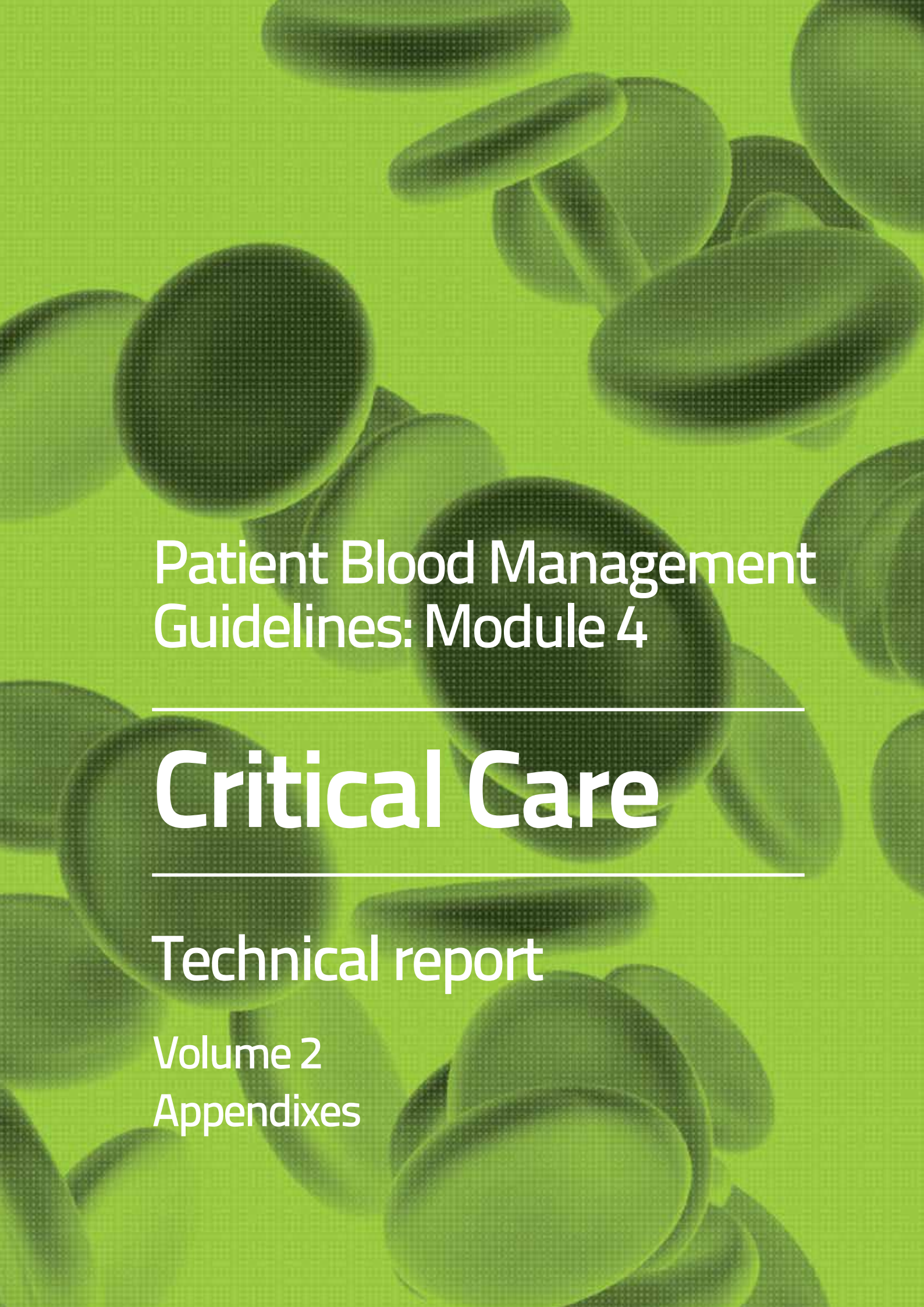

Patient Blood Management Guidelines: Module 4

Critical Care

Technical report

Volume 2
Appendixes

This volume presents appendixes to *Patient blood management guidelines: Module 4 – Critical care: Technical report – Volume 1 – Review of the evidence*.

Contents

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Appendix A Literature searches

A1 Literature search – Question 1

Table A1.1 EMBASE.com search for Level I evidence conducted 29 July 2010

#	Query	Results
#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*))	128412
#2	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	120228
#3	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	668
#4	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	788
#5	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	100123
#6	#2 OR #3 OR #4 OR #5	211369
#7	#2 OR #3 OR #4 OR #5 AND [1985-2011]/py	167384
#8	#1 AND #7	2497

Table A1.2 EMBASE.com search for Level II evidence conducted 16 May 2011

#	Query	Results
#1	'erythrocyte transfusion'/exp OR (blood:ab,ti OR erythrocyte:ab,ti OR 'red cell':ab,ti OR 'red blood cell':ab,ti OR rbc:ab,ti AND (transfus*:ab,ti OR infus*:ab,ti OR hypertransfus*:ab,ti OR retransfus*:ab,ti)) OR hemotransfus*:ab,ti OR haemotransfus*:ab,ti OR (transfus*:ab,ti OR retransfus*:ab,ti AND (trigger*:ab,ti OR level*:ab,ti OR threshold*:ab,ti OR rule*:ab,ti OR restrict*:ab,ti)) OR (transfusion:ab,ti AND (management:ab,ti OR practice*:ab,ti OR polic*:ab,ti OR strateg*:ab,ti OR guideline*:ab,ti OR indication*:ab,ti OR protocol*:ab,ti OR criteri*:ab,ti)) OR 'blood management':ab,ti OR 'management blood':ab,ti OR 'blood sparing':ab,ti OR 'cell salvage':ab,ti OR 'blood support':ab,ti OR 'blood requirement':ab,ti OR 'red cell management':ab,ti OR 'red cell sparing':ab,ti OR 'red cell support':ab,ti OR 'red cell requirement':ab,ti OR (blood NEXT/1 need):ab,ti OR leukodeplet*:ab,ti OR leukoreduc*:ab,ti OR leucodepl*:ab,ti OR leucodeplet*:ab,ti OR leucoreduc*:ab,ti OR leukofiltrat*:ab,ti OR leucofiltra*:ab,ti OR ((leukocyte* OR leucocyte*) NEXT/2 (remov* OR deplet* OR reduc* OR poor OR filtrat*)):ab,ti OR ((iron NEXT/5 (intravenous* OR iv)):ab,ti AND transfus*:ab,ti) OR ('blood transfusion'/exp OR 'blood component therapy'/exp NOT ('exchange blood transfusion'/exp OR 'plasma transfusion'/exp OR 'granulocyte transfusion'/exp OR	337496

	'amnioinfusion'/exp OR 'leukocyte transfusion'/exp OR 'intrauterine blood transfusion'/exp OR 'thrombocyte transfusion'/exp OR 'lymphocyte transfusion'/exp)) OR ('blood transfusion'/exp OR 'blood component therapy'/exp AND 'erythrocyte'/exp AND ('red cell':ab,ti OR 'red blood cell':ab,ti OR erythrocyte*:ab,ti)) OR 'red cell':ab,ti OR 'red blood cell':ab,ti OR erythrocyte*:ab,ti OR rbc*:ab,ti	
#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'	2312114
#3	#1 AND #2	49619
#4	#1 AND #2 AND [1-9-2009]/sd NOT [29-7-2010]/sd AND [2007-2011]/py	3506

Table A1.3 EMBASE.com search for Level III evidence conducted 6 June 2011

#	Query	Results
#1	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	131380
#2	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	862
#3	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	947
#4	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	111558
#5	#1 OR #2 OR #3 OR #4	232567
#6	mortality:ab,ti OR death*:ab,ti OR died:ab,ti OR ((cardiac OR heart OR coronary OR myocard*) NEXT/3 (infarct* OR attack OR occlusion)):ab,ti OR stroke:ab,ti OR ((cerebr* OR brain OR cranial) NEXT/3 (accident OR ischemia OR ischaemia OR infarct* OR hemorrhage OR haemorrhage)):ab,ti OR 'quality of life':ab,ti OR qol:ab,ti OR 'performance status':ab,ti OR 'functional status':ab,ti OR 'activities of daily living':ab,ti OR adl:ab,ti OR barthel:ab,ti OR karnofsky:ab,ti OR katz:ab,ti OR nottingham:ab,ti OR 'well being':ab,ti OR wellbeing:ab,ti OR disability:ab,ti OR 'health utility':ab,ti OR 'walk test':ab,ti OR 15d:ab,ti OR dasi:ab,ti OR ecog:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR facit:ab,ti OR fact:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 6mwt:ab,ti OR nhp:ab,ti OR qwb:ab,ti OR 'rand 36':ab,ti OR rand36:ab,ti OR 'sf 12':ab,ti OR sf12:ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'circulatory overload':ab,ti OR taco:ab,ti OR 'acute lung injury':ab,ti OR trali:ab,ti OR (hemolytic NEXT/4 reaction*):ab,ti OR 'transfusion reaction':ab,ti OR infection:ab,ti OR ('graft versus host' NEXT/2 (disease OR reaction)):ab,ti OR anaphyla*:ab,ti	2282519

#7	'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)	5774373
#8	#5 AND #6 AND #7	29531
#9	#5 AND #6 AND #7 AND [1-1-1985]/sd NOT [31-12-1994]/sd	3510
#10	#5 AND #6 AND #9 AND [1-1-1995]/sd NOT [31-10-2008]/sd	16619
#11	#5 AND #6 AND #9 AND [1-1-1995]/sd NOT [31-10-2008]/sd AND [medline]/lim	13990
#12	#10 NOT #11	2629
#13	#5 AND #6 AND #7 AND [1-11-2008]/sd NOT [29-7-2010]/sd	4816
#14	#9 OR #12 OR #13	10955

Table A1.4 Additional EMBASE.com search for Level III evidence with organ failure terms conducted 12 September 2011

#	Query	Results
#1	'blood transfusion'/exp OR blood NEAR/4 transfus* OR 'erythrocyte transfusion' OR 'erythrocyte transfusions' OR 'red blood cell' NEAR/1 'transfusion' OR 'rbc' NEAR/1 'transfusion' OR 'red blood cell' NEAR/1 'transfusions' OR 'rbc' NEAR/1 'transfusions' OR 'red cell' NEAR/1 'transfusion' OR 'normocyte transfusion' OR 'red cell' NEAR/1 'transfusions' OR 'red blood cell' NEAR/1 'exchange' OR 'rbc' NEAR/1 'exchange' OR 'red cell' NEAR/3 'exchange' OR 'red cells' NEAR/3 'exchange'	134189
#2	'restrictive transfusion trigger' OR restrictive NEAR/3 transfus* OR 'low' NEAR/3 'transfusion' OR 'low' NEAR/3 'transfusions'	901
#3	liberal AND transfus* OR 'high' NEAR/3 'transfusion' OR 'high' NEAR/3 'transfusions'	984
#4	transfusion NEAR/1 (threshold* OR trigger* OR strateg* OR polic* OR practice* OR protocol* OR guideline*) OR 'hemoglobin blood level'/exp OR ('hemoglobin'/exp OR hemoglobin OR haemoglobin AND (level* OR threshold* OR concentration* OR content)) OR 'blood hemoglobin' OR 'blood haemoglobin' OR 'plasma hemoglobin' OR 'plasma haemoglobin' OR 'serum hemoglobin' OR 'serum haemoglobin'	115522
#5	#1 OR #2 OR #3 OR #4	238967
#6	'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)	5872351
#7	'organ failure':ab,ti OR 'organ dysfunction':ab,ti	18675
#8	#5 AND #6 AND #7	697
#13	#5 AND #6 AND #7 AND [1-1-1985]/sd NOT [29-7-2010]/sd	564

Table A1.5 Cochrane library: search conducted 2 August 2010

#	Query	Results
#1	MeSH descriptor Erythrocyte Transfusion explode all trees	414
#2	MeSH descriptor Blood Transfusion explode all trees	2921
#3	blood NEAR/3 transfusion	4797
#4	'erythrocyte transfusion' OR 'erythrocyte transfusions'	509
#5	('red blood cell' OR rbc) NEAR/1 transfusion*	166
#6	'red cell' NEAR/1 transfusion*	3
#7	'normocyte transfusion' OR 'normocyte transfusions'	0
#8	('red blood cell' OR rbc) NEAR/1 exchange	2
#9	('red cell' OR 'red cells') NEAR/3 exchange	4
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	5313
#11	(restrictive AND transfus*)	57
#12	(restrictive OR low) NEAR/3 transfusion*	232
#13	(#11 OR #12)	253
#14	(liberal AND transfus*)	39
#15	(liberal OR high) NEAR/3 transfusion*	170
#16	(#14 OR #15)	182
#17	'transfusion threshold' OR 'transfusion thresholds'	45
#18	transfusion NEAR/1 trigger*	61
#19	'transfusion strategy' OR 'transfusion strategies'	40
#20	'transfusion policy' OR 'transfusion policies'	23
#21	'transfusion practice' OR 'transfusion practices'	57
#22	'transfusion protocol' OR 'transfusion protocols'	55
#23	transfusion NEAR/1 guideline*	34
#24	'hemoglobin threshold' OR 'hemoglobin trigger'	5
#25	'haemoglobin threshold' OR 'haemoglobin trigger'	6
#26	'hb threshold' OR 'hb trigger'	8
#27	'haemoglobin thresholds' OR 'haemoglobin triggers'	2
#28	'hb thresholds' OR 'hb triggers'	2
#29	(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)	1310
#30	(#10 OR #13 OR #16 OR #29)	6647

#31	#30 limited to: 'Cochrane Reviews', 'Other Reviews', and 'Technology Assessments'	567
#32	#32 limited to: 'Clinical Trials'	4367

A2 Literature search – Question 2

Table A2.1 EMBASE.com search for Level I and II studies conducted 15 September 2010

#	Query	Results
#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*))	130797
#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'	2189274
#3	'erythropoietin'/exp OR erythropoietin OR 'recombinant erythropoietin'/exp OR erthropoietin OR 'erythropoiesis stimulating' OR 'erythropoietic factor' OR hematopoietin OR hemopoietin OR haematopoietin OR haemopoietin OR 'dynepo'/exp OR 'epoch'/exp OR 'epoconn'/exp OR 'epoetin'/exp 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'	37726
#4	'iron'/exp OR iron	198707
#5	#3 OR #4	229488
#6	'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	537276
#7	#5 AND #6	4750
#8	# 5AND #6 AND [1985-2011]/py	4498
#9 (Level I)	#1 AND #8	127
#10 (Level II)	#2 AND #8 NOT #9	1145

Table A2.2 Cochrane library database search conducted 15 September 2010

#	Query	Results
#1	intensive NEAR/5 (care OR therap* OR treatment* OR recovery) OR icu OR critical* NEAR/5 (ill* OR care OR patient* OR condition*) OR subacute NEAR/5 care OR 'close monitoring' OR 'special care' OR 'high dependency unit' OR 'coronary care unit' OR ccu OR itu OR hdu	20854
#2	MeSH descriptor Erythropoietin explode all trees	1370
#3	(erthropoietin OR 'erythropoiesis stimulating factor')	4

#4	'erythropoietic NEAR/1 factor'	0
#5	(hematopoietin OR hemopoietin)	2
#6	(haematopoietin OR haemopoietin)	1
#7	(dynepo OR epoch OR epoconn OR epoetin OR epog?n)	904
#8	(epoietin OR epoxitin OR eprex OR erantin OR erypo)	65
#9	(espo OR exprex OR globuren OR hemax OR marogen)	35
#10	(neorecormon OR procrit OR recormon OR recormone)	52
#11	(rHuEPO OR 'rHu EPO' OR 'r Hu EPO')	396
#12	MeSH descriptor Iron explode all trees	1445
#13	iron	3679
#14	(#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	5292
#15	(#1 AND #14)	147
	Cochrane reviews, other reviews, tech assessments	43
	Clinical trials	91

A3 Literature search – Question 3

Table A3.1 EMBASE.com search for Level III studies conducted on 11 July 2011, limited to publication up to 15 September 2010

#	Query	Results
#1	'blood component therapy'/exp OR 'blood transfusion'/exp OR 'transfusion'/exp OR transfus* OR 'blood exchange' OR 'blood infusion' OR 'blood replacement' OR hemotherapy OR hematherapy OR hematotherapy OR haemotherapy OR haematherapy OR haematotherapy OR multitransfusion OR polytransfusion OR retransfus* AND [1-1-1901]/sd NOT [15-9-2010]/sd	241230
#2	'blood component'/exp OR 'blood component' OR 'blood components' OR 'blood product' OR 'blood products' OR 'transfusion product' OR 'transfusion products' OR 'blood constituent' OR 'blood constituents' AND [1-1-1901]/sd NOT [15-9-2010]/sd	32262
#3	'fresh frozen plasma'/exp OR 'plasma'/exp OR 'fresh frozen plasma' OR ffp AND [1-1-1901]/sd NOT [15-9-2010]/sd	71509
#4	'plasma transfusion'/exp OR 'plasma transfusion' OR 'plasma infusion' OR 'serum transfusion' AND [1-1-1901]/sd NOT [15-9-2010]/sd	2248
#5	'cryoprecipitate'/exp OR 'cryoprecipitate coagulum' OR cryoprecipitate OR 'cryo precipitate' AND [1-1-1901]/sd NOT [15-9-2010]/sd	2739
#6	'fibrinogen'/exp OR fibrinogen OR 'factor 1' OR 'factor i' AND [1-1-1901]/sd NOT [15-9-2010]/sd	136709
#7	'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' AND [1-1-1901]/sd NOT [15-9-2010]/sd	12602
#8	'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) AND [1-1-1901]/sd NOT [15-9-2010]/sd	5512674
#9	#2 OR #3 OR #5 OR #6	233595
#10	#1 AND #9	35312
#11	#4 OR #7 OR #10	38997
#12	'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 AND [1-1-1901]/sd NOT [15-9-2010]/sd	536356
#13	#11 AND #12	4867
#14	#8 AND #13	3217

Table A3.2 Cochrane library database search conducted 15 September 2010

#	Query	Results
#1	intensive NEAR/5 (care OR therap* OR treatment* OR recovery) OR icu OR critical* NEAR/5 (ill* OR care OR patient* OR condition*) OR subacute NEAR/5 care OR 'close monitoring' OR 'special care' OR 'high dependency unit' OR 'coronary care unit' OR ccu OR itu OR hdu	20854
#2	MeSH descriptor Blood Component Transfusion explode all trees	730
#3	MeSH descriptor Blood Transfusion explode all trees	2867
#4	*transfus*	7519
#5	'blood exchange' OR 'blood infusion'	47
#6	'blood replacement'	68
#7	hemotherapy OR hematherapy OR hematotherapy	61
#8	haemotherapy OR haematherapy OR haematotherapy	7
#9	(#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	7763
#10	'blood component' OR 'blood components'	459
#11	'blood product' OR 'blood products'	687
#12	'transfusion product' OR 'transfusion products'	8
#13	'blood constituent' OR 'blood constituents'	14
#14	(#10 OR #11 OR #12 OR #13)	1103
#15	(#9 AND #14)	721
#16	MeSH descriptor Plasma explode all trees	327
#17	'fresh frozen plasma' OR FFP	383
#18	(#16 OR #17)	625
#19	(#9 AND #18)	312
#20	'plasma transfusion'	33
#21	'plasma infusion' OR 'serum transfusion'	19
#22	(#19 OR #20 OR #21)	336
#23	cryoprecipitate OR 'cryo precipitate'	67
#24	(#23 AND #9)	39
#25	fibrinogen OR 'factor 1' OR 'factor I'	4731
#26	(#9 AND #25)	312
#27	MeSH descriptor Platelet Transfusion explode all trees	228
#28	MeSH descriptor Blood Platelets explode all trees	1435
#29	(#9 AND #28)	140
#30	platelet* NEAR/3 transfusion*	599

#31	'thrombocyte transfusion' OR 'thrombocytic transfusion'	41
#32	(#27 OR #29 OR #30 OR #31)	668
#33	(#15 OR #22 OR #24 OR #26 OR #32)	1639
#34	(#1 AND #33)	243
	Cochrane reviews, other reviews, and tech assessments	53
	Clinical trials	162

A4 Literature search – Question 4

Cell Salvage

Table A4.1 EMBASE.com search for Level I studies conducted 14 October 2010

#	Query	Results
#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*))	132299
#2	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	14972
#3	#1 AND #2	278

Table A4.2 EMBASE.com search for Level II studes conducted 20 October 2010

#	Query	Results
#1	'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'	2207212
#2	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	15021
#3	#1 AND #2	4341

Table A4.3 Cochrane library database search for Level I and II studies conducted 14 October 2010

#	Query	Results
#1	'salvage therapy' OR 'blood salvage' OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'Cell savers'	696
Level I	Cochrane reviews, other reviews, tech assessments	26
Level II	Clinical trials	628

Table A4.4 EMBASE.com search for Level III studies conducted 18 March 2011

#	Query	Results
#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*))	140626

#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'	2278244
#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)	5690878
#4	'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	566442
#5	'blood salvage'/exp OR 'blood salvage' OR 'salvage therapy'/exp OR 'salvage therapy' OR 'cell salvage' OR 'erythrocyte salvage' OR 'cell saver' OR 'cell savers'	15751
#6	#4 AND #5	1333
#7	#1 OR #2	2340040
#8	#3 AND #6	955
#9	#6 AND #7	419
#10	#8 NOT #9	594

Tranexamic acid and epsilon aminocaproic acid

Table A4.5 EMBASE.com search for Level I and II studies conducted 17 March 2011

#	Query	Results
#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*))	140626
#2	aminocaproic:ab,ti OR aminohexanoic:ab,ti OR 'amino caproic':ab,ti OR '6 amino n hexanoic acid':ab,ti OR acikaprin:ab,ti OR afibrin:ab,ti OR amicar:ab,ti OR capracid:ab,ti OR capramol:ab,ti OR caprocid:ab,ti OR caprogel:ab,ti OR caprolest:ab,ti OR caprolisine:ab,ti OR caprolysin:ab,ti OR capromol:ab,ti OR eaca:ab,ti OR ecapron:ab,ti OR ekaprol:ab,ti OR epsamon:ab,ti OR epsicapron:ab,ti OR epsikapron:ab,ti OR epsilcapramin:ab,ti OR 'amino caproate':ab,ti OR aminocaproate:ab,ti OR epsilonaminocaproic:ab,ti OR ethaaminocaproic:ab,ti OR hemocaprol:ab,ti OR hepin:ab,ti OR ipsilon:ab,ti OR neocaprol:ab,ti OR tachostyptan:ab,ti	3175
#3	tranexamic:ab,ti OR '4 amino methylcyclohexane carboxylate':ab,ti OR '4	6149

	aminomethylcyclohexanecarbonic acid':ab,ti OR '4 aminomethylcyclohexanecarboxylic acid':ab,ti OR amca:ab,ti OR amcha:ab,ti OR amchafibrin:ab,ti OR amikapron:ab,ti OR 'aminomethyl cyclohexane carboxylic acid':ab,ti OR 'aminomethyl cyclohexanecarboxylic acid':ab,ti OR 'aminomethylcyclohexane carbonic acid':ab,ti OR 'aminomethylcyclohexane carboxylic acid':ab,ti OR 'aminomethylcyclohexanecarbonic acid':ab,ti OR 'aminomethylcyclohexanecarboxylic acid':ab,ti OR 'aminomethylcyclohexanocarboxylic acid':ab,ti OR 'aminomethylcyclohexanoic acid':ab,ti OR amstat:ab,ti OR anvitoff:ab,ti OR 'cis 4 aminomethylcyclohexanecarboxylic acid':ab,ti OR 'cis aminomethyl cyclohexanecarboxylic acid':ab,ti OR cyclocapron:ab,ti OR cyclokapron:ab,ti OR cyklocapron:ab,ti OR exacyl:ab,ti OR frenolyse:ab,ti OR hexacapron:ab,ti OR hexakapron:ab,ti OR 'para aminomethylcyclohexane carboxylic acid':ab,ti OR tranex:ab,ti OR tranexanic:ab,ti OR 'trans 1 aminomethylcyclohexane 4 carboxylic acid':ab,ti OR 'trans 4 (aminomethyl) cyclohexane 1 carboxylic acid':ab,ti OR 'trans 4 (aminomethyl) cyclohexane carbonic acid':ab,ti OR 'trans 4 (aminomethyl) cyclohexanecarboxylic acid':ab,ti OR 'trans 4 aminomethylcyclohexane 1 carboxylic acid':ab,ti OR 'trans 4 aminomethylcyclohexane carboxylic acid':ab,ti OR 'trans 4 aminomethylcyclohexanecarboxylic acid':ab,ti OR 'trans achma':ab,ti OR 'trans amcha':ab,ti OR 'trans aminomethyl cyclohexane carboxylic acid':ab,ti OR 'trans aminomethylcyclohexane carboxylic acid':ab,ti OR 'trans aminomethylcyclohexanecarboxylic acid':ab,ti OR transamin:ab,ti OR 'transaminomethylcyclohexane carboxylic acid':ab,ti OR transexamic:ab,ti OR ugurol:ab,ti OR txa:ab,ti	
#4	#2 OR #3	9029
#5 (Level I)	#1 AND #4	126
#6	'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'	2278244
#7	#4 AND #6	1425
#8 (Level II)	#7 NOT #5	1317

Table A4.6 Cochrane library database search conducted 17 March 2011

#	Query	Results
#1	MeSH descriptor Tranexamic Acid explode all trees	274
#2	tranexamic OR '4 amino methylcyclohexane carboxylate' OR '4 aminomethylcyclohexanecarbonic acid' OR '4 aminomethylcyclohexanecarboxylic acid' OR amca OR amcha OR amchafibrin OR amikapron OR 'aminomethyl cyclohexane carboxylic acid' OR 'aminomethyl cyclohexanecarboxylic acid' OR 'aminomethylcyclohexane carbonic acid' OR 'aminomethylcyclohexane carboxylic acid' OR 'aminomethylcyclohexanecarbonic acid' OR 'aminomethylcyclohexanecarboxylic acid' OR 'aminomethylcyclohexanocarboxylic acid' OR 'aminomethylcyclohexanoic	516

	acid' OR amstat OR anvitoff OR 'cis 4 aminomethylcyclohexanecarboxylic acid' OR 'cis aminomethyl cyclohexanecarboxylic acid' OR cyclocapron OR cyclokapron OR cyklocapron OR exacyl OR frenolyse OR hexacapron OR hexakapron OR 'para aminomethylcyclohexane carboxylic acid' OR tranex OR tranexanic OR 'trans 1 aminomethylcyclohexane 4 carboxylic acid' OR 'trans 4 (aminomethyl) cyclohexane 1 carboxylic acid' OR 'trans 4 (aminomethyl) cyclohexane carbonic acid' OR 'trans 4 (aminomethyl) cyclohexanecarboxylic acid' OR 'trans 4 aminomethylcyclohexane 1 carboxylic acid' OR 'trans 4 aminomethylcyclohexane carboxylic acid' OR 'trans 4 aminomethylcyclohexanecarboxylic acid' OR 'trans achma' OR 'trans amcha' OR 'trans aminomethyl cyclohexane carboxylic acid' OR 'trans aminomethylcyclohexane carboxylic acid' OR 'trans aminomethylcyclohexanecarboxylic acid' OR transamin OR 'transaminomethylcyclohexane carboxylic acid' OR transexamic OR ugurol OR txa	
#3	MeSH descriptor 6-Aminocaproic Acid explode all trees	92
#4	aminocaproic OR aminohexanoic OR 'amino caproic' OR '6 amino n hexanoic acid' OR acikaprin OR afibrin OR amicar OR capracid OR capramol OR caprocid OR caprogel OR caprolest OR caprolisine OR caprolysin OR capromol OR eaca OR ecapron OR ekaprol OR epsamon OR epsicapron OR epsikapron OR epsilcapramin OR 'amino caproate' OR aminocaproate OR epsilonaminocaproic OR ethaaminocaproic OR hemocaprol OR hepin OR ipsilon OR neocaprol OR tachostyptan	245
#5	#1 OR #2 OR #3 OR #4	693
Level I	Cochrane reviews, other reviews, tech assessments	72
Level II	Clinical trials	608

Appendix B Excluded studies

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

B1 Studies excluded from question 1

The literature search encompassed both the medical and critical care populations. As such, this list includes excluded citations relevant to both the medical and critical care populations.

Level I evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

The Norwegian Knowledge Centre for the Health Services (2005). Transfusion and alternative treatment in acute haemorrhage (Structured abstract). Oslo : The Norwegian Knowledge Centre for the Health Services :119.

Not available/unable to be retrieved

Healthcare Insurance Board/ (2002). TACTICS: Transfusion Associated Complications or Transfusion Induced Complications - primary research (Brief record). Diemen : Healthcare Insurance Board/College voor Zorgverzekeringen .

University HealthSystem Consortium (1997). Red blood cell transfusion guidelines (Structured abstract). Oak Brook , Illinois : University Healthsystem Consortium :138.

Superseded/duplicate data/withdrawn

Carson JL, Hill S, Carless P, Hebert P, Henry D (2002). Transfusion Triggers: A systematic review of the literature. Transfusion Medicine Reviews 16(3):187-199.

Hill SR, Carless PA, Henry DA, Carson JL, Hebert PC, McClelland DB, et al. (2002). Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane database of systematic reviews (Online) (2):CD002042.

Hill S, Carless PA, Henry DA, Carson JL, Hebert-Paul PC, Henderson KM, et al. (2000). Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database of Systematic Reviews .

Hirst C, Wang WC (2002). Blood transfusion for preventing stroke in people with sickle cell disease. Hirst Ceri , Wang Winfred C Blood transfusion for preventing stroke in people with sickle cell disease Cochrane Database of Systematic Reviews: Reviews 2002 Issue 1 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD003146 .

Mahomed K (2007). WITHDRAWN: Prophylactic versus selective blood transfusion for sickle cell anaemia during pregnancy. Cochrane database of systematic reviews (Online) (3):CD000040.

Riddington C, Wang W (2002). Blood transfusion for preventing stroke in people with sickle cell disease. Cochrane database of systematic reviews (Online) (1):CD003146.

Erratum/not relevant

Marik PE, Corwin HL (2008). Erratum: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. (Critical Care Medicine (2008) 36 (2667-2674)). Critical Care Medicine 36(11):3134.

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Abstract Presentations from the AABB Annual Meeting and TXPO (2009). Transfusion 49.

Fredrickson (2010). Acute Physiological Effects of Red Blood Cell Transfusion in Preterm Infants Transfused Using Liberal or Restrictive Guidelines. Pediatric Academic Society http://www.abstracts2view.com/pas/.

Colomo A, Hernandez G, Muñiz DE, Madoz P, Aracil C, Álvarez UC, et al. (2008). Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding. Hepatology 48:413A.

Colomo A, Hernandez-Gea V, Madoz P, Carles A, varez-Urturi C, Poca M, et al. (2009). Hemodynamic changes and transfusion strategies in cirrhotic patiens with acute variceal bleeding. Hepatology 50:403A.

Duplicate data

Kennedy MS, Kalish LA, Mohandas K, Gernsheimer T, Townsend-McCall D (2002). The transfusion trigger and number of units transfused in patients with HIV: associations with disease stage and functional status. Transfusion 42(4):456-461.

Includes < 100 subjects

Zygun DA, Nortje J, Hutchinson PJ, Timofeev I, Menon DK, Gupta AK (2009). The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury. Critical Care Medicine 37(3):1074-1078

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Abstract only

Ahmed AH, Kojicic M, Li G, Kashyap R, Thakur S, Herasevich V, et al. (2009). Transfusion as a risk factor for hospital-acquired acute respiratory distress syndrome (ARDS) in Olmsted County Minnesota. Chest 136(4).

Andrzejewski C, Popovsky MA, Provencher JL, Stec TC, O'Hearn L (2009). Characteristics of patients with transfusion reactions associated with fluid challenges. Transfusion 49:196A-197A.

Badami K, Merriman EG, Dagger J (2009). FNHTR and infection/infammation may be related. Transfusion 49:195A.

Barrailler S, Decourcelle V, Guidez T, Braun S, Bauchart JJ, Auffray JL, et al. (2010). Prognostic value of anemia and haemoglobin changes in patients with acute coronary syndrome. Fundamental and Clinical Pharmacology 24:22.

Buckstein R, Alibhai S, Lam A, Zhang L, Cheung M, Callum J, et al. (2009). Hemoglobin has the greatest impact on Quality Of Life (QOL) in MDS patients -a tertiary care cross sectional and longitudinal study. Leukemia Research 33:S111-S112.

Garcia Monje MJ, Mourelo Farina M, ler Fernandez V, Fernandez Ugidos P, Galeiras R, Tabuyo Bello T, et al. (2009). Traumatic brain injury: Epidemiology, mortality risk factors and outcome. Intensive Care Medicine 35:S73.

Goldberg SL, Chen E, Corral M, Guo A, Laouri M (2009). Influence of RBC transfusions on clinical outcomes among USA Medicare beneficiaries with newly diagnosed myelodysplastic syndromes. Leukemia Research 33:S116.

Hearnshaw SA, Card T, Logan RFA, Travis SPL, Palmer KR, Murphy MF (2009). Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. Gut 58:A33-A34.

Natukunda BM, Schonewille H, Brand A (2009). Red blood cell alloimmunization in sickle cell disease patients in Uganda. Transfusion 49:126A.

Sada F, Belegu M, Zhubi B, Geci A, Hashimi M (2009). Anemia, red blood cell transfusion and clinical outcomes in ICU patients. Transfusion Alternatives in Transfusion Medicine 11:30.

Not in English

Afonin AN, Karpun NA (2010). Acute transfusion-related lung injury in patients after cardiac surgery. Anesteziologiia i reanimatologiia (2):27-30.

Hernandez-Gutierrez P, Grife-Coromina A, De la Garza-Estrada VA (1997). Scales to evaluate mortality of patients with trauma and adult respiratory distress syndrome. Salud Publica de Mexico 39(3):201-206.

Mukagatare I, Monfort M, de Marchin J, Gerard C (2010). The effect of leukocyte-reduction on the transfusion reactions to red blood cells concentrates. Transfusion Clinique et Biologique 17(1):14-19.

No/insufficient adjustment for confounding variables

Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS (2008). Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut 57(6):814-820.

Bijlsma TS, Schure PJCM, Leenen LPH, Van Der Graaf Y, Van Der Werken C (2005). The influence of blood transfusion on mortality in multiply injured patients. European Journal of Trauma 31(2):154-157.

Ciesla DJ, Moore EE, Johnson JL, Sauaia A, Cothren CC, Moore JB, et al. (2004). Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure. Archives of Surgery 139(6):590-595.

Graves TA, Cioffi WG, Mason J, McManus WF, Pruitt J (1989). Relationship of transfusion and infection in a burn population. Journal of Trauma 29(7):948-954.

Keller-Stanislawski B, Reil A, Gunay S, Funk MB (2010). Frequency and severity of transfusion-related acute lung injury - German haemovigilance data (2006-2007). Vox Sanguinis 98(1):70-77.

Previdi JK, Cayten CG, Byrne DW (1996). Early predictors of sepsis in the motor-vehicle crash trauma victim. Prehospital and disaster medicine : the official journal of the National Association of EMS Physicians and the World Association for Emergency and Disaster Medicine in association with the Acute Care Foundation 11(1):27-36.

Svennevig JL, Bugge-Asperheim B, Geiran OR, Vaage J, Pillgram-Larsen J, Fjeld NB, et al. (1986). Prognostic factors in blunt chest trauma. Analysis of 652 cases. Annales Chirurgiae et Gynaecologiae 75(1):8-14.

Taylor RW, Manganaro L, O'Brien J, Trottier SJ, Parkar N, Veremakis C (2002). Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. Critical Care Medicine 30(10):2249-2254.

Includes < 100 subjects

Chen B, Xiao Y, Qian G, Chen L, Zhong Q, Wang X (2006). Risk factors associated with ARDS following cardiopulmonary bypass. Chinese Journal of Emergency Medicine 15(5):429-432.

Cohen AR, Martin MB, Silber JH, Kim HC, Ohene-Frempong K, Schwartz E (1992). A modified transfusion program for prevention of stroke in sickle cell disease. Blood 79(7):1657-1661.

Cornet AD, Zwart E, Kingma SDK, Groeneveld ABJ (2010). Pulmonary effects of red blood cell transfusion in critically ill, non-bleeding patients. Transfusion Medicine 20(4):221-226.

de Montalembert M, Beauvais P, Bachir D, Galacteros F, Girot R (1993). Cerebrovascular accidents in sickle cell disease. Risk factors and blood transfusion influence. European Journal of Pediatrics 152(3):201-204.

Fenwick JC, Cameron M, Naiman SC, Haley LP, Ronco JJ, Wiggs BR, et al. (1994). Blood transfusion as a cause of leucocytosis in critically ill patients. The Lancet 344(8926):855-856.

Fidone C, Travali S, Garozzo G, Antolino A, Bennardello F, Manenti O, et al. (2006). Clinical effects of different types of red cell concentrates in patients with thalassaemia. Blood Transfusion 4(4):311-326.

Flores JM, Jimenez PI, Rincon MD, Marquez JA, Navarro H, Arteta D, et al. (2001). Early risk factors for sepsis in patients with severe blunt trauma. Injury 32(1):5-12.

Freedland M, Wilson RF, Bender JS, Levison MA (1990). The management of flail chest injury: Factors affecting outcome. Journal of Trauma 30(12):1460-1468.

Fuller B, Gajera M, Schorr C, Zanotti S, Gerber D, Dellinger RP, et al. (2009). The impact of packed red blood cell transfusion on clinical outcomes in patients with septic shock treated with early goal directed therapy. Intensive Care Medicine 35:S68.

George ME, Skarda DE, Watts CR, Pham HD, Beilman GJ (2008). Aggressive red blood cell transfusion: No association with improved outcomes for victims of isolated traumatic brain injury. Neurocritical Care 8(3):337-343.

Holguin F, Ramadan B, Gal AA, Roman J (2008). Prognostic factors for hospital mortality and ICU admission in patients with ANCA-related pulmonary vasculitis. American Journal of the Medical Sciences 336(4):321-326.

Jansen AJG, Caljouw MAA, Hop WCJ, Van Rhenen DJ, Schipperus MR (2004). Feasibility of a restrictive red-cell transfusion policy for patients treated with intensive chemotherapy for acute myeloid leukaemia. Transfusion Medicine 14(1):33-38.

Lee SW, Lee TY, Chang CS, Ko CW, Yeh HZ, Yang SS (2010). Independent factors associated with early outcome in Chinese cirrhotic patients after cessation of initial esophageal variceal hemorrhage. Journal of Clinical Gastroenterology 44(6):e123-e127.

Mackinnon S, Burnett AK, crawford RJ, Cameron S, Leask BGS, Sommerville RG (1988). Seronegative blood products prevent primary cytomegalovirus infection after bone marrow transplantation. Journal of Clinical Pathology 41(9):948-950.

Matsushima K, Eastman A, Shafi S, Burris A, Tyner T, Frankel H (2009). Transfusion increases infection without affecting neurologic outcome in spontaneous subarachnoid hemorrhage. Critical Care 13:S41-S43.

Melchior JC, Poupon RE, Verrier J (1987). Analysis of factors related to early death due to digestive hemorrhage in portal hypertension. Gastroenterologie Clinique et Biologique 11(5):402-408.

Musau P (2006). Risk indicators of morbidity and mortality in abdominal injuries. East African medical journal 83(12):644-650.

Schenk JF, Stephan B, Morsdorf S, Tilev K, Krischek B, Wenzel E, et al. (2000). Rational use of blood and blood components in hematology and oncology. Infusionstherapie und Transfusionsmedizin 27(4):190-194.

Shalev O, Manny N, Sharon R (1993). Posttransfusional hemolysis in recipients of glucose-6-phosphate dehydrogenase deficient erythrocytes. Vox Sanguinis 64(2):94-98.

Slim R, Yaghi C, Honein K, Bou Jaoude J, El Khoury S, Sayegh R (2005). Factors predictive of clinical outcome in upper gastrointestinal bleeding. Journal Medical Libanais 53(3):143-150.

Stoll VM, Medd P, Peniket A, Vyas P, Littlewood T, Hatton C (2010). Analysis of factors affecting outcome in recipients of bone marrow transplantation for myelodysplasia; A single centre's experience over a nine year period. British Journal of Haematology 149:81-82.

Tan FLS, Tan YM, Chung AYF, Cheow PC, Chow PKH, Ooi LL (2006). Factors affecting early mortality in spontaneous rupture of hepatocellular carcinoma. ANZ Journal of Surgery 76(6):448-452.

Wood J, Pandit D (2009). Outcome of severe sepsis in the ICU is independent of haemoglobin levels. Critical Care 13:S143.

Inconsistent results

Croce MA, Tolley EA, Claridge JA, Fabian TC (2005). Transfusions result in pulmonary morbidity and death after a moderate degree of injury. Journal of Trauma - Injury, Infection and Critical Care 59(1):19-24.

Wrong intervention/comparator

Inoue Y, Wada Y, Motohashi Y, Koizumi A (2010). History of blood transfusion before 1990 is associated with increased risk for cancer mortality independently of liver disease: A prospective long-term follow-up study. Environmental Health and Preventive Medicine 15(3):180-187.

Duplicate data

Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC (1994). Early predictors of post-injury multiple organ failure. Archives of Surgery 129:39-45.

B2 Studies excluded from question 2

For question 2 there were no studies that were excluded for reasons other than not meeting the PICO criteria.

B3 Studies excluded from question 3

Level III evidence

No/insufficient adjustment for confounding variables

Gajic, O., M. Yilmaz, R. Iscimen, D. J. Kor, J. L. Winters, S. B. Moore, and B. Afessa, 2007, Transfusion from male-only versus female donors in critically ill recipients of high plasma volume components: Critical Care Medicine, v. 35, no. 7, p. 1645-1648.

B 4 Studies excluded from question 4

Cell Salvage

Level II evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Drenovski V, Stankev M, Chervenkov V (1995). The results of resection treatment in infrarenal aneurysms of the abdominal aorta over the last 5 years (1989-1993). Khirurgiia 48(1):29-33.

Mazur AP (2009). Technology of blood preservation in the surgery of the abdominal aorta. Klinichna khirurhiia / Ministerstvo okhorony zdorov'ia Ukra?ny, Naukove tovarystvo khirurhiv Ukra?ny (10):40-43.

Level III evidence

The following studies were excluded for reasons other than not meeting the PICO criteria:

Not in English

Klaue P (1982). Experiences with the haemonetics-cell-saver. Anasthesie Intensivtherapie Notfallmedizin 17(4):220-224.

No useable data

Catling SJ, Freites O, Krishnan S, Gibbs R (2002). Clinical experience with cell salvage in obstetrics: 4 Cases from one UK centre. International Journal of Obstetric Anesthesia 11(2):128-134.

Gardner A, Gibbs N, Evans C, Bell R (2000). Relative cost of autologous red cell salvage versus allogeneic red cell transfusion during abdominal aortic aneurysm repair. Anaesthesia and Intensive Care 28(6):646-649.

Horst HM, Dlugos S, Fath JJ, Sorensen VJ, Obeid FN, Bivins BA (1992). Coagulopathy and intraoperative blood salvage (IBS). Journal of Trauma 32(5):646-653.

Hughes LG, Thomas DW, Wareham K, Jones JE, John A, Rees M (2001). Intra-operative blood salvage in abdominal trauma: A review of 5 years' experience. Anaesthesia 56(3):217-220.

Timberlake GA, McSwain J (1988). Autotransfusion of blood contaminated by enteric contents: A potentially life-saving measure in the massively hemorrhaging trauma patient? Journal of Trauma 28(6):855-857.

Tranexamic acid and epsilon aminocaproic acid

The following studies were excluded for reasons other than not meeting the PICO criteria:

Level I evidence

No useable data

Curry N, Hopewell S, Doree C, Hyde C, Brohi K, Stanworth S (2011). The acute management of trauma hemorrhage: A systematic review of randomized controlled trials. Critical Care :R92.

Henry DA, O'Connell DL (1989). Effects of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. British Medical Journal 298(6681):1142-1146.

Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S (2010). Haemostatic drugs for traumatic brain injury. Cochrane database of systematic reviews (Online) (1):CD007877.

Level II evidence

Not in English

Broemster D, Brostroem O, Engqvist A (1977). Tranexamic acid in severe gastrointestinal hemorrhage - a controlled trial. Aktuelle Gastrologie 6(3):225-228.

