



RBC Transfusion:

Applying evidence-based transfusion care
Jeannie Callum, MD, FRCPC

Disclosure

- ▶ Research funding from Canadian Blood Services, Octapharma Canada, and Defense Research and Development
- ▶ This is a talk about using red cell transfusions for adult patients



Outline

- ▶ 2 Cases
- ▶ Red blood cell basics
- ▶ Key risks of red blood cell transfusion
- ▶ When should you give red cell transfusions?
 - ▶ Multiple randomized trials and meta-analyses to guide your decisions



Rwanda Oncology Doctor: Global Community Must "Reduce the Disparities in Cancer Care" - Partners In Health Canada (pihcanada.org)

Case 1

- ▶ 27 year old female, 2 days post C-section complicated by moderate post-partum hemorrhage
- ▶ Pre-delivery hemoglobin was 10.5 g/dL
- ▶ Hemoglobin this morning is 5.7 g/dL
- ▶ Heart rate 87. blood pressure 102/56.
- ▶ She is pale and tired but no pre-syncope or lightheadedness
- ▶ You have ordered a dose of intravenous iron
- ▶ Plan is for discharge today
- ▶ Should you transfuse 1 unit of RBCs before sending her home?



Case 2

- ▶ 76 year old woman 4 days post-op from hip fracture surgery (after fracture from a fall)
- ▶ Plan to discharge tomorrow
- ▶ Hemoglobin 7.1 g/dL
- ▶ Asymptomatic, vitals stable
- ▶ No cardiac history
- ▶ Should you transfuse red blood cells?





Red blood cell basics

- ▶ Volume ~300 mL, hematocrit 50-65%, anticoagulant SAG-M
 - ▶ Some units may have lower volumes so ensure you include the volume required on your order (~5 mL/kg for an adult dose)
- ▶ Each unit increases hemoglobin by 1.0 g/dL
- ▶ Small amount of residual plasma
- ▶ Acceptable for transfusion for 42 days from donation
- ▶ Red cells in Rwanda not routinely leukoreduced, but can be requested on an as-needed basis
 - ▶ Leukoreduction reduces the risk of transfusion reactions (marginally), reduces the risk of HLA alloimmunization (important only for patients undergoing aggressive chemotherapy), and prevents some infectious transmissions (HTLV, CMV)



Irradiated red blood cells

PATIENTS REQUIRING IRRADIATED BLOOD ¹²⁹

- ◆ Patients with severe T-cell congenital immunodeficiency states
- ◆ Intrauterine transfusions (IUT)
- ◆ Neonatal exchange transfusions for infants with prior IUT
- ◆ Neonatal top-up transfusion if there has been a previous IUT
- ◆ Patients with Hodgkin's lymphoma
- ◆ Patients undergoing bone marrow or stem cell transplants
 - It is reasonable to continue providing irradiated products until immunosuppression discontinued
- ◆ Recipients of directed transfusions from family members
- ◆ Recipients of HLA-matched platelets
- ◆ Patients treated with purine analogs (e.g., fludarabine), purine antagonists (e.g., bendamustine), alemtuzumab and anti-thymocyte globulin



If not available, transfuse red blood cells over 14 days from collection
[Kopolovic I, et al. Blood. 2015 Jul 16;126(3):406-14]



Visit Rwanda on Twitter: "What better way to tackle your fears and enjoy adventure than rock climbing! Summit to the top of Kamonyi District's natural rocks and experience stunning panoramic views with @BeautifulRwand1. Visit <https://t.co/2922jdjeDM> for more information. #TemberaURwanda RW <https://t.co/G7pg7lqpBD>" / Twitter

