid (1mg/day) *patients with serum ferritin < 50ng/dL also received oral ferrous sulphate (6mg/kg).	Placebo + oral folic acid (1mg/day) *patients with serum ferritin < 50ng/dL also received oral ferrous sulphate (6mg/kg).			
Population characteristics				
Children with human immunodeficiency virus infection (HIV) or AIDS who also have anaemia. Anaemia was defined according to The Anaemia HIV Working Group (haemoglobin level <12g/dL in men and <11g/dL in women).				
Length of follow-up	Outcomes measured			
NA	Primary outcomes: death Secondary outcomes: haematological values (Hb and haematocrit), number of patients transfused, number of RBCs transfused, quality of life (sleep disorders, time to return to usual activities, quality of life scales regardless of their validation status), length of hospital stay, adverse events, adverse drug reactions			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Studies were pooled where appropriate and tests for heterogeneity applied. As only one study was considered in this review, a discussion of heterogeneity was not applicable. The included RCT had an unclear risk of bias as insufficient information was provided to judge the randomisation, allocation concealment, blinding of subjects or blinding of outcome assessment.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs placebo				
Death 1 trial (Rendo 2001) (N=21)	1/10 (10.0%)	1/11 (9.1%)	RR 1.10 [0.08, 15.36]	No significant difference *P* = 0.94 Heterogeneity NA
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children with HIV or AIDS who also have anaemia.				
Applicability				
Evidence probably applicable to Australian health-care context with some caveats. (Level C).				
Comments				
Five of the six included RCTs were in adult patients. Only one (Rendo 2001) was performed in paediatric patients.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis;NA, not applicable; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.
a 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%.

STUDY DETAILS: SR/MA				
Citation				
Mystakidou, K., Potamianou, A., and Tsilika, E. (2007) Erythropoietic growth factors for children with cancer: A systematic review of the literature. Curr.Med.Res.Opin. 23 (11) 2841-2847				
Affiliation/Source of funds				
Assistance in performing the literature search and preparing the manuscript were funded by Janssen-Cilag.				
Study design	Level of evidence	Location/setting		
Systematic review of randomised and pseudo randomised controlled trials	Level I	Various (individual trial locations not specified)		
Intervention	Comparator			
rHuEPO	Placebo or no treatment			
Population characteristics				
Children aged 0-18 years with cance receiving chemotherapy.				
Length of follow-up	Outcomes measured			
NA	RBC transfusions, amount transfused, donor exposures, haematocrit, haemoglobin, quality of life, adverse events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The authors only searched Medline, explaining that since an identified Cochrane review (2006) had searched several databases, these detailed searches were not repeated. They did hand search the reference list of this Cochrane review and other previously published literature reviews. RCTs, case-control studies and an open-label uncontrolled study were included. However, only the 5 RCTs are relevant to this review. The quality of the included studies is not reported. The authors briefly mention that studies involving rHuEPO in paediatric cancer patients are "often small and rarely randomised" but no further details are provided. A meta-analysis was not conducted; hence, tests for heterogeneity are not applicable.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs control				
Transfusion requirements 1 trial (N=15) (Csaki 1998)	NR	NR	NR	Non-significant trend towards reduction by 3 months (reported in text) *P* = NR Heterogeneity not applicable
Number of patients requiring blood transfusions 1 trial (N=15) (Csaki 1998)	4/8 (50.0%)	3/7 (42.9%)	NR	Significance not reported *P* = NR Heterogeneity not applicable
Haematocrit (%) at week 8 1 trial (N=15) (Csaki 1998)	39.3	33.2	NR	Favours rHuEPO (reported in text) *P* = NR Heterogeneity not applicable

Haemoglobin (g/dL) at week 8 1 trial (N=15) (Csaki 1998)	13.11	11.06	NR	Favours rHuEPO (reported in text) *P* = NR Heterogeneity not applicable
Haemoglobin post-treatment (g/dL) 1 trial (N=15) (Csaki 1998)	13.11	11.6	NR	Significance not reported *P* = NR Heterogeneity not applicable
Transfusion independent 1 trial (N=222) (Razzouk 2006)	38.7%	22.5%	NR	Favours rHuEPO *P* = 0.01 Heterogeneity not applicable
Number of patients requiring blood transfusions 1 trial (N=222) (Razzouk 2006)	72/111 (64.9%)	86/111 (77.5%)	NR	Significance not reported *P* = NR Heterogeneity not applicable
Increases in haemoglobin 1 trial (N=222) (Razzouk 2006)	NR	NR	NR	Favours rHuEPO (reported in text) *P* = NR Heterogeneity not applicable
Haemoglobin increases of at least 2g/dL 1 trial (N=222) (Razzouk 2006)	56%	35%	NR	Favours rHuEPO *P* = 0.002 Heterogeneity not applicable
Haemoglobin increases of at least 2g/dL 5-7 year age group 1 trial (N=47) (Razzouk 2006)	92%	41%	NR	Favours rHuEPO (reported in text) *P* = NR Heterogeneity not applicable
Haemoglobin post-treatment (g/dL) trial (N=222) (Razzouk 2006)	11.2	10.5	NR	Significance not reported *P* = NR Heterogeneity not applicable
Number of patients requiring blood transfusions 1 trial (N=34) (varan)	1/17 (5.9%)	8/17 (47.1%)	NR	Favours rHuEPO *P* = 0.008 Heterogeneity not applicable
Haemoglobin post-treatment (g/dL) 1 trial (N=34) (Varan)	10.21	8.41	NR	Favours rHuEPO (reported in text) *P* = NR Heterogeneity not applicable
rHuEPO + iron vs placebo + iron				
Number of RBC transfusions 1 trial (N=20) (Porter)	4.5 (median)	13 (median)	NR	Favours rHuEPO + iron (reported in text) *P* = NR Heterogeneity not applicable

RBC transfusions (amount transfused) (mL/kg) 1 trial (N=20) (Porter)	23 (median)	80 (median)	NR	Favours rHuEPO + iron (reported in text) *P* = NR Heterogeneity not applicable
rHuEPO + G-CSF vs G-CSF				
Number of blood transfusions required 1 trial (N=38) (Wagner)	NR	NR	NR	No significant difference (reported in text) *P* = NR Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children aged 0-18 years with cancer.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.				
Comments				
This systematic review did not pool data, with results presented by study for the 5 included RCTs. The authors conclude that rHuEPO is safe and effective in paediatric cancer patients with 3 of the 5 RCTs in children with solid tumours showing significantly reduced transfusion requirements and in the other study, a non-significant trend towards reduction. The trials which reported haemoglobin levels showed a significant increase with rHuEPO treatment.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

STUDY DETAILS: SR/MA		
Citation		
Ohlsson, A. and Aher, S. M. (2012) Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 9 CD004863-		
Affiliation/Source of funds		
Internal sources: Mount Sinai Hospital, Toronto, Canada External sources: Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA. Editorial support of the Cochrane Neonatal Review Group has been funded with Federal Funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C.		
Study design	Level of evidence	Location/setting
Systematic review of RCTs	Level I	Various European countries (Maier 1994, Maier 2002, Obladen 1991), Canada (Al-Kharfy 1996), Turkey (Arif 2005), South Africa (Avent 2002), Italy (Carnielli 1992, Carnielli 1998, Romagnoli 2000), China (Chang 1998, He 2008), Switzerland (Fauchére 2008), Austria (Haiden 2005), Mexico (Lima-Rogel 1998), New Zealand (Meyer 2003), USA (Ohls 1995, Ohls 1997, Ohls 2001A, Ohls 2001B, Ohls 2013, Shannon 1995), Chile (Salvado 2000), Greece (Soubasi 1993, Soubasi 1995, Soubasi 2000), Bangladesh (Yasmeen 2012), Singapore (Yeo 2001)
Intervention	Comparator	
1. Early initiation of rHuEPO (initiated before 8 days of ag, using any dose, route or duration of treatment) + iron[a] 2. Early initiation of darbepoetin + iron	1. Placebo or no intervention + iron[a] 2. Placebo + iron	
Population characteristics		
Preterm (<37 weeks) and/or low birthweight (<2500 g) neonates less than eight days of age.		
Length of follow-up	Outcomes measured	
NA	Primary outcomes: the proportion of infants exposed to one or more RBC transfusions Secondary outcomes: total volume (mL/kg) of blood transfused per infant, number of transfusions per infant, number of donors to whom the infant was exposed, mortality during initial hospital stay (all causes of mortality), retinopathy of prematurity (ROP) (any stage and stage ≥3), proven sepsis (clinical symptoms, signs of sepsis and positive blood culture for bacteria or fungi), necrotising enterocolitis (NEC) (Bell's stage II or more, or stage not reported), intraventricular haemorrhage (IVH), all grades and grades III and IV, periventricular leukomalacia (PVL), length of hospital stay (days), bronchopulmonary dysplasia (BPD) (supplementary oxygen at 28 days of age or at 36 weeks postmenstrual age (PMA) with or without compatible X-ray), sudden infant death after discharge, neutropenia, hypertension, long-term outcomes (assessed at any age beyond one year of age by a validated cognitive, motor; language or behavioural, school, social interaction, adaptation test), cerebral palsy, post-hoc analysis of any side effects reported in the trials.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Good

Description: Randomised and quasi-randomised trials were included. Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied. 27 RCTs were included in the systematic review. These RCTs were of variable quality and were assessed using the Cochrane risk of bias tool. Not all studies reported proper random sequence generation or allocation concealment and sample sizes were generally small.

Subgroup analyses were performed for low (≤500 IU/kg/week) and high (>500 IU/kg/week) doses of rHuEPO and low (≤5mg/kg/day) and high (> 5mg/kg/day) doses of supplemental iron by any route (co-intervention). Any amount of iron given intravenously was classified as high dose iron.

Iron was administered in all studies but one (Fauchere 2008). The authors were still awaiting on iron information from He 2008 (article not published in English).

RESULTS

Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO + iron vs placebo/no treatment + iron				
Transfusion incidence				
Use of one or more RBC transfusions (low and high doses of rHuEPO) 16 trials (N=1661)	437/862 (50.7%)	545/799 (68.2%)	RR 0.79 [0.73, 0.85]	Favours rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.01 (I^2=54%)
Use of one or more RBC transfusions (high dose of rHuEPO) 14 trials (n=1228)	335/629 (55.8%)	417/599 (69.9%)	RR 0.79 [0.73, 0.85]	Favours rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.02 (I^2 =81%)
Use of one or more red blood cell transfusions (low dose rHuEPO) 4 trials(n=484)	102/233 (43.8%)	144/251 (57.4%)	RR 0.77 [0.65, 0.91]	Favours rHuEPO *P* = 0.0026 No significant heterogeneity *P* = 0.74 (I^2 =0.0%)
Use of one or more RBC transfusions (high dose rHuEPO, high dose iron) 11 trials (n=863)	252/452 (55.8%)	287/411 (69.8%)	RR 0.84 [0.77, 0.92]	Favours rHuEPO *P* = 0.00014 Moderate heterogeneity *P* = 0.16 (I^2 =32%)
Use of one or more RBC transfusions (high dose rHuEPO, low dose iron) 3 trials (n=365)	83/177 (46.9%)	130/188 (69.1%)	RR 0.66 [0.55, 0.80]	Favours rHuEPO *P* < 0.00001 Substantial heterogeneity *P* = 0.02 (I^2 =75%)
Use of one or more red blood cell transfusions (low dose rHuEPO, high dose iron) 2 trials (n=322)	67/157 (42.7%)	94/165 (57.0%)	RR 0.75 [0.61, 0.93]	Favours rHuEPO *P* = 0.0091 No significant heterogeneity *P* = 1.00 (I^2 =0.0%)
Use of one or more red blood cell transfusions (low dose rHuEPO, low dose iron) 2 trials (n=162)	35/76 (46.1%)	50/86 (58.1%)	RR 0.80 [0.60, 1.07]	No significant difference *P* = 0.13 Substantial heterogeneity *P* = 0.07 (I^2 =70%)

Mortality during initial hospital stay (all causes of mortality) 16 trials (N=1656)	79/864 (9.1%)	80/792 (10.1%)	RR 0.91 [0.68, 1.22]	No significant difference *P* = 0.53 No significant heterogeneity *P* = 0.95 (I^2=0%)
Retinopathy of prematurity (all stages or stage not reported) 8 trials (N=982)	131/505 (26.0%)	129/477 (27.0%)	RR 0.99 [0.81, 1.21]	No significant difference *P* = 0.94 No significant heterogeneity *P* = 0.99 (I^2=0.0%)
Retinopathy of prematurity (stage ≥3) 7 trials (N=801)	38/410 (9.3%)	26/391 (6.6%)	RR 1.37 [0.87, 2.17]	No significant difference *P* = 0.18 No significant heterogeneity *P* = 0.77 (I^2=0%)
Necrotising enterocolitis (stage not reported) 11 trials (N=1347)	52/678 (7.7%)	45/669 (6.7%)	RR 1.07 [0.73, 1.57]	No significant difference *P* = 0.73 No significant heterogeneity *P* = 0.77 (I^2=0%)
Bronchopulmonary dysplasia Supplemental oxygen at 28 days of age 1 trial (N=100)	9/50 (18%)	12/50 (24%)	RR 0.75 [0.35, 1.62]	No significant difference *P* = 0.46 Heterogeneity not applicable
Bronchopulmonary dysplasia Supplemental oxygen at 36 weeks 5 trials (N=542)	107/282 (37.9%)	98/260 (37.7%)	RR 0.99 [0.81, 1.21]	No significant difference *P* = 0.94 No significant heterogeneity *P* = 0.99 (I^2 =0.0%)
Bronchopulmonary dysplasia Age at diagnosis not stated 5 trials (N=528)	30/269 (11.2%)	25/259 (9.7%)	RR 0.98 [0.61, 1.56]	No significant difference *P* = 0.92 No significant heterogeneity *P* = 0.74 (I^2 =0.0%)
Mental developmental index (MDI) < 70 at 18-22 months corrected age (in children examined) 1 trial (N=90)	14/45 (31.1%)	16/45 (35.6%)	RR 0.88 [0.49, 1.57]	No significant difference *P* = 0.66 Heterogeneity not applicable
Psychomotor developmental index (PDI) <70 at 18-22 months corrected age (in children examined) 1 trial (N=90)	14/45 (31.1%)	6/45 (13.3%)	RR 2.33 [0.98, 5.53]	No significant difference *P* = 0.054 Heterogeneity not applicable
Any neurodevelopmental impairment at 18-22 months corrected age (in children examined) 1 trial (N=99)	21/48 (43.8%)	23/51 (45.1%)	RR 0.97 [0.62, 1.51]	No significant difference *P* = 0.89 Heterogeneity not applicable

Use of one or more RBC transfusions (in NICUs using mostly satellite units of RBCs) 4 trials (N=501)	166/253 (65.6%)	182/248 (73.4%)	RR 0.89 [0.80, 0.99]	Favours rHuEPO *P* = 0.035 No significant heterogeneity *P* = 0.52 (I^2=0%)
Retinopathy of prematurity (stage>/= 3) in infants treated with rHuEPO before or after 8 days of age 10 trials (N=1303)	70/689 (10.2%)	40/614 (6.5%)	RR 1.48 [1.02, 2.13]	Favours placebo/no treatment *P* = 0.038 No significant heterogeneity *P* = 0.75 (I^2=0%)
	Mean ± SD	Mean ± SD		
Total volume (mL/kg) of blood transfused per infant 7 trials (N=581)	NR	NR	MD -6.82 [-11.52, -2.11]	Favours rHuEPO + iron *P* = 0.0045 Substantial heterogeneity *P* = 0.01 (I^2=63%)
Number of RBC transfusions per infant 13 trials (N=951)	NR	NR	MD -0.27 [-0.42, -0.12]	Favours rHuEPO + iron *P* = 0.00036 Substantial heterogeneity *P* = 0.00087 (I^2=64%)
Neonatal Behavioural Neurological Assessment at 40 weeks PMA (post menstrual age) 1 trial (N=44)	36.2 ± 0.75	34.4 ± 1.05	MD 1.80 [1.26, 2.34]	Favours rHuEPO + iron *P* < 0.00001 Heterogeneity not applicable
BSID-III cognitive scores at 18-22 months 1 trial (N=54)	98 ± 14	88 ± 12	MD 10.0 [3.06, 16.94]	Favours rHuEPO + iron *P* = 0.0047 Heterogeneity not applicable
Darbepoetin alfa + iron vs placebo/no treatment + iron				
	n/N (%)	n/N (%)		
Use of one or more RBC transfusions 1 trial (Ohls 2013; N=66)	13/33 (39.4%)	21/33 (63.6%)	RR 0.62 [0.38, 1.02]	No significant difference *P* = 0.058 Heterogeneity not applicable
Mortality during initial hospital stay (all causes of mortality 1 trial (Ohls 2013; N=66)	1/33 (3.0%)	3/33 (9.1%)	RR 0.33 [0.04, 3.04]	No significant difference *P* = 0.33 Heterogeneity not applicable
Retinopathy of prematurity (all stages) 1 trial (Ohls 2013; N=62)	12/32 (37.5%)	12/30 (40.0%)	RR 0.94 [0.50, 1.75]	No significant difference *P* = 0.84 Heterogeneity not applicable
Retinopathy of prematurity (stage ≥3) 1 trial (Ohls 2013; N=62)	2/32 (6.3%)	4/30 (13.3%)	RR 0.47 [0.09, 2.37]	No significant difference *P* = 0.36 Heterogeneity not applicable

Necrotising enterocolitis (> stage 2) 1 trial (Ohls 2013; N=62)	2/32 (6.3%)	2/30 (6.7%)	RR 0.94 [0.14, 6.24]	No significant difference *P* = 0.95 Heterogeneity not applicable
Bronchopulmonary dysplasia (Supplemental oxygen at 36 weeks PMA) 1 trial (Ohls 2013; N=62)	22/32 (68.8%)	20/30 (66.7%)	RR 1.03 [0.73, 1.46]	No significant difference *P* = 0.86 Heterogeneity not applicable
	Mean ± SD	Mean ± SD		
Total volume (mL/kg) of blood transfused per infant 1 trial (Ohls 2013; N=66)	30 ± 58	51 ± 65	MD -21.0 [-50.72, 8.72]	No significant difference *P* = 0.17 Heterogeneity not applicable
Number of blood transfusions per infant 1 trial (Ohls 2013; N=66)	1.2 ± 2.4	2.4 ± 2.9	MD -1.2 [-2.48, 0.08]	No significant difference *P* = 0.067 Heterogeneity not applicable
BSID-III cognitive scores at 18-22 months 1 trial (Ohls 2013; N=51)	97 ± 8	88 ± 12	MD 9.0 [3.33, 14.67]	Favours placebo *P* = 0.0019 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to preterm (<37 weeks) and/or low birth weight (<2500 g) neonates less than eight days of age.				
Applicability				
Evidence applicable to Australian health-care context with few caveats. Studies were conducted in UK, Europe, New Zealand and Canada (Level B), USA, China, Singapore and Chile (Level C) and Mexico, Bangladesh, Iran and South Africa (Level D).				
Comments				
Iron was administered in all studies but Fauchére (2008). The study by He (2008) was written in Chinese, with only the abstract available in English to the review authors. The authors state they are waiting on further information from He (2008) following a request sent to the authors of that trial. The abstract did not specify whether participants were given iron or not. In most studies both the intervention and the control groups received iron. However, Carnielli 1992 and Carnielli 1998 did not administer iron to the control groups, only the intervention groups.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a. 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%.

STUDY DETAILS: SR/MA				
Citation				
Ross, S. D., Allen, I. E., Henry, D. H., Seaman, C., Sercus, B., and Goodnough, L. T. (2006) Clinical benefits and risks associated with epoetin and darbepoetin in patients with chemotherapy-induced anemia: a systematic review of the literature. Clin.Ther. 28 801-831				
Affiliation/Source of funds				
Amgen Inc. provided funding to MetaWorks for this study. The authors are affiliated with MetaWorks, Inc., Medford, Massachusetts, Joan Karnell Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania and Stanfiord University Medical Center, Stanford, California.				
Study design	Level of evidence	Location/setting		
Systematic review	Level I	Various (individual trial locations not specified)		
Intervention	Comparator			
1. ESP (erythropoiesis stimulating protein)– epoetin alfa, epoetin beta or darbepoetin) 2. ESP (epoetin) *Only data for comparison 1 was applicable to this review	1. Standard care (typically transfusions), placebo/no treatment or both 2. Another ESP (darbepoetin) *Only data for comparison 1 was applicable to this review			
Population characteristics				
Children with cancer treated for chemotherapy-induced anaemia (ie. baseline haemoglobin < 11g/dL).				
Length of follow-up	Outcomes measured			
NA	Clinical efficacy and effectiveness (transfusions and quality of life) and safety (VTE and all-cause or treatment-associated death)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Appropriate search strategies used, search terms provided and inclusion/exclusion criteria detailed. Randomised and non-randomised studies were included but only randomised trials were utilised for this review. Study quality was assessed using the Jadad method. However, scores were presented collectively per treatment comparison, rather than by individual study. Meta-analyses were conducted for several outcomes, with the Cochran Q test specified for quantifying heterogeneity. Although the results of this test are not presented, the authors state that several covariates were examined using meta-regression analyses. Detailed results of these investigations are not presented.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs placebo/no treatment				
Transfusion incidence 1 trial (N=20) (Porter 1996)	9/10 (90%)	10/10 (100%)	OR 0.30 [0.01, 8.33]	No significant difference *P* = 0.479 Heterogeneity not applicable
Transfusion incidence 1 trial (N=34) (Varan 1999)	1/17 (5.9%)	8/17 (47.1%)	OR 0.07 [0.01, 0.66]	Favours rHuEPO *P* = 0.020 Heterogeneity not applicable
Death rate 1 trial (N=21) (Porter 1996)	1/10 (10%)	1/11 (9.1%)	OR 1.11 [0.06, 20.49]	No significant difference *P* = 0.944 Heterogeneity not applicable

Death rate 1 trial (N=34) (Varan 1999)	0/17 (0%)	0/17 (0%)	OR 1.00 [0.01, 84.36]	No significant difference *P* = 1.000 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children with cancer being treated for chemotherapy-induced anaemia.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.				
Comments				
Both adults and children were included in this study but only the paediatric data has been presented above.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

STUDY DETAILS: SR/MA				
Citation				
Tonia, Thomy, Mettler, Annette, Robert, Nadège, Schwarzer, Guido, Seidenfeld, Jerome, Weingart, Olaf, Hyde, Chris, Engert, Andreas, and Bohlius, Julia (2012) Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst.Rev.				
Affiliation/Source of funds				
Internal sources: Department of Internal Medicine I, University of Cologne, Germany, Cochrane Haematological Malignancies Group (CHMG), Germany, Institute of Social and Preventative Medicine, University of Bern, Switzerland. External sources: Department of Health, UK.				
Study design	Level of evidence		Location/setting	
Systematic review of RCTs	Level I		Various (individual trial locations not specified)	
Intervention	Comparator			
1. ESAs 2. ESAs and RBC transfusion as necessary 3. ESAs + conventional-dose cancer therapy (non-myeloablative chemotherapy and/or radiotherapy) 4. ESAs and RBC transfusion as necessary + conventional-dose cancer therapy	1. Placebo or not treatment 2. observation and RBC transfusion as necessary, alone or with placebo 3. Identical therapy alone or with placebo 4. Observation and RBC transfusion as necessary plus identical therapy, alone or with placebo			
Population characteristics				
Children diagnosed with malignant disease, using clinical and histological/cytological criteria, regardless of type or stage of the disease or previous therapy. All study participants had to be anaemic or at risk for anaemia from chemotherapy, radiotherapy or combination therapy, or the underlying disease. Other causes of anaemia, such as haemolysis, iron deficiency and occult bleeding, had to have been excluded. Trials were excluded if more than 80% of participants were diagnosed with an acute leukaemia.				
Length of follow-up	Outcomes measured			
NA	Primary outcomes: haematological response, patients receiving RBC transfusions, number of RBC units transfused per patient, overall survival, on-study mortality Secondary outcomes: tumour response (complete response), changes in quality of life including cancer-related fatigue and anaemia symptoms, adverse events (thromboembolic events, hypertension, haemorrhage/thrombocytopenia, rash/irritation/pruritus, seizures)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied. 91 RCTs were included but only one trial included children (Razzouk 2006). This RCT had a low risk of bias.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Erythropoietin vs placebo				
Haematologic response (increase in Hb of ≥2g/dL, or ≥6% point increase in Hct) (children <18 years) 1 trial (N=222)	63/111 56.8%	39/111 35.1%	RR 1.62 [1.20, 2.18]	Favours erythropoietin *P* = 0.0018 Heterogeneity not applicable

Participants receiving RBC transfusions (children < 18 years) 1 trial (N=222)	72/111 64.9%	86/111 77.5%	RR 0.84 [0.71, 0.99]	Favours erythropoietin *P* = 0.040 Heterogeneity not applicable
Overall survival (children < 18 years) 1 trial (N=222)	2/112 1.8%	2/110 1.8%	OR 0.98 [0.14, 7.03]	No significant difference *P* = 0.98 Heterogeneity not applicable
On-study mortality (children) 1 trial (N=222)	2/112 1.8%	2/110 1.8%	OR 0.98 [0.14, 7.03]	No significant difference *P* = 0.98 Heterogeneity not applicable
Thrombotic events (children) 1 trial (N=222)	6/112 5.4%	2/110 1.8%	RR 2.95 [0.61, 14.28]	No significant difference *P* = 0.18 Heterogeneity not applicable
	Mean ± SD	Mean ± SD		
Change in haemoglobin level (children < 18 years) 1 trial (N=222)	1.3 ± 2.38 (111)	1 ± 1.9 (111)	MD 0.30 [-0.27, 0.87]	No significant difference *P* = 0.30 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children with malignant disease.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.				
Comments				
This review included studies with patients of all ages. Subgroup analyses were performed to distinguish the different study populations. Only one study included children, hence it was the only study which provided the data in the table above.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

STUDY DETAILS: SR/MA				
Citation				
Vamvakas, E. C. and Strauss, R. G. (2001) Meta-analysis of controlled clinical trials studying the efficacy of EPO in reducing blood transfusions in the anemia of prematurity. Transfusion 41 (3) 406-415				
Affiliation/Source of funds				
Supported in part by Program Project Grant P01 HL46925 from the NIH (National Institutes of Health).				
Study design	Level of evidence	Location/setting		
Systematic review	Level I	Various (individual trial locations not specified)		
Intervention	Comparator			
rHuEPO + iron (intravenously or orally)	Not treated with rHuEPO + iron (intravenous or orally) *one study did not administer iron to the control group			
Population characteristics				
Infants under four months of age with the anaemia of prematurity				
Length of follow-up	Outcomes measured			
NA	Number of transfusions per infant odds ratio, ~~OD of RBC transfusion,~~ mean difference in the volume (mL/kg) of blood transfused, mean difference in the number of transfusions per infant			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Only one data base was searched and search terms were not reported. 20 of the 21 included studies used random allocation. However, the remaining study compared three sequentially enrolled groups receiving various doses of rHuEPO with a concurrent control group. Quality assessments clear and pre-determined. Data could not be pooled into a single meta-analysis, rather outcomes were selectively combined. Studies were pooled if the variation in results was sufficiently modest to be attributed to chance ($P > 0.10$ for the Q test statistic). Twelve variables were suitable for meta-analysis. The number of available studies was insufficient to explore heterogeneity. 21 studies were included and assessed using the Jadad score, with quality scores ranging from 1 to 5 (out of a maximum of 5).				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI) OR (95%CI) MD ± SE	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO + oral iron (2-4mg/kg/day) vs oral iron (2-4mg/kg/day) only				
Transfusion incidence (N=83) (Obladen 1991)	NR	NR	0.85 (0.35-2.060)	No significant difference p=NR Heterogeneity not applicable
Transfusion incidence (N=20) (Shannon 1991)	NR	NR	0.38 (0.05-2.77)	No significant difference p=NR Heterogeneity not applicable
Transfusion incidence (N=19) (Ohls 1991)	NR	NR	0.04 (0.002-0.97)	Favours rHuEPO + iron $P < 0.05$ Heterogeneity not applicable
Transfusion incidence (N=8) (Shannon 1992)	NR	NR	0.11 (0.005-2.730)	No significant difference p=NR Heterogeneity not applicable

Transfusion incidence (N=241) (Maier 1994)	NR	NR	0.49 (0.29-0.83)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Transfusion incidence (N=79) (Meyer 1994)	NR	NR	0.18 (0.06-0.51)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Transfusion incidence (N=24) (Ronnestad 1994)	NR	NR	0.05 (0.004-0.49)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity NR
Transfusion incidence (N=157) (Shannon 1995)	NR	NR	0.61 (0.32-1.17)	No significant difference p=NR Heterogeneity not applicable
Transfusion incidence (N=20) (Ohls 1995)	NR	NR	0.11 (0.01-0.84)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Transfusion incidence (N=29) (Bader 1996)	NR	NR	0.12 (0.02-0.72)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Transfusion incidence (N=24) (Samanci 1996)	NR	NR	0.17 (0.03-0.98)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=241) (Maier 1994)	NR	NR	0.4 ± 0.2	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=157) (Shannon 1995)	NR	NR	0.5 ± 0.3	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=20) (Ohls 1995)	NR	NR	1.2 ± 0.4	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=24) (Samanci 1996)	NR	NR	0.7 ± 0.3	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=83) (Obladen 1991)	NR	NR	2.4 ± 4.20	No significant difference p=NR Heterogeneity not applicable

Volume of blood transfused (mL/kg) 1 trial (N=157) (Shannon 1995)	NR	NR	7.4 ± 3.9	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=20) (Ohls 1995)	NR	NR	15.3 ± 4.8	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
rHuEPO + oral iron (≥6mg/kg/day) vs oral iron (≥6mg/kg/day) only				
Transfusion incidence (N=23) (Emmerson 1993)	NR	NR	0.13 (0.01-1.28)	No significant difference p=NR Heterogeneity not applicable
Transfusion incidence (N=29) (Bechensteen 1993)	NR	NR	0.10 (0.005-2.14)	No significant difference p=NR Heterogeneity not applicable
Transfusion incidence (N=30) (Kumar 1998)	NR	NR	0.05 (0.005-0.46)	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=55) (Al-Kharfy 1996)	NR	NR	2.2 ± 0.5	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=30) (Kumar 1998)	NR	NR	0.7 ± 0.2	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=36) (Giannakopoulou 1998)	NR	NR	5.5 ± 0.7	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=32) (Giannakopoulou 1998)	NR	NR	2.8 ± 0.7	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=30) (Kumar 1998)	NR	NR	10.7 ± 3.0	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=36) (Giannakopoulou 1998)	NR	NR	65.1 ± 10.9	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable

Volume of blood transfused (mL/kg) 1 trial (N=32) (Giannakopoulou 1998)	NR	NR	42.6 ± 7.9	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
rHuEPO + intravenous iron vs intravenous iron only				
Number of transfusions per patient 1 trial (N=22) (Carnielli 1992)	NR	NR	2.3 ± 0.8	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Number of transfusions per patient 1 trial (N=24) (Ohls1997)	NR	NR	2.8 ± 1.3	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=22) (Carnielli 1992)	NR	NR	34.2 ± 12.9	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
Volume of blood transfused (mL/kg) 1 trial (N=24) (Ohls 1997)	NR	NR	42.0 ± 20.3	Favours rHuEPO + iron *P* < 0.05 Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to infants under four months of age with the anaemia of prematurity.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Individual trial locations were not specified.				
Comments				
Before performing a meta-analysis, the authors evaluated the size of variation between studies using the Q test statistic. Following this calculation, it was decided that it was not appropriate to pool all available data into a single meta-analysis, rather outcomes were selectively combined. Studies were pooled if the variation in results was sufficiently modest to be attributed to chance (*P* > 0.10 for the Q test statistic). Twelve variables were suitable for meta-analysis.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

STUDY DETAILS: SR/MA				
Citation				
Xu XJ, Huang HY, Chen HL (2014) Erythropoietin and retinopathy of prematurity: a meta-analysis. European Journal of Pediatrics.				
Affiliation/Source of funds				
The authors declare no competing financial interest.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs, cohort and case-control studies	Level I/III	USA (Ohls 2013, Ohls 2001, Shannon 1995), multicentre Europe (Maier 2002), Italy (Romagnoli 2000), Germany (Fauchere 2008).		
Intervention	Comparator			
rHuEPO *All patients received iron, except those enrolled in Fauchere 2008	Placebo or no treatment			
Population characteristics				
Preterm neonates.				
Length of follow-up	Outcomes measured			
28 days.	Primary outcomes: ROP or severe (stage 3-4) ROP Secondary outcomes:			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: 14 studies were identified, which included 6 RCTs (Ohls 2013, Fauchere 2008, Maier 2002, Ohls 2001, Romagnoli 2000, Shannon 1995) 4 cohort studies and 3 case-control studies. Multiple databases were searched (PubMed and ISI databases) and search terms were provided. Manual searching of references from all eligible studies and review articles was conducted. Evaluation for inclusion, data extraction and qualitative assessment was carried out by two independent reviewers, with disagreements resolved by discussion between the two. Quality of RCTs was assessed according to the Jadad scale. Five out of six RCTs scored 4/5, and one study scored 3/5 (Romagnoli 2000). In the absence of significant heterogeneity, studies were pooled using a fixed-effect model. If heterogeneity was observed, a random effects model was used. Publication bias was assessed by visual inspection of a funnel plot, the Egger's regression test and Begg's adjusted rank correlation test. The funnel plot showed no asymmetry and the two tests suggested that there was no significant publication bias. Sensitivity analysis was performed for included RCTs. Subgroup analyses were performed by administration dose (high dose >500units/kg/week and low dose <500units/kg/week), and administration time (early 0-7 days and late 8-28 days).				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
rHuEPO vs placebo / no treatment				
ROP (11 studies*)	563/1221 (46.1%)	420/1134 (37.0%)	OR 1.59 [0.90, 2.81]	No significant difference *P* = NR I^2=82.9%
Severe ROP (9 studies*)	192/1298 (14.8%)	166/1199 (13.8%)	OR 1.20 [0.76, 1.90]	No significant difference *P* = NR I^2=63.8%
Sensitivity analysis: RCTs only				

ROP (5 studies: Ohls 2013**, Fauchere 2008, Maier 2002, Romagnoli 2000, Shannon 1995; N=)	NR	NR	OR 1.11 [0.61, 2.01]	No significant difference *P* = 0.74 I^2=55.4%
Severe ROP (4 studies: Ohls 2013**, Fauchere 2008, Ohls 2001, Romagnoli 2000; N=)	NR	NR	OR 1.35 [0.76, 2.40]	No significant difference *P* = 0.30 I^2=18.3%
Subgroup analysis: high dose rHuEPO (RCTs only, calculated post-hoc using RevMan 5.1)				
ROP (4 studies: Ohls 2013, Fauchere 2008, Maier 2002, Romagnoli 2000; N=555)	140/321 (43.6%)	77/234 (32.9%)	OR 1.29 [0.62, 2.65]	No significant difference *P* = 0.50 I^2=66%
Severe ROP (4 studies: Ohls 2013, Ohls 2001, Fauchere 2008, Romagnoli 2000; N=625)	49/318 (15.4%)	33/307 (10.7%)	OR 1.53 [0.92, 2.57]	No significant difference *P* = 0.10 I^2=6%
Subgroup analysis: low dose rHuEPO (RCTs only, calculated post-hoc using RevMan 5.1)				
ROP (2 studies: Ohls 2013, Shannon 1995; N=224)	13/111 (11.7%)	15/113 (13.3%)	OR 0.81 [0.32, 2.02]	No significant difference *P* = 0.65 I^2=0%
Severe ROP (1 study: Ohls 2013; N=66)	2/33 (6.1%)	4/33 (12.1%)	OR 0.47 [0.08, 2.75]	No significant difference *P* = 0.40 I^2=NA
Subgroup analysis: early rHuEPO (RCTs only, calculated post-hoc using RevMan 5.1)				
ROP (1 study: Fauchere 2008; N=39)	2/24 (8.3%)	2/15 (13.3%)	OR 0.59 [0.07, 4.71]	No significant difference *P* = 0.62 I^2=NA
Severe ROP (1 study: Fauchere 2008; N=39)	1/24 (4.2%)	0/15 (0%)	OR 1.98 [0.08, 51.76]	No significant difference *P* = 0.68 I^2=NA
Subgroup analysis: late rHuEPO (RCTs only, calculated post-hoc using RevMan 5.1)				
ROP (2 studies: Maier 2002, Romagnoli 2000; N=449)	126/263 (47.9%)	63/186 (33.9%)	OR 1.59 [0.54, 4.70]	No significant difference *P* = 0.40 I^2=86%
Severe ROP (1 study: Romagnoli 2000; N=230)	20/115 (17.4%)	9/115 (7.8%)	OR 2.48 [1.08, 5.71]	Favours placebo/no treatment *P* = 0.03 I^2=NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm neonates (Level A).				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats (Level B).				
Comments				

*Includes cohort and case-control studies.

**Ohls 2013 provided two sets of data: rHuEPO vs no rHuEPO and darbepoetin alfa vs no darbepoetin alfa.

The authors concluded that rHuEPO treatment is not associated with the development of ROP in preterm infants; however, this conclusion should be confirmed by further high quality researches.

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

Oral and/or parenteral iron

<table>
<tr><td colspan="3">STUDY DETAILS: SR/MA</td></tr>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Okebe, J. U., Yahav, D., Shbita, R., and Paul, M. (2011) Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev (10) CD006589-</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">Internal sources: UK Department for International Development (DFID), UK. The editorial base for the Cochrane Infectious Diseases Group is funded by the UK Department for International Development (DFID) for the benefit of developing countries. Dafna Yahav received funding from the editorial base.
External sources: The Nuffield Foundation, Afghanistan. Dr Juliana U Ojukwu was awarded a Reviews for Africa Programme Fellowship (www.mrc.ac.za/cochrane/rap.htm), funded by a grant from the Nuffield Commonwealth Programme, through The Nuffield Foundation. Micronutrients Unit, Department of Nutrition for Health and Development, World Health Organization, Switzerland (Grant to support the 2011 update).</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Systematic review of RCTs and cluster-randomised trials</td><td>Level I</td><td>Ethiopia (Adam 1997, Gebresellassie 1996), India (Aggarwal 2005, Bhatia 1993, Devaki 2007, Gopaldas 1983, Kapur 2003, Kashyap 1987, Nagpal 2004, Sarma 1977, Seshadri 1982, Seshadri 1984), Bolivia (Aguayo 2000, Berger 1997), Indonesia (Angeles 1993, Chwang 1988, Fahmida 2007, Irdjradinata 1993, Lind 2004, Palupi 1997, Smuts 2005, Soemantri 1989, Soewondo 1989), Mali (Ayoya 2009, Hall 2002), Bangladesh (Bacqui 2003), Togo (Berger 2000), Vietnam (Berger 2006), Thailand (Charoenlarp 1973, Wasantwisut 2006), Sri Lanka (de Silva 2003, Hettiarachchi 2008), Kenya (Desai 2003, Latham 1990, Lawless 1994, Olsen 2006, Verhoef 2002), Benin (Dossa 2001a, Dossa 2001b), Zambia (Greisen 1986), Papua New Guinea (Harvey 1989), Iran (Kianfar 1999), Tanzania (Massaga 2003, Mebrahtu 2004, Menendez 1997, Mwanri 2000, Sazawal 2006a, Sazawal 2006b), Guatemala (Mejia 1988), Gambia (Powers 1983, Smith 1989), Peru (Richard 2006), Mexico (Rosado 1997), Philippines (Roschnik 2004), Nepal (Shah 2002), Ghana (Zlotkin 2003).</td></tr>
<tr><td colspan="2">Intervention</td><td>Comparator</td></tr>
<tr><td colspan="2">1. Iron
2. Iron + folic acid
3. Iron + antimalarial treatment
4. Iron
Note: only data for interventions 1 and 2 have been extracted for this review</td><td>1. Placebo or no treatment
2. Placebo or no treatment
3. Placebo
4. Control in the treatment of proven anaemia</td></tr>
<tr><td colspan="3">Population characteristics</td></tr>
<tr><td colspan="3">Children (<18 years) living in a hypoendemic, mesoendemic, hyperendemic, or holoendemic area for malaria.
Studies were included if ≥ 70% of the included children lived in endemic regions. Studies were excluded if it was specifically stated in the publication, or information was obtained from the authors, that the trial was conducted in an area or period without malaria activity.
Children with or without anaemia, malaria or parasitaemia at baseline were included.</td></tr>
<tr><td>Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td>NA</td><td colspan="2">death from, haemoglobin levels, prevalence of anaemia (as defined in the study), infections other than malaria (including diarrhoea, pneumonia, sepsis, meningitis, measles and pertussis, expressed as episodes per child-month), weight (absolute values), height (absolute values).</td></tr>
<tr><td colspan="3">INTERNAL VALIDITY</td></tr>
<tr><td colspan="3">Overall quality assessment (descriptive)</td></tr>
</table>

Rating: Good

Description: Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. Pooling of data was appropriate and tests for heterogeneity applied. 71 RCTs were included in the systematic review. 57 of these provided data for interventions 1 and 2 and are included in this review. These RCTs were of variable quality and were assessed using the Cochrane risk of bias tool. Many of the included RCTs did not adequately report randomisation and allocation concealment methods, were not blinded and did not completely report outcome data (particularly for the outcome of mortality).

RESULTS

Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Iron vs placebo/no treatment				
All-cause mortality 22 trials (N=8644)	38/4294 (0.9%)	36/4350 (0.8%)	RD 0.00 [0.00, 0.00]	No significant difference *P* = 0.87 No significant heterogeneity *P* = 1.00 (I^2=0%)
Subgroup analysis: malaria endemicity				
13 trials conducted in hyper– or holoendemic 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 mesoendemic 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%
Laboratory measures				
Haemoglobin, end of treatment (anaemic children at baseline)11 trials (N= 2692)	NR	NR	MD 1.59 [0.93, 2.26]	Favours iron *P* =< 0.00001 Substantial heterogeneity *P* < 0.00001 (I^2 =98%)
Haemoglobin, end of treatment (non-anaemic children at baseline) 29 trials (N=5852)	NR	NR	MD 0.64 [0.48, 0.80]	Favours iron *P* < 0.00001 Substantial heterogeneity *P* < 0.00001 (I^2 =86%)
Haemoglobin, end of treatment (all children) 35 trials (N=8544)	NR	NR	MD 0.87 [0.64, 1.09]	Favours iron *P* =< 0.00001 Substantial heterogeneity *P* < 0.00001 (I^2 =95%)
Haemoglobin, change from baseline, end of treatment 20 trials (N=4205)	NR	NR	MD 0.61 [0.41, 0.80]	Favours iron *P* < 0.00001 Substantial heterogeneity *P* < 0.00001 (I^2=88%)
Growth measures				

Weight, end value 16 trials (N=4604)	NR	NR	SMD 0.01 [-0.05, 0.07]	No significant difference *P* = 0.79 Moderate heterogeneity *P* = 0.12 (I^2=26%)
Weight, change from baseline 11 trials (N=1162)	NR	NR	SMD 0.19 [0.07, 0.30]	Favours iron *P* = 0.0020 Substantial heterogeneity *P* < 0.00001 (I^2=84%)
Height, end value 16 trials (N=4911)	NR	NR	SMD 0.00 [-0.05, 0.06]	No significant difference *P* = 0.91 No significant heterogeneity *P* = 0.91 (I^2=0%)
Height, change from baseline 11 trials (N=1162)	NR	NR	SMD 0.18 [0.06, 0.30]	Favours iron *P* = 0.0027 Substantial heterogeneity *P* < 0.00001 (I^2=74%)
Iron + folic acid vs placebo/no treatment				
All-cause mortality 5 trials (N=18 107)	153/9045 (1.69%)	137/9062 (1.51%)	RD 0.00 [0.00, 0.01]	No significant difference *P* = 0.31 No significant heterogeneity *P* = 0.68 (I^2=0%)
Subgroup analysis: malaria endemicity				
3 trials conducted in hyper– or holoendemic 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 mesoendemic settings N=209	0/137	0/72	RD 0.00 [-0.02, 0.02]	*No significant difference* *P* = 1.0
Laboratory measures				
Haemoglobin, end of treatment (anaemic children at baseline) 4 trials (n=273)	NR	NR	MD 1.10 [0.30, 1.91]	Favours iron *P* = 0.0074 Substantial heterogeneity *P* < 0.00001 (I^2 =89%)
Haemoglobin, end of treatment (non-anaemic children at baseline) 2 trials (n=867)	NR	NR	MD 0.95 [0.32, 1.59]	Favours iron *P* = 0.0032 Substantial heterogeneity *P* < 0.00001 (I^2 =90%)
Haemoglobin, end of treatment (all children) 6 trials (n=1140)	NR	NR	MD 1.03 [0.56, 1.49]	Favours iron *P* = 0.000018 Substantial heterogeneity *P* < 0.00001 (I^2 =88%)
Growth measures				
Weight, end value 2 trials (N=1730)	NR	NR	SMD -0.02 [-0.12, 0.07]	No significant difference *P* = 0.66 Substantial heterogeneity *P* = 0.003 (I^2=83%)

Height, end value 2 trials (N=1730)	NR	NR	SMD -0.02 [-0.11, 0.08]	No significant difference *P* = 0.72 No significant heterogeneity *P* = 0.40 (I^2=0%)
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children under 18 years of age living in a hypoendemic, mesoendemic, hyperendemic, or holoendemic area for malaria.				
Applicability				
Evidence not applicable to Australian healthcare context. Studies were conducted developing countries where malaria has been described and include: India (Level C), Indonesia , Ethiopia, Bolivia, Mali, Bangladesh, Togo, Vietnam, Thailand, Sri Lanka, Kenya, Benin, Zambia, Papua New Guinea, Iran, Tanzania, Guatemala, Gambia, Peru, Mexico, Philippines, Ghana (Level D)				
Comments				
The authors highlight potential bias in the reporting of mortality data. Only 30 of the total 71 studies reported mortality data, with most of these trials only reporting mortality among the children available for analysis at the end of the study or follow-up period. Instead, they state data should have been assessed among all children randomised, that is, including those lost to follow-up.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

STUDY DETAILS: SR/MA				
Citation				
Pasricha, S. R., Hayes, E., Kalumba, K., and Biggs, B. A. (2013) Effect of daily iron supplementation on health in children aged 4-23 months: A systematic review and meta-analysis of randomised controlled trials. Lancet Global Health 1 (2) e77-e86				
Affiliation/Source of funds				
Funding: Victoria Fellowship (Government of Victoria, Australia); CRB Blackburn Scholarship (Royal Australasian College of Physicians); Overseas Research Experience Scholarship, University of Melbourne). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs	Level I	Various (individual trial locations not specified but most studies were conducted in low-income or middle-income settings)		
Intervention	Comparator			
Daily oral iron	No iron			
Population characteristics				
Community or outpatient, otherwise well children aged 4-23 months. Studies that compared daily oral iron supplements with control were eligible. Studies that combined iron supplements with a second intervention were eligible when the co-intervention was applied identically (without iron) in the control group. Studies comparing multiple micronutrients containing iron with control were excluded.				
Length of follow-up	Outcomes measured			
NA	Primary outcomes: haemoglobin (g/L), anaemia (defined by study investigators), iron status (iron indices, including ferritin), iron deficiency (defined by study investigators), iron deficiency anaemia (IDA, defined by study investigators), cognitive and psychomotor development, physical growth and safety (i.e. gastrointestinal effects, infections such as malaria, mortality). Secondary outcomes: included effects of iron on other micronutrients (e.g. zinc, vitamin A).			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Search terms, characteristics of the included studies and their risk of bias are not presented in the main article in detail. However, readers are referred to an appendix online for more information. The appendix gives more detailed information on the Scopus search strategy, risk of bias assessment tool and the results of the full text eligibility screening. A full list of included studies is also provided, accompanied by the characteristics of these RCTs and their risk of bias as judged using the Cochrane risk of bias tool. The inclusion/exclusion criteria are detailed, pooling of data was appropriate and tests for heterogeneity applied. 35 RCTs were included, with 9 considered to have a low risk of bias. Hb 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 Ferritin trials: 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 (n=20?)				
RESULTS				
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Iron vs no iron				
Primary outcome				

