

Kenneth Goldsmith Lecture

Blood, Sweat, and Tears: are we ready for personalised transfusion practice?

Tim Walsh

Professor of Critical Care, Edinburgh University









Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co- Morbidities CVD Respiratory Neurological Haemato- Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy chemotherapy Chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution	Blood transfusion Volume No. units Target Hb RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

Critical and acute illness: the ideal model for studying transfusion practice?

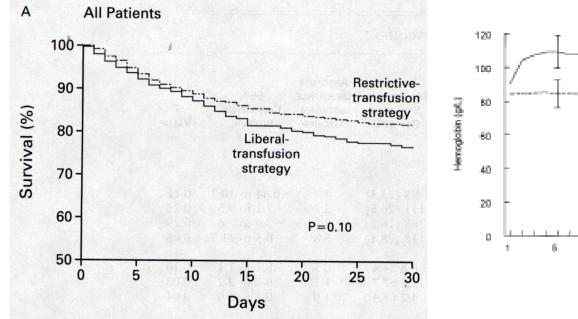
- High prevalence of anaemia
- High transfusion requirement
- Strong biological plausibility that keeping oxygen delivery high decreases organ failures and other complications
- High 'event rates' relevant to transfusion
 - Mortality ≈20%
 - High illness costs ≈£1500 per day
 - High burden of symptoms relevant to anaemia

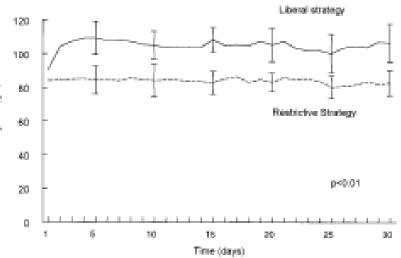
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.Sc., ELIZABETH YETIS'R, M.Sc., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

"TRICC" NEJM 1999



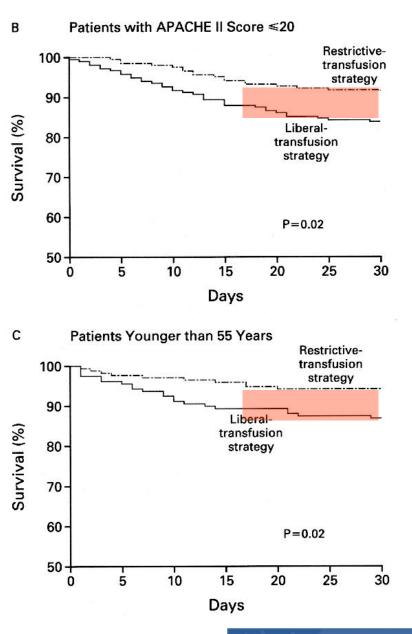




Aggregate mortality at 60 days 25% Difference in mortality at 60 days 3-8% overall

Main differences: [1] Degree of anaemia [2] Exposure to stored nonleucodepleted red cells

Mean time in study 11 days Difference in RBC exposure 2.7 units Difference in proportion exposed 33%



Edinburgh Critical Care Research Group

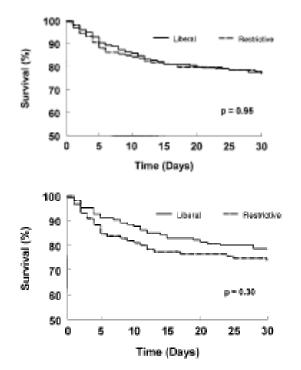
OUTCOME MEASURE	RESTRICTIVE- TRANSFUSION STRATEGY (N=418)	LIBERAL- TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% Confidence Interval	P Value
			р	ercent	
Death — no. (%)					
30-day	78 (18.7)	98 (23.3)	4.7	-0.84 to 10.2	0.11
60-day†	95 (22.7)	111 (26.5)	3.7	-2.1 to 9.5	0.23
ICU	56 (13.4)	68 (16.2)	2.3	-2.0 to 7.6	0.29
Hospital	93 (22.2)	118 (28.1)	5.8	-0.3 to 11.7	0.05
Multiple-organ-dysfunction score					
Unadjusted score	8.3±4.6	8.8±4.4	0.5	0.1 to 1.1	0.10
Adjusted score‡	10.7 ± 7.5	11.8 ± 7.7	1.1	0.8 to 2.2	0.03
Change from base-line score§	3.2 ± 7.0	4.2±7.4	1.0	0.1 to 2.0	0.04
No. of organs failing no. (%)					
0	100 (23.9)	82 (19.5)			
1	136 (32.5)	149 (35.5)			
2 3	109 (26.1)	108 (26.0)			
3	51(12.2)	63 (15.0)			
>3	22 (5.3)	18 (4.3)	1.8¶	-3.4 to 7.1¶	0.53¶
Length of stay — days		18 62	5 5 5	â	
ICU	11.0 ± 10.7	11.5 ± 11.3	0.5	-1.0 to 2.1	0.53
Hospital	34.8 ± 19.5	35.5 ± 19.4	0.7	-1.9 to 3.4	0.58

Patient	Condition	Complication	Intervention	Outcomes
Age	Trauma	Major Bleeding	<section-header><text><text><text></text></text></text></section-header>	Mortality
Gender	Sepsis	Trauma		Timing
Co-	Cancer	GI bleeding		Illness severity
Morbidities	Surgery	Surgery		Organ failures
CVD	Radiotherapy	Anaemia		Quality of Life
Respiratory	chemotherapy	Bleeding		QALYS
Neurological	chemotherapy	Acute marrow		Patient
Haemato-	Cobstetrics	impairment		symptoms
Logical	Liver disease	Blood sampling		Fatigue
Marrow failure	Illness severity	Haemodilution		Breathlessness
Oncology	Physiological	Anaemia		Resource
Other	disturbance	Severity		Length of stay
anaemias	Organ failure	<100g/L		Costs

Possible explanations

- Transfusion is harmful
 - White cells
 - Storage lesion
- Anaemia is beneficial
 - Blood rheology/flow
 - Oxygen supply to tissues is not limited at Hb values >70g/L despite critical illness
- Do these effects apply to the entire 'logic model'?