Risks of RBCs

- ▶ Transfusion associated circulatory overload (TACO) – 1 in 50 to 1 in 100
 - ▶ *300 mL of RBCs is not the same as 300 mL of saline*
- ▶ Transfusion-related acute lung injury (TRALI) – 1 in 10,000
- ▶ Acute and delayed hemolytic transfusion reactions
 - ▶ ABO-immune hemolysis (by mistake) – 1 in 40,000
 - ▶ RBC alloantibodies 1 in 13 (Hemolytic disease of the newborn risk for girls and young women)
 - ▶ Delayed hemolytic transfusion reactions 1 in 7000
- ▶ Anaphylaxis – 1 in 20,000
- ▶ More bleeding (from GI bleeding trials)
- ▶ HLA alloimmunization (leading to long waits for organ transplants)

It's not because of a worry about HIV

<1 in 1,000,000	Transmission of West Nile Virus
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 7,500,000	Transmission of hepatitis B virus per unit of component
1 in 7,600,000	Transmission of HTLV per unit of component
1 in 13,000,000	Transmission of hepatitis C virus per unit of component
1 in 21,000,000	Transmission of human immunodeficiency virus (HIV) per unit of component

Rwanda

Trends and Gaps in National Blood Transfusion Services — 14 Sub-Saharan African Countries, 2014–2016 | MMWR (cdc.gov)

Country	HIV population prevalence (%)			Prevalence (%) of TTIs in collected blood units								
				HIV			Other TTIs			All TTIs		
	2014 2015 2016						HBV, HCV, and syphilis			HIV, HBV, HCV, and syphilis		
				2014	2015	2016	2014	2015	2016	2014	2015	2016
Côte d'Ivoire	3.0	2.8	2.7	0.3	0.04	0.2	8.6	9.0	8.9	9.0	9.0	9.1
Ethiopia	1.1	1.1	0.9	2.1	1.2	1.1	4.4	4.6	4.2	5.2	5.1	4.5
Ghana	1.7	1.6	1.6	0.7	0.5	0.3	9.7	7.1	11.6	11.8	8.3	12.7
Kenya	5.7	5.6	5.4	0.6	0.8	0.6	2.8	4.3	2.5	3.5	5.2	3.2
Lesotho	24.7	24.9	25	2.6	2.4	2.5	3.6	3.8	5.0	6.2	6.2	7.6
Mozambique	13.0	12.7	12.3	5.2	4.8	4.0	8.2	8.8	6.9	13.4	13.6	11.0
Nigeria	3.1	3.0	2.9	1.4	1.4	1.5	11.3	11.7	13.1	12.9	13.2	14.6
Rwanda	3.2	3.2	3.1	0.1	0.1	0.2	2.6	2.7	3.4	2.8	2.9	3.6
South Africa	18.8	18.9	18.9	0.2	0.2	0.1	0.3	0.3	0.5	0.5	0.5	0.7

Risk of donor
Testing positive

TACO

- ▶ Rate of TACO increases with increasing age:
 - ▶ aged 80 yr+: 7.4%
 - ▶ aged 70-79 yr: 5.2%
 - ▶ aged 60-69 yr: 4.2%
 - ▶ aged 50-59 yr: 3.3%
 - ▶ aged 49 yr or less: 2.0%
- ▶ Increased rate of TACO with increasing amount of volume transfused ($P < 0.001$) and increasing total fluid balance ($P < 0.001$)
- ▶ Odds ratio of death for TACO cases compared with transfused controls of 3.8 (95% CI, 2.2 to 6.7) ($P < 0.001$)

Pre-transfusion RBC checklist

Red Blood Cell Pre-Transfusion Checklist

Alternatives failed or have been ordered?

- Anemia investigations completed (e.g., CBC, blood film, ferritin, iron saturation, vitamin B12, reticulocyte count)
- Iron (oral and IV), vitamin B12, erythropoietin ordered or not indicated

Consent?

Patient advised of risks of:

- TACO 1 in 100
- Hemolytic reaction 1 in 7,000
- TRALI 1 in 10,000
- Major allergic reaction 1 in 40,000
- Bacterial infection 1 in 250,000



Pre-transfusion RBC Checklist

Female under 45?

- Order Kell-negative units **Rwanda: Kell+ donors deferred**
- Inform recipient of the potential risk of transfusion causing hemolytic disease of the newborn in future pregnancies

At risk for FATAL transfusion-associated Graft vs. Host Disease?