Mortality 2 trials (N=NR)	NR	NR	Rate Ratio 1.10 [0.91, 1.34]	No significant difference *P* = 0.33 No significant heterogeneity *P* = NR (I^2=0%)
Secondary outcomes				
Haemoglobin (Hb)				
Hb (g/L) 26 trials (N=5479)	NR (2808)	NR (2671)	MD 7.22 [4.87, 9.57]	Favours iron *P* < 0.0001 Substantial heterogeneity *P* = NR (I^2=94%)
Sub-analysis: breastfeeding status				
- Hb (breastfed) 8 trials (n=1972)	NR	NR	MD 7.20 [3.89, 10.51]	Favours iron *P* < 0.0001 I^2=92%
- Hb (mixed/unreported) 18 trials (n=3507)	NR	NR	MD 7.21 [3.93, 10.48]	Favours iron *P* < 0.0001 I^2=95%
Sub-analysis: baseline Hb				
- Hb (anaemic patients) 3 trials (n=635)	NR	NR	MD 14.14 [7.36, 20.92]	Favours iron *P* < 0.0001 I^2=94%
- Hb (non-anaemic patients) - 4 trials (n=228)	NR	NR	MD 11.64 [-5.00, 28.28]	No significant difference *P* = 0.17 I^2=99%
- Hb (mixed/unreported) 20 trials (n=4616)	NR	NR	MD 5.81 [3.96, 7.66]	Favours iron *P* < 0.00001 I^2=88%
Sub-analysis: baseline iron status				
- Hb (iron deficient patients) 2 trials (n=115)	NR	NR	MD 10.35 [-4.62, 25.33]	No significant difference *P* = 0.18 I^2=96%
- Hb (iron replete patients) 4 trials (n=243)	NR	NR	MD 11.05 [-5.48, 27.57]	No significant difference *P* = 0.19 I^2=99%
- Hb (mixed/unreported iron status) 21 trials (n=5121)	NR	NR	MD 6.49 [4.62, 8.36]	Favours iron *P* < 0.00001 I^2=88%
Sub-analysis: iron dose				
- Hb (≤12.5mg) 16 trials (n=3889)	NR	NR	MD 5.72 [3.48, 7.96]	Favours iron *P* < 0.00001 I^2=93%
- Hb (12.6-30mg) 6 trials (n=796)	NR	NR	MD 12.77 [3.30, 22.24]	Favours iron *P* = 0.008 I^2=98%
- Hb (31-60mg) 1 trial (n=491)	NR	NR	MD 8.76 [6.81, 10.72]	Favours iron *P* < 0.00001 I^2=NA
- Hb (≥61mg) 1 trial (n=150)	NR	NR	MD 8.06 [3.79, 12.33]	Favours iron *P* = 0.0002 I^2=NA

- Hb (mixed/unspecified) 2 trials (n=153)	NR	NR	MD 2.35 [-0.66, 5.36]	No significant difference *P* = 0.13 I^2=48%
Sub-analysis: iron duration				
- Hb (1-3 months) 11 trials (n=1742)	NR	NR	MD 6.37 [3.49, 9.25]	Favours iron *P* < 0.0001 I^2=93%
- Hb (>3 months) 14 trials (n=3505)	NR	NR	MD 7.54 [3.87, 11.20]	Favours iron *P* < 0.0001 I^2=96
- Hb (mixed/unspecified) 1 trial (n=232)	NR	NR	MD 5.45 [3.09, 7.81]	Favours iron *P* < 0.00001 I^2=NA
Sub-analysis: iron combination				
- Hb (iron vs control) 17 trials (n=2063)	NR	NR	MD 6.88 [2.99, 10.77]	Favours iron *P* = 0.0005 I^2=96%
- Hb (iron + X vs X alone) 12 trials (n=3416)	NR	NR	MD 7.53 [4.87, 10.19]	Favours iron *P* < 0.00001 I^2=90%
Sub-analysis: malaria endemicity				
- Hb (endemic) 3 trials (n=866)	NR	NR	MD 6.29 [2.18, 10.40]	Favours iron *P* = 0.0003 I^2=86%
- Hb (non-endemic) 2 trials (n=1118)	NR	NR	MD 9.59 [5.56, 13.61]	Favours iron *P* < 0.00001 I^2=86%
- Hb (unstated) 21 trials (n=3495)	NR	NR	MD 7.05 [3.93, 10.16]	Favours iron *P* < 0.0001 I^2=95%
Ferritin				
Ferritin (ng/mL) 23 trials (N=4236) *corrected appendix reports 24 trials, N=4526 and MD 20.94 [16.84, 25.04]	NR (2196)	NR (2040)	MD 21.42 [17.25, 25.58]	Favours iron *P* < 0.0001 Substantial heterogeneity *P* = NR (I^2=98%)
Sub-analysis: breastfeeding status				
- Ferritin (breastfed) 8 trials (n=1680)	NR	NR	MD 26.61 [20.22, 33.01]	Favours iron *P* < 0.00001 I^2=93%
- Ferritin (mixed/unreported) 15 trials (n=2556)	NR	NR	MD 18.43 [12.85, 24.01]	Favours iron *P* < 0.00001 I^2=99%
Sub-analysis: baseline Hb				
- Ferritin (anaemic patients) 2 trials (n=136)	NR	NR	MD 22.24 [-12.43, 56.91]	No significant difference *P* = 0.21 I^2=96%
- Ferritin (non-anaemic patients) 5 trials (n=384)	NR	NR	MD 15.71 [-0.80, 32.22]	No significant difference *P* = 0.06 I^2=83%

- Ferritin (mixed/unreported) 17 trials (n=3716)	NR	NR	MD 22.95 [18.60, 27.30]	Favours iron *P* < 0.0001 I^2=98%
Sub-analysis: baseline iron status				
- Ferritin (iron deficient patients) 2 trials (n=115)	NR	NR	MD 30.65 [3.79, 57.51]	Favours iron *P* = 0.03 I^2=93%
- Ferritin (iron replete patients) 4 trials (n=243)	NR	NR	MD 22.42 [7.26, 37.57]	Favours iron *P* = 0.004 I^2=83%
- Ferritin (mixed/unreported iron status) 18 trials (n=3878)	NR	NR	MD 21.16 [16.55, 25.77]	Favours iron *P* < 0.00001 I^2=99%
Sub-analysis: iron dose				
- Ferritin (≤12.5mg) 15 trials (n=3295)	NR	NR	MD 24.43 [20.06, 28.81]	Favours iron *P* < 0.00001 I^2=98%
- Ferritin (12.6-30mg) 6 trials (n=788)	NR	NR	MD 12.52 [6.74, 18.31]	Favours iron *P* < 0.00001 I^2=85%
- Hb (mixed/unspecified) 2 trials (n=153)	NR	NR	MD 15.43 [-9.71, 40.56]	No significant difference *P* = 0.23 I^2=99%
Sub-analysis: iron duration				
- Ferritin (1-3 months) 8 trials (n=788)	NR	NR	MD 12.52 [6.74, 18.31]	Favours iron *P* = 0.001 I^2=96%
- Ferritin (>3 months) 13 trials (n=3002)	NR	NR	MD 26.52 [21.81, 31.23]	Favours iron *P* < 0.00001 I^2=98%
- Ferritin (mixed/unspecified) 2 trial (n=437)	NR	NR	MD 18.04 [2.52, 33.57]	Favours iron *P* = 0.02 I^2=92%
Sub-analysis: iron combination				
- Ferritin (iron vs control) 17 trials (n=2109)	NR	NR	MD 18.18 [12.77, 23.58]	Favours iron *P* < 0.00001 I^2=94%
- Ferritin (iron + X vs X alone) 9 trials (n=2417)	NR	NR	MD 24.38 [18.23, 30.53]	Favours iron *P* < 0.00001 I^2=99%
Sub-analysis: malaria endemicity				
- Ferritin (endemic) 1 trial (n=163)	NR	NR	MD 50.80 [33.45, 68.15]	Favours iron *P* < 0.00001 I^2=NA
- Ferritin (non-endemic) 3 trials (n=1325)	NR	NR	MD 31.17 [21.69, 40.66]	Favours iron *P* < 0.00001 I^2=84%
- Ferritin (unstated) 19 trials (n=2748)	NR	NR	MD 17.83 [13.10, 22.57]	Favours iron *P* < 0.00001 I^2=99%
Bayley's mental development index (MDI) score				

Bayley's MDI score 6 trials (Akman 2004, Idjradinata 1993, Lind 2003, Lozoff 1982, Walter 1989, Yalcin 2000) N=1093	NR	NR	MD 1.65 [-0.63, 3.94]	No significant difference *P* = 0.16 Substantial heterogeneity *P* = NR (I^2=66%)
Sub-analysis: breastfeeding status				
- Bayley's MDI (mixed/unreported) 6 trials (n=1093)	NR	NR	MD 1.65 [-0.63, 3.94]	No significant difference *P* = 0.16 I^2=66%
Sub-analysis: baseline Hb				
- Bayley's MDI (anaemic patients) 3 trials (n=113)	NR	NR	MD 4.46 [-9.32, 18.24]	No significant difference *P* = 0.53 I^2=80%
- Bayley's MDI (non-anaemic patients) 5 trials (n=325)	NR	NR	MD 1.49 [-1.08, 4.07]	No significant difference *P* = 0.25 I^2=28%
- Bayley's MDI (mixed/unreported) 1 trial (n=655)	NR	NR	MD 0.49 [-2.45, 3.43]	No significant difference *P* = 0.74 I^2=74%
Sub-analysis: baseline iron status				
- Bayley's MDI (iron deficient patients) 3 trials (n=281)	NR (149)	NR (132)	MD 5.90 [1.81, 10.00]	Favours iron *P* = 0.005 I^2=34%
- Bayley's MDI (iron replete patients) 3 trials (n=90)	NR (41)	NR (49)	MD 0.65 [-1.59, 2.88]	No significant difference *P* = 0.57 I^2=0%
- Bayley's MDI (mixed/unreported iron status) 2 trials (n=722)	NR (357)	NR (365)	MD -0.14 [-3.14, 2.85]	No significant difference *P* = 0.93 I^2=66%
Sub-analysis: iron dose				
- Bayley's MDI (≤12.5mg) 3 trials (n=790)	NR	NR	MD 1.49 [-0.95, 3.94]	No significant difference *P* = 0.23 I^2=73%
- Bayley's MDI (12.6-30mg) 1 trial (n=40)	NR	NR	MD 6.26 [1.54, 10.98]	Favours iron *P* = 0.009 I^2=NA
- Bayley's MDI (31-60mg) 2 trials (n=263)	NR	NR	MD -1.84 [-7.70, 4.01]	No significant difference *P* = 0.54 I^2=16%
Sub-analysis: iron duration				
- Bayley's MDI (≤1 month) 2 trials (n=263)	NR	NR	MD -1.84 [-7.70, 4.01]	No significant difference *P* = 0.54 I^2=16%
- Bayley's MDI (1-3 months) 1 trial (n=16)	NR	NR	MD 0.40 [-2.08, 2.88]	No significant difference *P* = 0.75 I^2=NA
- Bayley's MDI (>3 months) 3 trials (n=814)	NR	NR	MD 2.91 [-0.40, 6.23]	No significant difference *P* = 0.08 I^2=80%
Sub-analysis: iron combination				

- Bayley's MDI (iron vs control) 5 trials (n=438)	NR	NR	MD 2.35 [-1.33, 6.04]	No significant difference *P* = 0.21 I^2=67%
- Bayley's MDI (iron + X vs X alone) 1 trial (n=655)	NR	NR	MD 0.49 [-2.45, 3.43]	No significant difference *P* = 0.74 I^2=74%
Sub-analysis: malaria endemicity				
- Bayley's MDI (unstated) 6 trials (n=1093)	NR	NR	MD 1.65 [-0.63, 3.94]	No significant difference *P* = 0.16 I^2=66%
Bayley's psychomotor development index (PDI) score				
Bayley's PDI score 6 trials (Akman 2004, Idjradinata 1993, Lind 2003, Lozoff 1982, Walter 1989, Yalcin 2000) N=1086	NR	NR	MD 1.05 [-1.36, 3.46]	No significant difference *P* = 0.39 Substantial heterogeneity *P* = NR (I^2=67%)
Sub-analysis: breastfeeding status				
- Bayley's PDI (mixed/unreported) 6 trials (n=1086)	NR	NR	MD 1.05 [-1.36, 3.46]	No significant difference *P* = 0.39 I^2=67%
Sub-analysis: baseline Hb				
- Bayley's PDI (anaemic patients) 3 trials (n=113)	NR	NR	MD 4.20 [-9.88, 18.29]	No significant difference *P* = 0.56 I^2=78%
- Bayley's PDI (non-anaemic patients) 5 trials (n=325)	NR	NR	MD 0.04 [-1.80, 1.88]	No significant difference *P* = 0.96 I^2=0%
- Bayley's PDI (mixed/unreported) 1 trial (n=655)	NR	NR	MD 0.49 [-4.41, 5.39]	No significant difference *P* = 0856 I^2=89%
Sub-analysis: baseline iron status				
- Bayley's PDI (iron deficient patients) 3 trials (n=281)	NR	NR	MD 3.76 [-3.14, 10.66]	No significant difference *P* = 0.29 I^2=72%
- Bayley's PDI (iron replete patients) 3 trials (n=90)	NR	NR	MD 0.11 [-1.95, 2.17]	No significant difference *P* = 0.92 I^2=0%
- Bayley's PDI (mixed/unreported iron status) 2 trials (n=715)	NR	NR	MD 0.00 [-4.15, 4.16]	No significant difference *P* = 1.00 I^2=79%
Sub-analysis: iron dose				
- Bayley's PDI (≤12.5mg) 3 trials (n=790)	NR	NR	MD 1.56 [-1.54, 4.66[	No significant difference *P* = 0.32 I^2=83%
- Bayley's PDI (12.6-30mg) 1 trial (n=40)	NR	NR	MD -0.23 [-7.07, 6.61]	No significant difference *P* = 0.95 I^2=NA
- Bayley's PDI (31-60mg) 2 trials (n=256)	NR	NR	MD -0.55 [-5.88, 4.77]	No significant difference *P* = 0.84 I^2=0%

Sub-analysis: iron duration				
- Bayley's PDI (≤1 month) 2 trials (n=256)	NR	NR	MD -0.55 [-5.88, 4.77]	No significant difference *P* = 0.84 I^2=0%
- Bayley's PDI (1-3 months) 1 trial (n=16)	NR	NR	MD 0.00 [-2.26, 2.26]	No significant difference *P* = 1.00 I^2=NA
- Bayley's PDI (>3 months) 3 trials (n=814)	NR	NR	MD 1.80 [-2.06, 5.65]	No significant difference *P* = 0.36 I^2=82%
Sub-analysis: iron combination				
- Bayley's PDI (iron vs control) 5 trials (n=431)	NR	NR	MD 1.43 [-1.80, 4.66]	No significant difference *P* = 0.39 I^2=54%
- Bayley's PDI (iron + X vs X alone) 1 trial (n=655)	NR	NR	MD 0.49 [-4.41, 5.39]	No significant difference *P* = 0.85 I^2=89%
Sub-analysis: malaria endemicity				
- Bayley's PDI (unstated) 6 trials (n=1086)	NR	NR	MD 1.05 [-1.36, 3.46]	No significant difference *P* = 0.39 I^2=67%
Growth measures				
Weight (kg) 8 trials (N=2702)	NR	NR	MD -0.02 [-0.09, 0.05]	No significant difference *P* = 0.56 Moderate heterogeneity *P* = NR (I^2=25%)
Weight-for-age (Z-score) 8 trials (N=3237)	NR	NR	MD -0.02 [-0.08, 0.03]	No significant difference *P* = 0.43 No significant heterogeneity *P* = NR (I^2=0%)
Change in weight 8 trials (N=868)	NR	NR	SMD -1.12 [-1.91, -0.33]	Favours no iron *P* = 0.0005 Substantial heterogeneity *P* = NR (I^2=96%)
Length (cm) 7 trials (N=2470)	NR	NR	MD -0.13 [-0.33, 0.07]	No significant difference *P* = 0.20 No significant heterogeneity *P* = NR (I^2=0%)
Length-for-age (Z-score) 8 trials (N=3237)	NR	NR	MD 0.01 [-0.04, 0.06]	No significant difference *P* = 0.71 No significant heterogeneity *P* = NR (I^2=4%)
Change in length 8 trials (N=868)	NR	NR	SMD -0.83 [-1.53, -0.12]	Favours no iron *P* = 0.02 Substantial heterogeneity *P* = NR (I^2=95%)
Weight-for-length (Z-score) 5 trials (N=2763)	NR	NR	MD 0.03 [-0.06, 0.12]	No significant difference *P* = 0.50 Moderate heterogeneity *P* = NR (I^2=46%)

EXTERNAL VALIDITY
Generalisability
The study is generalisable to healthy children at risk of anaemia aged 4-23 months.
Applicability
Evidence probably applicable to Australian healthcare context with some caveats. Most studies were conducted in low-income or middle-income settings.
Comments
The authors note that the findings of the study are most relevant to developing nations as the majority of studies were conducted in low and middle-income countries. The study also reported a decrease in weight and length gain among participants in the iron groups, inferring that daily oral iron supplementation may impair growth. However, no significant differences were reported in the final weight or length measurements. The authors urge caution when drawing conclusions from the study due to the scarcity of data available regarding growth of children (both from this study and others) and the quality of the included RCTs with few reporting the methodology of randomisation and allocation concealment and only nine considered to have a low risk of bias.

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

[a] 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%.

Hydroxyurea

STUDY DETAILS: SR/MA				
Citation				
Mulaku, M., Opiyo, N., Karumbi, J., Kitonyi, G., Thoithi, G., and English, M. (2013) Evidence review of hydroxyurea for the prevention of sickle cell complications in low-income countries. Arch.Dis.Child. 98 (11) 908-914				
Affiliation/Source of funds				
M Mulaku and J Karumbi were supported by funds awarded to the SIRCLE collaboration by the Kenyan Consortium for National Health Research. N Opiyo was supported by funds from a Wellcome Trust Strategic Award (#084538). M English is supported by a Wellcome Trust Senior Fellowship (#097170). The funding source had no role in the conduct of the review and writing of the report.				
Study design	Level of evidence		Location/setting	
Systematic review	Level I		USA (Wang 2011, Ware 2012)	
Intervention	Comparator			
Hydroxyurea	Placebo or standard supportive care (without hydroxyurea)			
Population characteristics				
Children below 5 years of age with sickle cell disease *The authors note that although the focus of the review was on children under 5 years, studies enrolling children up to 18 years were also included as there is a paucity of data on younger children. Ware 2012 compared hydroxyurea/ phlebotomy (alternative treatment) and transfusions/chelation (standard treatment). This does not meet our PICO criteria.				
Length of follow-up	Outcomes measured			
NA	Primary outcomes – mortality and stroke. Secondary outcomes – vasoocclusive events (painful crises, infarcts and ischaemia)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Appropriate search strategies used and inclusion/exclusion criteria detailed. Quality assessments clear and pre-determined. A systematic review, RCTs and observational studies were included. However, only the 2 RCTs are relevant to this review. Although the RCTs were described, baseline demographic and clinical characteristics were not reported for patients in the individual studies. The authors note that heterogeneity was present (due to the different study designs, e.g. RCTs vs observational studies and outcome measures). As such, pooling the data was considered inappropriate so a meta-analysis was not conducted.				
RESULTS				
Outcome No. trials (No. patients)	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Hydroxyurea vs placebo/standard supportive care				
Mortality in 24 months follow-up 1 trial (N=NR)	0	0	NR	No significant difference *P* = not applicable Heterogeneity not applicable
Prevention of secondary stroke 1 trial (Ware 2012, N=133)[b]	NR	NR	NR	No significant difference (reported in text) *P* = NR Heterogeneity not applicable

Stroke 1 trial (Ware 2012; N=133)[b]	7/67 (10.45%)	0/66 (0%)	NR	No significant difference (reported in text) *P* = NR Heterogeneity not applicable
Number of transfusions 1 trial (Wang 2011; N=193)	204 per 1000 (20.4%)	340 per 1000 (34.0%)	HR 0.55 [0.32, 0.96]	Favours hydroxyurea *P* = NR Heterogeneity not applicable
Vasoocclusive pain episodes over 24 months follow-up 1 trial (N=193)	583 per 1000 (58.3%)	773 per 1000 (77.3%)	HR 0.59 [0.42, 0.83]	Favours hydroxyurea *P* < 0.002 Heterogeneity not applicable
Acute chest syndrome 1 trial N=193	71 per 1000 (7.1%)	186 per 1000 (18.6%)	HR 0.36 (0.15 to 0.87)	No significant difference *P* = NR Heterogeneity not applicable
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children up to 18 years of age with sickle cell disease.				
Applicability				
Evidence applicable to Australian health-care context with few caveats. Studies were conducted in the USA (Level C).				
Comments				
The results of this systematic review were presented as a narrative summary, as statistical pooling of data was considered inappropriate (as described above). The authors note that a consistent feature among the studies was the provision of high quality supportive care, in addition to hydroxyurea, and the use of regular haematological monitoring.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

a 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%.

b. Individual n's given as 66 and 67 but total N given as 161

Level II evidence

ESAs (with or without iron)

STUDY DETAILS: RCT		
Citation		
Andropoulos DB, Brady K, Easley RB et al (2013) Erythropoietin neuroprotection in neonatal cardiac surgery: A phase I/II safety and efficacy trial. The Journal of Thoracic and Cardiovascular Surgery, 146(1): 124-31.		
Affiliation/Source of funds		
The study was supported by grants/funding from the National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Development, Baylor College of Medicine General Clinical Research Centre, and the Texas Children's Hospital Anesthesiology Research Fund. The authors report that they have nothing to disclose with regard to commercial support.		
Study design	Level of evidence	Location/setting
RCT	Level II	USA
Intervention	Comparator	
Intravenous rHuEPO (500units/kg) preoperatively, and on postoperative days 1 and 3.	Normal saline (placebo)	
Population characteristics		
62 neonates aged <30 days scheduled for cardiac surgery with hypothermic CPB for >60 minutes. Exclusion criteria: <35 weeks gestational age, <2kg birth weight, known recognizable dysmorphic syndrome, surgery not requiring CPB, preoperative cardiac arrest, hypertension, polycythemia, thrombocytosis, evidence of hypercoagulability, patient/maternal history of major thrombosis, inability to enrol patient >12 hours preoperatively, cases where aortic cross-clamping was not used, CPB times anticipated to be <60 minutes, planned nadir temperature on bypass >30°C, patients with contraindications to rHuEPO administration.		
Length of follow-up	Outcomes measured	
12 months	Primary: dural sinovenous thrombosis (DSVT), other major thrombosis, hypertension, thrombocytosis, polycythemia. Secondary: MRI brain injury pre– and postoperatively, Bayley III scores at 12 months follow-up.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: An RCT of 62 neonates aged <30 days scheduled for cardiac surgery in the US, to assess the effect of rHuEPO compared with placebo on clinical and neurodevelopmental outcomes. Randomisation was performed by computer-generated random number assignment to rHuEPO or placebo, and patients were stratified within each of three anatomic groups: (1) hypoplastic left heart syndrome or variant undergoing Norwood Stage I palliation, (2) D-transposition of the great vessels undergoing arterial switch operation, (3) interrupted aortic arch with ventricular septal defect or other complete 2-ventricle anatomic repair. Surgical, anaesthetic and CPB techniques were standardised. Blinding of groups was maintained until the final patient had undergone 12-month Bayley III assessment. The authors noted that the study was not powered to detect statistically significant differences in neurodevelopmental outcomes including Bayley III scores. Aprotinin was administered to the first 21 patients for antifibrinolysis. Aprotinin marketing was suspended in December 2007, and ε-aminocaproic acid was administered to the final 38 patients in the study. 104 patients met inclusion criteria but only 62 (60%) were enrolled and randomised. The remaining patients either declined to be enrolled (n=24), were enrolled in another study (n=2), or the investigator was not available for consent / patient lived too far away (n=16). Three patients did not receive intended surgery and were excluded, leaving 59 for data analysis. In the intervention group, seven patients withdrew and three patients died before 12 month follow-up, and in the control group, four patients withdrew and three patients died.		
RESULTS		
Population analysed	Intervention (rHuEPO)	Comparator (Placebo)
Randomised (n=62)	35	27

Efficacy analysis (ITT) (n=59)	32 (clinical data) 22 (Bayley III scores at follow-up)		27 (clinical data) 20 (Bayley III scores at follow-up)	
Efficacy analysis (PP)	NR		NR	
Safety analysis (n=59)	32		27	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO vs placebo:				
Mortality	3/32 (9.4%)	3/27 (11.1%)	NR	NR
Preoperative cerebral infarction (all)	6/32(18.8%)	2/27 (7.4%)	NR	*No significant difference* *P* = 0.269
Preoperative cerebral infarction (mild)	4/32 (12.5%)	2/27 (7.4%)	NR	NR
Preoperative cerebral infarction (moderate)	1/32 (3.1%)	0/27 (0%)	NR	NR
Preoperative cerebral infarction (severe)	1/32 (3.1%)	0/27 (0%)	NR	NR
Postoperative cerebral infarction (all)	3/32 (9.4%)	5/27 (18.5%)	NR	*No significant difference* *P* = 0.450
Postoperative cerebral infarction (mild)	3/32 (9.4%)	5/27 (18.5%)	NR	NR
Postoperative cerebral infarction (moderate)	0/32 (0%)	0/27 (0%)	NR	NA
Postoperative cerebral infarction (severe)	0/32 (0%)	0/27 (0%)	NR	NA
Preoperative DSVT (all)	0/32 (0%)	0/27 (0%)	NR	NA
Postoperative DSVT (all)	3/32 (9.4%)	3/27 (11.1%)	NR	*No significant difference* *P* = 0.997
Postoperative DSVT (mild)	2/32 (6.3%)	2/27 (7.4%)	NR	NR
Postoperative DSVT (moderate)	1/32 (3.1%)	1/27 (3.7%)	NR	NR
Postoperative DSVT (severe)	0/32 (0%)	0/27 (0%)	NR	NA
	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)		
Neurodevelopmental outcomes at 12 months follow-up				
Bayley III composite score (cognitive)	101.1 ± 13.6	106.3 ± 10.8	NR	*No significant difference* *P* = 0.187
Bayley III composite score (language)	88.5 ± 12.8	92.4 ± 12.4	NR	*No significant difference* *P* = 0.329
Bayley III composite score (motor)	89.9 ± 12.3	92.6 ± 14.1	NR	*No significant difference* *P* = 0.506
Bayley III questionnaire score (social-emotional)	95.0 (92.5, 105.0)	100.0 (96.3, 108.8)	NR	*No significant difference* *P* = 0.249
Bayley III questionnaire score (behavioural)	93.2 ± 10.7	97.3 ± 15.7	NR	*No significant difference* *P* = 0.342
Bayley III questionnaire score (conceptual)	98.7± 13.6	99.2 ± 13.1	NR	*No significant difference* *P* = 0.906

Bayley III questionnaire score (social)	97.2 ± 11.4	100.7 ± 15.6	NR	*No significant difference* *P* = 0.423
Bayley III questionnaire score (practical)	89.5 ± 9.1	92.8 ± 12.6	NR	*No significant difference* *P* = 0.352
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants scheduled for cardiac surgery with some caveats (Level B).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site was USA. (Level C)				
Comments				
Subgroup analyses of the three anatomic groups were also performed; no statistically significant differences were observed (data not extracted). The authors concluded that the safety profile for rHuEPO was not different than placebo. Neurodevelopmental outcomes were not different between groups; however, this pilot study was not powered to definitively address these outcomes. Other limitations noted by the authors include the small sample size and the change in rHuEPO dosing levels, which may not be neuroprotective. An FDA mandate determined the decrease in rHuEPO dose from 1000 units/kg intravenously, to 500units/kg intravenously. The first 33 patients received the higher rHuEPO dose and the final 26 received the lower dose. Similarly, the first 21 patients in the trial received aprotinin for antifibrinolysis, whereas the final 38 patients received ε-aminocaproic acid. These changes are reflected in the full results of the study (data not extracted), with separate analyses conducted.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Bechensteen AG, Haga P, Halvorsen S et al (1993) Erythropoietin, protein, and iron supplementation and the prevention of anaemia of prematurity. Archives of Disease in Childhood, 69: 19-23.		
Affiliation/Source of funds		
Financial support and provision of Eprex was received from Cilag. Financial support for the preparation of the freeze dried human milk protein was received from Semper AB. AGB is the recipient of a research fellowship from the Norwegian Cancer Society.		
Study design	Level of evidence	Location/setting
RCT	Level II	4x hospitals, Norway.
Intervention	Comparator	
Subcutaneous rHuEPO (100units/kg) 3x per week from 3 to 7 weeks of age + oral iron supplementation (iron fumarate) at 18mg/day regardless of weight. Note: if serum iron fell <16.0umol/L, the iron dose was increased to 36mg/day.	Oral iron supplementation (iron fumarate) at 18mg/day regardless of weight. Note: if serum iron fell <16.0umol/L, the iron dose was increased to 36mg/day.	
Population characteristics		
29 VLBW (900-1400 g) preterm infants aged 3 weeks, with birth weight above the 3rd centile for gestational age. Exclusion criteria: ongoing ventilator treatment, fractional inspired oxygen >40%, previous or present steroid medication, blood transfusion <96hrs before start of study, ongoing infection with antibiotic treatment started <96hrs before start of study, obvious signs/symptoms of neurological impairment, ABO/Rh incompatibility or other haematological disease, other disease or illness (renal or heart disease, syndromes etc.), parenteral nutrition.		
Length of follow-up	Outcomes measured	
Until 16 weeks of age.	Laboratory measures (Hb, reticulocyte count, packed cell volume, serum iron concentration, WBC count, neutrophil count), growth (weight, length, head circumference), transfusion requirements, adverse events.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: An RCT of 29 VLBW otherwise healthy preterm infants in Norway, to examine the effect of rHuEPO plus oral iron compared with oral iron only, on laboratory measures and transfusion requirements. Infants were randomised separately at each centre to the intervention or control group. Randomisation was performed by pre-numbered sealed envelopes. All infants also received human milk (170–180 mL/kg/day) from week 3 to week 8 fortified with pasteurised freeze dried human milk protein at 9g/L to achieve total protein intake ~3.0 g/kg/day. Indications for blood transfusion were: (1) Hb<80 g/L or (2) at the discretion of clinician according to signs and symptoms. All but three infants (two intervention, one control) required an increase in iron dosage due to serum iron concentration falling <16.0 μmol/L. One infant in the control group was excluded at age 6 weeks due to suspected septicaemia. Data for this infant (3–6 weeks) were included in the analyses. No adverse events were observed during the study. The analyses of all main variables were repeated in a subgroup analysis which eliminated data from the excluded infant and from the infants with initial haemoglobin concentrations above 150 g/l or below 90 g/l. Results were very close to those obtained for the complete data set. Note: statistical power required 15 infants per group, but there were only 14 infants in the intervention group.		
RESULTS		
Population analysed	Intervention (rHuEPO + iron)	Comparator (iron only)
Randomised	14	15
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs iron only				
Blood transfusion	0/14 (0%)	4/15 (26.7%)	NR	NR
Hb (g/L) at age 6 weeks (estimated from graph)	~120	~100	NR	Favours rHuEPO + iron *P* < 0.001
Hb (g/L) at age 8 weeks (estimated from graph)	~115	~105	NR	Favour rHuEPO + iron *P* < 0.01
Hb (g/L) at age 5 weeks	112 g/l	NR	NR	NR
Hb (g/L) at age 7 weeks	NR	98 g/l	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants with some caveats (Level B).				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site Norway (Level B).				
Comments				
The authors concluded that instable VLBW infants with optimal iron and protein intakes, moderate dose rHuEPO can produce significant gains in red cell products that may be clinically useful.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Bierer R, Roohi M, Peceny C, Ohls RK. Erythropoietin increases reticulocyte counts and maintains hematocrit in neonates requiring surgery. J Pediatr Surg 2009;44(8):1540-5.		
Affiliation/Source of funds		
Supported by grants from National Institutes of Health HD00988 and M01 RR 00997.		
Study design	Level of evidence	Location/setting
RCT	Level II	New Mexico, USA

Intervention	Comparator
rHuEPO (200 units/kg/day IV added to their TPN solution or 400units/kg SC three times weekly) + oral iron supplementation when enteral feeds reached 60 mL/kg/day	Placebo (IV with TPN or SC sham dosing) + oral iron supplementation when enteral feeds reached 60 mL/kg/day

Population characteristics
Infants who were less than 28 days old at the time of study entry and had a diagnosis of a disease requiring major surgery (defined as surgery requiring at least 15 minutes of general anaesthesia or surgery where anticipated blood loos was 10 mL/kg body weight or greater). Infants were ineligible if it was deemed unlikely that they would survive more than 72 hours, if they required extracorporeal membrane oxygenation, if they had Coombs-positive haemolytic disease, if they had evidence of disseminated intravascular coagulation, if clinical seizures were present, if they had systolic blood pressure greater than 100 mmHg (while not on pressor support) during the first 96 hours after birth, if their haematocrit was greater than 50% or if they were receiving rHuEPO clinically.

Length of follow-up	Outcomes measured
15 days	Reticulocyte count, haemoglobin, haematocrit, phlebotomy losses, number of transfusions and transfusion volumes, donor exposure.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description: Participants were randomised using a random number list and stratified by weight (≥1500 g and <1500 g). No attempt at allocation concealment was reported. The study was conducted in a "double-masked fashion". Baseline patient characteristics and demographics were similar between the groups but infants in the rHuEPO group were sicker than those in the placebo group. Loss to follow-up was not reported but the authors note that data for all enrolled infants is reported so it is assumed all infants completed the study. It is not reported if outcome assessment was blinded to treatment allocation but all outcomes were objective. No subgroup analyses were reported.

RESULTS

Population analysed	Intervention		Comparator	
Randomised	10		10	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				
Transfusions during study (number per patient)	0.8 ± 0.3	0.1 ± 0.4	NR	No significant difference *P* = 0.07
Transfusions during hospitalisation (number per patient)	2.1 ± 0.5	0.5 ± 0.2	NR	*P* = NR

Volume transfused during study (mL/kg)	17 ± 4	4 ± 4	NR	*P* = NR
Volume transfused during hospitalisation (mL/kg)	43 ± 15	16 ± 7	NR	*P* = NR
Haematocrit (day 15) (%)	37 ± 2	33 ± 2	NR	No significant difference (reported in text) *P* = NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to infants requiring major surgery.				
Applicability				
Evidence probably applicable to Australian health-care context with some caveats. The study was conducted in the USA (Level C).				
Comments				
A strict transfusion protocol was used to administer blood transfusions during the study period (transfusion criteria is provided in the paper). Participants were not transfused to replace blood lost through phlebotomy. The authors note that infants in the rHuEPO group were sicker than those in the placebo group because of the more critical nature of their illness. Although this was not intentional it did result in these infants requiring more frequent laboratory evaluation and a greater number and volume of blood transfusions. The authors recommend a longer administration period in order to more accurately test for differences in transfusions.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Chicella MF, Krueger KP (2006) Prospective Randomized Double-Blind Placebo Controlled Trial of Recombinant Human Erythropoietin Administration to Reduce Blood Transfusions in Anemic Pediatric Intensive Care Patients. J Pediatr Pharmacol Ther, 11: 101-106.				
Affiliation/Source of funds				
The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single PICU, USA	
Intervention	Comparator			
Intravenous rHuEPO (300units/kg/day) + oral ferrous sulphate (6mg elemental iron/kg/day)	Placebo (normal saline, equivalent volume) + oral ferrous sulphate (6mg elemental iron/kg/day)			
Population characteristics				
27 critically ill children ≤18 years of age admitted to PICU with Hct ≤30%. Exclusion criteria: complications associated with anaemia such as congestive heart failure, end-organ dysfunction, lactic acidosis, and/or hypovolemic shock; hypertension; sickle cell anaemia; thalassemia; malignancy; renal insufficiency (serum creatinine >2x the upper limit of age-related normal values); liver failure; imminent risk of death; sensitivity to rHuEPO or other mammalian cell derived products; patients prohibited from received blood transfusions and pregnant females.				
Length of follow-up	Outcomes measured			
NR (longest length of therapy was 23 days)	Primary: number of patients given RBC transfusion, number of RBC transfusions per patient Secondary: % Hct change, final Hct, % reticulocyte count change			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: a randomised, double-blind placebo-controlled trail of 27 critically ill anaemic children to examine the effect of rHuEPO + oral iron compared with iron only on the need for RBC transfusion. PICU attending physicians were blinded to the patient's treatment arm. No protocol was used to determine when to transfuse. RBC transfusions were administered on a case-by-case basis, based on the physician's impression of the patient's clinical status. However, the following guidelines were suggested: Hct <25% and the presence of metabolic acidosis, tachycardia, hypoxia and/or need for surgery. The study aimed to enrol 100 patients; however due to difficulty enrolling patients, the study was stopped prematurely. Analyses were underpowered due to the small sample sizes. Patients in the rHuEPO group remained in the study for a mean 9 days (SD 6), compared with 13 days for the control group (SD 8). This difference was not statistically significant (p=0.15).				
RESULTS				
Population analysed	Intervention (rHuEPO + iron)		Comparator (iron only)	
Randomised (n=27)	14		13	
Efficacy analysis (ITT)	14		13	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	rHuEPO+ iron n/N (%) Mean ± SD	Iron only n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				
Patients who received a RBC transfusion	3/14 (21%)	4/13 (31%)	NR	No significant difference *P* = 0.68
RBC transfusions per patient	0.2 ± 0.4 (14)	0.6 ± 1.2 (13)	NR	No significant difference *P* = 0.49

% Hct change	3.9 ± 4 (14)	1.2 ± 4.3 (13)	NR	No significant difference *P* = 0.14
Final Hct	30.3 ± 3.6 (14)	26.8 ± 4.8 (13)	NR	No significant difference *P* = 0.06
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill anaemic children (Level A).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA. (Level C).				
Comments				
The authors concluded that in this small group of anaemic paediatric intensive care unit patients, prophylactic rHuEPO administration did not reduce the number of patients who received RBC transfusions. Furthermore, it did not significantly increase Hct or reticulocyte count when compared with placebo.				

rHuEPO, recombinant human erythropoietin; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
El-Ganzoury M, Awad H, El-Farrash R, El-Gammasy T, Ismail E, Mohamed H and Suliman S. (2014) Enteral Granulocyte-Colony stimulating factor and Erythropoietin early in life improves feeding tolerance in preterm infants: A randomised controlled trial. The Journal of Pediatrics				
Affiliation/Source of funds				
The authors declare no conflicts of interest				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multiple NICUs, Egypt	
Intervention	Comparator			
rhG-CSF, rHuEPO, or both	Placebo (distilled water)			
Population characteristics				
90 preterm infants born at ≤33 weeks gestation age				
Length of follow-up	Outcomes measured			
7 days	Day of successful start of enteral feedings after drug/placebo administration, time to the end of total parental nutrition (TPN), weight gain, incidence of NEC, NEC related death, length of hospital stay, hospital readmission, adverse effects of treatment.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An interventional randomised control trial was conducted in 90 preterm infants born at ≤33 weeks gestational age. The neonates were randomly assigned to 4 groups: 20 received rhG-CSF, 20 received rHuEPO, 20 received both, and 30 received distilled water (placebo control). Allocation was via a predetermined schedule generated from random numbers in a 1:1 manner based on a computer-generated randomisation sequence maintained within the investigational drug pharmacy. Allocation concealment was achieved with the use of opaque sequentially numbered sealed envelopes. The study was double-blinded, but not stated whether outcome assessors were blind to treatment allocation. Serum granulocyte colony-stimulating factor and erythropoietin levels were measured on days 0 and 7 of treatment. A sample size of at least 20 neonates in each group was sufficient to detect a 30% difference in the time needed to achieve feedings.				
RESULTS				
Population analysed	Intervention (rHuEPO)		Comparator (Placebo)	
Randomised	20		30	
Efficacy analysis (ITT)	20		30	
Efficacy analysis (PP)	NR		NR	
Safety analysis	20		30	
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO vs placebo				
Mortality (n=50)	2/20 (10%)	3/30 (10%)	NR	No significant difference *P* = 0.92
NEC (n=50)	0/20 (0%)	3/30 (10%)	NR	No significant difference *P* = 0.165
Haemoglobin (g/dL) (n=50)	17.7 ± 5.5	15.4 ± 2.9	NR	No significant difference *P* = 0.27
rHuEPO + G-CSF vs G-CSF				

Mortality (n=40)	1/20 (5%)	2/20 (10%)	NR	No significant difference *P* = 0.92
NEC (n=40)	0/20 (0%)	0/20 (0%)	NR	No significant difference *P* = 0.165
Haemoglobin (g/dL) (n=40)	16.6±5.1	16.8±4.3	MD -0.20 [-3.12, 2.72)[a]	No significant difference *P* = 0.89[a]
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats (Level B).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site Egypt (Level C).				
Comments				
Note: we calculated p-values post-hoc using RevMan 5.1 and the data provided, and found values did not match those reported by the authors [insert values found]. The authors concluded that the risk of NEC was reduced from 10% in the placebo group to 0% in all treatment groups. The next step is to investigate the use of these growth factors as therapy in large randomised trials that include preterm infants with early-stage NEC and postoperative infants.				

rhG-CSF, growth– colony stimulating factor; ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; rHuEPO, recombinant human erythropoietin; SD, standard deviation.
a. Calculated post-hoc using RevMan 5.1

STUDY DETAILS: RCT				
Citation				
Fearon JA, Weinthal J (2002) The Use of Recombinant Erythropoietin in the Reduction of Blood Transfusion Rates in Craniosynostosis Repair in Infants and Children. Plastic and Reconstructive Surgery, 109(7): 2190-6.				
Affiliation/Source of funds				
The study was supported by a grant from Ortho Biotech Products, which makes erythropoietin.				
Study design	Level of evidence		Location/setting	
RCT	Level II		North Texas Hospital for Children, USA	
Intervention	Comparator			
Subcutaneous rHuEPO (epoetin alfa) at 600units/kg once per week for 3 weeks before surgery + oral elemental iron (4mg/kg/day)	No rHuEPO + oral elemental iron (4mg/kg/day)			
Population characteristics				
31 infants and children <8 years of age undergoing primary cranial vault remodelling. Exclusion criteria: re-operative cases.				
Length of follow-up	Outcomes measured			
NR	Primary: RBC transfusion Secondary: Hb level			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: an RCT of 31 infants and children undergoing primary cranial vault remodelling in the US, to examine the effect of rHuEPO + iron compared with no rHuEPO + iron on the need for RBC transfusion. A single craniofacial surgeon operated on all patients. All caregivers responsible for administering blood were blinded to treatment groups. There were strict criteria for blood transfusions: - Intraoperative: Hb <7.0 g/dL (Hct <21%), or Hb <8.0 gdL + a base deficit <-5.0mmol/L, sustained mean arterial blood pressure <50mmHg, urine output <0.25cc/kg/hr for 2hrs, significant decrease in oxygen saturation without a known respiratory cause, or loss of a dicrotic notch on the arterial line tracing. - Postoperative: Hb <7.0 g/dL, or <8.0 g/dL + haemodynamic instability. 67 children were eligible for inclusion; 28 did not participate due to earlier than planned surgery, and eight parents of children declined. Of the 31 patients who participated, 29 completed the study (one patient developed a respiratory infection leading to a delay in surgery, and one patient was excluded after lab results detected alpha-thalassemia). No adverse events related to rHuEPO were observed. No patient withdrew from the study.				
RESULTS				
Population analysed	Intervention (rHuEPO + iron)		Comparator (No rHuEPO + iron)	
Randomised	14		15	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs no rHuEPO + iron				
Patients who received a blood transfusion	8/14 (57.1%)	14/15 (93.3%)	NR	Favours rHuEPO + iron *P* = 0.03
Mean Hb (g/dL)	13.1	11.8	NR	NR

Mean difference in Hb level pre– and post-treatment (g/dL)	1.0	0.0	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric surgical patients undergoing primary cranial vault remodelling with some caveats (Level B).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA. (Level C)				
Comments				
The authors concluded that the preoperative administration or rHuEPO significantly raised Hb levels and reduced the need for a blood transfusion with craniosynostosis correction.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Griffiths G, Lall R, Chatfield S et al (1997) Randomized controlled double blind study of role of recombinant erythropoietin in the prevention of chronic lung disease. Archives of Disease in Childhood, 76: F190-2.				
Affiliation/Source of funds				
GG was funded by the Yorkshire Regional Health Authority.				
Study design	Level of evidence		Location/setting	
RCT	Level II		4x NICUs in Yorkshire, England.	
Intervention	Comparator			
rHuEPO (480units/kg/week) + oral iron (3.0mg/kg/day) from four weeks after birth.	Placebo (4% human serum albumin) + oral iron (3.0mg/kg/day) from four weeks after birth.			
Population characteristics				
43 VLBW (≤1500 g) and/or preterm (≤32 weeks gestational age) infants requiring mechanical ventilation and/or supplemental oxygen from birth until 7-14 days of life. Exclusion criteria: severe renal, hepatic or coagulation disorders, major congenital malformation, lack of written informed consent.				
Length of follow-up	Outcomes measured			
6 months of age.	Primary: number of days on mechanical ventilation and/or supplemental oxygen after randomisation. Secondary: incidence of chronic lung disease, number of blood transfusions, and volume to weight ratio of blood transfused.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A multicentre RCT in 4x NICUs in England of 43 VLBW and/or preterm infants requiring mechanical ventilation and/or supplemental oxygen, to examine the effect of rHuEPO plus oral iron compared with placebo on clinical outcomes. 43 infants were randomised. Stratified randomisation was used, accounting for participating centres, gestational age, and multiple births. Blinding was maintained throughout the study. One infant in the treatment group was ineligible and was subsequently excluded from analysis. One infant in the placebo group was discontinued after parental consent was withdrawn, but this infant was still included in the final analysis. The first injection was given on the day of randomisation (allocation concealment). The two groups were broadly similar at baseline, although the placebo group may have had more severe respiratory illness, as suggested by the higher proportion of infants in intermittent positive pressure ventilation. There were only a small number of infants remaining in the study at 3 months. A sensitivity analysis was carried out to assess the impact of deaths, by setting the duration of respiratory support for all infants who died to the maximum recorded. There were a total of 41 different types of adverse events, with infection (positive blood cultures), pneumonia, and patent ductus arteriosus being the most common.				
RESULTS				
Population analysed	Intervention (rHuEPO + iron)		Comparator (placebo)	
Randomised (n=43)	22		21	
Efficacy analysis (ITT)	21		21	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				
Chronic lung disease	7/21 (33.3%)	12/21 (57.1%)	Difference in proportions -0.24 [-53, 5.4]	NR