Heinzl S (2010). Arresting hemorrhage in accident casualties: Tranexamic acid reduces mortality. Deutsches Arzteblatt 107(33):A1575.

Pascal JP, Tournut R, Clanet J, Hilary P, Rouzaud P, Louis A (1978). [Treatment of upper gastrointestinal hemorrhage (portal hypertension excluded) by intragastric infusion of hemostatic solution. A controlled trial (author's transl)]. Gastroentérologie clinique et biologique 2:357-364.

Studies already included in identified systematic reviews

Barer D, Ogilvie A, Henry D, Dronfield M, Coggon D, French S, et al. (1983). Cimetidine and tranexamic acid in the treatment of acute upper-gastrointestinal-tract bleeding. The New England journal of medicine 308:1571-1575.

Bergqvist D, Dahlgren S, Hessman Y (1980). Local inhibition of the fibrinolytic system in patients with massive upper gastrointestinal hemorrhage. Upsala Journal of Medical Sciences 85:173-178.

Biggs JC, Hugh TB, Dodds AJ (1976). Tranexamic acid and upper gastrointestinal haemorrhage--a double-blind trial. Gut 17:729-734.

Cormack F, Chakrabarti RR, Jouhar AJ, Fearnley GR (1973). Tranexamic acid in upper gastrointestinal haemorrhage. The Lancet 1:1207-1208.

Engqvist A, Brostrom O, Von Feilitzen F (1979). Tranexamic acid in massive haemorrhage from the upper gastrointestinal tract: A double blind study. Scandinavian Journal of Gastroenterology 14(7):839-844.

Hawkey GM, Cole AT, McIntyre AS, Long RG, Hawkey CJ (2001). Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut 49:372-379.

Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. The Lancet 376(9734):23-32 (PM:20554319).

von-Holstein CC, Eriksson SB, Källén R (1987). Tranexamic acid as an aid to reducing blood transfusion requirements in gastric and duodenal bleeding. British Medical Journal 294:7-10.

von-Holstein CC, Eriksson SB, Källén R (1987). Tranexamic acid in gastric and duodenal bleeding. Scandinavian journal of gastroenterology Supplement 137:71-74.

Appendix C Literature search results

C1 Search results – Question 1

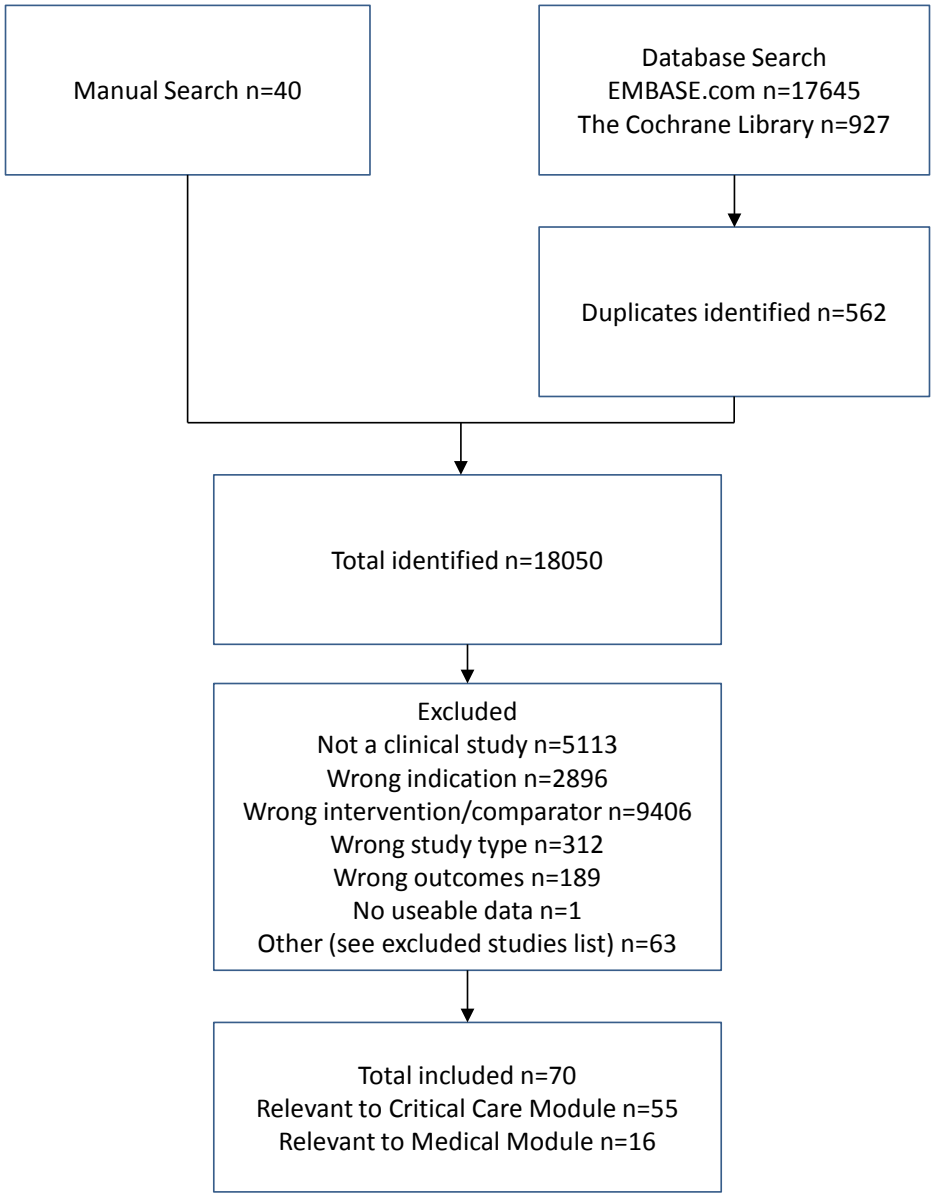

Figure C1 Search results – Question 1

C2 Search results – Question 2

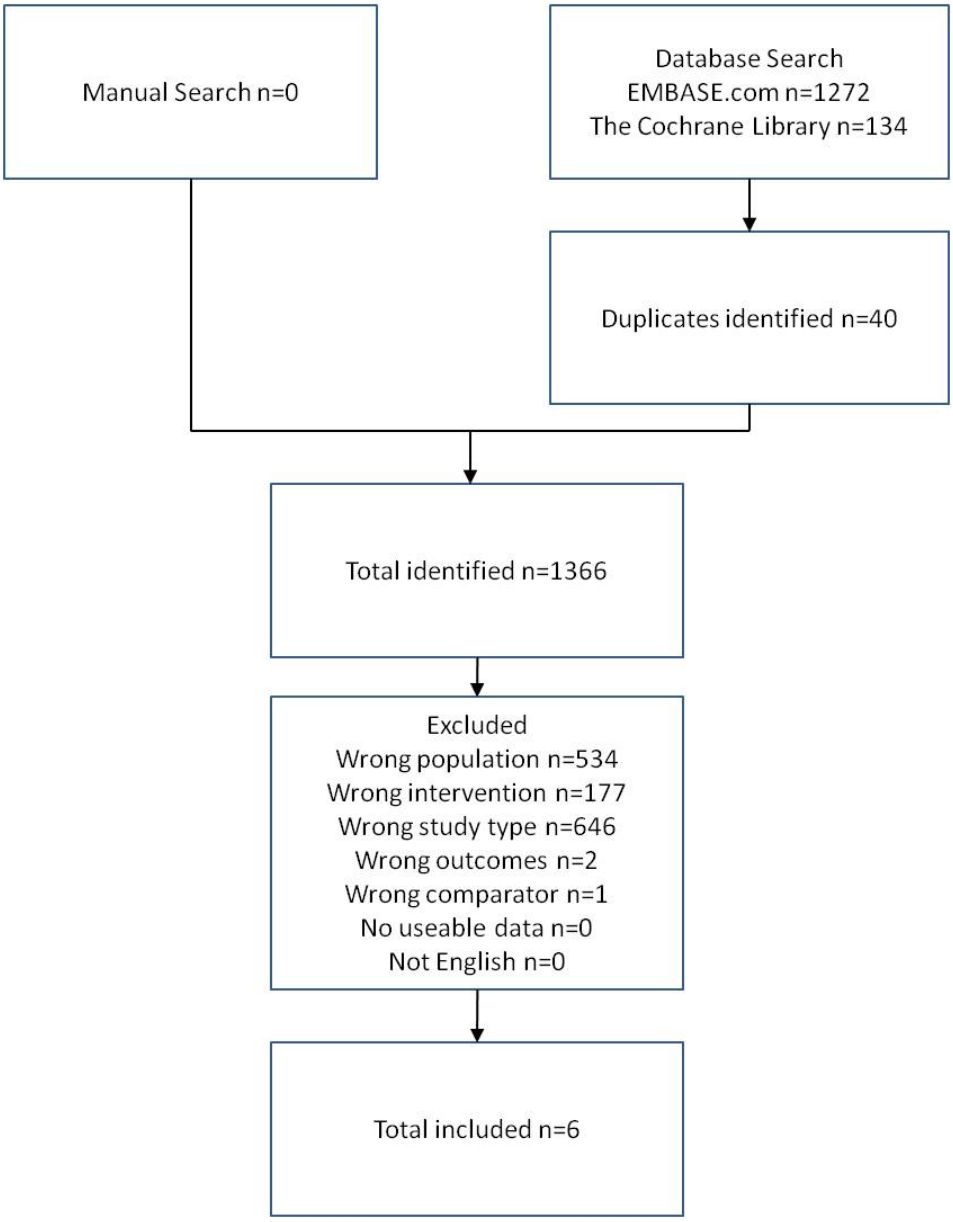

Figure C2 Search results – Question 2

C3 Search results – Question 3

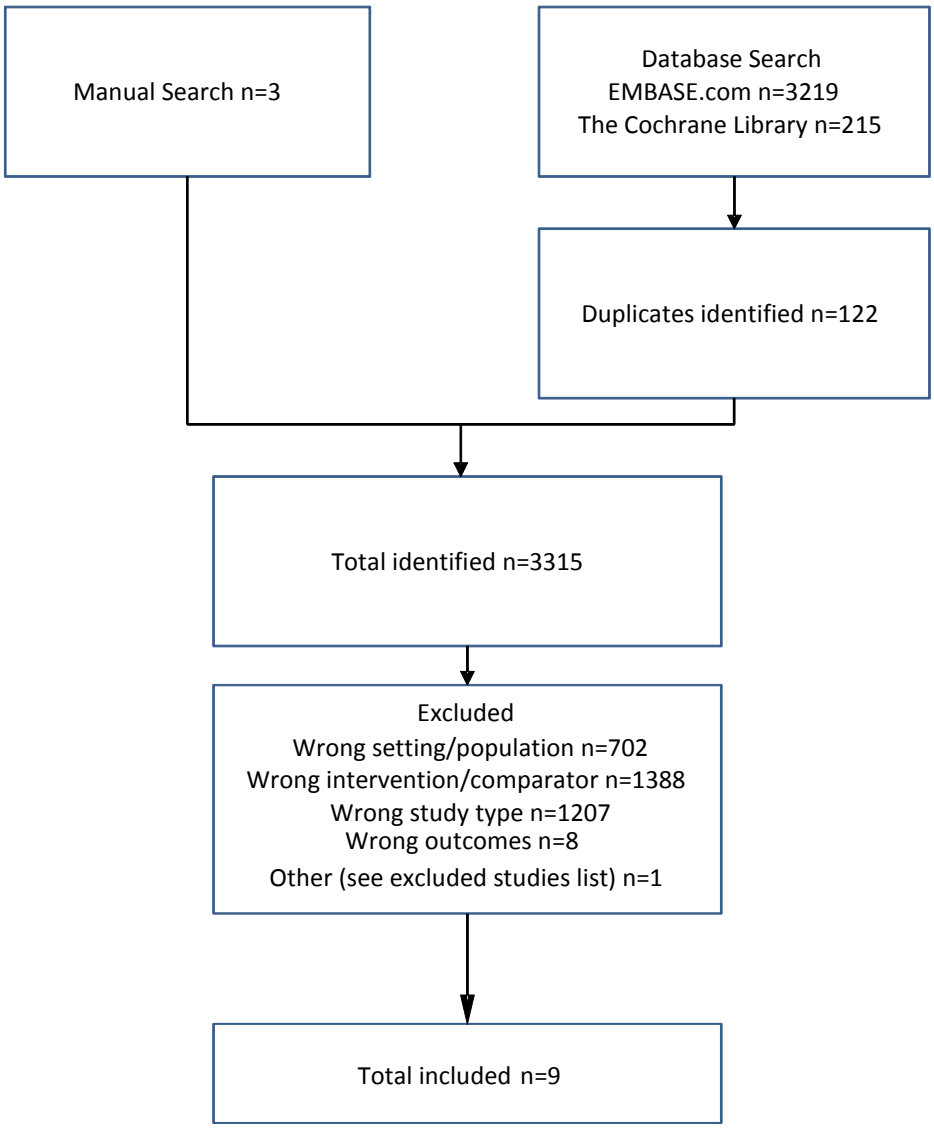

Figure C3 Search results – Question 3

C4 Search results – Question 4

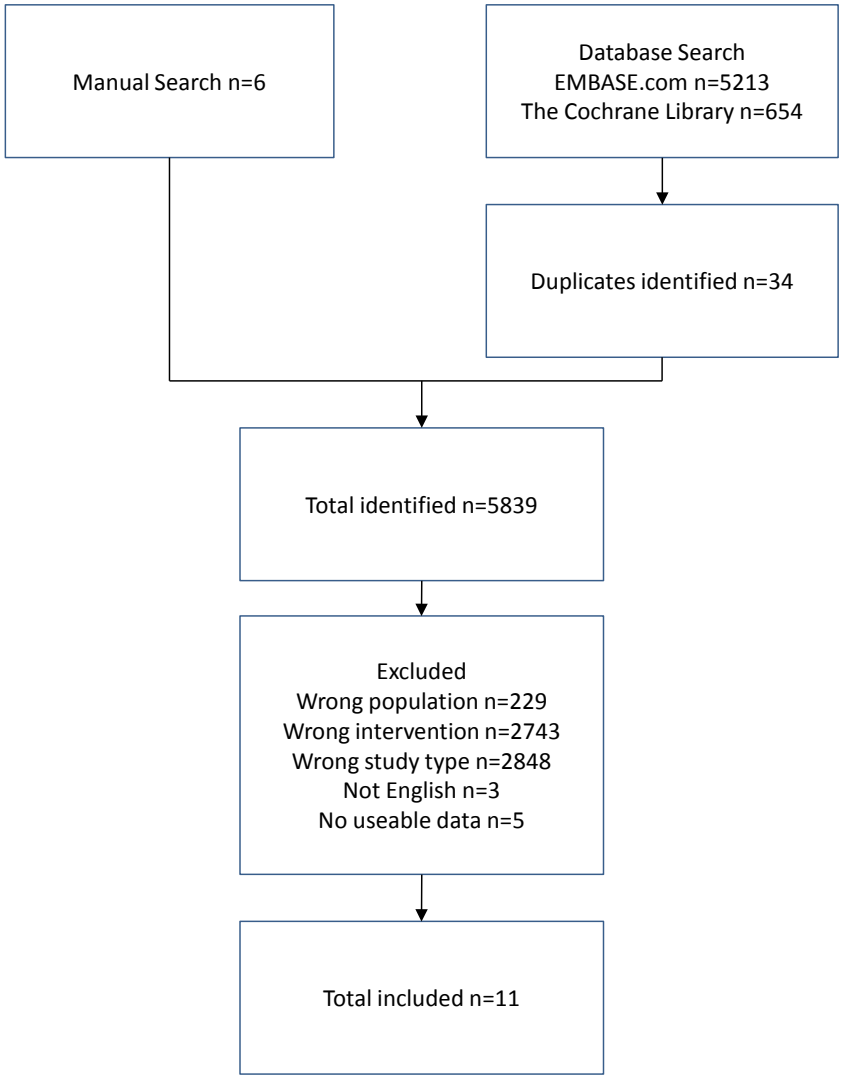

Figure C4 Search results – Question 4, Cell salvage

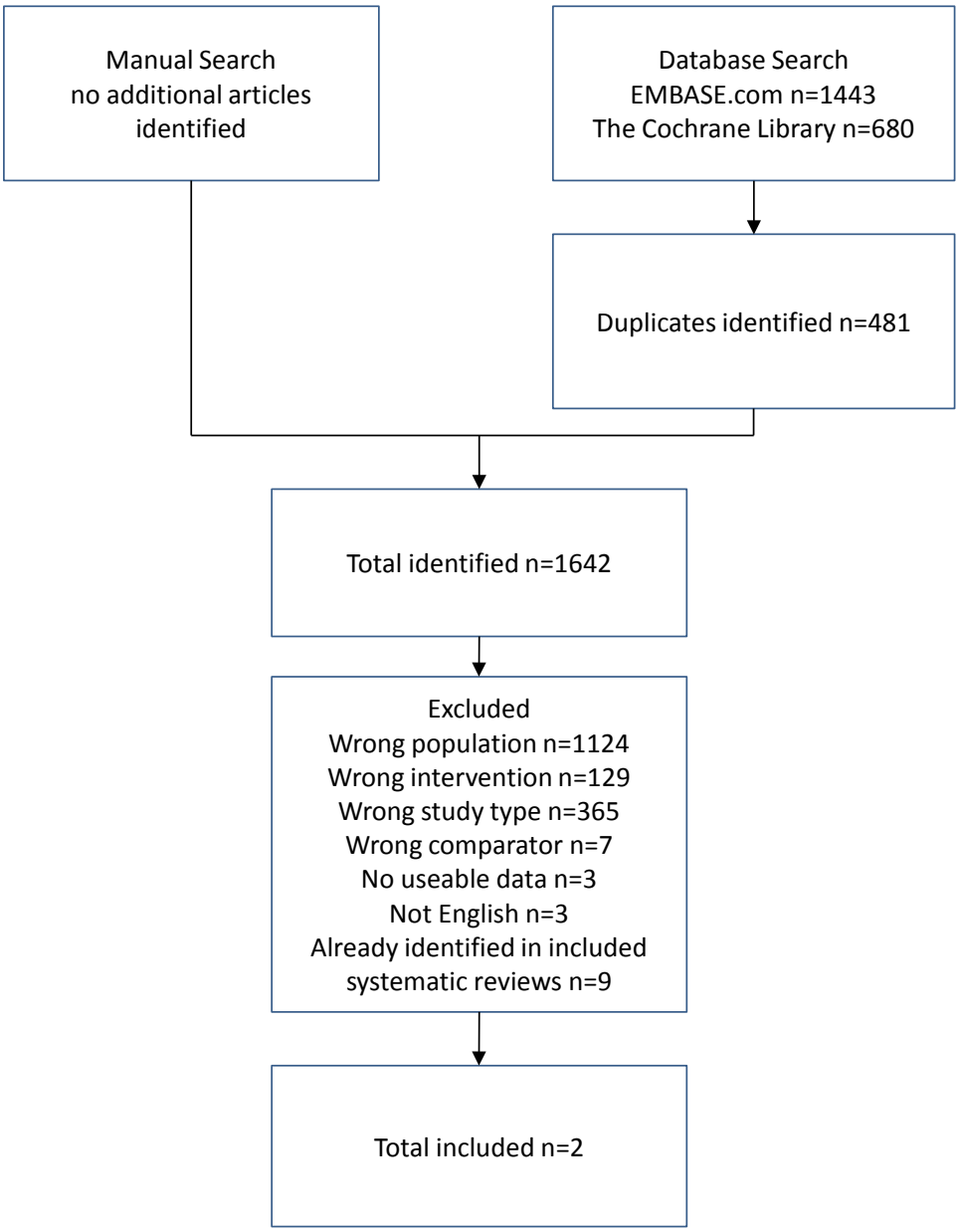

Figure C5 Search results – Question 4, TXA and EACA

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 and in the systematic review (Volume 1) the corresponding evidence statements are described as 'unknown'. These evidence statements are not numbered or included in the main body of the guideline.

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

D1 Evidence – Question 1

Key question(s): In a critical care population, what is the effect of RBC (allogeneic) transfusion versus no transfusion (or different dose) on mortality?		Evidence matrix: EM1.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level III: One systematic review of 13 cohort studies (Marik 2008; fair quality) Level III-2: 4 Studies that were included in the Marik review (Corwin 2004 fair; Dunne 2004 fair; Malone 2003 good; Vincent 2002 fair). 7 studies not included in the Marik review (Hébert 1997 fair; Rüttinger 2007, Good; Salim 2008 fair; Vincent 2008 Good; Zilberberg 2008 fair; Engoren 2009 fair; Rachoin 2009 Fair). Three studies which assessed transfusion dose (Bochicchio 2008 fair; Müller 2008 fair; Spinella 2008 fair)	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')*		
Marik review: 13 cohort studies increased risk of mortality with RBC transfusion Additional studies: 3 studies found increased risk of mortality with transfusion; 3 studies found decreased risk or no difference. Rüttinger 2007 found increased risk and no difference depending on what variables were included in the multivariate analysis. Three dose studies showed consistent results; increased mortality risk/decreased survival).	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)*		
Marik review: increased risk of mortality with RBC transfusion OR 1.69 (1.46, 1.92) Additional studies: - 3 studies found increased risk of mortality with transfusion OR 1.3-2.19 (2 studies did not adjust for organ dysfunction and 1 study adjusted for admission APACHE II) - 3 studies found decreased risk or no difference. OR 0.57-0.74 (all studies included some adjustment for organ dysfunction using SOFA, APACHE II etc) - Rüttinger 2007 found both increased risk and no difference depending on what variables were included in the multivariate analysis. Adjustment for variables associated with organ dysfunction during hospitalisation showed no relationship between RBC transfusion and mortality. Transfusion dose studies showed increased risk of mortality in two studies (OR 1.05 and 1.10) and decreased survival in one study (OR 0.77) per unit 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?)*		
Rüttinger and Müller studies conducted in surgical critical care patients; Salim study conducted in patients with traumatic brain injury; all other studies conducted in a broad critical care population (ICU and trauma).	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Studies carried out in USA, Western Europe, Canada, Germany and Iraq.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats

	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The results suggest that analyses should include both admission variables and variables for organ dysfunction and disease severity during hospital stay.
Since none of the studies stratified by Hb levels, this evidence does not provide any information on triggers for transfusion (in contrast to the situation with the medical 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	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	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, the effect of RBC transfusion on mortality is uncertain.

Key question(s): In a critical care population, what is the effect of RBC (allogeneic) transfusion versus no transfusion (or different dose) on infection (pneumonia and infectious complications)?			Evidence matrix: EM1.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	Pneu	Infect comp	
Level III: One systematic review of 9 cohort studies (Marik 2008; fair quality) Level III-2: Two studies that were included in the Marik review (Claridge 2002 poor; Shorr 2004 fair). The Claridge 2002 study was not included in the meta-analysis of infections in the Marik review. One study not included in the Marik review (Rachoin 2009 fair). Four studies assessed transfusion dose (Agarwal 1993 fair; Bochicchio 2008 fair; Duane 2008 poor; Palmieri 2006 poor).	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 a significantly increased risk of transfusion-related adverse event (pneumonia and infection) with RBC transfusion	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)*			
Pneumonia: OR 1.89 (1.33, 2.68) [Shorr 2004] Infection: OR 1.88 (1.52, 2.24) [Marik 2008; pooled]; OR 1.084 (1.028, 1.142) [Claridge 2002]; OR 1.6 (1.4, 1.8) [Rachoin 2009] Four studies found increased risk of infection with increasing transfusion dose: p<0.001 [Agarwal1993]; OR 2.8 (1.96, 3.94) [Bochicchio 2008]; OR 1.26 (1.06, 1.50) [Duane 2008]; OR 1.13 [Palmieri 2006].	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?)*			
The Marik review included four trauma/ICU studies and five studies in general surgery populations in the infectious complications analysis. The study by Duane enrolled patients with blunt head trauma and the study by Palmieri enrolled patients with acute burn injuries. All other individual studies included in the review were conducted in a broad critical care population (ICU and trauma).	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 health-care context in terms of health services/delivery of care and cultural factors?)*			
Studies included in the Marik review were carried out at various locations. The studies by Claridge, Rachoin, Agarwal, Bochicchio, Duane and Palmieri were carried out in USA. Applicability was downgraded for pneumonia because the Schorr study was published in 2004 and transfusion practise has changed. Applicability was downgraded for infectious complications because most studies did not provide a clear definition of infection.	A	A	Evidence directly applicable to Australian health-care context
	B	B	Evidence applicable to Australian health-care context with few caveats
	C	C	Evidence probably applicable to Australian health-care context with some caveats
	D	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Marik review included four trauma/ICU studies and five studies in general surgery populations in the infectious complications 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.

	Rating		
Component	Pneu	Infect comp	Description
1. Evidence base	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
2. Consistency	NA	A	Not applicable (one study only) / All studies consistent
3. Clinical impact	B	B	Substantial
4. Generalisability	A	A	Evidence directly generalisable to target population
5. Applicability	C	C	Evidence probably applicable to Australian health-care context with some caveats

EVIDENCE STATEMENT

In critically ill patients, RBC transfusion may be independently associated with an increased risk of ventilator-associated pneumonia.

In critically ill patients, RBC transfusion may be independently associated with an increased risk of infection.

Key question(s): In a critical care population, what is the effect of RBC (allogeneic) transfusion vs no transfusion (or different dose) on ARDS and ALI?		Evidence matrix: EM1.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level III: One systematic review of 6 cohort studies (Marik 2008; fair quality) Level III-2: Three studies that were included in the Marik review (Gong 2005 fair; Khan 2007 fair; Zilberberg 2007 fair).	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')*		
The pooled analysis in the Marik review and the Gong and Zilberberg studies found increased risk of ARDS with RBC transfusion. The study by Khan found no difference in ARDS/ALI; however, this was a smaller, single-centre study and the direction of the point estimates was consistent.	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)*		
Marik review: pooled analysis of ARDS OR 2.5 (1.66, 3.34) Gong 2005: ARDS OR 2.19 (1.42, 3.36) Zilberberg 2007: ARDS OR 2.797 (1.899, 4.120) Khan 2007: ARDS/ALI OR 1.39 (0.79, 2.43)	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 Marik review included only trauma/ICU studies in the ARDS analysis. All individual studies included in the review were conducted in a broad critical care population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
All studies carried out in USA	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The Khan study included subjects who may have received FFP and platelets in addition to RBC 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	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	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, RBC transfusion may be independently associated with an increased risk of ARDS or ALI.

Key question(s): In a critical care population, what is the effect of RBC (allogeneic) transfusion vs no transfusion (or different dose) on organ failure?		Evidence matrix: EM1.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level III-2: One study (Ciesla 2005 fair).	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Transfusion dose (12-hr > 6 vs ≤ 6 units) OR 3.40 (2.53, 4.58) 12-hr per unit OR 1.07 (1.05, 1.09)	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 conducted in surgical ICU patients only so may not be generalisable to the broader critical care setting.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Carried out in the US so likely to be applicable to the Australian setting.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, the effect of RBC transfusion on organ failure is uncertain.

Key question(s): In a critical care population, what is the effect of restrictive versus liberal RBC transfusion strategies on mortality?		Evidence matrix: EM1.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II: 5 fair quality publications of two studies (Hebert 1995; Hebert 1999; Hebert 2001; McIntyre 2004; McIntyre 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')*		
Overall critical care population - 2 papers 2 studies; both show no significant difference between restrictive and liberal transfusion Age <55 - 1 RCT only; restrictive transfusion reduces 30-day mortality **APACHEII ≤20** - 1 RCT only; restrictive transfusion reduces 30-day mortality Cardiovascular disease - 2 papers 1 study; both show no significant difference Trauma - 2 papers 1 study; both show no significant difference Closed head injury - 1 paper 1 study; no significant difference Severe infection/septic shock - 1 paper 1 study; 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Age <55 - restrictive transfusion reduces 30-day mortality RD -0.073 (-0.135, -0.011) APACHEII ≤20 - restrictive transfusion reduces 30-day mortality RD -0.074 (-0.136, -0.01) All other subgroups and overall critical care population showed no significant difference.	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	No difference and underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Both studies were conducted in a broad critical care population	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Both studies carried out in Canada	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

According to the power calculations reported by the authors, the Hebert 1999 study is likely to be underpowered.
A lower incidence of mortality was seen in the restrictive transfusion group, but this difference was not statistically significant.

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 and underpowered to detect a difference
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on mortality.

Key question(s): In a critical care population, what is the effect of restrictive versus liberal strategies for RBC (allogeneic) transfusion on organ failure/dysfunction?		Evidence matrix: EM1.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II: 5 fair quality publications of two studies (Hebert 1995; Hebert 1999; Hebert 2001; McIntyre 2004; McIntyre 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')*		
Overall critical care population 2 papers 2 studies; 1 showed no significant difference and 1 showed significant reductions in MOD score with restrictive transfusion. Both found no significant difference in the proportion of subjects with ≥3 organ failures. Age <55 - 1 study; significantly lower MOD score with restrictive **APACHEII ≤20** - 1 RCT only; significantly lower MOD score with restrictive Cardiovascular disease - 2 papers 1 study; no difference in all except change in MOD in patients with cardiovascular disease (1 study). Trauma - 2 papers 1 study; both show no significant difference Closed head injury - 1 paper 1 study; no significant difference Severe infection/septic shock - 1 paper 1 study; 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Overall critical care population Hebert 1999 - MOD score MD -1.1 (- 2.2, -0.08); change from baseline in MOD score MD -1.0 (-2.0, -0.1) No significant difference in the proportion of patients with ≥3 organs failed. Age <55 - significantly lower MOD score with restrictive; p=0.03 **APACHEII ≤20** - significantly lower MOD score with restrictive; p=0.01	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	No difference and underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Both studies were conducted in a broad critical care population	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Both studies carried out in Canada	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

According to the power calculations reported by the authors, the Hebert 1999 study is likely to be underpowered.
A lower incidence of organ failure was seen in the restrictive transfusion group, but this difference was not statistically significant.

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 and underpowered to detect a difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on organ failure and dysfunction.

Key question(s): In a critical care population, what is the effect of restrictive versus liberal strategies for RBC (allogeneic) transfusion on pulmonary AEs?		Evidence matrix: EM1.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II: 1 fair quality publication of one study (Hebert 1999).	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 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)*		
All pulmonary AEs - 1 study; no significant difference; RD -0.037 (-0.097, 0.023) ARDS - 1 study; no significant difference; RD -0.038 (-0.078, 0.002)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	No difference and underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The study was conducted in a broad critical care population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was carried out in Canada.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

According to the power calculations reported by the authors, the Hebert 1999 study is likely to be underpowered.
A lower incidence of ARDS was seen in the restrictive transfusion group, but this difference was not statistically significant.

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 or underpowered to detect a difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on pneumonia and ARDS.

Key question(s): In a critical care population, what is the effect of restrictive versus liberal strategies for RBC (allogeneic) transfusion on infectious AEs?		Evidence matrix: EM1.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II: 3 fair quality publications of one study (Hebert 1999; McIntyre 2004; McIntyre 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 infectious AEs - 3 papers 1 study no significant difference No difference in any of the individual infection types	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 infectious AEs - 3 papers 1 study no significant difference; all infectious AEs RD -0.019 (-0.061, 0.024) Pneumonia - RD 0.003 (-0.051, 0.058) Bacteraemia - RD -0.023 (-0.061, 0.014) Catheter-related sepsis - RD 0.01 (-0.018, 0.038) Septic shock - RD 0.029 (-0.008, 0.067)	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	No difference and underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The study was conducted in a broad critical care population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was carried out in Canada.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

According to the power calculations reported by the authors, the Hebert 1999 study is likely to be underpowered.

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 and underpowered to detect a difference
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on a broad range of infection outcomes.

Recommendation(s) for RBC transfusion in critically ill patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE MATRIX**
In critically ill patients, a restrictive transfusion strategy should be employed.	B	EM1.E, EM1.F, EM1.G, EM1.H

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	
Are there any resource implications associated with implementing this recommendation?	YES	
Ongoing education, monitoring, and feedback of transfusion practice is required		
Will the implementation of this recommendation require changes in the way care is currently organised?		NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	
Cost of developing an implementation program to educate clinical staff		
What could help to facilitate implementation of the recommendation?	YES	NO

D2 Evidence – Question 2

Key question(s): In anaemic patients who are critically ill, what is the effect of ESAs vs no ESAs on mortality?			Evidence matrix: EM2.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
Level I evidence: Zarychanski 2007 (good quality; EPO vs no EPO): Overall (9 trials [2 good, 3 fair, 4 poor]; N=3314), restrictive transfusion studies (3 trials [1 good, 1 fair, 1 poor]; N=1694) Subsequently published Level II evidence: 2 RCTs: Endre 2010 (fair quality; N=162; EPO vs placebo); Nirula 2010 (poor quality; N=16; EPO vs placebo)	Non -trauma	Trauma	
	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')*			
Overall There was no significant heterogeneity (P*het*=0.91; I^2=0). Studies that used a restrictive transfusion protocol There was no significant heterogeneity (P*het*=NR; I^2=0). Trauma studies There was no significant heterogeneity (*Phet*=0.53; I^2=0) Other medical and surgical ICU There was no significant heterogeneity (*Phet*=0.98; I^2=0)	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 in the space below 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*			
Updated meta-analysis for mortality (N=3561): 14.3% vs 16.0%; RR 0.90; 95% CI 0.77, 1.05; no significant difference Mortality for studies that used a restrictive transfusion practice (N=1694; Zarychanski 2007): OR 0.73; 95% CI 0.53, 1.00; favours EPO Mortality for studies that used a liberal transfusion practice (N=1547): RR 0.97 (0.79, 1.19); no difference Mortality for trauma patients (N=1439): RR 0.51 (0.33, 0.80); favours EPO Mortality for burns unit patients (N=40): RR 1.11 (0.17, 7.09); no difference Mortality for long-term acute care patients (N=86): RR 0.52 (0.20, 1.41); no difference Mortality for other ICU patients (N=1927): RR 1.01 (0.85, 1.19); no difference	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?)*			
Overall: one RCT (N=40) in a burns unit population (Still 1995), one RCT (N=86) in long-term acute care patients (Silver 2006), and eight RCTs in mixed (medical and surgical) ICU populations. Restrictive transfusion studies: One RCT (N=86) in long-term acute care patients (Silver 2006) and two RCTs (N=1608) in mixed (medical and surgical) ICU populations	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 health-care context in terms of health services/delivery of care and cultural factors?)*			
Overall: The studies were conducted in the USA (Corwin 1999; Corwin 2002; Corwin 2007; Silver 2006; Still 1995; Nirula 2010), Netherlands (van Iperen 2000), Greece (Georgopoulos 2005), New Zealand (Endre 2010) Restrictive transfusion studies: The studies were conducted in the USA (Corwin 2007, Silver 2006) and Greece (Georgopolous 2005)	A	A	Evidence directly applicable to Australian health-care context
	B	B	Evidence applicable to Australian health-care context with few caveats
	C	C	Evidence probably applicable to Australian health-care context with some caveats
	D	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In the Corwin 2007 study, the definition of liberal vs restrictive was applied in a post hoc analysis; therefore it not possible to make conclusions on influence of transfusion strategy on the effect of EPO on mortality. Recent studies published after the TRICC trial (which are likely to have employed a restrictive transfusion strategy) showed no effect and failed to describe the transfusion strategy used.
The Corwin study also contained a large number of trauma patients. It is difficult to determine how much of the effect on mortality is due to the population or the transfusion strategy.

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	Non-trauma	Trauma	Description
1. Evidence base	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
2. Consistency	A	A	All studies consistent
3. Clinical impact	NA	B	Substantial/no difference
4. Generalisability	A	B	Evidence directly generalisable to target population /Evidence directly generalisable to target population with some caveats
5. Applicability	B	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In a heterogeneous population of critically ill patients, ESAs have no effect on mortality.

In critically ill trauma patients with anaemia, ESAs may be associated with decreased mortality.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; ICU, intensive care unit; MI, myocardial infarction; NR, not reported; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RR, relative risk

Key question(s): In anaemic patients who are critically ill, what is the effect of ESAs vs no ESAs on blood transfusion?				Evidence matrix: EM2.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*				
Level I evidence: Zarychanski 2007 (good quality; EPO vs no EPO): transfusion incidence (7 trials [3 good, 3 fair, 1 poor]; N=3243), transfusion volume (5 trials [3 good; 2 poor]; N=3020) Restrictive transfusion: 3 RCTs [1 good, 1 fair, 1 poor] Trauma:: 2 RCTs [both good] Other ICU: 6 RCTs [2 good, 3 fair, 1 poor]	Restrictive transfusion	Trauma	Non-trauma	
	A	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	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	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	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')*				
Transfusion incidence Overall population: There was substantial heterogeneity (P*het*=NR; I^2=54.7). All studies agreed in direction. Three studies significantly favoured EPO (N=1536) and four studies (N=1707) found no significant difference between treatment arms. Restrictive transfusion practice: Substantial heterogeneity reflecting the differences in study design (*Phet*=0.003; I^2=83%) Liberal transfusion practice: No significant heterogeneity (*Phet*=0.96, I^2=0) Trauma: The two studies (Corwin 2002, Corwin 2007) are mildly heterogeneous (P=0.24; I^2=26), possibly due to differences in RBC transfusion practice Other critical ill: No significant heterogeneity (P=0.34; I^2=12), however the results from Corwin 2002 and Corwin 2007 are not consistent, reflecting differences in transfusion practice. Transfusion volume: Substantial heterogeneity (P*het*=NR; I^2=79.2).	A	A	A	All studies consistent
	B	B	B	Most studies consistent and inconsistency can be explained
	C	C	C	Some inconsistency, reflecting genuine uncertainty around question
	D	D	D	Evidence is inconsistent
	NA	NA	NA	Not applicable (one study only)

3. Clinical impact *(Indicate in the space below 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*				
<u>Incidence of RBC transfusion</u> Overall population (N=3243): 46.3% vs 54.4%; OR 0.73; 95% CI 0.64, 0.84; <u>favours EPO</u> Restrictive transfusion practice (N=1694): RR 0.68; 95% CI 0.43, 1.07; <u>no difference</u> Trauma (N=1423): RR 0.92; 95% CI 0.82, 1.02; <u>no difference</u> Other ICU (N=1734): RR 0.81; 95% CI 0.72, 0.91; <u>favours EPO</u> <u>Volume of RBCs transfused, units</u> Overall population (N=3020): WMD -0.41[b]; 95% CI -0.74, -0.10; <u>Favours EPO</u>	A	A	A	Very large
	B	B	B	Substantial
	C	C	C	Moderate
	D	D	D	Slight/Restricted
	NA	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?)*				
Transfusion incidence: one RCT (N=86) in long-term acute care patients (Silver 2006) and six RCTs (N=3157) in mixed (medical and surgical) ICU populations. Transfusion volume: One RCT (N=86) in long-term acute care patients (Silver 2006) and four RCTs (N=2934) in mixed (medical and surgical) ICU populations.	A	A	A	Evidence directly generalisable to target population
	B	B	B	Evidence directly generalisable to target population with some caveats
	C	C	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	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 health-care context in terms of health services/delivery of care and cultural factors?)*				
Transfusion incidence: The RCTs were conducted in Austria (Gabriel 1998), USA (Corwin 1999; Corwin 2002; Corwin 2007; Silver 2006), Greece (Georgopoulos 2005), and Belgium (Vincent 2006) Transfusion volume: The RCTs were conducted in USA (Corwin 2002; Corwin 2007; Silver 2006) Greece (Georgopoulos 2005), and Netherlands (van Iperen 2000) Results are dependent on local transfusion practices.	A	A	A	Evidence directly applicable to Australian health-care context
	B	B	B	Evidence applicable to Australian health-care context with few caveats
	C	C	C	Evidence probably applicable to Australian health-care context with
	D	D	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*				
The possible reduction in transfusion observed in non trauma patients is most likely related to the choice of transfusion strategy, rather than the effect of ESAs.				

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	Restrictive transfusion	Trauma	Non-trauma	Description
1. Evidence base	B	A	A	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	C	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	NA	NA	C	No difference/no difference/moderate
4. Generalisability	A	A	A	Evidence directly generalisable to target population
5. Applicability	B	B	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In a heterogeneous population of critically ill patients, ESAs do not appear to reduce the incidence of RBC transfusion, when a restrictive transfusion strategy is employed

In critically ill non-trauma patients, the effect of ESAs on the incidence of RBC transfusion is uncertain.

In critically ill trauma patients, ESAs appear to have no effect on the incidence of RBC transfusion.

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; ICU, intensive care unit; NA, not applicable; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; WMD, weighted mean difference

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] This point estimate decrease represents a transfusion savings of less than 0.5 units per patient.

Key question(s): In anaemic patients who are critically ill, what is the effect of ESAs vs no ESAs on thromboembolic events?		Evidence matrix: EM2.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level I evidence: Zarychanski 2007 (good quality; EPO vs no EPO): MI (1 trial [good]; N=1460); stroke (2 trials [1 good, 1 poor]; N=1608); DVT (5 trials [2 good, 1 fair, 2 poor]; N=3110) Subsequently published Level II evidence: DVT: 2 RCTs: Endre 2010 (fair quality, EPO vs placebo, general ICU); Nirula 2010 (poor quality, EPO vs placebo; traumatic brain injury) Pulmonary embolism, stroke, MI, and other thromboembolism: 1 RCT: Endre 2010 (fair quality, EPO vs placebo; general ICU)	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')*		
Thromboembolic events (trauma patients): Substantial heterogeneity[a] (*Phet*=0.11; I^2=62)[b] DVT (overall): No significant heterogeneity[a] (*Phet*=0.29; I^2=19)[b] DVT (restrictive transfusion practice): Substantial heterogeneity[a] (*Phet*=0.14; I^2=55) MI: No significant heterogeneity[a] (*Phet*=0.51; I^2=0)[b] Stroke: Substantial heterogeneity[a] (P*het*=0.06; I^2=72%)[b]	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 in the space below 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*		
DVT (N=3288): RR 1.06; 95% CI 0.69, 1.64; no difference DVT (Corwin 2007; N=1460): RR 1.49; 95% CI 1.02, 2.17; favours no ESA (differs from the results of the other studies due to size, study design, and transfusion practice. Corwin 2007 was restrictive) Stroke (N=1770): RR 0.76; 95% CI 0.41, 1.41; no difference MI (N=1622): RR 0.80; 95% CI 0.05, 13.82; no difference Thromboembolic events (trauma patients; N=1423): RR 1.07 (0.69, 1.65); no difference	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?)*		
MI: The RCTs were in mixed (medical and surgical) ICU populations. Stroke: The RCTs were in mixed (medical and surgical) ICU populations. DVT: One RCT (Still 1995) was in burns unit setting, one RCT (Nirula 2010) was in patients with traumatic head injury, the other RCTs were in mixed (medical and surgical) ICU populations	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
MI: The RCTs were conducted in the USA (Corwin 2007) and New Zealand.(Endre 2010) Stroke: The RCTs were conducted in Greece (Georgopolous 2005) and USA (Corwin 2007). DVT: International (including USA, New Zealand, Greece) Other thromboembolic events (trauma): The RCT was conducted in the USA.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
The RCTs were not powered to detect a significant difference in thromboembolic events. The largest and best quality study (Corwin 2007) demonstrated a significant increase in DVT and a near significant increase in MI. Note henereogeneity when meta-analysing with smaller studies. Also harm in other patient populations.		

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	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In a heterogeneous population of critically ill patients, ESAs may increase the risk of thromboembolic events.

CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; ICU, intensive care unit; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] Calculated for the purpose of this systematic review using Review Manager.

Key question(s): In anaemic patients who are critically ill, what is the effect of iron therapy vs no iron therapy on mortality?		Evidence matrix: EM2.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Pieracci 2009 (poor quality; N=200; oral iron vs placebo); van Iperen 2000 (poor quality; N=24; iron and folic acid vs folic acid 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')*		
The studies agreed in direction and neither study found a significant difference between treatment arms. There was no significant heterogeneity (P=0.46; 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 in the space below 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*		
Meta-analysis (N=224) 10.1% vs 12.2%; RR 0.81; 95% CI 0.39, 1.71; no significant difference	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?)*		
Pieracci 2009 included anaemic patients who are critically ill following surgery. van Iperen 2000 included anaemic patients admitted to ICU.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in the USA (Pieracci 2009) and the Netherlands (van Iperen 2000).	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
The studies were not powered to detect a difference in mortality.		