- Order irradiated blood if patient has any history of the following:
- Hodgkin's lymphoma
 - Allogeneic or autologous stem cell transplant
 - Ever treated with fludarabine, cladribine, bendamustine, alemtuzumab, anti-thymocyte globulin (ATG)
 - Congenital immunodeficiencies

Or units > 14 days



Pre-transfusion RBC Checklist

Diuretics?



Does my patient have a history of:

- Age greater ≥ 70 years
- Renal dysfunction
- Left ventricular dysfunction
- Prior or current CHF
- Severe euvolemic anemia (hemoglobin < 50 g/L)

- If YES to any of the above: prescribe PO/IV furosemide pre-transfusion (*unless currently hypovolemic*)

Rate and Dose?

- Specify rate of infusion (default rate is over 2 hours per unit; inpatients and patients at risk for TACO (need diuretics) infuse over 3-4 hours)
- Order 1 unit at a time (unless bleeding)

JACC Journal of the American College of Cardiology

Novem

nature

414, 673-828 13 December 2

Cell

Volume 104 Number 5 Pages 631-800 Mar

nature genetics

vol. 39 no. 10 october 2007

pp 1175-1285

121

PEDIATRICS

JANUARY 2008

JACC Journal of the American College of Cardiology

Genes & Development

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VOLUME 137

Science not the “Art of Medicine”