Is low transfusion threshold safe in critically ill patients with cardiovascular disease? Hebert PC et al. Crit Care Med 2001; 29: 227



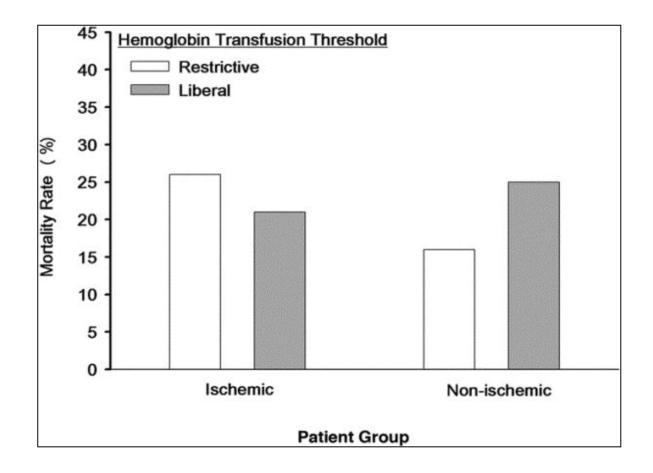
Subgroup of 357 patients with cardiovascular disease

Subgroup of 257 patients with ischaemic heart disease 30 day mortality

Difference –4.9% (-15.3% to 5.6%)

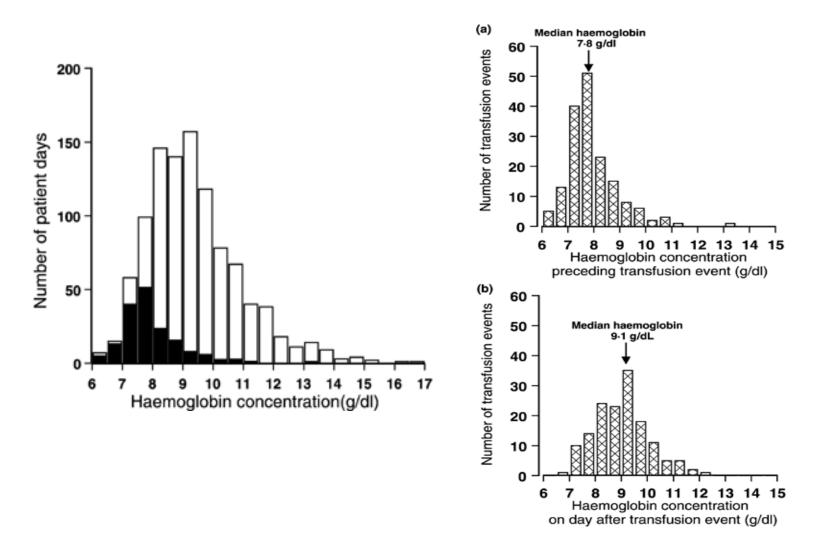
Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols *.

Deans, Katherine et al. Critical Care Medicine. 35(6):1509-1516, June 2007. DOI: 10.1097/01.CCM.0000266584.40715.A6

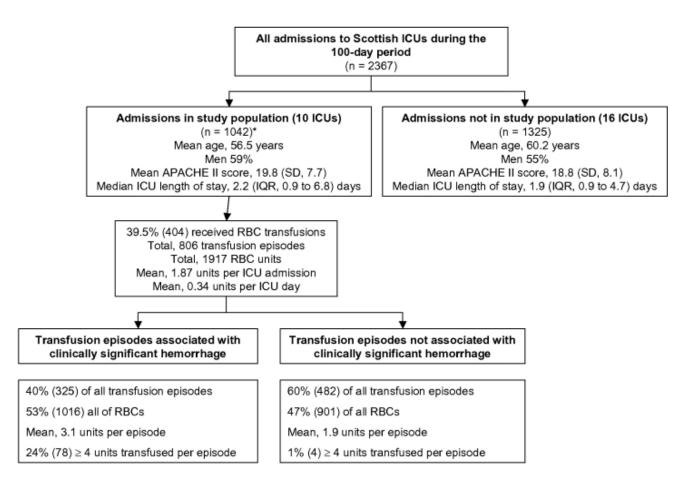


Practice misalignment in "fixed" intervention trials

Red cell transfusion practice following the transfusion requirements in critical care (TRICC) study: prospective observational cohort study in a large UK intensive care unit



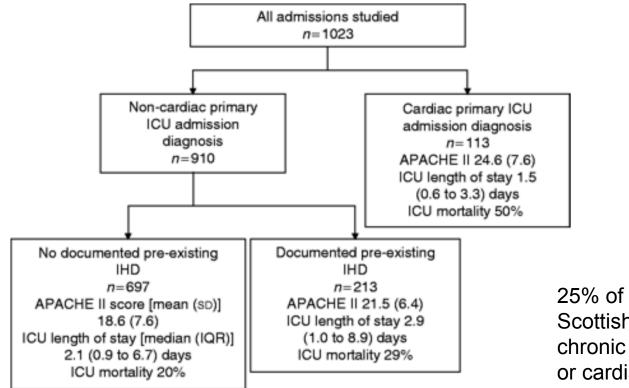
Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines



Transfusion Vol 44: pages 1405-1411, 22 SEP 2004 DOI: 10.1111/j.1537-2995.2004.04085.x

Prevalence of ischaemic heart disease at admission to intensive care and its influence on red cell transfusion thresholds: multicentre Scottish Study