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	Two level II studies with a high risk of bias
2. Consistency	A	Both studies consistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, the effect of iron therapy on mortality is uncertain.

CI, confidence interval; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, relative risk

Key question(s): In anaemic patients who are critically ill, what is the effect of iron therapy vs no iron therapy on blood transfusion?		Evidence matrix: EM2.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Level II evidence: 2 RCTs: Pieracci 2009 (poor quality; N=200; oral iron vs placebo); van Iperen 2000 (poor quality; N=24; iron and folic acid vs folic acid 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')*		
The results of the studies were inconsistent due to issues with powering and study quality.	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 in the space below 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*		
Incidence of RBC transfusion (Pieracci 2009; N=200): 29.9% vs 44.7%; RR=NR; P=0.03; favours iron therapy Mean (SD) volume of blood transfused, units (van Iperen 2000; N=24): 5 (7) vs 12 (14); MD -7; 95% CI -15.86, 1.86; no significant difference	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?)*		
Pieracci 2009 included anaemic patients who are critically ill following surgery. van Iperen 2000 included anaemic patients admitted to ICU.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in the USA (Pieracci 2009) and the Netherlands (van Iperen 2000).	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Both studies were poor quality and van Iperen 2000 was underpowered. Pieracci 2009 was not blinded, and patients received ESAs at the discretion of the attending physician.		

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	One level II study with a high risk of bias
2. Consistency	D	Evidence is inconsistent
3. Clinical impact	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients, the effect of oral iron therapy on RBC transfusion is uncertain.

CI, confidence interval; MD, mean difference; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RBC, red blood cell; RR, relative risk

Recommendation(s) for the use of ESAs in critically ill patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
ESAs should not be routinely used in critically ill anaemic patients.	B	EM2.A, EM2.B, EM2.C

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?		NO
Are there any resource implications associated with implementing this recommendation?		NO
Will the implementation of this recommendation require changes in the way care is currently organised?		NO
Are the guideline development group aware of any barriers to the implementation of this recommendation		NO
What could help to facilitate implementation of the recommendation?	YES	NO

D3 Evidence – Question 3

Key question(s): In patients with trauma, what is the effect of different FFP transfusion strategies on mortality?		Evidence matrix: EM3.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level III study of good quality (Inaba et al 2010), 1 Level III study of fair quality (Bochicchio et al 2008b) and 2 Level III studies of poor quality (Spinella et al 2008; Watson et al 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')*		
Two studies reported that FFP transfusion was significantly and independently associated with mortality (Bochicchio et al 2008b; Spinella et al 2008). Both Inaba et al (2010) and Watson et al (2009) reported no significant association between FFP transfusion and mortality, although Inaba et al (2010) reported a trend for greater mortality in patients treated with FFP.	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)*		
Bochicchio et al (2008b) found that FFP transfusion was significantly and independently associated with mortality: OR 1.03 (95% CI 1.02, 1.05; P<0.001) Spinella et al 2008) found that FFP transfusion was significantly and independently associated with in-hospital mortality: OR 1.22 (95% CI 1.0, 1.48; P=0.05)	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 included studies examined patients with trauma; however, it should be noted that the study by Spinella et al (2008) looked specifically at combat victims who received one or more units of any blood product, who did not receive massive transfusion, while Watson et al (2009) studies severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Three of the studies were undertaken in US centres are therefore reasonably applicable to the Australian health-care context (Inaba et al 2010; Bochicchio et al 2008b; Watson et al 2009). One study (Spinella et al 2008) was undertaken in a combat support hospital in Iraq.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the 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	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	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, the effect of FFP on mortality is uncertain.

Key question(s): In patients with trauma, what is the effect of different FFP transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level III study of good quality (Inaba et al 2010), 2 Level III studies of fair quality (Bochicchio et al 2008a; Bochicchio et al 2008b) and 1 Level III study of poor quality (Watson et al 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')*		
All 5 studies reported that FFP transfusion was significantly and independently associated with a range transfusion related serious adverse events; however, the individual studies reported different specific types of events.	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)*		
For most adverse outcomes, Inaba et al (2010) reported a trend suggesting greater harm in patients treated with FFP. For overall complications [OR 1.7 (95% CI 1.1, 2.4; P=0.016)] and ARDS [OR 3.0 (95% CI 1.4, 6.2; P=0.004)], this effect was statistically significant. Bochicchio et al (2008a) found that FFP transfusion was significantly and independently associated with VAP: OR 3.34 (95% CI 1.18, 9.43; P=0.23). Bochicchio et al (2008b) found that FFP transfusion was significantly and independently associated with infection: OR 1.02 (95% CI 1.01, 1.04; P<0.001). Watson et al (2009) found that FFP transfusion was significantly and independently associated with ARDS [HR 1.021 (95% CI 1.001, 1.049; P=0.38)] and MOF [OR 1.021 (95% CI 1.002, 1.04; P=0.029)] but not nosocomial infection.	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 included studies examined patients with trauma; however, it should be noted that the study by Bochicchio et al (2008a) focused on patients who also received MV, while Watson et al (2009) studies severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
All four studies were undertaken in US centres are therefore reasonably applicable to the Australian health-care context (Bochicchio et al 2008a; Bochicchio et al 2008b; Watson et al 2009).	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the analysis.

Although all five studies reported that FFP transfusion was significantly and independently associated with a range transfusion related serious adverse events; the individual studies reported different specific types of 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	D	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	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, FFP may be associated with transfusion related serious adverse events.

Key question(s): In non-trauma patients, what is the effect of different FFP transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level III study of poor quality (Sarani et al 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')*		
N/A	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)*		
Sarani et al (2008) found that FFP transfusion was significantly and independently associated with the incidence of infectious complications [OR 1.039 (95% CI 1.013, 1.067; P<0.01)].	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 results of the study are generalisable to patients in a surgical ICU without trauma.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in US centres and is therefore reasonably applicable to the Australian health-care context	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context
Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the 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	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	D	Slight/restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In non-trauma patients, FFP may be associated with transfusion related serious adverse events.

Key question(s): In critically ill elderly patients, what is the effect of different FFP transfusion strategies on mortality?		Evidence matrix: EM3.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 (Dara et al 2005)	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')*		
Not applicable (one study 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Dara et al (2005) did not report a significant association between FFP transfusion and mortality [OR 0.94 (95% CI 0.36, 2.39)].	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The study included patients with abnormal coagulation (INR ≥ 1.5 times normal), with an average age of 70.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in a 24-bed medical ICU in the USA, and is therefore applicable to the Australian health-care context.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the 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	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	Not applicable/no difference/underpowered
4.	Generalisability	B	Evidence directly generalisable to target population with some caveats
5.	Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill elderly patients, the effect of FFP on mortality is uncertain.

Key question(s): In critically ill elderly patients, what is the effect of different FFP transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.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 (Khan et al 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')*		
Not applicable (one study 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Khan et al (2007) found that FFP transfusion was significantly and independently associated with ARDS/ALI: OR 2.48 (95% CI: 1.29, 4.74).	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 included elderly patients admitted to a medical ICU.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in a 24-bed general medical non-cardiac medical ICU (MICU) in the USA.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the 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	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	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill elderly patients, transfusion of FFP may be independently associated with the development of ARDS or ALI.

Key question(s): In patients with traumatic brain injury, what is the effect of different FFP transfusion strategies on mortality?		Evidence matrix: EM3.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II studies of good quality (Etemadrezaie et al 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 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 increase in the risk of mortality in patients treated with FFP (RR 1.83; 95% CI: 1.16, 2.88; p=0.009).	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 is in patients with severe closed head injury, and the results are probably generalisable to this target population.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Since this study was undertaken in Iran, the results are likely to have limited applicability to current Australian clinical practice.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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
1. Consistency	NA	Not applicable (one study only)
2. Clinical impact	B	Substantial
3. Generalisability	A	Evidence directly generalisable to target population
4. Applicability	D	Evidence not applicable to Australian health-care context

EVIDENCE STATEMENT

FFP is not commonly used in Australia for this indication, and the results of this study therefore have limited applicability to the Australian critical care setting. Therefore, no evidence statements have been made in relation to this subpopulation.

Key question(s): In patients with traumatic brain injury, what is the effect of different FFP transfusion strategies on bleeding events?		Evidence matrix: EM3.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level II study of good quality (Etemadrezaie et al 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There was a significantly increased risk of intracerebral haemorrhage in patients treated with FFP compared to normal saline (RR 17.76; 95% CI: 1.06, 298.69). There was no significant benefit associated with FFP treatment for: the development of new lesions, subarachnoid haemorrhage, intraventricular haemorrhage or extraaxial haematoma.	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 is in patients with severe closed head injury, and the results are probably generalisable to this target population. The outcome of intracerebral haemorrhage is probably not generalisable to all bleeding events.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Since this study was undertaken in Iran, the results are likely to have limited applicability to current Australian clinical practice.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	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	D	Evidence not applicable to Australian health-care context

EVIDENCE STATEMENT

FFP is not commonly used in Australia for this indication, and the results of this study therefore have limited applicability to the Australian critical care setting. Therefore, no evidence statements have been made in relation to this subpopulation.

Key question(s): In patients with trauma, what is the effect of different fibrinogen/cryoprecipitate transfusion strategies on mortality?		Evidence matrix: EM3.H
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 (Watson et al 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')*		
N/A	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 did not report a significant association between cryoprecipitate transfusion units and mortality (P=0.828)	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 included severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in seven institutions in the USA and is reasonably applicable to the Australian health-care context.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	Not applicable/no difference/underpowered
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, the effect of cryoprecipitate on mortality is uncertain.

Key question(s): In patients with trauma, what is the effect of different fibrinogen/cryoprecipitate transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.I
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 (Watson et al 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')*		
N/A	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 that an increase in cryoprecipitate transfusion units was independently and significantly associated with MOF [HR 0.956 (95 % CI 0.923–0.989; P=0.01)], but not ARDS or nosocomial infection.	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 included severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in seven institutions in the USA and is reasonably applicable to the Australian health-care context.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, the effect of cryoprecipitate on transfusion related serious adverse events is uncertain.

Key question(s): In patients with trauma, what is the effect of different platelet transfusion strategies on mortality?		Evidence matrix: EM3.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 2 Level III studies of poor quality (Bochicchio et al 2008b; Watson et al 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')*		
Both studies reported no significant association between platelet 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 unknown 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 association between platelet 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?)*		
The included studies examined patients with trauma; however, it should be noted that the study by Watson et al (2009) looked specifically at severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Both studies were undertaken in US centres are therefore reasonably applicable to the Australian health-care context (Bochicchio et al 2008b; Watson et al 2009).	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to platelet transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the 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	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2.	Consistency	A	All studies consistent
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 health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, the effect of platelet transfusion on mortality is uncertain.

Key question(s): In patients with trauma, what is the effect of different platelet transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 3 Level III studies of poor quality (Bochicchio et al 2008a; Bochicchio et al 2008b; Watson et al 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')*		
Only one study reported that platelet transfusion was significantly and independently associated with a range transfusion related serious adverse events (Bochicchio, 2008a); however, it should be noted that the individual studies reported different specific types of events. The other studies reported no significant effect for serious adverse event outcomes.	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)*		
Bochicchio et al (2008a) found that platelet transfusion was significantly and independently associated with VAP: OR 4.19 (95% CI 1.37, 12.83; 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?)*		
The included studies examined patients with trauma; however, it should be noted that the study by Bochicchio et al (2008a) focused on patients who also received MV, while Watson et al (2009) studies severely injured blunt trauma patients with haemorrhagic shock.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
All three studies were undertaken in US centres are therefore reasonably applicable to the Australian health-care context (Bochicchio et al 2008a; Bochicchio et al 2008b; Watson et al 2009).	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to platelet transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the analysis.

There are three poor quality studies with one showing an effect on harms.

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	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients with trauma, the effect of platelet transfusion on transfusion related serious adverse events is uncertain.

Key question(s): In critically ill elderly patients, what is the effect of different platelet transfusion strategies on transfusion related serious adverse events?		Evidence matrix: EM3.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes 1 Level III study (Khan et al 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')*		
N/A	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)*		
Khan et al (2007) found that platelet transfusion was significantly and independently associated with ARDS/ALI: OR 3.89 (95% CI 1.36, 11.52).	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 included critically ill elderly patients admitted to a medical ICU.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The study was undertaken in a 24-bed general medical non-cardiac medical ICU in the USA	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill elderly patients, the effect of platelet transfusion on transfusion related serious adverse events is uncertain.

Recommendation(s) for the use of blood components in critical care patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
No recommendation made for this question.		

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
What could help to facilitate implementation of the recommendation?	YES	NO

D4 Evidence – Question 4

Key question(s): In trauma patients, what is the effect of cell salvage on mortality?		Evidence matrix: EM4.A
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Bowley 2006, Fair) and three Level III studies (Brown 2010, fair; Jurkovich 1984, poor; Ozmen 1992, poor).	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')*		
The studies by Bowley, Brown and Jurkovich found similar mortality rates in patients whose surgery did or did not include cell salvage (Bowley p=1.0, Brown p=0.56, Jurkovich27% vs. 25%). Ozmen 1992 reported a higher mortality rate with cell salvage (10% vs. 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Three studies (Bowley, Brown and Jurkovich) found no difference in mortality rates with cell salvage and one poor quality study (Ozmen) found a higher mortality rate with cell salvage.	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 conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Bowley 2006 was conducted in South Africa. The remaining three studies were conducted in the US.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In the Jurkovich 1984 study the control group had a significantly higher hematocrit at baseline. The Ozmen 1992 study provided very little baseline demographic information, making it difficult to assess whether the two treatment groups were comparable,

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	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In trauma patients, the use of cell salvage does not appear to have an effect on mortality.

Key question(s): In trauma patients, what is the effect of cell salvage on allogeneic transfusion volume?		Evidence matrix: EM4.B
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level II study (Bowley 2006, Fair) and three Level III studies (Brown 2010, fair; Jurkovich 1984, poor; Ozmen 1992, poor).	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')*		
The studies by Bowley and Brown found significant reductions in total allogeneic transfusion volume in patients who received cell salvage (Bowley p=0.008; Brown p<0.001). Jurkovich and Ozmen found that patients who had cell salvage had increased allogeneic 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The Bowley (Level II, good) and Brown (Level III, fair) studies found a significant reduction in allogeneic transfusion volume with cell salvage.	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 conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
Bowley 2006 was conducted in South Africa. The remaining three studies were conducted in the US.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In the Jurkovich 1984 study the control group had a significantly higher hematocrit at baseline. The Ozmen 1992 study provided very little baseline demographic information, making it difficult to assess whether the two treatment groups were comparable.

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	A	Very large
4. Generalisability	C	Evidence not directly generalisable to the target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In trauma patients, use of intra-operative cell salvage reduces allogeneic transfusion volume.

Key question(s): In non-trauma critical care patients, what is the effect of cell salvage on mortality?		Evidence matrix: EM4.C
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes six Level III studies (Alonso-Perez 1999, Poor; Alonso-Perez 2001, Poor; Markovic 2009, Poor; Posacioglu 2002, Poor; Serracino-Inglott 2005, Poor; Tawfick 2008, Poor)	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')*		
Five studies found no significant difference in mortality between cell salvage and no salvage groups, although three studies reported a lower mortality rate with cell salvage. Tawfick 2008 did not report 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Five studies found no significant difference 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?)*		
All six studies examined a population of patients undergoing emergency abdominal aortic aneurysm repair.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in a number of locations including Spain, France, Portugal, United States, Brazil, Chile, Serbia, Turkey, and the United Kingdom.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical impact	D	Slight/restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on mortality is uncertain.

Key question(s): In non-trauma critical care patients, what is the effect of cell salvage on allogeneic transfusion volume?		Evidence matrix: EM4.D
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes four Level III studies (Markovic 2009, Poor; Posacioglu 2002, Poor; Shuhaiber 2003, Poor; Tawfick 2008, Poor)	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 found that patients who had cell salvage had lower mean allogeneic RBC transfusion volume. Posacioglu (2002) found a higher mean RBC transfusion volume with cell salvage.	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)*		
Tawfick 2008 reported a lower mean allogeneic transfusion volume in emergency surgery patients who had cell salvage (6 units) compared to patients who did not have cell salvage (12 units). Markovic reported lower mean total allogeneic RBC transfusion with cell salvage (1890.1 mL ±1186) compared to no cell salvage (2755.9 mL±1265). Posacioglu reported higher mean total allogeneic RBC transfusion with cell salvage (5.8±3.84 units) than without cell salvage (3.63±2.87 units).	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 a population of patients undergoing emergency abdominal aortic aneurysm repair.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in Serbia, Turkey, Ireland and the United Kingdom.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

In Posacioglu (2002) the use of cell salvage depended on the surgeon's preference, availability of the device and rarity of patient's blood type.

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	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	C	Evidence probably applicable to Australian health-care context with some caveats

EVIDENCE STATEMENT

In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, cell salvage may reduce allogeneic transfusion volume.

Key question(s): In non-trauma critical care patients, what is the effect of cell salvage on allogeneic transfusion incidence?		Evidence matrix: EM4.E
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes three Level III studies (Markovic 2009, Poor; Shuhaiber 2003, Poor; Tawfick 2008, Poor)	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')*		
Suhaiber reported that all patients were transfused. Markovic and Tawfic reported lower transfusion rates in patients treated with cell salvage.	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)*		
Markovic and Tawfick reported a very slightly lower RBC and plasma transfusion incidence with cell salvage. Suhaiber reported that all patients were transfused. It is likely that these studies are underpowered to detect a 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?)*		
All studies examined a population of patients undergoing emergency abdominal aortic aneurysm repair.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The studies were conducted in Serbia, Ireland and the United Kingdom.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	NA	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on allogeneic RBC transfusion incidence is uncertain.

Key question(s): In trauma patients, what is the effect of tranexamic acid on mortality?		Evidence matrix: EM4.F
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Roberts 2011, good) that reviews 2 RCTs with 20451 subjects.	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 the overall mortality outcome, the CRASH-2 RCT showed a significant reduction in mortality with TXA. The RCT by Yutthakasemsunt 2010 did not find a significant reduction in mortality with TXA, however the point estimate for the effect favoured TXA treatment. For all other mortality outcomes the data was drawn only from the CRASH-2 RCT.	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)*		
Meta-analysis of data from two RCTs showed a significant reduction in the risk of overall mortality with TXA treatment: RR 0.90 (95% CI 0.85, 0.97). This effect was largely due to differences in mortality from myocardial infarction (RR 0.32; 95% CI 0.14, 0.75) and from bleeding (RR 0.85; 95% CI 0.76, 0.96) in the CRASH-2 study. In the CRASH-2 study if treatment was more than 3 hours after injury there was no effect of TXA on mortality (RR 1.00; 95% CI 0.86, 1.17).	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 RCTs reviewed were conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCTs had subjects from 40 countries including Australia.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

The RCT by Yutthakasemsunt 2010 was only available as an abstract. This study was included as it had been included in the Cochrane review Roberts 2011. It is a small study and only contributes to the overall mortality 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	B	Most studies consistent and inconsistency can be explained
3.	Clinical impact	B	Substantial
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	A	Evidence directly applicable to Australian health-care context

EVIDENCE STATEMENT

In acutely bleeding critically ill trauma patients, treatment with TXA within three hours of injury reduces the risk of mortality.

Key question(s): In trauma patients, what is the effect of tranexamic acid on allogeneic transfusion incidence?		Evidence matrix: EM4.G
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Roberts 2011, good) that reviews 2 RCTs with 20451 subjects.	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')*		
Only one RCT (CRASH-2) reported 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)*		
Data from one RCT (N=20211) showed no significant difference in transfusion incidence with TXA treatment: RR 0.98 (95% CI 0.96, 1.01).	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 CRASH-2 RCT was conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCTs had subjects from 40 countries including Australia.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	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	NA	Not applicable (one study only)
3.	Clinical impact	D	Slight/Restricted
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	A	Evidence directly applicable to Australian health-care context

EVIDENCE STATEMENT

In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion incidence.

Key question(s): In trauma patients, what is the effect of tranexamic acid on allogeneic transfusion volume?		Evidence matrix: EM4.H
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Roberts 2011, good) that reviews 2 RCTs with 20451 subjects.	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')*		
Only one RCT (CRASH-2) reported 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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Data from one RCT (N=20211) showed no significant difference in transfusion volume with TXA treatment: WMD -0.17 units (95% CI -0.39, 0.05)	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 CRASH-2 RCT reviewed were conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCT had subjects from 40 countries including Australia.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	NA	Not applicable (one study only)
3. Clinical impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian health-care context

EVIDENCE STATEMENT

In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion volume.

Key question(s): In trauma patients, what is the effect of tranexamic acid on thromboembolic events?		Evidence matrix: EM4.I
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study (Roberts 2011, good) that reviews 2 RCTs with 20451 subjects.	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')*		
Only one RCT (CRASH-2) reported 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 <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Data from one RCT (N=20211) showed no significant difference in the incidence of all vascular occlusive events (MI, stroke, PE, DVT) with TXA treatment: RR 0.84 (95% CI0.68, 1.02). There was a significant reduction in the risk of MI with TXA treatment: RR 0.64 (95% CI 0.42, 0.97). There was no significant effect on stroke (RR 0.86; 95% CI 0.61, 1.23), PE (RR1.01; 95% CI0.73, 1.41) or DVT (RR 0.98; 95% CI0.63, 1.51).	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 CRASH-2 RCT reviewed were conducted in populations of adult trauma patients.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCT had subjects from 40 countries including Australia.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	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	NA	Not applicable (one study only)
3.	Clinical impact	C	Moderate
4.	Generalisability	A	Evidence directly generalisable to target population
5.	Applicability	A	Evidence directly applicable to Australian health-care context

EVIDENCE STATEMENT

In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on the risk of stroke, pulmonary embolism or deep vein thrombosis, and reduces the incidence of myocardial infarction.

Key question(s): In non-trauma critical care patients, what is the effect of tranexamic acid on mortality?		Evidence matrix: EM4.J
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study: Gluud 2008 (Good, 7 RCTs N=1654)	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')*		
Gluud 2008 reported a significant decrease in all-cause mortality rates in patients with gastrointestinal bleeding treated with TXA: RR 0.61 (95% CI 0.42, 0.89). Six out of seven of the included studies reported a point estimate for the effect that favoured TXA treatment.	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)*		
Gluud 2008 reported a significant decrease in all-cause mortality rates in patients with gastrointestinal bleeding treated with TXA: RR 0.61 (95% CI 0.42, 0.89) .	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 Level I study examined a population with upper gastrointestinal bleeding.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCTs had subjects from various countries. Gluud 2008 included a RCT that had patients from Australia, however a number of these studies were old.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients with upper gastrointestinal bleeding, treatment with TXA may reduce the risk of mortality.

Key question(s): In non-trauma critical care patients, what is the effect of tranexamic acid on allogeneic transfusion incidence?		Evidence matrix: EM4.K
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study: Gluud 2008 (Good, 7 RCTs N=1654)	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 (GI bleeding)
	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')*		
The review reported no significant difference in transfusion incidence in patients treated with or without TXA.	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)*		
Gluud 2008 reported no significant difference in transfusion incidence in patients with gastrointestinal bleeding treated with or without TXA: RR 1.0 (95% CI 0.93, 1.11) Ferrer 2009 reported that no subjects in its' included RCTs 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?)*		
The two Level I studies examined populations with post-partum bleeding and upper gastrointestinal bleeding.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCTs had subjects from various countries. Gluud 2008 included a RCT that had patients from Australia, however a number of these studies were old.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component		Rating	Description
1.	Evidence base	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	A	Evidence directly generalisable to target population
5.	Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients with upper gastrointestinal bleeding, treatment with TXA does not appear to affect allogeneic transfusion incidence.

Key question(s): In non-trauma critical care patients, what is the effect of tranexamic acid on thromboembolic events?		Evidence matrix: EM4.L
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Includes one Level I study: Gluud 2008 (Good, 7 RCTs N=1654)	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')*		
Gluud 2008 reported no significant difference in thromboembolic events in patients with upper GI 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 unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Gluud 2008: upper GI bleeding: MI/PE/Stroke (RR 1.4; 95% CI 0.36, 5.28); DVT (RR 2.3; 95% CI 0.61, 8.94)	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 review examined a population with upper gastrointestinal bleeding.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability *(Is the body of evidence relevant to the Australian health-care context in terms of health services/delivery of care and cultural factors?)*		
The included RCTs had subjects from various countries. Gluud 2008 included a RCT that had patients from Australia, however a number of these studies were old.	A	Evidence directly applicable to Australian health-care context
	B	Evidence applicable to Australian health-care context with few caveats
	C	Evidence probably applicable to Australian health-care context with some caveats
	D	Evidence not applicable to Australian health-care context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	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	Not applicable/no difference/underpowered
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian health-care context with few caveats

EVIDENCE STATEMENT

In critically ill patients with upper gastrointestinal bleeding, the effect of TXA on the risk of thromboembolic events is uncertain.

Recommendation(s) for the use of tranexamic acid in critically ill trauma patients

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
In acutely bleeding, critically ill trauma patients TXA should be administered within 3 hours of injury.	B	EM4.F

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	
Are there any resource implications associated with implementing this recommendation?	YES	
Education training and monitoring		
Will the implementation of this recommendation require changes in the way care is currently organised?		NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	
Cost of pharmaceutical plus costs associated with education training and monitoring		
What could help to facilitate implementation of the recommendation?	YES	NO

Recommendation(s) for the use of tranexamic acid in critically ill patients with GI bleeding

RECOMMENDATION *What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.*	**GRADE**	**RELEVANT EVIDENCE TABLE**
In critically ill patients with upper GI bleeding consider the use of TXA.	C	EM4.J

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	
Are there any resource implications associated with implementing this recommendation?	YES	
Education training and monitoring		
Will the implementation of this recommendation require changes in the way care is currently organised?		NO
Are the guideline development group aware of any barriers to the implementation of this recommendation	YES	NO
Cost of pharmaceutical plus costs associated with education training and monitoring		
What could help to facilitate implementation of the 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 developed for Phase II 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

Transfusion vs. no transfusion (or different doses)

Level III evidence

Study type	Systematic review	
Citation	Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008 Sep;36(9):2667-74.	
Rating	Quality criteria	Error rating[b]
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Some	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Some	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
Y	Was a test for heterogeneity applied?	III-IV
Y	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	Search terms were quite brief. No quality assessment or explanation of populations.	
Quality rating	*Fair*	

Study type:				Cohort study	
Citation:				Agarwal N, Murphy JG, Cayten G, Stahl WM (1993) Blood transfusion increases the risk of infection after trauma. Arch Surg 128: 171-177.	
Y	N	NR	NA	Quality criteria	
				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:				5434 eligible for inclusion but 67 excluded for missing data on some element of the Revised Trauma Score and 1 excluded for missing units of transfusion data; infection identified via ICD-9-CM codes (no inter-rater reliability tested for measurement of outcome between multiple nurse-abstractors); stepwise logistic regression used to identify significant predictors to include in the multivariable model.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Bochicchio GV, Napolitano L, Joshi M, Bochicchio K, Meyer W, Scalea TM (2008) Outcome analysis of blood product transfusion in trauma patients: a prospective, risk-adjusted study. World J Surg 32: 2185-2189.	
Y	N	NR	NA	Quality criteria	
				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:				1172 consecutive patients included; CDC definitions used to diagnose infection; adjusted for a number of potential confounders.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A (2005) A 12-year prospective study of post-injury organ failure. Archives of Surgery 140: 432-440.Jul;68(7):566-72.	
Y	N	NR	NA	Quality criteria	
				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:				Included data from 1344 patients collected over a 12-year period; year and a number of other variables adjusted for in the analysis; no details on how many patients not included in/excluded from the analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg. 2002 Jul;68(7):566-72.	
Y	N	NR	NA	Quality criteria	
				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:				Two groups were not matched. The transfused patients were significantly older (p=0.003), had significantly more men (p=0.037) and had nearly double the ISS scores of the non-transfused group (P<0.0001). Analysis is stratified but no multivariate analysis for transfused vs. not transfused for mortality. Multivariate analysis for infection outcome only.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. Crit Care Med. 2004 Jan;32(1):39-52.	
Y	N	NR	NA	Quality criteria	
				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:				No presentation of baseline characteristics in transfused vs. not transfused groups. No reporting of how many patients were excluded or lost to follow-up. An additional analysis was performed in which patients were matched by propensity score.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Duane TM, Mayglothling J, Grandhi R et al (2008) The effect of anemia and blood transfusions on mortality in closed head injury patients. Journal of Surgical Research 147: 163-167.	
Y	N	NR	NA	Quality criteria	
				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
✓ Mortality	✓ Infection			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 cohort study; little information given in methodology section; unclear whether both mortality and infection analyses adjusted for the same variables.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Dunne JR, Malone DL, Tracy JK, Napolitano LM. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt). 2004 Winter;5(4):395-404.	
Y	N	NR	NA	Quality criteria	
				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]				Fair	

Study type:				Cohort study	
Citation:				Engoren M, Arslanian-Engoren C. Long-term survival in the intensive care unit after erythrocyte blood transfusion. Am J Crit Care. 2009 Mar;18(2):124-31.	
Y	N	NR	NA	Quality criteria	
				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:				Cohort study of ICU patients at a single medical centre. Multivariate analysis of mortality at a number of time points after admission.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med. 2005 Jun;33(6):1191-8.	
Y	N	NR	NA	Quality criteria	
				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:				Prospective cohort study using multiple logistic regression model. Patients screened and included quite well described and assessors blinded	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, Blajchman M, Schweitzer I, Pagliarello G. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. Am J Respir Crit Care Med. 1997 May;155(5):1618-23.	
Y	N	NR	NA	Quality criteria	
				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:				Combined retrospective and prospective cohort analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest. 2007 May;131(5):1308-14.	
Y	N	NR	NA	Quality criteria	
				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 risk of ALI/ARDS was higher in patients who had received platelets and FFP than in those who received only RBCs.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A et al (2001) Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 119: 1461-1468.	
Y	N	NR	NA	Quality criteria	
				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:				Prospective cohort study; patients excluded if they had infection prior to transfusion; a large number of potential confounders assessed; follow-up appears to be during hospitalisation.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma. 2003 May;54(5):898-905; discussion 905-7.	
Y	N	NR	NA	Quality criteria	
				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:				Large cohort study performed at a single centre. Study uses multiple logistic regression analysis to adjust for confounding variables.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Müller MH, Moubarak P, Wolf H et al (2008) Independent determinants of early death in critically ill surgical patients. Shock 30(1): 11-16.	
Y	N	NR	NA	Quality criteria	
				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 cohort study; no details on amount of missing data; adjusted for a number of potential confounders including interactions; 4-day follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Palmieri TL, Caruso DM, Foster KN et al (2006) Effect of blood transfusion on outcome after major burn injury: a multicenter study. Critical Care Medicine 34(6): 1602-1607.	
Y	N	NR	NA	Quality criteria	
				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:				Data collected for 666 patients; 46 excluded from analysis as they dies within the first 24 hours after admission; excluded patients older and had sustained massive, unsurvivable burns; survival analysis adjusted for a number of potential confounders – not clear if these were also included in the infection analysis; no adjustment for Hb/Hct or organ failure.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Rachoin JS, Daher R, Schorr C, Milcarek B, Parrillo JE, Gerber DR. Microbiology, time course and clinical characteristics of infection in critically ill patients receiving packed red blood cell transfusion. Vox Sang. 2009 Nov;97(4):294-302.	
Y	N	NR	NA	Quality criteria	
				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 had a nosocomial infection prior to or less than 24 h following their first transfusion and were considered as non-transfused for the purpose of the analysis.	
Quality rating: [Good/Fair/Poor]				Fair	

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Study type:				Cohort study	
Citation:				Rüttinger D, Wolf H, Küchenhoff H, Jauch KW, Hartl WH. Red cell transfusion: an essential factor for patient prognosis in surgical critical illness? Shock. 2007 Aug;28(2):165-71.	
Y	N	NR	NA	Quality criteria	
				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:				Large 12-year retrospective cohort study of surgical ICU patients from a single centre in Germany.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Salim A, Hadjizacharia P, DuBose J, Brown C, Inaba K, Chan L, Margulies DR. Role of anemia in traumatic brain injury. J Am Coll Surg. 2008 Sep;207(3):398-406.	
Y	N	NR	NA	Quality criteria	
				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:				Large cohort study that used logistic regression to analyse results. The raw data was presented in a slightly confusing way but the results of the regression analysis were clear.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Shorr AF, Duh MS, Kelly KM, Kollef MH; CRIT Study Group. Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med. 2004 Mar;32(3):666-74.	
Y	N	NR	NA	Quality criteria	
				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:				Subgroup analysis of VAP in patients requiring mechanical ventilation from the CRIT study	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Spinella PC, Perkins JG, Grathwohl KW et al (2008) Effects of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. Journal of Trauma 64: S69-S78.	
Y	N	NR	NA	Quality criteria	
				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 cohort study; included 567/708 transfused patients (excluded those with massive transfusion); adjusted for a number of potential confounders including GCS and Hct.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. JAMA. 2002 Sep 25;288(12):1499-507.	
Y	N	NR	NA	Quality criteria	
				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:				Not much explanation of how missing data was handled.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology. 2008 Jan;108(1):31-9.	
Y	N	NR	NA	Quality criteria	
				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:				Large multicentre cohort study of ICU patients admitted during a 2-week time period.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Zilberberg MD, Carter C, Lefebvre P, Raut M, Vekeman F, Duh MS, Shorr AF. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care. 2007;11(3):R63.	
Y	N	NR	NA	Quality criteria	
				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:				Subgroup analysis of the CRIT study (Corwin) No presentation of baseline characteristics in transfused vs. not transfused groups. No reporting of how many patients were excluded or lost to follow-up.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Zilberberg MD, Stern LS, Wiederkehr DP, Doyle JJ, Shorr AF. Anemia, transfusions and hospital outcomes among critically ill patients on prolonged acute mechanical ventilation: a retrospective cohort study. Crit Care. 2008;12(2):R60.	
Y	N	NR	NA	Quality criteria	
				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]				Fair	

Restrictive vs. liberal RBC transfusion: Critical Care/Trauma

Level I evidence

Study type	Systematic review	
Citation	Kramer AH, Zygun DA. Anemia and red blood cell transfusion in neurocritical care. Crit Care. 2009;13(3):R89.	
Rating[a]	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
N	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
NR	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
N	Was the quality of the studies reported?	III
N	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Some	Were the characteristics of the individual studies reported?	II-III
N	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
NA	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
NA	Was a test for heterogeneity applied?	III-IV
NA	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	No meta-analysis of data. The search terms were minimal and may not have captured all the literature.	
Quality rating	Poor	

Level II

Study type:				Randomised controlled trial	
Citation:				Hébert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, Blajchman M. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group. JAMA. 1995 May 10;273(18):1439-44.	
Y	N	NR	NA	Quality criteria	
				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:				Not blinded, but outcome assessment not affected by this; small pilot study underpowered to show non-inferiority.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17.	
Y	N	NR	NA	Quality criteria	
				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; open-label but objective outcome; underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Hébert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001 Feb;29(2):227-34.	
Y	N	NR	NA	Quality criteria	
				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:				Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.	
Quality rating: [Good/Fair/Poor]				Fair	

				Study type:	Randomised controlled trial
				Citation:	McIntyre L, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, Blajchman MJ; Canadian Critical Care Trials Group. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? J Trauma. 2004 Sep;57(3):563-8; discussion 568.
Y	N	NR	NA	Quality criteria	
				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:	Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.
				Quality rating: [Good/Fair/Poor]	Fair

			Study type:	Randomised controlled trial	
			Citation:	McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, Hare GM, Hébert PC. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocrit Care. 2006;5(1):4-9.	
Y	N	NR	NA	Quality criteria	
				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:	Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.	
			Quality rating: [Good/Fair/Poor]	Fair	

Restrictive vs. liberal RBC transfusion: Mixed/General Population

Level I evidence

Study type	Systematic review	
Citation	Carless et al (2010) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD002042. DOI: 10.1002/14651858.CD002042.pub2.	
Rating	Quality criteria	Error rating
	A. Was an adequate search strategy used?	
Y	Was a systematic search strategy reported?	I
Y	Were the databases searched reported?	III
Y	Was more than one database searched?	III
Y	Were search terms reported?	IV
Y	Did the literature search include hand searching?	IV
	B. Were the inclusion criteria appropriate and applied in an unbiased way?	
Y	Were inclusion/exclusion criteria reported?	II
Y	Was the inclusion criteria applied in an unbiased way?	III
Y	Was only the appropriate study type included?	I-IV
	C. Was a quality assessment of included studies undertaken?	
Y	Was the quality of the studies reported?	III
Y	Was a clear, pre-determined strategy used to assess study quality?	IV
	D. Were the characteristics and results of the individual studies appropriately summarised?	
Y	Were the characteristics of the individual studies reported?	II-III
Y	Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
Y	Were the results of the individual studies reported?	III
	E. Were the methods for pooling the data appropriate?	
Y	If appropriate, was a meta-analysis conducted?	III-IV
	F. Were the sources of heterogeneity explored?	
Y	Was a test for heterogeneity applied?	III-IV
Y	If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments	*Thorough literature search conducted; included RCTs only; quality of studies assessed; individual study results reported; meta-analysis conducted including all studies; heterogeneity assessed and discussed.*	
Quality rating	*Good*	

E2 Quality analysis – Question 2

ESAs

Level I evidence

Study type:				Systematic review	
Citation:				Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA. (2007) Erythropoietin-receptor agonist in critically ill patients: a meta-analysis of randomized controlled trails. CMAJ 177(7):725-34.	
Y	N	NR	NA	Quality criteria	
				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?	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?	IV
		✓		• If there was heterogeneity, was this discussed or the reasons explored?	IV
Comments:				No test for heterogeneity was applied, but there was sufficient detail provided to calculate using Review Manager	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Two good (Corwin 2007; Corwin 2002); fair (Corwin 1999; Silver 2006; Vincent 2006); poor (Still 1995; Gabriel 1998; van Iperen 2000; Georgopoulos 2005)	

Study type:				Systematic review	
Citation:				Turaga KJ, Sugimoto JT, Forse RA. (2007) A meta-analysis of randomized controlled trials in critically ill patients to evaluate the dose-response effect of erythropoietin. Journal of Intensive Care Medicine 22(5): 270-82.	
Y	N	NR	NA	Quality criteria	
				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?	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 included double counting	
Quality rating: [Good/Fair/Poor]				Systematic review: poor	
				Included studies:	

Study type:				Systematic review	
Citation:				Napolitano LM, Fabian TC, Kelly KM, Bailey JA, Block EF, Langholff W, Enny C, Corwin HL.(2008) Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. Journal of Trauma Injury, Infection, and Critical Care 65:285-299.	
Y	N	N R	N A	Quality criteria	
				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?	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:				Although not technically a systematic review, this study was included as it supplied a sub-group meta-analysis that was not otherwise available.	
Quality rating: [Good/Fair/Poor]				Systematic review: fair	
				Included studies: Corwin 2002 and Corwin 2007	

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ, Hutchison R, Mehrtens JE, Robinson JM, Schollum JBW, Westhuyzen J, Celi LA, McGinley RJ, Campbell IJ, George PM. (2010) Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney International 77:1020-30.	
Y	N	NR	NA	Quality criteria	
				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:				Concealment was by pharmacist More patients in the placebo group (n=31, 40%) had acute kidney injury on randomization as compared with that in the EPO group (n=23, 27%), according to the Acute Injury Network (AKIN) creatinine changes criteria (not significant). The EPO group patients were older (P=0.011); less likely to have had neurological surgery, injury or seizure or intracranial haemorrhage (P<0.05); and more likely to have had sepsis (P<0.05)	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Randomised controlled trial	
Citation:				Nirula R, Diaz-Arrastia R, Brasel K, Weigelt JA, Waxman K. (2010) Safety and efficacy of erythropoietin in traumatic brain injury patients: a pilot randomized trial. Critical Care Research and Practice doi:10.1155/2010/209848.	
Y	N	NR	NA	Quality criteria	
				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:				30.4% loss to follow-up. Length of follow-up for mortality NR.	
Quality rating: [Good/Fair/Poor]				Poor	

Iron therapy

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Pieracci FM, Henderson P, Rocco J, Rodney M,Holena DN, Genisca A, Ip I, Steven Benkert S, Hydo LJ, Eachempati SR, Shou J, Barie PS (2009) Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. Surgical Infection 10 (1): 9-19.	
Y	N	NR	NA	Quality criteria	
				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?	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:				All involved parties with the exception of the investigational pharmacist were blinded to the identity of the study drug. Trends were observed toward a greater likelihood of RBC transfusion prior to enrolment in the placebo group than the iron group (18.6% vs. 9.3%, respectively; p ——————————— 0.06), as well as a larger quantity of RBCs received prior to enrolment in the placebo than the iron group (mean 303 mL vs. 135 mL, respectively; p = 0.07). Outcomes that occurred after hospital discharge were not reported	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Randomised controlled trial	
Citation:				van Iperen CE, Gaillard CAJ, Kraaigenhagen RJ, Braam BG, Marx JJM, van de Wiel A. (2000) Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Car Med 28:2773-2778.	
Y	N	NR	NA	Quality criteria	
				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?	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:				P<0.05 for comparison between control and iron groups and control and EPO groups for length of stay in ICU.	
Quality rating: [Good/Fair/Poor]				Poor	

E3 Quality analysis – Question 3

FFP transfusion strategies for patients with trauma

Level III evidence

Study type:				Cohort study	
Citation:				Inaba K, Branco BC, Rhee P, Blackbourne LH, Holcomb JB, Teixeira PG, Shulman I, Nelson J, Demetriades D. Impact of plasma transfusion in trauma patients who do not require massive transfusion. J Am Coll Surg. 2010 Jun;210(6):957-65.	
Y	N	NR	NA	Quality criteria	
				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:				Some patients in the non-plasma group therefore received plasma, but not in the first 12 hours of admission.	
Quality rating: [Good/Fair/Poor]				Good	

Study type:				Cohort study	
Citation:				Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Shih, D., Meyer, W., & Scalea, T. M. 2008a, Blood product transfusion and ventilator-associated pneumonia in trauma patients, Surgical Infections, vol. 9, no. 4, pp. 415-422.	
Y	N	NR	NA	Quality criteria	
				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 number of patients with VAP was small (n = 26). The analysis did not adjust for other potential risk factors for pneumonia; e.g. brain injury or brain Abbreviated Injury Score (AIS), chest injury or chest AIS, aspiration of gastric contents, or enteral vs. parenteral nutrition.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Meyer, W., & Scalea, T. M. 2008b, Outcome analysis of blood product transfusion in trauma patients: A prospective, risk-adjusted study, World Journal of Surgery, vol. 32, no. 10, pp. 2185-2189.	
Y	N	NR	NA	Quality criteria	
				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:				There is a dose dependent correlation between blood product transfusion (PRBCs, FFP) and adverse outcome (mortality, infection) in critically ill trauma patients after appropriate stratification for all other variables that affect trauma outcome.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Spinella, P. C., Perkins, J. G., Grathwohl, K. W., Beekley, A. C., Niles, S. E., McLaughlin, D. F., Wade, C. E., & Holcomb, J. B. 2008, Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries, The Journal of trauma, vol. 64, no. 2 Suppl, p. S69-S77.	
Y	N	NR	NA	Quality criteria	
				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:				This retrospective study is the first to indicate that the amount of plasma transfused to patients with traumatic injuries who require any amount of blood products is independently associated with improved in-hospital survival. A subset analysis of patients who did not require a massive transfusion also indicated an independent association between the amount of plasma transfused and survival. In the overall population, primary surgical procedures were recorded for 647 patients. The most common procedures required for these 647 patients who required blood products were celiotomy 31%, craniectomy 16%, vascular repair 13%, and skeletal fixation 11%.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Watson, G. A., Sperry, J. L., Rosengart, M. R., Minei, J. P., Harbrecht, B. G., Moore, E. E., Cuschieri, J., Maier, R. V., Billiar, T. R., & Peitzman, A. B. 2009, Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome, Journal of Trauma - Injury, Infection and Critical Care, vol. 67, no. 2, pp. 221-227.	
Y	N	NR	NA	Quality criteria	
				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 population includes some patients who received massive transfusion.	
Quality rating: [Good/Fair/Poor]				Poor	