Blood transfusions	NR	NR	Difference in medians -2 [-4, 0]	NR
Volume : weight ratio (mL/kg) of blood transfused	NR	NR	Difference in medians -31 [-56, 4]	NR
Mortality (all)	6/21 (28.6%)	3/21 (14.3%)	NR	NR
Mortality due to septicaemia	3/21 (14.3%)	0/21 (0%)	NR	NR
Mortality due to CLD	2/21 (9.5%)	0/21 (0%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. Study site England (Level B).				
Comments				
The authors concluded that although there was a reduction in the need for blood transfusion, the dose of rHuEPO used in the study was relatively low. The authors could not explain why more deaths occurred in the treatment group, but in view of the small numbers involved, reported that it could be due to chance. rHuEPO seemed to reduce the number of days in oxygen for ill VLBW infants.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; rHuEPO, recombinant human erythropoietin; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Jacobs BR, Lyons K, Brilli RJ (2003) Erythropoietin therapy in children with bronchiolitis and anemia. Pediatric Critical Care Medicine, 4(1): 44-8.		
Affiliation/Source of funds		
The study was supported in part by a research grant from Ortho Biotech Products.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single PICU, USA
Intervention	Comparator	
Intravenous rHuEPO in a daily dose of 200 units/kg + enteral elemental iron (3mg/kg/day)	Intravenous albumin in a daily dose of 0.1mL/kg + enteral elemental iron (3mg/kg/day)	
Population characteristics		
44 critically ill children aged 1 month to 2 years diagnosed with bronchiolitis, acute respiratory failure, and anaemia. Bronchiolitis was defined as the presence of respiratory distress along with three of the following criteria: (a) history of upper respiratory tract infection within last 7 days, (b) bilateral expiratory wheezing and/or rales on auscultation, (c) hyperinflation along with patchy areas of infiltration or atelectasis on chest radiograph, (d) positive nasopharyngeal culture or endotracheal fluorescent antibody test for respiratory syncytial virus, parainfluenza or influenza. Anaemia was defined as haematocrit <2 SD below normal for age. Exclusion criteria: respiratory failure secondary to apnoea that was not preceded by respiratory distress, respiratory distress secondary to other known aetiologies, underlying chronic lung diseases, concurrent infections with other organisms, history of seizures, documented iron deficiency or haemolytic anaemia, treatment with experimental drugs within the past 30 days, known hypersensitivity to albumin or mammalian cell derived products, history of clinically significant isoimunisation, history of uncontrolled hypertension.		
Length of follow-up	Outcomes measured	
Patients discontinued dosing when their haematocrit was ≥35%. Additional lab data and blood transfusion requirement information were recorded until hospital discharge.	Primary: percentage of children requiring a blood transfusion. Secondary: haematocrit, reticulocyte count, ferritin, circulating rHuEPO, adverse events, PICU length of stay, ventilator days, oxygen days, change in heart rate.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: an RCT of 44 critically ill anaemic children with bronchiolitis and acute respiratory failure, to examine the effect of rHuEPO plus iron compared with placebo plus iron on transfusion requirement and other clinical outcomes. Upon entry into the study, patients were randomised using a random numbers table technique. Physicians and nurses were blinded to patient treatment group. The hospital pharmacists were unblinded and responsible for assigning patients to a treatment group according to the randomisation schedule. All patients received routine care for bronchiolitis and acute respiratory failure under the direction of the primary health care team. Transfusions were given when Hct fell <25% and who had a persistent supplemental oxygen requirements. Decisions to transfuse patients with Hct ≥25% were at the discretion of the primary care team. One child in the control group received a transfusion for a Hct ≥25% (26.5%), compared with no patients in the rHuEPO group. The study was stopped early after the interim analysis revealed no difference between the groups in terms of the primary outcome variable.		
RESULTS		
Population analysed	Intervention (rHuEPO + iron)	Comparator (placebo + iron)
Randomised	22	22
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Intervention n/N (%) Mean ± SD (n)	Comparator n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				
Mortality	0/22 (0%)	0/22 (0%)	NR	NA
Patients who received 1+ RBC transfusions	10/22 (45.5%)	11/22 (50.0%)	NR	No significant difference *P* > 0.05
RBC transfusion volume (mL/kg)	9.6 ± 0.5 (22)	10.4 ± 0.6 (22)	NR	No significant difference *P* > 0.05
Number of transfusions per patient	0.6 ± 0.2 (22)	0.7 ± 0.2 (22)	NR	No significant difference *P* > 0.05
Increase in Hct from admission to discharge (%)	7.1	4.4	NR	NR
Increase in serum ferritin from admission to discharge (ng/mL)	16.3	21.5	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill anaemic children with bronchiolitis and acute respiratory failure with some caveats (Level B).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors concluded that despite a favourable reticulocyte and circulating rHuEPO response, RBC transfusion requirements were not significantly diminished by rHuEPO treatment in children with bronchiolitis and respiratory failure. rHuEPO cannot be routinely recommended for this patient population.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Jim, W. T., Chen, L. T., Huang, F. Y., and Shu, C. H. (2000) The early use of recombinant human erythropoietin in anemia of prematurity. Clin.Neonatol. 7 (2) 12-16				
Affiliation/Source of funds				
Financial support was provided by the Premature Baby Foundation of Taiwan.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Taiwan	
Intervention	Comparator			
rHuEPO (SC injections of 200IU/kg 3 times a week for 6 weeks, beginning at 7 days of age) + oral iron (3mg/kg/day from 21 days of age)	Placebo (saline on the same schedule) + iron (3mg/kg/day from 21 days of age)			
Population characteristics				
23 premature infants <33 weeks gestation with birth weights <1500 g. Inclusion criteria: postnatal age >7days at the beginning of the study, no history if significant haemolytic disease caused by ABO or Rh incompatibility, absence of acquired or congenital infection, absence of seizures, absence of congenital malformations, absence of intraventricular haemorrhage above grade II, no severe renal , hepatic or homeostatic dysfunction, no respiratory distress syndrome requiring high concentrations of oxygen.				
Length of follow-up	Outcomes measured			
Six weeks	Laboratory data (haemoglobin, reticulocytes, haematocrit, neutrophils, platelets, iron metabolism), clinical monitoring (vital signs, blood pressure, weight gain), biochemical monitoring (liver function, renal function, electrolytes), volume of blood withdrawn for tests and frequency and volume of transfusions.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The study reports that infants were randomly assigned to two groups but the method of randomisation is not reported. Similarly, no method of allocation concealment is discussed in the article. The authors do not report if the study participants or investigators were blinded, or if outcomes assessed were blind to treatment allocation. Baseline characteristics and demographics were similar between treatment groups. No loss to follow-up is reported in the study but it is assumed all participants are included in the final analysis.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	12		11	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO vs placebo				
Number of transfusions per infant	1.3	1.8	NR	Favours rHuEPO $P < 0.05$
Volume of transfusions per infant (mL)	23	29	NR	Favours rHuEPO $P < 0.05$

Haemoglobin (g/dL) • After week 4 *data presented graphically for weeks 1-6	11.1	8.9	NR	Favours rHuEPO at weeks 4, 5 and 6 *P* < 0.05
Haematocrit (%) • After week 5 *data presented graphically for weeks 1-6	34.1	26.6	NR	Favours rHuEPO at weeks 5 and 6 *P* < 0.05
Serum ferritin (ng/mL) *data presented graphically for weeks 1-6	NR	NR	NR	Favours placebo at weeks 2, 4 and 6 *P* < 0.05
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to premature infants less than 33 weeks gestation and birth weight less than 1500 g.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in Taiwan (Level C).				
Comments				
The authors conclude that rHuEPO was well tolerated and resulted in a reduction in the number and volume of transfusions required. However, they also discuss the decrease in serum ferritin levels, acknowledging that the iron supplements used in the study may not have been adequate for optimal erythropoiesis. It is stated that further multicentre trials in this field are required, highlighting the importance of iron supplementation in such studies.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Juul SE (2003) Enterally dosed recombinant human erythropoietin does not stimulate erythropoiesis in neonates. The Journal of Pediatrics, 143(3): 321-6.				
Affiliation/Source of funds				
None reported. A portion of this work was conducted through the Clinical Research Center Facility at the University of Washington and supported by the National Institutes of Health, grants M01-RR– 00037 and RR00082.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single NICU, USA	
Intervention	Comparator			
rHuEPO (500unit/kg) 2x per day for 14 days + supplemental iron (1.0mg/kg/day)	Placebo (D_5W) for 14 days + supplemental iron (1.0mg/kg/day)			
Population characteristics				
VLBW (700–1500 g) neonates, receiving ≥ 30 mL/kg/day enteral feeding of human milk or infant formula and deemed noninfected by the attending neonatologist. Exclusion criteria: neonates receiving parenteral rHuEPO for prevention or treatment of anaemia of prematurity, if they had abdominal surgery during the first week of life, or if they had any congenital malformations involving the GI tract.				
Length of follow-up	Outcomes measured			
2 weeks.	Primary: corrected reticulocyte count at 14 days (% reticulocyte count x Hct/45) Secondary: Hct, serum Epo concentration, ZnPP/H (used to assess iron status), transfusion requirements.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: RCT of 32 VLBW neonates admitted to NICU in the US, to examine the effect of rHuEPO plus supplemental iron compared with placebo plus supplemental iron on clinical outcomes including transfusion requirements. Blinding and randomisation were reported, but details were not provided on who was blinded or the method of randomisation. 36 subjects were enrolled, and 32 completed the study (two subjects from each group withdrew). Eleven infants weighed between 700 and 1000 g at birth, and 21 infants weighed between 1001 and 1500 g. Infants in the rHuEPO group ranged from 2 to 8 weeks postnatal age at study entry, with a median of 4 weeks, whereas infants in the placebo group ranged from 1 to 7.4 weeks postnatal age, with a median of 2 weeks. By NICU policy, on admission, infants weighing ≤1000 g birth weight were assigned 1 unit of packed RBCs divided into 8 aliquots. Transfusions for all infants were given when Hct <20%, or Hct <30% or <35% with additional oxygen requirements. Note: data for Hct at baseline, 7 and 14 days were provided in graph form (not presented here).				
RESULTS				
Population analysed	Intervention (rHuEPO + iron)		Comparator (Placebo + iron)	
Randomised	15		17	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs Placebo + iron				
RBC transfusion volume (mL), during study (all patients)	9 ± 14	7 ± 12	NR	NR

RBC transfusion volume (mL), during study (patients 750-1000 g, n=11)	9 ± 11	16 ± 15	NR	NR
RBC transfusion volume (mL), during study (patients 1001-1500 g, n=21)	9 ± 15	2 ± 6	NR	NR
RBC transfusion volume (mL), after study (all patients)	15 ± 25	12 ± 24	NR	NR
RBC transfusion volume (mL), after study (patients 750-1000 g, n=11)	20 ± 33	22 ± 36	NR	NR
RBC transfusion volume (mL), after study (patients 1001-1500 g, n=21)	13 ± 21	6 ± 13	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW neonates with some caveats (Level B).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors concluded that enterally dosed rHuEPO (1000 units/kg/day) does not significantly influence erythropoiesis or iron utilisation when given for a 2-week period, nor does it elevate serum Epo concentration in preterm or term infants. Oral administration of rHuEPO is not an effective substitute for parenteral administration.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Khatami SF, Mamouri G, Torkaman M (2008) Effects of Early Human Recombinant Erythropoietin Therapy on the Transfusion in Healthy Preterm Infants. Indian Journal of Pediatrics, 75(12): 1227-30.				
Affiliation/Source of funds				
None reported. The authors are affiliated with Tehran University of Medical Sciences, Mashad University of Medical Sciences and Baghiatolah University of Medical Science.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Iran	
Intervention	Comparator			
Subcutaneous rHuEPO (500units/kg) 2x per week for 4 weeks or until discharge/transfer, plus enteral elemental iron (ferrous sulphate) at 3mg/kg/day.	No treatment plus enteral elemental iron (3mg/kg/day) from the second week of age.			
Population characteristics				
40 preterm infants (>28 and <34 weeks gestational age) with birth weight >1000 g to <1750 g, 48 to 96 hours old at study entry and likely to survive >72hrs as per the attending neonatologist. Informed consent from a parent or guardian was required. Exclusion criteria: major congenital malformation, evidence of coagulopathy, severe asphyxia, IVH grade 3 or 4, a positive antiglobulin test with clinical symptoms of haemolytic anaemia, surgical problems, exchange transfusion, severe cardiopulmonary disease requiring >40% head box oxygen or dependent on mechanical ventilation, systolic blood pressure >100mmHg (in the absence of pressor support), absolute neutrophil counts <500/μL.				
Length of follow-up	Outcomes measured			
4 weeks or until discharge/transfer.	Final Hct, final reticulocyte count, WBC count, platelet count, blood transfusion, transfusion number, weight gain, days of hospitalisation.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 40 preterm infants with birth weight 1001g to 1749g, to examine the effect of rHuEPO plus enteral elemental iron compared with no treatment plus enteral elemental iron on clinical outcomes including need for transfusion. Patients were randomised by means of numbered, sealed envelopes. Criteria for stopping rHuEPO administration in the treatment group included: neutropenia (ANC<500/μl), Hct >45% not attributable to transfusion with a reticulocyte count of 200,000 cells/μl or hypertension. rHuEPO was restarted when these conditions resolved. Treatment was also stopped when clinical seizures occurred or when hypertension or neutropenia persisted. All infants were enterally fed at a minimum of 100kcal/kg and received enteral supplements of folic acid (50μg/day), and a daily multivitamin containing Vitamin A (1500IU), vitamin D (400U), vitamin E (50U) and vitamin C (35mg). Guidelines for RBC transfusions were based on the relatively strict existing policy in the nursery. Infants who met transfusion criteria received a transfusion of 10-15 mL/kg RBCs. Note: the study population consisted of preterm infants who were growing and were in a stable condition at study commencement, and therefore had a lower risk of transfusion.				
RESULTS				
Population analysed	Intervention (rHuEPO + iron)		Comparator (No treatment + iron)	
Randomised	20		20	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs no treatment + iron				

Volume of RBC transfused per patient (mL)	4.02 ± 1.31	9.55 ± 5.85	NR	Borderline favours rHuEPO + iron *P* = 0.05
Number of transfusions per patient	2.20 ± NR	8.20 ± NR	NR	NR
Final Hct (%)	34.23 ± 6.6	29.73 ± 5.5	NR	Favours rHuEPO + iron *P* = 0.02
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats (Level B).				
Applicability				
Evidence not applicable to the Australian healthcare context. Study site Iran (Level D).				
Comments				
The authors concluded that the combination of early rHuEPO and iron as administered in the present study stimulated erythropoiesis and decreased RBC transfusion in premature infants who were 1000-1750 g birth weight. The enrolment of larger and healthier preterm infants, who were at lower risk of transfusion, is a limitation of the present study.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Kremenopoulos, G., Soubasi, V., Tsantali, C., Diamanti, E., and Tsakiris, D. (1997) The best timing of recombinant human erythropoietin administration in anemia of prematurity: A randomized controlled study. Int.J.Pediatr.Hematol.Oncol. 4 (4) 373-383				
Affiliation/Source of funds				
The authors are affiliated with the Department of Neonatology, First Pediatric Clinic, Renal Unit, University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Greece	
Intervention	Comparator			
Group A: rHuEPO (3 x 250U/kg/wk SC)+ oral iron supplements (3mg/kg/day) from the 15th day of life Group B: rHuEPO (3 x 200U/kg/wk SC)+ oral iron supplements (3mg/kg/day) from the 15th day of life	Group A: no rHuEPO early after birth for (3-7 days) for 6 weeks + oral iron supplements (3mg/kg/day) from the 15th day of life Group B: no rHuEPO after their problems had been resolved (3.4 ± 2.3 weeks of life until discharge and when they were receiving full enteral feeding + oral iron supplements (3mg/kg/day) from the 15th day of life			
Population characteristics				
Very low birth weight preterm infants. Inclusion criteria: gestational age at birth ≤31 weeks, birth weight ≤1500 g, no history of significant haemolytic disease caused by glucose-6-phosphate dehydrogenase deficiency, ABO or Rh incompatibility or other haemoglobinopathies and clinical stability at entry as judged by the absence of electrolyte-acid base disturbances, absence of acquired or congenital infections, good oxygenation either in mechanical ventilation or not and absence of seizures and hypertension.				
Length of follow-up	Outcomes measured			
Seven weeks	Daily vital signs including blood pressure recordings, number and duration of apnoeic episodes, bradycardias or tachycardias, daily weights, caloric intake and transfusion requirements			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: The study reports that infants were allocated to group A or B based on consecutive admission to the nursery. The authors report randomly assigning infants to either the intervention or control arm within each group, but the method of randomisation is not reported. Similarly, no method of allocation concealment is discussed in the article. The authors do not report if the study participants or investigators were blinded, or if outcomes assessed were blind to treatment allocation. Baseline characteristics and demographics were similar between treatment groups except for birth weight, which was higher in the control neonates without complications than the corresponding rHuEPO group. No loss to follow-up is reported in the study but it is assumed all participants are included in the final analysis. A subgroup analysis compared the neonates in Group A without complications and those with complications.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	Group A: 24 Group B: 20		Group A: 26 Group B: 15	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD (n)	Comparator n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs iron only				

Patients receiving transfusions				
-Group A Without complications	2/10 (20%)	9/12 (75%)	NR	Favours rHuEPO *P* < 0.01
-Group A With complications	14/14 (100%)	14/14 (100%)	NR	No significant difference[a]
-Group B	4/20 (20%)	13/15 (87%)	NR	NR
Transfusions per patient				
-Group A Without complications	0.2 ± 0.4 (10)	1 ± 0.7 (12)	NR	Favours rHuEPO *P* < 0.01
-Group A With complications	5 ± 2.5 (14)	4.9 ± 2.4 (14)	NR	No significant difference
-Group B	0.4 ± 0.9 (20)	1.8 ± 1.3 (15)	NR	Favours rHuEPO *P* = NR
Haemoglobin (g/L) (at end of treatment)				
-Group A Without complications	100 ± 9 (10)	87 ± 12 (12)	NR	Favours rHuEPO *P* < 0.05
-Group A With complications	111 ± 16 (14)	92 ± 21 (14)	NR	Favours rHuEPO *P* < 0.05
-Group B	96 ± 13 (20)	102 ± 24 (15)	NR	No significant difference *P* = NR
Haematocrit (%) (at end of treatment)				
-Group A Without complications	0.32 ± 0.03 (10)	0.26 ± 0.04 (12)	NR	Favours rHuEPO *P* < 0.01
-Group A With complications	0.36 ± 0.05 (14)	0.29 ± 0.07 (14)	NR	Favours rHuEPO *P* < 0.01
-Group B	0.29 ± 0.04 (20)	0.26 ± 0.03 (15)	NR	Favours rHuEPO *P* < 0.01
Ferritin (µg/L) (at end of treatment)				
-Group A Without complications	193 ± 161 (10	313 ± 139 (12)	NR	No significant difference *P* = NR
-Group A With complications	334 ± 165 (14)	470 ± 250 (14)	NR	No significant difference *P* = NR
-Group B	237 ± 184 (20)	267 ± 185 (15)	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to very low birth weight infants (≤1500 g) with gestational age at birth ≤31 weeks.				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. The study was conducted in Greece (Level B).				
Comments				
The neonates in group A were retrospectively classified into those without or with complications (mechanical ventilation ± sepsis). Neonates without or with minimal signs of respiratory distress and with no signs of sepsis were considered without complications. Neonates requiring mechanical ventilation (respiratory distress syndrome and sepsis based on positive blood cultures) for more than three days were classified as having complications. The authors concluded that rHuEPO should only be administered in neonates without complications or when complications				

have been resolved and full enteral feeding has been established. The authors suggest that rHuEPO therapy should be given until neonates are discharged from hospital.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation
a. Authors report that after rHuEPO was discontinued, rHuEPO group with complications had significantly lower need for transfusions than respective controls (0.2 ± 0.4 vs 1.4 ± 1.9) ($P < 0.05$)

STUDY DETAILS: RCT				
Citation				
Meister B, Maurer H, Simma B, Kern H, Ulmer H, Hittmair A, Fink FM (1997) The Effect of Recombinant Human Erythropoietin on Circulating Hematopoietic Progenitor Cells in Anemic Premature Infants. Stem Cells, 15:359-363				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Innsbruck University Hospital, Austria	
Intervention	Comparator			
rHuEPO (300IU/kg) 3x per week for 4 weeks + oral iron (6mg/kg/day) for 2 weeks, then 8mg/kg/day for 2 weeks.	Oral iron (6mg/kg/day) for 2 weeks, then 8mg/kg/day for 2 weeks.			
Population characteristics				
Thirty VLBW preterm infants, aged five to ten days, including those on ventilation or continuous positive airway pressure.				
Length of follow-up	Outcomes measured			
4 weeks	Volume of blood transfused, reticulocyte count, haematocrit, haemoglobin and erythrocyte values.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 30 VLBW preterm neonates, to examine the effect of rHuEPO + oral iron compared with oral iron only, on the volume of blood transfused and other laboratory measures. Infants were randomly assigned to the intervention or control group using a computerised random numbers generator. Blinding was not reported. Guidelines for transfusion: infants breathing spontaneously, whose fraction of inspired oxygen was <0.4, and signs of anaemia with Hb <11g/dL; or infants with no signs of anaemia, Hb <9g/dL and Hct <27%. A p-value <0.05 was considered statistically significant. One patient in the control group was withdrawn from the study because of development of intraventricular haemorrhage grade IV on study day 6.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	15		15	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	15		14	
Safety analysis	15		15	
Outcome	Intervention Median (IQR)	Comparator Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs iron				
Cumulative volume of blood transfused (mL/kg/day) (N=30)	0.0 (0.0, 0.47)	0.86 (0.5, 1.1)	NR	Favours rHuEPO + iron *P* = 0.038
Haematocrit (N=30)	NR	NR	NR	Favours rHuEPO + iron *P* = 0.003
Haemoglobin (N=30)	NR	NR	NR	Favours rHuEPO + iron *P* = 0.004
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				

Applicability
Evidence applicable to the Australian healthcare context with few caveats. Study site Austria (Level B).
Comments
The authors conclude using a relatively high dose of rHuEPO in premature infants, no significant in vivo effect on circulating peripheral blood progenitor or neutrophil count could be detected.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Ohls Robin K., Richard A. Ehrenkranz, Abhik Das, Anna M. Dusick, Kimberly Yolton, Elaine Romano, Virginia Delaney-Black, Lu-Ann Papile, Neal P. Simon, Jean J. Steichen and Kimberly G. Lee for the National Institute of Child Health and Human Development Neonatal Research Network (2004) Neurodevelopmental Outcome and Growth at 18 to 22 Months' Corrected Age in Extremely Low Birth Weight Infants Treated With Early Erythropoietin and Iron. Pediatrics 2004;114;1287 DOI: 10.1542/peds.2003-1129-L				
Affiliation/Source of funds				
This work was supported by a grant from the National Institutes of Health, National Institute of Child Health and Human Development, through cooperative agreements with the authors' institutions.				
Study design	Level of evidence		Location/setting	
RCT (follow-up of Ohls 2001)	Level II		Multicentre, USA	
Intervention	Comparator			
rHuEPO (23±10 doses at 400units/kg administered over an 8-10 week period) + parenteral iron (2±1 doses at 5mg/kg/week) 53% of rHuEPO doses were administered intravenously.	Parenteral iron (2±1 doses at 1mg/kg/week)			
Population characteristics				
102 ELBW (<1000 g) infants who were enrolled in the NICHD Neonatal Research Network Trial (Ohls 2001), followed up 18-22 months later.				
Length of follow-up	Outcomes measured			
18 to 22 months corrected age	Growth: weight, length, head circumference Neurodevelopmental outcomes: Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI), cerebral palsy, blindness, hearing loss, any neurodevelopmental impairment Post-discharge events: number transfused, number re-hospitalised			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: A follow-up of the Ohls 2001 RCT, to assess clinical outcomes of surviving ELBW infants who had been randomly assigned to either rHuEPO + parenteral iron or parenteral iron only at birth, to assess measures of morbidity including anthropometric and neurodevelopmental outcomes, and post-discharge events at 18-22 months corrected age. The original trial was a randomised, double-blinded multicentre trial. Full details were not reported in the current paper; readers should refer to Ohls 2001. Outcomes were assessed by certified examiners masked to treatment group. Fifteen patients from each group died before discharge. A limitation of this study was that only 70% of survivors were evaluated. Follow-up investigators generally seek to assess at least 80% of the potential study population to ensure that findings are generalisable, not affected by acquisition bias, and not prone to type I or II errors.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	Original trial: 87 Available for follow-up evaluation: 72		Original trial: 85 Available for follow-up evaluation: 70	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	51		51	
Safety analysis	15		15	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + Iron vs Iron only: reported in Ohls 2001:				

Mortality before discharge (N=172)	15/87 (17.2%)	15/85 (17.6%)	NR	NR
NEC (N=140)	4/72	6/68	NR	NR
BPD (N=140)	41/72	38/68	NR	NR
ROP ≥stage 3 (N=140)	13/72	10/68	NR	NR
Haematocrit at study end (%) (N=140)	35.0 (4.9)	30.3 (4.7)	NR	NR
Ferritin at study end (ng/mL) (N=140)	394 (1443)	417 (332)	NR	NR
At 18-22 month follow-up				
Number transfused between discharge and 18-22 month follow-up (N=102)	0/51 (0%)	0/51 (0%)	NR	NR
MDI <70 at 18-22 month follow-up (N=90)	14/45 (31.1%)	16/45 (35.6%)	NR	NR
PDI <70 at 18-22 months follow-up (N=90)	14/45 (31.1%)	6/45 (13.3%)	NR	NR
Any neurodevelopmental impairment at 18-22 month follow-up (N=99)	21/48 (43.8%)	23.51 (45.1%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW preterm infants (Level A).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA. (Level C)				
Comments				
The authors conclude that treatment of ELBW infants with early rHuEPO and iron does not significantly influence anthropometric measurements need for rehospitalisation and transfusions after discharge or developmental outcome at 18 to 22 months' corrected age.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Ovali Fahri, Nedim Samanci and Türkan Dağoğlu (1995) Management of Late Anemia in Rhesus Hemolytic Disease: Use of Recombinant Human Erythropoietin (A Pilot Study) Pediatric Research (1996) 39, 831–834;				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		NR	
Intervention	Comparator			
rHuEPO (200U/kg) 3x per week for 6 weeks + iron (3mg/kg/day)	Placebo (saline) 3x per week for 6 weeks + iron (3mg/kg/day)			
Population characteristics				
Twenty preterm infants aged 14 days who had Rh isoimmunisation diagnosed in utero.				
Length of follow-up	Outcomes measured			
4 months	Erythrocyte transfusion, Hb level, reticulocyte, platelet and neutrophil counts.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 20 preterm infants with Rhesus Haemolytic Disease to examine the effect of rHuEPO + iron compared with placebo + iron on the need for RBC transfusion. The study is reported as a double blind, placebo-controlled randomised pilot study. The drugs were prepared in sets of small vials and numbered randomly from 1 to 20. Only the pharmacist was aware of the content of the vials, the investigators and the administrators were blinded. The number of intrauterine and exchange transfusions and demographic data were similar in both groups at baseline.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	10		10	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				
RBC transfusions per patient (N=20)	1.8	4.2	NR	Favours rHuEPO + iron $P < 0.05$
Hb level (mmol/L) at 10 weeks *estimated from graph.	~1.8	~1.6	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with Rhesus Haemolytic Disease (Level A).				
Applicability				
Evidence may or may not be applicable to Australian healthcare context. Study site not specified.				
Comments				
The authors concluded that rHuEPO treatment decreases the need for erythrocyte transfusions in late anaemia of infants with Rh isoimmunisation.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Pape L, Ahlenstiel T, Kreuzer M et al (2009). Early erythropoietin reduced the need for red blood cell transfusion in childhood haemolytic uremic syndrome – a randomised prospective pilot trial. Pediatric Nephrology, 24: 1061-4.				
Affiliation/Source of funds				
The study was supported by a grant from Hoffmann la Roche AG Germany.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Single centre, Germany		
Intervention	Comparator			
Early administration of rHuEPO within 3 hours of hospital admission, plus rHuEPO (33 I.E./kg/week) for four weeks.	Conservative therapy without rHuEPO (standard therapy)			
Population characteristics				
10 children aged 1 to 6 years with proven enterohemorrhagic *E. coli* (EHEC)-positive haemolytic uremic syndrome (HUS), or likely EHEC infection and bloody diarrhoea. Exclusion criteria: children who had received transfusions for any other disease in the 90 days prior to study commencement, children with pre-existing renal disease or secondary/recurrent HUS.				
Length of follow-up	Outcomes measured			
4 weeks.	Primary: RBC transfusion Secondary: adverse events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 10 children in Germany with EHEC infection and HUS, to examine the effect of early administration of rHuEPO compared with no rHuEPO on RBC transfusion requirements. The sample size was calculated by power analysis suspecting a 50% reduction of the need for RBC transfusions in patients in the intervention group. The median age of children was 2 years in the treatment group (range 1-3 years), and 2 years in the control group (range 1-6 years). Hb levels between groups were comparable at baseline. RBC transfusion (10 mL/kg) was performed when Hb dropped <5mg/dl. One child in each group received no dialysis therapy. There were no protocol violations. No side effects, adverse events or central nervous system events were recorded in either group.				
RESULTS				
Population analysed	Intervention (Early rHuEPO)		Comparator (No rHuEPO	
Randomised	5		5	
Efficacy analysis (ITT)	5		5	
Efficacy analysis (PP)	5		5	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO vs placebo: Clinical outcomes				
Children who received one or more RBC transfusions	1/5 (20%)	4/5 (80%)	NR	NR
Mean number of RBC transfusions per child	0.2	1.4	NR	Favours early rHuEPO *P* = 0.04
Haemoglobin (mg/dL) at discharge	9.2	8.4	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				

Evidence directly generalisable to children with haemolytic uremic syndrome with some caveats (Level B).
Applicability
Evidence applicable to Australian healthcare context with few caveats. Study site was Germany (Level B).
Comments
The authors concluded that the early administration of rHuEPO at the time of HUS and beginning of renal failure may attenuate renal anaemia in children with EHEC-induced HUS and thereby reduce the number of RBC transfusions required. The authors note that results should be confirmed in a larger multicentre trial.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Porter JC, Leahey A, Polise K, Bunin G, Manno CS (1996) Recombinant human erythropoietin reduces the need for erythrocyte and platelet transfusions in pediatric patients with sarcoma: A randomized, double-blind, placebo-controlled trial. The Journal of Pediatrics, 129(5): 656-60.		
Affiliation/Source of funds		
Support was received from Ortho Biotech, New Jersey.		
Study design	Level of evidence	Location/setting
RCT	Level II	USA
Intervention		Comparator
Subcutaneous rHuEPO (150units/kg) 3x per week for 16 weeks + oral iron as ferrous sulphate (6mg/kg/day) Note: If the patient required transfusion or did not maintain Hb>11.5mg/dL after 4 weeks, rHuEPO dose was increased by increments of 50units/kg (max 300units/kg). If Hb increased to >16.5mg/dL, rHuEPO was withheld until Hb decreased to <11.5mg/dL. Iron therapy was discontinued if serum ferritin exceeded 1000 ng/mL.		Placebo (saline) + oral iron as ferrous sulphate (6mg/kg/day) Note: iron therapy was discontinued if serum ferritin exceeded 1000 ng/mL.
Population characteristics		
24 pediatric patients aged 6 months to 18 years with malignant sarcomas and receiving cyclic chemotherapy, with Hb<10.5mg/dL, anaemia unrelated to blood loss, haemolysis or vitamin deficiency. Exclusion criteria: clinically unstable for 1 month preceding study start, abnormal blood pressure (>90%) for age, history of any primary hematologic disease, seizure disorder, serum creatinine >2.0mg/dL, cerebral or bone metastases.		
Length of follow-up	Outcomes measured	
16 weeks.	Primary: RBC transfusion requirements Secondary: platelet transfusion requirements	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: An RCT of 24 pediatric cancer patients with anaemia and receiving chemotherapy, to examine the effect of rHuEPO + iron compared with iron only, on the need for RBC transfusion. Due to poor enrolment during the first 8 months, the protocol was amended to allow either subcutaneous or intravenous administration or rHuEPO. 24 children were enrolled. Patients were randomised using a computer-generated list of random numbers. Single-dose vials of rHuEPO and placebo were labelled identically. At the end of the 16 week study period, the patient's treatment assignment was revealed to both the patient and the investigator. The median dose of rHuEPO received during the 16-week period was 198units/kg 3x per week. Four patients did not complete the study and were unavailable for final analysis; reasons provided: conflicting drug protocols, protocol violation, parental request, death as a result of progressive malignancy. The study estimated 10 patients would be required per treatment arm to achieve 80% power to detect a 70% risk reduction in RBC transfusions.		
RESULTS		

Population analysed	Intervention (rHuEPO + iron)		Comparator (Placebo + iron)	
Randomised (n=24)	NR		NR	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	10		10	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Median (range)	Comparator n/N (%) Median (range)	Risk estimate (95% CI)	Statistical significance *P*-value
rHuEPO + iron vs placebo + iron				

Patients receiving RBC transfusion	9/10 (90%)	10/10 (100%)	NR	NR
Patients receiving a platelet transfusion	3/10 (30%)	9/10 (90%)	NR	NR
Units of RBCs transfused	4.5 (0-9)	13 (2-22)	NR	Favours rHuEPO + iron *P* = 0.01
Volume or RBCs transfused (mL/kg)	23 (0-118)	80 (18-226)	NR	Favours rHuEPO + iron *P* = 0.02
Units of platelets transfused	0 (0-3)	4 (0-17)	NR	Favours rHuEPO + iron *P* = 0.005
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric cancer patients with anaemia (Level A).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA. (Level C)				
Comments				
The authors concluded that treatment with rHuEPO and iron significantly reduces RBC transfusions in pediatric patients receiving concomitant chemotherapy for malignant sarcomas. A decrease in the number of platelet transfusions was also seen and deserves further study.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Warady, B. A., Kausz, A., Lerner, G., Brewer, E. D., Chadha, V., Brugnara, C., Dahl, N. V., and Watkins, S. L. (2004) Iron therapy in the pediatric hemodialysis population. Pediatr.Nephrol. 19 (6) 655-661				
Affiliation/Source of funds				
The study was supported by a grant from Watson Laboratories. The authors are affiliated with the Section of Nephrology, Children's Mercy Hospital, Kansas City, Missouri, USA.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Pediatric nephology centres, USA	
Intervention	Comparator			
12 doses of weekly IV iron dextran (infused over 30-60 mins at weekly intervals for 6 weeks, weight-based dosing <20kg: 25mg/week, 20-40kg: 50mg/week, >40kg: 100mg/week)	Daily oral ferrous fumarate (4-6mg/kg/day of elemental iron)			
Population characteristics				
Paediatric patients with end stage renal disease (ESRD) who were >1 year to <20 years of age, had received chronic haemodialysis for >2 months, had a baseline serum transferrin saturation >20%, were receiving maintenance doses of rHuEPO by the IV or SC route with a stable dose for >4 weeks prior to study entry and had a single pool Kt/V_{urea} >1.2 or a urea reduction ratio >60%. Exclusion criteria: anaemia of non-renal aetiology, the presence of active infection or inflammation (including sepsis, bacteraemia and graft/line infection within 4 weeks of enrolment), human immunodeficiency virus infection, malignancy, a history of a serious adverse reaction to IV iron, iron overload (serum ferritin >800ng/mL) at study initiation, severe hyperparathyroidism (intact parathyroid hormone >1000pg/mL) and uncontrolled hypertension (defined as repeated systolic and/or diastolic blood pressure >95th percentile for age post dialysis, despite the use of antihypertensive medication. There were no restrictions with respect to concomitant therapy, except for the use of oral iron supplements during IV iron therapy. Patients in either treatment group may have received IV iron prior to study entry.				
Length of follow-up	Outcomes measured			
16 weeks	Laboratory assessments (haematocrit, haemoglobin, serum iron status, serum ferritin, serum transferrin saturation, reticulocyte haemoglobin content, intact parathyroid hormone, pre and post dialysis blood urea nitrogen level), adverse events.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Patients were randomised using a random numbers table but no method of allocation concealment was described. It is not reported whether subjects and investigators were blinded to treatment arm. Baseline characteristics were similar between the groups. Loss to follow-up was not reported but it is assumed that all patients completed the study. Participants were recruited from the dialysis units of five paediatric nephrology centres. However, results are only reported collectively, rather than by recruitment site so it is not known if results were comparable.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	17		18	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
IV iron vs oral iron				
Blood transfusion	0	0	NR	*P* = NR

Haemoglobin (g/dL) change from beginning to end of study	-0.15 ± 2.55	-0.17 ± 1.89	NR	*P* = NR
Haematocrit (%) change from beginning to end of study	-0.48 ± 7.71	-0.81 ± 5.98	NR	*P* = NR
Ferritin (ng/mL) change from beginning to end of study	120.6 ± 133.7	-16.7 ± 94.3	NR	Favours IV iron *P* = 0.001
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to paediatric patients with end stage renal disease (ESRD) receiving chronic haemodialysis.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in the USA (Level C).				
Comments				
The doses of rHuEPO were adjusted every two weeks during the trial, as per standard clinical practice, to maintain target haemoglobin and haematocrit levels. All patients in the IV iron group received rHuEPO by the IV route, while 5 patients in the oral iron group received rHuEPO by the SC route. It was reported that all patients were compliant with the allocated treatment.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Oral and/or parenteral iron

STUDY DETAILS: RCT				
Citation				
Berseth, C. L., Van Aerde, J. E., Gross, S., Stolz, S. I., Harris, C. L., and Hansen, J. W. (2004) Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier. Pediatrics 114 (6) e699-e706				
Affiliation/Source of funds				
This study was supported by a grant from Mead Johnson Nutritionals.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Multicentre study, Canada and USA	
Intervention	Comparator			
Iron fortified powdered human milk fortifier test product (HMF-T)	Powdered commercially available human milk fortifier control product (HMF-C)			
Population characteristics				
Very low birth weight infants (≤1500 g), a gestational age ≤33 weeks postmenstrual age and an enteral intake of at least 100 mL/kg/day of unfortified human milk. Exclusion criteria: underlying disease or congenital malformation that was likely to interfere with growth or tolerance of fortified human milk, a 5 minute AGPAR score ≤4, undergone major surgery or received a diagnosis of grade 3 or 4 intraventricular haemorrhage before or on study day 0, received pharmacologic doses of glucocorticoids on >4 different days before study day 0 or on or within 72 hours of study day 0, consumed any marketed human milk fortifier (HMF) before or on study day 0, a feeding intolerance to human milk, received erythropoietin therapy, oral vitamin D, minerals or iron on study day 0 or ventilator dependence on study day 0 (≤40% fraction of inspired supplemental oxygen and/or nasal continuous positive airway pressure were allowed).				
Length of follow-up	Outcomes measured			
28 days	Growth, enteral and parenteral intake, serum chemistry and haematologic values, clinical histories, including the administration of blood transfusions, feeding tolerance, respiratory outcomes and morbidities.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Infants were stratified by gender and birthweight (≤1000 or >1000 g) before being randomised. A randomisation schedule was used to maintain a balance between each stratification level. However, no further detail was provided on the method of randomisation, nor was any attempt at allocation concealment reported. The study was double-blind and baseline characteristics were similar between treatment groups. The study was conducted across multiple sites but the results are presented collectively, rather than by study location, so it is not possible to determine if the results were comparable for all sites. A subgroup analysis of infants who met more stringent criteria is presented for the outcomes of growth and energy intake only.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	96		85	
Efficacy analysis (ITT)	96		85	
Efficacy analysis (PP)	55		39	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD Median (IQR)	Comparator n/N (%) Mean ± SD Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
Human milk fortifier test (HMF-T) vs human milk fortifier control (HMF-C)				
Receiving blood transfusions				

-From study day 0 through to 14	30/96 (31.3%)	27/85 (31.8%)	NR	No significant difference (reported in table) *P* = NR
-From study day 15 through to 28	12/96 (12.5%)	20/85 (23.5%)[a]	NR	Favours HMF-T *P* = 0.014
Suspected necrotising enterocolitis	6/96 (6.3%)	4/85 (4.7%)	NR	*P* = NR
Confirmed necrotising enterocolitis	1/96 (1.0%)	1/85 (1.2%)	NR	*P* = NR
Apnea or bradycardia or required supplemental oxygen or mechanical ventilation	*quantitative data not reported	*quantitative data not reported	NR	No significant difference (reported in text) *P* = NR
Laboratory measures				
Haematocrit (%) -Study day 14 *HMF-T: n=67 *HMF-C: n=55	30.0 (26.2-34.0)	29.4 (25.1-34.0)	NR	No significant difference (reported in table) *P* = NR
Haematocrit (%) -Study day 28 *HMF-T: n=43 *HMF-C: n=32	27.0 (24.0-29.6)	26.0 (24.0-31.0)	NR	No significant difference (reported in table) *P* = NR
Ferritin (ng/mL) -Study day 0 *HMF-T: n=80 *HMF-C: n=78	207.5 (155-325)	272.5 (175-350)	NR	No significant difference (reported in table) *P* = NR
Ferritin (ng/mL) -Study day 14 *HMF-T: n=66 *HMF-C: n=53	100.0 (54-200)	120.0 (68-205)	NR	No significant difference (reported in table) *P* = NR
Ferritin (ng/mL) -Study day 28 *HMF-T: n=22 *HMF-C: n=19	77.0 (37-155)	92.0 (33-110)	NR	No significant difference (reported in table) *P* = NR
Growth measures				
Weight gain (g/kg per day)	17.5 ± 0.53	17.3 ± 0.59	NR	No significant difference *P* = 0.63
Weight gain (g/kg per day) Subgroup analysis	17.4 ± 0.60	17.6 ± 0.63	NR	No significant difference *P* = NR
Achieved weight	*only reported graphically	*only reported graphically	NR	No significant difference *P* = NR
Achieved length	*only reported graphically	*only reported graphically	NR	No significant difference *P* = NR
Achieved head circumference	*only reported graphically	*only reported graphically	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to very low birth weight infants.				

Applicability
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in the Canada (Level B) and the USA (Level C).
Comments
The HMF-T and HMF-C products were administered as a supplement to the infant's human milk feedings.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.
a. Reported as 32% in study report

STUDY DETAILS: RCT				
Citation				
Franz, A. R., Mihatsch, W. A., Sander, S., Kron, M., and Pohlandt, F. (2000) Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. Pediatrics 106 (4 I) 700-706				
Affiliation/Source of funds				
No source of funds listed. The authors are affiliated with the Department of Pediatrics, Division of Neonatology and Pediatric Critical Care and the Department of Biometry and Medical Documentation, University of Ulm, Ulm, Germany.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Germany, neonatal referral centre	
Intervention	Comparator			
Early enteral iron supplementation (enteral iron supplementation starting at 2mg/kg/day as soon as 100 mL/kg/day of enteral feedings were tolerated) *The dose was increased to 4mg/kg/day when haematocrit fell below .30	Late enteral iron supplementation (enteral iron supplementation of 2mg/kg/day at 61 days of life) *The dose was increased to 4mg/kg/day if iron deficiency was diagnosed at any time			
Population characteristics				
Infants with a birthweight of <1301g. Exclusion criteria: major anomalies, haemolytic disease, twin-to-twin transfusion syndrome and missing parental consent.				
Length of follow-up	Outcomes measured			
61 days	Primary outcomes: ferritin, number of infants who fulfilled the criteria of iron deficiency at any time Secondary outcomes: transferrin saturation, haematocrit, reticulocyte count, mean corpuscular volume, mean corpuscular haemoglobin, number of infants who required transfusions and blood volume transfused			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Infants were assigned to 1 of 2 strata, depending on the need for blood transfusions within the first 7 days of life (stratum 1: no blood transfusion, stratum 2: ≥ 1 transfusion within the first 7 days of life). At day 7 of life, infants were randomised in blocks of 10 within each stratum to the treatment groups. However, the method of randomisation is not reported. Similarly, no attempt at allocation concealment is reported in the study. The participants were not blinded but laboratory staff were reported to be unaware of treatment allocation. Baseline characteristics were similar across a number of variables including gestational age, birthweight and markers of nutritional iron status. However, there was a trend towards more infants with chronic lung disease and severe retinopathy of prematurity in the late iron group. Loss to follow-up was reported and appropriately accounted for in the analysis.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	105		99	
Efficacy analysis (ITT)	105		99	
Efficacy analysis (PP)	68		65	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD Median (Range)	Comparator n/N (%) Mean ± SD Median (Range)	Risk estimate (95% CI)	Statistical significance *P*-value
Early iron vs late iron				
Infants transfused after day 14	41/105 (39.0%)	53/99 (53.5%)	NR	No significant difference *P* = 0.068

Infants transfused after day 14 (study completed)	29/68 (42.6%)	44/65 (67.7%)	NR	Favours early iron *P* = 0.0052
Volume transfused day 14 to 68 (mL/kg)	15.4 ± NR 0 (0-99)	25.7 ± NR 21 (0-128)	NR	Favours early iron *P* = 0.023[a]
Volume transfused day 14 to 68 (mL/kg) (study completed)	15.8 ± NR 0 (0-78)	31.7 ± NR 27 (0-108)	NR	Favours early iron *P* = 0.0014[a]
Mortality (all-cause)	2/105	2/99	NR	NR
Infants with iron deficiency	10/68 (14.7%)	26/65 (40.0%)	NR	*P* = NR
Ferritin at day 61	87.8 ± NR 45 (9-478) n=65	74.2 ± NR 51 (9-682) n=60	NR	No significant difference *P* = 0.98
Haematocrit at day 61 (L/L)	0.291 ± NR 0.28 (0.21-0.44) n=67	0.295 ± NR 0.28 (0.20-0.42) n=63	NR	No significant difference *P* = 0.77
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to infants with a birth weight <1301g.				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. The study was conducted in Germany (Level B).				
Comments				
Infants of both treatment groups received either protein and energy enriched milk from their mother or an iron fortified preterm infant cow's milk formula. In both treatment groups, iron was administered with the milk feeds. Loss to follow-up was high (>30% in each treatment arm).				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.
a. Not clear which value (mean / median) the p-value refers.