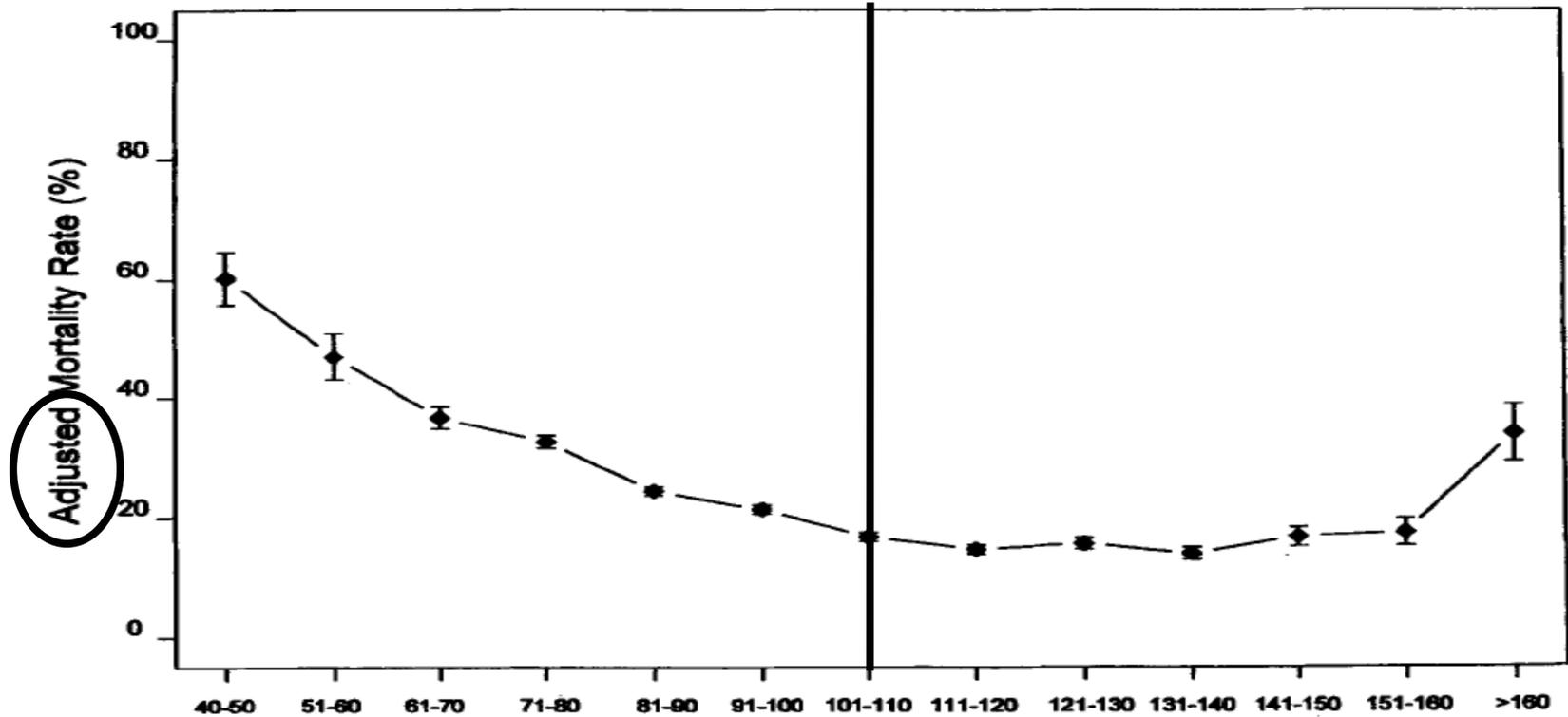
47 RCTs with 20,967 patients

restrictive (7.0-7.5-8.0) vs. liberal (9.0-9.5-10.0)

Clinical trials.gov – 14 ongoing studies that will add an additional 15,000 patients

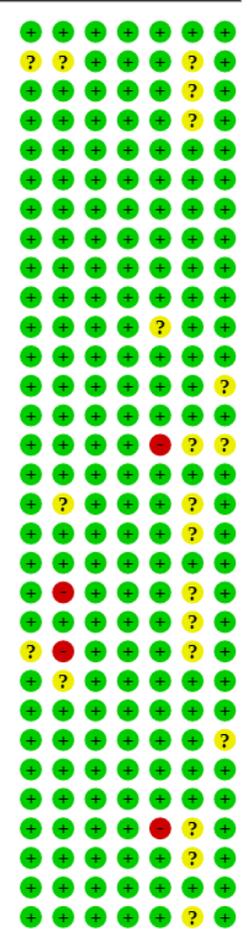
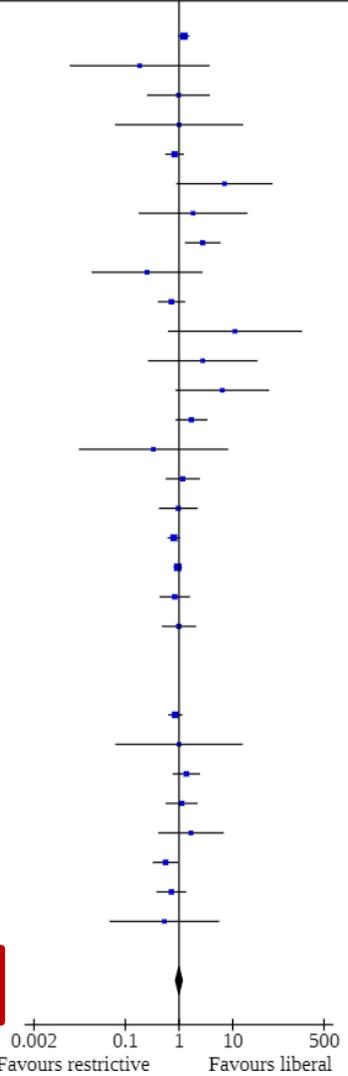
Pre-TRICC

Hebert P, et al. Am J Resp CCM 1997; 155: 1618-23



Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99 , 1.55]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40 , 1.28]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26 , 28.95]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.5%	0.95 [0.80 , 1.13]
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44 , 1.57]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Laine 2018	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76 , 2.46]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32 , 0.97]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]

Total (95% CI)	8321	8408	100.0%	0.99 [0.86 , 1.15]
Total events:	670	689		
Heterogeneity: Tau ² = 0.03; Chi ² = 40.06, df = 28 (P = 0.07); I ² = 30%				
Test for overall effect: Z = 0.07 (P = 0.94)				



Carson JL, et al. Cochrane Database Syst Rev. 2021;12(12):CD002042.