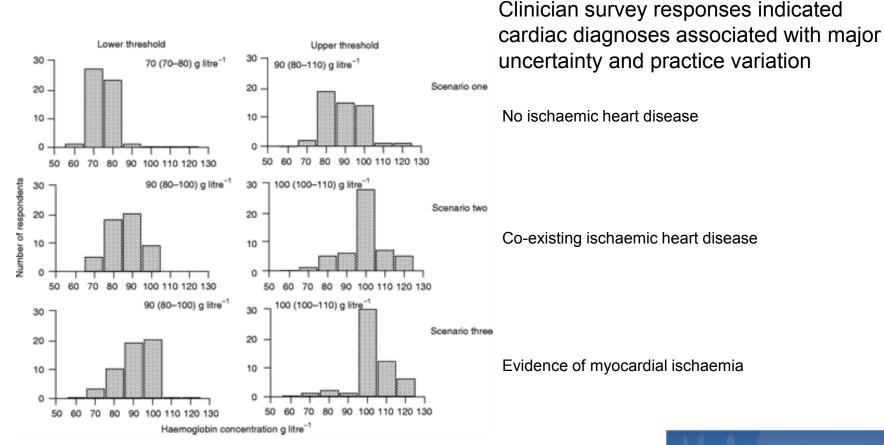
Br J Anaesth. 2005;94(4):445-452. doi:10.1093/bja/aei073



25% of patients admitted to Scottish ICUs had a history of chronic ischaemic heart disease or cardiac failure

Clinicians modified transfusion trigger according to chronic or acute cardiac diagnoses

	Group 1: non-cardiac ICU admission diagnosis, no documented IHD (<i>n</i> =697)	Group 2: non-cardiac ICU admission diagnosis, with documented IHD (n=213)	Group 3: cardiac ICU admission diagnosis (n=113)
Adjusted mean (SE) pre-transfusion haemoglobin concentration	74 (2.2)	77 (2.3)	79 (3.1)*



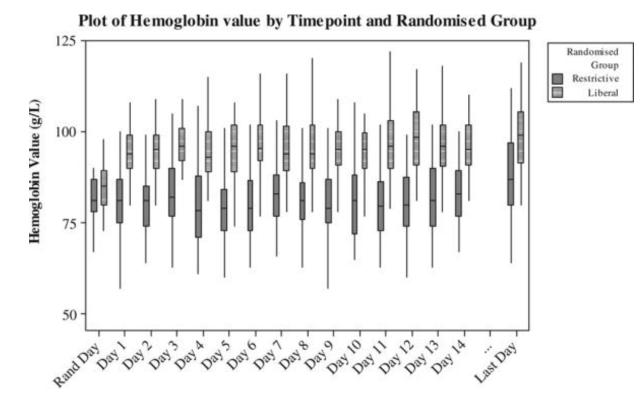
Br J Anaesth. 2005;94(4):445-452. doi:10.1093/bja/aei073

Restrictive Versus Liberal Transfusion Strategies for Older Mechanically Ventilated Critically III Patients: A Randomized Pilot Trial*.

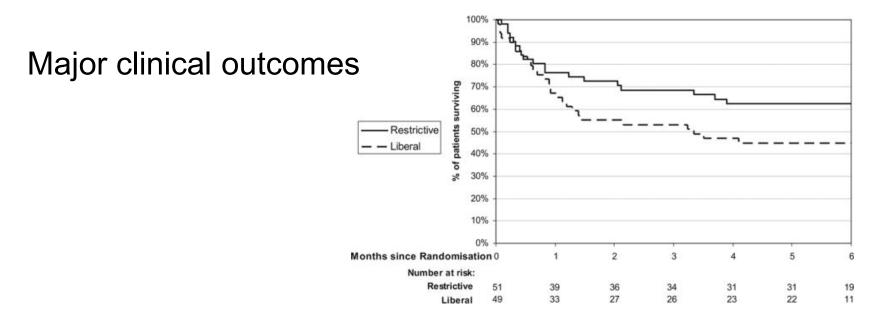
Walsh, Timothy; Boyd, Julia; Watson, Douglas; et al Critical Care Medicine. 41(10):2354-2363, October 2013. DOI: 10.1097/CCM.0b013e318291cce4

Patients Aged >55 years At least 4 days of MV Hb 90g/L

All leucodepleted RCC







Restrictive Transfusion Group (<i>n</i> = 51)	Liberal Transfusion Group (<i>n</i> = 49)	Mean Difference (95% CI)
14 (27.5)	17 (34.7)	0.79 (0.44 to 1.43)
19 (37.3)	24 (49.0)	0.76 (0.48 to 1.2)
12 (23.5)	16 (32.7)	0.72 (0.38 to 1.36)
14 (27.5)	22 (44.9)	0.61 (0.36 to 1.05)
19 (37.3)	27 (55.1)	0.68 (0.44 to 1.05)
		Difference in median (95% CI)
5 (0, 12; 0–15)	6 (3, 9; 0-14)	-0.32 (-3.2 to 2.60)
13 (7, 15; 0–15)	10 (5, 12; 0–15)	1.9 (—1.0 to 4.9)
26 (20, 33; 13–43)	29 (25, 39; 20–46)	-2.5 (-11.2 to 6.2)
30 (24, 40; 12–54)	31 (24, 39; 20–44)	-1.2 (-8.9 to 6.5)
	Transfusion Group (n = 51) 14 (27.5) 19 (37.3) 12 (23.5) 14 (27.5) 19 (37.3) 5 (0, 12; 0–15) 13 (7, 15; 0–15) 26 (20, 33; 13–43)	Transfusion Group $(n = 51)$ Transfusion Group $(n = 49)$ 14 (27.5)17 (34.7)19 (37.3)24 (49.0)12 (23.5)16 (32.7)14 (27.5)22 (44.9)19 (37.3)27 (55.1)5 (0, 12; 0-15)6 (3, 9; 0-14)13 (7, 15; 0-15)10 (5, 12; 0-15)26 (20, 33; 13-43)29 (25, 39; 20-46)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 3, 2013

VOL. 368 NO. 1

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D., Cristina Alvarez-Urturi, M.D., Jordi Gordillo, M.D., Carlos Guarner-Argente, M.D., Miquel Santaló, M.D., Eduardo Muñiz, M.D., and Carlos Guarner, M.D.