STUDY DETAILS: RCT				
Citation				
Fujiu T, Maruyama K, Koizumi T (2004) Oral iron supplementation in preterm infants treated with erythropoietin. Pediatrics International, 46: 635-9.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		NICU at Gunma Children's Medical Center, Japan.	
Intervention	Comparator			
Oral iron supplementation (4mg/kg/day) + subcutaneous rHuEPO 2x per week at 200 IU/kg for 8 weeks, or until hospital discharge.	Subcutaneous rHuEPO 2x per week at 200 IU/kg for 8 weeks, or until hospital discharge.			
Population characteristics				
24 VLBW (750-1499g) preterm infants with postnatal age 14-28 days and Hb <12g/dL. Exclusion criteria: major congenital malformation disease involving any of the major organ systems, haemolytic disease, culture-proven infection, or need for aggressive respiratory support (FiO_2>0.4, peak inspiratory pressure >20mmHg, or dependence on high frequency oscillatory ventilation). Infants were also excluded who did not have written parental consent.				
Length of follow-up	Outcomes measured			
1 month	Treatment success (no need for transfusion and Hb concentration never <8g.dL), need for RBC transfusion, Hb concentration, reticulocyte count, corpuscular volume, changes in iron status (ferritin, serum iron, transferrin saturation), adverse events including BPD and ROP.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: an RCT of 24 VLBW preterm anaemic infants, to examine the effect of oral iron supplementation + rHuEPO compared with rHuEPO only, on the need for RBC transfusion and Hb concentration. All infants were fed with either human milk or premature formula which contained 1.5mg iron per 100 mL. Packed RBC (10mg/kg) were given when Hb fell <7g/dL, or when infants displayed signs of anaemia e.g. need for additional oxygen supplementation +5% due to respiratory distress. One infant in the control group had a blood transfusion before study entry. The median (range) number of doses of rHuEPO administered were 15 (10-21) in the iron group and 16 (12-22) in the control group (p=0.68).				
RESULTS				
Population analysed	Intervention (Iron + rHuEPO)		Comparator (rHuEPO only)	
Randomised	12		12	
Efficacy analysis (ITT)	12		12	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Median (IQR)	Comparator n/N (%) Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
Iron + rHuEPO vs rHuEPO only				
Treatment success (no need for transfusion and Hb >8g/dL)	9/12 (75.0%)	8/12 (66.7%)	NR	No significant difference *P* > 0.99
RBC transfusion	0/12 (0%)	0/12 (0%)	NR	NA
ROP	3/12 (25.0%)	7/12 (58.3%)	NR	No significant difference *P* = 0.21

BPD (oxygen dependence at 36 weeks postconceptual age)	1/12 (8.3%)	2/12 (16.7%)	NR	No significant difference *P* > 0.99
Mortality	1/12 (8.3%)	0/12 (0%)	NR	NR
Hb (g/dL), 2 weeks	10.3 (9.8–10.4)	9.3 (8.9–10.1)	NR	No significant difference *P* = 0.16
Hb (g/dL), 4 weeks	9.3 (8.9–10.0)	9.4 (8.2–9.9)	NR	No significant difference *P* = 0.64
Hb (g/dL), 8 weeks (study exit)	9.9 (9.5–10.0)	9.7 (9.2–10.1)	NR	No significant difference *P* = 0.73
Hb (g/dL), 1 month follow-up	10.9 (10.6–12.1)	11.8 (10.6–12.4)	NR	No significant difference *P* = 0.59
Ferritin (ug/dL), 2 weeks	167 (94–296)	125 (60–276)	NR	No significant difference *P* = 0.46
Ferritin (ug/dL), 4 weeks	115 (79–146)	66 (42–139)	NR	No significant difference *P* = 0.25
Ferritin (ug/dL), 8 weeks (study exit)	104 (87–176)	52 (40–80)	NR	Favours iron + rHuEPO *P* = 0.03
Ferritin (ug/dL), 1 month follow-up	69 (52–91)	34 (21–45)	NR	Favours iron + rHuEPO *P* = 0.01
Serum iron (ng/mL), 2 weeks	52 (31–62)	54 (51–60)	NR	No significant difference *P* = 0.75
Serum iron (ng/mL), 4 weeks	57 (45–63)	68 (55–86)	NR	No significant difference *P* = 0.17
Serum iron (ng/mL), 8 weeks (study exit)	69 (60–86)	87 (71–103)	NR	No significant difference *P* = 0.15
Serum iron (ng/mL), 1 month follow-up	83 (61–94)	65 (59–83)	NR	No significant difference *P* = 0.59
Transferrin saturation (%), 2 weeks	36.1 (30.8–46.9)	28.4 (22.3–34.6)	NR	No significant difference *P* = 0.08
Transferrin saturation (%), 4 weeks	43.9 (31.4–51.6)	35.5 (29.0–40.5)	NR	No significant difference *P* = 0.27
Transferrin saturation (%), 8 weeks (study exit)	36.4 (29.4–53.5)	38.8 (27.3–50.5)	NR	No significant difference *P* = 0.54
Transferrin saturation (%), 1 month follow-up	24.4 (20.6–28.4)	20.0 (17.1–24.2)	NR	No significant difference *P* = 0.33
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants (Level A).				
Applicability				
Evidence applicable to Australian healthcare context with few caveats. Study site Japan. (Level B)				
Comments				
The authors concluded that there is not a clear advantage in a moderate dose or oral iron supplementation on erythropoiesis in rHuEPO-treated VLBW infants. Whether a higher dose would lead to enhanced erythropoiesis remains to be answered.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Taylor TA and Kennedy K A. Randomized Trial of Iron Supplementation versus Routine Iron Intake in VLBW Infants. (2013). Pediatrics 2013;131;e433; originally published online January 21, 2013; DOI: 10.1542/peds.2012-1822				
Affiliation/Source of funds				
Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose. Funding: No external funding.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Children's Memorial Hermann Hospital, USA	
Intervention	Comparator			
Iron supplementation (2mg/kg/day) + feeding with routine iron fortified milk (formula or fortified mother's milk) equivalent to ≥2mg/kg/day	No iron supplementation + feeding with routine iron fortified milk (formula or fortified mother's milk) equivalent to ≥2mg/kg/day			
Population characteristics				
150 VLBW (<1500 g) preterm infants (inborn or outborn) who reached 120 mL/kg/day of feedings before 32 weeks postmenstrual age. Exclusion criteria: infants with bowel resection or cyanotic heart disease. Written informed parental consent was required for all infants before enrolment.				
Length of follow-up	Outcomes measured			
Until 36 weeks postmenstrual age (PMA) or discharge	Primary: Hct at ≥36 weeks PMA Secondary: Mortality, number of blood transfusions, Bronchopulmonary dysplasia (BPD), sepsis, necrotising enterocolitis (NEC), apnoea of prematurity and growth.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: An RCT of 150 VLBW (<1500 g) preterm infants to determine if iron supplementation of 2 mg/kg per day, in addition to routine iron fortified formula or mother's milk, increased haematocrit (Hct) at 36 weeks' postmenstrual age (PMA). Infants were assigned to 1 of 2 strata according to gestational age (GA) by dates of birth (<27 weeks GA and ≥27 weeks GA). Once infants reached 120 mL/kg/day of feedings, they were randomly allocated via a computer-generated randomisation table with variable block size to the intervention or control group in a 1:1 ratio. Enrolling investigators were masked to the allocation sequence. Study investigators, clinicians, and parents were masked to group assignment until study data collection was complete. It is possible that bedside nurses who administered the medication could have identified differences in the appearance or smell of the preparations with and without iron, but there were no known episodes of unmasking of physicians or nurse practitioners. Multiple births were randomly assigned separately. A sample size of 75 per group was calculated to achieve 80% power to detect a difference in Hct of 2% between groups. Compliance with the study intervention and transfusion guideline was monitored during the intervention period.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	76		74	
Efficacy analysis (ITT)	76		74	
Efficacy analysis (PP)	69		67	
Safety analysis	1		1	
Outcome	Intervention n/N (%) Mean ± SD (n) Median (IQR)	Comparator n/N (%) Mean ± SD (n) Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
Iron supplementation vs no iron supplementation				
Mortality (N=150)	1/76 (1.3%)	1/74 (1.4%)	NR	*P* = NR

Transfusion incidence (N=150)	47/76 (61.8%)	53/74 (71.6%)	NR	*P* = NR
BPD (N=145)	27/74 (36%)	27/71 (38%)	RR 0.96 [0.63, 1.46]	No significant difference *P* = 0.85
Medical NEC (N=150)	7/76 (9%)	6/74 (8%)	RR 1.14 [0.40, 3.22]	No significant difference *P* = 0.81
Surgical NEC (N=150)	5/76 (7%)	2/74 (3%)	RR 2.43 [0.49, 12.16]	No significant difference *P* = 0.26
Number of transfusions per patient (N=150)	1 (0–2)	1 (0–2)	Median difference 0 (0–1)	No significant difference *P* = 0.64
Haematocrit at 36 weeks PMA (N=150)	29.2 ± 6 4.0 (75)	28.3 ± 4.5 (73)	Mean difference 0.9 (-0.5–2.3)	No significant difference *P* = 0.21
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW (<1500 g) preterm infants with some caveats (Level B).				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. Study site USA (Level C).				
Comments				
The authors concluded that among VLBW (<1500 g) infants, iron supplementation, in addition to routine iron intake, did not significantly increase the 36-week Hct or the decrease number of transfusions.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Tielsch, J. M., Khatry, S. K., Stoltzfus, R. J., Katz, J., Leclerq, S. C., Adhikari, R., Mullany, L. C., Shresta, S., and Black, R. E. (2006) Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: Community-based, cluster-randomised, placebo-controlled trial. Lancet 367 (9505) 144-152				
Affiliation/Source of funds				
The authors declare that they have no conflict of interest. This study was done with grants from the National Institutes of Health, Bethesda, MD, USA and the Bill and Melinda Gates Foundation, Seattle, Washington, DC, USA and a Cooperative Agreement between John Hopkins University and the Office of Health and Nutrition, US Agency for International Development, Washington, DC, USA.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Southern Nepal	
Intervention	Comparator			
1. Iron (12.5mg) + folic acid (50μg) (one tablet daily or half a tablet if < 1 year old) 2, Iron (12.5 mg) + folic acid (50 μg)+ zinc (10 mg) (one tablet daily or half a tablet if < 1 year old) *All children older than 6 months also received vitamin A (those aged 12 months or older were given 200 000IU every 6 months and those aged 6-12 months were given 100 000UI)	Placebo *All children older than 6 months also received vitamin A (those aged 12 months or older were given 200 000IU every 6 months and those aged 6-12 months were given 100 000UI)			
Population characteristics				
Children aged 1-36 months of age who lived in households in the study area. All children born into households in the study area were eligible once 1 month old if that house was their primary residence.				
Length of follow-up	Outcomes measured			
36 months	Primary outcome: all-cause mortality Secondary outcomes: cause-specific mortality, incidence and severity of diarrhoea, dysentery and acute respiratory illness in two subsamples of children			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Children were randomised by sector, stratified by geographic area and in blocks of four. To prevent the investigators from determining treatment allocation, a data file was given to an independent systems analyst who replaced the individual identifiers with a new, random set of identification numbers, filed the linked information in a secure location and replaced all treatment codes with the actual treatment received. Baseline characteristics were similar between the groups. Loss to follow-up was reported and appropriately accounted for the in the analysis. A subgroup analysis was conducted using a subset of participants from the trial who were younger than 24 months of age.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	8324		8663	
Efficacy analysis (ITT)	8128		8411	
Efficacy analysis (PP)	2787		3111	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD Median (IQR)	Comparator n/N (%) Mean ± SD Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value

Iron + folic acid vs placebo				
Deaths (overall)	112/8128 *9210.7 person-years	115/8411 *9798.6 person-years	HR 1.03 [0.78, 1.37]	No significant difference *P* > 0.10
Deaths (by gender) Male	41 *4827.5 person-years	52 *4909.0 person-years	HR 0.80 [0.52, 1.22]	No significant difference *P* > 0.10
Deaths (by gender) Female	71 *4383.2 person-years	63 *4889.5 person-years	HR 1.25 [0.87, 1.79]	No significant difference *P* > 0.10
Deaths (by age group) 1-5 months	34 *1211.5 person-years	28 *1282.7 person-years	1.28 [0.79, 2.08]	No significant difference *P* > 0.10
Deaths (by age group) 6-11 months	24 *1612.3 person-years	24 *1720.0 person-years	1.06 [0.59, 1.92]	No significant difference *P* > 0.10
Deaths (by age group) 12-23 months	34 *3247.2 person-years	37 *3429.2 person-years	0.97 [0.57, 1.64]	No significant difference *P* > 0.10
Deaths (by age group) 24-36 months	20 *3140.2 person-years	26 *3367.2 person-years	0.82 [0.45, 1.51]	No significant difference *P* > 0.10
Substudy (N=339): Iron + folic acid: n=152; Placebo: n=187				
Haemoglobin (g/L) < 70	1/152 (0.7%)	11/187 (5.9%)	NR	*P* = NR
Haemoglobin (g/L) 70-89	5/152 (3.3%)	18/187 (9.6%)	NR	*P* = NR
Haemoglobin (g/L) 90-110	63/152 (41.4%)	87/187 (46.5%)	NR	*P* = NR
Haemoglobin (g/L) > 110	83/152 (54.6%)	71/187 (38.0%)	NR	*P* = NR
Haemoglobin (g/L)	11.11 (1.18)	10.31 (1.71)	0.71 [0.34, 1.09]	Favours iron + folic acid *P* = 0.007
Serum ferritin (µg/L) *Iron + folic acid: n=146 *Placebo: n=159	53.57 (47.12)	19.58 (24.54)	34.25 [22.82, 45.69]	*P* = NR
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children aged 1-36 months.				
Applicability				
Evidence not applicable to Australian healthcare context. The study was conducted in Nepal (Level D).				
Comments				
This was a three arm trial, with one group receiving iron and folic acid, one receiving iron, folic acid and zinc and the last group receiving placebo. The iron and folic acid containing groups were stopped early based on a recommendation from the data and safety monitoring board as interim data showed there was no evidence of a beneficial effect. A lower mortality rate than expected resulted in insufficient statistical power to detect significant between group differences in mortality by the time study recruitment and follow-up were to be completed. The study continue to enrol participants in the zinc only and placebo arms. This study was a parallel trial to Sazawal 2006, conducted in Zanzibar.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Sankar, M. J., Saxena, R., Mani, K., Agarwal, R., Deorari, A. K., and Paul, V. K. (2009) Early iron supplementation in very low birth weight infants – A randomized controlled trial. ACTA PAEDIATR.INT.J.PAEDIATR. 98 (6) 953-958				
Affiliation/Source of funds				
The authors have no conflict of interest to declare. A financial grant from Indian Council of Medical Research (ICMR), New Delhi was obtained to procure the kits used for estimating serum ferritin.				
Study design	Level of evidence		Location/setting	
RCT	Level II		India, tertiary neonatal care unit	
Intervention	Comparator			
Oral iron at a dose of either 3mg/kg/day (birthweights 1000-1500 g) or 4mg/kg/day (birthweights <1000mg) from 2 weeks. Administered using a colloidal iron preparation (25mg elemental iron per mL), which also contained folic acid (200 µg/mL) and vitamin B12 (5 µmg/mL).	Control (no iron until 60 days)			
Population characteristics				
Preterm very low birthweight (<1500 g) infants who reached at least 100 mL/kg/day of oral feeds by day 14. Those with major anomalies and Rh haemolytic disease were excluded.				
Length of follow-up	Outcomes measured			
60 days	Primary outcome: serum ferritin Secondary outcomes: haematologic and anthropometric parameters, composite outcome (including chronic lung disease, necrotising enterocolitis, periventricular leucomalacia and retinopathy of prematurity) and requirement of blood transfusion.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Randomisation and allocation concealment strategies were detailed and adequate. The investigators were not blinded. However, the laboratory staff who estimated serum ferritin and other parameters were masked to treatment groups. The authors do not specify whether this was the case for all outcome variables. Baseline characteristics were similar between the groups except for the incidence of late-onset sepsis, which was higher in the control group. Loss to follow-up is reported and accounted for in the analysis. There were no subgroup analyses reported.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	22		24	
Efficacy analysis (ITT)	22		24	
Efficacy analysis (PP)	21		23	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Early iron vs no iron				
Requirement for blood transfusion	2/21 (9.5%)	3/23 (13.0%)	NR	No significant difference *P* = 0.63
Necrotising enterocolitis	1/21 (4.8%)[a]	0/21 (%)	NR	No significant difference *P* = 0.49

Retinopathy of prematurity requiring treatment	2/21 (9.5%)	3/23 (13.0%)	NR	No significant difference *P* = 0.57
Chronic lung disease	1/21 (4.8%)	1/23 (4.3%)	NR	No significant difference *P* = 0.88
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
Haemoglobin at 60 days (g/dL)	10.8 ± 1.	10.2 ± 2.	NR	No significant difference *P* = 0.36
Haematocrit at 60 days (%)	32.5 ± 5.3	30.8 ± 6.3	NR	No significant difference *P* = 0.35
Weight at 60 days (g)	2272 ± 756	2215 ± 736	NR	No significant difference *P* = 0.30
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to very low birthweight infants.				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. The study was conducted in India (Level C).				
Comments				
Infants on predominant expressed breast milk feeds (>50% of daily intake) were supplemented with a human milk fortifier that contains all the vitamins and minerals except iron. For infants on predominant formula feeds, no human milk fortifier was added and the dose of iron was adjusted to meet the required daily dose.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.
a. Reported by authors as 4.5%

STUDY DETAILS: RCT				
Citation				
Sazawal, S., Black, R. E., Ramsan, M., Chwaya, H. M., Stoltzfus, R. J., Dutta, A., Dhingra, U., Kabole, I., Deb, S., Othman, M. K., and Kabole, F. M. (2006) Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: Community-based, randomised, placebo-controlled trial. Lancet 367 (9505) 133-143				
Affiliation/Source of funds				
The authors declare that they have no conflict of interest. The study was supported by WHO Department of Child Health and Adolescent Health and Development with funds from United Nations Foundation, the John Hopkins Family Health and Child Survival and Global Research Activity Cooperative Agreements with US Agency for International Development and the Bill and Melinda Gates Foundation through its support for micronutrient research to the John Hopkins Bloomberg School of Public Health.				
Study design	Level of evidence		Location/setting	
RCT *Cluster-randomised	Level II		Pemba, Zanzibar	
Intervention	Comparator			
1. Iron (12.5mg) + folic acid (50µg) (one tablet daily or half a tablet if < 1 year old) 2. Iron (12.5mg) + folic acid (50µg) + zinc (10 mg) (one tablet daily or half a tablet if < 1 year old) Note: only intervention 1 included here	Placebo *			
Population characteristics				
Children aged 1-35 months, likely to remain resident on the island and not having severe malnutrition needing rehabilitation. All new births were also invited into enrol in the study at age 1 month. *All children were given vitamin A (those aged 12 months or older were given 200 000IU every 6 months and those aged younger than 12 months were given 100 000IU)				
Length of follow-up	Outcomes measured			
18 months (maximum duration of follow-up)	Serious adverse events (composite of hospital admissions and death), death during follow-up or within 30 days of stopping supplementation and hospital admission.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Children were randomised to one of four groups using a permuted block allocation sequence, with a block length of 16. Strips of supplements were labelled with 16 letter codes, which were hidden in the batch number of each strip of tablets before each child was assigned a code. Baseline characteristics were similar between the groups. Loss to follow-up was reported and appropriately accounted for in the analysis. There were limitations regarding the classification of cause-specific effects, as noted by the authors. Lumbar puncture, coma scoring, blood cultures or blood gas analytics were not available in the hospitals on the island and as such, it is possible that misclassifications occurred regarding meningitis, septicaemia with acidosis and cerebral malaria. However, alternate methods of diagnosis are detailed in the trial for these conditions. A subgroup analysis was conducted using a subset of the participants from the trial stratified by baseline anaemia, iron status and anthropometry.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	7950		8006	
Efficacy analysis (ITT)	7950		8006	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value

Iron + folic acid vs placebo				
Deaths (overall)	149/7950 *8402 child-years follow-up	130/8006 *8574 child-years follow-up	RR 1.16 [0.92, 1.47]	No significant difference *P* = 0.21
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to children aged 1-35 months.				
Applicability				
Evidence not applicable to Australian healthcare context. The study was conducted in Zanzibar (Level D).				
Comments				
This was a three arm trial, with one group receiving iron and folic acid, one receiving iron, folic acid and zinc, and the last group receiving placebo. The iron and folic acid containing groups were stopped early based on a recommendation from the data and safety monitoring board, leaving only two groups to continue (zinc alone and placebo). Significantly ($p < 0.05$) higher rates of total adverse effects were observed in the iron and folic acid containing groups, leading to the recommendation to discontinue these groups. The trial continued with the two remaining groups. *Note: Mortality results stratified by age and haemoglobin results are not usable here as they include iron/folic acid and iron/folic acid + zinc groups (combined) vs placebo				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
van den Hombergh J, Dalderop E, Smit Y. (1996) Does Iron Therapy Benefit Children with Severe Malaria-associated Anaemia? A Clinical Trial with 12 Weeks Supplementation of Oral Iron in Young Children from the Turiani Division, Tanzania. Journal of Tropical Pediatrics, 42: 220-7.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Turiani Hospital, Tanzania	
Intervention	Comparator			
Oral iron as ferrous sulphate (200mg/day), for 12 weeks	No Iron			
Population characteristics				
100 children younger than 30 months with severe malaria-associated anaemia (Hb ≤5 g/dL) attending the outpatient department or admitted to the paediatric ward of the study hospital Exclusion criteria: children with cerebral malaria, non-falciparum malaria or sickle cell anaemia, or children in whom the malarial anaemia was not the main medical problem.				
Length of follow-up	Outcomes measured			
Follow-up examination of all study children was carried out at the hospital's child health clinic (MCH) after 2, 4, 8, and 12 weeks.	Haemoglobin, haematocrit, reticulocyte count and a blood smear for malaria parasites. After 2 weeks respiratory rate was measured and at the end of the follow-up period(12 weeks) splenic function and bodyweight were measured.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 100 children with malaria-associated anaemia (Hb ≤5 g/dL) in Tanzania, to examine the effect of daily oral iron supplementation for 12 weeks compared with no iron, on laboratory, clinical and anthropometric measures. Simple randomisation was used to allocate children to the iron or control group. The diagnosing physician was not blinded to treatment group. All children were treated with the standard oral second-line malaria drug regimen in the hospital: Quinine sulphate (10mg/kg) 3x per day for 3 days, and Fansidar (sulphadoxin 500mg + pyrimethamin 25mg) as a single dose. Treatment was provided in case of clinical symptoms. At baseline, 20 children from each group (40%) had received a blood transfusion. Subgroup analyses were performed accounting for this variable. Follow-up was reported to be 100%; however between 5 and 8 children were not included in the analyses at 2, 4, 8 and 12 weeks. Reasons for these exclusions were not reported. Extra follow-up attendances by mothers because of an illness of their child was higher in the iron group; an observation which is not likely to be observer-biased.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	50		50	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Intervention n/N (%) Mean ± SD	Comparator n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Iron supplementation vs no iron				
Mortality	1/50 (2%)	1/50 (2%)	NR	No significant difference *P* = NR
Children who had received blood transfusion at baseline: iron, n=20; no iron n=20				
Hb (g/dL) at week 2	9.4 ± 1.1	9.6 ± 2.1	NR	NR

Hb (g/dL) at week 4	9.7 ± 1.5	9.9 ± 1.5	NR	NR
Hb (g/dL) at week 8	8.6 ± 2.8	8.4 ± 1.8	NR	NR
Hb (g/dL) at week 12	10.1 ± 1.5	9.4 ± 2.1	NR	NR
Children who had not received blood transfusion at baseline: iron, n=30; no iron n=30				
Hb (g/dL) at week 2	8.1 ± 1.4	8.1 ± 1.4	NR	NR
Hb (g/dL) at week 4	8.9 ± 1.2	8.7 ± 1.8	NR	NR
Hb (g/dL) at week 8	9.0 ± 1.8	8.1 ± 1.9	NR	NR
Hb (g/dL) at week 12	9.2 ± 1.5	9.0 ± 1.5	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply (Level D).				
Applicability				
Evidence not applicable to the Australian healthcare context. Study site Tanzania (Level D).				
Comments				
The authors concluded that infants and young children recover from severe anaemia associated with malaria within 2 weeks of effective malaria treatment, with or without iron supplementation.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Jain DL, Sarathi V, Desai S, Bhatnagar M, Lodha A. (2012) Low fixed-dose Hydroxyurea in severely affected Indian children with sickle cell disease. Hemoglobin, 36(4): 323–332.				
Affiliation/Source of funds				
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single tertiary care hospital, India	
Intervention	Comparator			
Oral hydroxyurea (HU) 10mg/kg/day for 18 months.	Placebo (powdered glucose capsules)			
Population characteristics				
Sixty severe sickle cell anaemia children (5–18 years) with more than three episodes of vasoocclusive crises or blood transfusions per year. Exclusion criteria: seropositivity for HIV or any chronic illness that could potentially enhance HU toxicity.				
Length of follow-up	Outcomes measured			
18 months	Primary: decrease in the frequency of vasoocclusive crises per patient per year. Secondary: a decrease in frequency of blood transfusions and hospitalisations, an increase in Hb F levels.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 60 child/adolescent patients with severe sickle cell anaemia, to examine the effect of hydroxyurea treatment compared with placebo on the frequency of vasoocclusive crises per patient per year. Subjects were randomised using randomisation tables. Trial was double-blinded; the laboratory technician and the clinician who assessed patients were not aware of the treatment arm. The study had sufficient statistical power (90%) to detect a mean difference in the primary outcome of 1.9 per patient per year with a SD of 0.5, assuming an alpha error or 0.05. Compliance was assessed by counting the total number of capsules remaining at the monthly follow-up visit.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	30		30	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	5		0	
Outcome	Intervention Mean ± SD	Comparator Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
[HU] vs [placebo]				
Vasoocclusive crises (N=60)	0.60 ±1.37	10.2 ± 3.24	NR	Favours hydroxyurea *P* < 0.001
Blood transfusions (N=60)	0.13 ± 0.43	1.98 ± 0.82	NR	Favours hydroxyurea *P* < 0.001
Hb (g/dL) (N=60)	9.29 ± 0.55	7.90 ± 0.58	NR	Favours hydroxyurea *P* < 0.001
Hb F (%) (N=60)	24.00 ± 5.90	18.92 ± 5.77	NR	Favours hydroxyurea *P* < 0.001
EXTERNAL VALIDITY				
Generalisability				

Evidence directly generalisable to children with severe sickle cell anaemia (Level A)..
Applicability
Evidence probably applicable to the Australian context with some caveats. Study site India (Level C).
Comments
The authors concluded that low fixed dose HU was an effective therapy for the treatment of severe sickle cell anaemia in Indian children.

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, Rana S, Thornburg CD, Rogers ZR, Kalpatthi RV, Barredo JC, Brown RC, Sarnaik SA, Howard TH, Wynn LW, Kutlar A, Armstrong FD, Files BA, Goldsmith JC, Waclawiw MA, Huang X, Thompson BW, for the BABY HUG investigators (2011) Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 2011; 377: 1663–72.		
Affiliation/Source of funds		
Funding was received from The US National Heart, Lung, and Blood Institute; and the National Institute of Child Health and Human Development. Role of the funding source: The NHLBI provided an initial draft of the study design. The study sponsors did not collect, analyse, report, or interpret data. Two employees of the NHLBI (JCG, MAW) contributed to the writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors declare no conflicts of interest.		
Study design	Level of evidence	Location/setting
RCT	Level II	13 centres, USA
Intervention	Comparator	
Hydroxycarbamide (20mg/kg/day) for 2 years	Placebo	
Population characteristics		
Infants with sickle cell anaemia (HbSS) or Sβ^{0}thalassemia of all clinical severities, aged 9–18 months at randomisation. Exclusion criteria: transfusion within 2 months; height, weight or head circumference less than the 5th percentile; mental developmental index (MDI) <70; abnormal transcranial Doppler ultrasound (TCD) velocity.		
Length of follow-up	Outcomes measured	
2 years	Primary: Splenic function, renal function Secondary: laboratory measures (blood counts, fetal haemoglobin concentration, chemistry profiles), spleen function biomarkers, urine osmolality, pulmonary function, neurodevelopment, TCD ultrasonography, growth, mutagenicity, adverse events (pain, dactylitis, acute chest syndrome, hospitalisation rates, and transfusion), toxicity	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: A large multicentre RCT in the US of 193 infants with sickle cell anaemia or sickle beta thalassemia, to examine the effect of hydroxyurea compared with placebo on splenic function, renal function and other clinical/laboratory measures. Patients were randomly assigned to either the treatment or placebo group in a 1:1 ratio. The randomisation sequence was pre-decided by a randomisation schedule developed for each clinical site by the medical coordinating centre. Double-blind randomisation was done with an automated telephone response system and the use of a random three digit kit number for each enrolled participant. The kit number, which was linked to the assignment sequence, was used by the drug distribution centre to shift the appropriate study drug to the clinical site pharmacy. Participants, caregivers, and medical coordinating centre staff were masked to treatment allocation. The study required a sample size of 100 patients per group to provide greater than 95% power to detect an estimated proportion with worsening spleen function of 0.6 in the control group vs 0.3 in the HU group, assuming a two-sided type I error of 4%, and to detect a 60% difference in the exit vs baseline GFR measurements with a two-sided type I error of 1%. A group sequential design was used to adjust for 6-month interim analysis reviews done by an independent data safety and monitoring board. Interim boundaries were widely set to enable the most powerful comparison to be done at the end of the study, should an interim boundary not be crossed during the trial. For secondary endpoints, a p-value ≤0.01 was considered significant.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	96	97
Efficacy analysis (ITT)	96	97
Efficacy analysis (PP)	83	84
Safety analysis	96	97

Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Hydroxyurea vs placebo				
Stroke	0/96 (0%)	1/97 (1.0%)	NR	No significant difference *P* = 0.31
Number of patients who received a transfusion	20/96 (20.8%)	33/97 (34.0%)	HR 0.55 [0.32, 0.96]	No significant difference *P* = 0.03
Number of transfusion events	35	63		
Number of patients who experienced pain alone	37/96 (38.5%)	55/97 (56.7%)	HR 0.54 [0.36, 0.83]	Favours hydroxyurea *P* = 0.004
Number of pain alone events	63	121		
Number of patients who experienced pain (all reports)	62/96 (64.6%)	75/97 (77.3%)	HR 0.59 [0.42, 0.83]	Favours hydroxyurea *P* = 0.002
Number of pain events (all reports)	177	375		
Number of patients with acute chest syndrome	7/96 (7.3%)	18/97 (18.6%)	HR 0.36 [0.15, 0.87]	No significant difference *P* = 0.02
Number of acute chest syndrome events	8	27		
Haemoglobin at exit (g/L)	91 (n=79)	86 (n=79)	NR	NR
Mean change in haemoglobin from baseline	3%	-7%	MD 0.9 [0.5, 1.3]	Favours hydroxyurea *P* < 0.0001
Bayley MDI at exit	97 (n=85)	94 (n=85)	NR	NR
Mean change in Bayley MDI from baseline	1%	-3%	MD 3 [-2, 8]	No significant difference *P* = 0.22
Bayley motor PDI at exit	101 (n=85)	99 (n=85)	NR	NR
Mean change in Bayley motor PDI from baseline	5%	2%	MD 2 [-3, 7]	No significant difference *P* = 0.22
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to infants with sickle-cell anaemia or sickle beta thalassemia (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study sites USA (Level C).				
Comments				
The authors conclude that on the basis of the safety and efficacy data from this trial, hydroxycarbamide can now be considered for all very young children with sickle-cell anaemia. 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.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; TCD transcranial Doppler ultrasound.

F3 Evidence summaries – Question 3

Level I evidence

STUDY DETAILS: SR/MA		
Citation		
Estcourt L, Stanworth S, Doree C, Hopewell S, Murphy MF, Tinmouth A, Heddle N. (2012) Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation (Review). Cochrane Database of Systematic Reviews, Issue 5 CD004269.		
Affiliation/Source of funds		
Internal sources: NHS Blood and Transplant, Research and Development, UK External sources: German Ministry of Education and Research, Germany		
Study design	Level of evidence	Location/setting
Systematic review of RCTs	I	US (Murphy 1982)
Intervention		Comparator
1. Prophylactic platelet transfusion (PPT) 2. PPT with one trigger level 3. PPT with one dose schedule 4. Platelet transfusion (prophylactic or therapeutic)		6. Therapeutic platelet transfusion (TPT) 7. PPT with another trigger level 8. PPT with another dose schedule 9. Alternative treatment e.g. artificial platelet substitute
Population characteristics		
Patients of all ages with haematological disorders receiving treatment with myelosuppressive chemotherapy and/or stem cell transplantation.		
Length of follow-up	Outcomes measured	
NR	Primary: number of bleeding episodes, number of days bleeding occurred. Secondary: mortality (all causes), mortality secondary to bleeding, number of platelet transfusions, number of RBC transfusions, disease-free survival, proportion of patients achieving complete remission, time in hospital, adverse treatment effects.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating (SR): Good Description: Of the 13 included studies, one (Murphy 1982) met all the criteria for this overview. The review authors rated Murphy 1982 as having an overall unclear risk of bias, predominantly due to poor reporting. A high risk of bias was noted for selective outcome reporting and potential for others bias. Murphy 1982 compared prophylactic and therapeutic platelet transfusion regimes. No provision of description of the method of random allocation was provided. Primary (survival) and secondary (bleeding events, days bleeding and transfusion requirements) outcomes were reported. Patients followed up until death or 1st July, 1976 (mean period approx. 20 months). Details were not reported for allocation concealment and blinding (patient, clinician or assessor), although given the nature of the outcomes this may not have been feasible. Loss to follow up and outcome data was not reported. The review authors noted high risk of bias for selective reporting and poorly backed up statements. Other bias included unbalanced group numbers and lack of reporting of patient characteristics. Note: the authors identified another study in paediatric patients (Roy 1973), although the comparison was high dose prophylactic platelet transfusions compared with lower dose prophylactic platelet transfusions. There were three studies in both adults and children (Diedrich 2005, Sensebe 2004, Slichter 2010); however, results were pooled for both age groups.		
RESULTS:		

Outcome No. trials (No. patients)	TPT n/N (%) Mean ± SD (N)	PPT n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	*Statistical significance* *P*-value Heterogeneity *P*-value (I2)
No. patients with ≥1	11/21 (52.4%)	10/35 (28.6%)	RR 1.66	No significant difference

significant bleeding event (ALL and AML patients) N=56			[0.9, 3.04]	*P* = 0.10 Substantial heterogeneity I^2=69% (subgroups)
No. patients with ≥1 significant bleeding event: subgroup (ALL) N=43	7/15 (46.7%)	5/28 (17.9%)	RR 2.61 [1.00, 6.83]	Favours PPT *P* = 0.05 Heterogeneity NA
No. patients with ≥1 significant bleeding event: subgroup (AML) N=13	4/6 (66.7%)	5/7 (71.4%)	RR 0.93 [0.45, 1.95]	No significant difference *P* = 0.85 Heterogeneity NA
No. of days with significant bleeding (ALL and AML) N = no. of days	46/13028	68/21185	RR 0.90 [0.62, 1.32]	No significant difference *P* = 0.60 I^2=0.0%
No. of days with significant bleeding: subgroup (ALL)	14/9863	31/17654	RR 0.81 [0.43, 1.52]	No significant difference *P* = 0.51
No. of days with significant bleeding: subgroup (ALL)	32/3166	37/3531	RR 0.96 [0.60, 1.54]	No significant difference *P* = 0.88
Mortality (all causes) N=56	7/21 (33.3%)	12/35 (34.3%)	RR 0.97 [0.46, 2.08]	No significant difference *P* = NR Heterogeneity NA
Mortality from bleeding N=56	2/21 (9.5%)	1/35 (2.9%)	RR 3.33 [0.32, 34.56]	No significant difference *P* = NR Heterogeneity NA
Mean number of platelet transfusions per course of chemotherapy N=56	1.0 ± 0 (21)	2.2 ± 0 (35)	Mean difference 0.0 [0.0, 0.0]	No significant difference *P* = NR Heterogeneity NA
Number of patients with platelet refractoriness N=56	1/21 (4.8%)	5/35 (14.3%)	RR 0.33 [0.04, 2.66]	No significant difference *P* = 0.30 Heterogeneity NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with haematological disorders.				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study sites USA (Level C).				
Comments				
The review authors summary in respect to Murphy 1982: Prophylactic versus therapeutic platelet transfusions – no significant difference in bleeding, effect on mortality (overall and due to bleeding), transfusion requirements and incidence of platelet refractoriness. There was a reduction in the platelet units required in the therapeutic group. Power of studies was generally inadequate to detect differences. Authors conclude there is insufficient evidence to determine whether prophylactic platelet transfusion is superior to therapeutic. Note: All transfusions involved platelet concentrates, prepared either from individual units of whole blood or by apheresis, given prophylactically to prevent bleeding.				

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CI, confidence interval

STUDY DETAILS: SR/MA				
Citation				
Osborn DA, Evans NJ. (2004) Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database of Systematic Review, Issue 2 CD002055				
Affiliation/Source of funds				
Internal: RPA Newborn Care, Royal Prince Alfred Hospital, Sydney, Australia. External: NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.				
Study design	Level of evidence		Location/setting	
Systematic review	Level I		Not reported	
Intervention	Comparator			
Volume expansion using normal saline, fresh frozen plasma (FFP), albumin, plasma substitute or blood	Control (no treatment)			
Population characteristics				
Very preterm infants born ≤ 32 weeks gestation or ≤ 1500 g and enrolled and treated in the first 72 hours after birth.				
Length of follow-up	Outcomes measured			
N/A	Primary: neonatal mortality and mortality to discharge, peri/intraventricular haemorrhage (P/IVH) (any or severe grades), periventricular leukomalacia, neurodevelopmental disability (either neurological abnormality including cerebral palsy, developmental delay or sensory impairment) Secondary: use of inotropes (in first 72 hours), failure to correct low SB, failure to correct systemic hypotension, patent ductus arteriosus, renal impairment (creatinine ≥ 120micromol/L, oliguria ≤ 0.5 mL/kg/hour), airleak, chronic lung disease (at 28 days postnatal or near term postmenstrual age), proven necrotising enterocolitis, retinopathy of prematurity (any stage and severe)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Eight RCTs were included of which four (Beverley 1985; Ekblad 1991; Gottuso 1976; NNNI 1996b) were relevant to the target question, comparing FFP to control (either no treatment or maintenance fluid). Appropriate search strategies and inclusion criteria applied in an unbiased way. The review authors noted that the study had a power of 80% to detect a 9% absolute difference in rates of combined death and severe disability between intervention and control groups at a significance level of 5%. Three studies (Beverley 1985; Gottuso 1976; NNNI 1996b) reported adequate randomisation procedures and adequate allocation concealment. Ekblad 1991 did not report method of randomisation, and allocation concealment was unclear. None of these studies reported blinding, however given the nature of the interventions, it is probable that caregivers were not blinded. Ekblad 1991 reported outcomes for the same cohort of infants in two papers. Two studies (Beverley 1985; NNNI 1996b) reported blinding measurement of outcomes. Three studies reported loss to follow-up clearly (no loss to follow-up in Gottuso 1976 and NNNI 1996b; seven patients (12.5%) in Beverley 1985). Ekblad 1991 reported outcome data for 38/40 infants in one paper and 35/40 infants in another. No statistically significant heterogeneity was found in any of the analyses.				
RESULTS				
Outcome No. trials (No. patients)	FFP n/N (%)	No treatment n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Death 3 trials (N=654)	76/321 (23.7%)	78/333 (23.4%)	RR 1.05 [0.81, 1.36]	No significant difference *P* = 0.69 No significant heterogeneity *P* = 0.94 (I^2=0.0%)

Any P/IVH in infants randomised 2 trials (N=120)	11/59 (18.6%)	20/61 (32.8%)	RR 0.58 [0.30, 1.11]	No significant difference *P* = 0.099 Moderate heterogeneity *P* = 0.22 (I^2=33%)
Any P/IVH in survivors examined 1 trial (N=282)	42/135 (31.1%)	38/147 (25.9%)	RR 1.20 [0.83, 1.74]	No significant difference *P* = 0.33 Heterogeneity NA
P/IVH grade 2-4 in infants randomised 1 trial (N=80)	5/38 (13.2%)	13/42 (31.0%)	RR 0.43 [0.17, 1.08]	No significant difference *P* = 0.072 Heterogeneity NA
P/IVH grade 2-4 in survivors examined 1 trial (N=282)	12/135 (8.9%)	14/147 (9.5%)	RR 0.93 [0.45, 1.95]	No significant difference *P* = 0.85 Heterogeneity NA
P/IVH grade 3-4 in infants randomised 1 trial (N=80)	5/38 (13.2%)	10/42 (23.8%)	RR 0.55 [0.21, 1.47]	No significant difference *P* = 0.24 Heterogeneity NA
Death or P/IVH in infants randomised 1 trial (N=80)	10/38 (26.3%)	20/42 (47.6%)	RR 0.55 [0.30, 1.03]	Borderline significance favouring FFP *P* = 0.061 Heterogeneity NA
Death or P/IVH in survivors examined 1 trial (N=404)	78/201 (38.8%)	74/203 (36.5%)	RR 1.06 [0.83, 1.37]	No significant difference *P* = 0.63 Heterogeneity NA
Death or P/IVH grade 3-4 in infants randomised 1 trail (N=80)	8/38 (21.2%)	13/42 (31.0%)	RR 0.68 [0.32, 1.46]	No significant difference *P* = 0.32 Heterogeneity NA
Death or P/IVH grade 3-4 in survivors examined 1 trial (N=404)	51/201 (25.4%)	51/203 (25.1%)	RR 1.01 [0.72, 1.41]	No significant difference *P* = 0.95 Heterogeneity NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to very preterm infants born ≤ 32 weeks gestation or ≤ 1500 g.				
Applicability				
Evidence may or may not be applicable to the Australian healthcare context (study sites not reported).				
Comments				
The review authors conclude the overall rate of mortality was not different between infants who received FFP compared to no treatment. Evidence of a reduced rate of P/IVH in one study was not supported by the overall meta-analysis or any other study. There is 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.				

CI, confidence interval; FFP, fresh frozen plasma; NA, not applicable; P/IVH, peri/intraventricular haemorrhage; RR, risk ratio

Level II evidence

STUDY DETAILS: RCT		
Citation		
F Galas, J. de Almeida, J. Fukushima, J Vincent, E. Osawa, S Zeferino, L. Camara, V Guimaraes, M Jatene and L. Hajjar. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: A randomized pilot trial. 2014 The Journal of Thoracic and Cardiovascular Surgery c Volume 148, Number 4.		
Affiliation/Source of funds		
The trial was supported by CSL Behring Ltd. (Sao Paulo, Brazil), which provided the study drug and the testing of clotting factors and thromboelastometry. Authors have nothing to disclose with regard to commercial support.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single centre, Brazil
Intervention	Comparator	
Fibrinogen concentrate (60 mg/kg) (pasteurised human fibrinogen concentrate)	Cryoprecipitate (10 mL/kg)	
Population characteristics		
Patients younger than age 7 years scheduled for elective cardiac surgery with CPB were preoperatively screened for eligibility. Eligible patients were included in the study after heparin neutralisation if 2 inclusion criteria were fulfilled: diffuse bleeding from capillary beds at wound surfaces requiring haemostatic therapy and plasma fibrinogen concentration<1 g/L. Exclusion criteria: inability to receive blood products, enrolment in another study, chronic anaemia (preoperative haemoglobin <10 g/dL), a history of coagulopathy or preoperative coagulopathy (platelet count <100,000 mL/mm^3 or prothrombin time >14.8 seconds), active infection, or hypersensitivity to fibrinogen concentrate.		
Length of follow-up	Outcomes measured	
7 days	Primary: postoperative blood losses during the 48 hours after surgery. Secondary: percentage of patients exposed to allogeneic blood products (RBCs, FFP, platelet concentrate, and cryoprecipitate), duration of mechanical ventilation, vasopressor requirement, and incidence of acute myocardial infarction, stroke, acute kidney injury requiring dialysis, septic shock, reoperation, peripheral artery occlusion, deep venous thrombosis, and pulmonary embolism, death up to postoperative day 7 or hospital discharge, ICU and hospital length of stay, coagulation parameters, ROTEM values, and fibrinogen dose before and after intervention.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: A total of 688 patients were assessed for eligibility and 63 fulfilled the inclusion criteria. Thirty patients were randomised to the fibrinogen group and 33 to the cryoprecipitate group. No patients in either group were lost to follow-up or withdrew from the study. There were no between group differences in baseline demographics and intraoperative characteristics. Exclusion criteria were inability to receive blood products, enrolment in another study, chronic anaemia (preoperative haemoglobin<10 g/dL), a history of coagulopathy or preoperative coagulopathy (platelet count <100,000 mL/mm3 or prothrombin time>14.8 seconds), active infection, or hypersensitivity to fibrinogen concentrate. Patients were randomly assigned in a 1:1 ratio. Opaque envelopes arranged using a random number table were prepared by the chief statistician and opened sequentially to determine the patient's treatment group. The research coordinator enrolled the participants and obtained informed consent. Outcome assessors and patients were unaware of study group assignments but the authors acknowledge that not all personnel were blinded because it was not feasible to mask the assigned therapy. No subgroup analyses were reported. Limitations of the study include the small sample size and single centre design.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	30	33
Efficacy analysis (ITT)	30	33
Efficacy analysis (PP)	30	33
Safety analysis	30	33

Outcome	Fibrinogen concentrate n/N (%)	Cryoprecipitate n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality	0 (0%)	0 (0%)	NR	NR
Postoperative transfusion	26/30 (86.7%)	33/33 (100.0%)	NR	Favours fibrinogen concentrate *P* = 0.046
Transfusion (RBC)	25/30 (83.3%)	32/33 (97.0%)	NR	No significant difference *P* = 0.094
Transfusion (platelets)	0/30 (0%)	3/33 (9.1%)	NR	No significant difference *P* = 0.240
Transfusion (FFP)	3/30 (10.0%)	8/33 (24.2%)	NR	No significant difference *P* = 0.137
Transfusion (cryoprecipitate)	13/30 (43.3%)	14/33 (42.4%)	NR	No significant difference *P* = 0.942
Stroke	0 (0%)	0 (0%)	NR	NR
Acute myocardial infarction	2/30 (6.7%)	5/33 (15.2%)	NR	Favours cryoprecipitate *P* = 0.429
Deep venous thrombosis	0 (0%)	0 (0%)	NR	NR
Pulmonary embolism	0 (0%0	0 (0%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric cardiac surgery patients with some caveats (Level B).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. The study was conducted in Brazil (Level C). 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.				
Comments				
Anaesthesia was induced with fentanyl, ketamine and pancuronium. Maintenance was performed with sevoflurane in oxygen and fentanyl as needed. Dobutamine or milrinone were used as inotropic drugs, and norepinephrine or epinephrine as vasopressors. Methylprednisolone and cefuroxime were administered intravenously at the introduction of anaesthesia. All patients received antifibrinolytic prophylaxis with ε-aminocaproic acid. Anticoagulation therapy was established with an initial dose of heparin. Additional heparin was administered intermittently to titrate clotting times during bypass. Transfusion protocols were in place. The preliminary results of our study showed that the use of fibrinogen concentrate was as efficient and safe as cryoprecipitate in the management of bleeding children undergoing cardiac surgery. The authors concluded that fibrinogen concentrate reduces perioperative bleeding without compromising outcomes.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; NR, not reported; P/IVH, peri/intraventricular haemorrhage; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry; RR, risk ratio

STUDY DETAILS: RCT				
Citation				
Lee JW, Yoo YC, Park HK, Bang SO, Lee KY, and Bai SJ. (2013) Fresh frozen plasma in pump priming for congenital heart surgery: Evaluation of effects on postoperative coagulation profiles using a fibrinogen assay and rotational thromboelastometry. Yonsei Med.J. 54 (3) 752-762.				
Affiliation/Source of funds				
This study was supported by a faculty research grant of Yonsei University College of Medicine for 2008 (4-2008-0562). The authors report no financial conflict of interest.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Single centre, South Korea		
Intervention	Comparator			
Fresh frozen plasma in pump priming	20% human albumin in pump priming			
Population characteristics				
Paediatric patients, aged 1 month to 16 years who were scheduled for elective cardiac surgery with CPB. Exclusions: neonates (<1 month of age), previously diagnosed coagulation disorders of non-cardiovascular origin, and any metabolic disorders leading to abnormalities in plasma protein profiles. ICU transfers with hemodynamic instability or reoperation for post-op bleeding.				
Length of follow-up	Outcomes measured			
Until first postoperative day	Haematological assays, including functional fibrinogen level and rotational thromboelastometry, transfusion requirements and postoperative bleeding			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 123 paediatric patients comparing FFP to 20% albumin in pump priming. Sealed envelopes were used as a method of randomisation and allocation concealment. The patient cohort was divided by age, with infants (<12 months age) and children (> 12 months) analysed separately for all outcomes. The anaesthesiologists, surgeons and ICU staff were blinded to treatment assignment, but perfusionists were not. Two patients were excluded after recruitment due to hemodynamic instability, leaving a total of 121 patients in the final analysis. Patient characteristics were similar between treatment groups for both infants and children.				
RESULTS				
Population analysed	Intervention Infants	Intervention Children	Comparator Infants	Comparator Children
Randomised	27	34	28	34
Efficacy analysis (ITT)	NR	NR	NR	NR
Efficacy analysis (PP)	NR	NR	NR	NR
Safety analysis	26	34	28	33
Outcome	FFP in pump prime Median (IQR)	Albumin in pump prime Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
After heparin reversal: bleeding (mL/kg) - Infants - Children	 12.3 (7.8, 16.7) 10 (6, 13.1)	 12.2 (9.6, 18.3) 10 (6.4, 16.1)	NR	No significant difference *P* = 0.677 *P* = 0.893
Transfusion volume or incidence (intraoperative bleeding)				

Pump priming: FFP (mL) - Infants - Children	 150 (150, 150) 300 (150, 300)	 0 (0, 0) 0 (0, 0)	NR	 *P* < 0.001 *P* < 0.001
Pump priming: RBC (mL) - Infants - Children	 125 (125, 125) 125 (0, 250)	 125 (125, 125) 250 (0, 250)	NR	No significant difference for either group *P* = 1.000 *P* = 0.203
Pump priming: additional RBC into CPB circuit (mL) - Infants - Children	 125 (125, 250) 0 (0, 125)	 125 (125, 125) 0 (0, 250)	NR	Favours albumin (infants) *P* = 0.002 No significant difference (children) *P* = 0.742
After heparin reversal: transfusion RBC (mL) - Infants - Children	 40 (0, 70) 5 (0, 375)	 2.5 (0, 37.5) 125 (0, 412.5)	NR	Favours albumin (infants) *P* = 0.047 No significant difference (children) *P* = 0.302
After heparin reversal: transfusion FFP (mL) - Infants - Children	 0 (0, 0) 0 (0, 11.3)	 0 (0, 43.1) 150 (0, 300)	NR	Favours FFP (infants and children) *P* = 0.042 *P* = 0.002
After heparin reversal: transfusion platelet (mL) - Infants - Children	 0 (0, 0) 0 (0, 0)	 0 (0, 0) 0 (0, 0)	NR	No significant difference (infants and children) *P* = 0.342 *P* = 0.717
After heparin reversal: transfusion salvaged blood (mL) - Infants - Children	 25 (0, 32.5) 100 (30, 505)	 15 (0, 53.8) 230 (60, 415)	NR	No significant difference (infants and children) *P* = 0.946 *P* = 0.368
Total transfusion requirements (mL/kg) - Infants - Children	 94.2 (76.1, 128.4) 32.4 (20.2, 52.8)	 61.7 (47.4, 83.6) 34.4 (20.1, 65.7)	NR	Favours albumin (infants) *P* = 0.001 No significant difference (children) *P* = 0.857
Total transfusion requirements (mL/kg) excluding FFP in pump priming - Infants - Children	 64 (52.5, 86.3) 21.8 (12.9, 41.3)	 61.7 (47.4, 83.6) 34.4 (20.1, 65.7)	NR	No significant difference (infants and children) *P* = 0.497 *P* = 0.060
Transfusion volume or incidence (during 24 hours in the ICU)				
Transfusion RBC (mL) - Infants - Children	 5 (0, 42.5) 0 (0, 120)	 12.5 (0, 66.8) 0 (0, 125)	NR	No significant difference (infants and children) *P* = 0.567 *P* = 0.975

Transfusion FFP (mL) - Infants - Children	 0 (0, 38.8) 0 (0, 242.5)	 32.5 (0, 50) 0 (0, 157)	NR	No significant difference (infants and children) *P* = 0.102 *P* = 0.598
Transfusion platelet (mL) - Infants - Children	 0 (0, 31.3) 0 (0, 20)	 0 (0, 36) 0 (0, 30)	NR	No significant difference (infants and children) *P* = 0.944 *P* = 0.955
Transfusion pump blood (mL) - Infants - Children	 0 (0, 3.8) 0 (0, 145)	 0 (0, 18.8) 0 (0, 15)	NR	No significant difference (infants and children) *P* = 0.386 *P* = 0.718
Total transfusion requirements (mL/kg) - Infants - Children	 7.9 (0.4, 14.4) 6.3 (1.9, 15.3)	 15.9 (4.6, 33.5) 10 (0, 14.6)	NR	No significant difference (infants and children) *P* = 0.065 *P* = 0.863
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric cardiac surgery patients undergoing cardiopulmonary bypass.				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study site South Korea (Level C).				
Comments				
The authors noted that the significantly higher volume of fresh frozen plasma added to the pump prime in the treatment groups is reasonable and expected given the nature of the study. The authors concluded improvements to hemodilution-related coagulation dysfunction were shown with the inclusion of FFP in pump priming for congenital heart surgery immediately after weaning from CPB and after heparin reversal. The clinical effects and benefits were not clear and were not shown to continue to the 24h in ICU.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; IQR, interquartile range; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial

STUDY DETAILS: RCT		
Citation		
McCall MM, Blackwell MM, Smyre JT, Sistino JJ, Ascell JR, Dorman H, Bradley SM. (2004) Fresh Frozen Plasma in the Pediatric Pump Prime: A Prospective, Randomized Trial. Ann Thorac Surg 77: 983-7.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Surgery unit at a single hospital in South Carolina, USA.
Intervention	Comparator	
One unit of fresh frozen plasma (FFP) added to pump prime.	No FFP added to pump prime (more albumin than intervention group)	
Population characteristics		
Infant patients <8kg scheduled for cardiac surgery with CPB. Patients with pre-existing coagulopathy, receiving a medication known to alter coagulation, or for whom CPB was a reoperation, were excluded.		
Length of follow-up	Outcomes measured	
24 hours.	Transfusion requirements and fibrinogen levels.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: An RCT of FFP compared to no FFP for reducing transfusion requirements and hypofibrinogenaemia in infants undergoing cardiopulmonary bypass surgery. 20 patients were randomised the day before surgery using sealed envelopes. Blinding was not reported for clinicians, investigators or outcome assessors. Patient characteristics were similar between groups although 3 were cyanotic in the FFP group compared with 2 patients in the no FFP group. The study was underpowered and the authors noted the small size of the study did not allow for detecting differences between cyanotic/acyanotic patients or those undergoing simple/complex operations. Loss to follow-up not explicitly reported although analysis occurred in all 20 patients recruited. Note: patients in the intervention group received less albumin in the pump prime than patients in the control group due to the colloid osmotic pressure of FFP.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	10	10
Efficacy analysis (ITT)	10	10
Efficacy analysis (PP)	10	10
Safety analysis	NR	NR