FFP transfusion strategies for non-trauma patients

Level III evidence

Study type:				Cohort study	
Citation:				Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med. 2008 36(4):1114-8	
Y	N	NR	NA	Quality criteria	
				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:				Study excluded non trauma patients. Only four variables were included in the multivariate analysis.	
Quality rating: [Good/Fair/Poor]				Poor	

FFP transfusion strategies for critically ill elderly patients

Level III evidence

Study type:				Cohort study	
Citation:				Dara, S. I., Rana, R., Afessa, B., Moore, S. B., & Gajic, O. 2005, Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy, Critical Care Medicine, vol. 33, no. 11, pp. 2667-2671.	
Y	N	NR	NA	Quality criteria	
				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:				Of relevance, patients in whom international normalized ratio was corrected received a larger dose (median, 17 mL/kg) than those who failed to correct (median, 10 mL/kg). In this sample, the rate of new bleeding episodes was uncommon and did not differ between the groups that did and did not receive prophylactic FFP transfusions. The use of FFP was associated with the development of acute lung injury, however this outcome was not analysed using logistic regression.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Khan, H., Belsher, J., Yilmaz, M., Afessa, B., Winters, J. L., Moore, S. B., Huhmayr, R. D., & Gajic, O. 2007, Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients, Chest, vol. 131, no. 5, pp. 1308-1314.	
Y	N	NR	NA	Quality criteria	
				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 risk of ALI/ARDS was higher in patients who had received platelets and FFP than in those who received only RBCs.	
Quality rating: [Good/Fair/Poor]				Good	

FFP transfusion strategies for patients with traumatic brain injury

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Etemadrezaie H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B. The effect of fresh frozen plasma in severe closed head injury. Clin Neurol Neurosurg 2007; 109:166-71.	
Y	N	NR	NA	Quality criteria	
				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 was a relatively large, well-reported and well-designed study.	
Quality rating: [Good/Fair/Poor]				Good	

E7 Analysis – Question 4

Cell Salavge

Level II evidence

Study type:				Randomised controlled trial	
Citation:				Bowley DM, Barker P, Boffard KD (2006) Intraoperative blood salvage in penetrating abdominal trauma: A randomised, controlled trial. World J Surg 30(6):1074-80.	
Y	N	NR	NA	Quality criteria	
				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:				A RCT of intraoperative cell salvage compared to allogenic transfusion in 44 abdominal trauma patients. Length of follow-up was not reported. The study may not be sufficiently powered to detect differences in survival, as the primary outcome was transfusion volume. Blinding was not reported, and it is assumed that the trial was not blinded due to the differences in the surgical procedures in the two groups.	
Quality rating:				Fair	

Level III studies

Study type:				Cohort study	
Citation:				Alonso-Perez M, Segura RJ, Pita S, Cal L (1999) Surgical treatment of ruptured abdominal aortic aneurysms in the elderly. Ann Vasc Surg 13(6):592-8.	
Y	N	NR	NA	Quality criteria	
				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 data for the cell salvage and non-cell salvage groups was not given.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Alonso-Perez M, Segura RJ, Sanchez J, Sicard G, Barreiro A, Garcia M, Diaz P, Barral X, Cairols MA, Hernandez E, Moreira A, Bonamigo TP, Llagostera S, Matas M, Allegue N, Kramer AH, Mertens R (2001) Factors increasing the mortality rate for patients with ruptured abdominal aortic aneurysms. Ann Vasc Surg 15(6):601-7.	
Y	N	NR	NA	Quality criteria	
				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 data for the cell salvage and non-cell salvage groups was not given.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Brown CVR, Foulkrod KH, Sadler HT, Richards EK, Biggan DP, Czysz C, Manuel T (2010) Autologous blood transfusion during emergency trauma operations. Arch Surg 145(7):690-4.	
Y	N	NR	NA	Quality criteria	
				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 matched cohort study of 94 trauma patients undergoing emergency surgery for trauma. 47 patients had intraoperative cell salvage and 47 patients did not. For the blood loss outcome the data for the control group was estimated, not measured.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Jurkovich GJ, Moore EE, Medina G. Autotransfusion in trauma. A pragmatic analysis. Am J Surg; 1984; 148(6):782-785	
Y	N	NR	NA	Quality criteria	
				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 cohort study of 85 adult trauma patients undergoing emergency surgery. 22 patients had surgery with cell salvage. 63 patients did not receive cell salvage due to inadequate blood retrieval, contamination or death. Blood loss was estimated, not measured.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Markovic M, Davidovic L, Savic N, Sindjelic R, Ille T, Dragas M (2009) Intraoperative cell salvage versus allogeneic transfusion during abdominal aortic surgery: Clinical and financial outcomes. Vascular 17(2):83-92.	
Y	N	NR	NA	Quality criteria	
				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:				Historically controlled cohort study of 180 patients having surgery with or without cell salvage. 60 patients had ruptured abdominal aortic aneurysm. Univariate analysis only	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Ozmen, V; McSwain, NE; Nichols, RL; Smith, J; Flint, LM. Autotransfusion of Potentially Culture-Positive Blood (CPB) in Abdominal Trauma: Preliminary Data from a Prospective Study. Journal of Trauma-Injury Infection & Critical Care. 32(1):36-39, January 1992.	
Y	N	NR	NA	Quality criteria	
				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 cohort study of 85 adult abdominal trauma patients undergoing surgery with or without cell salvage. Very little of baseline demographic provided.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Posacioğlu H, Apaydin A, Calkavur T, Uç H.(2002) Adverse effects of cell saver in patients undergoing ruptured abdominal aortic aneurysm repair. Ann Vasc Surg. 2002 Jul;16(4):450-5	
Y	N	NR	NA	Quality criteria	
				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:				Allocation to study arm was by surgeon's preference, availability of the device and rarity of patient's blood type. Follow-up length not reported.	
Quality rating: [Good/Fair/Poor]				Fair	

Study type:				Cohort study	
Citation:				Serracino-Inglott F, Awad S, Barclay A, Nasim A (2005) The use of a cell saver during repair of ruptured abdominal aortic aneurysms increases early survival. Ann R Coll Surg Engl 87(6):475.	
Y	N	NR	NA	Quality criteria	
				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:				Cohort study of 154 patients undergoing surgery with or without cell salvage for ruptured abdominal aortic aneurysm. Short report in a journal technical section. Poor reporting of transfusion volume and survival data.	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Shuhaiber JH, Whitehead SM (2003) The impact of introducing an autologous intraoperative transfusion device to a community hospital. Ann Vasc Surg 17(4):424-9.	
Y	N	NR	NA	Quality criteria	
				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:				Some parts of blood loss were estimated	
Quality rating: [Good/Fair/Poor]				Poor	

Study type:				Cohort study	
Citation:				Tawfick WA, O'Connor M, Hynes N, Sultan S (2008) Implementation of the Continuous AutoTransfusion System (C.A.T.S) in open abdominal aortic aneurysm repair: An observational comparative cohort study. Vasc Endovasc Surg 42(1):32-9.	
Y	N	NR	NA	Quality criteria	
				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 cohort study of 187 patients undergoing abdominal aortic aneurysm repair, including 55 patients who underwent emergency surgery. Length of follow-up and loss to follow-up were not reported. Control patients were significantly younger (mean difference 3 years, p=0.010).	
Quality rating: [Good/Fair/Poor]				Fair	

Tranexamic acid

Level I evidence

Study type:				Systematic review	
Citation:				Gluud LL, Klingenberg SL, Langholz SE (2008) Systematic review: Tranexamic acid for upper gastrointestinal bleeding. Aliment Pharmacol Ther 27(9):752-8.	
Y	N	NR	NA	Quality criteria	
				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?	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 strategy was published as a protocol in the Cochrane Library, reference given in text but detailed terms not written up in the article.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: 7 RCTs of good to poor quality	

Study type:				Systematic review	
Citation:				Roberts I, Shakur H, Ker K, Coats T, -on-behalf-of-the-CRASH- (2011) Antifibrinolytic drugs for acute traumatic injury. Roberts Ian, Shakur Haleema , Ker Katharine , Coats Tim , on behalf of the CRASH 2 Trial collaborators Antifibrinolytic drugs for acute traumatic injury Cochrane Database of Systematic Reviews: Reviews 2011 Issue 1 John Wiley & Sons , Ltd Chichester, UK.	
Y	N	NR	NA	Quality criteria	
				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?	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:				Subjects' baseline demographics not provided.	
Quality rating: [Good/Fair/Poor]				Systematic review: Good	
				Included studies: Tranexamic acid: 1 Good quality RCT, 1 Fair quality RCT	

Appendix F Evidence summaries

F1 Evidence summaries – Question 1

Transfusion vs. no transfusion (or different doses)

Level III evidence

STUDY DETAILS: SR/MA				
Citation				
Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008 Sep;36(9):2667-74.				
Affiliation/Source of funds				
Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University, Philadelphia, PA; Section of Critical Care Medicine, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH. Dr. Corwin is a consultant, has received research support, and is a speaker for Ortho Biotech and Johnson and Johnson PRD. Ortho Biotech and Johnson and Johnson manufacture and distribute Procrit®. Dr. Marik has not disclosed any potential conflicts of interest.				
Study design	Level of evidence	Location/setting		
Systematic review of Level III studies	Level I/III	Various		
Intervention/risk factor	Comparator			
RBC transfusion	No transfusion			
Population characteristics				
Forty-five observational studies of high-risk hospitalized patients with a median of 687 patients/study (range, 63–78,974) were analysed. The studies included trauma, general surgery, cardiac surgery, and neurosurgery, orthopaedic, cardiac, and general ICU patients.				
Length of follow-up	Outcomes measured			
Various	Mortality, infections, multiorgan dysfunction syndrome, and acute respiratory distress syndrome.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Fair Systematic review of observational studies that used multivariate analysis to assess the risk of mortality, infection, ARDS or MODS. No assessment of the quality of the included studies and no baseline demographics or details about the population of individual studies.				
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)
Mortality Pooled analysis 14 studies	NR	NR	OR 1.69 (1.46, 1.92)	Blood transfusion is significantly associated with <u>increased</u> mortality P=NR

Infectious complications Pooled analysis 9 studies	NR	NR	OR 1.88 (1.52, 2.24)	Blood transfusion is significantly associated with increased infectious complications P=NR
ARDS Pooled analysis 6 studies	NR	NR	OR 2.5 (1.66, 3.34)	Blood transfusion is significantly associated with increased ARDS P=NR
ACS				
Mortality Wu 2001 HCT>36 N=NR *Retrospective cohort*	NR	NR	OR 1.38 (1.05, 1.80)	*RBC transfusion is associated with an increased risk of mortality in patients with ACS and HCT>36.* *P=NR*
Mortality Wu 2001 HCT<33 N=NR *Prospective cohort*	NR	NR	OR 0.6 (0.47, 0.76)	*RBC transfusion is associated with a decreased risk of mortality in patients with ACS <33.* *P=NR*
Mortality Rao 2004 N=24,112 *Prospective cohort*	NR	NR	OR 3.94 (3.26, 4.75)	*RBC transfusion is associated with an increased risk of mortality in patients with ACS.* *P=NR*
Mortality Yang 2005 N=74,271			OR 1.67 (1.48, 1.88)	*RBC transfusion is associated with an increased risk of mortality in patients with ACS.* *P=NR*
Trauma				
Outcome No. trials (No. patients)	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality Malone 2003 N=15,534 *Prospective cohort*	NR	NR	OR 2.83 (1.82, 4.42)	*RBC transfusion is associated with an increased risk of mortality in trauma patients.* *P=NR*
Mortality Dunne 2004 N=9539 *Prospective cohort*	NR	NR	OR 4.23 (3.07, 5.84)	*RBC transfusion is associated with an increased risk of mortality in trauma patients.* *P=NR*

Mortality Silverboard 2005 N=102 *Prospective cohort*	NR	NR	OR 1.08 (1.04, 1.15)	*RBC transfusion is associated with an increased risk of mortality in trauma patients.* *P=NR*
Mortality Croce 2005 N=9126 *Prospective cohort*	NR	NR	OR 2.46 (2.0, 3.2)	*RBC transfusion is associated with an increased risk of mortality in trauma patients.* *P=NR*
Infectious complications Edna 1992 N=484 *Retrospective cohort*	NR	NR	OR 1.60 (0.70, 3.70)	*RBC transfusion is not associated with an increased risk of infection in trauma patients.* *P=NR*
Infectious complications Croce 2005 N=9126 *Prospective cohort*	NR	NR	OR 2.94 (2.04, 4.20)	*RBC transfusion is associated with an increased risk of infection in trauma patients.* *P=NR*
ARDS Silverboard 2005 N=102 *Prospective cohort*	NR	NR	OR 14.4 (3.2, 78.7)	*RBC transfusion is associated with an increased risk of ARDS in trauma patients.* *P=NR*
ARDS Croce 2005 N=9126 *Prospective cohort*	NR	NR	OR 3.42 (2.02, 34.2)	*RBC transfusion is associated with an increased risk of ARDS in trauma patients.* *P=NR*
ICU				
Outcome No. trials (No. patients)	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality Vincent 2002 N=1136 *Prospective cohort*	NR	NR	OR 1.37 (1.02, 1.84)	*RBC transfusion is associated with an increased risk of mortality in ICU patients.* *P=NR*
Mortality Corwin 2004 N=4892 *Prospective cohort*	NR	NR	OR 1.48 (1.07, 2.05)	*RBC transfusion is associated with an increased risk of mortality in ICU patients.* *P=NR*

Mortality Gong 2005 N=688 *Prospective cohort*	NR	NR	OR 1.2 (1.06, 1.34)	*RBC transfusion is associated with an increased risk of mortality in ICU patients.* *P=NR*
Infectious complications Taylor 2004 N=1717 *Retrospective cohort*	NR	NR	OR 1.18 (1.04, 1.34)	*RBC transfusion is associated with an increased risk of infection in ICU patients.* *P=NR*
Infectious complications Shorr 2005 N=NR *Prospective cohort*	NR	NR	OR 2.23 (1.43, 2.68)	*RBC transfusion is associated with an increased risk of infection in ICU patients.* *P=NR*
ARDS Gajic 2004 N=332 *Retrospective cohort*	NR	NR	OR 2.97 (1.56, 5.9)	*RBC transfusion is associated with an increased risk of ARDS in ICU patients.* *P=NR*
ARDS Gong 2005 N=688 *Prospective cohort*	NR	NR	OR (2.19 (1.42, 3.36)	*RBC transfusion is associated with an increased risk of ARDS in ICU patients.* *P=NR*
ARDS Zilberberg 2007 N=NR *Prospective cohort*	NR	NR	OR 2.8 (1.9, 4.12)	*RBC transfusion is associated with an increased risk of ARDS in ICU patients.* *P=NR*
ARDS Khan 2007 N=841 *Retrospective cohort*	NR	NR	OR 1.39 (0.79, 2.43)	*RBC transfusion is <u>not</u> associated with an increased risk of ARDS in ICU patients.* *P=NR*
Trauma and ICU				
Outcome No. trials (No. patients)	Transfusion n/N (%)	No transfuison n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
ARDS 6 studies (N=NR) *Prospective and retrospective cohorts*	NR	NR	OR 2.5 (1.66, 3.34)	*RBC transfusion is associated with an increased risk of ARDS in trauma and ICU patients.* *P=NR* *Q statistic <1, no heterogeneity*
EXTERNAL VALIDITY				
Generalisability				

The results of this study are generalisable to a population of ACS, trauma and ICU patients.
Applicability
The included studies were carried out in a variety of locations and may be applicable to the Australian context.
Comments
The authors conclude that RBC transfusion is associated with increased morbidity and mortality in high-risk hospitalised patients.

ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; HCT, hematocrit; MODS, multiorgan dysfunction syndrome; OR, odds ratio; SIRS, systematic inflammatory response syndrome; ACS, acute coronary syndrome; NR, not reported.

STUDY DETAILS: Cohort study			
Citation			
Agarwal N, Murphy JG, Cayten G, Stahl WM (1993) Blood transfusion increases the risk of infection after trauma. Arch Surg 128: 171-177.			
Affiliation/Source of funds			
Institute for Trauma and Emergency Care, New York Medical College, USA. Study supported in part by a grant from the Centers for Disease Control and Prevention.			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III-2	Eight hospitals (3 were Level I trauma centres); USA	
Risk factor/s assessed	Potential confounding variables measured		
Total amount of blood transfused (log transformed in multivariable analysis due to being highly skewed)	The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.		
Population characteristics (including size)			
5366 patients with trauma admitted to one of eight hospitals in New York and Connecticut; male 59.9%; mean age ~ 43-64 across transfusion groups.			
Length of follow-up	Outcomes measured		
Until discharge	Infection (major and minor)		
Method of analysis			
Stepwise logistic regression analysis used.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: 5434 eligible for inclusion but 67 excluded for missing data on some element of the Revised Trauma Score and 1 excluded for missing units of transfusion data; infection identified via ICD-9-CM codes (no inter-rater reliability tested for measurement of outcome between multiple nurse-abstractors); stepwise logistic regression used to identify significant predictors to include in the multivariable model.			
RESULTS			
Population	With risk factor (Transfusion)	Without risk factor (No Transfusion)	
Available	5434		
Analysed	5366		
Outcome (continuous)	RBC transfused	Risk estimate (95% CI)	Significance P-value
Infection (all trauma) N=5366	Total units transfused	NR	*Total RBC transfusion is a significant predictor of infection in all trauma patients* P<0.001
Infection (penetrating trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of infection in penetrating trauma patients* P<0.001

Infection (blunt trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of infection in blunt trauma patients* P<0.001
Infection (low fall trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of infection in low fall trauma patients* P<0.001
Major infection (all trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of major infection in all trauma patients* P<0.001
Major infection (penetrating trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of major infection in penetrating trauma patients* P<0.001
Major infection (blunt trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of major infection in blunt trauma patients* P<0.001
Major infection (low fall trauma) N=NR	Total units transfused	NR	*Total RBC transfusion is a significant predictor of major infection in low fall trauma patients* P<0.001
Major infection (all trauma) N=NR	Total units transfused in first 24 hours	NR	*Total RBC transfusion in the first 24 transfusion is a significant predictor of major infection in all trauma patients* P<0.001
Major infection (penetrating trauma) N=NR	Total units transfused in first 24 hours	NR	*Total RBC transfusion in the first 24 hours transfusion is a significant predictor of major infection in penetrating trauma patients* P<0.001
Major infection (blunt trauma) N=NR	Total units transfused in first 24 hours	NR	*Total RBC transfusion in the first 24 hours transfusion is a significant predictor of major infection in blunt trauma patients* P<0.001
Major infection (low fall trauma) N=NR	Total units transfused in first 24 hours	NR	*Total RBC transfusion in the first 24 hours transfusion is <u>not</u> a significant predictor of major infection in low fall trauma patients* P≥0.05

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a population of trauma patients.
Applicability
This study was carried out in the USA and is likely to be applicable to the Australian setting.
Comments
The authors conclude that 'blood transfusion in the injured patient is an important predictor of infection'. The authors note a number of limitations of their study including: (i) the retrospective nature of the data collection; (ii) the lack of intra-rater or inter-rater reliability tests for identifying infection; (iii) the lack of information on severity of infection; and (iv) a lack of data on other blood components.

CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NR, not reported;; RBC, red blood cell; USA, United States of America.

STUDY DETAILS: Cohort study			
Citation			
Bochicchio GV, Napolitano L, Joshi M, Bochicchio K, Meyer W, Scalea TM (2008) Outcome analysis of blood product transfusion in trauma patients: a prospective, risk-adjusted study. World J Surg 32: 2185-2189.			
Affiliation/Source of funds			
R Adams Cowley Shock Trauma Center, Baltimore, US; University of Maryland School of Medicine, Baltimore, US. Funding not stated.			
Study design	Level of evidence	Location/setting	
Prospective cohort study	Level III-2	Single trauma centre/US	
Risk factor/s assessed	Potential confounding variables measured		
Units of PRBC transfused (also FFP and platelets)	Adjusted for age, sex, race, Injury Severity Score, admission Glasgow Coma Scale, units of FFP and units of platelets.		
Population characteristics (including size)			
1172 patients admitted for > 48 hours to the ICU of the R Adams Cowley Shock Trauma Center from 2002-2004. 74% male, mean age 43, mean ISS 24, mean admission Glasgow Coma Score 12.			
Length of follow-up	Outcomes measured		
Until discharge	Mortality and infection		
Method of analysis			
Multiple logistic regression was used.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: 1172 consecutive patients included; CDC definitions used to diagnose infection; adjusted for a number of potential confounders.			
RESULTS			
Population	With risk factor (Transfusion)	Without risk factor (No Transfusion)	
Available	1172		
Analysed	1172		
Outcome (continuous)	RBC transfused	Risk estimate (95% CI)	Significance P-value
Mortality N=1172	Per unit RBC transfused	OR 1.05 (1.03, 1.07)	*A 1-unit increase in RBC transfusion is a significant predictor of increased mortality in trauma patients* P<0.001
Infection N=1172	Per unit RBC transfused	OR 2.8 (1.96, 3.94)	*A 1-unit increase in RBC transfusion is a significant predictor of increased infection in trauma patients* P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of trauma patients.			

Applicability
This study was carried out in the USA and is likely to be applicable to the Australian setting.
Comments
The authors conclude that 'there is a dose-dependent correlation between blood product transfusion and adverse outcome (increased mortality and infection) in trauma patients.' FFP (but not platelets) was also significantly associated with mortality and infection. The authors note the limitations of using the Injury Severity Scale but used it because it 'remains the standard in the majority of trauma studies.'

CDC, Centers for Disease Control and Prevention; CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A (2005) A 12-year prospective study of post-injury organ failure. Archives of Surgery 140: 432-440.				
Affiliation/Source of funds				
Denver health Medical Center and the University of Colorado Health Sciences Center, Denver; US. Supported in part by grants from the National Institutes of Health, Bethesda and the Jourdan Block Trauma Research and Development Foundation, Denver; US.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level III-2		Single Level I trauma centre/US	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion (continuous and categorical [> 6 units])		Continuous analysis adjusted for: year, age, Injury Severity Score. Categorical analysis adjusted for: year, age, Injury Severity Score.		
Population characteristics (including size)				
1344 trauma patients admitted to the Rocky Mountain regional Trauma Center's surgical ICU between May 1992 and Dec 2003. Had to have a ISS > 15, survive for at least 48 hours after injury, be admitted to the ICU within 24 hours of injury and be aged ≥ 15 years. 73% male; mean age 37.5; mean ISS 29.3.				
Length of follow-up		Outcomes measured		
Daily physiologic and laboratory data collected through ICU day 28 and clinical events recorded thereafter until hospital discharge or death.		Multiple organ failure (defined as a total score of ≥ 4 on the Denver MOF scoring system occurring 48 hours after injury)		
Method of analysis				
Multivariate analyses were conducted using logistic regression for categorical variables and standard linear regression for continuous variables.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Included data from 1344 patients collected over a 12-year period; year and a number of other variables adjusted for in the analysis; no details on how many patients not included in/excluded from the analysis.				
RESULTS				
Population	With risk factor (Transfusion)		Without risk factor (No Transfusion)	
Available	1344			
Analysed	1344			
Outcome (categorical)	12-hr RBC transfusion > 6 units n/N	12-hr RBC **transfusion ≤ 6** units n/N	Risk estimate (95% CI)	Significance P-value
Multiple organ failure (N=1344)	NR	NR	OR 3.40 (2.53, 4.58)	*12-hr transfusion of > 6 units is significantly associated with an increased risk of multiple organ failure* *P<0.001*

Outcome (continuous)	12-hr RBC transfusion	Risk estimate (95% CI)	Significance P-value
Multiple organ failure (N=1344)	Per unit RBC transfused	OR 1.07 (1.05, 1.09)	*A 1-unit increase in 12-hr RBC transfusion is significantly associated with an increased risk of multiple organ failure* P<0.001
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of trauma patients.			
Applicability			
This study was carried out in the US and is likely to be applicable to the Australian setting.			
Comments			
The authors conclude that 'the present study has confirmed that age, injury severity, and the use of blood transfusion during resuscitation are significant risk factors for postinjury MOF.'			

CI, confidence interval; hr, hour; ICU, intensive care unit; ISS, injury severity score; MOF, multiple organ failure; NR, not reported; OR, odds ratio; RBC, red blood cell; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg. 2002 Jul;68(7):566-72.				
Affiliation/Source of funds				
Department of Surgery, University of Virginia Health System, Charlottesville 22908-0709, USA				
Study design	Level of evidence	Location/setting		
Prospective cohort study	Level III	Single trauma centre, USA		
Risk factor/s assessed	Potential confounding variables measured			
pRBC transfusion within 48 hours	Sex, ICU admissions, GCS, APACHE II score, Ps, ISS, age, units of RBC transfused within 48 hours.			
Population characteristics (including size)				
1593 patients admitted to the trauma centre from November 1996 to December 1999. The decision to transfuse was made by the attending trauma specialist and/or the head of the trauma unit. Indications for transfusion were hemodynamic instability, haematocrit <30 in a patient with coronary risk factors, haematocrit <25 in a previously health patient and significant or ongoing blood loss. Mean initial Glasgow Coma Score was 13.1±0.1 and mean Injury Severity Score was 15.5±0.3.				
Length of follow-up	Outcomes measured			
Until discharge	Mortality (not adjusted so not included here) Infections (includes infections not transmitted by transfusion) length of stay, hospital charges			
Method of analysis				
Univariate analysis with unpaired two-tailed Student's T, chi-squared or Fisher's exact tests. Multivariate analysis with backwards step-wise logistic regression performed for infection outcome.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Unmatched cohort study. Analysis does stratify by ISS but does not use multivariate analysis of transfused vs. not transfused for mortality. Multivariate analysis used for infection outcome only.				
RESULTS				
Population	With risk factor (Transfusion)		Without risk factor (No Transfusion)	
Available	1593			
Analysed	309		1284	
Outcome (categorical)	Transfusion within 48 hours n/N (%) or mean±SD	No transfusion within 48 hours n/N (%) or mean±SD	Risk estimate (95% CI)	Significance P-value
Infection N=1593	102/309 (33)	98/1284 (7.6)	OR 1.084 (1.028, 1.142)	*pRBC transfusion is significantly associated with an increased risk of infection* P=0.0028
Hospital charges (1000$)	58.0±4.4	13.9±0.7	NR	-

Hospital charges (1000$), ISS <15	28.0±4.7	8.12±0.05	NR	-
Hospital charges (1000$), ISS 15-24	45.4 ± 4.0	15.4±1.1	NR	-
Hospital charges (1000$), ISS ≥24	78.6 ± 7.939	39.1 ± 4.2	NR	-
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of trauma patients.				
Applicability				
This study was carried out in the USA and is likely to be applicable to the Australian setting.				
Comments				
The authors conclude that 'multivariate analysis further demonstrated that pRBCs were an independent risk factor for the development of infections.'				

CI, confidence interval; ISS, injury severity score; NR, not reported; NS, not significant; GSC, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; Ps, survival probability; RBC, red blood cell.

[a] Affected patient numbers calculated post hoc form percentage values

STUDY DETAILS: Cohort study				
Citation				
Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ. The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. Crit Care Med. 2004 Jan;32(1):39-52.				
Affiliation/Source of funds				
Dartmouth-Hitchcock Medical Center, Lebanon, NH; Stanford University Medical Center, Palo Alto, CA; University of Pittsburgh Medical Center, Pittsburgh, PA; Rhode Island Hospital, Providence, RI; St. Louis University Health Science Center, St. Louis, MO; University of Colorado Medical Center, Denver, CO; Duke University Medical Center, Durham, NC; Cedar- Sinai Medical Center, Los Angeles, CA; and Analysis Group, Boston, MA. Supported, in part, by Ortho Biotech Products.				
Study design	Level of evidence	Location/setting		
Multi-centre prospective cohort study	Level III	284 ICUs in 213 hospitals in the United States		
Risk factor/s assessed	Potential confounding variables measured			
RBC transfusion	Logistic regression analysis: unclear but include baseline Hb and mean age of transfused blood. Propensity analysis: propensity for transfusion (patients demographics, baseline APACHE II and SOFA scores, origin of admission, admitting diagnoses, medical history and hospital LOS)			
Population characteristics (including size)				
4892 ICU patients enrolled during August 2000 and April 2001. Inclusion criteria included: age of18 yrs; admission to ICU and an anticipated ICU stay of 48 hrs. Exclusion criteria included: admission to a pediatric, cardiothoracic, cardiac, neurologic, or burn ICU; renal failure on dialysis; patients prohibited from receiving RBC transfusions.				
Length of follow-up	Outcomes measured			
30 days or until discharge.	Mortality, transfusion-related AEs (not shown here as not adjusted analysis)			
Method of analysis				
Multivariate logistic regression analysis used to assess association between RBC transfusion and mortality. Matched propensity analysis also used.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Large multi-centre prospective cohort study. No presentation of baseline characteristics in transfused vs. not transfused groups. No reporting of how many patients were excluded or lost to follow-up.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	4892			
Analysed	2358		2534	
Outcome (categorical)	Transfusion n/N (%)	No Transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value

Mortality (1-2 units vs 0 units) N=NR *Logistic regression analysis*	NR	NR	OR 1.48 (1.07, 2.05)	*Transfusion of 1-2 units of RBCs is significantly associated with an increased risk of mortality compared with no transfusion* P=0.018
Mortality (3-4 units vs 0 units) N=NR *Logistic regression analysis*	NR	NR	OR 2.62 (1.80, 3.81)	*Transfusion of 3-4 units of RBCs is significantly associated with an increased risk of mortality compared with no transfusion* P<0.0001
Mortality (>4 units RBCs vs 0 units) N=NR *Logistic regression analysis*	NR	NR	OR 4.01 (2.74, 5.87)	*Transfusion of >4 units of RBCs is significantly associated with an increased risk of mortality compared with no transfusion* P<0.0001
Mortality N=2118 *Propensity analysis*	NR	NR	MR 1.65 (1.35, 2.03)	*RBC transfusion is significantly associated with an increased risk of mortality* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of ICU critical care patients				
Applicability				
The study was carried out in the United States and is likely to be applicable to the Australian setting.				
Comments				
Incomplete reporting of transfused vs. not transfused for baseline characteristics and outcomes.				

AE, adverse event; ANOVA, analysis of variance; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RBC, red blood cell; NR, not reported; MR, mortality ratio.

STUDY DETAILS: Cohort study			
Citation			
Duane TM, Mayglothling J, Grandhi R et al (2008) The effect of anemia and blood transfusions on mortality in closed head injury patients. Journal of Surgical Research 147: 163-167.			
Affiliation/Source of funds			
Virginia Commonwealth University Medical Center, Richmond, US. Funding not stated.			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III-2	Single Level I trauma centre/United States	
Risk factor/s assessed	Potential confounding variables measured		
Blood transfusion (total units transfused)	Adjusted for: age, neurosurgical procedure and minimum Hct.		
Population characteristics (including size)			
788 patients aged ≥ 16 years admitted between Jan 2001 and Dec 2006 with primarily isolated head trauma as defined by having a head abbreviated injury severity score (AIS) of ≥ 2 and all other AIS scores ≤ 1. Patients with penetrating trauma were excluded. Mean age 47.8 years; mean ISS 15.3, mean AIS 3.8, mean GCS 12.6.			
Length of follow-up	Outcomes measured		
Hospitalisation	Infection (diagnosis of infection not defined)		
Method of analysis			
Multivariate analysis was performed to determine predictors of mortality. Multivariate analysis also performed for infection, although not stated in methods.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: Retrospective cohort study; little information given in methodology section; unclear whether both mortality and infection analyses adjusted for the same variables.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	788		
Analysed	788		
Outcome (continuous)	Total PRBCs transfused	Risk estimate (95% CI)	Significance P-value
Infection N=788	Per unit RBC transfusion	OR 1.26 (1.06, 1.50)	*RBC transfusion is significantly associated with a 26% increased risk of infection per unit transfused* P=0.009
EXTERNAL VALIDITY			
Generalisability			
The results of this study are generalisable to a population of patients with isolated blunt head trauma.			
Applicability			
The study was carried out in the United States and is likely to be applicable to the Australian context.			
Comments			

The analysis of infection showed that age, neurosurgical procedure, minimum Hct and total PRBCs transfused were all significant predictors of infection.

AIS, abbreviated injury severity score; CI, confidence interval; GCS, Glasgow coma scale; Hct, haematocrit; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Dunne JR, Malone DL, Tracy JK, Napolitano LM. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt). 2004 Winter;5(4):395-404.				
Affiliation/Source of funds				
University of Maryland School of Medicine and The R. Adams Cowley Shock Trauma Center, Baltimore, Maryland.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level III		Single trauma centre, United States	
Risk factor/s assessed		Potential confounding variables measured		
Blood transfusion		Age, ISS, GCS, race, and gender.		
Population characteristics (including size)				
9539 patients admitted to the trauma centre between Jan 1997 and Jul 1999. Patients were stratified by age, gender, Glasgow coma score, and mechanism of injury. Injury severity was assessed using the injury severity score. Blood transfusion data in the first 24 h were collected prospectively in the trauma registry and included data capture for total transfused blood volume.				
Length of follow-up		Outcomes measured		
Hospitalisation		Mortality and systemic inflammatory response syndrome, ICU admission and resource utilisation including length of stay (not included here).		
Method of analysis				
Discrete variables were compared using Pearson's Chi square analysis. Continuous variables were compared using Student's t-test and ANOVA. Differences were considered significant when $p<0.05$. Multiple logistic regression analysis was used to identify if blood transfusion was a risk factor for systemic inflammatory response syndrome, mortality, and ICU admission. Patients who were transfused were significantly older and had significantly higher ISS and lower GCS.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Large prospective cohort study of trauma patients in a single centre. Multiple logistic regression analysis used to control for differences between groups.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	9539			
Analysed	954		8585	
Outcome (categorical)	Blood transfusion in the first 24 hours	No blood transfusion in the first 24 hours	Risk estimate (95% CI)	Significance P-value
Mortality N=9539	212/954 (22.2)	120/8585 (1.4)	OR 4.23 (3.07, 5.84)	*RBC transfusion in the first 24 hours is significantly associated with an increased risk of mortality* P<0.0001
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to a population to trauma patients.
Applicability
The study was carried out in the United States and is likely to be applicable to the Australian context.
Comments

CI, confidence interval; GCS, Glasgow coma scale; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; SIRS, systemic inflammatory response syndrome; ANOVA, analysis of variance.

STUDY DETAILS: Cohort study				
Citation				
Engoren M, Arslanian-Engoren C. Long-term survival in the intensive care unit after erythrocyte blood transfusion. Am J Crit Care. 2009 Mar;18(2):124-31.				
Affiliation/Source of funds				
Departments of Anesthesiology and Internal Medicine, St Vincent Mercy Medical Center; Department of Anesthesiology, University of Toledo Health Sciences College, Toledo, Ohio; School of Nursing, University of Michigan, Ann Arbor.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study, database review	Level III		The cardiac ICU, the burn ICU, the neurological and neurosurgical ICU, and the combined medical-surgical ICU at a single medical centre in the United States.	
Risk factor/s assessed	Potential confounding variables measured			
RBC transfusion	Sex, type of ICU, intubation and reintubation, cardiac arrest, surgery, mechanical ventilation, tracheostomy, central venous catheter, pulmonary artery catheter, haemodialysis, continuous venovenous haemofiltration, readmission to ICU, admitting service, Glasgow Coma Score, age, APACHE II score, urea nitrogen, creatinine, Hb, height, weight, days in ICU.			
Population characteristics (including size)				
2123 patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002.				
Length of follow-up		Outcomes measured		
4.74-5.99 years.		Mortality		
Method of analysis				
The $\chi 2$ test and the Fisher exact test were used to compare categorical variables. A t test was used to compare normally distributed continuous variables. Cox proportional hazard modelling was used to determine the predictors of mortality. Models were analysed further by using a case-control method, in which the control patients (who did not receive a transfusion) were matched to the case patients (who did receive a transfusion) with respect to APACHE II scores and propensity to receive a transfusion.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Cohort study of ICU patients at a single medical centre. Multivariate analysis of mortality at a number of time points after admission.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	2213			
Analysed	404 (278 matched analysis)		1809 (278 matched analysis)	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
30-day mortality N=2213	101/404 (25)	265/1809 (15)	HR 1.11 (0.86, 1.42)	*RBC transfusion is not associated with 30-day mortality* P=0.42

30-day mortality N=556 *Matched analysis*	52/278 (19)	67/278 (24)	NR	*RBC transfusion is not associated with 30-day mortality* P=NR
30-180-day mortality N=1847	49/303	149/1544	HR 1.14 (0.83, 1.58)	*RBC transfusion is not associated with 30-180-day mortality* P=0.41
30-180-day mortality N=437 *Matched analysis*	31/226	36/211	NR	*RBC transfusion may be associated with 30-180-day mortality* P=NR
Mortality after 180 days N=1649	126/254	352/1395	HR 0.75 (0.57, 0.99)	*RBC transfusion is significantly associated with decreased 180+ day mortality* P=0.04
Mortality after 180 days N=370 *Matched analysis*	63/195	74/175	HR 0.71 (0.50, 0.99)	*RBC transfusion is significantly associated with decreased 180+ day mortality* P=0.046
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a broad population of ICU patients.				
Applicability				
The study was carried out in the United States and is likely to be applicable to the Australian setting.				
Comments				

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; GCS, Glasgow Coma Scale; Hb, haemoglobin; HR, hazard ratio; ICU, intensive care unit; NR, not reported; RBC, red blood cell.

STUDY DETAILS: Cohort study				
Citation				
Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med. 2005 Jun;33(6):1191-8.				
Affiliation/Source of funds				
Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Environmental Health Department (Occupational Health Program) and Department of Biostatistics, Harvard School of Public Health, Boston, MA; and Division of Pulmonary, Sleep and Critical Care Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY Supported, in part, by research grant RO1 HL60710 from the National Heart, Lung, and Blood Institute; grant K23 HL67197 from the National Heart, Lung, and Blood Institute; and grant T32 HL07874, Massachusetts General Hospital..				
Study design		Level of evidence		Location/setting
Prospective cohort study		Level III		Neurologic, cardiac, medical and surgical ICUs of a single hospital, United States
Risk factor/s assessed	Potential confounding variables measured			
RBC Transfusion	Age, APACHE III score, trauma, diabetes, direct pulmonary injury, transfer from another hospital, haematologic failure, heart rate >99 beats per minute, respiratory rate >33 breaths per minute, haematocrit >37.5%, arterial pH <7.33, albumin ≤2.3 g/dL.			
Population characteristics (including size)				
Patients admitted to the ICU between Sept 1999 and Aug 2002 with at least one defined risk factor for ARDS and no exclusion criteria were eligible for the study. Exclusion criteria: age <18 yrs, diffuse alveolar haemorrhage or chronic lung disease, directive to withhold intubation, neutropenia not secondary to sepsis, immunosuppression secondary to medication or diseases such as HIV, treatment with granulocyte colony-stimulating factor or inhibitors of tumour necrosis factor. Outcome assessment was blinded to transfusion status. 688 patients were included.				
Length of follow-up		Outcomes measured		
NR		ARDS		
Method of analysis				
Univariate: Fisher's exact test for dichotomous variables and Wilcoxon rank sum for continuous variables. Multivariate: Multiple logistic regression model using a backward elimination algorithm.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective cohort study using multiple logistic regression model. Patients screened and included quite well described and assessors blinded.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	688			
Analysed	362		326	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value

ARDS N=688	134/362 (37.0)	87/326 (26.7)	OR 2.19 (1.42, 3.36)	*RBC transfusion is significantly associated with an increased risk of ARDS* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a general population of ICU patients.				
Applicability				
The study was carried out in the United States and is likely to be applicable to the Australian context.				
Comments				

APACHE III, Acute Physiology and Chronic Health Evaluation III; ARDS, acute respiratory distress syndrome; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell.

STUDY DETAILS: Cohort study				
Citation				
Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, Blajchman M, Schweitzer I, Pagliarello G. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. Am J Respir Crit Care Med. 1997 May;155(5):1618-23.				
Affiliation/Source of funds				
Critical Care Programs of the University of Ottawa, Ottawa, Ontario, University of British Columbia, Vancouver, British Columbia, University of Western Ontario, London, Ontario, University of Toronto, Toronto, Ontario; Clinical Epidemiology Unit, University of Ottawa, Ottawa, Ontario; and Department of Pathology, McMaster University, Hamilton, Ontario, Canada Supported by the Medical Research Council of Canada, the Canadian Red Cross Society, Blood Services, the Physicians' Services Incorporated, and an unrestricted grant from Bayer Inc.				
Study design	Level of evidence		Location/setting	
Combined retrospective and prospective cohorts	Level III		Six ICUs, Canada	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion (increasing units) vs. none		Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status		
Population characteristics (including size)				
4470 patients admitted to six ICUs during 1993. The study excluded patients who were less than 16 yr of age or who met brain death criteria within 24 hr of admission.				
Length of follow-up		Outcomes measured		
Until ICU discharge		ICU mortality		
Method of analysis				
Univariate: chi-squared or student's t tests. Multivariate: logistic regression				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Combined retrospective and prospective cohort analysis.				
RESULTS				
Population	Transfusion		No transfusion	
Available	3838			
Analysed	1386 (330 cardiovascular diagnosis)		3084 (1035 cardiovascular diagnosis)	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
All patients				

ICU mortality (1-3 units) N=3838	191/754 (25.3)	585/3084 (19.0)	OR 0.74 (0.57, 0.96)	*RBC transfusion of 1-3 units is significantly associated with a reduction in mortality compared with no transfusion* P=0.01
ICU mortality (4-6 units) N=3406	98/322 (30.4)	585/3084 (19.0)	OR 0.71 (0.50, 0.99)	*RBC transfusion of 4-6 units is significantly associated with a reduction in mortality compared with no transfusion* P=0.02
ICU mortality (7-10 units) N=3229	56/145 (38.6)	585/3084 (19.0)	OR 0.93 (0.59, 1.46)	*RBC transfusion of 7-10 units is <u>not</u> significantly associated with mortality compared with no transfusion* P=0.37
ICU mortality (>10 units) N=3249	71/165 (43.0)	585/3084 (19.0)	OR 0.90 (0.59, 1.38)	*RBC transfusion of >10 units is <u>not</u> significantly associated with mortality compared with no transfusion* P=0.32
Patients with a cardiovascular diagnosis				
ICU mortality (1-3 units) N=1236	49/201 (24.4)	181/1035 (17.5)	OR 0.61 (0.37, 1.00)	*RBC transfusion of 1-3 units is significantly associated with a reduction in mortality compared with no transfusion* P=0.0256
ICU mortality (4-6 units) N=1103	16/68 (23.5)	181/1035 (17.5)	OR 0.49 (0.23, 1.03)	*RBC transfusion of 4-6 units is significantly associated with a reduction in mortality compared with no transfusion* P=0.0304
ICU mortality (7-10 units) N=1069	16/34 (47.1)	181/1035 (17.5)	OR 0.96 (0.39, 2.41)	*RBC transfusion of 7-10 units is <u>not</u> significantly associated with mortality compared with no transfusion* P=0.47

ICU mortality (>10 units) N=1062	14/27 (51.9)	181/1035 (17.5)	OR 0.64 (0.24, 1.69)	*RBC transfusion of >10 units is <u>not</u> significantly associated with mortality compared with no transfusion* P=0.184
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult ICU patients.				
Applicability				
The study was carried out in Canada and is likely to be applicable to the Australian context.				
Comments				

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; OR, odds ratio; RBC, red blood cell.