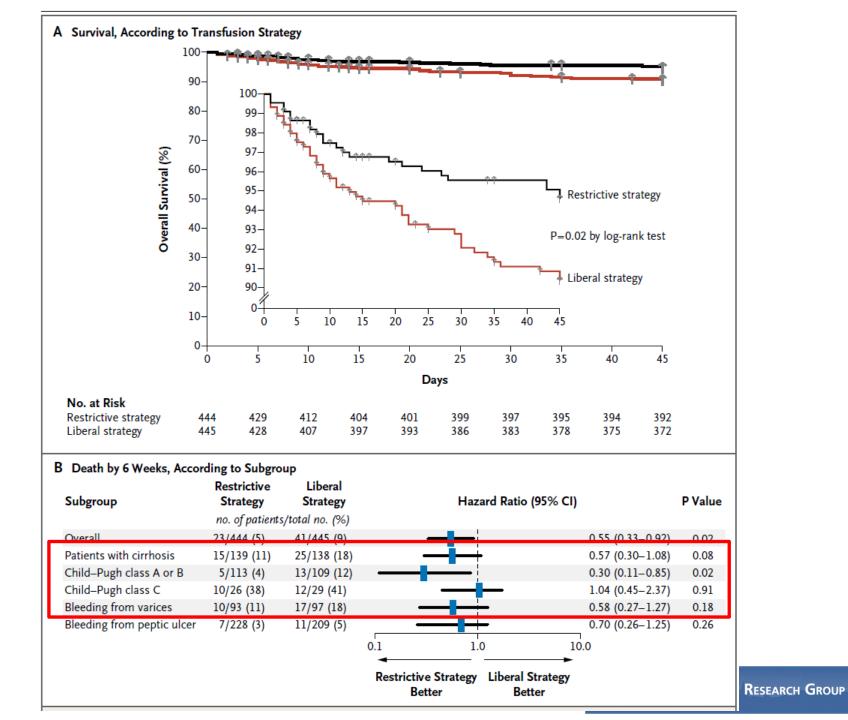
Exclusions

- Massive exsanguinating bleeding
- Cardiovascular disease

Stratified for presence of cirrhosis

- Single unit transfusions
- 31% cirrhosis; 49% peptic ulcer bleeding

Hb 70g/L versus 90g/L



Outcomes

- Overall <u>excess</u> deaths in liberal group from uncontrolled bleeding (0.7 vs 3.1%)
- More re-bleeding and rescue therapy in liberal group
- Small (significant) increase in PPG in liberal group vs no change in restrictive group
- More pulmonary oedema and cardiac adverse events in liberal group



Factors associated with prophylactic plasma transfusion before vascular catheterization in non-bleeding critically ill adults with prolonged prothrombin time: a case-control study

D. P. Hall¹, N. I. Lone^{1,2}, D. M. Watson³, S. J. Stanworth⁴ and T. S. Walsh^{1*}, for the Intensive Care Study of Coagulopathy (ISOC) Investigators

Factors associated with greater use of FFP

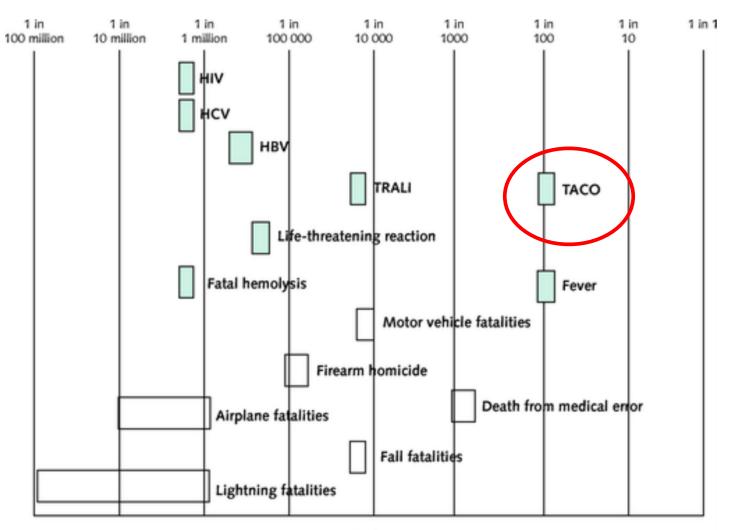
- Chronic liver disease; high bilirubin
- Concurrent RBC transfusion
- Worse coagulation tests (low platelets; higher APTT)

A national clinical scenario-based survey of clinicians' attitudes towards fresh frozen plasma transfusion for critically ill patients. Transfusion Med 2011; 21: 124-129