Reduces the risk of transfusion: 0.54
(0.47- 0.63; $P < 0.001$)

And the number of units transfused
(mean difference -1.43 unit, (-2.01 to
-0.86; $P < 0.001$)

Cost to put a single RBC unit into a patient US\$741 in 2010



RBC - TRICC Study

- ▶ NEJM 1999; 340:409-17 - Hebert et al
 - ▶ n=838 non-bleeding, ICU patients, Hb <9 g/dL
 - ▶ RCT - transfusion Hb <7 vs <10
 - ▶ **Non-leukoreduced RBCs**
 - ▶ Stratified by APACHE 2 score
 - ▶ Groups equal with respect to baseline characteristics
 - ▶ Average patient: 58 year old male, with 1-2 organ failure, mechanically vented, admitted to the ICU from the OR

Outcome - Mortality

Outcome	<7 g/dL	<10 g/dL	P value
30-day	18.7%	23.3%	P=0.11
Hospital	22.2%	28.1%	P=0.05

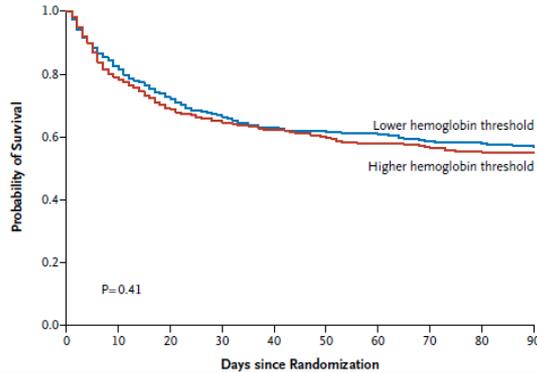
NNT = 17 patients to prevent one in-hospital death

Morbidity Outcomes in TRICC

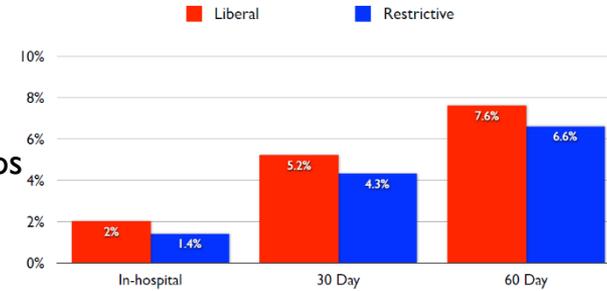
	Restrictive N (%)	Liberal N (%)	P Value
MI	3 (0.7)	12 (2.9)	0.02
Pulmonary Edema	22 (5.3)	45 (10.7)	0.01
ARDS	32 (7.7)	48 (11.4)	0.06

Key RBC Trials

TRISS
 Holst
 NEJM 2014
 Septic Shock
 n=998
 7 vs 9 g/dL
 No subgroups



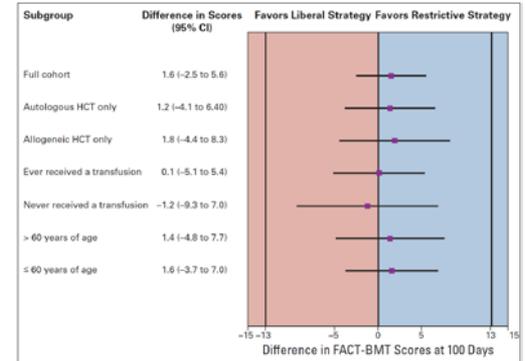
FOCUS
 Carson
 NEJM 2011
 Fractured hips
 Periop
 n=2016
 8 vs 10



TRICS III
 Mazer
 NEJM 2017
 CVSx
 n=5035
 7.5 vs 9.5 g/dL
 No subgroups

Composite: 0.90 (0.76-1.07)
Death: 0.85 (0.62-1.16)
Stroke: 0.92 (0.61-1.38)
MI: 1.00 (0.79-1.27)
Kidney Failure: 0.84 (0.60-1.19)