Outcome	FFP Mean ± SD	No FFP Mean ± SD	Risk estimate (95% CI)	Significance *P*-value
Mean chest tube output over first 24 hr (mL/kg)	10 ± 7	10 ± 5	NR	*No significant difference* *P* = 0.9
Donor exposures per patient (RBC)	1.8 ± 0.4	2.1 ± 0.3	NR	*No significant difference* *P* = 0.09
Donor exposures per patient (platelets)	0.9 ± 0.7	1.0 ± 0.7	NR	*No significant difference* *P* = 0.8
Donor exposures per patient (FFP)	1.0 ± 0.0	0.3 ± 0.5	NR	*Favours no FFP* *P < 0.001*

Donor exposures per patient (cryoprecipitate)	0.4 ± 0.8	2.0 ± 0.9	NR	*Favours FFP* *P* < 0.001
Total donor exposures per patient	4.1 ± 1.5	5.4 ± 1.4	NR	*No significant difference* *P* = 0.06
Patients receiving FFP post-operative prior to ICU admission	0/10 (0%)	3/10 (30%)	NR	NR
Patients receiving cryoprecipitate post-operative prior to ICU admission	2/10 (20%)	0/10 (0%)	NR	NR
Patients receiving platelets post-operative prior to ICU admission	1/10 (10%)	1/10 (10%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to infants weighing less than 8kg requiring cardiopulmonary bypass surgery.				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats (Level C).				
Comments				
The authors concluded that the use of FFP in the pump prime significantly limited dilutional hypofibrinogenaemia, decreased the transfusion of cryoprecipitate after bypass, and tended to decrease the overall mean patient exposure to blood products.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial

STUDY DETAILS: RCT		
Citation		
The Northern Neonatal Nursing Initiative (NNNI) Trial Group (1996a) A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. European Journal of Pediatrics, 155(7): 580-8.		
Affiliation/Source of funds		
The scientific co-ordination of the trial was funded as part of the European Community Concerted Action programme. The Perinatal Trials Service and the National Perinatal Epidemiology Unit are funded by the Department of Health, UK.		
Study design	Level of evidence	Location/setting
RCT	Level II	Multi-centre, UK (maternity units from 18 hospitals)
Intervention	Comparator	Comparator 2
Fresh frozen plasma (FFP) 20 mL/kg infused over 15min with 10 mL/kg 24 h later	Gelatin plasma substitute 20 mL/kg infused over 15min with 10 mL/kg 24 h later	Glucose as a 10% dextrose or dextrose saline 60-120 mL/kg infused for at least 24 hours (control)
Population characteristics		
Preterm infants born before 32 weeks gestation who were <2 hours old. The fundamental entry criterion was that the responsible clinician was uncertain whether or not to use the plasma volume expansion. Exclusion criteria: none specified however there were 190 potentially eligible babies who did not enter the trial. The authors reported that 61 of these were judged too small or ill to justify enrolment at birth (all of whom died). A further 24 babies who did not enrol 24 also died before discharge. Other non-entry reasons include delays in ethics approval, parent non-consent, and administrative errors.		
Length of follow-up	Outcomes measured	
6 weeks (planned 2 years) * Current paper only reports on 6-week outcomes. The final analyses planned for 2 years post intervention is reported elsewhere (see NNNI 1996b).	Primary: death before 6 weeks, survival with severe disability at the age of 2 years. Secondary: death before discharge, survival with major or minor cerebral ultrasound abnormality at 6 weeks (e.g. intraventricular haemorrhage (IVH), ventriculomegaly, parenchymal abnormality)	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: A three-armed RCT comparing FFP to either a gelatin plasma substitute or glucose (control) in 776 preterm infants <2 hrs old on mortality and severe morbidity. The authors sought analysis from four main comparisons (FFP compared with Control; FFP compared with Gelatin; FFP or Gelatin compared with Control; and Gelatin compared with Control) however results of comparative data were not presented. Randomisation reported via a telephone call to a central randomisation service. Allocation concealment not reported and treating clinicians not blinded to treatment. Outcome assessors were usually unaware of (but not formally "blind" to) the baby's original trial allocation. Patient characteristics were similar between groups. Protocol violations adequately reported. All randomised babies included in the analysis but selective reporting for some outcomes also included. A sample size of 600 was needed to detect (80% power) a 25% rate of the primary outcome at 2 years in the control group and a 15% rate in the intervention group – the authors state this 10% decrease between groups was 'plausible and clinically significant'. The 25% rate was based on previous studies. An interim analysis was conducted 1 year after recruitment to check assumptions of power calculations and as mortality was lower than anticipated the sample size was revised to 700.		
RESULTS		

Population analysed	FFP	Gelatin plasma substitute	Glucose (control)
Randomised	257	261	258
Efficacy analysis (ITT)	257	261	258
Efficacy analysis (PP)	204	228	257

Safety analysis	NR		NR		NR
Outcome	FFP n/N (%) Mean ± SD (n)	Gelatin n/N (%) Mean ± SD (n)	Control n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value
Mortality before 6 weeks	43/257 (16.7%)	54/261 (20.7%)	43/258 (16.7%)	NR	
Mortality before discharge (total)	49/257 (19.1%)	58/261 (22.2%)	47/258 (18.2%)	NR	No significant difference *P* = NR
Mortality before discharge due to respiratory distress	27/257 (10.5%)	27/261 (10.3%)	28/258 (10.9%)	NR	No significant difference *P* = NR
Mortality before discharge due to IVH	15/257 (5.8%)	16/261 (6.1%)	8/258 (3.1%)	NR	No significant difference *P* = NR
Mortality before discharge due to NEC	5/257 (1.9%)	9/261 (3.4%)	7/258 (2.7%)	NR	No significant difference *P* = NR
Mortality before discharge due to other reasons	2/257 (0.8%)	6/261 (2.3%)	4/258 (1.6%)	NR	No significant difference *P* = NR
IVH (all)	44/147 (29.9%)	33/142 (23.2%)	42/161 (26.1%)	NR	No significant difference *P* = NR
Severe IVH	13/147 (8.8%)	15/142 (10.6%)	16/161 (9.9%)	NR	No significant difference *P* = NR
Sepsis	59/257 (23.0%)	34/261 (13.0%)	36/258 (14.0%)	RR 1.70[1.25-2.33]	Favours no FFP *P* = NR
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to preterm infants born before 32 weeks gestation less than 2 hours old.					
Applicability					
Evidence applicable to the Australian healthcare context with few caveats. Study site UK (Level B)					
Comments					
The authors concluded that neither early prophylactic volume expansion, nor a coagulation factor supplement, had any detectable effect on short-term outcome in this large multicentre trial. Note regarding the per-protocol analysis: FFP (n=257) – 204 as allocated, 3 given non-allocated treatment, 10 never given FFP, 26 FFP delayed >2h, 14 treatment not completed; Gelatin (n=261) – 228 as allocated, 1 given non-allocated treatment, 3 never given gelatin, 6 treatment delayed >2h, 23 treatment not completed; Glucose control (n=258) – 257 as allocated, 1 given non-allocated treatment.					

CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial

STUDY DETAILS: RCT		
Citation		
The Northern Neonatal Nursing Initiative (NNNI) Trial Group (1996b) Randomized trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Lancet, 348: 229-32.		
Affiliation/Source of funds		
Funding received from the Department of Health, UK. The Northern Maternity Survey Office was funded by the Northern Regional Health Authority.		
Study design	Level of evidence	Location/setting
RCT	Level II	Multi-centre, UK (maternity units from 18 hospitals)
Intervention	Comparator	Comparator 2
Fresh frozen plasma (FFP) 20 mL/kg infused over 15min with 10 mL/kg 24h later	Gelatin plasma substitute 20 mL/kg infused over 15min with 10 mL/kg 24h later	Glucose as a 10% dextrose or dextrose saline 60-120 mL/kg infused for at least 24 hours (control)
Population characteristics		
Preterm infants born before 32 weeks gestation who were <2hrs old involved in the earlier study (NNNI 1996a) who were followed up at 2 years of age.		
Length of follow-up	Outcomes measured	
2 years from start of original study (NNNI 1996a).	Primary: mortality before 2 years Secondary: visual impairment (including retinopathy of prematurity (ROP)), auditory impairment, and neuromotor impairment at 2 years.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: A three-armed RCT comparing FFP to a gelatin plasma substitute to glucose (control) in preterm infants <2hrs old on mortality and severe morbidity. Outcomes were sought from: 1. FFP compared with Control 2. FFP compared with Gelatin 3. FFP or Gelatin compared with Control 4. Gelatin compared with Control Follow-up study involved a formal independent neurodevelopmental assessment of all survivors at the age of 2 years. Families who participated in the original trial were aware of the 2 year follow-up study and intermittent contact was maintained with trial staff. Randomisation was reported. In the follow-up study independent neurodevelopmental assessment was performed by one paediatrician who reviewed all children prior to hospital records and reports being abstracted and were blinded to treatment group allocation of the children. No loss to follow-up was reported. The trial was designed to detect (80% power) an increase from 75% to 85% in the proportion of babies surviving without severe disability.		

RESULTS					
Population analysed	FFP		Gelatin plasma substitute		Glucose (control)
Randomised	257		261		258
Efficacy analysis (ITT)	257		261		258
Efficacy analysis (PP)	NR		NR		NR
Safety analysis	NR		NR		NR
Outcome	FFP n/N (%) Mean ± SD (n)	Gelatin n/N (%) Mean ± SD (n)	Control n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value

Mortality before 2 years	54/257 (21.0%)	65/261 (24.9%)	53/258 (20.5%)	NR	No significant difference *P* = NR
Mortality (age 1-23 months) due to chronic lung disease	7/257 (2.7%)	7/261 (2.7%)	5/258 (1.9%)	NR	No significant difference *P* = NR
Mortality (age 1-23 months) due to sudden unexpected death	4/257 (1.6%)	5/261 (1.9%)	1/258 (0.4%)	NR	No significant difference *P* = NR
Mortality (age 1-23 months) due to infection	2/257 (0.8%)	2/261 (0.8%)	2/258 (0.8%)	NR	No significant difference *P* = NR
Death or severe disability at age 2 years (FFP versus Gelatin and Control)	NR	NR	NR	RR 0.94 [0.74, 1.15]	No significant difference *P* = NR
Death or severe disability at age 2 years (FFP or Gelatin versus Control)	NR	NR	NR	RR 1.00 [0.80, 1.24]	No significant difference *P* = NR
Mortality (age 1-23 months) due to other	1/257 (0.4%)	2/261 (0.8%)	2/258 (0.8%)	NR	No significant difference *P* = NR
EXTERNAL VALIDITY					
Generalisability					
The results are mostly generalisable to preterm infants born before 32 weeks gestation.					
Applicability					
The results are mostly applicable to the Australian setting.					
Comments					
The authors concluded that there is no evidence that the routine early use of FFP, or some other form of intravascular volume expansion, affects the risk of death or disability in babies born more than 8 weeks before term. Developmental quotients were similar between groups at age 2 years. *This is part 2 of the NNNI 1996a study, reporting on 2 year outcomes.					

CI, confidence interval; FFP, fresh frozen plasma; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; ROP, retinopathy of prematurity; RR, risk ratio

STUDY DETAILS: RCT				
Citation				
Oliver WC, Beynen FM, Nuttall GA , Schroeder DR, Ereth MH, Dearani JA, Puga FJl. (2003) Blood Loss in Infants and Children for Open Heart Operations: Albumin 5% Versus Fresh-Frozen Plasma in the Prime. Ann Thorac Surg 75:1506-12.				
Affiliation/Source of funds				
Financial support was received from the Mayo Foundation.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Surgery unit at a single hospital in Minnesota, USA.		
Intervention	Comparator			
One unit of fresh frozen plasma in the prime.	200 mL of 5% albumin in the prime.			
Population characteristics				
Paediatric patients weighing 10kg or less who required cardiopulmonary bypass surgery. Patients with hematologic diseases, coagulation defect, severe liver dysfunction, and blood transfusion within 24hrs of operation were excluded.				
Length of follow-up	Outcomes measured			
24 hours.	Primary: Blood loss in the ICU 24hrs postoperatively, recorded as mediastinal chest tube drainage (MCTD). Secondary: Blood product usage intraoperatively and 24hrs postoperatively, coagulation tests, intubation and ICU duration.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT conducted with 56 patients comparing fresh frozen plasma to 5% albumin for reducing blood loss in paediatric patients undergoing cardiopulmonary bypass surgery. Method of randomisation was not reported. All personnel associated with the perioperative care of patients (except perfusionists) were blinded to treatment group. Patient characteristic were similar between groups. No loss to follow-up was noted, although analysis was conducted on the same number of patients recruited. A sample size of 28 patients per group was required to provide statistical power of 80% to detect a 30 mL/kg difference in mean 24hr ICU blood loss between groups.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	28		28	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	FFP n/N (%) Mean ± SD (n)	5% Albumin n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value
MCTD (mL/kg) 24hrs postoperatively (all patients)	32.4 ± 17.6 (28)	51.0 ± 38.3 (28)	NR	*No significant difference* *P* = 0.152
MCTD (mL/kg) 24hrs postoperatively (simple surgery patients)	36 (estimated from graph)	22 (estimated from graph)	NR	*No significant difference* *P* = 0.21

MCTD (mL/kg) 24hrs postoperatively (complex surgery patients)	30 (estimated from graph)	68 (estimated from graph)	NR	*Favours FFP* *P* = 0.003
MCTD (mL/kg) 24hrs postoperatively (acyanotic patients)	32 (estimated from graph)	40 (estimated from graph)	NR	*No significant difference* *P* = 0.933
MCTD (mL/kg) 24hrs postoperatively (cyanotic patients)	35 (estimated from graph)	70 (estimated from graph)	NR	*Favours FFP* *P* = 0.035
Units of blood transfused intraoperatively and 24hrs postoperatively (including intervention FFP)	8.0 ± 4.2 (28)	6.1 ± 4.5 (28)	NR	*Favours no FFP* *P* = 0.035
Blood products used (Units) in the operating room and 24hrs postoperatively (excluding intervention FFP)	7.0 ± 4.2 (28)	6.1 ± 4.5 (28)	NR	*No significant difference* *P* > 0.10
Total RBC units transfused	2.6 ± 0.7 (28)	2.5 ± 0.6 (28)	NR	*No significant difference* *P* > 0.10
Total FFP units transfused (excluding intervention FFP)	0.3 ± 0.5 (28)	0.6 ± 0.7 (28)	NR	*Favours FFP* *P* = 0.038
Total platelet concentrate units transfused	2.1 ± 1.7 (28)	1.3 ± 1.6 (28)	NR	*No significant difference* *P* = 0.069
Total cryoprecipitate units transfused	0.1 ± 0.8 (28)	0.1 ± 0.4 (28)	NR	*No significant difference* *P* > 0.10
Total fibrin glue units transfused	1.9 ± 2.1 (28)	1.6 ± 2.5 (28)	NR	*No significant difference* *P* > 0.10
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients 10kg or less who require cardiopulmonary bypass surgery.				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study conducted in the USA (Level C)				
Comments				
Total transfusion requirements were less for acyanotic compared with cyanotic patients (*P* < 0.001) but after adjustment for cyanosis were not significantly associated with either intervention or control. Multivariate analysis found the effect of prime type was found to be dependent on surgical complexity (p=0.002) e.g. greater MCTD with 5% albumin than FFP in complex surgery. Similarly, greater MCTD with cyanotic patients with albumin 5% than with FFP. The authors concluded that substituting 5% albumin for FFP in the prime of acyanotic patients weighting 10kg or less who undergo noncomplex operations requiring CBP significantly reduces perioperative transfusions without increasing blood loss. Note: this conclusion (reported in text) does not reflect the data presented in tables and figures which showed no statistical difference between prime type, acyanotic patients and simple operations.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ICU, intensive care unit; ITT, intention-to-treat; MCTD, mediastinal chest tube drainage; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Baer VL, Lambert DK, Henry E et al. (2007) Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopaenic neonates in a multihospital healthcare system. Journal of Perinatology, 27: 790-796.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Multiple NICUs, USA
Risk factor/s assessed	Potential confounding variables measured	
Platelet transfusion	Platelet count, birth weight, ethnicity, gestational age, Apgar score (1 and 5 min), days intubated, NEC, bacterial or fungal sepsis, meningitis, grade 3 or 4 IVH.	
Population characteristics (including size)		
A retrospective cohort study of 1600 neonates with thrombocytopenia in the USA, to examine the effect of platelet transfusion on mortality. Neonates were included who were admitted to one of the Intermountain Healthcare NICUs with a birth date between 1 January 2002 and 31 December 2005. There were uniform guidelines for administering platelet transfusions across all the participating NICUs. The following platelet transfusion guidelines in NICU were in place: - Transfuse patients on ECMO when platelet count falls <100,000 μL^{-1} or immediately pre– or post-surgery - Transfuse unstable patients (mechanical ventilation or vasopressors) when platelet count falls <50,000 μL^{-1} - Transfuse stable patients when platelet count falls <20,000 μL^{-1} Exclusion criteria: mortality within 48 hrs of NICU admission.		
Length of follow-up	Outcomes measured	
Data was obtained retrospectively for the period 1 January 2002 to 31 December 2005.	Mortality	
Method of analysis		
Differences in categorical variables were assessed using Fisher's exact test. A Student's t-test was used to assess continuous variables. Statistical significance was set as $P < 0.05$. The sensitivity analysis began with a linear logistic regression model using the equation; logit(mortality) = a + b(#transfusions) + g(unmeasured) + error, where 'a' is the number of platelet transfusions given, 'b' is the relationship between platelet transfusions and mortality rate after adjusting for the unmeasured covariate, and 'g' is the relationship between mortality rate and the unmeasured covariate. The correlation between '#transfusions' and the 'unmeasured covariate' is expressed as 'r', and 'b' is then estimated for different values of 'g' and 'r'. A g=0.6 corresponds to an effect equal to the number of transfusions *before* adjusting for the unobserved predictor. In this model, a positive coefficient indicates a higher probability that platelet transfusions are responsible for death. Nonlinear relationships between number of platelet transfusions and mortality were also investigated. The sensitivity analysis assumes a model where number of transfusions and unmeasured variables are predictors of mortality. The unmeasured variables might include such factors as level of illness and genetic predisposition. The unmeasured variables were assumed to be normally distributed with mean 0 and SD of 1 (with larger values indicating sicker infants).		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: There was no difference in gender or ethnicity between the groups but participants who received platelet transfusions had lower birth weights and gestational age than those who did not received platelet transfusions. The authors report that there was no correlation between birth weight and the number of transfusions given. There were uniform guidelines for administering platelet transfusions across all the participating NICUs. The authors conducted 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.		
RESULTS (calculated post-hoc from data (%) reported by authors in table 1a, 1b and table 2)		

Population	Intervention (n)		Comparator (n)	
Available 1-2 transfusions: 3-10 transfusions: >10 transfusions:	494 278 167 49		1106	
Analysed 1-2 transfusions: 3-10 transfusions: >10 transfusions:	494 278 167 49		1106	
Outcome	Platelet transfusion n/N (%)	No platelet transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality (unadjusted)				
All patients	82/494 (16%)	20/1106 (2%)	NR	NR
Patients who received 1-2 transfusions compared with control	31/278 (11%)	20/1106 (2%)	NR	Favours no platelet transfusion P≤0.001
Patients who received 3-10 transfusions compared with control	34/167 (20%)	20/1106 (2%)	NR	Favours no platelet transfusion P≤0.001
Patients who received >10 transfusions compared with control	17/49 (35%)	20/1106 (2%)	NR	Favours no platelet transfusion P≤0.001
IVH grade 3-4 (unadjusted)				
All patients	99/494 (20%)	44/1106 (4%)	NR	NR
Patients who received 1-2 transfusions compared with control	39/278 (14%)	44/1106 (4%)	NR	Favours no platelet transfusion P≤0.001
Patients who received 3-10 transfusions compared with control	50/167 (30%)	44/1106 (4%)	NR	Favours no platelet transfusion P≤0.001
Patients who received >10 transfusions compared with control	10/49 (20%)	44/1106 (4%)	NR	Favours no platelet transfusion P≤0.001
Bacterial sepsis (unadjusted)				
All patients	112/494 (23%)	55/1106 (5%)	NR	NR
Patients who received 1-2 transfusions compared with control	47/278 (17%)	55/1106 (5%)	NR	Favours no platelet transfusion P≤0.001
Patients who received 3-10 transfusions compared with control	43/167 (26%)	55/1106 (5%)	NR	Favours no platelet transfusion P≤0.001
Patients who received >10 transfusions compared with control	22/49 (45%)	55/1106 (5%)	NR	Favours no platelet transfusion P≤0.001
Fungal sepsis (unadjusted)				
All patients	30/494 (6%)	22/1106 (2%)	NR	NR

Patients who received 1-2 transfusions compared with control	8/278 (3%)	22/1106 (2%)	NR	No significant difference *P* = NR
Patients who received 3-10 transfusions compared with control	12/167 (7%)	22/1106 (2%)	NR	Favours no platelet transfusion P≤0.02
Patients who received >10 transfusions compared with control	10/49 (20%)	22/1106 (2%)	NR	Favours no platelet transfusion P≤0.001
Linear regression model				
Mortality with each additional platelet transfusion	NA	NA	OR 1.14 (1.10, 1.18)	Favours no platelet transfusion *P* = NR
Logistic regression model				
Mortality (infants who received ≤10 platelet transfusions)	NA	NA	OR 1.45	Favours no platelet transfusion *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to neonates with thrombocytopenia. (Level A)				
Applicability				
Evidence applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The sensitivity analysis tested 48 hypothetical scenarios combining the risk of additional platelet transfusions and unmeasured variables on mortality. A g-value of 0.6 corresponded to an effect equal to the number of transfusions before adjusting for the unmeasured variable. 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 g<0.6, there was a statistically significant adverse effect of additional platelet transfusions on mortality, beyond the effect of the observed variable. Platelet transfusions were also significantly associated with mortality when an unmeasured variable that had a ≤0.75 correlation with the number of platelet transfusions and a log odds ratio of 0.6 existed. Only in the bottom right of the table was the OR significantly below 1, indicating a beneficial effect of transfusions on mortality rate. This could only occur if an unmeasured variable exists that had at least a 0.75 correlation with the number of transfusions and has a log odds ratio of 1 or greater for increasing the mortality rate. The results of the sensitivity analysis suggested that the platelet transfusions themselves are harmful, and are very likely responsible for some fraction of the increasing mortality rate (refer to Table 3 in paper for full results). The authors concluded that the number of platelet transfusions administered in the NICU predicts the mortality rate. Some of this correlation is ascribable to unknown and unmeasured factors such as level of illness. However, 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.				

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell

STUDY DETAILS: Case-control study		
Citation		
Bonifacio L, Petrova A, Nanjundaswamy S and Mehta R. (2007) Thrombocytopenia related neonatal outcome in preterms. Indian Journal of Pediatrics, 74(3): 269-74.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
Nested case-control study.	Level III-2	Single NICU, USA
Risk factor/s assessed	Potential confounding variables measured	
Severity of thrombocytopenia (mild, moderate, severe), age of thrombocytopenia onset (early, late), gestational age (<28 weeks, 28-32 weeks), platelet transfusion.	Ethnicity, parity, plurality, mode of delivery, chronic maternal disease, smoking, alcohol and drug use, Apgar score, maternal and neonatal treatment, haematological abnormalities, blood and cerebral spinal fluid cultures.	
Population characteristics (including size)		
A case-control study of 164 preterm infants aged ≤ 32 weeks gestation with thrombocytopenia defined as a platelet count of ≤150x10^9/L (cases) or without thrombocytopenia (controls) with the aim of examining the effect of thrombocytopenia severity, gestational age and platelet transfusion on clinical outcomes. There were 94 preterm infants with thrombocytopenia and 70 preterm infants without thrombocytopenia. Exclusion criteria: diagnosed congenital anomalies, transfer-in from another NICU, transfer-out to another facility.		
Length of follow-up	Outcomes measured	
Until hospital discharge	IVH (days 7 and 14 of life), sepsis, NEC, thrombocytopenia-associated bleeding, mortality before discharge.	
Method of analysis		
The authors used the chi-square test to determine the difference in proportion, and analysis of variance to assess continuous data followed by the Tukey test. Two-sided *p*-values <0.05 were considered statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: There were 114 available cases and 80 controls, but 28 infants (18 cases, 10 controls) were excluded as per the exclusion criteria. A comparison was made between those participants who had thrombocytopenia (cases) and those who did not (controls) to establish the similarity between the groups at baseline. A comparison of those who received platelets compared with no platelet transfusion was also made, with the authors noting that infants who received platelet transfusions were significantly more likely to be < 28 weeks gestational age and have lower birth weights than those who did not received platelet transfusions; and that the transfusion rate was higher among infants between 28–32 weeks gestational age with more severe thrombocytopenia. Of the 94 included thrombocytopenia cases, 12 were defined as mild (100-150x10^9/L), 34 as moderate (50-100x10^9/L), and 48 as severe (<50x10^9/L). Only data for moderate to severe thrombocytopenia is presented below. The authors collected data for potential confounding variables from maternal and neonatal medical charts. Not stated whether these were adjusted for in analyses. For data extraction, the authors utilised clinical notes as well as results of the instrumental and laboratory tests.		
RESULTS		

Population	Intervention (n)		Comparator (n)	
Available	60		22	
Analysed	60		22	
Outcome	Platelet transfusion n/N (%)	No platelet transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Gestational age <28 weeks (n=56) (unadjusted)				
IVH	34/49 (69.4)	4/7 (57.2)	NR	No significant difference *P* = NR

Sepsis	31/49 (63.3)	5/7 (71.4)	NR	No significant difference *P* = NR
Mortality	25/49 (51.0)	1/7 (14.3)	NR	*P* = NR[a]
Gestational age 28-32 weeks (n=26) (unadjusted)				
IVH	3/11 (27.3)	3/15 (20.0)	NR	No significant difference *P* = NR
Sepsis	3/11 (27.3)	5/15 (33.3)	NR	No significant difference *P* = NR
Mortality	4/11 (36.4)	3/15 (20.0)	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that platelet transfusions did not lower mortality in very premature born infants with moderate and severe thrombocytopenia during the NICU admission. a. 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.				

CI, confidence interval; FFP, fresh frozen plasma; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported

STUDY DETAILS: Cohort study		
Citation		
Christensen RD, Henry E, Wiedmeier SE et al. (2006) Thrombocytopenia among extremely low birth weight neonates: data from a multihospital healthcare system. Journal of Perinatology, 26: 384-353.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	Multiple NICUs, USA
Risk factor/s assessed	Potential confounding variables measured	
Platelet transfusion	Contributing factors used to explain thrombocytopenia: small for gestational age, DIC, bacterial or fungal infection, NEC, genetics, thrombus, drug-associated, alloimmune or autoimmune, cytomegalovirus, other viral infections.	
Population characteristics (including size)		
284 extremely low birth weight (ELBW) preterm infants (≤1000 g). Exclusion criteria: mortality within 48hrs of NICU admission.		
Length of follow-up	Outcomes measured	
NR	Mortality (during and after thrombocytopenia).	
Method of analysis		
Descriptive statistics were calculated using Statit. Means and standard deviations used to express values in groups that were normally distributed, and medians and ranges to express values in groups that were not. Differences in categorical variables were assessed using the X^2-test. A Student t-test was used to assess continuous variables. Statistical significance was set as $P < 0.05$. All hypotheses were two-tailed.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: a retrospective cohort study of 284 ELBW preterm infants from multiple NICUs in the USA, to examine the effect of platelet transfusion on mortality and bleeding. Data were collected from electronic medical records, case mix, pharmacy, and laboratory systems. Trained clinical personnel entered additional data, with data managed by authorised data analysts. In addition, the medical records (paper) of 208 neonates with thrombocytopenia were reviewed by the authors to determine reasons for ordering each platelet transfusion. There were 76 infants without thrombocytopenia; one received a platelet transfusion. Usable data was only reported for thrombocytopaenic patients (presented below).		
RESULTS		

Population	Intervention (n)		Comparator (n)	
Available	129		79	
Analysed	129		79	
Outcome	Platelet transfusion n/N (%)	No platelet transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Mortality in thrombocytopaenic patients	29/129 (23)	7/79 (9)	NR	Favours no platelet transfusion $P < 0.01$
Patients with thrombocytopenia and 1-5 platelet transfusions (unadjusted)				
Mortality (all)	19/95 (20)	7/79 (9)	NR	NR

Mortality after thrombocytopenia resolved	1/95 (1.1)	1/79 (1.3)	NR	NR
Mortality while thrombocytopenia was still a problem	18/95 (18.9)	6/79 (7.6)	NR	NR
Patients with thrombocytopenia and >5 platelet transfusions (unadjusted)				
Mortality	10/34 (29)	7/79 (9)	NR	NR
Mortality after thrombocytopenia resolved	2/34 (5.9)	1/79 (1.3)	NR	NR
Mortality while thrombocytopenia was still a problem	8/34 (23.5)	6/79 (7.6)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW preterm infants. (Level A)				
Applicability				
Evidence applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors reported that the mortality rate among those who received platelet transfusions was twice that of those that received no platelet transfusions ($P < 0.01$). The authors also reported that the rate of thrombocytopenia observed in this study population was more than twice that reported among the general NICU population.				

CI, confidence interval; DIC, disseminated intravascular coagulation ; ELBW, extremely low birth weight; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported

STUDY DETAILS: Cohort study		
Citation		
Church GD, Matthay MA, Liu K, Milet M & Flori HR (2009) Blood product transfusions and clinical outcomes in pediatric patients with acute lung injury. Pediatric Critical Care Medicine, 10(3): 297-302.		
Affiliation/Source of funds		
Support was received in part from the Children's Hospital and Research Center at Oakland's Pediatric Clinical Research Center. Dr Flori, Dr Liu and Dr Matthay received funding, but report that the sources had no involvement in the study design, data collection, analysis, interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. The authors did not disclose any potential conflict of interest.		
Study design	Level of evidence	Location/setting
Retrospective analysis of a prospective cohort study	Level III-2	PICUs at two children's hospitals, USA.
Risk factor/s assessed	Potential confounding variables measured	
Transfusion of RBC, FFP and/or platelets within the first 72hrs after diagnosis of acute lung injury	Age, sex, ethnicity, diagnosis associated with ALI, medical history, air leak, adjusted exhaled tidal volume, hematologic failure, DIC, thrombocytopenia, neutropenia, red cell, platelet, or FFP transfusions, peak inspiratory pressure, positive expiratory pressure, Pao2/FIo2, static respiratory compliance, pH, base excess, mean airway pressure, and presence of organ system failure. The authors also noted that haemolytic transfusion reactions and bacterial contaminant could confound the interpretation of results; however, that the incidence of these events was low so their contribution to results, if any, would be minimal.	
Population characteristics (including size)		
315 paediatric intensive care patients aged from 36 weeks corrected gestational age to 18 years with acute lung injury at any time during admission to the PICU. Patients were excluded if they received an exchange transfusion or plasmapheresis within the first 72 hrs after diagnosis of ALI. Patients who had pre-existing ALI at a hospital prior to transfer to study site hospital were also excluded.		
Length of follow-up	Outcomes measured	
NR	Primary: all-cause mortality in the PICU. Secondary: duration of unassisted ventilation.	
Method of analysis		
Univariate assessment of clinical risk factors associated with mortality was completed using Chi-squared and logistic regression analyses. Linear regression was used to test the association of transfusions with the duration of unassisted ventilation. Statistical analyses to evaluate for the presence of interactions between potential confounding variables (see above) were also carried out: all variables with a p-value <0.1 were included in backward, stepwise multivariate models. A p-value of <0.5 was considered statistically significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: a retrospective analysis of a prospectively gathered database of 315 paediatric intensive care patients with acute lung injury comparing those who received transfusion of blood products to those who did not on mortality and ventilation outcomes. Only blood transfusions administered in the first 72 hours after diagnosis of acute lung injury were included in the analysis. The authors note that one limitation to the study is that some patients may have received more than one blood product which may have complicated the effect of an individual blood product transfusion.		
RESULTS		
Population	With risk factor	Without risk factor
Available (n=328)	NR	NR
Analysed (n=315)	152[a]	163

Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Any transfusion compared with no transfusion				
PICU mortality	41/152 (27.0%)	28/163 (17.2%)	NR	Favours no transfusion *P* = 0.04
Platelet transfusion compared with no transfusion				
PICU mortality *Percentages estimated from graph (Figure 1 in Church 2009). N=216	NR/53 (36%)	NR/163 (18%)	NR	Favours no transfusion *P* < 0.005
FFP transfusion compared with no transfusion				
PICU mortality *Percentages estimated from graph (Figure 1 in Church 2009). N=203	NR/40 (50%)	NR/163 (17%)	NR	Favours no transfusion *P* < 0.001
Multivariate analysis (stepwise logistic regression analysis)				
Platelet transfusion[b] (mL/kg) and mortality			OR 1.85 [0.63, 5.46]	No significant difference *P* = 0.26
FFP (mL/kg/24 hr) and mortality			OR 1.08 [1.00, 1.18]	Favours no transfusion *P* = 0.04
Organ system dysfunction			OR 10.23 [4.89, 21.34]	Favours no transfusion *P* < 0.001
Pao2/FIo2 per 20-point decrease			OR 1.12 [1.03, 1.23]	Favours no transfusion *P* = 0.01
DIC			OR 0.74 [0.28, 1.90]	No significant difference *P* = 0.53
Multivariate analysis (alternate analysis)				
FFP and mortality (mL/kg/24 hr)			OR 1.08 [0.98, 1.19]	No significant difference *P* = 0.09
PRISM III (paediatric risk of mortality score)			OR 1.19 [1.13, 1.24]	Favours no transfusion *P* < 0.001
DIC			OR 0.62 [0.20, 1.88]	No significant difference *P* = 0.40
EXTERNAL VALIDITY				
Generalisability				
Evidence generalisable to critically ill paediatric patients aged from 36 weeks corrected gestational age with some caveats (Level B).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. Study sites are in the USA (Level C).				
Comments				

The authors noted that both platelet and FFP transfusions were significantly associated with increased mortality on univariate analysis. On multivariate analysis, the transfusion of FFP alone was associated with increased mortality, independent of the presenting oxygenation defect as measured by the Pao2/FIo2, or the presence of multi-organ system failure or DIC. The authors concluded that the transfusion of FFP is associated with an increased risk of mortality in children with ALI.

a. It is written in one section of text that 154 patients received a blood product transfusion; however, everywhere else this number is written as 152, which adds up to the total number of patients that were stated to have been analysed (315). There is no mention of two patients being lost to follow-up or not being included in the analysis, so we have assumed the 154 to be an error.

b. It is unclear whether platelet transfusion was included in this multivariate analysis. In Table 2 it is not included, but in text it is described together with the other variables.

ALI, acute lung injury; CI, confidence interval; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; OR, odds ratio; NEC, necrotising enterocolitis; NR, not reported; PICU, paediatric intensive care unit

STUDY DETAILS: Cohort study		
Citation		
Karam O, Lacroix J, Robitaille N, Rimensberger PC & Tucci M (2013) Association between plasma transfusions and clinical outcome in critically ill children: a prospective observational study. Vox Sanguinis, 104: 342-9.		
Affiliation/Source of funds		
Funding was received by the Fonds de la Recherche en Sante du Quebec (grant # 24460).		
Study design	Level of evidence	Location/setting
Prospective cohort study.	Level III-2	Single PICU, Canada.
Risk factor/s assessed	Potential confounding variables measured	
Transfusion of FFP or FP (leukoreduced).	Weight, PRISM score and international normalised ratio (INR) at admission, plasma transfusions prior to admission, need for extracorporeal life support (ECLS), RBC and platelet transfusions.	
Population characteristics (including size)		
831 pediatric intensive care patients aged <18 years (prospectively enrolled over a 1-year period). Exclusion criteria: need of plasma exchange therapy, prematurity (patient age <40 gestational weeks), age <3 days, pregnancy, post-partum admission and brain death at PICU admission.		
Length of follow-up	Outcomes measured	
28 days or until hospital discharge or death (whichever occurred first)	Primary: new or progressive MODS Secondary: nosocomial infections, ICU length of stay, 28-day mortality	
Method of analysis		
Fisher's exact test was used to undertake unadjusted univariate analysis of categorical variables and outcome. Student's t-test was used for continuous variables. Correlations between two continuous variables were analysed with Pearson's correlation test. Logistic regression was used to compare odds ratios for development of the primary and secondary outcomes, and adjustments were made for weight as well as variables associated with the primary outcome (see above). Age was not included in the logistic models as it was co-linear with weight. The usefulness of the model in predicting outcome was assessed using a Nagelkerte R2 test. The model was also evaluated with an area under the ROC curve.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: a prospective cohort study of 831 paediatric intensive care patients to assess the risk of FFP transfusion on new or progressive MODS, as well as infection, PICU length of stay and mortality. There were 911 patients available for analysis however 80 patients did not meet the eligibility criteria. There were no formal transfusion guidelines in the PICU. Patient characteristics varied among groups notably in age, weight and severity of illness, with those receiving transfusions being younger, smaller and with more severe illness than those who did not receive a transfusion. The authors stated that this is the only prospective epidemiological study that describes the clinical impact of plasma transfusions in critically ill children. Regression modelling was used which rigorously included several clinically significant covariables that had not been considered in a previous paediatric plasma study (Church 2009). Results were adjusted for weight, severity score and coagulopathy at admission, plasma prior to admission, need for ECLS, RBC and platelet transfusions. All deaths were considered related to progressive MODS. There was no reporting of whether outcomes were assessed blind to risk factor exposure, and it is assumed they were not.		
RESULTS		

Population	Intervention (with risk factor)		Comparator (without risk factor)	
Available (n=911)	NR		NR	
Analysed	94		737	
Outcome	FFP n/N (%)	No FFP n/N (%)	Risk estimate (95% CI)	Significance *P*-value

Nosocomial infections	16/94 (17.0%)	27/737 (3.7%)	UR 5.4 [2.8, 10.4] AR 2.3 [1.0, 5.3]	Borderline favours no FFP *P* = NR
28-day mortality	15/94 (16.0%)	13/737 (1.8%)	UR 10.6 [4.9, 23.1] AR 2.2 [0.5, 8.6]	No significant difference *P* = NR
New or progressive MODS	39/94 (41.5%)	61/738 (8.3%)	UR 7.9 [4.8, 12.8] AR 3.2 [1.6, 6.6]	Favours no FFP *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to critically ill paediatric patients.				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site Canada (Level B).				
Comments				
The authors noted that in critically ill children, plasma transfusions seemed to be independently associated with an increased occurrence of new or progressive MODS, nosocomial infections and prolonged length of stay. The authors noted that their internal validity is strengthened by other studies corroborating both the direction and magnitude of their results (Sarani 2008, Church 2009, Watson 2009). A significant limitation of this study is the heterogeneity of the study population and the difference in severity of illness between the two groups.				

AR, adjusted risk; CI, confidence interval; ECLS, extracorporeal life support; FFP, fresh frozen plasma; MODS, multiple organ dysfunctions; NR, not reported; PICU, paediatric intensive care unit; RBC, red blood cell; UR, unadjusted risk

STUDY DETAILS: Cohort study		
Citation		
Nacoti M, Cazzaniga S, Lorusso F et al (2012) The impact of perioperative transfusion of blood products on survival after pediatric liver transplantation. Pediatric Transplantation, 16: 357-66.		
Affiliation/Source of funds		
The authors stated they had no conflicts of interest to declare.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	General Hospital of Bergamo, Italy.
Risk factor/s assessed	Potential confounding variables measured	
Perioperative transfusion of blood products (RBC, fibrinogen and FFP).	Age, sex, weight, height, BMI, indication for transplantation, PELD score, lab tests, PICU's variables.	
Population characteristics (including size)		
243 paediatric liver transplant patients aged <18 years from deceased brain-dead donors. Exclusion criteria: Combined organ transplantations were excluded.		
Length of follow-up	Outcomes measured	
1 year	Primary: patient and graft survival in the first year after transplantation	
Method of analysis		
Kaplan–Meier product-limit estimator was used to compute cumulative survival rates. Univariate analysis with log-rank test was used to assess survival differences among variables categories. Continuous variables were categorised using their median or tertiles as cut-off points. All variables with a p-value ≤ 0.1 in the univariate analysis were included in a multivariate analysis to assess which factors influenced patient and graft survival. Cox proportional hazard regression with forward stepwise selection was used to identify main risk factors. Complications in the first year were considered in survival analysis to adjust for postoperative confounders. Effects of identified factors were presented as hazard ratios with 95% confidence interval together with their p-values. Propensity score analysis was used to adjust risk factors for selection biases in the use of blood products. Multivariate logistic regression with stepwise selection was used to assess propensity score function. All statistical tests were considered significant for p-values ≤ 0.05.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a retrospective cohort study of 243 consecutive paediatric liver transplant patients aged <18 years at a single hospital in Italy, to assess the risk of perioperative transfusion of RBC and FFP on patient and graft survival in the first year after transplantation. Seven hepatobiliary surgeons performed all the liver transplants with two involved in each procedure. Fifteen anaesthesiologists were involved throughout the study period. Transfusion policy was based on clinical assessment, therefore subject to bias. Due to the nature of the study blinding to outcome was not feasible. Missing data were <2%. 39 patients stopped follow-up within one year. 26 patients died. One year patient survival was significantly associated with the number of allogenic RBC and FFP units transfused during surgery. Limitations of the study included retrospective nature, inability to distinguish whether survival was related to massive transfusion due to different triggers.		
RESULTS[a]		
RBC transfusion		

Population analysed N=243	High RBC transfusion (n) ≥3 units (intra-op) ≥0.1 unit (post-op)	Med RBC transfusion (n) 2 units (intra-op)	Low/no RBC transfusion (n) ≤1 unit (intra-op) 0 units (post-op)
During surgery	39 (16%)	75 (30.9%)	129 (53.1%)
Within 48 hours after liver transplant	64 (23.3%)	NA	179 (73.7%)

Outcome	High transfusion n/N (%)	Med transfusion n/N (%)	Low transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Patient survival at 1 year (univariate)					
RBC during surgery	27/39 (69.9%)	67/75 (89.1%)	122/129 (94.3%)	NR	Favours low RBC *P* < 0.001
RBC within 48 hours after liver transplant	55/64 (86.6%)	NA	160/179 (89.5%)	NR	No significant difference *P* = 0.548
Patient survival at 1 year (multivariate)					
RBC during surgery (2 units) (≤ 1 unit reference category)				HR 1.847 [0.647, 5.267]	No significant difference *P* = 0.251
RBC during surgery (≥3 units) (≤ 1 unit reference category)				HR 3.146 [1.097, 9.022]	Favours low RBC *P* = 0.033
Patient survival at 1 year (propensity score-adjusted[b]) (≤ 1 unit reference category)					
RBC during surgery (2 units) (≤ 1 unit reference category)				HR 2.170 [0.747, 6.301]	No significant difference *P* = 0.154
RBC during surgery (≥3 units) (≤ 1 unit reference category)				HR 3.010 [1.009, 8.979]	Favours low RBC *P* = 0.048
FFP transfusion					
Population analysed N=243	High FFP transfusion (n) ≥3 units (intra-op) ≥1 unit (post-op)		Med FFP transfusion (n) 2 units (intra-op)		Low/no FFP transfusion (n) ≤1 unit (intra-op) 0 units (post-op)
During surgery	63 (25.9%)		60 (24.7%)		120 (49.4%)
Within 48 hours after liver transplant	51 (21.0%)		NA		192 (79.0%)
Outcome	High transfusion n/N (%)	Med transfusion n/N (%)	Low transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Patient survival at 1 year (univariate)					
FFP during surgery	48/63 (75.8%)	55/60 (91.3%)	113/120 (94.0%)	NR	Favours low FFP *P* = 0.001
FFP within 48 hours after liver transplant	41/51 (79.7%)	NA	175/192 (91.3%)	NR	Favours no FFP *P* = 0.022
Patient survival at 1 year (multivariate[b])					
FFP during surgery (2 units) (≤ 1 unit reference category)	NR	NR	NR	HR 1.124 (0.341, 3.705)	No significant difference *P* = 0.848

FFP during surgery (≥ 3 units) (≤ 1 unit reference category)	NR	NR	NR	HR 3.346 (1.196, 9.364)	Favours low FFP *P* = 0.021
Patient survival at 1 year (propensity score-adjusted[b]) (≤ 1 unit reference category)					
FFP during surgery (2 units)	NR	NA	NR	HR 1.111 (0.336, 3.680)	No significant difference *P* = 0.863
FFP during surgery, ≥ 3 units	NR	NA	NR	HR 2.808 (0.927, 8.505)	No significant difference *P* = 0.068
Platelet transfusion					
Population analysed	High PLT transfusion (n) ≥181x1000/cc (pre-op) ≥1 unit (intra– or post-op)		Med PLT transfusion (n) 91-180x1000/cc (pre-op)		Low PLT transfusion (n) ≤90x1000/cc (pre-op) 0 units (intra– or post-op)
Before surgery (N=237)	79 (33.3%)		82 (34.6%)		76 (32.1%)
During surgery (N=243)	11 (4.5%)		NA		232 (95.5%)
Within 48 hours after liver transplant (N=243)	15 (6.2%)		NA		228 (93.8%)
Outcome	High PLT transfusion n/N (%)	Med PLT transfusion n/N (%)	Low PLT transfusion n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Patient survival at 1 year (univariate)					
Platelets before surgery	70/79 (88.1%)	73/82 (88.5%)	69/76 (90.2%)	NR	No significant difference *P* = 0.929
Platelets during surgery	9/11 (81.8%)	NA	207/232 (89.1%)	NR	No significant difference *P* = 0.342
Platelets within 48 hours after liver transplant	12/15 (79.4%)	NA	204/228 (89.4%)	NR	No significant difference *P* = 0.237
Fibrinogen					
Population analysed N=241	High fibrinogen ≥221 mg/dL		Med fibrinogen 141-220 mg/dL		Low fibrinogen ≤140 mg/dL
Before surgery	82 (34.0%)		80 (33.2%)		79 (32.8%)
Outcome	High fibrinogen n/N (%)	Med fibrinogen n/N (%)	Low fibrinogen n/N (%)	Risk estimate (95% CI)	Significance *P*-value
Patient survival at 1 year (univariate)					
Fibrinogen before surgery	70/82 (84.9%)	71/80 (88.4%)	74/79 (93.4%)	NR	No significant difference *P* = 0.308
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to paediatric liver transplant patients (Level A).					
Applicability					
Evidence applicable to the Australian healthcare context with few caveats. Study site Italy (Level B).					

Comments
Although a relationship between number of units transfused and infant survival was observed, the authors noted this may not be considered causal but rather a surrogate marker for sicker patients. The multiple regression analysis (controlling for potential confounding factors) confirmed the negative and independent impact of blood products on one year survival. The propensity score adjusted analysis controlled for selection bias, and confirmed the results from the multivariate analysis. The authors concluded that most mortality and graft loss occurred in the first few months after transplantation, confirming findings of earlier studies. Decreasing early surgical complications and perioperative transfusion will improve the overall long-term patient and graft survival after paediatric liver transplantation. a. Only percentage values were reported. Patient numbers were back-calculated from total N. Values do not match due to rounding. b. Forty-one risk factors were investigated, of which five were identified as predicting one year patient survival, when analysed using a multivariate Cox regression model. These included recipients age, total ischaemia time, number of RBC units transfused during surgery, number of FFP units transfused during surgery, and biliary complications. c. Propensity score analysis was used to control for confounding factors that could potentially influence the use of blood products. Outcome for propensity score was defined as children with overall blood components transfused above the median value of 700 mL vs. children below this value.