Annals of Internal Medicine

ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

Ann Intern Med. 2012;157(1):49-58. doi:10.7326/0003-4819-157-1-201206190-00429



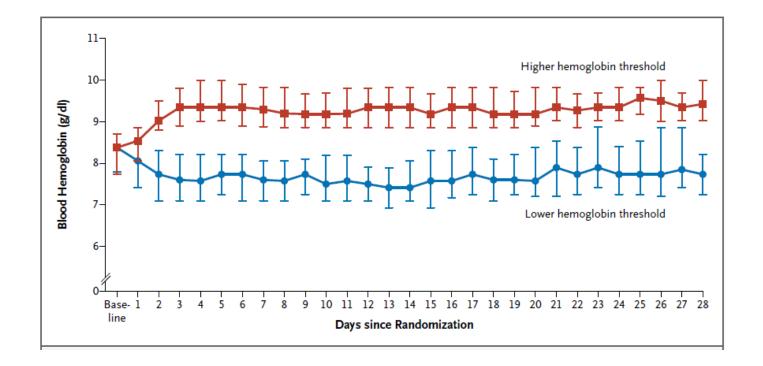
Risk

ORIGINAL ARTICLE

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

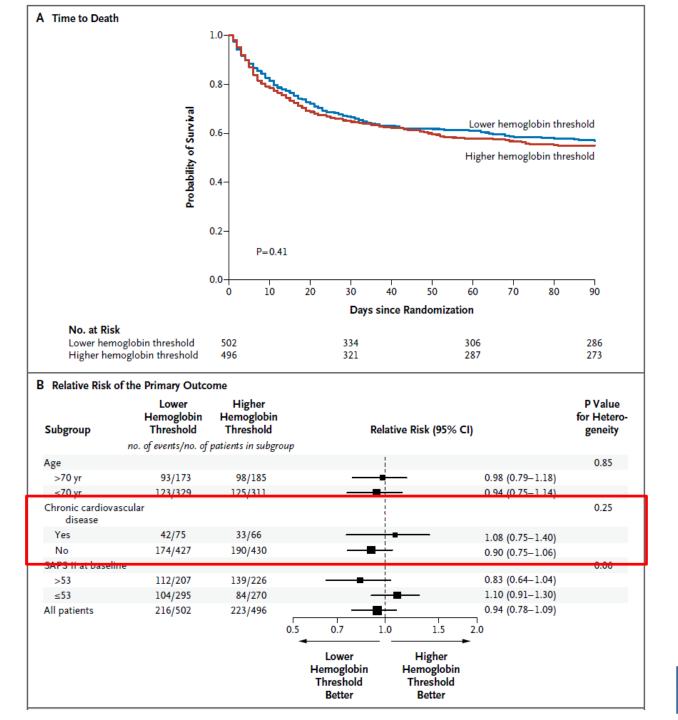
Hb 70g/L vs 90g/L

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Ian Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D.,



Transfusion exposure: restrictive liberal

64% (median 1 unit) 99% (median 3 units)



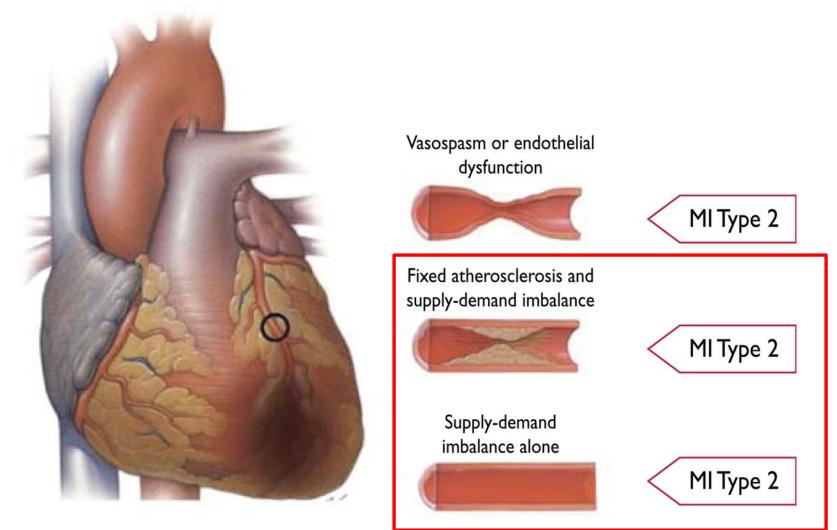
Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis

Lars B Holst et al. BMJ 2015; 350 doi: http://dx.doi.org/10.1136/bmj.h1354

	No of ever	nts/total							
Study or subgroup	Restrictive transfusion	Liberal transfusion			atio M-H to n (95% Cl)		Weight (%)	Risk ratio M-H to random (95% CI)	Risk of bias
1.2.1 Low risk of bias					1		. ,		
Carson 1998 ³²	5/42	2/42		10			1.0	2.50 (0.51 to 12.17)	$\bullet \bullet $
Carson 2011 ²⁵	66/1001	76/998			+		16.5	0.87 (0.63 to 1.19)	$\odot \odot \odot$
Cooper 2011 ⁷¹	2/24	1/21				_	0.5	1.75 (0.17 to 17.95)	
Foss 2009 ²⁸	5/60	0/60				-	→ 0.3	11.00 (0.62 to 194.63)	$\overline{\mathbf{\Theta}}$
Hébert 1999 ⁴	95/416	111/419			4		23.2	0.86 (0.68 to 1.09)	$\overline{\mathbf{\Theta}}$
Holst 2014 ⁹	216/502	223/496			.		35.2	0.96 (0.83 to 1.10)	$\overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}}$
Lacroix 2007 ⁵	14/320	14/317		-	4		4.4	0.99 (0.48 to 2.04)	$\overline{\mathbf{\Theta}}$
Villanueva 2013 ⁶	23/444	41/445			4		8.5	0.56 (0.34 to 0.92)	$\overline{0}$
Walsh 2013 ¹⁰	19/51	27/49		-	4		10.4	0.68 (0.44 to 1.05)	$\overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{O}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{\Theta}} \overline{\mathbf{O}} \overline{\mathbf{O}}$
Subtotal	445/2860	495/2847			4		100.0	0.86 (0.74 to 1.01)	
Test for heterogeneity: $\tau^2 {=} 0.01, \chi^2 {=} 1$	0.96, df=8, P=0	0.20, l ² =27%	ia.						eration (selection bias) alment (selection bias) onnel (performance bias) isment (detection bias) me data (attrition bias) porting (reporting bias) Baseline imbalance Sponsor bias Academic bias
rest for overall effect: z=1./9, P=0.0,	(-						and the second sec
Total (95% CI)	445/2860	495/2847			4		100.0	0.86 (0.74 to 1.01)	(selection t (selection t erformance (detection t (reporting t (reporting t Sponsor Academic
Test for hoterogeneity: $\tau^2 = 0.01$, $\chi^2 = 1$	0.96, df-8, P-	0.20, l ² -27%	_				_		A A A
Test for overall effect: z=1.79, P=0.02	7								eneration (selection cealment (selection risonnel (performance essment (detection come data (attrition reporting (reporting Baseline imba Sponsol Academic
Test for subgroup differences: not ap	plicable		0.01	0.1	1	10	100		sonr sonr sonr ssm epol
			Favours restricti	ve strategy	li	Fav beral stra	ours tegy		tence generation (selection ion concealment (selection s and personnel (performance ome assessment (detection tete outcome data (attrition elective reporting (reporting Baseline imba Sponsoi Academic