STUDY DETAILS: Cohort study				
Citation				
Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest. 2007 May;131(5):1308-14.				
Affiliation/Source of funds				
Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, and the Department of Laboratory Medicine and Pathology, Division of Transfusion Medicine, Mayo Clinic College of Medicine, Rochester, MN. This research was supported in part by National Heart, Lung, and Blood Institute grant No. K23 HL78743–01A1.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III		Single medical ICU, United States	
Risk factor/s assessed		Potential confounding variables measured		
Transfusion (includes RBC, FFP and platelets) vs. none		Haematocrit, APACHE III score, age, INR, sepsis, aspiration, pancreatitis, and pneumonia, and the propensity for transfusion with particular blood products.		
Population characteristics (including size)				
Consecutive critically ill patients who had been admitted to the medical ICU between March 2004 and March 2005 screened for inclusion criteria. Patients who had pulmonary oedema (hydrostatic or ALI/ARDS) on ICU admission and those who had been admitted to the ICU for <24 h were excluded from the study. Also, patients who declined research authorization were excluded from the study. 1673 patients were eligible to be included and after application of the exclusion criteria 841 patients were included in the study and were followed up for the development of ALI/ARDS. Daily portable chest radiographs were independently reviewed by study investigators (intensivists) who were blinded to the predictor variables.				
Length of follow-up		Outcomes measured		
In-hospital		ARDS/ALI		
Method of analysis				
Wilcoxon rank sum, the Fisher exact test, or the chi-squared test. Risk factors for ALI/ARDS were considered for multivariable logistic regression models if they (1) were statistically significant in univariate analysis ($p<0.05$), (2) had high odds ratios (ORs) [≥2]; or (3) were biologically plausible. Because of co-linearity, each of the blood product types (i.e. RBCs, FFP, or platelets) was also included into separate logistic models.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Well described and controlled retrospective cohort study.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	298 (includes other transfusion types)		543	
Analysed	262 (RBC)		543	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
ALI/ARDS N=805	NR	97/543	OR 1.39 (0.79, 2.43)	*Transfusion of RBCs is not associated with an increased risk of ALI/ARDS* P=NR

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a population of medical ICU patients.
Applicability
The study was carried out in the United States and is likely to be applicable to the Australian context.
Comments
Of the 262 patients transfused with RBCs, some will also have received FFP and platelet transfusion.

APACHE II, Acute Physiology and Chronic Health Evaluation II; ALI, acute lung injury; ARDS, Acute respiratory distress syndrome; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; INR, international normalised ratio; NR, not reported; OR, odds ratio; RBC, red blood cell; FFP, fresh-frozen plasma.

STUDY DETAILS: Cohort study				
Citation				
Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A et al (2001) Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 119: 1461-1468.				
Affiliation/Source of funds				
Hospital Universitario 'Virgen del Rocío,' Seville, Spain. No funding stated.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level III-2		Single ICU/Spain	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion ≥ 4 units		Univariate analysis showed the following potential confounders: mechanical ventilation ≥ 48 hours, transfusion ≥ 4 U blood components, transfusion ≥ 4 U RBC, arterial hypotension, reintervention, transfusion ≥ 2 U plasma, reintubation and neurologic dysfunction. Final multivariate analysis adjusted for: Reintubation, mechanical ventilation ≥ 48 hours, neurologic dysfunction, arterial hypotension.		
Population characteristics (including size)				
738 patients admitted to ICU following cardiac/vascular surgery. Mean age 58.4 years; 61% male; APACHE II score at admission to ICU 10.7.				
Length of follow-up		Outcomes measured		
Hospitalisation		Pneumonia		
Method of analysis				
Variables with P<0.05 on univariate analysis included in a logistic regression analysis with stepwise elimination.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective cohort study; patients excluded if they had infection prior to transfusion; a large number of potential confounders assessed; follow-up appears to be during hospitalisation.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	738			
Analysed	299		439	
Outcome (categorical)	RBC transfusion **≥ 4** units	RBC transfusion < 4 units	Risk estimate (95% CI)	Significance P-value
Pneumonia N=738	NR	NR	OR 2.6 (1.1, 5.8)	*RBC transfusion ≥ 4 units is significantly associated with an increased risk of pneumonia compared with RBC transfusion < 4 units* P=0.016
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to a population of surgical ICU patients following cardiac surgery.
Applicability
The study was carried out in Spain may be applicable to the Australian setting.
Comments
The authors conclude that 'the administration of blood derivatives, mainly RBCs, was associated in a dose dependent manner with the development of SPIs, primarily nosocomial infection.' The authors note that there is the possibility of residual confounding, particularly if transfusion is a marker for another confounding factor.

APACHE, Acute Physiology and Chronic Health Evaluation ; CI, confidence interval.; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; SPI, severe postoperative infection.

STUDY DETAILS: Cohort study				
Citation				
Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma. 2003 May; 54(5):898-905; discussion 905-7.				
Affiliation/Source of funds				
From the Departments of Surgery and Epidemiology, University of Maryland School of Medicine and R Adams Cowley Shock Trauma Center, Baltimore, Maryland.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level III		Single trauma centre, United States	
Risk factor/s assessed		Potential confounding variables measured		
Transfusion in first 24 hours vs. no transfusion in first 24 hours		Anaemia at admission, admission base deficit, serum lactate, and shock index, age, gender, race, Glasgow coma scale score and injury severity score.		
Population characteristics (including size)				
15534 patients aged ≥18 years who were admitted to the trauma centre between Jan 1998 and Dec 2000. Patient who were transfused within the first 24 hours were older, had higher injury severity and Glasgow coma scale scores and lower haematocrit at admission.				
Length of follow-up		Outcomes measured		
Until discharge		Mortality		
Method of analysis				
Univariate: chi-squared test; Multivariate: multiple logistic regression analysis using stepwise backward elimination procedure (gender, race, and anemia group did not meet statistical requirements for being retained in the model).				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Large single-institution cohort study. Study uses multiple logistic regression analysis to adjust for confounding variables.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	15,534			
Analysed	1703		13,831	
Outcome (categorical)	Transfusion in the first 24 hours	No transfusion in the first 24 hours	Risk estimate (95% CI)	Significance P-value
Hospital mortality N=15,534	377/1703 (22.1)	313/13,831 (2.3)	OR 2.83 (1.82, 4.40)	*RBC transfusion in the first 24 hours is significantly associated with an increased risk of mortality* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of trauma patients.				
Applicability				

The study was carried out in the United states and is likely to be applicable to the Australian setting.
Comments
The authors conclude that blood transfusion is a significant independent predictor of mortality in trauma patients. Transfusion was also an independent predictor of ICU admission and length of ICU stay.

CI, confidence interval.; ICU, intensive care unit; NR, not reported; OR, odds ratio.

STUDY DETAILS: Cohort study			
Citation			
Müller MH, Moubarak P, Wolf H et al (2008) Independent determinants of early death in critically ill surgical patients. Shock 30(1): 11-16.			
Affiliation/Source of funds			
Ludwig-Maximillian University, Munich, Germany No funding stated.			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III	Single surgical ICU/Germany	
Risk factor/s assessed	Potential confounding variables measured		
RBC transfusion (units transfused)	A backward selection algorithm was used to construct the final model. The final model was adjusted for: age, admission APACHE II score, admission day need for ventilation, admission SBP, admission PTT, body temperature at admission, vascular operation, interaction between RBC units transfused and APACHE II score.		
Population characteristics (including size)			
4214 cases admitted to ICU immediately after surgery. From Mar 1993 to Feb 2005. Age ~ 66 years.			
Length of follow-up	Outcomes measured		
During ICU	4-day survival		
Method of analysis			
All binary variables, all continuous variables after appropriate modeling, and all relevant interactions were combined into a multivariate GAM. A backward selection algorithm was used to construct the final model. The algorithm included five consecutive steps: (a) calculation of the complete multivariate GAM including all variables; (b) elimination of the variable with the highest P value from the model; (c) calculation of AIC statistics, if AIC of the subsequent model was less than that of the preceding one, the last model was retained; (d) steps (b) and (c) were repeated as long as there was no further AIC reduction by the subsequent model; and (e) smoothed terms were replaced by linear terms for the sake of simplification; linear terms were retained in the final model if this procedure further reduced the AIC value. Model adequacy was described as the proportion deviance explained.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Retrospective cohort study; no details on amount of missing data; adjusted for a number of potential confounders including interactions; 4-day follow-up.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	4217		
Analysed	4214 (discrepancy between abstract and text)		
Outcome (continuous)	RBC transfusion	Risk estimate (95% CI)	Significance P-value
Infection N=4214	Per unit transfused	1.10 (1.02, 1.17)	*RBC transfusion is significantly associated with increased risk of mortality of 10% per unit transfused* P=NR

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a population of patients admitted to ICU immediately following surgery..
Applicability
The study was carried out in Germany and is likely to be Applicable to the Australian context.
Comments
The authors note that they 'identified four variables that had an independent effect on acute outcome and that would also be amenable to treatment: systolic blood pressure, partial thromboplastin time, body temperature, and the number of transfused red blood cells.' With regards specifically to RBC transfusions, they note that 'We found a linear association between the number of red blood cell units transfused on admission day and 4-day mortality, indicating that a threshold effect does not seem to exist. The importance of red blood cell transfusion for acute prognosis is further supported by the significant interaction between APACHE II score and red blood cell transfusion on admission day.' The authors note a number of limitations including the fact the study was conducted at a single centre and the possibility of residual confounding.

AIC, Akaike information criterion; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; GAM, generalised additive models; NR, not reported; OR, odds ratio; PTT, partial thromboplastic time; RBC, red blood cell; SBP, systolic blood pressure.

STUDY DETAILS: Cohort study			
Citation			
Palmieri TL, Caruso DM, Foster KN et al (2006) Effect of blood transfusion on outcome after major burn injury: a multicenter study. Critical Care Medicine 34(6): 1602-1607.			
Affiliation/Source of funds			
21 Burn centres in the US. No funding stated. Noted that the authors have no financial interests to disclose.			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III	21 burn centres, United States	
Risk factor/s assessed	Potential confounding variables measured		
RBC transfusion (units transfused)	Infection analysis assumed to be adjusted for the same variables as survival analysis: age, sex, total body surface area, inhalation injury, number of infections, number of operations, admission to first operation, admission to first transfusion, admission to last transfusion, escharotomies, cardiac disease, ARDS, blood stream infection.		
Population characteristics (including size)			
620 patients with acute burn injury ≥ 20% of TBSA admitted to a participating burn centre from Jan 2002 to Dec 2002. Patients admitted > 72 hrs after the injury were excluded. Mean age 32.1; male 76%; mean TBSA 36.4%.			
Length of follow-up	Outcomes measured		
During hospitalisation	Infection (included UTI, pneumonia, BSI, wound infection and central venous catheter infection as defined by the CDC) Also included analysis of mortality by number of transfusions (not included here).		
Method of analysis			
Multivariate adjusted logistic regression was used to calculate the OR between number of units transfused and infectious episodes.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Poor Description: Data collected for 666 patients; 46 excluded from analysis as they dies within the first 24 hours after admission; excluded patients older and had sustained massive, unsurvivable burns; survival analysis adjusted for a number of potential confounders – not clear is these were also included in the infection analysis; no adjustment for Hb/Hct or organ failure.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	666		
Analysed	620		
Outcome (continuous)	Blood transfusion	Risk estimate (95% CI)	Significance P-value
Infection N=620	Per unit transfused	OR 1.13	*Blood transfusion is significantly associated with increased risk of infection of 13% per unit transfused* P<0.001

EXTERNAL VALIDITY
Generalisability
The results of this study are generalisable to a population of patients with burns > 20% TBSA.
Applicability
The study was carried out in the United States and is likely to be Applicable to the Australian context.
Comments
The authors conclude that transfusion was associated with increased infection even after factoring indices of burn severity. They note a number of limitations of their study including: (i) the small sample size which might have resulted in undetected associations; and (ii) the possibility of residual confounding.

ARDS, acute respiratory distress syndrome; BSI, bloodstream infection; CDC, Centers for Disease Control and Prevention; CI, confidence interval; OR, odds ratio; RBC, red blood cell; TBSA, total body surface area; US, United States of America; UTI, urinary tract infection.

STUDY DETAILS: Cohort study				
Citation				
Rachoin JS, Daher R, Schorr C, Milcarek B, Parrillo JE, Gerber DR. Microbiology, time course and clinical characteristics of infection in critically ill patients receiving packed red blood cell transfusion. Vox Sang. 2009 Nov;97(4):294-302.				
Affiliation/Source of funds				
Cooper University Hospital, Camden, New Jersey, USA; Robert Wood Johnson Medical School at Camden, University of Medicine and Dentistry of New Jersey, New Jersey, USA				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III		Single ICU, United States	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion		Nosocomial infections, prolonged ICU length of stay, prolonged hospital length of stay, in-hospital mortality, number of transfusions, APACHE II score, age, gender, use of pressors, need for mechanical ventilation and race.		
Population characteristics (including size)				
All patients 18 years or older and surviving more than 24 h in the ICU at Cooper University Hospital between July 2003 and September 2006 were eligible for inclusion in the analysis. The study population consisted of 2432 patients of which a total of 640 were transfused. Patients who had a nosocomial infection prior to or less than 24 h following their first transfusion were considered as non-transfused for the purpose of the analysis (n = 31).				
Length of follow-up		Outcomes measured		
During hospitalisation		Occurrence of nosocomial infection, type/site of infection, infecting organism, time from admission (hospital and ICU) to infection, ICU length of stay, hospital length of stay and in-hospital mortality.		
Method of analysis				
Categorical variables were compared using the chi-square test or Fisher exact test as appropriate. Continuous variables were tested for significance using the Mann–Whitney U-test. Logistic regression was used to assess the unique predictive effect of transfusion as an independent risk factor for these outcomes: nosocomial infections (at least one infection), prolonged ICU length of stay (> median), prolonged hospital length of stay (> median) and in-hospital mortality. For all outcomes, predictors included in the model were: transfusion status (number of occasions transfused), APACHE II score (dichotomized at median of 16), age (dichotomized at the median of 60), gender, use of pressors, need for mechanical ventilation and race (white vs. others). For the mortality risk model an age (x) transfusion interaction term was entered to account for the difference in mortality risk over age.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: This study reviews the experience in a single ICU to compare non-transfused and transfused patients for the distribution of causative organisms, source/site of infections and timing of the occurrence of infection in addition to the overall incidence of infection and outcomes.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	2432			
Analysed	609		1823	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value

Hospital mortality N=2432	81/609 (13.3)	158/1823 (8.7)	OR 1.3 (1.02, 1.5)	*RBC transfusion is significantly associated with increased mortality* P=0.03
Nosocomial infection N=2432	64/609 (10.5)	90/1823 (4.9)	OR 1.6 (1.4, 1.8)	*RBC transfusion is significantly associated with increased nosocomial infection* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of critically ill patients.				
Applicability				
The study was carried out in the United States and is likely to be Applicable to the Australian context.				
Comments				

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell.

STUDY DETAILS: Cohort study				
Citation				
Rüttinger D, Wolf H, Küchenhoff H, Jauch KW, Hartl WH. Red cell transfusion: an essential factor for patient prognosis in surgical critical illness? Shock. 2007 Aug;28(2):165-71.				
Affiliation/Source of funds				
Department of Surgery, Klinikum Grosshadern, and Institute of Statistics, Ludwig-Maximilian University Munich, Germany				
Study design	Level of evidence	Location/setting		
Retrospective cohort study	Level III-2	Single ICU, Germany		
Risk factor/s assessed	Potential confounding variables measured			
RBC transfusion vs. none	Limited analysis: Emergency admission, immediate post-operative admission, thoracic surgery, APACHE II score at admission, artificial ventilation on admission, renal replacement therapy on admission, blood pressure ≤80 mmHg at admission, HB <80 g/L at admission, pneumonia, peritonitis, severe sepsis Extended analysis: as above plus maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, and duration of renal replacement therapy			
Population characteristics (including size)				
3037 patients admitted to the surgical ICU between March 1993 and February 2005. The study included all consecutive surgical cases admitted to the ICU immediately or delayed after a surgical procedure. Only cases with an ICU stay of more than 1 day were included, thereby excluding patients with a rapidly fatal clinical course or with minimal disease severity. Patients who did not undergo surgery or were admitted only for medical reasons and patients who had a do-not-resuscitate order on admission were excluded. RBC transfusion was used when HB fell below 80-90 g/L, although cardiac high-risk patients were maintained at Hb 100 g/L. 'Mean age was 63.5 ± 15.8 years, 65.9% of the cases were men, 50.4% of the cases were emergency admissions, 79.1% came directly from the operating room, and 9.7% were readmissions. Most of the cases were abdominal surgery patients (53.6%), 20.2% came from vascular surgery service, 13.5% from thoracic surgery, and 11.1% from orthopedic surgery.'				
Length of follow-up	Outcomes measured			
Until ICU discharge	ICU mortality, ICU length of stay			
Method of analysis				
Univariate analysis and multivariate analysis using a stepwise logistic regression model. Patients who died during ICU stay were excluded from the length of stay analysis.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Large 12-year retrospective cohort study of surgical ICU patients from a single centre in Germany.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1244		1793	
Analysed	1244		1793	
Outcome (categorical)	RBC transfusion	No RBC transfusion	Risk estimate (95% CI)	Significance P-value
Limited analysis				

ICU mortality	Any RBC transfusion N=1793	No transfusion N=1244	OR 1.847 (1.263, 2.701)	*Favours no RBC transfusion* P=0.002
ICU mortality	1-2 RBC units in total N=676	No transfusion N=1244	OR 0.840 (0.494, 1.426)	*No difference* P=0.518
ICU mortality	3-4 RBC units in total N=345	No transfusion N=1244	OR 1.572 (0.902, 2.738)	*No difference* P=0.110
ICU mortality	5-8 RBC units in total N=301	No transfusion N=1244	OR 3.863 (2.383, 6.254)	*Favours no RBC transfusion* P<0.001
ICU mortality	>8 RBC units in total N=471	No transfusion N=1244	OR 5.372 (3.219, 8.965)	*Favours no RBC transfusion* P<0.001
ICU mortality	Maximum 1-2 RBC units on a single day	No transfusion	OR 1.281 (0.858, 1.913	*No difference* P=0.225
ICU mortality	Maximum 3-4 RBC units on a single day	No transfusion	OR 3.620 (2.191, 5.982)	*Favours no RBC transfusion* P<0.001
ICU mortality	Maximum >4 RBC units on a single day	No transfusion	OR 6.203 (3.511, 10.959)	*Favours no RBC transfusion* P<0.001
Extended analysis				
ICU mortality	Any RBC transfusion N=1793	No transfusion N=1244	OR 0.898 (0.532, 1.516)	*No difference* P=0.688
ICU mortality	1-2 RBC units in total N=676	No transfusion N=1244	OR 0.683 (0.351, 1.283)	*No difference* P=0.261
ICU mortality	3-4 RBC units in total N=345	No transfusion N=1244	OR 1.108 (0.515, 2.386)	*No difference* P=0.793
ICU mortality	5-8 RBC units in total N=301	No transfusion N=1244	OR 1.161 (0.598, 2.255)	*No difference* P=0.660
ICU mortality	>8 RBC units in total N=471	No transfusion N=1244	OR 0.737 (0.358, 1.514)	*No difference* P=0.406
ICU mortality	Maximum 1-2 RBC units on a single day	No transfusion	OR 0.780 (0.455, 1.337)	*No difference* P=0.366
ICU mortality	Maximum 3-4 RBC units on a single day	No transfusion	OR 0.812 (0.358, 1.844)	*No difference* P=0.619

ICU mortality	Maximum >4 RBC units on a single day	No transfusion	OR 0.812 (0.354, 1.863)	*No difference* P=0.623
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of surgical ICU patients.				
Applicability				
The study was carried out in Germany and is likely to be applicable to the Australian setting.				
Comments				
The study found that when variables reflecting organ dysfunction during ICU are controlled for there is no effect of RBC transfusion on mortality. The authors conclude that RBC transfusion during ICU stay may be a surrogate marker for disease severity and is not independently associated with ICU mortality.				

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unt; OR, odds ratio; RBC, red blood cell

STUDY DETAILS: Cohort study				
Citation				
Salim A, Hadjizacharia P, DuBose J, Brown C, Inaba K, Chan L, Margulies DR. Role of anemia in traumatic brain injury. J Am Coll Surg. 2008 Sep;207(3):398-406.				
Affiliation/Source of funds				
From the Department of Surgery, Division of Trauma and Critical Care, Cedars-Sinai Medical Center, and the Division of Trauma, Los Angeles County and University of Southern California Medical Center, Los Angeles, CA; and the Division of Trauma, Brackenridge Hospital, Austin, TX.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III		Single surgical ICU, United States	
Risk factor/s assessed		Potential confounding variables measured		
Transfusion vs. no transfusion		Head AIS (>3 versus ≤3), age (≥55 years versus <55), gender, ISS (≥16 versus <16), head injury, spinal column injury, systolic blood pressure on admission, and heart rate on admission.		
Population characteristics (including size)				
1150 patients with traumatic brain injury admitted to the surgical ICU between Jul 1998 and Dec 2005. All patients with serial haemoglobin measurements were included in the study. Patients who died within 48 hours of admission to the surgical ICU, patients with non-survivable head injuries (n=6), and patients with significant extracranial injuries (n=205), were excluded from analysis. Anaemia was defined as a haemoglobin level of less than 90 g/L for 3 consecutive measurements. The decision to transfuse blood was at the discretion of the trauma attending physician, typically occurring in response to significant haemorrhage, in an effort to correct anaemia or to increase oxygen delivery.				
Length of follow-up		Outcomes measured		
Until discharge		Hospital mortality, complications		
Method of analysis				
Logistic regression				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Large cohort study of traumatic brain injury patients at a single centre. Logistic regression was used to adjust for confounding variables. The raw data was presented in a slightly confusing way but the results of the regression analysis were clear.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1361			
Analysed	1150 (stated as included in analysis); 1123 included in multivariable model			
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
Hospital mortality N=1123	NR	NR	OR 2.19 (1.27, 3.75)	*RBC transfusion is significantly associated with an increased risk of mortality* P=0.0044

Complications (ARDS, acute renal failure, acute respiratory failure, bacteraemia/fungaemia, MOF, PE, pneumonia and sepsis) N=1123	NR	NR	OR 3.67 (2.18, 6.17)	*RBC transfusion is significantly associated with an increased risk of complications* P<0.0001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients with traumatic brain injury.				
Applicability				
The study was carried out in the United States and the results are likely to be applicable to the Australian context.				
Comments				
Complications included acute respiratory distress syndrome, acute renal failure, acute respiratory failure, bacteraemia or fungemia, multisystem organ failure, pulmonary embolism, pneumonia, and sepsis.				

AIS, abbreviated injury score; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio.

STUDY DETAILS: Cohort study				
Citation				
Shorr AF, Duh MS, Kelly KM, Kollef MH; CRIT Study Group. Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med. 2004 Mar;32(3):666-74.				
Affiliation/Source of funds				
From the Pulmonary and Critical Care Medicine Service, Walter Reed Army Medical Center, Washington, DC; Analysis Group , Boston, MA; Ortho Biotech (KMK), Bridgewater, NJ; Pulmonary and Critical Care Medicine, Barnes-Jewish Hospital, Washington University, St. Louis, MO. Ortho Biotech Products (Bridgewater, NJ) sponsored the CRIT Trial. No grant was provided to Dr. Shorr for his work on this analysis, but the analysis itself was funded by Ortho Biotech.				
Study design	Level of evidence	Location/setting		
Multi-centre cohort study	Level III	284 ICUs in the United States		
Risk factor/s assessed	Potential confounding variables measured			
Transfusion vs. none Transfusion (1-2 or >2 units) vs. none	Age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			
Population characteristics (including size)				
This is a subgroup analysis for patients in the CRIT study. 1518 patients without pneumonia at intensive care unit admission and who then required at least 48 hrs of mechanical ventilation. Patients admitted to ICU with pneumonia were excluded as the primary outcome for this study was ventilator-associated pneumonia.				
Length of follow-up			Outcomes measured	
Patients were followed until death, hospital discharge, or up to 30 days after ICU admission, whichever occurred first.			VAP, late-onset VAP	
Method of analysis				
Univariate: student's t test and chi-squared test. Multivariate logistic regression adjusting for time at risk for the outcome event was undertaken to determine independent risk factors for VAP.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Subgroup analysis of VAP in patients requiring mechanical ventilation from the CRIT study				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1563			
Analysed	801		717	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
VAP N=1518	181/801 (22.6)	130/717 (18.1)	OR 1.89 (1.33, 2.68)	*Transfusion is significantly associated with increased risk of VAP* P=0.0004

VAP (1-2 units vs 0 units) N=NR	NR	NR	OR 1.90 (1.28, 2.82)	*Transfusion of 1-2 units is significantly associated with increased risk of VAP compared with no transfusion.* P=0.0027
VAP (> 2 units vs 0 units) N=NR	NR	NR	OR 1.87 (1.24, 2.82)	*Transfusion is significantly associated with increased risk VAP.* P=0.0014
late-onset VAP N=1331	88/801	36/717	OR 2.16 (1.27, 3.66)	*Transfusion is significantly associated with increased risk of late-onset VAP* P=0.0043
late-onset VAP (1-2 units vs 0 units) N=NR	NR	NR	OR 1.96 (1.07, 3.58)	*Transfusion of 1-2 units is significantly associated with increased risk of VAP* P=0.0295
late-onset VAP (> 2 units vs 0 units) N=NR	NR	NR	OR 2.37 (1.31, 4.28)	*Transfusion of >2 units is significantly associated with increased risk of VAP* P=0.0041
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of ICU patients requiring mechanical ventilation.				
Applicability				
The study was carried out in the United States and is likely to be applicable to the Australian context.				
Comments				

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; VAP, ventilator associated pneumonia.

STUDY DETAILS: Cohort study			
Citation			
Spinella PC, Perkins JG, Grathwohl KW et al (2008) Effects of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. Journal of Trauma 64: S69-S78.			
Affiliation/Source of funds			
Connecticut Children's Medical Center, Hartford; Walter Reed Army Medical Center, Washington; Brooke Army Medical Center, Fort Sam Houston; Madigan Army Medical Center, For Lewis; US Army Institute of Surgical Research, Fort Sam Houston; US. Funding not stated.			
Study design	Level of evidence	Location/setting	
Retrospective cohort study	Level III-2	Iraq/1 combat support hospital	
Risk factor/s assessed	Potential confounding variables measured		
PRBC transfusion (per unit). Also included FFP and whole blood (not shown here)	Adjusted for confounding variables associated with survival on univariate analysis. Variables with P<0.02 on univariate analysis included in the model unless colinearity existed between variables. Adjusted for: FFP, ISS, GCS score ≤ 8, base deficit ≥ 4, admission temperature, SBP and Hct.		
Population characteristics (including size)			
Total population included 708 trauma patients admitted to a combat support hospital in Iraq between Nov 2003 and Dec 2004 who received blood transfusion (RBC, FFP or fresh whole blood). Subgroup analysis presented here includes 567 patients who did not receive massive transfusion.			
Length of follow-up	Outcomes measured		
During hospitalisation (i.e. prior to transfer or discharge)	In-hospital survival		
Method of analysis			
Used multivariate logistic regression analysis to adjust for potential confounding variables.			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Retrospective cohort study; included 567/708 transfused patients (excluded those with massive transfusion); adjusted for a number of potential confounders including GCS and Hct.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	708	-	
Analysed	567	-	
Outcome (continuous)	RBC transfusion	Risk estimate (95% CI)	Significance P-value
In-hospital survival N=567	Per unit pRBC	OR 0.77 (0.64, 0.92)	*RBC transfusion is significantly associated with a 23% decreased risk of survival per unit transfused* P=0.004
EXTERNAL VALIDITY			
Generalisability			

The results of this study are generalisable to a population of combat trauma patients who did not have massive transfusion.
Applicability
The study was carried out at a military hospital in Iraq and may not be applicable to the general Australian trauma setting.
Comments
The authors conclude that 'for trauma patients transfused at least one unit of a blood product, FFP and RBC amounts were independently associated with increased survival and decreased survival, respectively.' The authors suggest that the differential results for FFP and RBC suggest that it is possible to adequately adjust for severity of injury. They also note that the association between RBC and decreased survival 'may be related to the increased storage age of RBCs transfused to all patients in our study (33 days).' They note a number of limitations including: (i) the retrospective nature of the study; (ii) the lack of data on admission platelet concentration; and (iii) the fact that 30-day mortality could not be assessed as many foreign nationals were transferred to other facilities when they were stabilised.

CI, confidence interval; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; Hct, haematocrit; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; SBP, systolic blood pressure; US, United States of America.

STUDY DETAILS: Cohort study				
Citation				
Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. JAMA. 2002 Sep 25;288(12):1499-507.				
Affiliation/Source of funds				
Department of Intensive Care, Erasme University Hospital, Brussels, Belgium; Department of Anesthesiology, Hopital Broussais, Paris, France; Department of Anesthesiology, Klinikum FSU Jena, Jena, Germany; Istituto di Anestesia e Rianimazione, Ospedale Maggiore di Milano, Milan, Italy; Medical Intensive Care Unit, VU ziekenhuis, Amsterdam, the Netherlands; Department of Intensive Care, University College London Hospitals, London, England; Department of Anesthesiology and Intensive Care, Onze Lieve Vrouwziekenhuis, Aalst, Belgium.				
Study design	Level of evidence		Location/setting	
Prospective cohort study	Level III		146 ICUs in western Europe	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion		Admitting SOFA score, admitting APACHE II score, age and admitting Hb level.		
Population characteristics (including size)				
3534 patients admitted to ICU during a 2-week period (November 15, 1999, through November 29, 1999). Mean (SD) patient age was 61 (17) years, with 33.4% older than 70 years. The majority of patients (62%) were men. The mean admitting APACHE II score was 14.8 (7.9) and the mean admitting SOFA score was 5.2 (3.8).				
Length of follow-up		Outcomes measured		
Patients were followed up for 28 days or until hospital discharge, inter-institutional transfer, or death.		Mortality Frequency of blood drawing and associated volume of blood drawn, collected over a 24-hour period; hemoglobin levels, transfusion rate and organ dysfunction (assessed using the Sequential Organ Failure Assessment score), collected throughout a 2-week period.		
Method of analysis				
Descriptive statistics were computed for all study variables. Difference testing between groups was performed using the 2-tailed t test, analysis of variance (with Bonferroni post-hoc analyses), or chi squared test. Significance for main effects was tested at the 0.05 level. Logistic regression was conducted to assess determinants of mortality.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Fair quality prospective cohort study. Low levels of missing data.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	3534			
Analysed	1140		1896	
Outcome (categorical)	Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value

28-day mortality N=3534 *Logistic regression*	331/1140 (29.0)	283/1896 (14.9)	OR 1.37 (1.02, 1.84)	*Transfusion is significantly associated with increased risk of mortality* P=0.04
28-day mortality N=1032 *Matched analysis*	117/516 (22.7)	88/516 (17.1)	NR	*Transfusion is significantly associated with increased risk of mortality* P=0.02
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of ICU patients.				
Applicability				
The study was carried out at multiple centres in western Europe and is likely to be applicable to the Australian context.				
Comments				

CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; Hb, haemoglobin; SD, standard deviation; NR, not reported; OR, odds ratio.

STUDY DETAILS: Cohort study				
Citation				
Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology. 2008 Jan;108(1):31-9.				
Affiliation/Source of funds				
Department of Intensive Care, Erasme Hospital, Free University of Brussels. Department of Anesthesiology and Intensive Care, Friedrich-Schiller-University, Jena, Germany. Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, Jerusalem, Israel. Department of Anesthesia, Division of Acute Care Medicine, Stavanger University Hospital, Stavanger, Norway. Department of General Intensive Care, University Hospital Centre Sart-Tilman, Liege, Belgium.				
Study design	Level of evidence		Location/setting	
Multicentre prospective cohort study	Level III-2		198 ICUs in Europe	
Risk factor/s assessed		Potential confounding variables measured		
RBC transfusion		Age, sex, comorbid diseases, Simplified Acute Physiology Score II and Sequential Organ Failure Assessment score on admission, the type of admission (medical or surgical), the presence of sepsis during the ICU stay, and the country of origin.		
Population characteristics (including size)				
The study included all patients aged >15 years admitted to ICU between May 1 and May 15 2002. Patients who stayed in ICU for less than 24 hours for routine postoperative observation were excluded.				
Length of follow-up		Outcomes measured		
Until death, hospital discharge or 60 days.		Hospital mortality, ICU mortality		
Method of analysis				
Univariate: two-tailed t test, Mann–Whitney U test, chi-square test, and Fisher exact test as appropriate. Multivariate Cox proportional hazard model for time to in-hospital death right censored at 30 days. Extended analysis included adjusting for RBC transfusion as a time-dependent variable. Propensity scores were obtained through logistic regression of patient characteristics on blood transfusion status.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: Large multicentre cohort study of ICU patients admitted during a 2-week time period.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	1040		2107	
Analysed	1040		2107	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
30-day mortality (multivariate)	NR	NR	HR 0.89 (0.76, 1.05)	*No difference* P=0.159
30-day mortality (extended multivariate)	NR	NR	HR 0.69 (0.48, 1.01)	*No difference* P=0.055

Propensity matched patients				
30-day mortality	NR	NR	HR 0.73 (0.59, 0.90)	*Favours RBC transfusion.* P=0.004
30-day mortality (extended multivariate)	NR	NR	HR 0.57 (0.36, 0.90)	*Favours RBC transfusion.* P=0.016
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of ICU patients				
Applicability				
The study was carried out at multiple European centres and is likely to be applicable to the Australian setting.				
Comments				
The authors note that these results are contrary to their earlier study which had a highly similar population, study design and analysis. They speculate that improved blood preparation (eg. leukodepletion) may have reduced the risk of mortality associated with transfusion.				

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; NR, not reported; RBC red blood cell.

STUDY DETAILS: Cohort study			
Citation			
Zilberberg MD, Carter C, Lefebvre P, Raut M, Vekeman F, Duh MS, Shorr AF. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care. 2007;11(3):R63.			
Affiliation/Source of funds			
School of Public Health and Health Sciences, University of Massachusetts, Amherst, P.O. Box 303, Goshen, MA, USA; Ortho Biotech Clinical Affairs, LLC, 430 Route 22 East, Bridgewater, NJ, USA; Groupe d'analyse, 1080 Beaver Hall Hill, Suite 1810, Montreal, Quebec, Canada; Analysis Group, 111 Huntington Avenue, Tenth Floor, Boston, MA, USA; Washington Hospital Center, 110 Irving Street, NW, Washington, DC, USA. The Crit study and the current analyses were funded by Ortho Biotech Clinical Affairs, LLC.			
Study design		Level of evidence	Location/setting
Retrospective analysis of data from CRIT prospective cohort study		Level III	284 ICUs in the United States
Risk factor/s assessed	Potential confounding variables measured		
RBC transfusion vs. none	Gender; admitting diagnoses of neurological disorder, gastrointestinal disease, and chronic obstructive pulmonary disease; medical history of diabetes and malignancy; baseline APACHE II score; antibiotics use at baseline; total serum bilirubin of more than 2.0 mg/dl; serum creatinine of more than 2.0 mg/dl; admitting diagnosis; age; ICU type; SOFA score; H2 antagonists at baseline; continuous sedation; nutritional status; Hb level; Albumin ≤2.3 g/dL.		
Population characteristics (including size)			
An analysis of 4730 patients from the CRIT study Only incident cases of ARDS developing in the ICU were included in the analysis. Patients admitted to the ICU with a diagnosis of ARDS were excluded. For the ARDS cases, the pRBC transfusions were examined in the time period prior to or at the visit of the first recorded ARDS complication. For the control group, the pRBC transfusions were observed until the end of the study.			
Length of follow-up	Outcomes measured		
Until death, hospital discharge or 30 days after ICU admission	ARDS, duration of mechanical ventilation, ICU and hospital lengths of stay and hospital costs.		
Method of analysis			
Univariate: Student's t test and chi-squared test. Multivariate: stepwise logistic regression. Covariates included in the final regression model were those significant at an alpha level (determined a priori) of 10% (that is, p value of less than or equal to 0.10) or those with biologic plausibility of relating to ARDS (for example, age, pneumonia, and trauma).			
INTERNAL VALIDITY			
Overall quality assessment (descriptive)			
Rating: Fair Description: Retrospective sub-group analysis of a large multi-centre prospective cohort study. No presentation of baseline characteristics in transfused vs. not transfused groups. No reporting of how many patients were excluded or lost to follow-up.			
RESULTS			
Population	With risk factor	Without risk factor	
Available	4730		

Analysed	2056		2674	
Outcome (categorical)	Transfusion	No transfusion	Risk estimate (95% CI)	Significance P-value
ARDS, any RBC transfusion N=4730	164/2056 (8.0)	82/2674 (3.1)	OR 2.797 (1.899, 4.120	*RBC transfusion is significantly associated with an increased risk of ARDS* P<0.0001
ARDS (1-2 units vs. 0 units) N=NR	NR	NR	OR 2.191 (1.409, 3.407)	*RBC transfusion of 1-2 units is significantly associated with an increased risk of ARDS compared with no transfusion* P=0.0005
ARDS (>2 units vs. 0 units) N=NR	NR	NR	OR 3.784 (2.417, 5.924)	*RBC transfusion of >2 units is significantly associated with an increased risk of ARDS compared with no transfusion* P<0.0001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of ICU patients.				
Applicability				
The study was carried out in the United States and is likely to be generalisable to the Australian context.				
Comments				

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, Acute respiratory distress syndrome; CI, confidence interval; Hb, haemoglobin; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; pRBC, packed red blood cell; SOFA, Sequential Organ Failure Assessment.

STUDY DETAILS: Cohort study				
Citation				
Zilberberg MD, Stern LS, Wiederkehr DP, Doyle JJ, Shorr AF. Anemia, transfusions and hospital outcomes among critically ill patients on prolonged acute mechanical ventilation: a retrospective cohort study. Crit Care. 2008;12(2):R60.				
Affiliation/Source of funds				
School of Public Health and Health Sciences, University of Massachusetts, North Pleasant Street, Amherst, Massachusetts, USA, Analytica International, Park Avenue South, New York, New York, USA, Division of Pulmonary and Critical Care Medicine, Washington Hospital Center, Irving Street Northwest, Washington, District of Columbia, USA				
Study design	Level of evidence	Location/setting		
Retrospective cohort study	Level III	Review of Henry Ford Health System database which includes seven hospitals serving the primary and specialty health care needs of residents in the Midwestern USA.		
Risk factor/s assessed	Potential confounding variables measured			
RBC transfusion	age, sex, race, Charlson Comorbidity Index, baseline and nadir hemoglobin, hospital-acquired pneumonia, blood stream infection, gastrointestinal endoscopy, abdominal surgery, cardiac surgery (on and off bypass), and orthopaedic surgery. Mortality outcomes were adjusted additionally for hospital length of stay. Hospital length of stay and cost outcomes were adjusted for mortality.			
Population characteristics (including size)				
The study used data from all hospital admissions that took place between January 2000 and December 2005. Patients were included if they were 18 years old or older and had charges associated with at least one procedure code for insertion of an endotracheal tube for mechanical ventilation and at least one code for 96 continuous hours of ventilation. Patients on dialysis before the index admission and with a diagnosis code for chronic renal failure were excluded. The analysis identified 4344 eligible patients.				
Length of follow-up	Outcomes measured			
Until hospital discharge or death.	Mortality, resource utilization (hospital length of stay), hospital costs, discharge Hb, and discharge destination.			
Method of analysis				
Descriptive statistics, chi-squared and student's t tests, Mann-Whitney tests (for costs), linear (costs) and logistic (mortality) regression.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: A retrospective analysis of a large integrated claims database covering a 5-year period (January 2000 to December 2005) was conducted in adult patients receiving prolonged acute mechanical ventilation (mechanical ventilation for ≥ 96 hours).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	4334			
Analysed	2912		1432	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value

Hospital mortality N=4334	938/2912 (32.2)	342/1432 (23.9)	OR 1.21 (1.00, 1.48)	*Transfusion may be associated with increased risk of hospital mortality.* P=NR
Hospital costs ($) N=4334	NR	NR	$48,973 ($45,582, $52,478)	*Transfusion was associated with increased hospital costs.* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of critically ill patients on prolonged acute mechanical ventilation				
Applicability				
The study was carried out in the United States and is likely to be applicable to the Australian context.				
Comments				

CI, confidence interval; Hb, haemoglobin; NR, not reported; SD, standard deviation; OR, odds ratio.

Restrictive vs. liberal RBC transfusion: Critical Care/Trauma

Level I evidence

STUDY DETAILS: SR/MA				
Citation				
Kramer AH, Zygun DA. Anemia and red blood cell transfusion in neurocritical care. Crit Care. 2009;13(3):R89.				
Affiliation/Source of funds				
Departments of Critical Care Medicine & Clinical Neurosciences & Community Health Sciences, University of Calgary, Foothills Medical Center, Calgary, AB, Canada.				
Study design			Level of evidence	Location/setting
Systematic review of Level II and III studies			Level I/III	Various
Intervention/risk factor		Comparator		
1) RBC transfusion 2) Restrictive transfusion threshold		1) No transfusion 2) Liberal transfusion threshold		
Population characteristics				
Patients with traumatic brain injury or aneurysmal subarachnoid haemorrhage.				
Length of follow-up		Outcomes measured		
Various, most to discharge.		Mortality, nosocomial infections, complications, outcome at discharge and six months		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Poor Search of Medline only from inception to March 2009. Search terms used were very brief and definitely not exhaustive, retrieving 2137 english language publications. Little detail of inclusion/exclusion criteria and no assessment of study quality.				
RESULTS				
Outcome No. trials (No. patients)	RBC transfusion or Restrictive transfusion n/N (%)	No transfusion or Liberal transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Traumatic brain injury				
Carlson 2006, linear regression, N=169				
Outcome at discharge	NR	NR	NR	*Number of RBC units transfused was associated with worse discharge outcome.*
Duane 2008, logisitic regression (age, ISS, total blood products), N=788				
Mortality	NR	NR	NR	*RBC transfusions not associated with mortality.*
Nosocomial infection	NR	NR	NR	*RBC transfusions associated with nosocomial infections.*
Salim 2008, logistic regression (10 covariates), N=1150				

Hospital mortality	NR	NR	OR 2.2	*RBC transfusion is associated with hospital mortality.* *P=0.004*
Complications			OR 3.7	*RBC transfusion is associated with complications.* *P=0.0001*
George 2008, Cox proportional hazard regression (age, motor GCS, blood ethanol, lowest Na+, complications), N=82				
Mortality	Transfusion: 52%	No transfusion: 48%	NR	*RBC transfusion predicted mortality.* *P<0.05*
McIntyre 2006 – see separate data extraction form				
Aneurysmal subarachnoid haemorrhage				
Kramer 2008, Logistic regression (WFNS score, age, vasospasm, modified Fisher score), N=245				
Nosocomial infection	NR	NR	NR	*RBC transfusion is associated with nosocomial infection.* *P=NR*
Tseng 2008, Logistic regression (age, WFNS, IVH, postoperative deficits, sepsis, DIDs), N=160				
Poor outcome at discharge	NR	NR	OR 4.5	*RBC transfusion is associated with poor outcome at discharge.* *P=0.04*
Poor outcome at 6 months	NR	NR	NR	*RBC transfusion is <u>not</u> associated with poor outcome at 6 months.* *P=NR*
DeGeorgia 2005, abstract only, Logistic regression (Hunt-Hess, APACHE II), N=166				
Worse outcome at discharge, patients with vasospasm	NR	NR	OR 2.9 (1.1, 7.8)	*RBC transfusion is associated with worse outcome at discharge in patients with vasospasm.* *P=NR*
Worse outcome at discharge, patients without vasospasm	NR	NR	NR	*RBC transfusion is <u>not</u> associated with worse outcome at discharge in patients without vasospasm.* *P=NR*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to populations with traumatic brain injury and subarachnoid haemorrhage.				
Applicability				
The included studies were conducted in a range of countries and may be applicable to the Australian setting.				
Comments				
The authors conclude that 'although hemoglobin concentrations as low as 7 g/dL are well tolerated in most critical care patients, such a severe degree of anaemia could be harmful in brain-injured patients'.				

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; GCS, Glasgow Coma Scale; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial.