BMI, body mass index; CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; NA, not applicable; NR, not reported; PELD, paediatric end stage liver disease; PICU, paediatric intensive care unit; RBC, red blood cell

STUDY DETAILS: Cohort study		
Citation		
von Lindern JS, Hulzebos CV, Bos AF, Brand A, Walther FJ & Lopriore E (2012) Thrombocytopaenia and intraventricular haemorrhage in very premature infants: a tale of two cities. Arch Dis Child Fetal Neonatal Ed, 97: F348-F352.		
Affiliation/Source of funds		
None reported.		
Study design	Level of evidence	Location/setting
Retrospective cohort study.	Level III-2	2 NICUs, The Netherlands.
Risk factor/s assessed	Potential confounding variables measured	
Restrictive platelet transfusions (transfused only when active haemorrhage and platelet count <50x10^9/L); liberal platelet transfusions (transfused according to predefined platelet count thresholds).	Rate and severity of thrombocytopenia, gestational age at birth, birth weight, gender, Apgar score, days on respiratory support, sepsis, NEC grade 2 or above, major haemorrhage.	
Population characteristics (including size)		
679 premature infants with gestational age <32 weeks admitted to NICU. Exclusion criteria not reported.		
Length of follow-up	Outcomes measured	
NR	Primary: incidence and severity of IVH Secondary: mortality, major haemorrhage	
Method of analysis		
The t-test was used to analyse continuous variables and Fisher's exact test for nominal variables. Logistic regression analysis was performed for potential confounding factors. A p-value of <0.05 was considered significant.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: There were 689 infants eligible for inclusion. Ten infants died shortly after birth, before a cranial ultrasound or other tests (e.g., platelet counts) could be performed, and were therefore not included in the analysis. No cranial ultrasound scans were performed in 18 other infants (reasons not reported). Patients were also excluded from final analysis if their platelet count was unknown (n=8). There were no significant differences in patient demographic and clinical characteristics between the two units but among those with thrombocytopenia the incidence of NEC was higher in the restrictive transfusion unit (10%) compared with those in the liberal transfusion unit (4%). Blinding of outcome assessment is unclear (each NICU read their own scans). Due to the potential for differences in interpretation of cranial ultrasounds between centres, it would have been preferable for an independent reviewer to evaluate the ultrasound scans. There were two protocol violations in the restrictive transfusion group and one in the liberal transfusion group.		
RESULTS * The data is reported according to NICU transfusion policy, not specifically infants who received platelet transfusions		

Population	Restrictive platelet transfusion (first NICU)	Liberal platelet transfusion (second NICU)
Available (n=679)	353	326
Analysed (n=653)	330	323

Outcome	Restrictive n/N (%) Mean ± SD	Liberal n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality (overall)	25/353 (7%)	22/326 (7%)	NR	No significant difference *P* = 0.86
Mortality in infants who received a platelet transfusion	NR	NR	NR	"There was no difference in death rate in infants with and without a platelet transfusion"

IVH (all infants with available cranial ultrasound, n=653)	75/330 (23%)	63/323 (20%)	NR	No significant difference *P* = 0.31
IVH grade 1 in thrombocytopaenic patients	30/145 (21%)	15/141 (11%)	NR	Favours liberal transfusion unit *P* = 0.02
IVH grade 2 in thrombocytopaenic patients	2/145 (1%)	10/141 (7%)	NR	Favours restrictive transfusion unit *P* = 0.02
IVH grade 1 or 2 in thrombocytopaenic patients	32/145 (22%)	25/141 (18%)	NR	No significant difference *P* = 0.36
IVH grade 3 in thrombocytopaenic patients	2/145 (1%)	8/141 (6%)	NR	Borderline favours restrictive transfusion unit *P* = 0.06
IVH grade 4 in thrombocytopaenic patients	10/145 (7%)	8/141 (6%)	NR	No significant difference *P* = 0.67
IVH grade 3 or 4 in thrombocytopaenic patients	12/145 (8%)	16/141 (11%)	NR	No significant difference *P* = 0.38
Major haemorrhage other than IVH requiring one or more platelet transfusions	3/353 (0.85%) *gastrointestinal, adrenal post-surgery	2/326 (0.6%) *pulmonary	NR	NR
Transfusion incidence (RBC)[a]	159/353 (45%)	163/326 (50%)	NR	No significant difference *P* = 0.20
Platelet transfusion in thrombocytopaenic patients (N=288)	21/145 (15%)	44/141 (31%)	NR	Favours restrictive transfusion unit *P* < 0.001
Number of platelet transfusions per thrombocytopaenic patient (N=288)	0.2 ± 0.7	1.1 ± 3.0	NR	Favours restrictive transfusion unit *P* = 0.001
Number of platelet transfusions per transfused patient (N=65)	1.6 ± 0.9	3.6 ± 4.6	NR	Favours restrictive transfusion unit *P* = 0.05
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to premature infants <32 weeks gestational age.				
Applicability				
Evidence applicable to the Australian healthcare context with few caveats. Study site the Netherlands (Level B).				
Comments RBC transfusion incidence is baseline rate. The effect favouring restrictive transfusion unit for platelet transfusions is not included in the evidence report (vol.1). It is logical that infants in the more liberal platelet transfusion group will receive more platelets compared with those in the restrictive platelet transfusion group.				

The authors concluded that in the restrictive transfusion unit, the rate of platelet transfusions was significantly lower, but the incidence and severity of IVH was similar to the liberal transfusion unit. A restrictive platelet guideline is not associated with a higher incidence of IVH.

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 both thrombocytopenia (irrespective of severity) and gestational age <28 weeks.

a. Two infants in the restrictive transfusion unit also had pulmonary haemorrhage managed by mechanical ventilation with positive end-expiratory pressure and endotracheal xylomethazoline

CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; NR, not reported; PDA, patent ductus arteriosus; RBC, red blood cell; SD, standard deviation

F4 Evidence summaries – Question 4

Level I evidence

STUDY DETAILS: SR/MA		
Citation		
Arnold D M, Fergusson D A, Chan A K, Cook R J, Fraser G A, Lim W, Blajchman M A, Cook D J. (2006) Avoiding transfusions in children undergoing cardiac surgery: a meta-analysis of randomized trials of aprotinin. Anesthesia and Analgesia, 102(3): 731-737.		
Affiliation/Source of funds		
Author affiliations and sources of funding reported: Donald M. Arnold (Transfusion Medicine Fellow) funded by the Canadian Blood Services. Anthony Chan (Career Investigator) affiliated with the Heart and Stroke Foundation of Canada. Richard J. Cook (Canada Research Chair) affiliated with the Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario. Graeme A. Fraser (recipient of the Edith Turner Foundation Fellowship) affiliated with Centre for Gene Therapeutics, Department of Medicine, McMaster University; Juravinski Cancer Centre, Hamilton, Ontario, Canada. Wendy Lim (holder of Graduate Scholarship from the Canadian Institutes of Health Research) affiliated with the Department of Medicine, Canadian Blood Services. Deborah J. Cook (Canada Research Chair) affiliated with Departments of Medicine, Medicine & Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario.		
Study design	Level of evidence	Location/setting
Meta-analysis of Level II studies	I	NR
Intervention	Comparator	
Aprotinin	Placebo, No aprotinin, Other antifibrinolytic drugs (EACA)	
Population characteristics		
Paediatric patients aged <18 years with primary or redo open heart surgery with CPB for repair or palliation of CHD		
Length of follow-up	Outcomes measured	
NR	Proportion of paediatric patients requiring transfusion Amount of blood transfused Amount of chest drainage Red blood cell (RBC) or whole blood transfusion included unless the type of blood transfusion not specified	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Good

Description: Twelve RCTs in exclusively paediatric patients were included (Mossinger 2003; Chauhan 2000; Miller 1998; Davies 1997; Seghaye 1996; D'Errico 1996; Boldt 1994; Herynkopf 1994; Boldt 1993a; Boldt 1993b; Dietrich 1993; Gomar 1995). Chauhan 2000 was a four-armed RCT comparing aprotinin to EACA to aprotinin + EACA to no treatment. Participants in Mossinger (2003) were those undergoing primary sternotomy weighing <10 kg only, participants in Boldt (1994) and Herynkopf (1994) were those undergoing primary sternotomy only. The specific conditions of participants in other studies were not reported in the SR. The authors reported that screening and data extraction was performed by two independent reviewers. Methodological quality was determined by two independent reviewers blinded to the details of the studies, using the Jadad quality assessment scale. Areas assessed included adequacy of allocation concealment and the use of an objective, predefined transfusion protocol. The authors reported that the methodological quality of most included studies were poor, mainly due to inadequate description of the methods (e.g. attrition, allocation concealment, the use of an objective transfusion protocol) or potential bias in the funding sources. Meta-analyses were conducted but the authors reported that heterogeneity was high for the outcomes volume of blood transfused and volume of chest tube drainage.

RESULTS

Outcome	Aprotinin n/N (%)	Placebo or no treatment n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Volume of blood transfused (mL/kg) 7 studies (Chauhan 2000[a], Davies 1997, D'Errico 1996, Seghaye 1996, Herynkopf 1994, Boldt 1993a x2[b]) N = 404	NR	NR	WMD -8.42 [-19.86, 3.02]	No significant difference *P* = NR Substantial heterogeneity *P* = NR (I^2=96%)
Volume of chest tube drainage (mL/kg) 11 studies (Mossinger 2003, Chauhan 2000[a], Miller 1998, Davies 1997, D'Errico 1996, Gomar 1995, Boldt 1994, Boldt 1993a x2[b], Boldt 1993b, Dietrich 1993) N = 571	NR	NR	WMD -0.97 [-4.94, 2.99]	No significant difference *P* = NR Substantial heterogeneity *P* = NR (I^2=77%)
Proportion of children who received RBC or whole blood transfusions				
All studies 6 studies (Mossinger 2003, Miller 1998, Davies 1997, D'Errico 1996, Herynkopf 1994, Boldt 1994) N = 362	NR	NR	RR 0.67 [0.51, 0.89]	Favours aprotinin *P* = NR Mild heterogeneity *P* = NR (I^2=15%)
Good quality studies 4 studies (Mossinger 2003, D'Errico 1996, Davies 1997, Herynkopf 1994) N = 186	NR	NR	RR 0.60 [0.38, 0.95]	Favours aprotinin *P* = NR Heterogeneity NR

Studies using an objective transfusion protocol 3 studies (D'Errico 1996, Davies 1997, Herynkopf 1994) N = 126	NR	NR	RR 0.72 [0.58, 0.89]	Favours aprotinin *P* = NR Heterogeneity NR
Patients undergoing primary sternotomy 3 studies (Mossinger 2003, Boldt 1994, Herynkopt 1994) N = 120	NR	NR	RR 0.44 [0.26, 0.76]	Favours aprotinin *P* = NR Heterogeneity NR
Patients with mean weight >10 kg 5 studies (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
Patients with mean weight <10 kg 1 study (Mossinger 2003) N = 60	NR	NR	NR	Favours aprotinin *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with CHD undergoing open heart surgery with CPB (Level A).				
Applicability				
Evidence may or may not be applicable to the Australian healthcare context (study locations not reported) (Level C).				
Comments				
The authors concluded that, in paediatric patients, aprotinin reduced the proportion of patients who received allogeneic blood transfusions during cardiac surgery with CPB. However, aprotinin had no significant effect on the volume of blood transfused or on the amount of chest tube drainage. Among trials examining the effect of aprotinin in children, there is a need for consistency in reporting dosing regimens and transfusion volume and incidence using objective transfusion protocols. Before the routine use of aprotinin in children undergoing cardiac surgery can be recommended, further independent RCTs are needed to carefully examine clinically important outcomes including bleeding, reoperation rates, and death in addition to the need for perioperative transfusion.				

CBP, cardiopulmonary bypass; CHD, congenital heart defects; CI, confidence interval; EACA, Epsilon-aminocaproic acid; ITT, intention-to-treat; MA, meta-analysis; NA; not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SR, systematic review; WMD, weighted mean difference

a. Analysis included Chauhan 2000 which was a four-armed RCT comparing aprotinin to EACA to aprotinin + EACA to no treatment.

b. Boldt 1993a was analysed as two separate studies (children < and >10 kg).

Analysis includes studies 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.

STUDY DETAILS: SR/MA		
Citation		
Backes CH, Rivera BK, Haque U, Bridge JA et al. (2014) Placental transfusion strategies in very preterm neonates: a systematic review and meta-analysis. Obstetrics and Gynecology, 124(1): 47–56.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of RCTs.	Level I	NR
Intervention	Comparator	
Placental transfusion strategies including delayed cord clamping (DCC) >20 seconds after delivery, or cord milking defined as squeezing and pulling the umbilical cord toward the newborn at least 3x after delivery.	Early cord clamping (ECC) <15 seconds after delivery.	
Population characteristics		
Very preterm infants <32 weeks gestation.		
Length of follow-up	Outcomes measured	
Until hospital discharge.	Neonatal outcomes: IVH (all grades), severe IVH (grade 3-4), sepsis, or NEC (Bell's stage 2+) during initial hospitalisation, mortality before discharge.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: There were 12 included studies: Baenziger 2007, Hosono 2008, Oh 2002 (abstract only), Oh 2011, Gokmen 2011, Ibrahim 2000, Mercer 2003, Mercer 2006, Sommers 2012, March 2013, Kinmond 1993, McDonnell 1997 Appropriate search strategies and search terms were reported in the supplementary material (Appendix 1). Two authors independently assessed the eligibility of identified studies and extracted data using standardised forms. Trial authors were contacted for additional data when necessary. Any discrepancies were resolved via a third author, with the final decision agreed by consensus. The methodological quality of each study was also independently assessed using a modified version of the Jadad scale. Trials rated ≥10 were considered high quality. There were no disagreements between reviewers regarding trial quality. The characteristics of the individual studies were reported in the supplementary material (Appendix 3) but baseline demographics and characteristics of patients in these studies were not provided. Eight trials were rated high quality with a score of 10 (Kinmond 1993, McDonnell 1997, Ibrahim 2000, Mercer 2003, Mercer 2006, Hosono 2008, Sommers 2012, March 2013). Two trials were given a score of 9 due to not providing justification for sample size (Baezinger 2007, Gokmen 2011) and one trial was given a score of 8 as the description of inclusion/exclusion criteria and withdrawals were not clearly stated (Oh 2011). Oh 2002 was an abstract only and did not have enough detail to receive a quality rating.		
RESULTS:		

Outcome No. trials (No. patients)	Placental transfusion n/N (%) Mean ± SD (n)	ECC n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Significance *P*-value Heterogeneity *P*-value (I^2)

Transfusion incidence (Hosono 2008, Ibrahim 2000, Kinmond 1993, March 2013, McDonnell 1997, Mercer 2006). 6 studies, N=301	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%
No. of transfusions (Kinmond 1993, Ibrahim 2000, Oh 2002, Mercer 2006, Hosono 2008, Gokmen 2011) 6 studies, N=245	NR	NR	MD -1.14 (-2.01, -0.27)	Favours placental transfusion *P* = 0.01 Substantial heterogeneity I^2=64%
IVH all grades (McDonnell 1997, Ibrahim 2000, Oh 2002, Mercer 2003, Mercer 2006, Hosono 2008, Oh 2011, Gokmen 2011, March 2013) 9 studies, N=390	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%
Severe IVH grades 3-4 (McDonnell 1997, Oh 2002, Mercer 2003, Mercer 2006, Hosono 2008, March 2013) 6 studies, N=283	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%
Mortality before discharge (Kinmond 1993, McDonnell 1997, Oh 2002, Mercer 2003, Mercer 2006, Baenziger 2007, Hosono 2008, March 2013) 8 studies, N=373	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%
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats. (Level B)				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)				
Comments				

Sensitivity analyses using the leave-one-out method were performed across all measured outcomes. When the Mercer 2006 and March 2013 trials were excluded in the IVH (all grades) meta-analysis, the result became non-significant. Funnel plots suggested no presence of publication bias in these data, indicating that the loss of statistical significance with study deletion is more likely attributable to lower statistical power from smaller sample sizes. The authors concluded that enhanced placental transfusion (DCC or cord milking) at birth provides better neonatal outcomes than does ECC, most notably reductions in overall mortality, lower risk of IVH and decreased blood transfusion incidence. The optimal umbilical cord clamping practice among neonates requiring immediate resuscitation remains uncertain.

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; IVH, intraventricular haemorrhage; MA, meta-analysis; MD, mean difference; NEC, necrotising enterocolitis; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SR, systematic review

STUDY DETAILS: SR/MA				
Citation				
Faraoni D, Willems A, Melot C, De Hert S, Van der Linden P. (2012) Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. European Journal of Cardio-Thoracic Surgery, 42: 781-6.				
Affiliation/Source of funds				
The authors report no declaration of interest. The authors were affiliated with the Departments of Anaesthesiology and Paediatric Intensive Care, Queen Fabiola Children's University Hospital (HUDERF), the Department of Emergency at Erasme University Hospital and the Department of Anaesthesiology at Ghent University Hospital, Brussels, Belgium.				
Study design	Level of evidence		Location/setting	
Meta-analysis of Level II studies	Level I		Turkey (Bulutcu 2005), India (Chauhan 2003, Chauhan 2004a, Chauhan 2004b), USA (Reid 1997), Canada (Zonis 1996), NR (Levin 2000, Shimizu 2011)*	
Intervention	Comparator			
Tranexamic acid (TXA)	Placebo			
Population characteristics				
Paediatric patients aged <18 years undergoing cardiac surgery.				
Length of follow-up	Outcomes measured			
NR	Blood loss; transfusion of RBCs, platelets (PLT) and fresh frozen plasma (FPP) at 24 hours; post-operative adverse effects; mechanical ventilation duration; length of stay in intensive care unit; mortality			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Eight RCTs were included (Bulutcu 2005; Chauhan 2003; Chauhan 2004a; Chauhan 2004b; Reid 1997; Zonis 1996; Levin 2000; Shimizu 2011). Chauhan 2004a was a five-armed RCT comparing four doses of TXA to placebo. The authors reported that the SR was performed in accordance with the Quality of Reporting of Meta-analyses (QUORUM) consensus. Screening and data extraction were performed by two authors. The methodological quality of included studies was assessed by study design, method of randomisation, blinding, transfusion policy and reporting of primary and secondary outcomes. Each study was assigned a level of recommendation and grade; however the range of possible grades and what these meant were not described. Meta-analyses were performed using both fixed and random effects models. Two sensitivity analyses were performed: one which excluded the five-armed RCT by Chauhan 2004a; and another which excluded all studies by Chauhan et al. This was to explore possible bias introduced by this research team, as they published nearly half of all identified studies. Note: where there was no heterogeneity, data for the fixed effects models will be presented below.				
RESULTS				
Outcome	TXA Mean ± SD	Placebo Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
24 hr postoperative blood loss (mL/kg) 11 studies (N = 848)[a]	NR	NR	Random effects: MD -3.61 [-8.08, 0.85]	No significant difference $P = 0.11$ Substantial heterogeneity $P < 0.00001$ (I^2=82%)

24 hr postoperative transfusion volume (mL/kg)				
RBC 9 studies (N = 710)[a]	NR	NR	Fixed effects: MD -6.38 [-8.28, -4.47]	Favours TXA *P* < 0.00001 No significant heterogeneity *P* = 0.46 (I^2=0%)
PLT 7 studies (N = 520)[a]	NR	NR	Fixed effects: MD -3.70 [-5.40, -2.00]	Favours TXA *P* < 0.0001 No significant heterogeneity *P* = 0.46 (I^2=0%)
FFP 8 studies (N = 669)[a]	NR	NR	Fixed effects: MD -5.52 [-7.54, -3.50]	Favours TXA *P* < 0.00001 No significant heterogeneity *P* = 0.60 (I^2=0%)
Sensitivity analysis: excluding Chauhan 2004a				
24hr postoperative blood loss (mL/kg) 7 studies (N = 608)	NR	NR	Random effects: MD -7.82 [-11.54, -4.10]	Favours TXA *P* = NR Substantial heterogeneity *P* = NR (I^2=57%)
RBC transfusion (mL/kg) at 24h 5 studies (N = 470)	NR	NR	Fixed effects: MD -7.57 [-10.17, -4.98]	Favours TXA *P* = NR No significant heterogeneity *P* = NR (I^2=0%)
PLT transfusion (mL/kg) at 24h 3 studies (N = 180)	NR	NR	Random effects: MD -3.12 [-7.09, 0.96]	No significant difference *P* = NR Substantial heterogeneity *P* = NR (I^2=53%)
FFP transfusion (mL/kg) at 24h 4 studies (N = 429)	NR	NR	Fixed effects: MD -6.19 [-8.87, -3.52]	Favours TXA *P* = NR No significant heterogeneity *P* = NR (I^2=4%)
Sensitivity analysis: excluding Chauhan 2004a, Chauhan 2004b & Chauhan 2003				
24hr postoperative blood loss (mL/kg) 5 studies (N = 388) (exclude all studies by Chauhan 2003, 2004a, b)[c]	NR	NR	Fixed effects: MD -5.22 [-8.16, -2.28]	Favours TXA *P* = NR No significant heterogeneity *P* = NR (I^2=0%)
RBC transfusion (mL/kg) at 24h 3 studies (N = 250)	NR	NR	Fixed effects: MD -8.83 [-13.48, -4.19]	Favours TXA *P* = NR Moderate heterogeneity *P* = NR (I^2=39%)

FFP transfusion (mL/kg) at 24h 2 studies (N = 209)	NR	NR	Random effects: MD -4.48 [-10.27, 1.31]	No significant difference *P* = NR Moderate heterogeneity *P* = NR (I^2=40%)
Subgroup analysis: acyanotic patients				
24 hr postoperative blood loss (mL/kg) 3 studies (N = 298)	NR	NR	NR	No significant difference *P* = 0.47 Heterogeneity NR *P* = NR (I^2=NR)
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients undergoing cardiac surgery with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that TXA reduces blood transfusion volume significantly in paediatric cardiac surgery although the clinical relevance of these results is not clear. As data on postoperative morbidity and mortality and on TXA-related side effects could not be evaluated in the available studies, they concluded that the evidence for the routine use of TXA in paediatric cardiac surgery remains weak. Further studies are needed to assess the potential beneficial effects of TXA on postoperative outcomes and to define the optimal dosage scheme for TXA. *NR in current study. Data pulled from primary studies.				

CBP, cardiopulmonary bypass; CI, confidence interval; FPP, fresh frozen plasma; ITT, intention-to-treat; MA, meta-analysis; MD, mean difference; NA, not applicable; NR, not reported; PP, per-protocol; PLT, platelets; RBC, red blood cells; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; TXA, tranexamic acid

a. Chauhan 2004a was analysed as four studies representing each of the active treatment arms (TXA doses). There were 60 patients per arm.

STUDY DETAILS: SR/MA				
Citation				
Ghavam S, Batra D, Mercer J, Kugelman A et al. (2013) Effects of placental transfusion in extremely low birthweight infants: meta-analysis of long– and short-term outcomes. Transfusion, 54: 1192–8.				
Affiliation/Source of funds				
The authors reported no conflicts of interest or funding sources.				
Study design	Level of evidence		Location/setting	
Systematic review and meta-analysis of RCTs or quasi-RCTs	Level I		NR	
Intervention	Comparator			
Delayed cord clamping (DCC) (greater than 20 second delay) and/or umbilical cord milking (UCM) (milking the cord toward the infant 2-3 times before clamping	Immediate cord clamping (ICC)			
Population characteristics				
Extremely low birth weight (ELBW, <1000 g) preterm neonates <30 weeks gestation. Exclusion criteria: observational studies or RCTs where weight-differentiated data were not available.				
Length of follow-up	Outcomes measured			
24 months.	Primary: standardised long-term neurodevelopmental outcomes Secondary: Hb and Hct on admission, number of blood transfusions, IVH, blood pressure, number of days on mechanical ventilation, sepsis.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: a systematic review and meta-analysis of 10 RCTs in ELBW preterm neonates, to examine the effect of delayed cord clamping compared to immediate cord clamping on long-term neurodevelopmental outcomes. RCTs and quasi-randomised trials were eligible for inclusion. Two independent investigators performed the literature search. Additional information was requested from authors if necessary. Data were obtained for all neonates <30 weeks and <1000 g from authors in which studies included a mixed cohort of neonates. Two observers extracted data. The quality of the included studies was not reported. Individual study results were also not provided, with only pooled data presented. Several meta-analyses were conducted but a test for heterogeneity was not applied. There were 10 included studies: Hosono 2008, Hosono 2009, Ibrahim 2000, Kugelman 2007, March 2011, Mercer 2006, Mercer 2010, Oh 2011, Rabe 2000 and Windrim 2011. Details of included and excluded studies were reported in supplementary materials.				
RESULTS:				
Outcome No. trials (No. patients)	DCC n/N (%)	ICC n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
RBC transfusion (no. of studies NR)	70/NR	79/NR	MD -2.22 (-2.52, -1.92)	Favours DCC *P* < 0.001 Heterogeneity NR
IVH	NR	NR	OR 0.56	No significant difference

(no. of studies NR)			(0.29, 1.07)*	*P* = 0.08 Heterogeneity NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to ELBW preterm infants. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that strategies to enhance placental transfusion may improve short-term outcomes of ELBW infants. However, paucity of data on neurodevelopmental outcomes and safety concerns tempers enthusiasm for these interventions. Appropriately designed RCTs to assess short-term and long-term outcomes are needed in ELBW infants. *As reported in text (in table reported as OR 0.56; 95%CI 0.29, 1.29)				

CI, confidence interval; DCC, delayed cord clamping; ELBW, extremely low birth weight; Hb, haemoglobin; Hct, haematocrit; ICC, immediate cord clamping; IVH, intraventricular haemorrhage; MA, meta-analysis; MD, mean difference; NR, not reported; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; SR, systematic review; UCM, umbilical cord milking

STUDY DETAILS: SR/MA				
Citation				
Ker K, Beecher D, Roberts I (2013). Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database of Systematic Reviews, Issue 7. Art No.: CD010562.				
Affiliation/Source of funds				
Funding was received from the National Institute for Health Research, UK. The authors declare no conflicts of interest.				
Study design	Level of evidence	Location/setting		
Meta-analysis of RCTs	Level I	Egypt (Albirmawy 2013)		
Intervention	Comparator			
Topical administration of TXA	No TXA or placebo			
Population characteristics				
People of all ages with bleeding of any severity. (Albirmaway 2013: children undergoing primary isolated adenoidectomy)				
Length of follow-up	Outcomes measured			
No restrictions.	Primary: blood loss, death Secondary: myocardial infarction, stroke, DVT, pulmonary embolism, blood transfusion			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Appropriate search strategies and inclusion/exclusion criteria detailed. The quality of included studies was assessed using the Cochrane Risk of Bias tool. The characteristics, patient demographics and results of the individual studies were presented. 29 studies were identified for inclusion, of which one was in children (Albirmawy 2013). Albirmawy 2013 was a randomised placebo-controlled trial of topical TXA (1g in 10 mL saline poured into nasopharynx) in 400 children undergoing primary isolated adenoidectomy. Outcomes included blood loss, frequency of post-operative bleeding and transfusion requirements. The review authors gave a low risk of bias to random sequence generation, a low/unclear risk of bias to blinding (participants, investigators and outcome assessors) and incomplete outcome data; and an unclear risk of bias to allocation concealment and selective reporting.				
RESULTS				
Outcomes No. RCTs (No. patients)	TXA n/N (%) Mean ± SD	Placebo n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Blood loss (mL) 1 trial (Albirmawy 2013) N=400	NR (200)	NR (200)	MD 0.73 (0.71, 0.76)	Favours TXA *P* = NR
Transfusion 1 trial (Albirmawy 2013) N=400	0/200 (0%)	2/200 (1%)	RR 0.20 (0.01, 4.14)	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				

The evidence is directly generalisable to paediatric patients undergoing primary isolated adenoidectomy (Level A).
Applicability
The evidence is probably applicable to the Australian healthcare context with some caveats (Level C).
Comments
The authors made no conclusions specific to the paediatric population. Overall they concluded that the topical application of TXA reduces bleeding and transfusion volume and incidence in surgical patients; however the effect on the risk of thromboembolic events is uncertain.

CI, confidence interval; DVT, deep vein thrombosis; MA, meta-analysis; MD, mean difference; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SR, systematic review; TXA, tranexamic acid

STUDY DETAILS: SR/MA		
Citation		
Louis D, More K, Oberoi S, Shah PS. Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: An updated systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2014.		
Affiliation/Source of funds		
The authors declared no competing interests. They are affiliated with the Division of Neonatology, Department of Pediatrics, University of Toronto, Division of Neonatology, Department of Pediatrics, Hospital for Sick Children, Division of Pediatric Hematooncology, The Hospital for Sick Children, Departments of Pediatrics, Mount Sinai Hospital, Institute of Health Policy, Management and Evaluation, University of Toronto, all Toronto, Ontario, Canada.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of RCTs and quasi-RCTs.	Level I	Various (individual trial locations not specified)
Intervention	Comparator	
IVIg (as prophylaxis or treatment, at any dose) *IVIg must have been used for the purpose of prevention or treatment or Rh or ABO incompatibility. The use of IVIg for other reasons was not included.	Placebo or no intervention	
Population characteristics		
Term and preterm neonates with isoimmune haemolytic disease secondary to Rh or ABO incompatibility. Neonates who had additional minor group incompatibility in addition to Rh or ABO incompatibility were included. Exclusion criteria: neonates who had isolated minor group incompatibility, studies including both Rh and ABO incompatibility but not providing results on these conditions.		
Length of follow-up	Outcomes measured	
NA	Primary outcome: need for exchange transfusion Secondary outcomes: number of exchange transfusion per infant, peak serum bilirubin levels, duration of phototherapy, duration of hospitalisation, need for top-up transfusions, neonatal mortality and adverse reactions requiring cessation of therapy	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Twelve studies were included in the review; three had a low risk of bias (Santos 2013, Smits-Wintjens 2011, Garcia 2004) and nine had a high risk of bias (Elalfy 2011, Nasseri 2006, Huang 2006, Miqdad 2004, Pishva 2000, Alpay 1999, Dagaglu 1995, Voto 1995, Rubo 1992). The search strategy was appropriate, with three databases searched and search terms reported in the supplementary material (Appendix 1). Inclusion/exclusion criteria were detailed. The authors intended to include RCTs and quasi-randomised trials but only RCTs were identified for inclusion. The quality of studies was assessed using the Cochrane Risk of Bias tool, with the overall risk of bias presented in the main article for each included study and more detail available in the supplementary material (Appendix 3). The characteristics and patient demographics of individual studies were reported in the supplementary material (Appendix 2). Due to clear differences in the risk of bias between studies, a meta-analysis was not conducted using all of the available studies. Instead, two meta-analyses were conducted for the primary outcome (need for exchange transfusion); one using studies with a low risk of bias and one using studies with a high risk of bias.		
RESULTS		

Outcome No. trials (No. patients)	IVIg n/N (%) Mean ± SD	Placebo or no intervention n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
All trials				
Mortality 12 trials (Santos 2013, Smits-Wintjens 2011, Garcia 2004, Elalfy 2011, Nasseri 2006, Huang 2006, Miqdad 2004, Pishva 2000, Alpay 1999, Dagaglu 1995, Voto 1995, Rubo 1992). N=NR	0	0	NA	NA
Rh isoimmunisation				
Need for exchange transfusion -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* < 0.00001 No significant heterogeneity *P* = 0.99 (I^2=0%)
Need for exchange transfusion -Low risk of bias 3 trials (Garcia 2004, Santos 2013, Smiths 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 *P* = 0.73 (I^2=0%)
No. of exchange transfusions per infant -High risk of bias 5 trials (NR) N=199	NR	NR	MD -0.9 [-1.5, -0.3]	Significance not reported *P* = NR Substantial heterogeneity *P* = NR (I^2=92%)
No. of exchange transfusions per infant -Low risk of bias 3 trials (NR) N=190	NR	NR	MD -0.02 [-0.14, 0.10]	Significance not reported *P* = NR No significant heterogeneity *P* = NR (I^2=0%)
Subgroup analysis: prophylactic IVIg				

Need for exchange transfusion -High risk of bias 3 trials (Dagoglu 1995, Psihva 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 No significant heterogeneity *P* = 0.77 (I^2=0%)
Need for exchange transfusion -Low risk of bias 3 trials (Garcia 2004, Santos 2013, Smiths 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 *P* = 0.73 (I^2=0%)
Subgroup analysis: preterm neonates				
Need for exchange transfusion -Low risk of bias 2 trials (Garcia 2004, Santos 2013) N=64	10/31 (32.3)	12/33 (36.4)	RR 0.73 [0.44, 1.19]	No significant difference *P* = 0.21 No significant heterogeneity *P* = 0.82 (I^2=0%)
ABO isoimmunisation				
Need for exchange transfusion -High risk of bias 5 trials (Alpay 1999, Huang 2006, Miqdad 2004, Nasseri 2006, Pishva 2000) N= 350	13/174 (7.5)	46/176 (26.1)	RR 0.31 [0.18, 0.55]	Favours IVIg *P* < 0.0001 No significant heterogeneity *P* = 0.63 (I^2=0%)
No. of exchange transfusions per infant -High risk of bias 3 trials (NR) N=226	NR	NR	MD -0.2 [-0.3, -0.1]	Significance not reported *P* = NR No significant heterogeneity *P* = NR (I^2=0%)
EXTERNAL VALIDITY				
Generalisability				
The study is directly generalisable to term and preterm neonates diagnosed with isoimmune haemolytic disease secondary to Rh or ABO incompatibility. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats (Level C). Individual trial locations were not specified.				
Comments				
The authors highlight the fact that the studies with a low risk of bias, which did not show a significant result, were small and it is therefore plausible that they lacked enough power to detect a true difference. The efficacy of IVIg is not conclusive in Rh haemolytic disease of the newborn with studies with a low risk of bias indicating no benefit and studies with a high risk of bias suggesting a benefit. The role of IVIg in ABO disease is not clear as studies that showed a benefit had a high risk of bias;				

CI, confidence interval; IVIg, intravenous immunoglobulin; MA, meta-analysis; MD, mean difference; NA, not applicable; NR, not reported; RCT, randomised controlled trial; Rh, rhesus; RR, risk ratio; SD, standard deviation; SR, systematic review.

STUDY DETAILS: SR/MA		
Citation		
Mathew JL. (2011) Timing of umbilical cord clamping in term and preterm deliveries and infant and maternal outcomes: a systematic review of randomized controlled trials. Indian Pediatrics, 48: 123–9.		
Affiliation/Source of funds		
The authors reported no conflicts of interest or funding sources.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of RCTs	Level I	UK (Aladangady 2006, Oh 2002), Europe (Baenziger 2007, Rabe 2000, Ultee 2008), USA (Mercer 2003, Mercer 006, Mercer 2010, Strauss 2008, Strauss 2007), South Africa (Hofmeyr 1988), Israel (Kugelman 2007, Kugelman 2009), Australia (McDonnell 1997).
Intervention	Comparator	
Delayed cord clamping (DCC) >30 seconds following delivery	Early cord clamping (ECC) ≤30 seconds following delivery	
Population characteristics		
Term and preterm neonates.		
Length of follow-up	Outcomes measured	
NR	Any short– and long-term outcomes reported in trials, e.g. mortality, neonatal morbidity, laboratory values (Hb, Hct).	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a systematic review and meta-analysis of 29 RCTs in preterm and term infants, to examine the effect of delayed cord clamping compared to early cord clamping on short– and long-term outcomes. There were 14 RCTs in preterm infants and 15 RCTs in term infants. There were no outcomes relevant to this overview presented for the term infant studies. Preterm infant studies: Aladangady 2006, Baenziger 2007, Hofmeyr 1988, Kugelman 2007, Kugelman 2009, McDonnell 1997, Mercer 2003, Mercer 2006, Mercer 2010, Oh 2002, Rabe 2000, Strauss 2008, Strauss 2007, Ultee 2008. Appropriate search strategy used and search terms reported. Inclusion/exclusion criteria detailed. Only RCTs included. The quality of studies was assessed using the Cochrane Risk of Bias Tool and reported in the supplementary material (Web Table 1). The outcomes for the individual studies were reported but not the results for each trial, with only pooled data presented. Although several meta-analyses were conducted, a test for heterogeneity was not applied. However, the authors briefly discuss potential heterogeneity, in relation to procedural differences between the trials, and suggest caution when interpreting results. The authors rated seven of the preterm studies as having a low risk of bias based on criteria in the Cochrane Risk of Bias tool (Kugelman 2007, Kugelman 2009, Mercer 2003, Mercer 2006, Mercer 2010, Strauss 2008, Strauss 2007). The remainder had moderate or high risk of bias. Risk of mortality and IVH were comparable among trials with low risk of bias, suggesting robust results. All the trials included fairly stable pregnant women, and babies likely to be at risk of adverse outcomes were generally excluded. The definition of ECC was fairly uniform across trials; however, DCC was defined in multiple ways with time ranging from 30 seconds to 5 minutes. The majority of trials used lower positioning of the infant with DCC. Only one trial (Rabe 2000) used lower positioning in both the DCC and ECC arms.		

RESULTS:				
Outcome No. trials (No. patients)	DCC n/N (%) Mean ± SD (N)	ECC n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Preterm infants				
Transfusion requirement 6 studies (NR) N=358	NR	NR	RR 0.72 (0.54, 0.96)	Favours DCC *P* = NR Heterogeneity NR
No. of transfusions administered 4 studies (NR) N=144	NR	NR	MD -0.92 (-1.78, -0.05)	Favours DCC *P* = NR Heterogeneity NR
Mortality 9 studies (NR) N=503	NR	NR	RR 0.55 (0.21, 1.46)	No significant difference *P* = NR Heterogeneity NR
IVH 7 studies (NR) N=408	NR	NR	RR 0.49 (0.32, 0.74)	Favours DCC *P* = NR Heterogeneity NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that DCC resulted in a significantly reduced incidence of IVH in preterm neonates. The risks and benefits of DCC for mothers delivering prematurely have not been explored.				

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; Hb, haemoglobin; Hct, haematocrit; IVH, intraventricular haemorrhage; MA, meta-analysis; MD, mean difference; NR, not reported; RCT, randomised controlled trial; RR, relative risk; SR, systematic review

STUDY DETAILS: SR/MA		
Citation		
McDonald SJ, Middleton P, Dowswell T, Morris PS. (2013) Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database of Systematic Reviews, Issue 7: CD004074.		
Affiliation/Source of funds		
Support was received from the University of Adelaide, The Department of Health and Ageing, NIHR, UK and the NHMRC, Australia; and the NIHR, UK. The contact author (McDonald) was the author of one of the included studies. The other review authors assessed this trial for potential inclusion and data extraction.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of RCTs.	Level I	Central/South America (Cernadas 2006), Africa (van Rheenen 2007).
Intervention		Comparator
Delayed cord clamping (DCC) >60 seconds after birth or when cord pulsation has ceased		Early cord clamping (ECC) <60 seconds after birth
Population characteristics		
Term infants (≥37 weeks gestational age) Exclusion criteria: preterm infants (<37 weeks gestational age), breech presentation, multiple pregnancies		
Length of follow-up	Outcomes measured	
NR	Primary: mortality Secondary: birth weight, 5-min Apgar score <7, NICU admission, respiratory distress, hypoxia, jaundice requiring phototherapy, clinical jaundice, cord Hb concentration, not breastfed at discharge, anaemia up to 4-6 months post birth, Hb concentration, Hct, neurodevelopmental outcomes, polycythaemia, ferritin concentration, symptoms of infection.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: Appropriate search strategies and inclusion/exclusion criteria detailed. Only RCTs were included in this review, quasi-randomised studies were excluded. At least two review authors independently assessed the full text of potential studies for inclusion. Data extraction was performed separately and double-checked for discrepancies. There was thorough discussion about the appropriateness of all studies for inclusion. Individual investigators were contacted if clarification was required before inclusion. Risk of bias was assessed using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. There were 15 included studies, however only two provided relevant data for this review (Cernadas 2006, van Rheenen 2007). Participants generally were healthy pregnant women expected to give birth vaginally. The van Rheenen 2007 trial was conducted in a malaria-endemic area. The timing of ECC was relatively consistent between studies (within 15 seconds of birth). The timing of DCC was variable, ranging from 1 minute post birth (Cernadas 2006) to when the cord stopped pulsating (van Rheenen 2007). Both studies attempted to blind the collection of at least some outcome data. Attrition was relatively low in Cernadas 2006, but high in van Rheenen 2007.		
RESULTS:		

Outcome No. trials (No. patients)	DCC n/N (%) Mean ± SD (N)	ECC n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)

Neonatal mortality[a] 2 trials (Cernadas 2006, van Rheenen 2007) N=381	3/239 (1.3)	1/142 (0.7)	RR 2.73 (0.29, 25.38)[b]	No significant difference *P* = 0.38 No significant heterogeneity I^2 = 0%
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to term infants. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that a more liberal approach to delaying clamping of the umbilical cord in healthy term infants appears to be warranted, particularly in light of growing evidence that DCC increases early Hb concentrations and iron stores in infants. DCC is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.				

CI, confidence interval; DCC, delayed cord clamping; ECC, early cord clamping; Hb, haemoglobin; Hct, haematocrit; IVH, intraventricular haemorrhage; MA, meta-analysis; NICU, neonatal intensive care unit; RCT, randomised controlled trial; RR, risk ratio; SR, systematic review

a. All events occurred in van Rheenen 2007.

b. RR recalculated post-hoc with intervention/comparator arms switched, to be consistent with other studies.

STUDY DETAILS: SR/MA		
Citation		
Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. (2012) Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews, Issue 8: CD003248.		
Affiliation/Source of funds		
There were potentially relevant studies for inclusion by the contact author (Rabe), which were assessed by the co-authors only. LD received a research grant.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of RCTs	Level I	Scotland (Aladangandy 2006, Baezinger 2007, Kinmond 1993), England (Rabe 2000), South Africa (Hofmeyr 1988, Hofmeyr 1993), The Netherlands (Ultee 2008), Israel (Kugelman 2007), Australia (McDonnell 1997), USA (Mercer 2003, Mercer 2006, Oh 2002, Strauss 2008), Japan (Hosono 2008), NR (Nelle 1998).
Intervention		Comparator
Delayed cord clamping (DCC) >30 seconds (cord milking studies with clamping <30s also included)		Immediate cord clamping (ICC) <30 seconds
Population characteristics		
Preterm infants <37 weeks gestation.		
Length of follow-up	Outcomes measured	
NR	Primary: mortality (before discharge, after discharge, overall), mortality or neurosensory disability at 2-3 years of age, IVH grade 3-4, periventricular leukomalacia. Secondary: requirement for resuscitation, Apgar score at 1, 5 and 10 mins, hypothermia during first hour of life or on admission to labour ward, RDS during first 36hrs of life, use of exogenous surfactant, days of oxygen dependency, oxygen dependency at 28d after birth and at 36 weeks gestation, CLD stage 2-4, volume administration or inotropic support for hypotension in first 24hrs of life, treatment for PDA, anaemia, number/volume of blood transfusions, hyperbilirubinaemia with phototherapy or exchange transfusion, Hb and ferritin at 6 and 12 months of age, IVH (all grades), NEC, length of hospital stay.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Good

Description: There were 15 included studies with 738 total infants: Aladangandy 2006, Baezinger 2007, Hofmeyr 1988, Hofmeyr 1993, Hosono 2008, Kinmond 1993, Kugelman 2007, McDonnell 1997, Mercer 2003, Mercer 2006, Nelle 1998 (abstract only), Oh 2002, Rabe 2000, Strauss 2008, Ultee 2008.

Appropriate search strategies and inclusion/exclusion criteria detailed. RCTs and cluster RCTs were included in the review. Two review authors independently assessed all potential studies for inclusion and performed data extraction. Any disagreement was resolved through discussion or, if required, with the consult of a third review author. Where trial information was unclear, authors of the original trials were contacted for further details. Two authors independently assessed risk of bias for each study using criteria in the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement was resolved through discussion or by involving a third assessor. Several subgroup analyses were conducted which investigated the impact of specific interventions (e.g. cord milking) and study quality (e.g. allocation concealment).

Quality of included studies: the methods of randomisation and allocation concealment were poorly described for most studies, with only three studies providing clear information (Mercer 2006, Strauss 2008, Oh 2002). Ultee 2008 was judged as having a high risk of bias for allocation concealment. Blinding of participants and investigators was not possible due to the nature of the intervention. Blinding of outcome assessment was judged to have an unclear or high risk of bias across all studies. Most outcome data across studies was collected soon after birth so loss to follow-up was not generally a problem. Three studies (Baezinger 2007, Strauss 2008, Ultee 2008) had a high risk of bias in this area due to post-randomisation exclusions leading to results which were difficult to interpret. There were no clear instances of outcome reporting bias.

RESULTS:

Outcome No. trials (No. patients)	DCC n/N (%) Mean ± SD (N)	ICC n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Mortality before discharge (13 studies[a]) N=668	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%
Severe IVH grade 3–4 (6 studies: Mercer 2003, Rabe 2000, Hofmeyr 1988, Mercer 2006, Hofmeyr 1993, Hosono 2008) N=305	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%
IVH all grades (10 studies [b]) N=539	35/260 (13.5)	56/279 (20.1)	RR 0.59 (0.41, 0.85)	Favours DCC *P* = 0.0048 No significant heterogeneity I^2=0%
Transfused for anaemia (7 studies: Strauss 2008, Kugelman 2007, McDonnell 1997, Kinmond 1993, Hosono 2008, Rabe 2000, Mercer 2006) N=392	44/186 (23.7)	75/206 (36.4)	RR 0.61 (0.46, 0.81)	Favours DCC *P* = 0.00053 No significant heterogeneity I^2=0%

No. of transfusions (5 studies: Oh 2002, Hosono 2008, Mercer 2006, Rabe 2000, Kinmond 1993) N=210	NR (104)	NR (106)	MD -1.26 (-1.87, -0.64)	Favours DCC *P* = 0.000061 No significant heterogeneity I^2=0%
Subgroup analysis: DCC without cord milking				
Mortality before discharge (12 studies [c]) N=628	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%
Severe IVH grade 3-4 (5 studies: Rabe 2000, Mercer 2003, Hofmeyr 1988, Mercer 2006, Hofmeyr 1993) N=265	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%
Subgroup analysis: Cord milking				
Mortality before discharge (1 study: Hosono 2008) N=40	2/20 (10.0)	3/20 (15.0)	RR 0.67 (0.12, 3.57)	No significant difference *P* = 0.64 Heterogeneity NA
Severe IVH grade 3-4 (1 study: Hosono 2008) N=40	2/20 (10.0)	4/20 (20.0)	RR 0.50 (0.10, 2.43)	No significant difference *P* = 0.39 Heterogeneity NA
Sensitivity analysis: low risk of bias for allocation concealment				
Mortality before discharge (2 studies: Oh 2002, Mercer 2006) N=105	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%
Severe IVH grade 3-4 (1 study: Mercer 2006) N=72	0/36 (0)	1/36 (2.8)	RR 0.33 (0.01, 7.92)	No significant difference *P* = 0.50 Heterogeneity NA
Sensitivity analysis: high/unclear risk of bias for allocation concealment				
Mortality before discharge (11 studies [d]) N=563	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%

Severe IVH grade 3-4 (5 studies: Rabe 2000, Hofmeyr 1988, Mercer 2003, Hosono 2008, Hofmeyr 1993) N=233	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%
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that providing additional placental blood to the preterm baby by either delaying cord clamping for 30-120s appears to be associated with reduced need for transfusion, better circulatory stability, less IVH (all grades) and lower risk for NEC. However, there were insufficient data for reliable conclusions about the comparative effects on any of the primary outcomes for this review.				