Study or subgroup	Restrictive	Liberal	Risk ratio M-H to	Weight	Risk ratio M-H to	Risk of bias
	transfusion		random (95% CI)	(%)	random (95% CI)	
2.14.1 Trauma and acute blood los						
Blair 1986 ²⁹	0/26	2/24		0.3	0.19 (0.01 to 3.67)	????
Zygun 2009 ⁴³	3/20	0/10		0.3	3.67 (0.21 to 64.80)	
Subtotal	3/46	2/34		0.6	0.85 (0.05 to 15.82)	
Test for heterogeneity: $\tau^2 = 2.22$, $\chi^2 =$		l6, l²=50%				
Test for overall effect: z=0.11, P=0	01					
2.14.2 Perioperative setting Almeida 2013 ¹¹	23/101	8/97		3.7	2.76 (1.30 to 5.87)	
Bush 1997 ³⁰	4/50	8/97 4/49		1.3	0.98 (0.26 to 3.70)	00000000
Carson 1998 ³²						
Carson 2011 ¹⁵	5/42 66/1001	2/42 76/998		1.0	2.50 (0.51 to 12.17)	
Cholette 2011 ³³				12.3	0.87 (0.63 to 1.19)	
Foss 2009 ²⁸	0/30 5/60	1/30 0/60		0.2	0.33 (0.01 to 7.87) 11.00 (0.62 to 194.63)	
Grover 2006 ³⁶	0/109	1/109		0.3	0.33 (0.01 to 8.09)	
				3.9		
Hajjar 2010 ⁷ Parker 2013 ¹²	15/249	12/253			1.27 (0.61 to 2.66)	
Shehata 2012 ⁴¹	26/100	27/100		7.9	0.96 (0.61 to 1.53)	
So-Osman 2010-13 ⁴⁵	4/25 1/299	1/25		0.5	4.00 (0.48 to 33.33)	
Villanueva 2013 ⁶		2/304			0.51 (0.05 to 5.58)	
Wu 2011 ⁴²	23/444	41/445		7.3	0.56 (0.34 to 0.92)	
	3/112	4/114		1.1	0.76 (0.17 to 3.33)	00000000
Subtotal Test for heterogeneity: $\tau^2=0.11$, $\chi^2=0.11$		179/2626		40.3	1.06 (0.76 to 1.49)	
Test for everall effects $\tau = 0.11, \chi =$		0.06,1 =41%		_		
2.14.3 Critical care						
Carson 2013 ⁸	7/54	1/55		0.6	7.13 (0.91 to 56.02)	?+??+++ +
Cooper 2011 ⁷¹	2/24	1/21		0.5	1.75 (0.17 to 17.95)	
Hébert 1995 ³⁷	13/33	11/36		4.8	1.29 (0.67 to 2.47)	0000000
Hébert 1999 ⁴	95/416	111/419	1	15.6	0.86 (0.68 to 1.09)	
Holst 2014 ⁹	216/502	223/496	1	20.3	0.96 (0.83 to 1.10)	
Lacroix 2007 ⁵	14/320	14/317		4.0	0.99 (0.48 to 2.04)	
Robertson 2014 ⁴⁰	14/99	17/101		4.8	0.84 (0.44 to 1.61)	
Walsh 2013 ¹⁰	19/51	27/49		8.5	0.68 (0.44 to 1.01)	
Subtotal		405/1494		59.1	0.92 (0.80 to 1.06)	
Test for heterogeneity: τ^2 =0.00, χ^2 =				37.1	0.92 (0.00 10 1.00)	bias) bias) bias) bias) bias) bias) tance
Test for overall effect: z=1.18, P=0.		0,1 -10 /8				
Total (95% CI)	558/4167	586/4154	1	100.0	0.95 (0.81 to 1.11)	(selection bias) (selection bias) erformance bias) (detection bias) (detection bias) (reporting bias) letine imbalance Sponsor bias
Test for heterogeneity: τ^2 =0.03, χ^2 =				100.0	0.00 (0.01 (0 1.11)	n (selection bias) tt (selection bias) (performance bias) tt (detection bias) ta (attrition bias) g (reporting bias) sellne imbalance sellne sponsor bias
Test for overall effect: z=0.64, P=0.				_		
Test for subgroup differences: $\chi^2=0$		$ ^2=0\%$	0.01 0.1 1 10 1	100		e generatic concealme d personnel assessmer autcome d ive reportir Ba
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Holst et al. BMJ						Random sequence generati Allocation concealme Blinding of participants and personnel Blinding of outcome assessme Incomplete outcome d Selective reporti

Differentiation between myocardial infarction (MI) types 1 and 2 according to the condition of the coronary arteries.