Level II evidence

STUDY DETAILS: RCT		
Citation		
Hébert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, Blajchman M. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group. JAMA. 1995 May 10;273(18):1439-44.		
Affiliation/Source of funds		
Critical Care Programs at the University of Ottawa; the University of Toronto; the University of Western Ontario, London, Ontario; and the University of British Columbia, Vancouver; the Clinical Epidemiology Unit, University of Ottawa; and the Department of Pathology, McMaster University, Hamilton, Ontario. This work was supported by the Canadian Red Cross Society, Blood Services, Ottawa, Ontario, and the Physicians' Services Incorporated, North York, Ontario. Dr Hebert is a Career Scientist with the Ontario Ministry of Health.		
Study design	Level of evidence	Location/setting
Multicentre RCT	Level II	5 ICUs in Canada
Intervention	Comparator	
Restrictive transfusion strategy – Hb levels maintained at 70-90 g/L and transfusion trigger of Hb 70-75 g/L	Liberal transfusion strategy – Hb levels maintained at 100-120 g/L and a transfusion threshold of 100-105 g/L	
Population characteristics		
The study enrolled 69 patients ≥16 years old who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of ≤ 90 g/L within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded if they were unable to receive blood products; were losing blood at enrolment (defined as evidence of ongoing blood loss and a decrease in the Hb of 30 g per litre or use of at least 3 units of packed RBC during the previous 12 hours); chronic anaemia (Hb <90 g/L at least once within the previous month); pregnancy; brain death or imminent brain death; a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. Patients were admitted between 15 March 1993 and 30 January 1994. All randomised patients completed the study.		
Length of follow-up	Outcomes measured	
NR	30-day mortality, 120-day mortality, ICU mortality, hospital mortality, multiple organ dysfunction Analysis: ITT; univariate with Fisher's exact test	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Fair quality. Not blinded, but outcome assessment not affected by this; small pilot study underpowered to show non-inferiority.		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	33	36
Efficacy analysis (ITT)	33	36
Safety analysis	33	36

Outcome	Restrictive n/N (%) Mean ± SD (N)	Liberal n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
ICU mortality N=69	5/33 (15)	7/36 (19)	RD -0.04 (-0.22, 0.14)[a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase ICU mortality compared with a liberal RBC transfusion trigger. P=0.64* [a]
30-day mortality N=69	8/33 (24)	9/36 (25)	RD -0.01 (-0.21, 0.20)[a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase 30-day mortality compared with a liberal RBC transfusion trigger. P=0.94* [a]
120-day mortality N=46 *Study-reported analysis*	13/24 (54)	11/22 (50)	RD 0.04 (-0.25, 0.33)[a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase 120-day mortality compared with a liberal RBC transfusion trigger. P=0.78* [a]
120-day mortality N=69 *Post-hoc review analysis*	21/33 (64)	25/36 (69)	RD -0.06 (-0.28, 0.16)[a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase 120-day mortality compared with a liberal RBC transfusion trigger. P=0.61* [a]
Multiple organ dysfunction score	9.3±3.6	10.0±3.8	MD -0.70 (- 2.4, 1.0) [a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase MODS compared with a liberal RBC transfusion trigger.* *P=0.44*
Multiple System Organ Failure (≥3 organ failures)	9/33 (27)	6/36 (17)	RD 0.106 (-0.09, 0.29) [a]	*A restrictive RBC transfusion trigger does <u>not</u> significantly increase Multiple System Organ Failure rates compared with a liberal RBC transfusion trigger.* *P=0.38*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of critical care patients.				
Applicability				
The study was carried out in Canada and is likely to be applicable to the Australian context.				
Comments				
The authors conclude that use of a restrictive transfusion strategy does not appear to increase mortality and organ failure rates in critical care patients, although the study may be underpowered.				

Hb, haemoglobin; ICU, intensive care unit; ITT, intention-to-treat; MODS, multiple-organ-dysfunction score; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation.

[a] Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Recalculated post hoc to show restrictive vs liberal.

STUDY DETAILS: RCT		
Citation		
Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17.		
Affiliation/Source of funds		
From the Critical Care Program and the Clinical Epidemiology Unit, University of Ottawa, Ottawa; the Department of Pathology, McMaster University, Hamilton, On; the Critical Care Program, University of Toronto, Toronto; the Critical Care Program, University of Western Ontario, London; and the Critical Care Program, University of British Columbia, Vancouver — all in Canada. Supported by the Medical Research Council of Canada and by an unrestricted grant from Bayer. Dr. Hébert is a Career Scientist of the Ontario Ministry of Health.		
Study design	Level of evidence	Location/setting
Multicentre RCT (TRICC)	Level II	25 intensive care units in Canada
Intervention	Comparator	
Restrictive transfusion strategy – Hb levels maintained at 70-90 g/L and transfusion given when Hb <70 g/L	Liberal transfusion strategy – Hb levels maintained at 100-120 g/L and a transfusion threshold of 100 g/L	
Population characteristics		
The study enrolled patients ≥16 years old who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of 90 g/L or less within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded if they were unable to receive blood products; were losing blood at enrolment (defined as evidence of ongoing blood loss and a decrease in the Hb of 30 g per litre or use of at least 3 units of packed RBC during the previous 12 hours); chronic anaemia (Hb <90 g/L at least once within the previous month); pregnancy; brain death or imminent brain death; a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. 6451 patients were assessed for eligibility and 838 patients were randomised, with 829 patients completing the study. Patients were stratified by centre and by APACHE II score (≤15 or >15). Adherence to transfusion protocol was required only during the patients' stay in ICU. Patients were admitted between November 1994 and November 1997.		
Length of follow-up	Outcomes measured	
Up to 60 days	30-day mortality, 60-day mortality, ICU mortality, hospital mortality, complications Analysis: ITT; univariate with Fisher's exact test; multivariate with forward stepwise logistic regression. Adjusted for age, APACHE II score, diagnosis, and coexisting illnesses	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Fair quality. Randomised; open-label but objective outcome; underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.		
RESULTS		
Population analysed	Intervention	Comparator

Randomised	418		420	
Efficacy analysis (ITT)	418		420	
Safety analysis				
Outcome	Restrictive n/N (%) Mean ± SD (N)	Liberal n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
30-day mortality N=838	78/418 (18.7)	98/420 (23.3)	RD -0.047 (-0.102, 0.0084)[c]	*No significant difference* *P=0.10*
			Unadjusted OR 0.75	*No significant difference* *P=0.09*
			Adjusted OR 0.72 (0.50, 1.07)[a]	*No significant difference* *P=0.07*
30-day mortality (cardiac disease patients only) N=326	31/151 (20.5)	40/175 (22.9)	RD -0.024 (-0.113, 0.067) [c]	*No difference* *P=0.69*
30-day mortality (severe infection or septic shock patients only) N=218	26/114 (22.8)	31/104 (29.8)	NR	*No difference* *P=0.36*
30-day mortality (trauma patients only) N=200	10/100 (10)	9/103[b] (8.8)	NR	*No difference* *P=0.81*
30-day mortality (aged ≥55 years) N=504	NR	NR	NR	*No difference* *P>0.36*
30-day mortality (aged <55 years) N=334	5.7%	13.0%	RD -0.073 (-0.135, -0.011)[a]	*Favours restrictive transfusion* *P=0.03*
30-day mortality (APACHE II score > 20) N=414	NR	NR	NR	*No difference* *P>0.36*
30-day mortality (APACHE II score ≤ 20) N=424	8.7%	16.1%	RD -0.074 (-0.136, -0.01)[a]	*Favours restrictive transfusion* *P=0.02*
60-day mortality N=838	95/418 (22.7)	111/420 (26.5)	RD -0.037 (-0.095, 0.021)[c]	*No difference* *P=0.23*

ICU mortality N=838	56/418 (13.4)	68/420 (16.2)	RD -0.023 (-0.076, 0.020)[c]	*No difference* *P=0.29*
Hospital mortality N=838	93/418 (22.2)	118/420 (28.1)	RD -0.058 (-0.117, 0.003)[c]	*No significant difference P=0.05*
Multiple-organ-dysfunction, ≥ 3 organ failures N=838	73/418 (17.5)	81/420 (19.3)	RD -0.02 (-0.07, 0.03)[c]	*No difference* *P=0.53*
Multiple-organ-dysfunction score (adjusted) N=838	10.7±7.5	11.8±7.7	MD -1.1 (-2.2, -0.8,)	*Favours restrictive transfusion* *P=0.03*
Multiple-organ-dysfunction score (change from baseline; adjusted) N=838	3.2±7.0	4.2±7.4	MD -1.0 (-2.0, -0.1)	*Favours restrictive transfusion* *P=0.04*
MOD score (aged ≥55 years, adjusted for those who died) N=504	NR	NR	NR	*No difference* *P>0.30*
MOD score (aged <55 years, adjusted for those who died) N=334	8.8 ± 5.7	10.3 ± 6.6	NR	*Favours restrictive transfusion* *P=0.03*
MOD score (APACHE II score > 20, adjusted for those who died) N=414	NR	NR	NR	*No difference* *P>0.30*
MOD score (APACHE II score ≤ 20, adjusted for those who died) N=424	8.3 ± 6.2	10.0 ± 7.2	NR	*Favours restrictive transfusion* *P=0.01*
Multiple-organ-dysfunction score (cardiac patients only) N=326	NR	NR	NR	*No difference* *P > 0.3*
Multiple-organ-dysfunction score (severe infection or septic shock patients only) N=218	NR	NR	NR	*No difference* *P > 0.3*

Multiple-organ-dysfunction score (trauma patients only) N=200	NR	NR	NR	*No difference* *P > 0.3*
Pulmonary complications N=838	106/418 (25.4)	122/420 (29.0)	RD -0.037 (-0.097, 0.023)[c]	*No difference* *P=0.22*
ARDS N=838	32/418 (7.7)	48/420 (11.4)	RD -0.038 (-0.078, 0.002)[c]	*No significant difference* *P=0.06*
Pneumonia N=838	87/418 (20.8)	86/420 (20.5)	RD 0.003 (-0.051, 0.058)[c]	*No difference* *P=0.92*
Infectious complications N=838	42/418 (10.0)	50/420 (11.9)	RD -0.019 (-0.061, 0.024)[c]	*No difference* *P=0.38*
Bacteraemia N=838	30/418 (7.2)	40/420 (9.5)	RD -0.023 (-0.061, 0.014)[c]	*No difference* *P=0.22*
Catheter-related sepsis N=838	21/418 (5.0)	17/420 (4.0)	RD 0.01 (-0.018, 0.038)[c]	*No difference* *P=0.50*
Septic shock N=838	41/418 (9.8)	29/420 (6.9)	RD 0.029 (-0.008, 0.067)[c]	*No difference* *P=0.13*
EXTERNAL VALIDITY				
Generalisability				
The results of the study are generalisable to a population of critical care patients.				
Applicability				
The study was carried out in Canada and the results are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that use of a restrictive transfusion protocol in intensive care does not result in increased mortality and reduces multi-organ failure. Initial powering estimates suggested that 2300 patients were required; this was revised to 1620 patients. Final included numbers were 838, so study may be underpowered.				

TRICC, transfusion requirements in critical care; APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, haemoglobin; ICU, intensive care unit; ITT, intention-to-treat; MODS, multiple-organ-dysfunction score; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation.

[a] Adjusted for age, APACHE II score, diagnosis, and coexisting illnesses.

[b] Incorrect number included in publication. Correct number taken from McIntyre 2004.

[c] Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Recalculated post hoc to show restrictive vs liberal.

STUDY DETAILS: RCT		
Citation		
Hébert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001 Feb;29(2):227-34.		
Affiliation/Source of funds		
From the Critical Care Programs at the University of Ottawa, Ottawa, ON, Canada; the University of Toronto, Toronto, ON; the University of Western Ontario , London, ON; the University of British Columbia , Vancouver, BC, Canada; the Clinical Epidemiology Unit, University of Ottawa; and the Departments of Pathology and Medicine, Mc- Master University, Hamilton, ON. Supported, in part, by the Medical Research Council of Canada and an unrestricted grant from Bayer Inc.		
Study design	Level of evidence	Location/setting
Multicentre RCT (TRICC)	Level II	25 intensive care units in Canada
Intervention	Comparator	
Restrictive transfusion strategy – Hb levels maintained at 70-90 g/L and transfusion given when Hb <70 g/L	Liberal transfusion strategy – Hb levels maintained at 100-120 g/L and a transfusion threshold of 100 g/L	
Population characteristics		
The study enrolled patients ≥16 years old who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of ≤ 90 g/L within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded if they were unable to receive blood products; were losing blood at enrolment (defined as evidence of ongoing blood loss and a decrease in the Hb of 30 g per litre or use of at least 3 units of packed RBC during the previous 12 hours); chronic anaemia (Hb <90 g/L at least once within the previous month); pregnancy; brain death or imminent brain death; a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. 6451 patients were assessed for eligibility and 838 patients were randomised, with 829 patients completing the study. Patients were stratified by centre and by APACHE II score (≤15 or >15). Adherence to transfusion protocol was required only during the patients' stay in ICU. 357 of the enrolled patients had cardiovascular disease. Patients were admitted between November 1994 and November 1997.		
Length of follow-up	Outcomes measured	
60 days, one patient with cardiovascular disease was lost to follow up at 60 days.	30-day mortality, 60-day mortality, ICU mortality, hospital mortality, complications Analysis: ITT; univariate with Fisher's exact test; multivariate with forward stepwise logistic regression. Adjusted for age, APACHE II score, diagnosis, and coexisting illnesses	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Fair quality. Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.		
RESULTS – Cardiovascular disease patients only		
Population analysed	Intervention	Comparator

Randomised	160 (111 for ischaemic heart disease)		197 (147 for ischaemic heart disease)	
Efficacy analysis (ITT)	160 (111 for ischaemic heart disease)		197 (147 for ischaemic heart disease)	
Safety analysis	160 (111 for ischaemic heart disease)		197 (147 for ischaemic heart disease)	
Outcome	Restrictive n/N (%) Mean ± SD (N)	Liberal n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
30-day mortality, all cardiovascular disease N=357	36/160 (23)	45/197 (23)	RD -0.003 (-0.091, 0.084)[a]	*No difference* *P=1.0*
			Unadjusted OR 1.14 (0.66, 1.96)	*No difference* *P=0.94*
			Adjusted OR 1.26 (0.70, 2.24)	*No difference* *P=0.68*
30-day mortality (ischaemic heart disease patients only) N=258	29/111 (26)	31/147 (21)	RD 0.049 (-0.056, 0.153)[a]	*No difference* *P=0.38*
60-day mortality N=356 *Study-reported analysis*	42/160 (26)	53/197 (27)	RD -0.008 (-0.10, 0.084)[a]	*No difference* *P=0.9*
60-day mortality (ischaemic heart disease patients only) N=258	32/111 (29)	36/147 (25)	RD 0.04 (-0.069, 0.149)[a]	*No difference* *P=0.48*
ICU mortality N=357	31/160 (19)	32/197 (16)	RD 0.031 (-0.048, 0.111)[a]	*No difference* *P=0.49*
ICU mortality (ischaemic heart disease patients only) N=258	26/111 (23)	25/147 (17)	RD 0.063 (-0.035, 0.162)[a]	*No difference* *P=0.27*
Hospital mortality N=357	43/160 (27)	56/197 (28)	RD -0.019 (-0.109, 0.069)[a]	*No difference* *P=0.81*
Hospital mortality (ischaemic heart disease patients only) N=258	32/111 (29)	39/147 (27)	RD 0.021 (-0.089, 0.132)[a]	*No difference* *P=0.78*

MODS N=351	8.6±4.9	9.0±4.4	MD 0.4 (-0.6, 1.4)[a]	*No difference* *P=0.4*
MODS (ischaemic heart disease only) N=258	9.1±5.0	9.1±4.5	MD 0.1 (-1.2, 1.2)[a]	*No difference* *P=0.98*
Change in MODS N=351	0.23±4.2	1.28±4.4	MD 1.1 (0.1, 2)[a]	*Favours restrictive transfusion* *P=0.023*
Change in MODS (ischaemic heart disease patients only) N=258	0.31±4.3	1.00±4.3	MD 0.7 (-0.4, 1.8)[a]	*No difference* *P=0.21*
MODS (nonsurvivors considered to have all organs failed at death) N=357	11.1±7.6	11.9±7.9	MD -0.7 (-2.4, 0.8)[a]	*No difference* *P=0.39*
MODS (ischaemic heart disease; nonsurvivors considered to have all organs failed at death) N=258	11.8±8.2	11.6±7.5	MD 0.3 (-1.7, 2.2)[a]	*No difference* *P=0.8*
Change in MODS (nonsurvivors considered to have all organs failed at death) N=357	2.7±6.9	4.0±7.3	MD -1.3 (-2.8, 0.2)[a]	*No significant difference* *P=0.081*
Change in MODS (ischaemic heart disease, nonsurvivors considered to have all organs failed at death) N=258	3.0±7.1	3.4±6.7	MD -0.4 (-2.2, 1.3)[a]	*No significant difference* *P=0.61*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of critical care patients with cardiovascular disease.				
Applicability				
The study was conducted in Canada and is likely to be applicable to the Australian context.				
Comments				

The authors conclude that a restrictive transfusion strategy is appropriate for haemodynamically stable critical care patients with cardiovascular disease. The authors acknowledge that the study may be underpowered for this subgroup. The numbers of patients with cardiovascular disease used here are different to the numbers used in the original TRICC publication (Hebert 1999).

TRICC, Transfusion Requirements in Critical Care; APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, haemoglobin; ICU, intensive care unit; ITT, intention-to-treat; MODS, multiple-organ-dysfunction score; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; OR, odds ratio.

a Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Reversed post hoc to show restrictive vs liberal.

STUDY DETAILS: RCT		
Citation		
McIntyre L, Hebert PC, Wells G, Fergusson D, Marshall J, Yetisir E, Blajchman MJ; Canadian Critical Care Trials Group. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? J Trauma. 2004 Sep;57(3):563-8; discussion 568.		
Affiliation/Source of funds		
Centre for Transfusion and Clinical Epidemiology Program, Ottawa Health Research Institute, Ottawa, Ontario. Supported by the Medical Research Council of Canada and by an unrestricted grant from Bayer.		
Study design	Level of evidence	Location/setting
Multicentre RCT (TRICC)	Level II	25 intensive care units in Canada
Intervention	Comparator	
Restrictive transfusion strategy – Hb levels maintained at 70-90 g/L and transfusion given when Hb <70 g/L	Liberal transfusion strategy – Hb levels maintained at 100-120 g/L and a transfusion threshold of 100 g/L	
Population characteristics		
The study enrolled patients ≥16 years old who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of ≤ 90 g/L 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded if they were unable to receive blood products; were losing blood at enrolment (defined as evidence of ongoing blood loss and a decrease in the Hb of 30 g per litre or use of at least 3 units of packed RBC during the previous 12 hours); chronic anaemia (Hb <90 g/L at least once within the previous month); pregnancy; brain death or imminent brain death; a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. 6451 patients were assessed for eligibility and 838 patients were randomised, with 829 patients completing the study. Patients were stratified by centre and by APACHE II score (≤15 or >15). Adherence to transfusion protocol was required only during the patients' stay in ICU. The trial included 203 trauma patients: 100 in the restrictive group and 103 in the liberal red blood cell transfusion group. One patient was lost to follow-up at 60 days. Patients were admitted between November 1994 and November 1997.		
Length of follow-up	Outcomes measured	
Up to 60 days	30-day mortality, 60-day mortality, ICU mortality, hospital mortality, complications Analysis: ITT; univariate with Fisher's exact test; multivariate with forward stepwise logistic regression. Adjusted for age, APACHE II score, diagnosis, and coexisting illnesses	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Fair quality. Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.		
RESULTS – Resuscitated trauma patients		
Population analysed	Intervention	Comparator
Randomised	100	103
Efficacy analysis (ITT)	100	103
Safety analysis	100	103

Outcome	Restrictive n/N (%) Mean ± SD (N)	Liberal n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
30-day mortality N=203	10/100 (10)	9/103 (9)	RD 0.01 (-0.07, 0.09) Unadjusted OR 0.86 (0.34, 2.22) Adjusted OR 0.72 (0.24, 2.19)	*No difference* *P=0.81*
60-day mortality N=203	10/100 (10)	10/103 (10)	RD 0.00 (-0.08, 0.08)[a]	*No difference* *P=1.00*
ICU mortality N=203	8/100 (8)	6/103 (6)	RD 0.02 (-0.05, 0.09)[a]	*No difference* *P=0.59*
Hospital mortality N=203	10/100 (10)	10/103 (10)	RD 0.00 (-0.08, 0.08)[a]	*No difference* *P=1.00*
MODS N=202	7.9±4.4	7.7±3.9	MD 0.00 (-0.08, 0.08)	*No difference* *P=0.69*
Change in MODS N=202	0.0±4.4	0.6±3.8	NR	*No difference* *P=0.29*
MODS (nonsurvivors considered to have all organs failed at death) N=203	9.2±6.3	9.0±6.0	NR	*No difference* *P=0.81*
Change in MODS (nonsurvivors considered to have all organs failed at death) N=203	1.2±6.1	1.9±5.7	NR	*No difference* *P=0.44*
Infection N=203	8/100 (8.0)	13/103 (12.6)	NR	*No difference* *0.28*
EXTERNAL VALIDITY				
Generalisability				
The study is generalisable to a population of critical care resuscitated trauma patients				
Applicability				
The study was carried out in Canada and the results are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that for critically ill resuscitated trauma patients, a restrictive transfusion strategy is appropriate.				

TRICC, Transfusion Requirements in Critical Care; APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, haemoglobin; ICU, intensive care unit; ITT, intention-to-treat; MODS, multiple-organ-dysfunction score; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation; CI, confidence interval.

[a] Calculated post-hoc for this review.

STUDY DETAILS: RCT		
Citation		
McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, Hare GM, Hébert PC. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocrit Care. 2006; 5:4-9.		
Affiliation/Source of funds		
Centre for Transfusion and Critical Care Research, Clinical Epidemiology Unit, Critical Care Program, University of Ottawa and Ottawa Health Research Institute; Departments of Critical Care and Pediatrics, Hospital for Sick Children, University of Toronto; Critical Care Program, The Ottawa Hospital; Department of Surgery, Critical Care Program, University of Toronto; University of Ottawa Heart Institute, Ottawa; Department of Anesthesia and Physiology, University of Toronto, St. Michael's Hospital. Supported by the Medical Research Council of Canada and by an unrestricted grant from Bayer. Dr. Hébert is a Career Scientist of the Ontario Ministry of Health.		
Study design	Level of evidence	Location/setting
Multicentre RCT (TRICC)	Level II	25 ICUs in Canada (13 ICUs contributed to this analysis)
Intervention	Comparator	
Restrictive transfusion strategy – Hb levels maintained at 70-90 g/L and transfusion given when Hb <70 g/L	Liberal transfusion strategy – Hb levels maintained at 100-120 g/L and a transfusion threshold of 100 g/L	
Population characteristics		
The study enrolled patients ≥16 years old who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of ≤ 90 g/L or less within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded if they were unable to receive blood products; were losing blood at enrolment (defined as evidence of ongoing blood loss and a decrease in the Hb of 30 g per litre or use of at least 3 units of packed RBC during the previous 12 hours); chronic anaemia (Hb <90 g/L at least once within the previous month); pregnancy; brain death or imminent brain death; a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. 6451 patients were assessed for eligibility and 838 patients were randomised, with 829 patients completing the study. Patients were stratified by centre and by APACHE II score (≤15 or >15). Adherence to transfusion protocol was required only during the patients' stay in ICU. Patients were admitted between November 1994 and November 1997. 67 of the enrolled patients sustained a closed head injury.		
Length of follow-up	Outcomes measured	
Up to 60 days	30-day mortality, 60-day mortality, ICU mortality, hospital mortality, complications Analysis: ITT; univariate with Fisher's exact test; multivariate with forward stepwise logistic regression. Adjusted for age, APACHE II score, diagnosis, and coexisting illnesses	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Fair quality. Subgroup analysis of TRICC trial; original trial underpowered to show non-inferiority; randomised approximately 50% of required number of patients estimated by sample size calculations.		
RESULTS – Trauma patients with closed head injury		

Population analysed	Intervention		Comparator	
Randomised	29		38	
Efficacy analysis (ITT)	29		38	
Safety analysis	29		38	
Outcome	Restrictive n/N (%) Mean ± SD (N)	Liberal n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
30-day mortality N=67	5/29 (17)	5/38 (13)	RD 0.041 (-0.134, 0.215)	*No difference* *P=0.64*
			Unadjusted OR 0.73 (0.19, 2.80)	*No difference* *P=0.74*
			Adjusted OR 0.76 (0.12, 4.93)	*No difference* *P=0.91*
60-day mortality N=67	5/29 (17)	5/38 (13)	RD 0.04 (-0.13, 0.22)[a]	*No difference* *P=0.64*
ICU mortality N=67	3/29 (10)	3/38 (8)	RD 0.02 (-0.12, 0.16)[a]	*No difference* *P=0.73*
Hospital mortality N=67	5/29 (17)	5/38 (13)	RD 0.04 (-0.13, 0.22)[a]	*No difference* *P=0.64*
MODS N=37	9.3 ± 3.7	8.6 ± 3.6	NR	*No difference* *P=0.40*
Change in MODS N=67	1.7 ± 3.8	1.3 ± 3.8	NR	*No difference* *P=0.68*
MODS (nonsurvivors considered to have all organs failed at death) N=67	12.1 ± 6.4	10.6 ± 6.3	NR	*No difference* *P=0.35*
Change in MODS (nonsurvivors considered to have all organs failed at death) N=67	4.5 ± 6.2	3.4 ± 6.2	NR	*No difference* *P=0.49*
Infection N=67	2/29 (6.9)	2/38 (5.3)	NR	*No difference* *P=0.78*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of trauma patients with closed head injury.				
Applicability				

The study was carried out in Canada and the results are likely to be applicable to the Australian setting.
Comments
The authors state that the study size is too small to make any conclusions about the best transfusion strategy in closed head injury trauma patients. Neurological recovery was not measured in the TRICC trial.

TRICC, Transfusion Requirements in Critical Care; APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, haemoglobin; ICU, intensive care unit; ITT, intention-to-treat; MODS, multiple-organ-dysfunction score; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation; CI, confidence interval.

[a] Calculated post-hoc for this review.

Restrictive vs. liberal RBC transfusion: Mixed/General Population

Level I evidence

STUDY DETAILS: SR/MA				
Citation				
Carless et al (2010) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD002042. DOI: 10.1002/14651858.CD002042.pub2.				
Affiliation/Source of funds				
University of Newcastle, Newcastle, Australia; Institute of Clinical Evaluative Sciences, Toronto, Canada; Robert Wood Johnson Medical School, New Brunswick, US; Ottawa General Hospital, Ottawa, Canada; Scottish National Blood Transfusion Service, Edinburgh, UK; London School of Hygiene and Tropical Medicine, London, UK.				
Study design	Level of evidence	Location/setting		
Systematic review/meta-analysis of RCTs	Level I	Various		
Intervention/risk factor	Comparator			
Restrictive red blood cell transfusion (allogeneic or autologous)	Liberal red blood cell transfusion (allogeneic and/or autologous)			
Population characteristics				
Any eligible (N=17 RCTs and 3746 subjects). Included trauma and critical care (6 RCTs), upper GI haemorrhage (2 RCTs), surgery (8 RCTs) and leukaemia (1 RCT).				
Length of follow-up	Outcomes measured			
Not stated but mortality at 120 days included as an outcome	Mortality and transfusion-related events including infection, pneumonia and renal failure. Other outcomes not included in this review.			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Good Thorough literature search conducted; included RCTs only; quality of studies assessed; individual study results reported; meta-analysis conducted including all studies; heterogeneity assessed and discussed.				
RESULTS				
Outcome No. trials (No. patients)	Restrictive RBC transfusion n/N (%)	Liberal RBC transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity[a] P value (I^2)
< 14-day mortality 2 RCTs (N=821) *Original analysis*	1/408 (0.2)	3/413 (0.7)	RR 0.44 (0.006, 2.96)	No difference P=0.40 (Phet=0.84; I^2=0%)
30-day mortality 9 RCTs (N=2461) *Original analysis*	113/1226 (9.2)	134/1235 (10.9)	RR 0.83 (0.66, 1.05)	No difference P=0.12 (Phet=0.65; I^2=0%)

30-day mortality 3 RCTs (N=1544) *Post-hoc analysis 1 – CC/trauma studies only*	100/771 (13.0)	121/773 (15.7)	RR 0.83 (0.66, 1.06)	No difference P=0.13 (Phet=0.80; I^2=0%)
30-day mortality 2 RCTs (N=907) *Post-hoc analysis 2 – CC/trauma studies only (excluding paediatric study)*	86/451 (19.1)	107/456 (23.2)	RR 0.81 (0.63, 1.05)	No difference P=0.11 (Phet=0.66; I^2=0%)
60-day mortality 2 RCTs (N=922) *Original analysis*	100/460 (21.7)	113/462 (24.5)	RR 1.09 (0.46, 2.60)	No difference P=0.85 (Phet=0.19; I^2=42%)
60-day mortality 1 RCT (N=838) *Post-hoc analysis 1 – CC/trauma studies only*	95/418 (22.7)	111/420 (26.4)	RR 0.86 (0.68, 1.09)	No difference P=0.21 (Phet=NA)
120-day mortality 1 RCT (N=69) *Original analysis (CC study only)*	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	No difference P=NR (Phet=NA)
120-day mortality 1 RCT (N=69) Post-hoc analysis (CC study only)	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	No difference P=0.44 (Phet=NA)
Hospital mortality 4 RCTs (N=1409) *Original analysis*	96/701 (13.7)	126/708 (17.8)	RR 0.78 (0.62, 0.98)	Favours restrictive transfusion P=0.031 (Phet=0.53; I^2=0%)
Hospital mortality 1 RCT (N=838) *Post-hoc analysis 1 – CC study only*	93/418 (22.2)	118/420 (28.1)	RR 0.79 (0.63, 1.00)	No significant difference P=0.05 (Phet=NA)
ICU mortality 3 RCTs (N=736) *Original analysis (CC studies only)*	19/373 (5.1)	15/363 (4.1)	RR 1.15 (0.59, 2.23)	No difference P=0.68 (Phet=0.52; I2=0%)
ICU mortality 2 RCTs (N=736) *Post-hoc analysis 2 – CC/trauma studies only (excluding paediatric study)*	8/53 (15.1)	7/46 (15.2)	RR 0.95 (0.34, 2.68)	No difference P=0.92 (Phet=0.31; I^2=3%)

Mortality (unspecified follow-up) 1 RCT (N=214) *Original analysis*	12/109 (11.0)	17/105 (16.2)	RR 0.68 (0.34, 1.35)	No difference P=NR (Phet=NA)
Pneumonia 4 RCTs (N=1679) *Original analysis*	99/840 (11.8)	100/839 (11.9)	RR 1.00 (0.78, 1.29)	No difference P=0.98 (Phet=0.68; I^2=0%)
Pneumonia 2 RCTs (N=1475) *Post-hoc analysis 1 – CC studies only*	98/738 (13.3)	96/737 (13.0)	RR 1.02 (0.79, 1.32)	No difference P=0.86 (Phet=0.88; I^2=0%)
Pneumonia 1 RCT (N=838) *Post-hoc analysis 1 – CC studies only (excluding paediatric CC study)*	87/418 (20.8)	86/420 (20.5)	RR 1.02 (0.78, 1.33)	No difference P=0.90 (Phet=NA)
Infection 4 RCTs (N=1788) *Original analysis*	94/891 (10.5)	124/897 (13.8)	RR 0.76 (0.60, 0.97)	Favours restrictive transfusion P=0.029 (Phet=0.43; I^2=0%)
Infection 1 RCT (N=637) *Post-hoc analysis 1 – CC studies only (paediatric study only)*	65/320 (20.3)	79/317 (24.9)	RR 0.82 (0.61, 1.09)	No difference P=0.17 (Phet=NA)
Renal failure 2 RCTs (N=1065) *Original analysis*	10/532 (1.9)	5/533 (0.9)	RR 1.86 (0.66, 5.22)	No difference P=0.24 (Phet=0.50; I^2=0%)
Renal failure 2 RCTs (N=637) *Post-hoc analysis 1 – CC studies only (paediatric study only)*	2/320 (0.6)	0/317 (0)	RR 4.95 (0.24, 102.77)	No difference P=0.30 (Phet=NA)
Pulmonary oedema 4 RCTs (N=1633) *Original analysis*	24/818 (2.9)	51/815 (6.3)	RR 0.49 (0.18, 1.31)	No difference P=0.16 Mild heterogeneity (Phet=0.30; I^2=19%)
EXTERNAL VALIDITY				
Generalisability				

The results of the overall analysis are generalisable to a broad population including medical, critical care and surgical patients. The results of the critical care/trauma analysis are generalisable to a population including trauma/critical care patients.
Applicability
The studies included in the overall analysis were conducted in a number of different locations and are likely to be applicable to the Australian setting.
Comments
The authors conclude that 'the existing evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease'.

CI, confidence interval; GI, gastrointestinal; Hct, haematocrit; ICU, intensive care unit; MI, myocardial infarction; NA, not applicable; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio;

F2 Evidence summaries – Question 2

ESAs

Level I evidence

STUDY DETAILS: SR/MA				
Citation				
Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA. (2007) Erythropoietin-receptor agonist in critically ill patients: a meta-analysis of randomized controlled trails. CMAJ 177(7):725-34.				
Affiliation/Source of funds				
None declared for Ryan Zarychanski, Alexis Turgeon and Lauralyn McIntyre. Dean Fergusson has received unrestricted grants and consultancy monies from Amgen and Ortho Biotech.				
Study design	Level of evidence		Location/setting	
SR of	I		US (Still 1995; Corwin 1999; Corwin 2002; Corwin 2007; Silver), Netherlands (van Iperen), Greece (Georgopoulos), Gabriel (Austria); Belgium (Vincent)	
Intervention		Comparator		
EPO		Placebo or no intervention		
Population characteristics				
Critically ill patients One study was in burn unit and the other 8 studies were in medical and surgical ICU.				
Length of follow-up		Outcomes measured		
21-30 days (Corwin 2002; Gabriel 1998; van Iperen 2000) 36-40 days (Still 1995; Corwin 1999) 84 days (Silver 2006) 140 days (Corwin 2007)		Mortality, RBC transfusion, thromboembolic events		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description:				
RESULTS				
Outcome No. trials (No. patients)	EPO n/N (%) Mean ± SD (N)	Control n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality, n/N (%) 9 trials (N=3314)	238/1695 (14.0)	255/1619 (15.8)	OR 0.86 (0.71, 1.05)	No difference P=0.14 *No significant heterogeneity*[a] Phet=NR (I^2=0)

Mortality (patients admitted to mixed medical and surgical units [the 2 trials that enrolled patients with burns (Still 1995) or patients admitted to long-term acute care hospital (Silver 2006) were excluded])	NR [can be calculated]	NR [can be calculated]	OR 0.88 (0.72, 1.07)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (40 000 U/wk EPO), n/N (%) (N=3020)	NR [can be calculated]	NR [can be calculated]	OR 0.82 (0.66, 1.02)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (> 40 000 U/wk EPO), n/N (%) N=354	NR	NR	OR 1.26 (0.74, 2.15)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (restrictive transfusion [haemoglobin ≤ 80 g/L]), n/N (%) N=1694	NR	NR	OR 0.73 (0.53, 1.00)	Favours EPO P=0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (liberal transfusion [haemoglobin ≥ 90 g/L]), n/N (%) N=NR	NR	NR	OR 1.18 (0.66, 2.11)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (high quality [as appraised by Zarychanski et al] RCTs), n/N (%) N=NR	NR	NR	OR 0.81 (0.65, 1.01)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=2.8)
Mortality (unblinded), n/N (%) N=NR	NR	NR	OR 1.03 (0.42, 2.53)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)
Mortality (adequate allocation concealment), n/N (%) N=NR	NR	NR	OR 0.84 (0.68, 1.04)	No difference P>0.05 *No significant heterogeneity*[a] Phet=NR (I^2=0)

MI, n/N (%) 1 trial (N=1460)	15/733 (2.1)	6/727 (0.8)	RR 2.48 (0.97, 6.36)[b]	No difference P=0.06
Stroke, n/N (%) 2 trials (N=1608)	18/833 (2.2)	19/775 (2.5)	RR 0.82 (0.43, 1.55)[b]	No difference P=0.54 *No significant heterogeneity*[a] Phet=0.71 (I^2=0)
DVT, n/N (%) 5 trials (N=3110)	85/1582 (5.4)	65/1528 (4.3)	RR 1.29 (0.94, 1.78)[b]	No difference P=0.11 *No significant heterogeneity*[a] P=0.48 (I^2=0)
Incidence of RBC transfusion, n/N (%) 7 trials (N=3243)	768/1658 (46.3)	862/1585 (54.4)	OR 0.73 (0.64, 0.84)	Favours EPO P<0.001 *Substantial heterogeneity*[a] P=NR (I^2=54.7)
Mean volume of RBCs transfused, units 5 trials (N=3020)	NR	NR	WMD -0.41 (-0.74, -0.10)	Favours EPO P<0.05 *Substantial heterogeneity*[a] P=NR (I^2=79.2) [This decrease represents a transfusion savings of less than 0.5 units per patient]
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to ICU patients.				
Applicability				
Mostly applicable to the Australian context.				
Comments				

DVT, deep vein thrombosis; EPO, erythropoietin; ICU, intensive care unit; ITT, intention-to-treat; CI, confidence interval; MA, meta-analysis; NR, not reported; OR, odds ratio; PP, per-protocol; RBC, red blood cell; 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] Calculated in Review Manager 5.

STUDY DETAILS: SR/MA				
Citation				
Turaga KJ, Sugimoto JT, Forse RA. (2007) A meta-analysis of randomized controlled trials in critically ill patients to evaluate the dose-response effect of erythropoietin. Journal of Intensive Care Medicine 22(5): 270-82.				
Affiliation/Source of funds				
Not reported				
Study design	Level of evidence		Location/setting	
Systematic review of RCTs	I		US (Still 1995; Corwin 1999; Corwin 2002), Netherlands (van Iperen), Greece (Georgopoulos)	
Intervention		Comparator		
EPO		No EPO		
Population characteristics				
Intensive care patients				
Length of follow-up		Outcomes measured		
21-42 days		RBC transfusion volume		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description:				
RESULTS				
Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
RBC transfusion volume, units 5 trials (N=1686)	NR	NR	WMD -1.64 (-2.61, -0.67)	No difference P<0.05 *Heterogeneity NR*
RBC transfusion volume (studies with 'higher'doses of EPO) 4 trials (N=333)	NR	NR	WMD -2.15 (-3.06, -1.24)	Favours EPO P<0.05 Heterogeneity NR
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to adult intensive care patient.				
Applicability				
Mostly applicable to the Australian context.				
Comments				

EPO, erythropoietin; ITT, intention-to-treat; CI, confidence interval; NR, not reported; MA, meta-analysis; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review; WMD, weighted mean difference.

STUDY DETAILS: RCT

Citation				
Napolitano LM, Fabian TC, Kelly KM, Bailey JA, Block EF, Langholff W, Enny C, Corwin HL.(2008) Improved survival of critically ill trauma patients treated with recombinant human erythropoietin. Journal of Trauma Injury, Infection, and Critical Care 65:285-299.				
Affiliation/Source of funds				
Study design	Level of evidence		Location/setting	
Meta-analysis (subgroups from 2 RCTs)	Level I		ICU	
Intervention	Comparator			
IV EPO (40,000 U/week) for a total of three or four doses	Placebo			
Population characteristics				
Trauma patients admitted to an ICU for at least 2 days with Hb < 120 g/L				
Length of follow-up	Outcomes measured			
29 days	Mortality, RBC transfusion, Thromboembolic events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Description: Subgroup analysis of the results from Corwin et al (2002) and Corwin et al (2007)				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised				
Efficacy analysis (ITT)				
Efficacy analysis (PP)				
Safety analysis				
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mortality (Corwin et al [2002]; prospective dataset), n/N (%) (N=630)	13/314 (4.1)	28/316 (8.9)	Unadjusted HR 0.46 (0.24, 0.89) Fully adjusted HR 0.55 (0.28, 1.08) Final best fit HR[i] 0.50 (0.26, 0.97)[i]	*Favours EPO* P<0.05

Mortality (Corwin et al [2002]; retrospective dataset[j]), n/N (%) (N=559)	11/289 (3.8)	18/270 (6.7)	Unadjusted HR 0.57 (0.27, 1.20) Fully adjusted HR 0.64 (0.28, 1.47) Final best fit HR[k] 0.65 (0.29, 1.44)	*No significant difference* P>0.05
Mortality (Corwin et al [2007]), n/N (%) (N=793)	14/402 (3.5)	26/391 (6.6)	Unadjusted HR 0.51 (0.27, 0.98) Fully adjusted HR 0.36 (0.18, 0.74) Final best fit HR[l] 0.38 (0.19, 0.74)	*Favours EPO* P<0.05
Mortality (ISS < 15), n/N (N=199)	4/103 (3.9)	4/96 (4.2)	RR 0.86 (0.10, 7.23)[g]	*No significant difference* P=0.92[g] *Moderate heterogeneity*[a] *P*het=0.20 (I^2=40)
Mortality (ISS 15-24), n/N (N=391)	6/200 (3.0)	8/191 (4.2)	RR 0.71 (0.25, 2.04)[g]	*No significant difference* P=0.53[g] *No significant heterogeneity*[a] P*het*=0.71 (I^2=0)
Mortality (ISS ≥ 25), n/N (N=753)	17/386 (4.4)	37/367 (10.1)	RR 0.45 (0.25, 0.79)[g]	*Favours ESA* P=0.005[g] *No significant heterogeneity*[a] P*het*=0.39 (I^2=0)
Mean (SD) time of death, days (N=1423)	NR	NR	MD -0.36 (-1.14, 0.42)[g]	*No significant difference* P=0.37[g] *No significant heterogeneity*[a] P*het*=0.46 (I^2=0)
Incidence of RBC transfusion (Corwin et al [2002]), n/N (%) (N=630)	168/314 (53.5)	195/316 (61.7)	RR 0.87 (0.76, 0.99)	*Favours EPO* P<0.05
Incidence of RBC transfusion (Corwin et al [2007]), n/N (%) (N=793)	215/402 (53.5)	216/391 (55.2)	RR 0.97 (0.85, 1.10)	*No significant difference* P>0.05
Mean (SD) volume of RBCs transfused (Corwin et al [2002]), units (N=363)	2.6 (4.9)	3.1 (5.3)	MD -0.5 (-1.30, 0.30)[d]	*No significant difference* P=0.22[d]

Mean (SD) volume of RBCs transfused (Corwin et al [2007]), units	4.3 (3.8)	4.3 (5.1)	MD 0.0 (-0.63, 0.63)[d]	*No significant difference* P=1.00
Mean (SD) volume of RBCs transfused (overall), units	NR	NR	MD -0.19 (-0.68, 0.30)	*No significant difference* P=0.45 *No significant heterogeneity* P*het*=0.33 (I^2=0)
Thromboembolic events (Corwin et al [2002]), n/N (%) (N=630)	35/314 (11.1)	42/316 (13.3)	RR 0.84 (0.56, 1.28)	*No significant difference* P>0.05
Thromboembolic events (Corwin et al [2007]), n/N (%) (N=793)	66/402 (16.4)	49/391 (12.5)	RR 1.31 (0.93, 1.85)	*No significant difference* P>0.05
Thromboembolic events (pooled), n/N (%) (N=1423)	101/716 (14.1)	91/707 (12.9)	RR 1.07 (0.69, 1.65)[a]	*No significant difference* P=0.77[a] *Substantial heterogeneity*[b] P*het*=0.11 (I^2=62)
Venous thromboembolic events (Corwin et al [2002]), n/N (%) (N=630)	30/314 (9.6)	28/316 (8.9)	RR 1.08 (0.66, 1.76)	*No significant difference* P>0.05
Venous thromboembolic events (Corwin et al [2007]), n/N (%) (N=793)	50/402 (12.4)	37/391 (9.5)	RR 1.31 (0.88, 1.96)	*No significant difference* P>0.05
Venous thromboembolic events (pooled), n/N (%) (N=793)	80/716 (11.2)	65/707 (9.2)	RR 1.21 (0.89, 1.66)[a]	*No significant difference* P=0.22[a] *No significant heterogeneity*[b] P*het*=0.54 (I^2=0)
Thromboembolic events (Corwin et al [2007]; subjects receiving heparin on study day 1), n/N (%) (N=300)	18/150 (12.0)	16/150 (10.7)	RR 1.13 (0.60, 2.12)	*No significant difference* P>0.05
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to adult intensive care patient.				
Applicability				
Mostly applicable to the Australian context.				