TRIST
 Tay
 JCO 2020
 Hematology
 n=300
 7 vs 9



No benefit in CVD patients

Study	No of events/ total No of patients		Risk ratio MH random effect (95% CI)	Weight (%)	Risk ratio MH random effect (95% CI)
	Restrictive transfusion	Liberal transfusion			
All studies					
Almeida 2015	7/22	0/12		0.9	8.48 (0.53 to 136.76)
Bush 1997	4/49	4/50		3.8	1.02 (0.27 to 3.85)
Carson 2011	43/1008	52/995		27.7	0.82 (0.55 to 1.21)
Carson 2013	7/55	1/55		1.6	7.00 (0.89 to 55.01)
Cooper 2011	2/24	1/21		1.3	1.75 (0.17 to 17.95)
Gregersen 2015	6/34	3/25		4.0	1.47 (0.41 to 5.32)
Hebert 1999	29/111	31/146		23.9	1.23 (0.79 to 1.91)
Holst 2014	33/75	24/66		26.5	1.21 (0.80 to 1.82)
Jairath 2015*	6/49	2/67		2.8	4.10 (0.86 to 19.47)
Parker 2013	4/70	4/67		3.7	0.96 (0.25 to 3.67)
Walsh 2013	3/17	4/15		3.8	0.66 (0.18 to 1.50)
Total	144/1514	126/1519		100.0	1.15 (0.88 to 1.50)

Test for heterogeneity: $\tau^2=0.03$, $\chi^2=11.58$, $df=10$, $P=0.31$, $I^2=14\%$

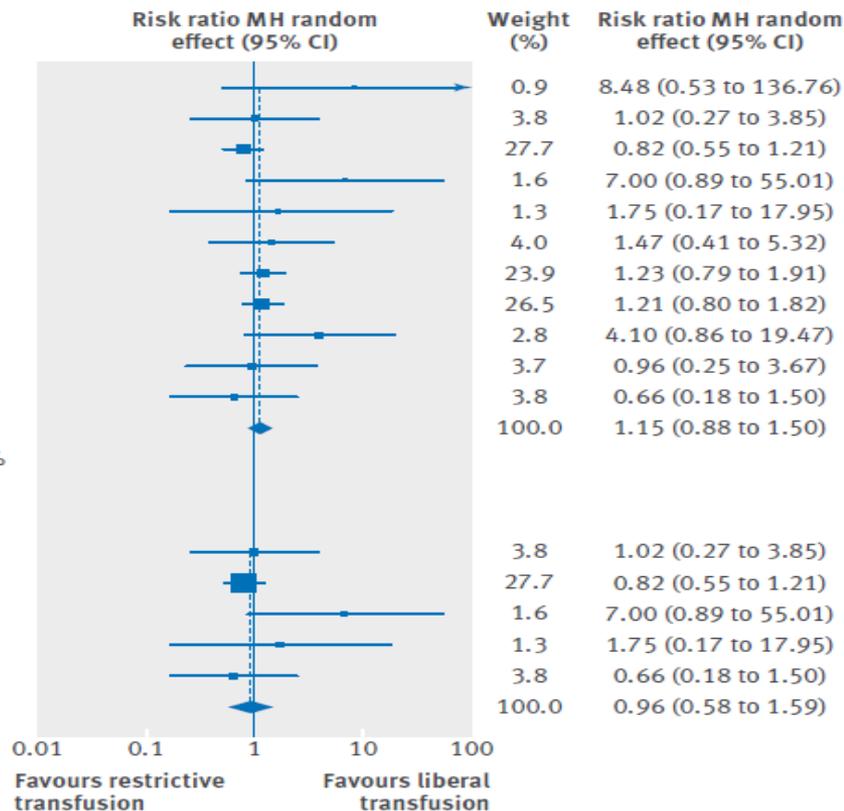
Test for overall effect: $z=1.04$, $P=0.30$