Thygesen K et al. Eur Heart J 2012;eurheartj.ehs184

Mortality in patients with chronic cardiovascular disease Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351

	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFGHI
1.1.1 All studies								
Almeida 2015	7	22	0	12	0.9%	8.48 [0.53, 136.76]		
Bush 1997	4	49	4	50	3.8%	1.02 [0.27, 3.85]		<u>,,,,,,,,,,,</u> ,,,,
Carson 2011	43	1008	52	995	27.7%	0.82 [0.55, 1.21]		
Carson 2013	7	55	1	55	1.6%	7.00 [0.89, 55.01]		
Cooper 2011	2	24	1	21	1.3%	1.75 [0.17, 17.95]		?
Gregersen 2015	6	34	3	25	4.0%	1.47 [0.41, 5.32]	-	? • • • • • ?
Hebert 1999	29	111	31	146	23.9%	1.23 [0.79, 1.91]		•••?
Holst 2014	33	75	24	66	26.5%	1.21 [0.80, 1.82]		
Jairath 2015	6	49	2	67	2.8%	4.10 [0.86, 19.47]	+	•••••
Parker 2013	4	70	4	67	3.7%	0.96 [0.25, 3.67]		? 🗣 ? ? 🗣 🗣 ? 🗬 🗬
Walsh 2013	3		4		3.8%	0.66 [0.18, 2.49]		
Subtotal (95% CI)		1514		1519	100.0%	1.15 [0.88, 1.50]	•	
Total events	144		126					
Test for overall effect 1.1.2 Randomised b		, – 0.5	.0)					
Bush 1997	4	49	4	50	12.8%	1.02 [0.27, 3.85]	+	?????+????+
Carson 2011	43	1008	52	995	64.1%	0.82 [0.55, 1.21]		
Carson 2013	7	55	1	55	5.7%	7.00 [0.89, 55.01]		
Cooper 2011	2	24	1	21	4.5%	1.75 [0.17, 17.95]		?
Walsh 2013	3	17	4	15	12.8%	0.66 [0.18, 2.49]		
waish 2013		1153		1136	100.0%	0.96 [0.58, 1.59]	•	
Subtotal (95% CI)		1155						
Subtotal (95% CI)	59	1155	62					
Subtotal (95% CI) Total events				P = 0.3	2); I² = 14	%		
	= 0.06; Ch	i ² = 4.67	7, df = 4 (P = 0.3	2); I² = 14	%		

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

(H) Assessment of Cardiovascular Event

(I) Definition of Cardiovascular Event

Mortality at 30 days: RR 1.15 (0.88 to 1.50)

Holst et al Systematic Review

All comers (including CVD): RR 0.86 (0.74 to 1.01)

Acute coronary syndrome and pulmonary oedema in patients with chronic cardiovascular disease Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351

A	Restric	tive	Liber	al		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	I A B C D E F G H I
Almeida 2015	0	22	0	12		Not estimable		
3ush 1997	2	49	1	50	3.4%	2.04 [0.19, 21.79]		- ?????????
Carson 2011	38	1008	23	1005	72.5%	1.65 [0.99, 2.74]	+	• • • • • • • • • •
Carson 2013	11	54	6	54	22.3%	1.83 [0.73, 4.60]	+	
Cooper 2011	1	24	0	21	1.9%	2.64 [0.11, 61.54]		
Holst 2014	6	75	2	66	0.0%	2.64 [0.55, 12.64]		
Parker 2013	0	70	0	67		Not estimable		? 🗣 ? ? 🗣 🗣 ? 🗬 🗬
Alalah 2013	1	17	0	15	0.0%	2.67 [0.12, 60.93]		
Fotal (95% CI)		1135		1130	100.0%	1.71 [1.11, 2.65]	•	
Fotal events	52		38					
Heterogeneity: Tau² =	•			P = 0.99	3); I² = 0%) 100
Test for overall effect:	Z=2.43 ((P = 0.0	1)				Favours Restrictive Favours L	
3	-							
-	Restri		Libe			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup			Events			M-H, Random, 95% Cl		
Carson 2013	7				23.0%	3.50 [0.76, 16.11]		- •••??•••••
Cooper 2011	2				24.3%	0.22 [0.05, 0.92]		
Hebert 1999	14	160				0.49 [0.27, 0.88]		
Parker 2013	1	70	2	67	13.6%	0.48 [0.04, 5.16]		<u>? ♥ ? ? ♥ ♥ ? ♥ ♥</u>
Total (95% CI)		309		340	100.0%	0.63 [0.22, 1.81]		
Total events	24		47					
Heterogeneity: Tau ² :	= 0.65; Ch	ni² = 7.4	2, df = 3 ((P = 0.0	6); l² = 60	%		100
Test for overall effect	t: Z = 0.86	(P = 0.3	39)				Favours restrictive Favours li	
<u>Risk of bias legend</u>								
(A) Random sequen	-			bias)				
(B) Allocation concea	alment (se	election	bias)					
(C) Blinding of partic	ipants and	d perso	nnel (per	forman	ce bias)		RR 1 71 (0 1	1 to 2.65); I ² 0%
(D) Blinding of outco	me asses	sment	(detectio	n bias)		//////	$1 \times 1 \times$	1.02.00, 1.070
(E) Incomplete outco	me data (attrition	bias)			Aheo	luta rick diffar	ence ≈2%; NNT ≈50
(F) Selective reportin	g (reportir	ng bias)					$CHUC \sim 2/0, ININI \sim 30$
(G) Other bias								
(H) Assessment of C			/ent					
 Definition of Cardi 	iovascular	Event						

bjh guideline

Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients

Andrew Retter,^{1,2} Duncan Wyncoll,¹ Rupert Pearse,³ Damien Carson,⁴ Stuart McKechnie,⁵ Simon Stanworth,⁶ Shubha Allard,⁷ Dafydd Thomas,⁸ Tim Walsh⁹ and British Committee for Standards in Haematology British Journal of Haematology, 2013, **160**, 445–464

JAMA | Special Communication

Clinical Practice Guidelines From the AABB Red Blood Cell Transfusion Thresholds and Storage

Jeffrey L. Carson, MD; Gordon Guyatt, MD; Nancy M. Heddle, MSc; Brenda J. Grossman, MD, MPH; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Terry Gernsheimer, MD; John B. Holcomb, MD; Lewis J. Kaplan, MD; Louis M. Katz, MD; Nikki Peterson, BA; Glenn Ramsey, MD; Sunil V. Rao, MD; John D. Roback, MD, PhD; Aryeh Shander, MD; Aaron A. R. Tobian, MD, PhD

JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185 Published online October 12, 2016.