Comments

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation. CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; ICU, intensive care unit; ISS, Injury Severity Score; HR, hazard ratio; NA, not applicable; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk

a Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2<25%; moderate heterogeneity if I2 between 25%-50%; substantial heterogeneity if I2>50%.

g Calculated for the purpose of this systematic review using Review Manager.

i Best fit model included the factors treatment group, age (<55 and ≥55), race, baseline creatinine, ferritin, and serum erythropoietin concentration.

j This retrospective population does not include 12 of the 47 deaths reported on or before day 28 in EPO 2 (Corwin et al [2002]), and the distribution of these missing deaths was uneven (10 placebo and 2 EPO).

k Retrospective best fit model included the factors treatment group, age (<55 and ≥55), race, baseline creatinine, ferritin, and serum erythropoietin

Level II evidence

STUDY DETAILS: RCT				
Citation				
Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ, Hutchison R, Mehrtens JE, Robinson JM, Schollum JBW, Westhuyzen J, Celi LA, McGinley RJ, Campbell IJ, George PM. (2010) Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). Kidney International 77:1020-30.				
Affiliation/Source of funds				
ZHE received non-directed research funding from Roche Pharmaceuticals. All the other authors declared no competing interests. This study was supported by Health Research Council of New Zealand grant 05/131 (Early intervention in acute renal failure). The oversight and ongoing direction provided by the HRC appointed DSMB is acknowledged. The dedication of John Dean and nursing staff at both centers and the Canterbury Health Laboratories made this study possible. Sources of support requiring acknowledgement: Health Research Council of New Zealand (ref.: HRC05/131).				
Study design	Level of evidence		Location/setting	
RCT	II		New Zealand	
Intervention		Comparator		
Daily IV EPO for 2 days		Matching placebo		
Population characteristics				
General ICU and cardiothoracic surgery patients				
Length of follow-up		Outcomes measured		
30 days		Mortality		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description:				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	84		78	
Efficacy analysis (ITT)	84		78	
Efficacy analysis (PP)	70		63	
Safety analysis	84		78	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Survival	NR	NR	HR 0.95 (0.52, 1.7)	*Favours EPO* P>0.05
Mortality (within 7 days), n/N (%)	9/84 (10.7)	13/78 (16.7)	NR	P=0.36

Mortality (within 30 days), n/N (%)	16/84 (19.0)	17/78 (21.8)	NR	P=0.70
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to ICU patients				
Applicability				
Applicable to the Australian context.				
Comments				

EPO, erythropoietin; HR, hazard ratio; ICU, intensive care unit; ITT, intention-to-treat; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT				
Citation				
Nirula R, Diaz-Arrastia R, Brasel K, Weigelt JA, Waxman K. (2010) Safety and efficacy of erythropoietin in traumatic brain injury patients: a pilot randomized trial. Critical Care Research and Practice doi:10.1155/2010/209848.				
Affiliation/Source of funds				
This research was funded by the American Association for the Surgery of Trauma Research and Education Foundation Scholarship Award.				
Study design	Level of evidence		Location/setting	
RCT	II		USA	
Intervention	Comparator			
IV EPO 40,000 units within 6 hours of the time of injury.	Placebo			
Population characteristics				
Blunt trauma patients with an admission GCS [Glasgow Coma Scale] < 13 and evidence of TBI [traumatic brain injury] on CT [x-ray computed tomography]				
Length of follow-up	Outcomes measured			
NR	Mortality, thromboembolic events			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description:				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	15		8	
Efficacy analysis (ITT)	11		5	
Efficacy analysis (PP)	11		5	
Safety analysis	11		5	
Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
In hospital deaths, n/N (%)	2/11 (18.2) [One patient died from his head injury and the other died from hypoxia from ARDS]	0/5 (0.0)		
DVT, n/N (%)	0/11 (0.0)	1/5 (20.0)		

EXTERNAL VALIDITY
Generalisability
The study is generalisable to traumatic brain injury patients
Applicability
The study is mostly applicable to the Australian context.
Comments

ARDS, acute respiratory distress syndrome; DVT, deep vein thrombosis; EPO, erythropoietin; ITT, intention-to-treat; IV, intravenous; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Iron therapy

Level II evidence

STUDY DETAILS: RCT		
Citation		
Pieracci FM, Henderson P, Rocco J, Rodney M,Holena DN, Genisca A, Ip I, Steven Benkert S, Hydo LJ, Eachempati SR, Shou J, Barie PS (2009) Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. Surgical Infection 10 (1): 9-19.		
Affiliation/Source of funds		
Acknowledgments Doctor Pieracci was supported by the Surgical Infection Society/Wyeth Evaluative Fellowship in Outcomes Research. He was the winner of the Surgical Infection Society 2008 New Member Award for this work. Author disclosure statement No conflicting financial interests exist.		
Study design	Level of evidence	Location/setting
RCT	II	USA
Intervention	Comparator	
325 mg oral iron three times a day until hospital discharge or for 42 days. + 500 mg oral ascorbic acid three times a day + 1 mg oral cyanobalamin daily + 1 mg folic acid daily	Placebo + 500 mg oral ascorbic acid three times a day until hospital discharge or for 42 days. + 1 mg oral cyanobalamin daily + 1 mg folic acid daily	
Population characteristics		
Critically ill surgical patients with anaemia (<13 g/dL) and an expected ICU length of stay of at least 5 days.		
Length of follow-up	Outcomes measured	
42 days or hospital discharge	Mortality RBC transfusion	
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description:		
RESULTS		

Population analysed	Intervention	Comparator
Randomised	97	103
Efficacy analysis (ITT)	97	103
Efficacy analysis (PP)	88	92
Safety analysis	97	103

Outcome	EPO n/N (%) Mean ± SD (N)	Placebo n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Incidence of RBC transfusion, n/N (%)	29/97 (29.9)	46/103 (44.7)	NR	P=0.03
Incidence of RBC transfusion (patients with iron-deficient erythropoiesis), n/N (%)	NR/NR (30.7)	NR/NR (68.4)	NR	P<0.01
Incidence of RBC transfusion (patients without iron-deficient erythropoiesis), n/N (%)	NR	NR	NR	P=0.86
Incidence of RBC transfusion (patients who had received a blood transfusion prior to study enrolment), n/N (%)	NR	NR	NR	P<0.01
Incidence of RBC transfusion (patients who had no received a blood transfusion prior to study enrolment), n/N (%)	NR/NR (29.6)	NR/NR (35.7)	NR	P=0.39
Incidence of RBC transfusion (patients with an APACHE II score higher than 12), n/N (%)	NR/NR (37.3)	NR/NR (59.6)	NR	P=0.02
Incidence of RBC transfusion (patients with an APACHE II score lower than 12), n/N (%)	NR	NR	NR	P=0.24

	Logistic regression analyses were conducted using the outcomes of both RBC transfusion and infection (Table 2). In the case of the former, we hypothesized that the increased risk of transfusion in the placebo than the iron group may have been secondary to the trend toward an increase in both baseline EBL and baseline RBC transfusion risk. In order to test this hypothesis, we fit a logistic regression model using the likelihood of RBC transfusion as the dependent variable and randomization status, baseline EBL (mL), baseline likelihood of RBC transfusion, and admission APACHE II score as independent variables. These covariates were selected because of their association ($p \leq 0.25$) with randomization status by univariable analysis. The model contributed significantly to predicting the variability in transfusion risk (likelihood $\chi^2 = 29.4$; $p < 0.01$). After controlling for baseline EBL, baseline likelihood of RBC transfusion, and admission APACHE II score, patients who received placebo remained nearly twiceas likely to receive a RBC transfusion during the study than patients who received iron (odds ratio [OR] = 1.95, 95% confidence interval [CI] 1.03, 3.71; p = 0.04).			
Incidence of EPO supplementation, n/N (%)	6/97 (6.3)	15/103 (14.6)	NR	P=0.06
Mortality, n/N (%)	9/97 (9.4)	10/103 (9.9)	NR	P=0.90
EXTERNAL VALIDITY				
Generalisability				
Applicability				
Comments				

APACHE, Acute Physiology and Chronic Health Evaluation; EBL, estimated blood loss; EPO, erythropoietin; ICU, intensive care unit; ITT, intention-to-treat; NR, notr reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; SD, standard deviation.

STUDY DETAILS: RCT		
Citation		
van Iperen CE, Gaillard CAJ, Kraaigenhagen RJ, Braam BG, Marx JJM, van de Wiel A. (2000) Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Car Med 28:2773-2778.		
Affiliation/Source of funds		
From the Departments of Internal Medicine and Intensive Care (Drs. van Iperen, Gaillard, and van de Wiel), Amersfoort, The Netherlands, and the Department of Internal Medicine (Drs. van Iperen and Braam and Prof. Dr. Marx), University Hospital Utrecht, Utrecht, The Netherlands. The epoetin alfa used was provided by Janssen-Cilag (Tilburg, The Netherlands) and the VAMP system was provided by Baxter Healthcare (Utrecht, The Netherlands).		
Study design	Level of evidence	Location/setting
RCT	II	The Netherlands

Intervention	Comparator
<u>Iron, EPO and folic acid</u> 1 mg/day IV folic acid for 21 days and 20 mg/day IV iron saccharate from Days 1 to 14 and 300 IU/kg sc EPO on Days 1, 3, 5, 7, and 9 <u>Iron and folic acid</u> 1 mg/day IV folic acid for 21 days and 20 mg/day IV iron saccharate from Days 1 to 14	1 mg/day IV folic acid for 21 days

Population characteristics	
ICU patients with anaemia (Hb < 11.2 g/dL or, in the case of cardiac disease, a haemoglobin concentration of < 12.1 g/dL)	
Length of follow-up	Outcomes measured
21 days	Mortality RBC transfusion

INTERNAL VALIDITY
Overall quality assessment (descriptive)
Rating: Poor Description:

RESULTS		
Population analysed	Intervention	Comparator
Randomised	<u>Iron and folic acid</u> 12	12
Efficacy analysis (ITT)	NR	NR
Efficacy analysis (PP)	NR	NR
Safety analysis	NR	NR

Outcome	Iron therapy n/N (%) Mean ± SD (N)	No iron therapy n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Mortality, n/N (%)	2/12 (16.7)	4/12 (33.3)	RR 0.50 (0.11, 2.23)	*No significant difference* P=0.36
Total volume of blood transfused, units	63	140	NR	NR
Mean (SD) volume of blood transfused, units	5 (7)	12 (14)	MD 7 (-2.37, 16.37)	*No significant difference* P>0.05
EXTERNAL VALIDITY				
Generalisability				
Somewhat generalisable to critically ill patients				
Applicability				
Mostly applicable to the Australian context				
Comments				

EPO, erythropoietin; Hb, haemoglobin; ITT, intention-to-treat; ICU, intensive care unit; IV, intravenous; MD, mean difference; NR, not reported; PP, per-protocol; RBC, red blood cell; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation.

F3 Evidence summaries – Question 3

FFP transfusion strategies for patients with trauma

Level III Evidence

<table>
<tr><td colspan="3">STUDY DETAILS: Cohort study</td></tr>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Inaba K, Branco BC, Rhee P, Blackbourne LH, Holcomb JB, Teixeira PG, Shulman I, Nelson J, Demetriades D. Impact of plasma transfusion in trauma patients who do not require massive transfusion. J Am Coll Surg. 2010 Jun;210(6):957-65.</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">NR</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Retrospective observational cohort study</td><td>Level III-2</td><td>Level I trauma centre in the USA (surgical ICU)</td></tr>
<tr><td colspan="2">Risk factor/s assessed</td><td>Potential confounding variables measured</td></tr>
<tr><td colspan="2">FFP during the first 12 hours after admission</td><td>Included in the propensity score model were all variables that differed significantly (at the p<0.05 level) between the plasma and no plasma cohorts (injury mechanism, ventilator requirements, systolic blood pressure and GCS on admission, ISS, Abbreviated Injury Scale, total volumes of PRBC, platelets, and cryoprecipitate received at 12 and 24 hours and during the total hospital stay).</td></tr>
<tr><td colspan="3">Population characteristics (including size)</td></tr>
<tr><td colspan="3">Trauma patients admitted to a Level I trauma centre (2000–2005) requiring a nonmassive transfusion (<10 U packed RBC within 12 hours of admission). Patients who died within the first 24 hours after hospital admission were excluded from the analysis to minimise the impact of survival bias.
N=1685 (including 516 patients who received FFP in the first 12 hours). After propensity score matching, 284 matched pairs were available for analysis.</td></tr>
<tr><td colspan="2">Length of follow-up</td><td>Outcomes measured</td></tr>
<tr><td colspan="2">NR</td><td>• In-hospital mortality
• In-hospital complications
• Ventilation days
• ICU LOS
• Hospital LOS</td></tr>
<tr><td colspan="3">Method of analysis</td></tr>
<tr><td colspan="3">The nonmassively transfused patients were divided into 2 cohorts; patients who received plasma during the first 12 hours after admission and those who received none. These 2 cohorts were compared for differences in demographics, clinical characteristics, and blood transfusion requirements using bivariate analysis. Chi-square or Fisher's exact tests were used to compare proportions and unpaired Student's t-test or Mann-Whitney U tests were used to compare means. Because the number of confounders was large in comparison with the number of events, patients receiving plasma were matched in a 1:1 ratio to patients who did not receive plasma using propensity scores.</td></tr>
<tr><td colspan="3">INTERNAL VALIDITY</td></tr>
<tr><td colspan="3">Overall quality assessment (descriptive)</td></tr>
</table>

Rating: Good

Description: The objective of this study was to determine the outcomes (in-hospital mortality and complications) of plasma administration in trauma patients who required blood but did not undergo a massive transfusion. A retrospective review of the institutional trauma registry and the Blood Bank Database at the Los Angeles County and University of Southern California Medical Centre was performed. All trauma patients admitted to the surgical ICU who received a PRBC transfusion between 2000 and 2005 were identified.

RESULTS

Population	With risk factor		Without risk factor	
Available	284		284	
Analysed	284		284	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
Mortality	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.3 (0.8,2.0)	*No significant effect* P=0.30
Overall complications	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.7 (1.1,2.4)	*FFP transfusion is significantly and independently associated with overall complications* P=0.016
ARDS	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	3.0 (1.4,6.2)	*FFP transfusion is significantly and independently associated with ARDS* P=0.004
MODS	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.8 (0.9,3.5)	*No significant effect* P=0.13
Pneumonia	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.7 (0.9,3.0)	*No significant effect* P=0.11
Sepsis	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.9 (1.0,3.6)	*No significant effect* P=0.08
Line sepsis	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.5 (0.4,5.4)	*No significant effect* P=0.75
Bacteraemia and fungemia	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	1.1 (0.5,2.8)	*No significant effect* P>0.99
ARF	FFP transfusion within 12 hours of admission	No FFP transfusion within 12 hours of admission	2.3 (0.7,7.5)	*No significant effect* P=0.27

EXTERNAL VALIDITY

Generalisability

The results of this study are generalisable to trauma patients requiring nonmassive transfusion

Applicability

The results of this study are applicable to the Australian healthcare system.
Comments
Matched patients received a mean of 2.9±2.2 U PRBC in the first 12 hours, 3.8±2.7 U in the first 24 hours, and 7.7±6.2 U during their total hospital stay. The mean number of units of apheresis platelets and cryoprecipitate transfused during their hospital stay was 0.7±2.2 U and 1.0±4.0 U, respectively. Patients who received plasma in the first 12 hours had a mean of 3.0±2.0 U transfused in the first 12 hours, 3.7±2.5 U in the first 24 hours, and 6.3±7.2 U during their total hospital stay. Patients who did not receive plasma in the first 12 hours had a mean of 0.6±1.5 U plasma transfused in the first 24 hours and 2.1±4.8 U during their total hospital stay. Some patients in the non-plasma group therefore received plasma, but not in the first 12 hours of admission.

USA, United States of America; FFP, Fresh Frozen Plasma; CI, Confidence Interval.

STUDY DETAILS: Cohort study				
Citation				
Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Shih, D., Meyer, W., & Scalea, T. M. 2008a, Blood product transfusion and ventilator-associated pneumonia in trauma patients, *Surgical Infections*, vol. 9, no. 4, pp. 415-422.				
Affiliation/Source of funds				
University of Maryland				
Study design	Level of evidence		Location/setting	
Prospective observational cohort study	Level III-2		Single site in the USA	
Risk factor/s assessed		Potential confounding variables measured		
FFP Platelets		Albumin Base deficit Creatinine Glasgow Coma Score Heart rate Systolic blood pressure		
Population characteristics (including size)				
Trauma patients admitted to the intensive care unit (ICU) who received mechanical ventilation (MV) for ≥ 48 hours and who did not have pneumonia on admission. N=766 (including 26 patients who were found to have VAP)				
Length of follow-up		Outcomes measured		
NR		Ventilator associated pneumonia (VAP). Late-onset VAP was defined as that occurring ≥ 72 h after MV.		
Method of analysis				
All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP (p < 0.20) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Prospective observational cohort study of 766 trauma patients admitted to the ICU, who received MV for ≥ 48 h, and who did not have pneumonia on admission. Late-onset VAP was defined as that occurring ≥ 72 h after MV. Only transfusions of red blood cell (RBC) concentrate, fresh-frozen plasma (FFP), or platelets before the onset of VAP were considered. Logistic regression analyses controlled for all variables related significantly to VAP by univariate analysis (sex, Injury Severity Score, and ventilator days and ICU length of stay prior to VAP).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	386		380	
Analysed	386		380	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

VAP	FFP transfusion	No FFP transfusion	3.34 (1.18, 9.43)	*FFP transfusion is significantly and independently associated with VAP* P=0.023
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to trauma patients who have received mechanical ventilation.				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				

VAP, Ventilated Assisted Pneumonia; FFP, Fresh Frozen Plasma; CI, Confidence Interval.

STUDY DETAILS: Cohort study				
Citation				
Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Meyer, W., & Scalea, T. M. 2008b, Outcome analysis of blood product transfusion in trauma patients: A prospective, risk-adjusted study, *World Journal of Surgery*, vol. 32, no. 10, pp. 2185-2189.				
Affiliation/Source of funds				
University of Maryland				
Study design	Level of evidence		Location/setting	
Prospective observational cohort study	Level III-2		Single site in the USA (R. Adams Cowley Shock Trauma Center)	
Risk factor/s assessed		Potential confounding variables measured		
FFP transfusion only Platelet transfusion only		Age Sex Injury Severity Score Admission Glasgow Coma Score Transfusion (combination) Packed RBC transfusion		
Population characteristics (including size)				
Consecutive trauma patients admitted >48 hours to the ICU during a 2-year period (2002–2004). N=1172 (including 56 patients who received FFP)				
Length of follow-up		Outcomes measured		
NR		Outcome assessment included infection rate, ventilator days (V days), ICU and hospital length of stay (LOS), and mortality.		
Method of analysis				
Multiple logistic regression analyses were used for binary outcomes, using the covariates age, sex, race, and ISS as adjusters. The blood product variables were entered into the regression equation so that the variance in outcome explained by these variables would be partialled out of the final model, thus allowing interpretation of the blood product of interest to be made independent of the effects of the other blood products. Continuous variables were compared by using Student's t test (to compare differences between transfused and non-transfused patients) and multiple linear regression analysis, using the same covariates as adjusters.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Studies have confirmed adverse outcome associated with transfusion of packed red blood cells in trauma; however, little data are available regarding other blood product transfusion, such as fresh frozen plasma (FFP) and platelets. The objective of this study was to examine risk-adjusted outcome in trauma with stratification by blood product type. Prospective data were collected daily for 1,172 consecutive trauma patients admitted to the intensive care unit (ICU) during a 2-year period, including transfusion rates of blood products (PRBCs, FFP, platelets).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	56		1116	
Analysed	56		1116	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

Infection	FFP transfusion	No FFP transfusion	1.02 (1.01,1.04)	*FFP transfusion is significantly and independently associated with infection* P<0.001
Hospital LOS	FFP transfusion	No FFP transfusion	1.3 (1.3,1.41)	*FFP transfusion is significantly and independently associated with hospital LOS* P<0.001
ICU LOS	FFP transfusion	No FFP transfusion	1.25 (1.2,1.31)	*FFP transfusion is significantly and independently associated with ICU LOS* P<0.001
Mortality	FFP transfusion	No FFP transfusion	1.03 (1.02,1.05)	*FFP transfusion is significantly and independently associated with mortality* P<0.001
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to trauma patients				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				
There is a dose dependent correlation between blood product transfusion (PRBCs, FFP) and adverse outcome (mortality, infection) in critically ill trauma patients after appropriate stratification for all other variables that affect trauma outcome.				

CI, Confidence Interval; ISS, Injury Severity Score; PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma; LOS, Length of Stay; ICU, Intensive Care Unit; NR, Not Recorded

STUDY DETAILS: Cohort study		
Citation		
Spinella, P. C., Perkins, J. G., Grathwohl, K. W., Beekley, A. C., Niles, S. E., McLaughlin, D. F., Wade, C. E., & Holcomb, J. B. 2008, Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries, *The Journal of trauma*, vol. 64, no. 2 Suppl, p. S69-S77.		
Affiliation/Source of funds		
NR		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	A combat support hospital in Iraq
Risk factor/s assessed	Potential confounding variables measured	
FFP (units)	Glasgow Coma Scale score, age, heart rate (bpm), systolic blood pressure (mm Hg), temperature, haematocrit, pH, base deficit, INR, red blood cell (units), massive transfusion, rFVIII% use, Injury Severity Score (ISS).	
Population characteristics (including size)		
The study population included combat victims who received one or more units of any blood product, including RBCs, FFP, and fresh whole blood (FWB). A subgroup analysis that included only those who did not receive a massive transfusion was also performed to provide another method to determine whether the effects measured in the primary analysis were predominantly influenced by patients who received massive transfusions. The study includes data from 2003-2004. N=708 (including 567 patients who did not receive massive transfusion of whom 215 received FFP transfusion)		
Length of follow-up	Outcomes measured	
24 hours	In-hospital mortality (survival)	
Method of analysis		
Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Variables with $p < 0.2$ on univariate analysis were included in the regression model unless colinearity existed between variables. Receiver operating curve analysis was used to determine appropriate cut off points for continuous variables chosen to be modelled as binary. Despite colinearity between RBC and FFP units transfused, both variables were included in the regression analysis because of clinical suspicion of potential independent effects on survival. A secondary subset analysis that included only those who did not receive a massive transfusion was also performed to provide another method to determine whether the effects measured in the primary analysis were predominantly influenced by patients who received massive transfusions. Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. For the nonmassively transfused population, additional variables included in the regression model were admission temperature, systolic blood pressure, and haematocrit.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		
Rating: Poor Description: A retrospective review of 708 patients transfused at least one unit of a blood product at one combat support hospital between November 2003 and December 2004. Admission vital signs, laboratory values, amount of blood products transfused in a 24-hour period, and Injury Severity Score (ISS) were analysed by multivariate logistic regression to determine independent associations with in-hospital mortality.		
RESULTS		
Population	With risk factor	Without risk factor
Available	215	352
Analysed	215	352

Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
Survival (excluding massive transfusion)	FFP transfusion (1 unit)	NA	1.22 (1.0, 1.48)	*An increase in FFP transfusion units is significantly and independently associated with improved survival* P=0.05
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to patients with combat trauma injuries, and are only somewhat generalisable to the broad trauma population.				
Applicability				
The study was set in a combat hospital in Iraq, and it is unclear if the results are applicable to the Australian healthcare setting.				
Comments				
This retrospective study is the first to indicate that the amount of plasma transfused to patients with traumatic injuries who require any amount of blood products is independently associated with improved in-hospital survival. A subset analysis of patients who did not require a massive transfusion also indicated an independent association between the amount of plasma transfused and survival. Are the results confounded by the fact that patients may have received FFP plus RBC transfusions? In the overall population, primary surgical procedures were recorded for 647 patients. The most common procedures required for these 647 patients who required blood products were celiotomy 31%, craniectomy 16%, vascular repair 13%, and skeletal fixation 11%.				

CI, Confidence Interval; FFP, Fresh Frozen Plasma; bpm, beats per minute; INR, International Normalization Ratio; RBC, Red Blood Cells; NR, Not Reported; NA, Not Applicable.

STUDY DETAILS: Cohort study		
Citation		
Watson, G. A., Sperry, J. L., Rosengart, M. R., Minei, J. P., Harbrecht, B. G., Moore, E. E., Cuschieri, J., Maier, R. V., Billiar, T. R., & Peitzman, A. B. 2009, Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome, *Journal of Trauma - Injury, Infection and Critical Care*, vol. 67, no. 2, pp. 221-227.		
Affiliation/Source of funds		
Supported by the National Institutes of Health (NIH NIGMS U54 GM062119-1 and NIH KL2 RR024154-03).		
Study design	Level of evidence	Location/setting
Prospective observational cohort study	Level III-2	Seven institutions in USA between November 2003 and November 2007.

Risk factor/s assessed	Potential confounding variables measured
Plasma-rich transfusion components including fresh frozen plasma (FFP), platelets (PLT), and cryoprecipitate.	Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

Population characteristics (including size)
Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion. Included patients survived beyond the initial 48-hours post-injury. Inclusion criteria for the overall cohort study included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (>6 mEq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the brain with an abbreviated injury score ≥2, allowing exclusion of patients with isolated traumatic brain injury. Patients <16 or >90 years of age and those with cervical spinal cord injury were also excluded from enrolment. Data were derived from the ongoing multicenter prospective cohort study known as the Inflammation and the Host Response to Injury Large Scale Collaborative Program (www.gluegrant.org), supported by the National Institute of General Medical Sciences (NIGMS), which is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure after traumatic injury and hemorrhagic shock. N= 1,175 (including 764 patients who were given FFP)

Length of follow-up	Outcomes measured
NR	Mortality Multiple organ failure Nosocomial infection Acute Respiratory Distress Syndrome

Method of analysis

Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: A multicenter prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. All patients required blood transfusion for enrollment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. Cox proportional hazard regression models were used to estimate the outcome risks (per unit) associated with plasma-rich transfusion requirements during the initial 24 hours after injury after controlling for important confounders.

There was no association with plasma-rich transfusion components and mortality or nosocomial infection. For every unit given, FFP was independently associated with a 2.1% and 2.5% increased risk of MOF and ARDS, respectively. Cryoprecipitate was associated with a 4.4% decreased risk of MOF (per unit), and platelets were not associated with any of the outcomes examined. When early deaths (within 48 hours) were included in the model, FFP was associated with a 2.9% decreased risk of mortality per unit transfused.

RESULTS

Population	With risk factor		Without risk factor	
Available	766		409	
Analysed	766		409	
Outcome (categorical)	Risk factor definition	No risk factor definition	Hazard ratio (95% CI)	Significance P-value
Mortality	FFP transfusion (1 unit)	NA	0.996 (0.96,1.03)	*An increase in FFP transfusion units is not independently associated with mortality* P=0.821
Multiple organ failure	FFP transfusion (1 unit)	NA	1.021 (1.002,1.04)	*An increase in FFP transfusion units is significantly and independently associated with multiple organ failure* P=0.029
Nosocomial infection	FFP transfusion (1 unit)	NA	1.013 (0.993,1.033)	*An increase in FFP transfusion units is not independently associated with nosocomial infection* P=0.198

Acute respiratory distress syndrome	FFP transfusion (1 unit)	NA	1.025 (1.001,1.049)	*An increase in FFP transfusion units is significantly and independently associated with acute respiratory distress syndrome* P=0.038
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to severely injured blunt trauma patients with haemorrhagic shock. The population includes some patients who received massive transfusion.				
Applicability				
The results of this study are broadly applicable to the Australian healthcare system.				
Comments				
Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study.				

NR, Not Reported; NA, Not Applicable; CI, Confidence Interval; RBC, Red Blood Cell; FFP, Fresh Frozen Plasma.

FFP transfusion strategies for non-trauma patients

Level III evidence

STUDY DETAILS: Cohort study				
Citation				
Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med. 2008 36(4):1114-8				
Affiliation/Source of funds				
NR				
Study design	Level of evidence		Location/setting	
Retrospective observational cohort study	Level III-2		The surgical intensive care unit (SICU) of the Hospital of the University of Pennsylvania	
Risk factor/s assessed		Potential confounding variables measured		
FFP transfusion		PRBCs, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and age.		
Population characteristics (including size)				
Patients admitted to the surgical intensive care unit (SICU) of the Hospital of the University of Pennsylvania between 2004 and 2005. Trauma patients were excluded due to confounders with identification based on medical record number. N=2438 (including 380 patients who received FFP and 2,058 patients who did not).				
Length of follow-up		Outcomes measured		
NR		Infectious complications, including ventilator associated pneumonia (VAP) and bloodstream infection (BSI).		
Method of analysis				
The relative risks of infectious complications for patients receiving and not receiving FFP were calculated. T-test allowed comparison of average units of FFP transfused to patients with and without infectious complications to describe a dose-response relationship. Chi square analysis was used to describe the relationship between risk of infection following FFP transfusion in patients who did and did not also receive PRBC transfusion. Multivariate logistic regression analyses with FFP, PRBCs, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and age were used to evaluate the association between FFP and infectious complication.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: A total of 380 non-trauma patients who received fresh frozen plasma from 2004 to 2005 were compared with 2,058 non-trauma patients who did not receive fresh frozen plasma. The relative risk of infectious complication for patients receiving and not receiving fresh frozen plasma was determined using multivariate logistic regression.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	380		2058	
Analysed	380		2058	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

Infectious complications	FFP transfusion (increasing units)	N/A	1.039 (1.013, 1.067)	*FFP transfusion is significantly and independently associated with infectious complications* P<0.01
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to non-trauma patients in surgical ICU				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				
The study excluded trauma patients. Only three variables were adjusted for in the multivariate analysis.				

USA, United States of America; FFP, Fresh Frozen Plasma; CI, Confidence Interval.

FFP transfusion strategies for critically ill elderly patients

Level III evidence

<table>
<tr><td colspan="4">STUDY DETAILS: Cohort study</td></tr>
<tr><td colspan="4">Citation</td></tr>
<tr><td colspan="4">Dara, S. I., Rana, R., Afessa, B., Moore, S. B., & Gajic, O. 2005, Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy, Critical Care Medicine, vol. 33, no. 11, pp. 2667-2671.</td></tr>
<tr><td colspan="4">Affiliation/Source of funds</td></tr>
<tr><td colspan="4">Supported in part by funds from the Mayo Foundation and a grant from the National Blood Foundation</td></tr>
<tr><td>Study design</td><td colspan="2">Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Retrospective cohort study</td><td colspan="2">Level III-2</td><td>24-bed medical intensive care unit in a tertiary referral centre</td></tr>
<tr><td colspan="2">Risk factor/s assessed</td><td colspan="2">Potential confounding variables measured</td></tr>
<tr><td colspan="2">FFP transfusion (median dose was 17 mL/kg)</td><td colspan="2">Age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III Score, INR level, indication</td></tr>
<tr><td colspan="4">Population characteristics (including size)</td></tr>
<tr><td colspan="4">All patients admitted to a medical intensive care unit during a 5-month period who had abnormal coagulation defined as an INR level ≥ 1.5 times normal, but without active bleeding. The average age of patients was 70.
N=115</td></tr>
<tr><td colspan="2">Length of follow-up</td><td colspan="2">Outcomes measured</td></tr>
<tr><td colspan="2">NR</td><td colspan="2">New bleeding episodes
FFP complications
Acute lung injury
Circulatory overload
Allergic reactions
Hospital mortality
ICU length of stay among survivors
Note: only hospital mortality was measured in the multivariate logistic regression analysis.</td></tr>
<tr><td colspan="4">Method of analysis</td></tr>
<tr><td colspan="4">Categorical outcome variables were compared between two groups based on the chi square test or Fisher's exact test. Continuous outcome variables were compared using Student's t-test or rank sum tests as appropriate. To determine the clinical characteristics associated with FFP transfusion, logistic regression analysis was performed with FFP transfusion as the dependent variable. The potentially significant variables identified in univariate analysis ($p<0.1$) and nonsignificant biologically plausible variables were entered in the analysis. The final model was chosen by stepwise forward selection method to achieve the best goodness of fit for the whole model. INR level, recent bleeding, Coumadin anticoagulation, liver insufficiency, RBC transfusion and invasive procedure were used as independent variables in the final model.</td></tr>
<tr><td colspan="4">INTERNAL VALIDITY</td></tr>
<tr><td colspan="4">Overall quality assessment (descriptive)</td></tr>
<tr><td colspan="4">Rating: Fair
Description: The objective of this retrospective cohort study in critically ill elderly patients was to determine if FFP transfusion in the intensive care unit is variable, and to assess the hypothesis that liberal use may not be associated with improved outcome. Data were collected on all patients admitted to a medical intensive care unit during a 5-month period who had abnormal coagulation, defined as an international normalised ratio (INR) ≥ 1.5 times normal.</td></tr>
<tr><td colspan="4">RESULTS</td></tr>
</table>

Population	With risk factor		Without risk factor	
Available	44		71	
Analysed	44		71	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
Hospital mortality	FFP transfusion	No FFP transfusion	0.94 (0.36,2.39)	*FFP transfusion is not independently associated with hospital mortality*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to critically ill elderly patients with abnormal coagulation parameters. The results are not applicable to patients experiencing active bleeding. It should be noted that 51% of patients were undergoing invasive procedures.				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				
Of relevance, patients in whom international normalized ratio was corrected received a larger dose (median, 17 mL/kg) than those who failed to correct (median, 10 mL/kg). In this sample, the rate of new bleeding episodes was uncommon and did not differ between the groups that did and did not receive prophylactic FFP transfusions. The use of FFP was associated with the development of acute lung injury, however this outcome was not analysed using logistic regression.				

CI, Confidence Interval; FFP, Fresh Frozen Plasma; INR, International Normalized Ratio; ICU, Intensive Care Unit

STUDY DETAILS: Cohort study		
Citation		
Khan, H., Belsher, J., Yilmaz, M., Afessa, B., Winters, J. L., Moore, S. B., Huhmayr, R. D., & Gajic, O. 2007, Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients, *Chest*, vol. 131, no. 5, pp. 1308-1314.		
Affiliation/Source of funds		
This research was supported in part by National Heart, Lung, and Blood Institute grant No. K23 HL78743–01A1.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	A 24-bed general medical non-cardiac medical ICU (MICU) in St. Mary's Hospital, Mayo Clinic, Rochester, MN, USA

Risk factor/s assessed	Potential confounding variables measured
FFP transfusion RBC transfusion Platelet transfusion	The ALI/ARDS risk factors that were studied included any transfusion, transfusion of individual blood products, sepsis, aspiration, pneumonia, drug overdose, disseminated intravascular coagulation (DIC), pancreatitis, alcohol use, cigarette smoking, and demographics. Except for smoking and alcohol abuse, risk factors for ALI/ARDS (including transfusions) were implicated only if they were present up to 48 h prior to the development of ALI/ARDS.
Population characteristics (including size)	
The study included data from consecutive patients admitted to an MICU. Patients who had received a transfusion with any blood product were compared with those who had not undergone transfusion. Patients who had pulmonary oedema (hydrostatic or ALI/ARDS) on MICU admission and those who had been admitted to the MICU for < 24 hours were excluded from the study. The mean age of patients included in the study was > 60 years. N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with FFP)	
Length of follow-up	Outcomes measured
NR	Development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) according to the standard American-European Consensus Conference on ARDS definition.
Method of analysis	
Continuous and categorical variables were compared using the Wilcoxon rank sum, the Fisher exact test, or the χ^2 test, as appropriate. Demographics, baseline characteristics, ALI/ARDS risk factors, and transfusion factors were compared between patients who had been exposed and had not been exposed to blood product transfusion. The comparisons were also made between patients in whom ALI/ARDS developed and those in whom it did not develop, excluding patients in whom hydrostatic pulmonary oedema developed. Risk factors for ALI/ARDS were considered for multivariable logistic regression models if they (1) were statistically significant in univariate analysis ($p < 0.05$), (2) had high odds ratios (≥2); or (3) were biologically plausible. Both factors associated with the probability of transfusion (i.e. the propensity score) and ALI/ARDS were included in the multivariate analysis. Because of colinearity, each of the blood product types (i.e. RBCs, FFP, or platelets) were also included into separate logistic models. In addition to nontransfusion risk factors, each model contained a probability of transfusion of specific blood products.	
INTERNAL VALIDITY	
Overall quality assessment (descriptive)	

Rating: Good Description: In this single-centre retrospective cohort study, 841 consecutive critically ill patients were studied for the development of ALI/ARDS. Patients who received blood product transfusions were compared with those who did not, in univariate and multivariate propensity analyses.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	122		543	
Analysed	122		543	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
ARDS/ALI	FFP transfusion	No transfusion	2.48 (1.29,4.74)	*FFP transfusion is significantly and independently associated with ARDS/ALI* P-value: NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to critically ill elderly patients				
Applicability				
The results of this study are broadly applicable to the Australian healthcare system.				
Comments				
The risk of ALI/ARDS was higher in patients who had received platelets and FFP than in those who received only RBCs.				

CI, Confidence Interval; FFP, Fresh Frozen Plasma; RBC, Red Blood Cells; NR, Not Reported; ARDS, Acute Respiratory Distress Syndrome; ALI, Acute Lung Injury

FFP transfusion strategies for patients with traumatic brain injury

Level II evidence

STUDY DETAILS: RCT				
Citation				
Etemadrezaie H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B. The effect of fresh frozen plasma in severe closed head injury. Clin Neurol Neurosurg 2007; 109:166-71.				
Affiliation/Source of funds				
The Research Counselor of Mashhad University of Medical Sciences.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Shahid Kamyab (Emdadi) Hospital, Mashhad, Iran	
Intervention	Comparator			
FFP 10-15 mL/kg	Normal saline 10-15 mL/kg			
Population characteristics				
Patients with severe closed head injury (Glasgow coma scale ≤ 8), no mass lesion required evacuation and no history of coagulopathy.				
Length of follow-up	Outcomes measured			
Unclear (time of patient discharge)	Reduction in the incidence of delayed traumatic intracerebral haematoma (DTICH) Glasgow outcome scale (GOS) CT scan changes Laboratory changes Mortality			
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Good Description: A double-blind randomised clinical trial in 90 patients with severe closed head injury. Patients were randomised to receive either FFP or normal saline.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	44		46	
Efficacy analysis (ITT)	44		46	
Efficacy analysis (PP)	NR		NR	
Safety analysis	44		46	
Outcome	FFP n/N (%)	Normal saline n/N (%)	Risk estimate (95% CI)	Significance P-value
Mortality	28/44 (64)	16/46 (35)	1.83 (1.16,2.88)	*Favours comparator* P=0.009

New lesion	9/44 (20)	4/46 (9)	2.35 (0.78,7.09)	*Favours comparator* P=0.13
Intracerebral haemorrhage	8/44 (18)	0/46 (0)	17.76 (1.06,298.69)	*Favours comparator* P=0.05
Subarachnoid haemorrhage	2/44 (5)	2/46 (4)	1.05 (0.15,7.10)	*No significant effect* P=0.96
Intraventricular haemorrhage	1/44 (2)	0/46 (0)	3.13 (0.13,74.93)	*No significant effect* P=0.96
Extraaxial haematoma	0/44 (0)	1/46 (2)	0.35 (0.01,8.33)	*No significant effect* P=0.51
EXTERNAL VALIDITY				
Generalisability				
The study results are generalisable to patients with severe closed head injury.				
Applicability				
Since this study was undertaken in Iran, the results are likely to be poorly applicable in the Australian setting.				
Comments				
This was generally a well-designed and well-reported study. The study was adequately powered to detect mortality and bleeding given the high level of mortality in the patient population.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; CI, Confidence Interval; FFP, Fresh Frozen Plasma; CT, Computerised Tomography

Fibrinogen/cryoprecipitate transfusion strategies for patients with trauma

Level III evidence

<table>
<tr><td colspan="3">STUDY DETAILS: Cohort study</td></tr>
<tr><td colspan="3">Citation</td></tr>
<tr><td colspan="3">Watson, G. A., Sperry, J. L., Rosengart, M. R., Minei, J. P., Harbrecht, B. G., Moore, E. E., Cuschieri, J., Maier, R. V., Billiar, T. R., & Peitzman, A. B. 2009, Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome, Journal of Trauma - Injury, Infection and Critical Care, vol. 67, no. 2, pp. 221-227.</td></tr>
<tr><td colspan="3">Affiliation/Source of funds</td></tr>
<tr><td colspan="3">Supported by the National Institutes of Health (NIH NIGMS U54 GM062119-1 and NIH KL2 RR024154-03).</td></tr>
<tr><td>Study design</td><td>Level of evidence</td><td>Location/setting</td></tr>
<tr><td>Prospective observational cohort study</td><td>Level III-2</td><td>Seven institutions in USA between November 2003 and November 2007.</td></tr>
<tr><td>Risk factor/s assessed</td><td colspan="2">Potential confounding variables measured</td></tr>
<tr><td>Plasma-rich transfusion components including fresh frozen plasma (FFP), platelets (PLT), and cryoprecipitate.</td><td colspan="2">Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant (p <0.05).</td></tr>
<tr><td colspan="3">Population characteristics (including size)</td></tr>
<tr><td colspan="3">Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion. Included patients survived beyond the initial 48-hours post-injury.
Inclusion criteria for the overall cohort study included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (>6 mEq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the brain with an abbreviated injury score ≥2, allowing exclusion of patients with isolated traumatic brain injury. Patients <16 or >90 years of age and those with cervical spinal cord injury were also excluded from enrolment.
Data were derived from the ongoing multicenter prospective cohort study known as the Inflammation and the Host Response to Injury Large Scale Collaborative Program (www.gluegrant.org), supported by the National Institute of General Medical Sciences (NIGMS), which is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure after traumatic injury and hemorrhagic shock.
N= 1,175 (including 764 patients who were given FFP)</td></tr>
<tr><td colspan="2">Length of follow-up</td><td>Outcomes measured</td></tr>
<tr><td colspan="2">NR</td><td>Mortality
Multiple organ failure
Nosocomial infection
Acute Respiratory Distress Syndrome</td></tr>
<tr><td colspan="3">Method of analysis</td></tr>
</table>

Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: A multicenter prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. All patients required blood transfusion for enrollment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. Cox proportional hazard regression models were used to estimate the outcome risks (per unit) associated with plasma-rich transfusion requirements during the initial 24 hours after injury after controlling for important confounders.

There was no association with plasma-rich transfusion components and mortality or nosocomial infection. For every unit given, FFP was independently associated with a 2.1% and 2.5% increased risk of MOF and ARDS, respectively. Cryoprecipitate was associated with a 4.4% decreased risk of MOF (per unit), and platelets were not associated with any of the outcomes examined. When early deaths (within 48 hours) were included in the model, FFP was associated with a 2.9% decreased risk of mortality per unit transfused.

RESULTS

Population	With risk factor		Without risk factor	
Available	479		696	
Analysed	479		696	
Outcome (categorical)	Risk factor definition	No risk factor definition	Hazard ratio (95% CI)	Significance P-value
Mortality	Cryoprecipitate transfusion (1 unit)	NA	1.006 (0.96,1.06)	*An increase in cryoprecipitate transfusion units is not independently associated with mortality* P=0.828
Multiple organ failure	Cryoprecipitate transfusion (1 unit)	NA	0.956 (0.923,0.989)	*An increase in cryoprecipitate transfusion units is significantly and independently associated with multiple organ failure* P=0.01
Nosocomial infection	Cryoprecipitate transfusion (1 unit)	NA	0.997 (0.968,1.028)	*An increase in cryoprecipitate transfusion units is not independently associated with nosocomial infection* P=0.858

Acute respiratory distress syndrome	Cryoprecipitate transfusion (1 unit)	NA	1.03 (0.997,1.065)	*An increase in cryoprecipitate transfusion units is not independently associated with acute respiratory distress syndrome* P=0.076
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to severely injured blunt trauma patients with haemorrhagic shock. The population includes some patients who received massive transfusion.				
Applicability				
The results of this study are broadly applicable to the Australian healthcare system.				
Comments				
Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study. All patients also received RBC transfusion.				