CI, confidence interval; CLD, chronic lung disease; DCC, delayed cord clamping; Hb, haemoglobin; ICC, immediate cord clamping; IVH, intraventricular haemorrhage; MA, meta-analysis; MD, mean difference; NA, not applicable; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; RCT, randomised controlled trial; RDS, respiratory distress syndrome; RR, risk ratio; SR, systematic review

a. Mercer 2003, Kinmond 1993, Strauss 2008, Ultee 2008, Hofmeyr 1988, Hofmeyr 1993, Kugelman 2007, Rabe 2000, McDonnell 1997, Baezinger 2007, Oh 2002, Hosono 2008, Mercer 2006

b. Strauss 2008, McDonnell 1997, Oh 2002, Rabe 2000, Kugelman 2007, Mercer 2003, Hosono 2008, Hofmeyr 1993, Hofmeyr 1988, Mercer 2006

c. Strauss 2008, Ultee 2008, Mercer 2003, Kinmond 1993, Hofmeyr 1988, Hofmeyr 1993, Kugelman 2007, Rabe 2000, McDonnell 1997, Baezinger 2007, Oh 2002, Mercer 2006

d. Hosono 2008, Rabe 2000, Kugelman 2007, Strauss 2008, McDonnell 1997, Baezinger 2007, Kinmond 1993, Hofmeyr 1993, Mercer 2003, Hofmeyr 1988, Ultee 2008

STUDY DETAILS: SR/MA				
Citation				
Schouten ES, van de Pol AC, Schouten ANJ, Turner NM et al. (2009) The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery a meta-analysis. Pediatric Critical Care Medicine, 10(2): 182-190.				
Affiliation/Source of funds				
None reported.				
Study design	Level of evidence		Location/setting	
Meta-analysis of RCTs	Level I		NR	
Intervention		Comparator		
Aprotinin, TXA or ACA		Placebo or head-to-head with aprotinin, TXA or ACA		
Population characteristics				
Children aged 0-18 years undergoing cardiac or scoliosis surgery.				
Length of follow-up		Outcomes measured		
NR		Blood loss, transfusion of RBC, plasma or thrombocytes.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: There were 28 studies identified; 23 in cardiac surgery patients (n=1893) and 5 in scoliosis surgery patients (n=207). Thirteen of the cardiac surgery studies compared aprotinin with placebo, five compared TXA with placebo and three compared ACA with placebo. One study compared aprotinin and TXA with placebo, and another compared aprotinin and ACA with placebo. Of the scoliosis surgery studies, two studies compared aprotinin with placebo, two compared TXA with placebo and one compared ACA with placebo. Appropriate search strategies, with inclusion/exclusion criteria reported. The methodological quality of included studies was judged independently by two reviewers, with discrepancies resolved by discussion. Quality was judged in terms of allocation, blinding, and follow-up, whereby each criterion was assigned a score of two, one, or zero points. A combined score for allocation, blinding, and follow-up greater than four was considered good. Several meta-analyses were conducted and a test for heterogeneity was applied. The methodological quality of the cardiac studies was generally poor, with only 8 out of 23 studies scoring more than 4 points. Three studies provided an adequate description of the allocation concealment, seven studies were double-blinded, and 10 studies reported a follow-up of 80% or more. All patients were randomly allocated except for the large-dose aprotinin arm in the study by Miller et al, and this arm was excluded from analysis. All the scoliosis studies were good quality with a score of four points or more. They adequately described allocation concealment and had a follow-up of at least 80%. Note: for cardiac surgery patients, the outcomes of blood loss and thrombocyte transfusion with aprotinin and ACA were too heterogeneous to be meta-analysed. Similarly, the outcomes of RBC transfusion with ACA were too heterogeneous to be meta-analysed.				
RESULTS				
Outcomes No. RCTs (No. patients)	Antifibrinolytic n/N (%) Mean ± SD	Placebo n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
Cardiac surgery patients				
Aprotinin				

Transfusion of RBC (3 studies: Davies 1997, Chauhan 2000, Bulutcu 2005) N=250	NR	NR	WMD -4 (-7, -2)	Favours aprotinin *P* = NR No significant heterogeneity I^2=0%
Transfusion of plasma (2 studies: Chauhan 2000, Bulutcu 2005) N=228	NR	NR	WMD -5 (-8, -2)	Favours aprotinin *P* = NR No significant heterogeneity I^2=0%
Tranexamic acid				
Blood loss (mL/kg) (6 studies: Zonis 1996, Reid 1997, Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Bulutcu 2005) N=542	NR	NR	WMD -11 (-13, -8)	Favours TXA *P* = NR Moderate heterogeneity I^2=31%
Transfusion of RBC (5 studies: Reid 1997, Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Bulutcu 2005) N=460	NR	NR	WMD -7 (-10, -5)	Favours TXA *P* = NR Mild heterogeneity I^2=6%
Transfusion of plasma (4 studies: Chauhan 2003, Chauhan 2004a, Chauhan 2004b, Bulutcu 2005) N=419	NR	NR	WMD -7 (-9, -4)	Favours TXA *P* = NR No significant heterogeneity I^2=0%
Transfusion of thrombocytes (no. of studies NR; N=370)	NR	NR	WMD -5 (-7, -3)	Favours TXA *P* = NR No significant heterogeneity I^2=0%
Aminocaproic acid				
Transfusion of plasma (3 studies: Chauhan 2000, Rao 2000, Chauhan 2004) N=410	NR	NR	WMD -3 (-5, -1)	Favours ACA *P* = NR Mild heterogeneity I^2 = 20%
Scoliosis surgery patients				
Aprotinin				

Blood loss (mL) (1 study: Cole 2003) N=44	NR	NR	WMD -385 (-727, -42)	Favours aprotinin *P* = NR
Tranexamic acid				
Blood loss (mL) (2 studies: Sethna 2005, Neilipovitz 2001) N=84	NR	NR	WMD -682 (-1149, -214)	Favours TXA *P* = NR Mild heterogeneity I^2=24%
Transfusion of RBC (2 studies: Sethna 2005, Neilipovitz 2001) N=84	NR	NR	WMD -349 (-620, -77)	Favours TXA *P* = NR No significant heterogeneity I^2=0%
Transfusion of plasma (2 studies: Sethna 2005, Neilipovitz 2001) N=84	NR	NR	WMD -15 (-127, 98)	No significant difference *P* = NR Mild heterogeneity I^2=24%
Aminocaproic acid				
Blood loss (mL) (1 study: Florentino 2004) N=36	NR	NR	WMD -59 (-262, 144)	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
The evidence is directly generalisable to paediatric patients undergoing cardiac or scoliosis surgery (Level A).				
Applicability				
The evidence may or may not be applicable to the Australian healthcare context (study sites not reported).				
Comments				
The authors concluded that TXA appeared to be at least as effective as aprotinin in reducing blood loss and transfusion of blood products after major pediatric surgery. Evidence regarding ACA was insufficient to allow any inferences. Considering the potential side effects of aprotinin and the higher costs, the authors suggest that TXA should be the antifibrinolytic of choice in major pediatric surgery, and recently changed their antifibrinolytic protocol in line with this conclusion.				

ACA, aminocaproic acid; CI, confidence interval; MA, meta-analysis; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; WMD, weighted mean difference; TXA, tranexamic acid

STUDY DETAILS: SR/MA				
Citation				
Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. (2012) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database of Systematic Reviews, Issue 3 CD005011.				
Affiliation/Source of funds				
Internal: National Blood Service, Research and Development, UK; Canadian Blood Services, Canada; Department of Clinical Pathology, Sunnybrook Health Sciences Centre, Canada. External: No sources of support supplied.				
Study design	Level of evidence	Location/setting		
Systematic review of RCTs	I	Australia (Ekert 2006)		
Intervention	Comparator			
Use of rFVIIa to prevent, treat or control bleeding	No rFVIIa			
Population characteristics				
All populations without haemophilia or other haemostatic defects.				
Length of follow-up	Outcomes measured			
NR	Survival at fixed time periods with mortality evaluated by cause when possible, number and/or duration of bleeding episodes, severity of blood loss, RBC transfusion requirements, number of patients avoiding transfusions (for prophylactic studies), adverse events e.g. thrombosis			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Twenty-nine RCTs were included of which three were in paediatric populations. One study examined paediatric surgery patients and was relevant to this overview (Ekert 2006). One RCT (Hanna 2010) enrolled paediatric patients of ASA class I and II with congenital craniofacial malformations scheduled for reconstructive surgery (Hanna 2010) and one RCT (Chuansumrit 2005) examined the role of rFVIIa in the control of bleeding in children with Dengue haemorrhagic fever. Two authors screened all titles and abstracts of papers identified in the literature search. Two authors independently assessed papers at full text, with any discrepancies noted. Data extraction was performed by two authors using standardised forms, with any disagreement resolved through consensus. Quality of included studies was assessed based on criteria from the Cochrane Handbook for Systematic Reviews of Interventions (v 5.0.1). Domains assessed included random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors; reporting of outcome data and other potential threats to validity. Each domain was rated "Yes" (adequate), "Unclear" or "No" (clearly inadequate). A criterion was added to the table to indicate whether a power calculation was performed. Heterogeneity was assessed, with I^2 values greater than 25% indicating that pooled estimated should be interpreted with a high level of caution. When I^2 was below 25%, the authors explored the robustness of summary measures, particularly with respect to study quality. Quality of included studies: Ekert 2006 was a double-blind placebo-controlled RCT in Australia of infants <1 year of age with congenital heart disease requiring CPB. The authors examined prophylactic use of rFVIIa. Ekert 2006 received a low risk of bias for blinding and reporting of outcome data, and an unclear risk of bias for random sequence generation, allocation concealment and selective reporting.				
RESULTS				
Outcome No. trials (No. patients)	Prophylactic rFVIIa n/N (%) Mean ± SD (n_	Comparator n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)

Death 2 studies (Ekert 2006; N=76)	0/40 (0)	0/36 (0)	NA	No significant difference *P* = NA
Number of patients transfused 1 study (Ekert 2006; N=76)	30/40 (75.0)	29/36 (80.6)	RR 0.93 [0.73, 1.18]	No significant difference *P* = NR
Thromboembolic events 1 study (Ekert 2006; N=76)	0/40 (0.0)	0/36 (0.0)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to infants <1 year of age undergoing cardiac surgery with CPB. (Level A)				
Applicability				
Evidence applicable to the Australian healthcare context. (Level A)				
Comments				
*NR in SR. Data pulled from primary studies.				

CI, confidence interval; ITT, intention-to-treat; MA, meta-analysis; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

STUDY DETAILS: SR/MA		
Citation		
Song G, Yang P, Zhu S, Luo E et al. (2013) Tranexamic acid reducing blood transfusion in children undergoing craniosynostosis surgery. J Cradiofac Surg, 24: 299–303.		
Affiliation/Source of funds		
The authors report not conflicts of interest.		
Study design	Level of evidence	Location/setting
Systematic review and meta-analysis of level II-III studies.	Level I/III	USA (Goobie 2011, Maugans 2011), France (Dadure 2011).
Intervention	Comparator	
TXA administered intravenously.	Placebo or no treatment.	
Population characteristics		
Children undergoing craniosynostosis surgery.		
Length of follow-up	Outcomes measured	
NR	RBC transfusion and blood loss.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Included three trials, of which two were RCTs (Dadure 2011, Goobie 2011) and one was a retrospective comparative study (Maugans 2011). Maugans 2011 contained two studies within the one paper (Maugans 2011 (group a), Maugans 2011 (group b). The dose of TXA was 10 mg/kg/hr in two studies (Dadure 2011, Maugans 2011) and 5 mg/kg/hr in one study (Goobie 2011). Only controlled trials were included but they could be retrospective, prospective, randomised or non-randomised studies with a placebo/no treatment group. To be included, studies had to contain sufficient raw data for weighed mean difference with 95% confidence intervals. Studies were excluded which did not present raw data or which had no usable data. Data were extracted independently by two reviewers with disagreement resolved by consensus. Methodological quality was assessed using the Jadad composite scale. High quality trials scored more than 2 of a maximum possible score of 5. The characteristics of individual studies were reported but not baseline demographics / patient characteristics. The two RCTs provided detailed descriptions of the randomisation method (computer-generated), and scored 5/5 points. The main study limitations pertained to justification of sample size, allocation concealment and double blinding. Quality of the retrospective study (Maugans 2011) was not assessed.		
RESULTS:		

Outcome No. trials (No. patients)	TXA n/N (%) Mean ± SD (N)	No TXA n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)
RBC transfusion volume (3 studies: Maugans 2011, Dadure 2011, Goobie 2011) N=138	NR	NR	MD -10.81 (-16.84, -4.78)	Favours TXA *P* = 0.0004 No heterogeneity *P* = 0.45 (I^2=0%)

Perioperative blood loss (3 studies: Maugans 2011, Dadure 2011, Goobie 2011) N=138	NR	NR	MD -20.53 (-32.26, -8.80)	Favours TXA *P* = 0.0006 Substantial heterogeneity *P* = 0.08 (I^2=56%)
Sensitivity analysis: RCTs only				
RBC transfusion volume (2 studies: Dadure 2011, Goobie 2011) N=82*	NR	NR	MD -11.87 (-18.80, -4.95)	Favours TXA *P* = 0.0008 Substantial heterogeneity *P* = 0.14 (I^2=55%)
Perioperative blood loss (2 studies: Dadure 2011, Goobie 2011) N=82*	NR	NR	MD -30.79 (-71.72, 10.14)	No significant difference *P* = 0.14 Substantial heterogeneity *P* = 0.02 (I^2 = 82%)
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients undergoing craniosynostosis surgery. (Level A)				
Applicability				
Evidence probably applicable to Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that TXA can significantly reduce the transfusion of RBC in children undergoing craniosynostosis surgery. However, there is a controversy on the efficacy of TXA in reducing blood loss. *Data duplicated in other systematic reviews, not included in evidence summary tables (vol. 1).				

CI, confidence interval; IVH, intraventricular haemorrhage; MA, meta-analysis; MD, mean difference; RBC, red blood cell; RCT, randomised controlled trial; SR, systematic review; TXA, tranexamic acid

STUDY DETAILS: SR/MA				
Citation				
Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB. (2008) Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD006883. DOI: 10.1002/14651858.CD006883.pub2.				
Affiliation/Source of funds				
The authors declare the internal source of funding was Saltostall Fund for Pain Research, USA. The authors declare no external sources of funding supplied. The following declarations of interest were reported at the time of writing: – Prof D Carr worked at Javelin Pharmaceuticals and held his academic appointment at Tufts University School of Medicine. – Prof M Soledad Cepeda worked for Johnson & Johnson and still held her academic appointment at Tufts University School of Medicine. It was declared that neither Javelin Pharmaceuticals nor Johnson & Johnson produced antifibrinolytics.				
Study design	Level of evidence	Location/setting		
Systematic review of blinded and unblinded RCTs	Level I	NR		
Intervention	Comparator			
Antifibrinolytics (aprotinin, TXA, EACA)	Placebo			
Population characteristics				
Paediatric patients aged <18 years undergoing surgery for correction of primary or secondary scoliosis				
Length of follow-up	Outcomes measured			
1-10 days after surgery	Primary: mortality and number of patients transfused. Secondary: number of patients transfused with allogeneic blood, amount of total blood transfused, total blood loss and adverse events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Six RCTs were included (Cole 2002; Cole 2003; Florentino 2004 ; Khoshhal 2003; Neilipovitz 2001; Sethna 2005). The authors reported that data was extracted from each study by two independent reviewers with disagreements resolved through a third author. Trial authors were contacted for additional information on the method of randomisation, allocation concealment, period of outcome evaluation and measures of dispersion. Quality of the studies were assessed on the basis of method of randomisation, method of allocation concealment, blinding of the study, completeness of follow-up and the use of ITT analysis. They rated the studies using a scale of A to D, with D being the lowest quality (no allocation concealment used). The authors reported that three studies had low risk of bias (Cole 2003; Florentino 2004; Khoshhal 2003); and three had moderate risk of bias (Cole 2002;Neilipovitz 2001; Sethna 2005). Meta-analyses were performed using fixed effects models.				
RESULTS				
Outcome	Any antifibrinolytic n/N (%) Mean ± SD	Placebo n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value Heterogeneity *P*-value (I^2)

Number of patients transfused 4 studies (Khoshhal 2003, Neilipovitz 2001, Sethna 2005, Florentino 2004; N = 163)	42/79 (53.2)	53/84 (63.1)	RR 0.87 [0.67, 1.12]	No significant difference *P* = 0.28 No significant heterogeneity *P* = 0.77 (I^2=0%)
Total blood transfused 5 studies (Cole 2003, Khoshhal 2003, Neilipovitz 2001, Sethna 2005, Florentino 2004; N = 207)	NR	NR	MD -327.41 [-469.04, -185.78]	Favours antifibrinolytics *P* < 0.00001 No significant heterogeneity *P* = 0.68 (I^2=0%)
Total blood loss 5 studies (Cole 2003, Khoshhal 2003, Neilipovitz 2001, Sethna 2005, Florentino 2004; N = 207)	NR	NR	MD -426.53 [-602.51, -250.56]	Favours antifibrinolytics *P* < 0.00001 No significant heterogeneity *P* = 0.42 (I^2=0%)
Mortality 6 studies (N = 254)	0	0	NA	No significant difference *P* = NA Heterogeneity NR
Aprotinin vs placebo				
Number of patients transfused 1 study (Khoshhal 2003; N = 43)	8/15 (53.3)	20/28 (71.4)	RR 0.75 [0.44, 1.27]	No significant difference *P* = 0.28
Number of patients transfused with allogeneic blood 1 study (Khoshhal 2003; N = 43)	NR	NR	RR 0.71 [0.53, 0.90]	Favours aprotinin *P* = NR
Total blood transfused 2 studies (Cole 2003, Khoshhal 2003; N = 87)	NR	NR	MD -361.42 [-583.88, -138.96]	Favours aprotinin *P* = 0.0015 No significant heterogeneity *P* = 0.80 (I^2=0%)
Total blood loss 2 studies (Cole 2003, Khoshhal 2003; N = 87)	NR	NR	MD -450.32 [-726.35, -174.29]	Favours aprotinin *P* = 0.0014 No significant heterogeneity *P* = 0.53 (I^2=0%)
Postoperative DVT 1 study (Cole 2003; N = 44)	0/21 (0)	3/23 (13.0)	NR	Significance NR *P* = NR
TXA vs placebo				

Number of patients transfused 2 studies (Cole 2003; Khoshhal 2003; N = 84)	20/45 (44.4)	21/39 (53.8)	RR 0.84 [0.56, 1.27]	No significant difference *P* = 0.41 No significant heterogeneity *P* = 0.94 (I^2=0%)
Number of patients transfused with allogeneic blood 2 studies (Neilipovitz 2001; Sethna 2005; N = 84)	0	0	NA	No significant difference *P* = NR Heterogeneity NR
Total blood transfused 2 studies (Cole 2003; Khoshhal 2003; N = 84)	NR	NR	MD -395.14 [-687.55, -102.73]	Favours TXA *P* = 0.0081 No significant heterogeneity *P* = 0.51 (I^2=0%)
Total blood loss 2 studies (Cole 2003; Khoshhal 2003; N = 84)	NR	NR	MD -681.81 [-1149.12, -214.49]	Favours TXA *P* = 0.0042 Mild heterogeneity *P* = 0.25 (I^2=24%)
EACA vs placebo				
Number of patients transfused 1 study (Florentino 2004; N = 36)	14/19 (73.7)	12/17 (70.6)	RR 1.04 [0.69, 1.57]	No significant difference *P* = 0.84
Number of patients transfused with allogeneic blood 1 study (Florentino 2004; N = 36)	0	0	NA	No significant difference *P* = NR
Total blood transfused 1 study (Florentino 2004; N = 36)	NR	NR	MD -245.00 [-481.03, -8.97]	Favours EACA *P* = 0.042
Total blood loss 1 study (Florentino 2004; N = 36)	NR	NR	MD -325.00 [-586.83, -63.17]	Favours EACA *P* = 0.015
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients aged <18 years undergoing scoliosis surgery. (Level A)				
Applicability				
Evidence may or may not be applicable to the Australian healthcare context (study locations NR) (Level C).				
Comments				

The authors concluded that antifibrinolytic drugs reduced blood loss and the amount of blood transfused in paediatric patients undergoing scoliosis surgery. However, their effect on the number of children requiring blood transfusion remains unclear. Aprotinin, tranexamic acid and aminocaproic acid appeared to be similarly effective. The effect of antifibrinolytic drugs on mortality could not be assessed.

CI, confidence interval; DVT, deep vein thrombosis; EACA, Epsilon-aminocaproic acid; ITT, intention-to-treat; MA, meta-analysis; MD, mean difference; NA; not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SR, systematic review; TXA, tranexamic acid

Level II evidence

STUDY DETAILS: RCT				
Citation				
Aggarwal V, Kapoor PM, Choudhury M, Kiran U, Chowdhury U (2012) Utility of sonoclot analysis and tranexamic acid in tetralogy of Fallot patients undergoing intracardiac repair. Annals of Cardiac Anaesthesia, 15(1): 26–31.				
Affiliation/Source of funds				
The authors reported no sources of support or conflicts of interest.				
Study design	Level of evidence		Location/setting	
RCT	Level II		India	
Intervention	Comparator			
3x doses of TXA (10mg/kg): after induction of anaesthesia, during CPD and during heparin neutralisation.	3x doses of normal saline at the same time intervals.			
Population characteristics				
Children aged 1 to 12 years with tetralogy of Fallot (TOF) undergoing intracardiac repair. Exclusion criteria: antiplatelet or anticoagulation therapy in the two weeks prior to surgery, patients likely to have shorter CPB times.				
Length of follow-up	Outcomes measured			
NR	Coagulation parameters, D-dimer and DR_{15} values, blood loss.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: A double-blind RCT of 80 children with TOF undergoing intracardiac repair in India, to examine the effect of tranexamic acid compared to placebo on blood loss and coagulation parameters. Children were randomised using the random table method. Of the 94 children randomised, 80 completed the study. Of the 14 children excluded, three were receiving aspirin in the preceding 2 weeks, one had renal dysfunction and five in each group underwent intracardiac repair without pulmonary valvotomy and patch repair. There were no differences in baseline characteristics between groups.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	NR		NR	
Efficacy analysis (ITT)	40		40	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	TXA Mean ± SD (n) n/N (%)	Placebo Mean ± SD (n) n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Blood loss within 24 hrs post-surgery (mL/kg)	12 ± 3 (40)	21 ± 4 (40)	NR	Favours TXA $P < 0.01$
Excessive bleeding (>25 mL/kg) due to hyperfibrinolysis	2/40 (5.0)	5/40 (12.5)	NR	NR
EXTERNAL VALIDITY				

Generalisability
Evidence directly generalisable to paediatric cardiac surgery patients with some caveats. (Level B)
Applicability
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)
Comments
The authors concluded that Sonoclot analysis is a useful, point of care method for the monitoring of coagulation and fibrinolysis in patients with tetralogy of Fallot undergoing intracardiac repair.

CBP, cardiopulmonary bypass; CI, confidence interval; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; TOF, tetralogy of Fallot; TXA, Tranexamic acid; SD, standard deviation; SR, systematic review

STUDY DETAILS: RCT				
Citation				
Ahmed Z, Stricker L, Rozzelle A, Zestos M. (2014) Aprotinin and transfusion requirements in pediatric craniofacial surgery. Pediatric Anesthesia, 24: 141–5.				
Affiliation/Source of funds				
The authors reported no conflicts of interest.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, USA	
Intervention	Comparator			
Aprotinin (171.5 mL/m^2) administered intravenously over 30mins, followed by a maintenance infusion (40 mL/m^2/hr).	Placebo (normal saline)			
Population characteristics				
Paediatric patients aged 1 month to 3 years scheduled for major reconstructive craniofacial surgery. Exclusion criteria: history of trauma that required craniofacial reconstruction, major systemic disease, renal impairment or bleeding disorder, allergy to aprotinin, exposure to aprotinin within previous 6 months.				
Length of follow-up	Outcomes measured			
Until hospital discharge.	Primary: RBC transfusion requirements Other: other transfusion requirements, postoperative drain output, mortality, adverse events.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 26 young paediatric patients scheduled for major reconstructive craniofacial surgery in the USA, to examine the effect of aprotinin compared to placebo on RBC transfusion requirements. Method of randomisation not reported. Drug and placebo were prepared and labelled in double-blind fashion by an anaesthesiologist not involved in the clinical care of the patients. Baseline characteristics were similar between the groups. All randomised patients were included in final analyses.				
RESULTS				
Population analysed	Aprotinin		Placebo	
Randomised	13		13	
Efficacy analysis (ITT)	13		13	
Efficacy analysis (PP)	NR		NR	
Safety analysis	13		13	
Outcome	Aprotinin n/N (%) Mean ± SD (n)	Placebo n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
Transfusion incidence				
FFP	5/13 (38.5)	9/13 (69.2)	NR	No significant difference *P* = NR
RBC and/or platelet (postoperative)	2/13 (15.4)	3/13 (23.1)	NR	No significant difference *P* = NR

Transfusion volume (intraoperative)				
FFP (mL)	100 ± 150 (13)	220 ± 200 (13)	NR	No significant difference *P* = NR
FFP (mL/kg)	10 ± 20 (13)	20 ± 20 (13)	NR	No significant difference *P* = NR
RBC (mL)	380 ± 90 (13)	550 ± 200 (13)	NR	Favours aprotinin *P* = 0.004
RBC (mL/kg)	40 ± 10 (13)	60 ± 20 (13)	NR	Favours aprotinin *P* = 0.05
Albumin (mL)	110 ± 100 (13)	120 ± 100 (13)	NR	No significant difference *P* = NR
Bleeding				
Drain output (mL), 1 day post-surgery	60	103	NR	No significant difference *P* = NR
Drain output (mL), 2 days post-surgery	100	99	NR	No significant difference *P* = NR
Drain output (mL), average days 1 & 2	80 ± 30 (13)	101 ± 3 (13)	NR	No significant difference *P* = NR
Adverse events within 30 days post-surgery				
Mortality	0/13 (0)	0/13 (0)	NR	No significant difference *P* = NA
Thrombotic complications	0/13 (0)	0/13 (0)	NR	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients aged 1 month to 3 years scheduled for major reconstructive craniofacial surgery. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that aprotinin was associated with decreased RBC transfusion requirements in children undergoing craniofacial surgery, with no renal toxicity or death. Aprotinin is no longer available for clinical use in the USA because of adverse effects in adults; re-evaluation is warranted for its use in children scheduled for surgery involving potentially high blood loss.				

CI, confidence interval; FPP, fresh frozen plasma; ITT, intention-to-treat; NA; not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review

STUDY DETAILS: RCT		
Citation		
Alan S, Arsan S, Okulu E et al. (2014) Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born ≤1500 g: a prospective, randomized, controlled trial. J Pediatr Hematol Oncol, 36(8): e493-e498.		
Affiliation/Source of funds		
The authors declared no conflict of interest.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single NICU, Turkey.
Intervention	Comparator	
Umbilical cord milking (UCM)	Immediate cord clamping (ICC) <10s of delivery	
Population characteristics		
Preterm infants (≤32 weeks gestational age) with VLBW (≤1500 g). Exclusion criteria: suspected twin-to-twin transfusion syndrome, discordant twins, major congenital or chromosomal anomalies, vaginal bleeding due to placenta previa, abruption or placental tear, haemolytic disease of the fetus and newborn e.g. Rhesus sensitisation, intrauterine growth restriction, maternal gestational diabetes treated with insulin, hydrops fetalis, refused parental consent.		
Length of follow-up	Outcomes measured	
Until NICU discharge.	Primary: number and volume of RBC transfusions during the first 35 days of life Secondary: haemodynamic variables during the first 24hrs of life	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: an RCT of 48 VLBW preterm infants in Turkey, to examine the effect of UCM compared to ICC on transfusion requirements in the first 35 days of life. There were 48 infants randomised. Two infants were excluded from each group due to inappropriate milking technique in the UCM group, and major bleeding or death in the control group. After analysis on the first day, three infants from each group were lost to follow-up due to death or major bleeding. There were 19 infants per group in subsequent analyses. Patients were randomised using sequentially numbered sealed non-transparent envelopes. In case of twin pregnancies, the first one was randomised and the second one was automatically assigned to the opposite arm without randomisation. Umbilical cord milking was performed by one of the investigators (SA) who also took part in most of the deliveries. The intervention was unmasked for the attending neonatal and obstetric teams in the delivery room. Method of UCM: infants were placed at the level of placenta in caesarean deliveries and below the level of placenta in vaginal deliveries. The cord was held at 25-30cm from the baby and milked vigorously toward the umbilicus for 3x at the speed of approximately 5cm/sec by the attending neonatologist before clamping.		
RESULTS		
Population analysed	UCM (placental transfusion)	ICC
Randomised	24	24
Efficacy analysis (ITT)	22 (first analysis) 19 (subsequent analyses)	22 (first analysis) 19 (subsequent analyses)
Efficacy analysis (PP)	NR	NR
Safety analysis	24	24

Outcome	UCM n/N (%) Median (range)	ICC n/N (%) Median (range)	Risk estimate (95% CI)	Statistical significance *P*-value
RBC transfusion requirements				
RBC transfusion in first 3 days of life	2/21 (9.5)	4/21 (19.0)	NR	No significant difference *P* = 0.384
RBC transfusion during the study period	15/19 (78.9)	17/19 (89.5)	NR	No significant difference *P* = 0.380
No. of RBC transfusions in first 14 days of life	1 (0 – 3)	1 (0 – 4)	NR	No significant difference *P* = 0.828
Volume of RBC transfusion in first 14 days of life (mL/kg)	10 (0 – 40)	10 (0 – 45)	NR	No significant difference *P* = 0.773
No. of RBC transfusions in first 35 days of life	2 (0 – 6)	2 (0 – 7)	NR	No significant difference *P* = 0.840
Volume of RBC transfusion in first 35 days of life (mL/kg)	25 (0 – 78)	25 (0 – 75)	NR	No significant difference *P* = 0.885
No. of RBC transfusions during NICU stay	3 (0 – 7)	3 (0 – 8)	NR	No significant difference *P* = 0.813
Volume of RBC transfusion during NICU stay (mL/kg)	45 (0 – 103)	42 (0 – 116)	NR	No significant difference *P* = 0.872
Adverse events				
Major bleeding or death in the delivery room	0/24 (0)	2/24 (8.3)	NR	No significant difference *P* = NR
Major bleeding or death in days 2-7 of life	3/22 (13.6)	3/22 (13.6)	NR	No significant difference *P* = 1.000
IVH ≥ grade 3	NR (13.6)	0 (0)	NR	No significant difference *P* > 0.05
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to VLBW preterm infants. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that UCM in VLBW infants seems to be associated with potentially beneficial effects on hematologic and hemodynamic parameters during the first day of life. We suggest that these beneficial effects may become more prominent if phlebotomy losses are minimised and restricted transfusion strategies are utilised.				

CI, confidence interval; FPP, fresh frozen plasma; ICC, immediate cord clamping; ITT, intention-to-treat; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; UCM, umbilical cord milking; VLBW, very low birth weight

STUDY DETAILS: RCT		
Citation		
Brum MR, Miura MS, de Castro SF, Machado GM et al. (2012) Tranexamic acid in adenotonsillectomy in children: a double-blind randomized clinical trial. International Journal of Pediatric Otorhinolaryngology, 76: 1401–5.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single hospital, Brazil.
Intervention	Comparator	
TXA (10mg/kg) administered intravenously in the preoperative period and at the 8th and 16th hours of the postoperative period	Placebo (saline)	
Population characteristics		
Children aged 4-12 years with indication of adenotonsillectomy due to adenotonsillar hyperplasia and obstructive symptoms of the upper airways. Exclusion criteria: previously diagnosed blood dyscrasia, abnormal coagulation screening, history of bleeding disorder or spontaneous hematomas, evidence of other clinically significant disease.		
Length of follow-up	Outcomes measured	
10 days post-surgery.	Primary: intraoperative bleeding volume Secondary: primary and secondary postoperative bleeding, streaks of blood in saliva and no. of days this occurred. (2° postoperative bleeding defined as clinically significant bleeding requiring hospital readmission, blood transfusion or surgical reintervention).	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Good Description: A double-blind RCT of 95 children scheduled for adenotonsillectomy in Brazil, to examine the effect of TXA compared to placebo on intraoperative bleeding. Randomised blocks were used to keep a balanced number of patients in each group. Participants within blocks were given increasing numbers which identified a sealed opaque envelope containing treatment assignment. Each surgeon received a randomised block of four patients to operate on. At the time of surgery, the team contacted the hospital pharmacy and provided the patient's information and name of the surgeon. The pharmacist in charge opened the corresponding envelope containing the treatment assignment. Blinding of the surgeon, main investigator and patient/family were maintained until after study completion. An ITT analysis was performed as well as a per-protocol analysis where participants who did not receive the intervention or discontinued the intervention were excluded. There was no difference in six or age between the groups but weight in the TXA group was significantly less than the placebo group. One patient in the TXA group was lost to follow-up. Linear regression including weight, age and treatment showed no significant difference in bleeding between groups.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	47	48
Efficacy analysis (ITT)	47	48
Efficacy analysis (PP)	39	39

Safety analysis	NR		NR	
Outcome	TXA n/N (%) Mean ± SD (n)	Placebo n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
ITT analyses				
Total intraoperative bleeding (mL)	135.1 ± 71.4 (47)	158 ± 88.1 (48)	NR	No significant difference *P* = 0.197
Intraoperative bleeding (mL/kg)	5.84 ± 3.4 (47)	5.23 ± 3.29 (48)	NR	No significant difference *P* = 0.381
PP analyses				
Total intraoperative bleeding (mL)	131.92 ± 64.04 (39)	155 ± 86.2 (39)	NR	No significant difference *P* = 0.184
Intraoperative bleeding (mL/kg)	5.71 ± 3.44 (39)	5.46 ± 3.39 (39)	NR	No significant difference *P* = 0.742
Secondary outcomes				
Primary postoperative bleeding	NR	NR	NR	No significant difference *P* = 0.85
Secondary postoperative bleeding	0	0	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children scheduled for adenotonsillectomy with some caveats. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that there is no benefit in the use of TXA for reducing bleeding during the perioperative period of adenotonsillectomy in children. More studies with larger sample sizes are required to evaluation the benefit of TXA in postoperative bleeding.				

CI, confidence interval; ITT, intention-to-treat; NA; not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; TXA, Tranexamic acid

STUDY DETAILS: RCT				
Citation				
Caputo M, Patel N, Angelini GD, de Siena P et al. (2011) Effect of normothermic cardiopulmonary bypass on renal injury in pediatric cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg, 142: 1114–21.				
Affiliation/Source of funds				
Support was received from the British Heart Foundation, NIHR Bristol Biomedical Research Unit in Cardiovascular Medicine and Garfield Weston Trust.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, England.	
Intervention	Comparator			
Normothermia: temperature maintained at 35-37°C	Hypothermia: cooling to a nasopharyngeal temperature of 28°C			
Population characteristics				
Paediatric patients (median age 6.5 years) undergoing corrective cardiac surgery with CPB. Exclusion criteria: pre-existing renal dysfunction, neonates, patients requiring hypothermic circulatory arrest or complex repair of the pulmonary arterial system with periods of low-flow CPB.				
Length of follow-up	Outcomes measured			
NR	Urinary albumin, retinal binding protein and NAG; serum urea, creatinine, electrolytes, glucose and lactate; haematocrit, all-cause in hospital mortality and morbidity.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: an RCT of 59 paediatric patients undergoing corrective cardiac surgery with CPB in England, to examine the effect of normothermia compared to hypothermia on clinical and laboratory endpoints. Random treatment allocations were generated by computer in advance using block randomisation with varying block sizes. Allocation details were concealed in sequentially numbered, opaque sealed envelopes. Randomisation was revealed to the surgeon after the start of the operation. Urinary markers were measured in duplicate and in a blinded fashion. Patients were managed in the ICU by intensivists and cardiologists blinded to randomisation. Baseline characteristics were similar between groups. Loss to follow-up not reported, but infants were analysed by ITT. The study sample size was set at 29 patients per group based on previous experience in similar studies, for 80% power at a 5% significance level (two-tailed). There were only 28 patients in the normothermic group.				
RESULTS				
Population analysed	Normothermic		Hypothermic	
Randomised	28		31	
Efficacy analysis (ITT)	28		31	
Efficacy analysis (PP)	NR		NR	
Safety analysis	28		31	
Outcome	Normothermic n/N (%) Median (IQR)	Hypothermic n/N (%) Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
All-cause in hospital mortality	0/28 (0)	0/31 (0)	NA	No significant difference *P* = NA

RBC transfusion incidence	8/28 (29)	8/31 (26)	NR	NR
RBC transfusion (mL/kg)	9.6 (6.8–19.7)	9.5 (6.8–16.6)	NR	NR
Platelet/FFP transfusion incidence	6/28 (21)	5/31 (16)	NR	NR
Platelet/FFP transfusion (mL/kg)	9.9 (4.9–10.0)	5.2 (4.9–5.5)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients undergoing cardiac surgery with CPB. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)				
Comments				
The study was powered to detect changes in biochemical markers but not in clinical outcome. The authors concluded that normothermic CPB is associated with similar renal impairment to hypothermic CPB in children undergoing heart surgery.				

CI, confidence interval; ITT, intention-to-treat; NA; not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; ICU, intensive care unit; NAG, N-acetyl-b-D-glucosaminidase

STUDY DETAILS: RCT				
Citation				
Cholette JM, Powers KS, Alfieris GM, Angona R et al. (2013) Transfusion of cell saver salvaged blood in neonates and infants undergoing open heart surgery significantly reduces RBC and coagulant product transfusions and donor exposures: results of a prospective, randomised, clinical trial. Pediatr Crit Care Med, 14(2): 137–47.				
Affiliation/Source of funds				
The authors reported that no author had any financial or personal relationship with other people or organisations that could inappropriately influence this paper.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, USA	
Intervention		Comparator		
Cell saver salvaged blood stored at the bedside for 24hrs post-collection.		Crystalloid, colloid or albumin for volume replacement. RBCs were given for anaemia.		
Population characteristics				
Children ≤20kg scheduled for cardiac surgical repair/palliation with cardiopulmonary bypass (CPB). Exclusion criteria: parent/guardian who did not speak English or if consent could not be obtained.				
Length of follow-up		Outcomes measured		
7 days.		Postoperative allogeneic RBC transfusions and donor exposures, clinical outcomes.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: An RCT of 110 paediatric patients weighing ≤20kg scheduled for cardiac surgery with CPB at a single hospital in the USA, to examine the effect of cell salvaged blood compared to crystalloid, colloid or albumin on postoperative RBC transfusions and donor exposures. Block randomisation was used to randomize subjects. Subjects were stratified by weight (≤10kg or >10kg) and risk-adjusted congenital heart surgery (RACHS-1) score (1-3 = less severe; 4-6 = more severe). The cardiac surgeon was blinded to study group. Obvious differences in packaging and labelling of blood products prevented blinding of the attending physician, percussionists, anaesthesiologist, and PICU personnel. Knowledge of the treatment groups may have influenced the decision to transfuse RBCs. Baseline characteristics were similar between the groups. Of the 110 infants randomised, 106 participated (three patients had surgery performed off CPB and one patient had surgery postponed). Of the 53 patients in the cell saver group, 50 had cell saver blood collected and 49 had cell saver blood transfused. Subgroup analysis was performed with subjects divided according to low or high RACHS scores. There was no loss to follow-up and no protocol violations.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	55		55	
Efficacy analysis (ITT)	53		53	
Efficacy analysis (PP)	53		53	
Safety analysis	53		53	
Outcome	Cell salvage n/N (%) Mean ± SD (n)	No cell salvage n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value

RBC transfusion within 24hrs post-surgery	0.04 ± 0.19 (53)	0.51 ± 0.91 (53)	NR	Favours cell salvage *P* = 0.001
RBC transfusion within 48hrs post-surgery	0.19 ± 0.44 (53)	0.75 ± 1.2 (53)	NR	Favours cell salvage *P* = 0.003
RBC transfusion within 7 days post-surgery	0.64 ± 1.24 (53)	1.1 ± 1.4 (53)	NR	No significant difference *P* = 0.07
Platelet transfusion within 2 days post-surgery	0 ± 0 (53)	0.11 ± 0.38 (53)	NR	Favours cell salvage *P* = 0.03
FFP transfusion within 2 days post-surgery	0 ± 0 (53)	0.15 ± 0.46 (53)	NR	Favours cell salvage *P* = 0.02
Cryoprecipitate transfusion within 2 days post-surgery	0 ± 0 (53)	0.08 ± 0.27 (53)	NR	Favours cell salvage *P* = 0.04
Mortality	3/53 (5.7)	1/53 (1.9)	NR	No significant difference *P* = 0.310
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric cardiac surgery patients with CPB weighing ≤20kg. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The study was a pilot study and was not powered to assess differences in clinical outcomes. The authors concluded that cell saver blood can be safely stored at the bedside for immediate transfusion for 24 hours post-collection. Administration of cell saver blood significantly reduces the number of RBC and coagulant product transfusions and donor exposures in the immediate post-operative period.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hct, haematocrit; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; PICU, paediatric intensive care unit; PP, per-protocol; RACHS, risk-adjusted congenital heart surgery; RBC, red blood cell; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Coniff RF. (1998) The Bayer 022 Compassionate-Use Pediatric Study. Ann Thorac Surg, 65: S31–4.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Multicentre, USA

Intervention	Comparator
1. Aprotinin, high dose 2. Aprotinin, low dose 3. Aprotinin, pump prime only	Placebo

Population characteristics
Paediatric patients aged ≤16 years undergoing a procedure associated with CPB and with a definite increased risk of perioperative bleeding. Exclusion criteria: uncomplicated primary procedures and valve repairs.

Length of follow-up	Outcomes measured
NR	Donor blood and blood product requirements, thoracic drainage volumes, rates of reoperation due to diffuse bleeding.

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description: a four-armed RCT in 116 paediatric patients in the USA undergoing surgery with CPB and at increased risk of bleeding, to examine the effect of aprotinin at three doses compared to placebo on blood transfusion requirements. The randomisation method and blinding was not reported. Patients were stratified by primary or repeat sternotomy (there were 43 primary and 73 repeat sternotomies). There were only three patients aged ≤1 year randomised to high dose aprotinin which may have distorted results. The authors reported that the sample size was too small to permit formal statistical analysis of outcome data. Also, due to this being a compassionate use study, the authors did not do hands-on monitoring of the trial and reported that data may not be quite as clean as data from a more formal trial. Baseline characteristics and demographics were not reported. Loss to follow-up was not reported but it appeared that all randomised infants were included in analyses. The authors were completing another aprotinin dose-response study concurrently to the present study, which showed that the pump prime only regimen was not particularly effective. As a result of this finding, the pump prime only arm was discontinued from the present study which explains the smaller number of patients.

RESULTS				
Population analysed	High dose aprotinin	Low dose aprotinin	Aprotinin in pump prime only	Placebo
Randomised	31	33	18	34
Efficacy analysis (ITT)	31	33	18	34
Efficacy analysis (PP)	NR	NR	NR	NR
Safety analysis	31	33	18	34

Outcome	High n/N (%) Mean ± SD (n)	Low n/N (%) Mean ± SD (n)	PP n/N (%) Mean ± SD (n)	Placebo n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
Units of donor blood or blood product transfused	2.9 ± 8.5 (31)	6.0 ± 5.1 (33)	9.1 ± 12.6 (18)	11.3 ± 23.7 (34)	NR	NR
Patients requiring transfusion of donor blood or blood products	NR (93.5)	NR (93.9)	NR (88.9)	NR (85.3)	NR	NR
Patients requiring transfusion of ≥20 units of donor blood or blood products	NR (3.2)	NR (3.0)	NR (5.6)	NR (11.8)	NR	NR
Mortality	1/31 (3.2)	2/33 (6.1)	1/18 (5.6)	5/34 (14.7)	NR	NR
Subgroup analysis: patients undergoing redo operations (more prone to bleeding)						
Units of donor blood or blood product transfused	7.1 ± 10.4 (19)	7.4 ± 5.4 (22)	11.9 ± 16.3 (10)	15.2 ± 28.6 (22)	NR	NR
Patients requiring transfusion of donor blood or blood products	NR (94.7)	NR	NR	NR (90.9)	NR	NR
Patients requiring transfusion of ≥20 units of donor blood or blood products	NR (5.3)	NR (4.5)	NR (10.0)	NR (13.6)	NR	NR
Subgroup analysis: patients **aged ≤1 year**						
Units of donor blood or blood product transfused	7.3 ± 3.2 (3)	5.0 ± 3.1 (14)	14.1 ± 17.6 (8)	9.0 ± 6.5 (6)	NR	NR
Patients requiring transfusion of donor blood or blood products	NR	NR (92.9)	NR	NR	NR	NR
Patients requiring transfusion of ≥20 units of donor blood or blood products	NR	NR	NR (12.5)	NR (16.7)	NR	NR
Subgroup analysis: patients aged >1 and <17 years						
Units of donor blood transfused	2.6 ± 1.8 (28)	3.7 ± 2.3 (19)	2.8 ± 2.2 (10)	4.8 ± 6.5 (28)	NR	NR
Units of donor blood *and* blood product transfused	5.0 ± 8.9 (28)	6.8 ± 6.1 (19)	5.1 ± 4.5 (10)	11.8 ± 26.0 (28)	NR	NR
Patients requiring transfusion of donor blood	NR (92.9)	NR (94.7)	NR (80.0)	NR (82.1)	NR	NR

Patients requiring transfusion of donor blood *and* blood products	NR (92.9)	NR (94.7)	NR (80.0)	NR (82.1)	NR	NR
Patients requiring transfusion of ≥20 units of donor blood	NR (14.3)	NR (31.6)	NR (30.0)	NR (28.6)	NR	NR
Patients requiring transfusion of ≥20 units of donor blood *and* blood products	NR (3.6)	NR (5.3)	NR	NR (10.7)	NR	NR
EXTERNAL VALIDITY						
Generalisability						
Evidence directly generalisable to paediatric patients undergoing procedures with CPB and with an increased risk of perioperative bleeding. (Level A)						
Applicability						
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)						
Comments						
The authors concluded that there is a trend toward benefit with aprotinin use in a paediatric population, as measured by requirement for blood and blood product, in patients who are more than 1 year of age and in patients undergoing a repeat operation rather than a primary sternotomy operation.						

CI, confidence interval; NR, not reported; RCT, randomised controlled trial; ITT, intention-to-treat; PP, per-protocol; SD, standard deviation; PP, per-protocol; SD, standard deviation; NA; not applicable; NR, not reported; CPB, cardiopulmonary bypass

STUDY DETAILS: RCT				
Citation				
D'Errico CC, Munro HM, Buchman SR, Wagner D, Muraszko KM. (2003) Efficacy of aprotinin in children undergoing craniofacial surgery. J Neurosurg. 99:287-290.				
Affiliation/Source of funds				
Not reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		USA	
Intervention	Comparator			
IV aprotinin 240mg/m^2 over 20 mins, followed by infusion 56mg/m^2/hr	Placebo (saline)			
Population characteristics				
39 paediatric patients aged 1 month to 12 years undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement. Exclusion criteria: renal insufficiency/failure, pre-existing coagulation abnormality, aprotinin allergy, previous craniofacial surgery.				
Length of follow-up	Outcomes measured			
3 days post-surgery.	Perioperative blood loss, need for blood transfusion.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A double-blind RCT of 39 paediatric patients undergoing craniofacial reconstruction at a single hospital in the USA, to examine the effect of aprotinin compared to placebo on perioperative blood loss and blood transfusion requirements. Patients were assigned to a treatment group based on a computer-generated list of random numbers. The same surgical team performed all operative procedures; all were blinded to treatment allocation. Study drugs were prepared by the pharmacy and administered in a double-blind fashion. Only the pharmacist who kept a record of the patient's identification number and the randomisation list could identify which study drug was used in case of an emergency. Baseline patient characteristics were similar between groups, except for median age (higher in aprotinin group) and lowest Hct level (higher in aprotinin group). Loss to follow-up not explicitly reported, but assumed all patients remained in the study.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	18		21	
Efficacy analysis (ITT)	18		21	
Efficacy analysis (PP)	18		21	
Safety analysis	18		21	
Outcome	Aprotinin Mean ± SD (n) n/N (%)	Placebo Mean ± SD (n) n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Estimated blood loss (mL/kg)	28 ± 21 (18)	39 ± 25 (21)	NR	No significant difference *P* = 0.14

Intraoperative blood transfusion volume (mL/kg)	32 ± 25 (18)	52 ± 34 (21)	NR	Favours aprotinin *P* = 0.04
Postoperative RBC transfusion volume (mL/kg)	33 ± 24 (18)	57 ± 38 (21)	NR	Favours aprotinin *P* = 0.03
Platelet transfusion incidence	1/18 (5.6)	0/21 (0.0)	NR	No significant difference *P* = NR
FFP transfusion incidence	2/18 (11.1)	5/21 (23.8)	NR	No significant difference *P* = NR
Cryoprecipitate transfusion incidence	0/18 (0.0)	0/21 (0.0)	NA	No significant difference *P* = NA
Mortality	0/18 (0.0)	0/21 (0.0)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric craniofacial surgery patients. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that aprotinin decreased blood transfusion requirements in paediatric patients undergoing craniofacial reconstruction, thereby reducing the risks associated with exposure to banked blood products.				