Anaesthesia 2016, 71, 829-842

doi:10.1111/anae.13489

Guidelines

AAGBI guidelines: the use of blood components and their alternatives 2016

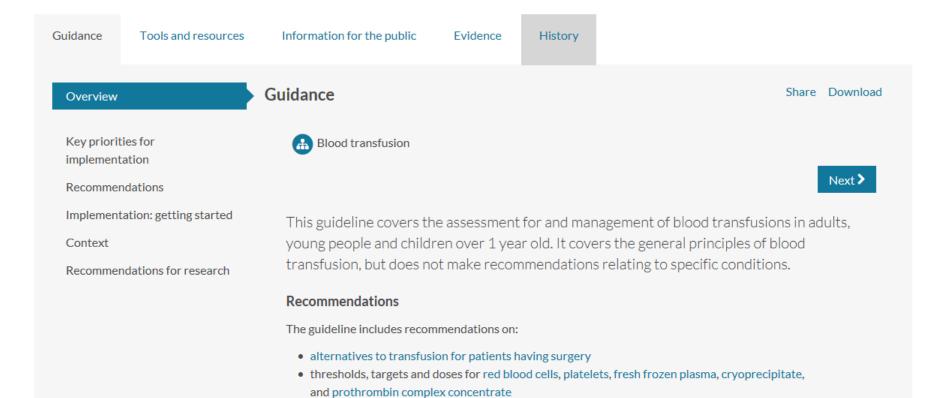
A. A. Klein,¹ P. Arnold,² R. M. Bingham,³ K. Brohi,⁴ R. Clark,⁵ R. Collis,⁶ R. Gill,⁷ W. McSporran,⁸
 P. Moor,⁹ R. Rao Baikady,¹⁰ T. Richards,¹¹ S. Shinde,¹² S. Stanworth¹³ and T. S. Walsh¹⁴

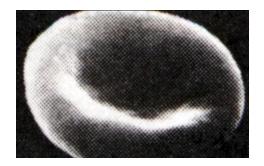
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	NICE National Institute for Health and Care Excellence	NICE Pathways	NICE Guidance	Standards and indicators	Evidence services	Sign in
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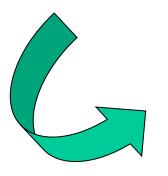
Blood transfusion

NICE guidelines [NG24] Published date: November 2015

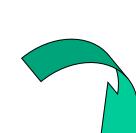




Membrane phospholipid vesiculation and blebbing Cytoskeletal remodelling Dissociation of membrane bi-layer from skeletal cytoskeleton Loss of membrane (?pro-thrombotic)







Damage and Loss of band 3 protein (increased susceptibility to oxidation) Increased cellular permeability

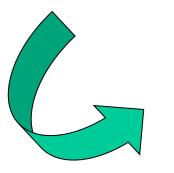
Accumulation of bioreactive substances (proinflammatory?)

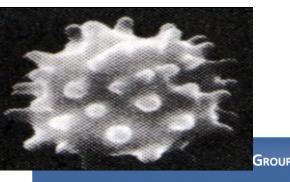
Depletion of cellular energy (ATP and total ATP/ADP/AMP stores) (impaired oxygen release) Lipid peroxidation Proteolysis Ca⁺⁺ influx

Physical loss of membrane (contains

lipids and cytoskeletal protein) Altered volume to surface area Micro-vesicle release Loss of deformability (?↓ transit) Increased interaction with endothelium (?↑ adherence)







RBC storage age and outcomes

Four large trials comparing fresher RBCs versus older RBCs (stored around 20 days) in different patient groups

- ABLE trial (critical care) N Engl J Med 2015
 - DOI: 10.1056/NEJMoa1500704
- RECESS trial (cardiac surgery) N Engl J Med 2015
 DOI: 10.1056/NEJMoa1414219
- INFORM trial (hospital wide) N Engl J Med 2016
 - DOI: 10.1056/NEJMoa160901
- TRANSFUSE trial (critical care) N Engl J Med 2017
 - DOI: 10.1056/NEJMoa170757
- No benefit from transfusing fresher over standard age (or older) RBCs in any clinical setting tested

Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co- Morbidities CVD Respiratory Neurological Haemato- Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy chemotherapy Chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy chemotherapy	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution	Blood transfusion Volume No. units Target Hb RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

Patient	Condition	Complication	Intervention	Outcomes
Age Gender CO- Morbidities CVD Respiratory Neurological Haemato- Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy chemotherapy Liver disease Liver disease Illness severity Physiological disturbance Organ failure	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution	Blood transfusion Volume No. units Target Hb RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co- Morbidities CVD Respiratory Neurological Haemato- Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy chemotherapy Obstetrics Liver disease Illness severity Physiological disturbance Organ failure	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution	<section-header><section-header><text></text></section-header></section-header>	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

Patient	Condition	Complication	Intervention	Outcomes
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Patient	Condition	Complication	Intervention	Outcomes
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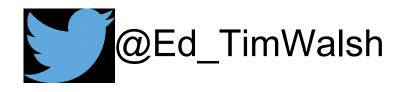
Personalised transfusion medicine: the major uncertainties

- Chronic cardiovascular disease
- Acute myocardial infarction (MINT trial)
- Acute brain injury
 - Traumatic brain injury (Hemotion trial)
 - Sub-arachnoid haemorrhage (SAHaRA trial)
- Chronic anaemia
 - Marrow failure
 - Post acute/critical illness
 - RBC transfusion versus iron/EPO

'Blut ist ein ganz besondrer Saft.' (Blood is a very special juice.) Faust. Goethe

'The best transfusion is the one that was never given'

Anon.



twalsh@staffmail.ed.ac.uk