NR, Not Reported; NA, Not Applicable; MOF, Multiple Organ Failure; ARDS, Acute Respiratory Distress Syndrome; CI, Confidence Interval; RBC, Red Blood Cell

Platelet transfusion strategies for patients with trauma

Level III evidence

STUDY DETAILS: Cohort study				
Citation				
Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Shih, D., Meyer, W., & Scalea, T. M. 2008a, Blood product transfusion and ventilator-associated pneumonia in trauma patients, *Surgical Infections*, vol. 9, no. 4, pp. 415-422.				
Affiliation/Source of funds				
University of Maryland				
Study design	Level of evidence		Location/setting	
Prospective observational cohort study	Level III-2		Single site in the USA	
Risk factor/s assessed		Potential confounding variables measured		
FFP (total amount of transfusion over entire hospital stay, in units) Platelets (total amount of transfusion over entire hospital stay, in units)		Albumin Base deficit Creatinine Glasgow Coma Score Heart rate Systolic blood pressure		
Population characteristics (including size)				
Trauma patients admitted to the intensive care unit (ICU) who received mechanical ventilation (MV) for ≥ 48 hours and who did not have pneumonia on admission. N=766 (including 26 patients who were found to have VAP)				
Length of follow-up		Outcomes measured		
NR		Ventilator associated pneumonia (VAP). Late-onset VAP was defined as that occurring ≥ 72 h after MV.		
Method of analysis				
All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP (p < 0.20) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Description: Prospective observational cohort study of 766 trauma patients admitted to the ICU, who received MV for ≥ 48 h, and who did not have pneumonia on admission. Late-onset VAP was defined as that occurring ≥ 72 h after MV. Only transfusions of red blood cell (RBC) concentrate, fresh-frozen plasma (FFP), or platelets before the onset of VAP were considered. Logistic regression analyses controlled for all variables related significantly to VAP by univariate analysis (sex, Injury Severity Score, and ventilator days and ICU length of stay prior to VAP).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	45		721	
Analysed	45		721	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

VAP	Platelet transfusion	No platelet transfusion	4.19 (1.37, 12.83)	*Platelet transfusion is significantly and independently associated with VAP* P=0.012
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to trauma patients who have received mechanical ventilation.				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				

VAP, Ventilated Assisted Pneumonia; CI, Confidence Interval.

STUDY DETAILS: Cohort study				
Citation				
Bochicchio, G. V., Napolitano, L., Joshi, M., Bochicchio, K., Meyer, W., & Scalea, T. M. 2008b, Outcome analysis of blood product transfusion in trauma patients: A prospective, risk-adjusted study, *World Journal of Surgery*, vol. 32, no. 10, pp. 2185-2189.				
Affiliation/Source of funds				
University of Maryland				
Study design	Level of evidence		Location/setting	
Prospective observational cohort study	Level III-2		Single site in the USA (R. Adams Cowley Shock Trauma Center)	
Risk factor/s assessed		Potential confounding variables measured		
FFP transfusion only (measured in number of units transfused) Platelet transfusion only (measured in number of units transfused)		Age Sex Injury Severity Score (ISS) Admission Glasgow Coma Score Transfusion (combination) Packed RBC transfusion		
Population characteristics (including size)				
Consecutive trauma patients admitted >48 hours to the ICU during a 2-year period (2002–2004). N=1172				
Length of follow-up		Outcomes measured		
NR		Outcome assessment included infection rate, ventilator days (V days), ICU and hospital length of stay (LOS), and mortality.		
Method of analysis				
Multiple logistic regression analyses were used for binary outcomes, using the covariates age, sex, race, and ISS as adjusters. The blood product variables were entered into the regression equation so that the variance in outcome explained by these variables would be partialled out of the final model, thus allowing interpretation of the blood product of interest to be made independent of the effects of the other blood products. Continuous variables were compared by using Student's t test (to compare differences between transfused and non-transfused patients) and multiple linear regression analysis, using the same covariates as adjusters.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Description: Studies have confirmed adverse outcome associated with transfusion of packed red blood cells in trauma; however, little data are available regarding other blood product transfusion, such as fresh frozen plasma (FFP) and platelets. The objective of this study was to examine risk-adjusted outcome in trauma with stratification by blood product type. Prospective data were collected daily for 1,172 consecutive trauma patients admitted to the intensive care unit (ICU) during a 2-year period, including transfusion rates of blood products (PRBCs, FFP, platelets).				
RESULTS				
Population	With risk factor		Without risk factor	
Available	4		1168	
Analysed	4		1168	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value

Infection	Platelet transfusion	No platelet transfusion	0.94 (0.96,1)	*Platelet transfusion is not independently associated with infection*
Hospital LOS	Platelet transfusion	No platelet transfusion	-0.15 (-0.023 ,0.07)	*Platelet transfusion is not independently associated with hospital LOS*
ICU LOS	Platelet transfusion	No platelet transfusion	-0.08 (-0.14,0.01)	*Platelet transfusion is not independently associated with ICU LOS*
Mortality	Platelet transfusion	No platelet transfusion	1.03 (1.02,1.04)	*Platelet transfusion is not significantly associated with mortality*
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to trauma patients				
Applicability				
The results of this study are applicable to the Australian healthcare system.				
Comments				
Only 4 patients had the risk factor (platelet transfusion) and it is therefore likely that the study was underpowered to detect significant associations.				

CI, Confidence Interval;; LOS, Length of Stay; ICU, Intensive Care Unit; NR, Not Reported

STUDY DETAILS: Cohort study		
Citation		
Watson, G. A., Sperry, J. L., Rosengart, M. R., Minei, J. P., Harbrecht, B. G., Moore, E. E., Cuschieri, J., Maier, R. V., Billiar, T. R., & Peitzman, A. B. 2009, Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome, *Journal of Trauma - Injury, Infection and Critical Care*, vol. 67, no. 2, pp. 221-227.		
Affiliation/Source of funds		
Supported by the National Institutes of Health (NIH NIGMS U54 GM062119-1 and NIH KL2 RR024154-03).		
Study design	Level of evidence	Location/setting
Prospective observational cohort study	Level III-2	Seven institutions in USA between November 2003 and November 2007.

Risk factor/s assessed	Potential confounding variables measured
Plasma-rich transfusion components including fresh frozen plasma (FFP), platelets (PLT), and cryoprecipitate.	Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

Population characteristics (including size)
Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion. Included patients survived beyond the initial 48-hours post-injury. Inclusion criteria for the overall cohort study included blunt mechanism of injury, presence of prehospital or emergency department systolic hypotension (<90 mm Hg) or an elevated base deficit (>6 mEq/L), blood transfusion requirement within the first 12 hours, and any body region exclusive of the brain with an abbreviated injury score ≥2, allowing exclusion of patients with isolated traumatic brain injury. Patients <16 or >90 years of age and those with cervical spinal cord injury were also excluded from enrolment. Data were derived from the ongoing multicenter prospective cohort study known as the Inflammation and the Host Response to Injury Large Scale Collaborative Program (www.gluegrant.org), supported by the National Institute of General Medical Sciences (NIGMS), which is designed to characterize the genomic and proteomic response in injured patients at risk for multiple organ failure after traumatic injury and hemorrhagic shock. N= 1,175 (including 764 patients who were given FFP)

Length of follow-up	Outcomes measured
NR	Mortality Multiple organ failure Nosocomial infection Acute Respiratory Distress Syndrome

Method of analysis

Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors). Clinically relevant interaction terms were tested and kept in the final model if statistically significant ($p < 0.05$).

INTERNAL VALIDITY

Overall quality assessment (descriptive)

Rating: Poor

Description: A multicenter prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. All patients required blood transfusion for enrollment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. Cox proportional hazard regression models were used to estimate the outcome risks (per unit) associated with plasma-rich transfusion requirements during the initial 24 hours after injury after controlling for important confounders.

There was no association with plasma-rich transfusion components and mortality or nosocomial infection. For every unit given, FFP was independently associated with a 2.1% and 2.5% increased risk of MOF and ARDS, respectively. Cryoprecipitate was associated with a 4.4% decreased risk of MOF (per unit), and platelets were not associated with any of the outcomes examined. When early deaths (within 48 hours) were included in the model, FFP was associated with a 2.9% decreased risk of mortality per unit transfused.

RESULTS

Population	With risk factor		Without risk factor	
Available	481		694	
Analysed	481		694	
Outcome (categorical)	Risk factor definition	No risk factor definition	Hazard ratio (95% CI)	Significance P-value
Mortality	PLT transfusion (1 unit)	NA	0.948 (0.83,1.08)	*An increase in PLT transfusion units is not independently associated with mortality* P=0.419
Multiple organ failure	PLT transfusion (1 unit)	NA	1.045 (0.978,1.117)	*An increase in PLT transfusion units is not independently associated with multiple organ failure* P=0.196
Nosocomial infection	PLT transfusion (1 unit)	NA	1.01 (0.942,1.082)	*An increase in PLT transfusion units is not independently associated with nosocomial infection* P=0.782

Acute respiratory distress syndrome	PLT transfusion (1 unit)	NA	1.073 (0.985,1.168)	*An increase in PLT transfusion units is not independently associated with acute respiratory distress syndrome* P=0.105
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to severely injured blunt trauma patients with haemorrhagic shock. The population includes some patients who received massive transfusion.				
Applicability				
The results of this study are broadly applicable to the Australian healthcare system.				
Comments				
Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study. All patients also received RBC transfusion.				

NR, Not Reported; NA, Not Applicable; CI, Confidence Interval; RBC, Red Blood Cell; PLT, platelet transfusion

Platelet transfusion strategies for critically ill elderly patients

Level III evidence

STUDY DETAILS: Cohort study		
Citation		
Khan, H., Belsher, J., Yilmaz, M., Afessa, B., Winters, J. L., Moore, S. B., Huhmayr, R. D., & Gajic, O. 2007, Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients, *Chest*, vol. 131, no. 5, pp. 1308-1314.		
Affiliation/Source of funds		
This research was supported in part by National Heart, Lung, and Blood Institute grant No. K23 HL78743–01A1.		
Study design	Level of evidence	Location/setting
Retrospective cohort study	Level III-2	A 24-bed general medical non-cardiac medical ICU (MICU) in St. Mary's Hospital, Mayo Clinic, Rochester, MN, USA
Risk factor/s assessed	Potential confounding variables measured	
FFP transfusion RBC transfusion Platelet transfusion	The ALI/ARDS risk factors that were studied included any transfusion, transfusion of individual blood products, sepsis, aspiration, pneumonia, drug overdose, disseminated intravascular coagulation (DIC), pancreatitis, alcohol use, cigarette smoking, and demographics. Except for smoking and alcohol abuse, risk factors for ALI/ARDS (including transfusions) were implicated only if they were present up to 48 h prior to the development of ALI/ARDS.	
Population characteristics (including size)		
The study included data from consecutive patients admitted to an MICU. Patients who had received a transfusion with any blood product were compared with those who had not undergone transfusion. Patients who had pulmonary oedema (hydrostatic or ALI/ARDS) on MICU admission and those who had been admitted to the MICU for < 24 hours were excluded from the study. The mean age of patients included in the study was > 60 years. N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with FFP)		
Length of follow-up	Outcomes measured	
NR	Development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) according to the standard American-European Consensus Conference on ARDS definition.	
Method of analysis		
Continuous and categoric variables were compared using the Wilcoxon rank sum, the Fisher exact test, or the χ^2 test, as appropriate. Demographics, baseline characteristics, ALI/ARDS risk factors, and transfusion factors were compared between patients who had been exposed and had not been exposed to blood product transfusion. The comparisons were also made between patients in whom ALI/ARDS developed and those in whom it did not develop, excluding patients in whom hydrostatic pulmonary oedema developed. Risk factors for ALI/ARDS were considered for multivariable logistic regression models if they (1) were statistically significant in univariate analysis ($p < 0.05$), (2) had high odds ratios (≥2); or (3) were biologically plausible. Both factors associated with the probability of transfusion (i.e. the propensity score) and ALI/ARDS were included in the multivariate analysis. Because of colinearity, each of the blood product types (i.e. RBCs, FFP, or platelets) were also included into separate logistic models. In addition to nontransfusion risk factors, each model contained a probability of transfusion of specific blood products.		
INTERNAL VALIDITY		
Overall quality assessment (descriptive)		

Rating: Good Description: In this single-centre retrospective cohort study, 841 consecutive critically ill patients were studied for the development of ALI/ARDS. Patients who received blood product transfusions were compared with those who did not, in univariate and multivariate propensity analyses.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	122		543	
Analysed	122		543	
Outcome (categorical)	Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
ARDS/ALI	Platelet transfusion	No platelet transfusion	3.89 (1.36–11.52)	*Platelet transfusion is significantly and independently associated with ARDS/ALI* P-value: NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to critically ill elderly patients				
Applicability				
The results of this study are broadly applicable to the Australian health-care system.				
Comments				
the risk of ALI/ARDS was higher in patients who had received platelets and FFP than in those who received only RBCs.				

CI, Confidence Interval; RBC, Red Blood Cells; NR, Not Reported; ARDS, Acute Respiratory Distress Syndrome; ALI, Acute Lung Injury

F4 Evidence summaries – Question 4

Cell Salvage

Level II evidence

STUDY DETAILS: RCT				
Citation				
Bowley DM, Barker P, Boffard KD (2006) Intraoperative blood salvage in penetrating abdominal trauma: A randomised, controlled trial. World J Surg 30(6):1074-80.				
Affiliation/Source of funds				
Witwatersrand medical school, Johannesburg, Republic of South Africa.				
Study design	Level of evidence		Location/setting	
RCT	Level II		Trauma unit, single hospital	
Intervention		Comparator		
Intraoperative cell salvage		Allogenic blood transfusion		
Population characteristics				
44 patients with penetrating torso injury requiring laparotomy who had hypotension and significant blood loss. All patients received prophylactic antibiotics. Patients under age 18 and those with injuries more than 6 hours old were excluded.				
Length of follow-up		Outcomes measured		
NR		Allogeneic transfusion volume, survival, costs.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: A RCT of intraoperative cell salvage compared to allogenic transfusion in 44 abdominal trauma patients.				
RESULTS				
Population analysed	Intervention		Comparator	
Randomised	21		23	
Efficacy analysis (ITT)	21		23	
Efficacy analysis (PP)	21		23	
Safety analysis	21		23	
Outcome	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value
Allogeneic transfusion volume (units) First 24 hours post-injury	6.47 ±5.14 (21)	11.17±6.06 (23)	NR	*Use of cell salvage is associated with significantly reduced allogeneic transfusion volume.* P=0.008

Survival (all subjects)	7/21 (33%)	8/23 (55%)	NR	*Use of cell salvage is not associated with improved survival.* P=1.0
Survival (subjects with enteric injury)	7/18 (38.8%)	4/17 (23.5%)	NR	*Use of cell salvage is not associated with improved survival.* P=0.47
Mean per-patient costs, £ Excludes capital and maintenance costs and cell salvage technician costs.	812.23±451.26	990.04±479.48	NR	*Use of cell salvage is not associated with changes in costs.* P=0.2
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult patients with penetrating abdominal trauma.				
Applicability				
The study was performed at a single trauma centre in South Africa. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that use of intraoperative cell salvage reduces demand for allogeneic blood transfusion and does not decrease survival rates. The study may not be sufficiently powered to detect differences in survival, as the primary outcome was transfusion volume. Blinding was not reported, and it is assumed that the trial was not blinded due to the differences in the surgical procedures in the two groups.				

ITT, intention-to-treat; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation.

Level III evidence

STUDY DETAILS: Cohort study				
Citation				
Alonso-Perez M, Segura RJ, Pita S, Cal L (1999) Surgical treatment of ruptured abdominal aortic aneurysms in the elderly. Ann Vasc Surg 13(6):592-8.				
Affiliation/Source of funds				
Collaborative Hospitals Group, A Coruna, Spain				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		21 hospitals in Spain	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		Not significant by univariate analysis so not considered in the multivariate analysis		
Population characteristics (including size)				
(Jan 1995 – Dec 1996) 112 patients aged 75 years or older undergoing surgery for ruptured abdominal aortic aneurysm.				
Length of follow-up		Outcomes measured		
NR – probably until death or discharge		Mortality		
Method of analysis				
Univariate using unpaired Student's t-test, Mann-Whitney test, and chi-squared test.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retrospective cohort study of 112 patients aged 75 or over undergoing emergency operations for ruptured abdominal aortic aneurysm.				
RESULTS				
Population	With risk factor		Without risk factor	
Available				
Analysed	8		104	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality	6/8 (75%)	NR	OR 1.8 (0.3, 9.5)	*Use of cell salvage is not significantly associated with mortality.* P=0.706
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of elderly patients with ruptured abdominal aortic aneurysms.				
Applicability				
The study was carried out at 21 hospitals in Spain. The results of this study are likely to be applicable to the Australian setting.				
Comments				

The authors conclude that use of cell salvage is not associated with mortality in elderly patients with ruptured abdominal aortic aneurysms.

CI, confidence interval.

STUDY DETAILS: Cohort study				
Citation				
Alonso-Perez M, Segura RJ, Sanchez J, Sicard G, Barreiro A, Garcia M, Diaz P, Barral X, Cairols MA, Hernandez E, Moreira A, Bonamigo TP, Llagostera S, Matas M, Allegue N, Kramer AH, Mertens R (2001) Factors increasing the mortality rate for patients with ruptured abdominal aortic aneurysms. Ann Vasc Surg 15(6):601-7.				
Affiliation/Source of funds				
Hospital Juan Canalejo. A Coruna, Hospital Covadonga, Oviedo, Hospital de Bellvitqe, Barcelona, Hospital Santa Creu i Sant Pau, Barcelona, Hospital Val1 d'Hebron, Barcelona, Spain Barnes Hospital, Washington University Medical Center, St. Louis, Missouri, United States Hopital Nord, Saint Etienne, France. Hospital Geral Santo Antonio, Porto, Portugal. Hospital de la Universidad Catolica de Chile, Santiago, Chile. Hospital San Francisco, Porto Alegre, Brazil.				
Study design	Level of evidence		Location/setting	
Cohort study	Level III-2		10 hospitals, Spain, France, Portugal, United States, Brazil, Chile	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		Not significant by univariate analysis so not considered in the multivariate analysis		
Population characteristics (including size)				
(Jan 1996 – Dec 1997) 144 patients undergoing emergency operations for ruptured abdominal aortic aneurysm.				
Length of follow-up		Outcomes measured		
NR – probably until discharge		Mortality		
Method of analysis				
Univariate using unpaired Student's t-test, Mann-Whitney test, and chi-squared test.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retropective cohort study of 144 patients undergoing emergency operations for ruptured abdominal aortic aneurysm.				
RESULTS				
Population	With risk factor		Without risk factor	
Available				
Analysed	42		102	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality	NR	NR	NR	*Use of cell salvage is not significantly associated with mortality.* P=0.45
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients with ruptured abdominal aortic aneurysms.				

Applicability
The study was carried out at 10 centres in Europe, the United Staes and South America. The results of this study are likely to be applicable to the Australian setting.
Comments
The authors conclude that use of cell salvage is not associated with mortality in ruptured abdominal aortic aneurysm patients.

CI, confidence interval.

STUDY DETAILS: Cohort study				
Citation				
Brown CVR, Foulkrod KH, Sadler HT, Richards EK, Biggan DP, Czysz C, Manuel T (2010) Autologous blood transfusion during emergency trauma operations. Arch Surg 145(7):690-4.				
Affiliation/Source of funds				
University Medical Center Brackenridge, and Capital Area Perfusionists, Austin, Texas, United States of America.				
Study design	Level of evidence	Location/setting		
Retrospective matched cohort study	Level III-2	Single trauma centre		
Risk factor/s assessed	Potential confounding variables measured			
Use of cell salvage	The cell salvage group was paired with controls according to the confounding variables of age (±5 years), sex, mechanism of injury (blunt or penetrating), Injury Severity Score (16-25 or >25), and operation performed.			
Population characteristics (including size)				
47 adult trauma patients who underwent urgent trauma surgery with cell salvage. These patients were matched to 47 adult trauma patients who underwent urgent trauma surgery without cell salvage.				
Length of follow-up	Outcomes measured			
NR	Allogeneic transfusion volume, blood loss, mortality, blood product cost			
Method of analysis				
Chi-squared and paired, 2-tailed t tests and nonparametric tests when appropriate.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective matched cohort study of 94 trauma patients undergoing emergency surgery for trauma. 47 patients had intraoperative cell salvage and 47 patients did not.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	47		47	
Analysed	47		47	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Intraoperative blood loss (mL, mean (SD))	1795 (1197) measured	978 (890) estimated	NR	*Use of intraoperative cell salvage is associated with significantly greater blood loss.* P<0.001
Mortality (n/N (%))	6/47 (13)	10/47 (21)	NR	*Use of intraoperative cell salvage is not associated with increased mortality.* P=0.56

Allogeneic transfusion volume (Units, mean (SD))	Preoperative	2 (2)	3 (1)	NR	*Use of intraoperative cell salvage is not associated with preoperative allogeneic transfusion volume.* P=0.16
	Intraoperative	2 (1)	4 (2)	NR	*Use of intraoperative cell salvage is associated with significantly lower intraoperative allogeneic transfusion volume.* P=0.002
	Total	4 (2)	8 (3)	NR	*Use of intraoperative cell salvage is associated with significantly lower total allogeneic transfusion volume.* P<0.001
Blood product costs per-patient, mean US$ Includes cell salvage machine operating costs.		1616	2584	NR	*Use of intraoperative cell salvage is associated with significantly lower blood product costs.* P=0.004
EXTERNAL VALIDITY					
Generalisability					
The results of this study are generalisable to a population of adult patients undergoing emergency surgery for trauma.					
Applicability					
The study was carried out at a single trauma centre in the United States. The results of this study are likely to be applicable to the Australian setting.					
Comments					
The authors conclude that cell salvage is associated with fewer transfusions of allogeneic red blood cells while providing a savings in total transfusion costs.					

CI, confidence interval; NR, not reported; SD, standard deviation.

STUDY DETAILS: Cohort study				
Citation				
Jurkovich GJ, Moore EE, Medina G. Autotransfusion in trauma. A pragmatic analysis. Am J Surg; 1984; 148(6):782-785				
Affiliation/Source of funds				
Denver General Hospital, Denver, Colorado, United States of America				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single hospital, United States	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage				
Population characteristics (including size)				
85 adult acute trauma patients undergoing surgery.				
Length of follow-up		Outcomes measured		
NR		Allogeneic transfusion volume, blood loss, mortality		
Method of analysis				
Descriptive statistics				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retrospective cohort study of 85 adult trauma patients undergoing emergency surgery. 22 patients had surgery with cell salvage. 63 patients did not receive cell salvage due to inadequate blood retrieval, contamination or death.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	22		63	
Analysed	22		63	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Blood loss, estimated (mL, mean (SD))	8600 (1500)	2900 (630)	NR	*Patients treated with cell salvage had a greater mean blood loss*. P=NR
Allogeneic transfusion volume (mL, mean (SD))	6800 (900)	3300 (580)	NR	*Patients treated with cell salvage had a greater mean allogeneic transfusion volume.* P=NR
Mortality (n/N (%))	6/22 (27)	16/63 (25)	NR	*Patients treated with and without cell salvage had similar mortality rates.* P=NR
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to an adult population of trauma patients undergoing emergency surgery.
Applicability
The study was conducted at a single hospital in the Unted States. The results of this study are likely to be applicable to the Australian setting.
Comments
The two patient groups had significant differences in their presentation haematocrit value and crystalloid requirements. Haematocrit was significantly higher in the control group ($p<0.01$).

CI, confidence interval; NR, not reported; SD, standard deviation.

STUDY DETAILS: Cohort study				
Citation				
Markovic M, Davidovic L, Savic N, Sindjelic R, Ille T, Dragas M (2009) Intraoperative cell salvage versus allogeneic transfusion during abdominal aortic surgery: Clinical and financial outcomes. Vascular 17(2):83-92.				
Affiliation/Source of funds				
Clinical Centre of Serbia, Belgrade and the University of Belgrade, Belgrade, Serbia.				
Study design	Level of evidence		Location/setting	
Historically controlled cohort study	Level III-3		Single centre, Serbia	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		NA		
Population characteristics (including size)				
Prospective cohort of 90 patients undergoing surgery with cell salvage during 2004 and 2005 and a historical cohort of 90 patients who had surgery without cell salvage during 2002. 30 patients in each cohort underwent emergency surgery for ruptured abdominal aortic aneurysm. There were no significant differences in baseline measurements of urea, creatinine, haematocrit, Hb, platelets and aneurysm size between the two emergency surgery groups. Allogeneic transfusion was not given to patients with Hb levels >100 g/L or haematocrit levels >30%.				
Length of follow-up		Outcomes measured		
Until discharge		Blood loss, allogeneic RBC transfusion, allogeneic plasma transfusion, mortality		
Method of analysis				
Descriptive statistics and univariate analysis				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Historically controlled cohort study of 180 patients having surgery with or without cell salvage. 60 patients had ruptured abdominal aortic aneurysm.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	30		30	
Analysed	30		30	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Intraoperative mortality	7/30	4/30	NR	P=NR
Postoperative mortality	5/30	10/30	NR	P=NR
Overall mortality	12/30	14/30	NR	*Use of cell salvage is not significantly associated with mortality.* P=0.62

Intraoperative blood loss (mL, mean ± SD)	4052.6±3186	3965.6±1708	NR	*Use of cell salvage is not significantly associated with blood loss.* P=NS
Intraoperative RBC transfusion (mL, mean ± SD)	913.8±602	1146.3±595	NR	*Favours cell salvage.* P=0.0380
Postoperative RBC transfusion (mL, mean ± SD)	976.3±927	1609.6±998	NR	*Favours cell salvage.* P=0.0097
Total allogeneic RBC transfusion (mL, mean ± SD)	1890.1±1186	2755.9±1265	NR	*Favours cell salvage.* P=0.0089
Intraoperative plasma transfusion (mL, mean ± SD)	627.8±508	817.0±551	NR	*Favours cell salvage.* P=0.240
Postoperative plasma transfusion (mL, mean ± SD)	595.6±1021	828.8±640	NR	*Favours cell salvage.* P=0.0410
Total allogeneic plasma transfusion (mL, mean ± SD)	1223.4±1223	1645.8±947	NR	*Favours cell salvage.* P=0.0062
Allogeneic RBC transfusion incidence	29/30	30/30	NR	P=NR
Allogeneic plasma transfusion incidence	25/30	30/30	NR	P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population undergoing surgery for ruptured abdominal aortic aneurysm.				
Applicability				
The study was carried out at a single centre in Serbia. The results fo this study may be applicable to the Australian context.				
Comments				
The authors conclude that the use of intraoperative cell salvage results in a significant reduction in the transfusion of allogeneic products with no effect on survival.				

CI, confidence interval; NR, not reported; SD, standard deviation.

STUDY DETAILS: Cohort study				
Citation				
Ozmen, V; McSwain, NE; Nichols, RL; Smith, J; Flint, LM. Autotransfusion of Potentially Culture-Positive Blood (CPB) in Abdominal Trauma: Preliminary Data from a Prospective Study. Journal of Trauma-Injury Infection & Critical Care. 32(1):36-39, January 1992.				
Affiliation/Source of funds				
Tulane University Scholl of Medicine, New Orleans, Louisiana, United States of America.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single hospital	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage				
Population characteristics (including size)				
70 patients with penetrating abdominal trauma, gastrointestinal tract injuries and a Penetrating Abdominal Trauma Index score ≥20.				
Length of follow-up		Outcomes measured		
NR		Allogeneic transfusion volume, mortality		
Method of analysis				
Chi-square test for discrete variables and student's *t* test for continuous variables.				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retrospective cohort study of 85 adult abdominal trauma patients undergoing surgery with or without cell salvage.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	20		50	
Analysed	20		50	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Allogeneic transfusion volume Total Mean (calculated pot hoc)	139 6.95	179 3.58	NR	*Patients treated with cell salvage had a greater mean allogeneic transfusion volume*. P=NR
Mortality, 72-hour (n/N (%))	2/20 (10)	0/50 (0)	NR	*Patients treated with cell salvage had a higher mortality rate*. P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult abdominal trauma patients undergoing emergency surgery.				
Applicability				

The study was carried out at a single centre in the United States. The results of this study are likely to be applicable to the Australian setting.
Comments
Very little of baseline demographic provided.

CI, confidence interval; NR, not reported.

STUDY DETAILS: Cohort study				
Citation				
Posacioğlu H, Apaydin A, Calkavur T, Uç H.(2002) Adverse effects of cell saver in patients undergoing ruptured abdominal aortic aneurysm repair. Ann Vasc Surg. 2002 Jul;16(4):450-5				
Affiliation/Source of funds				
Dept of Cardiovascular Surgery, Ege University, Izmir, Turkey				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single hospital, Turkey	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		Gross clamp level, graft type		
Population characteristics (including size)				
56 patients with ruptured abdominal aortic aneurysm undergoing surgical repair. Use of cell salvage depended on the surgeon's preference, availability of the device and rarity of patient's blood type. Age range was 35 to 85 years with a mean age of 68.2 years. 55 patients were male and 1 patient was female. The female patient was not given cell salvage. Blood transfusion requirements were determined according to the institutional protocol, which was not specified.				
Length of follow-up		Outcomes measured		
NR		Mortality, allogeneic transfusion volume, reoperation, complications (respiratory, renal, gastrointestinal), FFP transfusion and length of stay		
Method of analysis				
Descriptive statistics and univariate and multivariate logistic regression				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective cohort study of 56 patients with ruptured abdominal aortic aneurysm undergoing surgery with or without cell salvage.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	40		16	
Analysed	40		16	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Mortality	16/40 (40)	8/16 (50)	NR	*Use of cell salvage is not associated with mortality.* P=0.495
Allogeneic RBC transfusion volume (postoperative) (units, mean±SD)	5.8±3.84	3.63±2.87	NR	*Use of cell salvage is associated with increased allogeneic RBC transfusion volume* P=0.026

Allogeneic FFP transfusion volume (postoperative) (units, mean±SD)	4.45±4.03	1.5±1.37	NR	*Use of cell salvage is associated with increased allogeneic FFP transfusion volume* P=0.006
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients with ruptured abdominal aortic aneurysms.				
Applicability				
The study was carried out at a single centre in Turkey. The results of this study may be applicable to the Australian context.				
Comments				
The authors conclude that the use of cell salvage is associated with increased usage of allogenic blood.				

CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; RBC, red blood cell; SD, standard deviation

STUDY DETAILS: Cohort study				
Citation				
Serracino-Inglott F, Awad S, Barclay A, Nasim A (2005) The use of a cell saver during repair of ruptured abdominal aortic aneurysms increases early survival. Ann R Coll Surg Engl 87(6):475.				
Affiliation/Source of funds				
Wythenshawe Hospital, Manchester, United Kingdom				
Study design	Level of evidence		Location/setting	
Cohort study	Level III-2		Single hospital, United Kingdom	
Risk factor/s assessed		Potential confounding variables measured		
Use of call salvage		NR		
Population characteristics (including size)				
154 patients who underwent surgery for ruptured abdominal aortic aneurysm between January 2000 and June 2004. Cell salvage was used for 40 of these patients. The two groups had no differences in age, cardiac symptoms, respiratory symptoms, cardiac medication, myocardial infarction and diabetes.				
Length of follow-up		Outcomes measured		
NR		Survival, transfusion volume		
Method of analysis				
Descriptive statistics				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Cohort study of 154 patients undergoing surgery with or without cell salvage for ruptured abdominal aortic aneurysm.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	40		114	
Analysed	40		114	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Overall survival [a]	27/40 (68)	58/114 (51)	NR	*The use of cell salvage is not significantly associated with mortality.* P=0.07
Survival, excluding patients who died in theatre	79%	56%	NR	*Favours cell salvage* P=0.01
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients undergoing surgery for ruptured abdominal aortic aneurysm.				
Applicability				
The study was carried out at a single hospital in the United Kingdom. The results of this study are likely to be applicable to the Australian setting.				

Comments
The study is a short report in a journal technical section. Could not extract data on transfusion volume, as it was not stated whether the values presented were mean or median.

CI, confidence interval.

[a] Affected subject numbers calculated post hoc from percentages

STUDY DETAILS: Cohort study				
Citation				
Shuhaiber JH, Whitehead SM (2003) The impact of introducing an autologous intraoperative transfusion device to a community hospital. Ann Vasc Surg 17(4):424-9.				
Affiliation/Source of funds				
Conquest Hospital, Hastings and Rother NHS Trust, The Ridge St Leonards-on Sea, East Sussex, United Kingdom				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single hospital, United Kingdom	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		NA		
Population characteristics (including size)				
25 patients undergoing emergency abdominal aortic aneurysm repair. The study also reports results for 93 patients who had elective surgery. The authors report that the cell salvage machine was not used in ruptured or emergency cases but they have data for cell salvage in emergency AAA (4 subjects).				
Length of follow-up		Outcomes measured		
NR – probably until discharge		Blood loss, Allogeneic transfusion volume		
Method of analysis				
Student t test and Mann-Whitney U test				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Poor Description: Retrospective cohort study of 25 patients undergoing emergency abdominal aortic aneurysm repair.				
RESULTS				
Population	With risk factor		Without risk factor	
Available				
Analysed	4		21	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Blood loss, mL estimated (mean (SD))	2838 (1815)	4312 (2575)	NR	*Patients whose surgery included cell salvage had lower mean blood loss.* P=NR
Allogeneic transfusion volume, mL (mean (SD))	2800 (857)	3161 (2155)	NR	*Patients whose surgery included cell salvage had lower mean allogeneic transfusion volume.* P=NR
Allogeneic transfusion incidence	4/4	21/21	NR	*No difference* P=NR
EXTERNAL VALIDITY				

Generalisability
The results of this study are generalisable to a population of patients undergoing emergency abdominal aortic aneurysm repair.
Applicability
The study was carried out at a single centre in the United Kingdom. The results of this study are likely to be applicable to the Australian setting.
Comments

CI, confidence interval

STUDY DETAILS: Cohort study				
Citation				
Tawfick WA, O'Connor M, Hynes N, Sultan S (2008) Implementation of the Continuous AutoTransfusion System (C.A.T.S) in open abdominal aortic aneurysm repair: An observational comparative cohort study. Vasc Endovasc Surg 42(1):32-9.				
Affiliation/Source of funds				
University College Hospital and Galway Clinic, Galway, Ireland.				
Study design	Level of evidence		Location/setting	
Retrospective cohort study	Level III-2		Single centre, Ireland	
Risk factor/s assessed		Potential confounding variables measured		
Use of cell salvage		NR		
Population characteristics (including size)				
Patients undergoing open abdominal aortic aneurysm repairs received allogenic blood alone or blood from cell salvage (with further allogenic blood if needed). Allocation to the use of cell salvage was based on the availability of a Haemovigilance technician trained to operate the machine. Patients were considered to be controls if a Haemovigilance technician was not available at the time of surgery. Both elective and emergency surgeries were included.				
Length of follow-up		Outcomes measured		
NR		Blood loss, allogeneic transfusion volume and incidence, mortality, cost		
Method of analysis				
Descriptive statistics				
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Fair Description: Retrospective cohort study of 187 patients undergoing abdominal aortic aneurysm repair, including 55 patients who underwent emergency surgery.				
RESULTS				
Population	With risk factor		Without risk factor	
Available	101 (emergency and elective)		86 (emergency and elective)	
Analysed	27 (emergency)		28 (emergency)	
Outcome (categorical)	Risk factor definition	No risk factor definition	Risk estimate (95% CI)	Significance P-value
Blood loss, estimated (emergency surgery) (mL, mean (range))	3329 (756-20000)	2998 (835-18000)	NR	*Cell salvage is not associated with blood loss.* P=0.082
Allogeneic RBC transfusion volume (emergency surgery) (Units, mean (range))	6 (0-34)	12 (3-38)	NR	*Patients treated with cell salvage had a lower mean allogeneic transfusion volume.* P=NR

Allogeneic RBC transfusion incidence	20/27	28/28	NR	*Patients treated with cell salvage had a lower incidence of allogeneic transfusion.* P=NR
Mortality, 30-day (emergency surgery) (n/N (%))	6/27 (22)	9/28 (32)	NR	*Patients treated with cell salvage had a lower mortality rate.* P=NR
Mean per-patient cost, € Emergency and elective surgeries Includes transfusion costs, consumables and hospital bed costs.	13780.27	19016.77	Difference: 5236.50	*Patients treated with cell salvage had a lower mean mean cost per patient.* P=NR
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult patients underging surgery for abdominal aortic aneurysm repair.				
Applicability				
The study was carried out at a single centre in Ireland. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors conclude that cell salvage markedly reduced the amount of allogenic blood transfused. Although expensive to set up initially, cell salvage proved to be more cost-effective when it was used on a continuous basis in a mixed emergency and elective repair setup.				

CI, confidence interval, mL, millilitre; NR, not reported

Tranexamic acid

Level II evidence

STUDY DETAILS: SR/MA				
Citation				
Gluud LL, Klingenberg SL, Langholz SE (2008) Systematic review: Tranexamic acid for upper gastrointestinal bleeding. Aliment Pharmacol Ther 27(9):752-8.				
Affiliation/Source of funds				
Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen; Department of Internal Medicine, Gentofte University Hospital, Hellerup, Denmark.				
Study design	Level of evidence		Location/setting	
Systematic review	Level I		United Kingdom, Australia and Sweden.	
Intervention		Comparator		
Tranexamic acid (4-8g daily, intravenous and/or oral)		Placebo		
Population characteristics				
Seven RCTs, described in eight publications, were included.1654 patients with suspected upper gastrointestinal bleeding confirmed by gastriclavage, haematemesis or melaena were randomised. In total, 21% were withdrawn after randomisation. Reasons for exclusions included lack of verified bleeding, malignant disease, terminal illness, treatment administered too late or the patient was included too late after admission to hospital.				
Length of follow-up		Outcomes measured		
Varied, details not reported		Mortality, allogeneic transfusion frequency		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: SR,Good; Included studies, 7 RCTs of good to poor quality Description: Systematic review of the use of tranexamic acid in gastrointestinal bleeding.				
RESULTS				
Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
All-cause mortality 7 RCTs	5%	8%	RR 0.61 (0.42, 0.89)	*Favours tranexamic acid.* P=Significant No significant heterogeneity[a] P=0.87 (I^2=NR)
Mortality due to bleeding 7 RCTs	3%	5%	RR0.66 (0.40, 1.10)	No difference P=Not significant Heterogeneity[a] P=NR (I^2=NR)
Allogeneic transfusion frequency 4 RCTs	56%	57%	RR 1.0 (0.93, 1.11)	No difference P=Not significant No significant heterogeneity[a] P=0.59 (I^2=NR)

Thromboembolic events: myocardial infarction, pulmonary embolism, cerebral infarction 3 RCTs	5/522 (1.0)	4/526 (0.8)	RR 1.4 (0.36, 5.28)	No difference P=Not significant Heterogeneity[a] P=0.36 (I^2=NR)
Thromboembolic events: deep vein thrombosis	6/522 (1.1)	2/526 (0.4)	RR 2.3 (0.61, 8.94)	No difference P=Not significant No significant heterogeneity[a] P=0.96 (I^2=NR)
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of patients with upper gastrointestinal haemorrhage.				
Applicability				
The studies included in this review were carried out at centres in the United Kingdom, Sweden and Australia. The results of this study are likely to be applicable to the Australian setting.				
Comments				
The authors say they have assessed the quality of the included studies but don't give a rating for each study. Numbers of subjects included in each analysis were not routinely presented.				

ITT, intention-to-treat; CI, confidence interval; MA, meta-analysis; NR, not reported; PP, per-protocol; RCT, randomised controlled trial; SD, standard deviation; SR, systematic review.

STUDY DETAILS: SR/MA				
Citation				
Roberts I, Shakur H, Ker K, Coats T, -on-behalf-of-the-CRASH- (2011) Antifibrinolytic drugs for acute traumatic injury. Roberts Ian, Shakur Haleema , Ker Katharine , Coats Tim , on behalf of the CRASH 2 Trial collaborators Antifibrinolytic drugs for acute traumatic injury Cochrane Database of Systematic Reviews: Reviews 2011 Issue 1 John Wiley & Sons , Ltd Chichester, UK.				
Affiliation/Source of funds				
The Cochrane Collaboration				
Study design	Level of evidence	Location/setting		
Systematic review	Level I	40 countries		
Intervention		Comparator		
Tranexamic acid, 2g, given as a single dose in Yutthakasemsunt 2010 and in CRASH-2 2010 as loading dose 1g over 10 minutes then infusion of 1g over 8 hours.		Placebo		
Population characteristics				
CRASH-2 2010: 20,211 adult (>16 years) trauma patients with, or at risk of, significant bleeding. Yutthakasemsunt 2010: 240 adults patients (>16 years) with moderate to severe traumatic brain injury (Glasgow Coma Scale 4 to 12) within 8 hours of injury.				
Length of follow-up		Outcomes measured		
NR		Mortality, Thromboembolic events, allogeneic transfusion incidence and volume.		
INTERNAL VALIDITY				
Overall quality assessment (descriptive)				
Rating: Systematic review: Good; Included studies: Tranexamic acid: 1 Good quality RCT, 1 Fair quality RCT Description: A systematic review of the use of tranexamic acid in trauma patients. The review includes 2 RCTs with a total of 20451 subjects.				
RESULTS				
Outcome No. trials (No. patients)	<Intervention> n/N (%) Mean ± SD (N)	<Comparator> n/N (%) Mean ± SD (N)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Mortality due to vascular occlusion (includes MI, stroke and PE) 1 RCT N=20211	NR	NR	RR 0.69 (0.44, 1.07)	*No difference* P=0.096
Mortality due to stroke 1 RCT N=20211	NR	NR	RR 1.60 (0.52, 4.89)	*No difference* P=0.40
Mortality due to PE 1 RCT N=20211	NR	NR	RR 0.86 (0.46, 1.61)	*No difference* P=0.63

Mortality due to MI 1 RCT N=20211	NR	NR	RR 0.32 (0.14, 0.75)	*Favours tranexamic acid* P=0.0053
Mortality due to bleeding 1 RCT N=20211	NR	NR	RR 0.85 (0.76, 0.96)	*Favours tranexamic acid* P=0.0077
Mortality due to mulit-organ failure 1 RCT N=20211	NR	NR	RR 0.90 (0.75, 1.08)	*No difference* P=0.25
Mortality due to head injury 1 RCT N=20211	NR	NR	RR 0.97 (0.87, 1.08)	*No difference* P=0.60
Mortality due to other causes 1 RCT N=20211	NR	NR	RR 0.94 (0.74, 1.20)	*No difference* P=0.63
Mortality in patients treated ≤1 hour after injury 1 RCT N=20211	509/3747 (13.6)	581/3704 (15.7)	RR 0.87 (0.75, 1.00)	*Favours tranexamic acid* P=NR
Mortality in patients treated >1 to ≤3 hours after injury 1 RCT N=20211	463/3037 (15.2)	528/2996 (17.6)	RR 0.87 (0.75, 1.00)	*Favours tranexamic acid* P=NR
Mortality in patients treated >3 hours after injury 1 RCT N=20211	491/3272 (15.0)	502/3362 (14.9)	RR 1.00 (0.86, 1.17)	*No difference* P=NR
All-cause mortality 2 RCTs N=20451	1475/10180 (14.5)	1631/10187 (16.0)	Fixed effects: RR 0.90 (0.85, 0.97)	*Favours tranexamic acid* P=0.0025 No significant heterogeneity[a] P=0.38 (I^2=0%)
Stroke events 1 RCT N=20211	NR	NR	RR 0.86 (0.61, 1.23)	*No difference* P=0.42
PE events 1 RCT N=20211	NR	NR	RR1.01 (0.73, 1.41)	*No difference* P=0.93

DVT events 1 RCT N=20211	NR	NR	RR 0.98 (0.63, 1.51)	*No difference* P=0.91
MI events 1 RCT N=20211	NR	NR	RR 0.64 (0.42, 0.97)	*Favours tranexamic acid* P=0.035
Vascular occlusive events (MI, stroke, PE, DVT) 1 RCT N=20211	NR	NR	RR 0.84 (0.68, 1.02)	*No difference* P=0.084
Allogeneic transfusion incidence 1 RCT N=20211	5067/10060 (50.4)	5160/10067 (51.3)	Fixed effects: RR 0.98 (0.96, 1.01)	*No difference* P=0.21
Allogeneic transfusion volume 1 RCT N=20211	3.05±7.7	3.22±8.02	Fixed effects: WMD -0.17 (-0.39, 0.05)	*No difference* P=NS
EXTERNAL VALIDITY				
Generalisability				
The results of this study are generalisable to a population of adult (>16 years) trauma patients.				
Applicability				
The studies in this review were carried out at centres in 40 countries. The results of this review are likely to be applicable to the Australian setting.				
Comments				

ITT, intention-to-treat; CI, confidence interval; DVT, deep vein thrombosis; MA, meta-analysis; MI, myocardial infarction; NR, not reported; NS, not significant; PE, pulmonary embolism; PP, per-protocol; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; SR, systematic review; UK, United Kingdom; WMD, weighted mean difference.