CI, confidence interval; FFP, fresh frozen plasma; Hct, haematocrit; ITT, intention-to-treat; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Eldaba AA, Amr YM, Albirmawy OA. Effects of tranexamic acid during endoscopic sinsus surgery in children. Saudi J Anaesth 2013;7:229-33.		
Affiliation/Source of funds		
No source of funds reported. The authors are affiliated with the Department of Anesthesia and Surgical Intensive Care, ENT, Tanta University Hospital, Tanta University, Tanta, Egypt.		
Study design	Level of evidence	Location/setting
RCT	Level II	Egypt
Intervention	Comparator	
Intravenous 25mg/kg TXA diluted in 10 mL of normal saline (slow intravenous injection in 3-5 minutes)	10 mL of normal saline (slow intravenous injection within 3-5 minutes)	
Population characteristics		
100 children aged 5-10 years with chronic rhinosinusitis and undergoing FESS (functional endoscopic sinus surgery). Exclusion criteria: refusal of the parents, systematic diseases affecting the nose, medical treatment affecting the study or any congenital anomalies, patients with pre-existing renal and hepatic disorders, bleeding diathesis and abnormal prothrombin time, partial thromboplastin time (PTT) or platelet counts, usage of non-steroidal anti inflammatory drugs within 7 days of surgery.		
Length of follow-up	Outcomes measured	
NR (duration of surgery through to recovery)	Quality of the surgical field (level of bleeding), volume of bleeding, mean arterial blood pressure, heart rate, side effects	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: Randomisation was performed using a computer based random number generator in permuted blocks of varying sizes. Treatment allocations were entered in sealed envelopes that were not opened until consent was obtained. Anaesthesiologists, operating personnel, chief nurse and study staff were blinded to treatment groups. All surgical procedures were conducted by the same surgical team using the same technique. The surgical team was blinded to the study protocol. Baseline characteristics were similar between the groups. Loss to follow-up is not reported but it is assumed all participants were included in the final analysis. No subgroup analyses were reported. Quality of the surgical field (predefined scale adapted from Boezaart *et al* 1995: 0= No bleeding. 1= Minimal bleeding: not a surgical nuisance and no suction required. 2= Mild bleeding: occasional suction required but does not affect dissection. 3= Moderate bleeding: slightly compromises surgical field, frequent suction required. 4= Severe bleeding: significantly compromises surgical field, frequent suction required, bleeding threat field just after removal of suction. 5= Massive bleeding: prevent dissection.		
RESULTS		

Population analysed	TXA	Placebo
Randomised	50	50
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR

Safety analysis	NR		NR	
Outcome	TXA Mean ± SD (n) n/N (%)	Placebo Mean ± SD (n) n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
Volume of bleeding (mL)	102 ± 19 (50)	153 ± 23 (50)	NR	Favours TXA *P* < 0.0001
Quality of the surgical field 15 minutes after starting surgical procedure				
Grade 0	0/50 (0.0)	0/50 (0.0)	NA	No significant difference *P* = NA
Grade I	7/50 (14.0)	0/50 (0)	NR	Favours TXA *P* = 0.006
Grade II	35/50 (70.0)	26/50 (52.0)	NR	No significant difference *P* = 0.064
Grade III	8/50 (16.0)	24/50 (48.0)	NR	Favours TXA *P* = 0.0006
Grades IV and V	0/50 (0.0)	0/50 (0.0)	NA	No significant difference *P* = NA
Quality of the surgical field 30 minutes after starting surgical procedure				
Grade 0	1/50 (2.0)	0/50 (0)	NR	No significant difference *P* = NR
Grade I	10/50 (20.0)	1/50 (2.0)	NR	Favours TXA *P* = 0.004
Grade II	37/50 (74.0)	28/50 (56.0)	NR	No significant difference *P* = 0.059
Grade III	2/50 (4.0)	21/50 (42.0)	NR	Favours TXA *P* < 0.0001
Grades IV and V	0/50 (0.0)	0/50 (0.0)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to children with chronic rhinosinusitis undergoing FESS (Level A).				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C). The study was conducted in Egypt.				
Comments				
General anaesthesia was used for all patients. No complications/side effects of TXA were reported. The authors concluded that a single intravenous bolus dose of TXA in children during FESS improves quality of surgical field, reduces intraoperative bleeding and duration of surgery.				

CI, confidence interval; FESS, functional endoscopic sinus surgery; ITT, intention-to-treat; NA, not applicable; NR, not reported; PTT, partial thromboplastin time; RCT, randomised controlled trial; PP, per-protocol; SD, standard deviation; TXA, tranexamic acid

STUDY DETAILS: RCT		
Citation		
Ferreira CA, Vicente WV, Evora PRB, Rodrigues AJ et al. (2009) Does aprotinin preserve platelets in children with acyanogenic congenital heart disease undergone surgery with cardiopulmonary bypass? Rev Bras Cir Cardiovasc, 24(3): 373–81.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single hospital, Brazil
Intervention	Comparator	
Aprotinin (240mg/m^2), administered intravenously over 20-30 mins at the time of surgical incision, followed by continuous infusion of 56mg/m^2/hr throughout surgery. Aprotinin (240mg/m^2) was also added to the perfusate of the oxygenator.	No aprotinin	
Population characteristics		
Paediatric patients aged one month to four years scheduled for correction of acyanogenic congenital heart disease using CPB. Exclusion criteria: exposure to aprotinin in previous 6 months, use of salicylates up to 7 days before surgery, allergic immune disorders, hepatic, renal or coagulation disorders; episodes of cardiac arrest, sepsis or vasculitis in previous two months.		
Length of follow-up	Outcomes measured	
30 days or until discharge.	Surgical data: volumed of RBC, fresh plasma and packed platelets; TCA before, during and after CPB, complications. Postoperative data: PICU length of stay, duration of mechanical ventilation, bleeding, use of blood products, donor exposures.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: an RCT of 19 paediatric patients aged one month to four years scheduled for cardiac surgery with CPB in Brazil, to examine the effect of aprotinin compared to no aprotinin on clinical outcomes including transfusion volume and incidence. The method of randomisation was not reported. The study was unblinded. Transfusion of RBC was according to the PICU protocol (details not provided). Baseline characteristics were similar between the groups. Loss to follow-up not reported.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	10	9
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Aprotinin n/N (%) Mean ± SD Median	Control n/N (%) Mean ± SD Median	Risk estimate (95% CI)	Statistical significance *P*-value
Mortality	0/10 (0)	0/9 (0)	NA	No significant difference *P* = NA
Intraoperative RBCs (mL)	221 ± 55	248 ± 73	NR	No significant difference *P* = NR
Postoperative outcomes				
Bleeding in first 48 hrs (mL/kg)	17.6 ± NR	18.1 ± NR	NR	No significant difference *P* = NR
RBC transfusion incidence	1/10 (10)	0/9 (0)	NR	NR
Platelet concentrate transfusion incidence	0/10 (0)	2/9 (22)	NR	NR
Platelet concentrate (mL/kg)	0 ± 0	12 ± NR	NR	NR
Albumin (mL/kg)	27.58 ± 30.27	12.95 ± 18.58	NR	NR
Donor exposures	2	2	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients aged one month to four years undergoing cardiac surgery with CPB. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that aprotinin quantitatively preserved platelets, but did not affect postoperative bleeding significantly in children undergoing corrective surgery for congenital heart defects.				

CI, confidence interval; CPB, cardiopulmonary bypass; EBV, estimated blood volume; FFP, fresh frozen plasma; Hct, haematocrit; ITT, intention-to-treat; NR, not reported; PICU, paediatric intensive care unit; RBC, red blood cell; PT, prothrombin time; RCT, randomised controlled trial; PP, per-protocol; PV, prime volume; RBC, red blood cell

STUDY DETAILS: RCT				
Citation				
Flaujac C, Pouard P, Boutouyrie P, Emmerich J et al. (2007) Platelet dysfunction after normothermic cardiopulmonary bypass in children: Effect of high-dose aprotinin. Thromb Haemost, 98: 385–91.				
Affiliation/Source of funds				
Not reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, France	
Intervention		Comparator		
2x doses aprotinin (30,000 KIU/kg) administered intravenously after induction of anaesthesia, plus 8,000 KIU/kg/hr during CPB.		No aprotinin.		
Population characteristics				
Infants aged 4 days to 36 months undergoing primary corrective cardiac surgery with CPB.				
Length of follow-up		Outcomes measured		
NR		Platelet function, postoperative blood loss and transfusion requirements, laboratory measures.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 20 infants and newborns undergoing primary corrective cardiac surgery with CPB in France, to examine the effect of high dose aprotinin compared to no aprotinin on platelet function, postoperative blood loss and transfusion requirements. Method of randomisation not described. There were nine newborns aged ≤1 month and 11 infants aged 2-36 months. All patients weighed <15kg and none had a history of major heart surgery. Groups were similar at baseline. Surgeons were unaware of treatment allocation. Loss to follow-up not reported; however it appeared all randomised infants were included in analyses. Transfusion protocol: - RBC when Hct ~40% - Platelets in the case of bleeding when ≤50x10^9/L - FFP to maintain filling pressure when Hct and protein levels were reached - Prothrombin complex concentrate when prothrombin time >20 seconds - Albumin to maintain filling pressure when protidemia <50 g/L				
RESULTS				
Population analysed	Aprotinin		No aprotinin	
Randomised	10		10	
Efficacy analysis (ITT)	10		10	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Aprotinin n/N (%) Median (IQR)	Control n/N (%) Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value

24hr postoperative blood loss (mL/kg)	19.8 (12.6 – 21.3)	18.3 (9.1 – 30.1)	NR	No significant difference *P* = NR
Total 24hr postoperative transfusion requirements (mL/kg)	18 (9.0 – 25.8)	30 (25.8 – 39.3)	NR	Favours aprotinin *P* = 0.01
24hr postoperative transfusion incidence				
RBC	6/10 (60.0)	10/10 (100.0)	NR	Borderline favours aprotinin *P* = 0.06 [a]
Platelets	3/10 (30.0)	6/10 (60.0)	NR	No significant difference *P* = 0.21 [a]
FFP	2/10 (20.0)	3/10 (30.0)	NR	No significant difference *P* = 0.61 [a]
Albumin	0/10 (0.0)	4/10 (40.0)	NR	No significant difference *P* = 0.12 [a]
Prothrombin complex concentrate (prepared from FFP)	4/10 (40.0)	7/10 (70.0)	NR	No significant difference *P* = 0.20 [a]
Adverse events				
Thrombotic events	0/10 (0.0)	0/10 (0.0)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to infants and newborns undergoing primary corrective cardiac surgery with CPB. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that high dose aprotinin has a protective effect against platelet dysfunction in paediatric normothermic CPB.				

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; ITT, intention-to-treat; IQR, interquartile range; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

a. Calculated post-hoc using RevMan 5.1

STUDY DETAILS: RCT				
Citation				
Friesen RH, Perryman KM, Weigers KR, Mitchell MB, Friesen RM. (2006) A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants. Pediatric Anesthesia, 16: 429-435.				
Affiliation/Source of funds				
Supported by a grant from the National Center for Research Resources, NIH.				
Study design	Level of evidence		Location/setting	
RCT	Level II		USA	
Intervention	Comparator			
ANH, 15 mL/kg autologous whole blood collected prior to heparinisation, followed by intravenous infusion of 15 mL/kg 5% albumin	No ANH			
Population characteristics				
32 paediatric patients aged >1 month and <15 kg scheduled for non-complex open cardiac surgery with CPB. Exclusion criteria: known or suspected coagulopathy, including hepatic or renal disease or recent (within 7 days) antiplatelet or anticoagulation therapy; repeat open heart operations, complex procedures in which prolonged CPB and/or significant blood loss anticipated, cyanotic heart disease.				
Length of follow-up	Outcomes measured			
24 hours.	Primary: coagulation status Secondary: activation of fibrinolysis, haematocrit, 24 hr postoperative blood loss (mediastinal tube drainage), transfusion of homologous blood components during the intraoperative and 24 hr postoperative periods.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: an RCT of 32 paediatric patients scheduled for non-complex cardiac surgery with CPB, to examine the effect of ANH on coagulation, blood loss and transfusion requirements. Patients were randomised using sealed envelopes opened prior to induction of anaesthesia. How randomisation sequence was generation not stated. Blinding not reported, but assumed patients blinded due to timing of envelopes being opened. Blinding of surgeons and anaesthesiologists would not have been possible due to nature of intervention. No loss to follow-up. Homologous transfusion guidelines: component therapy if bleeding deemed clinically significant by anaesthesiologist and surgeon and if surgical bleeding had been excluded. Platelet concentrate was allowed first, followed by cryoprecipitate (if bleeding persisted and fibrinogen concentration <60%), followed by FFP (PT or aPTT >150%). RBC transfusion if blood loss persistent, exceeded 10 mL/kg and Hct <25%.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	16		16	
Efficacy analysis (ITT)	16		16	
Efficacy analysis (PP)	16		16	
Safety analysis	NR		NR	
Outcome	ANH n/N (%)	Control n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value

RBC transfusion during CPB	14/16 (87.5%)	13/16 (81.3%)	NR	NR
RBC transfusion post-CPB	3/16 (18.8%)	3/16 (18.8%)	NR	NR
FFP transfusion	1/16 (6.3%)	3/16 (18.8%)	NR	NR
Platelet transfusion	0/16 (0.0%)	3/16 (18.8%)	NR	NR
Cryoprecipitate transfusion	0/16 (0.0%)	0/16 (0.0%)	NR	NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients undergoing cardiac surgery with CPB with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that although fewer subjects in the treatment group received transfusions of homologous FFP and platelet concentrates, a larger study would be required to demonstrate any statistical significance. They noted that in older children with lower PV/EBV ratios, it is possible that a reduction of homologous RBC transfusion volumes could be achieved with ANH.				

ANH, acute normovolaemic haemodilution; aPTT, activated partial thromboplastin time; CI, confidence interval; CPB, cardiopulmonary bypass; EBV, estimated blood volume; FFP, fresh frozen plasma; Hct, haematocrit; ITT, intention-to-treat; NR, not reported; PT, prothrombin time; RCT, randomised controlled trial; PP, per-protocol; PV, prime volume; RBC, red blood cell

STUDY DETAILS: RCT				
Citation				
Hans P, Collin V, Bonhomme V, et al. (2000) Evaluation of acute normovolemic hemodilution for surgical repair of craniosynostosis. Journal of Neurosurgical Anesthesiology, 12(1): 33-6.				
Affiliation/Source of funds				
Not reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Belgium	
Intervention	Comparator			
ANH to achieve a haematocrit of 25%	No ANH			
Population characteristics				
Paediatric patients (mean age 7 months) scheduled for surgical repair of scaphocephaly or pachycephaly.				
Length of follow-up	Outcomes measured			
NR	Hct at end of surgery and before discharge, estimated blood loss / estimated blood volume (EBL/EBV), homologous transfusion volume and incidence.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: an RCT of 34 infants scheduled for craniofacial surgery in Belgium, to examine the effect of ANH on blood loss and transfusion requirements. The method of randomisation and blinding were not reported. All patients were operated by the same surgeon and managed by the same anaesthetist. There were no significant differences between groups at baseline. ANH method: blood removal via the arterial line to achieve a target Hct of 25% and simultaneous replacement with a 5% albumin solution to maintain the circulating volume.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	17		17	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	ANH n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Statistical significance *P*-value
EBL/EBV	21.35 ± 8.0	24.0 ± 6.6	NR	No significant difference *P* = NR
Homologous transfusion incidence	15/17 (88.2)	14/17 (82.4)	NR	No significant difference *P* = NR
Homologous transfusion volume	17.0 ± 4.7	19.6 ± 6.3	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				

Evidence directly generalisable to infants undergoing craniofacial surgery. (Level A)
Applicability
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)
Comments
The difference in blood requirement between the two groups amounted to 2.6% of the EBV in favour of the ANH group, but was not significant at the 0.05 level. The authors concluded that ANH does not reduce the incidence of homologous transfusion or the amount of homologous blood transfused in this patient group. The findings of this study may be explained by the low estimated blood volume and the low preoperative Hct value of included patients, as well as by a minimal amount of blood lost during surgery. In adults, guidelines for autologous transfusion recommend ANH only when the potential blood loss is likely to be greater than 20% of blood volume.

ANH, acute normovolaemic haemodilution; CI, confidence interval; CPB, cardiopulmonary bypass; EBL, estimated blood loss; EBV, estimated blood volume; FFP, fresh frozen plasma; Hct, haematocrit; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; PP, per-protocol; RBC, red blood cell; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Katheria AC, Leone TA, Woelkers D, Garey DM et al. (2014) The effects of umbilical cord milking on hemodynamic and neonatal outcomes in premature neonates. The Journal of Pediatrics, 164: 1045–50.				
Affiliation/Source of funds				
The authors declare no conflicts of interest.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single tertiary hospital, USA	
Intervention	Comparator			
Umbilical cord milking (UCM)	Immediate cord clamping (ICC)			
Population characteristics				
Preterm infants aged 23 to <32 weeks gestation. Exclusion criteria: monochorionic multiples, incarcerated mothers, placenta previa, concern for abruptions, refusal to perform the intervention by obstetrician.				
Length of follow-up	Outcomes measured			
NR	Primary: superior vena cava (SVC) flow Other: heart rate, blood pressure, other neonatal outcomes			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: An RCT of 60 preterm infants at a single tertiary hospital in the USA, to examine the effect of umbilical cord milking compared to immediate cord clamping on superior vena cava flow and other neonatal outcomes. Infants were randomised using opaque sealed envelopes immediately before delivery, with stratification by gestational age (23 to <29 or 29 to <32 weeks). Obstetricians and the neonatology team were aware of allocated groups before delivery. Assessment of the primary outcome was blinded. After randomisation, three infants from the UCM group and two infants from the ICC group were excluded due to predefined criteria. Baseline characteristics were similar between the two groups. Loss to follow-up was not reported, although it appeared no more infants were excluded from final analyses. A subgroup analysis was conducted based on gestational age. Method of UCM: infant was held below the mother's introitus at vaginal delivery or below the level of incision at caesarean delivery. Two seconds of milking was performed to about 20cm of the umbilical cord, with two repetitions.				
RESULTS				
Population analysed	UCM (placental transfusion)		ICC	
Randomised	33		32	
Efficacy analysis (ITT)	30		30	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	UCM n/N (%) Mean ± SD (n)	ICC n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
Transfusion incidence	11/30 (37)	22/30 (73)	NR	Favours placental transfusion *P* = 0.004

Age when transfusion given, days	12 ± 11 (30)	12 ± 13 (30)	NR	No significant difference *P* = NR
IVH	8/30 (27)	11/30 (37)	NR	No significant difference *P* = 0.29
Severe IVH	2/30 (7)	4/30 (13)	NR	No significant difference *P* = NR
Death	2/30 (7)	1/30 (3)	NR	No significant difference *P* = NR
Subgroup analysis: infants <29 weeks gestation				
Transfusion	9/14 (64)	14/14 (100)	NR	Favours placental transfusion *P* = 0.04
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to preterm infants with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that there is greater systemic blood flow in preterm neonates treated with UCM when compared to ICC. More evidence is needed to determine whether UCM reduces IVH and other long-term morbidities. They also note that although a significant difference in IVH was not observed, the study was not powered sufficiently to assess this outcome.				

CI, confidence interval; ICC, immediate cord clamping; ITT, intention-to-treat; IVH, intraventricular haemorrhage; NR, not reported; RCT, randomised controlled trial; PP, per-protocol; SD, standard deviation; SVC, superior vena cava; UCM, umbilical cord milking

STUDY DETAILS: RCT				
Citation				
Lisander B, Jonsson R, and Nordwall A. (1996) Combination of Blood-Saving Methods Decreases Homologous Blood Requirements in Scoliosis Surgery. Anaesth Intens Care, 24: 555-8.				
Affiliation/Source of funds				
The study was supported by grants from the County Council of Ostergotland and Goteborg Medical Society.				
Study design	Level of evidence	Location/setting		
RCT	Level II	Single hospital, Sweden		
Intervention	Comparator			
1. Preoperative haemodilution (ANH) 2. Cell salvaged blood recovered from the wound and returned to the patient 3. ANH + cell salvage 4. ANH + cell salvage + arterial hypotension	Intraoperative haemodilution (IHD), whereby volume losses were replaced by a plasma substitute (control).			
Population characteristics				
Paediatric patients (mean age 14.5 years) with idiopathic scoliosis scheduled for surgery with the Harrington rod procedure with fusion (all patients were ASA group I). Exclusion criteria: known coagulopathy.				
Length of follow-up	Outcomes measured			
NR	Blood loss and transfusion requirements.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: a five-armed pilot RCT of 57 paediatric patients scheduled for scoliosis surgery in Sweden, to examine the effect of various blood-saving methods on blood loss and transfusion requirements. Only data for ANH compared to control, and cell salvaged blood compared to control will be presented here. The method of randomisation and blinding were not reported. Patient baseline characteristics between groups were similar except for the number of segments fused during surgery which were significantly lower in the control group compared to the others ($P < 0.05$). All randomised patients were included in analyses. ANH: carried out immediately after induction of anaesthesia. Blood withdrawn with simultaneous replacement first with 500 mL 6% dextran 70 and later 3% dextran. Dilution carried out to a Hb 80 g/L. Blood stored at room temp and transfused during or immediately after surgery, in the reverse order to which collected. Recovery of wound blood: during surgery, red cells from the wound were recovered with a Cellsaver4, washed and returned to the patient. The aspirated blood was mixed with citrate in the suction tube and later washed with at least one litre of normal saline.				
RESULTS				
Population analysed	ANH	Cell salvage	Comparator	
Randomised	10	11	13	
Efficacy analysis (ITT)	10	11	13	
Efficacy analysis (PP)	NR	NR	NR	
Safety analysis	NR	NR	NR	
Outcome	Intervention Mean ± SD (n)	Control Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
ANH vs control				

Donor blood units transfused	4.9 ± 2.6	5.5 ± 2.2 (13)	NR	No significant difference *P* = NR
Cell salvage vs control				
Donor blood units transfused	4.1 ± 1.5 (11)	5.5 ± 2.2 (13)	NR	No significant difference *P* = NR
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric scoliosis surgery patients with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)				
Comments				
No signs of cardiovascular, respiratory, renal, hepatic, neurologic or metabolic complications were observed. The authors concluded that the combination of blood –saving methods (ANH + cell saver or ANH + cell saver + hypotension) resulted in a significant decrease in the use of banked blood in scoliosis surgery.				

CI, confidence interval; IHD, intraoperative haemodilution; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; PHD, preoperative haemodilution; PICU, paediatric intensive care unit; PP, per-protocol; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Mozol K, Haponiuk I, Byszewski A, Maruszewski B (2008) Cost-effectiveness of mini-circuit cardiopulmonary bypass in newborns and infants undergoing open heart surgery. Kardiologia Polska, 66: 9.				
Affiliation/Source of funds				
Not reported.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Poland	
Intervention	Comparator			
Miniaturised CPB systems	Conventional CPB systems			
Population characteristics				
Paediatric patients aged <1 year scheduled for cardiac surgery with CPB and extracorporeal circulation support.				
Length of follow-up	Outcomes measured			
NR	Postoperative complications including heart, respiratory or renal failure, multi-organ distress syndrome and neurological disorders; blood products and crystalloid volumes transfused; treatment costs.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: an RCT of 60 infants scheduled for cardiac surgery with CPB in Poland, to examine the effect of a miniaturised CPB compared to a conventional CPB system on postoperative complications and transfusion requirements. The method of randomisation and whether blinding was used were not reported. The anaesthetic technique and postoperative management were carried out according to the same protocols. Baseline characteristics were similar between the groups. Loss to follow-up was not reported and it was unclear whether all infants were included in final analyses.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	30		30	
Efficacy analysis (ITT)	NR		NR	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Miniaturised n/N (%) Mean ± SD (n)	Conventional n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
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
Intraoperative crystalloids transfused (mL)	313 ± 243.9	266 ± 262.9	NR	No significant difference *P* = NR
Postoperative crystalloids transfused (mL)	601 ±199.1	662.9 ± 159	NR	No significant difference *P* = NR
Mortality	0	0	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to infants scheduled for cardiac surgery with CPB and extracorporeal circulation support. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that miniaturisation of the extracorporeal circulation significantly improves post-operative outcomes in infants undergoing heart surgery. The mini-circuit also significantly reduced cost of treatment in this patient group.				

CI, confidence interval; CPB, cardiopulmonary bypass; ITT, intention-to-treat; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Precious DS, Splinter W, Bosco D. (1996) Induced hypotensive anaesthesia for adolescent orthognathic surgery patients. J Oral Maxillofac Surg, 54: 680–3.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single hospital, Canada
Intervention	Comparator	
Induced hypotensive anaesthesia (blood pressure maintained within 75% of baseline systolic values). Intermittent boluses of propranolol were given intravenously, up to 0.1mg/kg as required.	No hypotensive anaesthesia (blood pressure maintained within 10mm Hg of baseline systolic values)	
Population characteristics		
Adolescent patients aged 13 to 15 years requiring sagittal ramus split osteotomy, Le Fort I osteotomy, or genioplasty. Exclusion criteria: renal, hepatic, cardiac, vascular, hematologic or endocrine disease.		
Length of follow-up	Outcomes measured	
NR	Surgical field rating, estimated blood loss (EBL), length of surgery and anaesthesia.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: An RCT of 50 adolescent patients undergoing osteotomy or genioplasty surgery at a single hospital in Canada, to examine the effect of induced hypotension on intraoperative blood loss. The method of randomisation was not described. Patients were stratified and blocked according to their proposed surgery. The surgeon was unaware of treatment assignment, and was the one to estimate intraoperative blood loss (based on surgical experience). The anaesthetist also estimated blood loss via accurate tabulation of the volume of fluid within the suction containers minus the amount of irrigation fluids used throughout the procedure. The weight of blood in the sponges was measured and figured into the total estimate. Baseline characteristics were similar between the groups. Fromm'e Ordinal Scale of assessment of surgical field: 5=Massive uncontrollable bleeding 4=Bleeding, heavy but controllable, that significantly interfered with dissection 3=Moderate bleeding that moderately compromised surgical dissection 2=Moderate bleeding, a nuisance but without interference with accurate dissection 1=Bleeding, so mild that it was not even a surgical nuisance 0=No bleeding, virtually bloodless field		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	25	25
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Induced hypotension Mean ± SD (n) n/N (%)	Normotension Mean ± SD (n) n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value
EBL by surgeon (mL/kg)	5.0 ± 1.9	6.8 ± 3.0	NR	Favours induced hypotension *P* < 0.017
EBL by anaesthetist (mL/kg)	4.9 ± 2.4	7.9 ± 4.4	NR	Favours induced hypotension *P* < 0.003
EBL by Hct (mL/kg)	6.3 ± 3.4	8.9 ± 4.3	NR	Favours induced hypotension *P* < 0.02
Average EBL (mL/kg)	5.4 ± 2.0	7.9 ± 3.2	NR	Favours induced hypotension *P* < 0.002
Surgical field rating	1.2 ± 0.4	1.7 ± 0.6	NR	Favours induced hypotension *P* < 0.001
Blood transfusion	0/25 (0.0)	0/25 (0.0)	NR	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to adolescent surgical patients with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with few caveats. (Level B)				
Comments				
The authors concluded that induced hypotensive anaesthesia results in both reduced blood loss and improvement in surgical field.				

CI, confidence interval; EBL, estimated blood loss; Hct, haematocrit; ITT, intention-to-treat; NA, not applicable; NR, not reported; RCT, randomised controlled trial; PP, per-protocol; SD, standard deviation;

STUDY DETAILS: RCT		
Citation		
Sarupria A, Makhija N, Lakshmy R, Kiran U. (2013) Comparison of difference doses of e-aminoproic acid in children for tetralogy of Fallot sugery: clinical efficacy and safety. Journal of cardiothoracic and vascular anesthesia, 27(1): 23–9.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single centre, India

Intervention	Comparator
1. EACA (100 mg/kg), 3x doses (2x doses over 10-15 mins and 1x bolus) 2. EACA (75 mg/kg), 3x doses (1x dose over 10-15 mins, 1x maintenance infusion during surgery and 1x bolus)	3. No EACA

Population characteristics	
Children weighing 5-20kg undergoing corrective surgery with CPB for tetralogy of Fallot. Exclusion criteria: renal dysfunction, previous neurologic event, congenital bleeding disorder.	
Length of follow-up	Outcomes measured
NR	Primary: blood loss and transfusion requirements Secondary: safety measures: all-cause mortality, thrombosis, neurologic dysfunction, perioperative ST/T changes, renal dysfunction Other: coagulation variables

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Fair

Description: An RCT of 115 children weighing 5-20kg undergoing cardiac surgery with CPB in India, to examine the effect of two doses of EACA compared to no EACA on blood loss and transfusion requirements.

Children were randomised via a computer-generated randomisation list. Baseline characteristics were similar between groups except for platelet count, which was significantly higher in groups 2 and 3 (p=0.002). Anaesthesiologists were not blind to treatment allocation, but physicians involved in re-exploration were unaware of treatment allocation. Anaesthetic and surgical management were standardised in all groups, with operations all performed by the same team. A sample size of 40 children per group was calculated to have 80% power to show a difference with a p-value of 0.05. There were 120 children enrolled, but five excluded due to surgical cause of bleeding (n=2), use of multiple haemostatic agents (n=2) and the inability to be weaned from CPB (n=1).

RESULTS

Population analysed	Group 1	Group 2	Group 3 (control)
Randomised	40	40	40
Efficacy analysis (ITT)	38	40	37
Efficacy analysis (PP)	NR	NR	NR
Safety analysis	38	40	37

Outcome	Group 1 n/N (%) Mean ± SD (n)	Group 2 n/N (%) Mean ± SD (n)	Group 3 n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value

Transfusion incidence (donor exposure)					
RBC	34/38 (89.5)	30/40 (75.0)	36/37 (97.3)	NR	2 vs 3: favours 2 *P* = 0.01
FFP	34/38 (89.5)	29/40 (72.5)	37/37 (100)	NR	2 vs 3: favours 2 *P* = 0.01
Platelet concentrate	37/38 (97.4)	40/40 (100)	37/37 (100)	NR	No significant difference *P* = 1.00
Intraoperative transfusion requirements (mL/kg)					
RBC	22.47 ± 12.32 (38)	16.56 ± 12.49 (40)	32.38 ± 13.01 (37)	NR	1 vs 3: favours EACA *P* < 0.01 2 vs 3: favours EACA *P* < 0.01
FFP	10.33 ± 7.96 (38)	10.19 ± 7.63 (40)	17.00 ± 5.08 (37)	NR	1 vs 3: favours EACA *P* < 0.01 2 vs 3: favours EACA *P* < 0.01
Platelet concentrate	2.08 ± 1.054 (38)	2.31 ± 0.86 (40)	2.30 ± 0.82 (37)	NR	No significant difference *P* = 0.47
Total transfusion requirements (mL/kg)					
RBC	54.35 ± 27.42 (38)	24.47 ± 19.62 (40)	69.86 ± 23.91 (37)	NR	1 vs 2: favours 2 *P* < 0.01 2 vs 3: favours 2 *P* < 0.01 1 vs 3: favours 1 *P* < 0.05
FFP	27.60 ± 16.36 (38)	12.80 ± 9.82 (40)	42.98 ± 13.91 (37)	NR	1 vs 3: favours 1 *P* < 0.01 2 vs 3: favours 2 *P* < 0.01
Platelet concentrate	NR	NR	NR	NR	No significant difference *P* > 0.05
Cumulative postoperative blood loss (mL)					
6 hrs	108.45 ± 61.45 (38)	32.75 ± 26.02 (40)	137.84 ± 52.50 (37)	NR	1 vs 2: favours 2 *P* < 0.01 1 vs 3: favours 1 *P* < 0.05
12 hrs	172.37 ± 71.56 (38)	50.50 ± 42.30 (40)	192.16 ± 66.67 (37)	NR	1 vs 2: favours 2 *P* < 0.01 1 vs 3: no significant difference *P* > 0.05

24 hrs	223.95 ± 83.36 (38)	69.00 ± 50.01 (40)	235.41 ± 79.88 (37)	NR	1 vs 2: favours 2 *P* < 0.01 1 vs 3: no significant difference *P* > 0.05
Adverse events					
All-cause mortality	2/38 (5.3)	3/40 (7.5)	3/37 (8.1)	NR	No significant difference *P* = 0.88
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to paediatric patients weighing 5–20 kg undergoing cardiac surgery with CPB. (Level A)					
Applicability					
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)					
Comments					
The authors concluded that EACA was effective in reducing the postoperative blood loss and transfusion requirements in children undergoing corrective cardiac surgery on CPB for tetralogy of Fallot. The 75 mg/kg dose regimen (after induction, maintenance infusion during surgery, upon initiation of CPB) was optimal.					

CI, confidence interval; CPB, cardiopulmonary bypass; EACA, Epsilon-aminocaproic acid; FFP, fresh frozen plasma; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Singh R, Vellaichamy M, Gowda N, Kumar V et al. (2001) Aprotinin for open cardiac surgery in cyanotic heart disease. Asian Cardiovascular and Thoracic Annals, 9(2): 101–4.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	India
Intervention	Comparator	
1. Aprotinin 20,000 KIU/kg, 2x doses (during the pre-CPB period as a continuous infusion over 30mins, and in the pump prime). 2. Aprotinin 20,000 KIU/kg during the pre-CPB period only.	No aprotinin.	
Population characteristics		
Paediatric cyanotic patients with tetralogy of Fallot undergoing total correction with CPB (mean age 3.5 years).		
Length of follow-up	Outcomes measured	
NR	Perioperative laboratory tests, total blood loss (intraoperative and postoperative), chest tube drainage, blood and blood components administered to treat postoperative bleeding, renal function, mortality	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: an RCT of 75 paediatric cyanotic patients undergoing cardiac surgery with CPB in India, to examine the effect of two doses of aprotinin compared to one dose of aprotinin compared to no aprotinin, on total blood loss and transfusion requirements. Patients were randomised using computer-generated random numbers. Standard anaesthetic and surgical techniques were followed in all patients. Patients received aprotinin in a blinded fashion where the principle investigator was unaware of treatment allocation. Baseline characteristics were similar between the groups. Loss to follow-up not reported, although it appeared that all randomised patients were included in analyses. The significance reported below is based on a comparison between Group 1 or Group 2 to control. Postoperative transfusion criteria: Hct <28% or Hb <90 g/L.		

RESULTS					
Population analysed	Group 1	Group 2	Control		
Randomised	25	25	25		
Efficacy analysis (ITT)	25	25	25		
Efficacy analysis (PP)	NR	NR	NR		
Safety analysis	NR	NR	NR		
Outcome	Group 1 n/N (%) Mean ± SD	Group 2 n/N (%) Mean ± SD	Control n/N (%) Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value
Total blood loss (mL)	221.4 ± 60.3	254.2 ± 22.6	426.0 ± 92.0	NR	Favours aprotinin $P < 0.05$

Total 24hr chest tube drainage (mL)	164.3 ± 25.7	145.2 ± 20.5	321.0 ± 23.0	NR	Favours aprotinin *P* < 0.05
Blood transfusion (units)	1.1 ± 1.1	0.91 ± 0.75	2.2 ± 1.0	NR	Favours aprotinin *P* < 0.05
FFP transfusion (units)	2.0 ± 2.5	1.8 ± 1.3	4.8 ± 1.0	NR	Favours aprotinin *P* < 0.05
Platelet transfusion (units)	1.4 ± 3.8	1.6 ± 1.8	2.6 ± 2.0	NR	Favours aprotinin *P* < 0.05
Mortality	0	0	0	NR	No significant difference *P* = NA
EXTERNAL VALIDITY					
Generalisability					
Evidence directly generalisable to cyanotic paediatric patients with tetralogy of Fallot undergoing cardiac surgery with CPB. (Level A)					
Applicability					
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)					
Comments					
The authors concluded that a single dose of aprotinin before CPB is recommended in cyanotic patients undergoing intracardiac repair.					

CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hb, haemoglobin; Hct, haematocrit; ITT, intention-to-treat; NA, not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT				
Citation				
Thompson GH, Florentino-Pineda I, Poe-Kochert C. (2005) The role of Amicar in decreasing perioperative blood loss in idiopathic scoliosis. Spine, 30(17S):S94-S99.				
Affiliation/Source of funds				
The authors reported that no funds were received to support this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.				
Study design	Level of evidence		Location/setting	
RCT	Level II		USA	
Intervention	Comparator			
Amicar (EACA), administered intraoperatively before skin incision at 100mg/kg over 15 minutes (not to exceed 5 g). Amicar was then maintained at 10mg/kg/hr until wound closure.	No Amicar			
Population characteristics				
36 children aged 11 to 18 years with idiopathic scoliosis scheduled for posterior spinal fusion surgery with segmental spinal instrumentation. Exclusion criteria: patients with same-day or staged anterior procedures.				
Length of follow-up	Outcomes measured			
NR	Perioperative blood loss (estimated intraoperative blood loss + measured postoperative Hemovac suction drainage), intraoperative blood loss, postoperative blood loss (Hemovac suction drainage), transfusion requirements (autologous and allogeneic), complications (venous thrombosis or thromboemboli)			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: an RCT of 36 children with idiopathic scoliosis scheduled for surgery, to assess the effect of Amicar on perioperative blood loss and transfusion requirements. The pharmacy allocated patients to Amicar or control using random numbers. Baseline characteristics were reported to be similar between groups; however, individual patient characteristics were not presented. The anaesthesiologist and surgeon were blind to treatment group until study completion. Not reported whether outcome assessors were blind to treatment group. Transfusion was given when Hb<7g/dL. Methods of statistical analysis not reported.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	19		17	
Efficacy analysis (ITT)	19		17	
Efficacy analysis (PP)	19		17	
Safety analysis	19		17	
Outcome	EACA Mean ± SD (n) n/N (%)	Control Mean ± SD (n) n/N (%)	Risk estimate (95% CI)	Statistical significance *P*-value

Intraoperative blood loss (mL)	893 ± 166	952 ± 303	NR	No significant difference *P* = NR
Postoperative Hemovac drainage (mL)	498 ± 179	764 ± 284	NR	Favoured Amicar *P* < 0.05
Total perioperative blood loss (mL)	1391 ± 212	1716 ± 513	NR	Favoured Amicar *P* = 0.03
Autologous units transfused	1.1 ± 1.0	2.1 ± 1.3	NR	Favoured Amicar *P* = 0.002
Allogeneic transfusion incidence	0/19 (0.0)	0/17 (0.0)	NA	No significant difference *P* = NA
Venous thrombosis or thromboemboli	0/19 (0.0)	0/17 (0.0)	NA	No significant difference *P* = NA
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric idiopathic scoliosis surgery patients with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that Amicar is a safe, effective medication in idiopathic scoliosis. It decreased perioperative blood loss, but predominantly in the postoperative Hemovac drainage, and perhaps was mediated by the increased fibrinogen secretion. This decreased perioperative transfusion and the need for autologous donation, which lowered costs.				

CI, confidence interval; CPB, cardiopulmonary bypass; Hb, haemoglobin; ITT, intention-to-treat; NA, not applicable; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation

STUDY DETAILS: RCT		
Citation		
Vacharaksa K, Prakanrattana U, Suksompong S and Chumpathong S. (2002) Tranexamic acid as a means of reducing the need for blood and blood component therapy in children undergoing open heart surgery for congenital cyanotic heart disease. J Med Assoc Thai, 85(S3): S904-S909.		
Affiliation/Source of funds		
Not reported.		
Study design	Level of evidence	Location/setting
RCT	Level II	Single hospital, Thailand
Intervention	Comparator	
Intravenous TXA (15mg/kg) after induction of anaesthesia and at the end of CPB	Intravenous TXA (15mg/kg) after induction of anaesthesia plus normal saline (placebo) at the end of CPB	
Population characteristics		
Paediatric patients aged ≤14 years (mean age 6 years) with cyanotic CHD and a right-to-left shunt who were scheduled for open heart surgery. Exclusion criteria: history of allergy to TXA, history of liver or renal disease, history of coagulation disorder, surgery involving the cavopulmonary connection.		
Length of follow-up	Outcomes measured	
24 hours post-surgery.	Total blood loss volume collected in the chest tube drains at 6, 12 and 24hrs, starting from the time of chest closure; transfusion requirements, Hct, prothrombin time, partial thromboplastin time, platelet count, thrombotic complications, mortality.	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Fair Description: a double-blind RCT of 67 paediatric patients with cyanotic CHD undergoing cardiac surgery in Thailand, to examine the effect of two-dose TXA compared to single-dose TXA (and placebo) on total blood loss and transfusion requirements. The method of randomisation was not reported. There were 67 children enrolled, but five were excluded from the placebo group due to reoperation (n=3) and pleural effusion as a result of CHF (n=2) within 24hrs post-surgery. All TXA and placebo solutions were prepared in a blind manner by an individual not involved in the study. Although the study was described as being double-blinded, it was not reported who administered the intervention solution, or whether the surgeons/anaesthesiologists and/or outcome assessors were blind to treatment assignment. Baseline characteristics were similar between the groups. Blood and blood components were transfused intraoperatively according to the routing protocol for an abnormal coagulogram (PT>14s: add protamine 0.5mg/kg; PTT>34s: transfuse FFP 10 mL/kg; platelet count <10x10^3/mm^3: transfuse platelet concentrate 0.1unit/kg). When postoperative blood loss was >3mL/kg/hr and the Hct was <35%, a RBC transfusion was given to raise the Hct to 40%.		
RESULTS		
Population analysed	Intervention	Comparator
Randomised	33	34
Efficacy analysis (ITT)	33	29
Efficacy analysis (PP)	NR	NR
Safety analysis	33	29

Outcome	TXA n/N (%) Mean ± SD (n)	Placebo n/N (%) Mean ± SD (n)	Risk estimate (95% CI)	Statistical significance *P*-value
Total postoperative blood loss (mL)	195.63 ± 188.03 (33)	186.30 ± 163.78 (29)	NR	No significant difference *P* = 0.5
Postoperative blood loss (mL/kg/24hr)	12.51 ± 13.20 (33)	10.68 ± 6.38 (29)	NR	No significant difference *P* = 0.5
Mortality	0/33 (0.0)	0/29 (0.0)	NA	No significant difference *P* = NA
Thrombotic complications	0/33 (0.0)	0/29 (0.0)	NA	No significant difference *P* = NA
Postoperative transfusion requirements				
Total RBC (mL)	395.82 ± 160.50 (33)	434.04 ± 200.82 (29)	NR	No significant difference *P* = 0.4
RBC (mL/kg/24hr)	23.72 ± 10.61 (33)	27.05 ± 11.28 (29)	NR	No significant difference *P* = 0.2
Total FFP (mL)	294.22 ± 139.62 (33)	276.18 ± 152.80 (29)	NR	No significant difference *P* = 0.6
FFP (mL/kg/24hr)	19.39 ± 9.98 (33)	16.21 ± 6.98 (29)	NR	No significant difference *P* = 0.4
Platelets (units/kg/24hr)	0.12 ± 0.05 (33)	0.11 ± 0.05 (29)	NR	No significant difference *P* = 0.4
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients with cyanotic CHD undergoing cardiac surgery. (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that there was no significant difference in postoperative blood loss and transfusion requirements between children with cyanotic CHD undergoing open heart surgery who received a single dose of TXA compared with those who received two doses.				

CI, confidence interval; CHD, congenital heart disease; CHF, chronic heart failure; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hb, haemoglobin; Hct, haematocrit; ITT, intention-to-treat; NA, not applicable; NR, not reported; PP, per-protocol; RBC, red blood cell; PT, prothrombin time; PTT, partial thromboplastin time; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid

STUDY DETAILS: RCT				
Citation				
Verma K, Errico T, Diefenbach C, Hoelscher C, Peters A, Dryer J, et al. The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: A prospective randomized trial. J Bone Jt Surg Am Vol 2014;96(10):e80.				
Affiliation/Source of funds				
None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. One or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. Funding for this study was provided exclusively by departmental funds.				
Study design		Level of evidence		Location/setting
RCT		Level II		Single centre, USA
Intervention			Comparator	
TXA (loading dose 10mg/kg infused over 15 minutes, maintenance dose 1mg/kg/hr)	EACA (loading dose 100mg/kg infused over 15 minutes, maintenance dose 10mg/kg/hr)		Placebo (saline)	
Population characteristics				
125 patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis.				
Length of follow-up		Outcomes measured		
NR (followed through posterior spinal arthrodesis)		Primary outcomes: intraoperative blood loss and postoperative drainage Secondary outcomes: transfusion requirements, haematocrit changes both intraoperatively and postoperatively		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Patients were randomised using a computer-generated random assignment. Allocation assignments were blinded from all persons except the pharmacist and remained unchanged for the duration of the study. Unblinding from the study was allowed at any time for medical necessity. Allocation assignments favoured the saline solution group over the treatment groups when the allocation assignments were revealed. Baseline characteristics were similar between groups except for estimated blood volume, which was larger in the saline group. There was no loss to follow-up and all patients were included in the final analysis. Within each group patients were stratified according to mean arterial pressure (MAP) and a subgroup analysis was conducted among patients with low MAP (< 75mmHg).				
RESULTS				
Population analysed	Intervention TXA		Intervention EACA	Comparator
Randomised	36		42	47
Efficacy analysis (ITT)	36		42	47
Efficacy analysis (PP)	NR		NR	NR
Safety analysis	36		42	47
Outcome	Intervention Mean ± SD	Control Mean ± SD	Risk estimate (95% CI)	Statistical significance *P*-value

TXA vs placebo				
Overall total blood losses (mL)[a]	1531 ± 911	2116 ± 1201	NR	Favours TXA *P* = 0.015
Overall drain total (mL)	789 ± 449	1034 ± 559	NR	Favours TXA *P* = 0.027
Intraoperative estimated blood loss	785 ± NR	1080 ± NR	NR	No significant difference *P* = 0.058
Intraoperative estimated blood loss when MA*P* <75mmHg	715 ± NR	1124 ± NR	NR	Favours TXA *P* = 0.042
EACA vs placebo				
Overall total blood losses (mL)[a]	1775 ± 853	2116 ± 1201	NR	No significant difference *P* = 0.161
Overall drain total (mL)	1016 ± 422	1034 ± 559	NR	No significant difference *P* = 0.867
Intraoperative estimated blood loss	769 ± NR	1080 ± NR	NR	Favours EACA *P* = 0.037
Intraoperative estimated blood loss when MA*P* <75mmHg	761 ± NR	1124 ± NR	NR	No significant difference *P* = 0.061
TXA or EACA vs placebo				
Overall total blood losses (mL)[a]	1663.0 ± 882	2116.0 ± 1202	NR	Favours TXA or EACA *P* = 0.019
Overall drain total (mL)	912.0 ± 446	1034.0 ± 559	NR	No significant difference *P* = 0.187
Intraoperative estimated blood loss	776 ± NR	1080 ± NR	NR	Favours TXA or EACA *P* = 0.019
EXTERNAL VALIDITY				
Generalisability				
Evidence is directly generalisable to patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis (Level A)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
A transfusion threshold was utilised in the study. During surgery, the team was advised to transfuse only for haematocrit ≤25 in patients with ongoing bleeding. Postoperatively, a symptomatic patient with a haematocrit ≤22 received a transfusion. TXA and EACA reduced operative blood loss but not transfusion rate. TXA is more effective at reducing postoperative drainage and total blood losses compared with EACA.				

CI, confidence interval; CPB, cardiopulmonary bypass; EACA, Epsilon-aminocaproic acid; ITT, intention-to-treat; MAP, mean arterial pressure; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; TXA, tranexamic acid
a. Total losses consisted of the estimated blood loss and the drain total

STUDY DETAILS: RCT				
Citation				
Ye L, Lin R, Fan Y, Yang L et al. (2013) Effects of circuit residual volume salvage reinfusion on the postoperative clinical outcome for pediatric patients undergoing cardiac surgery. Pediatr Cardiol, 34: 1088–93.				
Affiliation/Source of funds				
Funding was received from the National Science and Technology Foundation of China, the Zhejiang Province innovation team for early screening and intervention of birth defects, the Health Bureau of Zhejiang Provincial Key Program, and the Ministry of Education.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Single hospital, China	
Intervention		Comparator		
Reinfusion of washed residual CPB circuit blood within 6hrs.		No cell salvage. Allogeneic RBCs were directly transfused post-surgery and the residual CPB circuit blood was discarded.		
Population characteristics				
Chinese paediatric patients aged 6 days to 13.16 years and weighing 2.4 to 36kg who underwent open heart surgery with CPB.				
Length of follow-up		Outcomes measured		
NR		Allogeneic RBC transfusion requirements, Hct on the first day in the ICU, postoperative chest tube drainage, intrahospital mortality, respiratory morbidity, renal dysfunction.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: An RCT of 309 paediatric patients undergoing open heart surgery with CPB at a single hospital in China, to examine the effect of cell salvage compared to no cell salvage on RBC transfusion requirements and other clinical outcomes. The method of randomisation and blinding were not reported. There were significantly more patients in the intervention group. There was only one blood cell saver machine in the hospital during the early stages of research. Another cell saver machine was purchased later which lead to an increased number of patients receiving this treatment. Baseline characteristics between groups were similar. Platelets, RBCs and FFP were given according to each anaesthesiologist's discretion as there were no universal criteria in place at the study hospital. No patients dropped out during the study and it appeared all randomised patients were included in analyses.				
RESULTS				
Population analysed	Cell salvage		No cell salvage	
Randomised	217		92	
Efficacy analysis (ITT)	217		92	
Efficacy analysis (PP)	NR		NR	
Safety analysis	NR		NR	
Outcome	Cell salvage n/N (%) Median (IQR)	No cell salvage n/N (%) Median (IQR)	Risk estimate (95% CI)	Statistical significance *P*-value
Perioperative allogeneic RBC transfusion, units	1.5 (1.5 – 2.5)	2.5 (2.5 – 3.0)	NR	Favours cell salvage *P* = 0.000

Mortality	1/217 (0.5)	2/92 (2.2)	NR	No significant difference *P* = 0.212
EXTERNAL VALIDITY				
Generalisability				
Evidence directly generalisable to paediatric patients undergoing cardiac surgery with CPB with some caveats. (Level B)				
Applicability				
Evidence probably applicable to the Australian healthcare context with some caveats. (Level C)				
Comments				
The authors concluded that reinfusion of washed CPB circuit residual blood significantly raised the postoperative Hct level, reduced the incidence of allogeneic blood transfusion, decreased the incidence of early postoperative renal dysfunction, and did not increase the chest tube drainage post cardiac surgery.				

CI, confidence interval; CPB, cardiopulmonary bypass; Hct, haematocrit; ICU, intensive care unit; ITT, intention-to-treat; IQR, interquartile range; FFP, fresh frozen plasma; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; PP, per-protocol; SD, standard deviation