Studies randomised by CVD

Bush 1997	4/49	4/50		3.8	1.02 (0.27 to 3.85)
Carson 2011	43/1008	52/995		27.7	0.82 (0.55 to 1.21)
Carson 2013	7/55	1/55		1.6	7.00 (0.89 to 55.01)
Cooper 2011	2/24	1/21		1.3	1.75 (0.17 to 17.95)
Walsh 2013	3/17	4/15		3.8	0.66 (0.18 to 1.50)
Total	59/1153	62/1136		100.0	0.96 (0.58 to 1.59)

Test for heterogeneity: $\tau^2=0.06$, $\chi^2=4.67$, $df=4$, $P=0.32$, $I^2=14\%$

Test for overall effect: $z=0.17$, $P=0.87$



No benefit for cardiac surgery patients

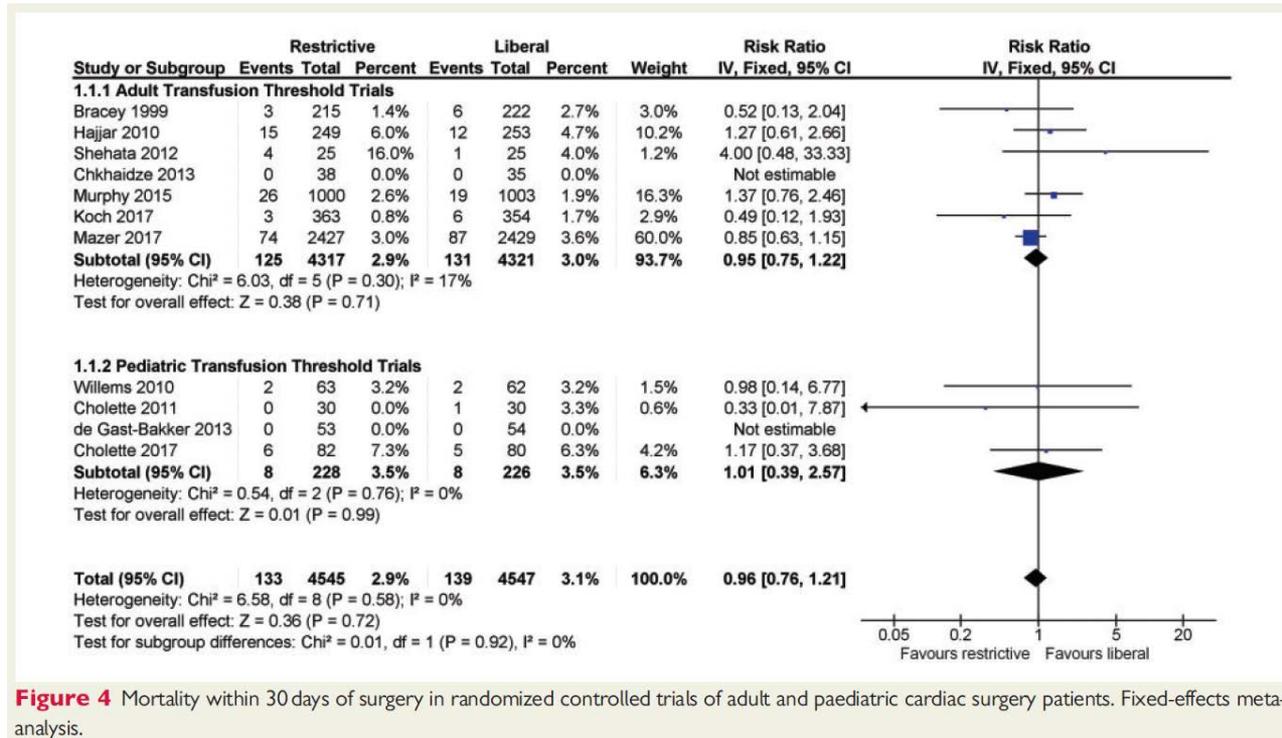


Figure 4 Mortality within 30 days of surgery in randomized controlled trials of adult and paediatric cardiac surgery patients. Fixed-effects meta-analysis.

OR 0.96 (0.76-1.21)

REALITY Trial – RCT 80 vs. 100 g/L in patients with acute myocardial infarction

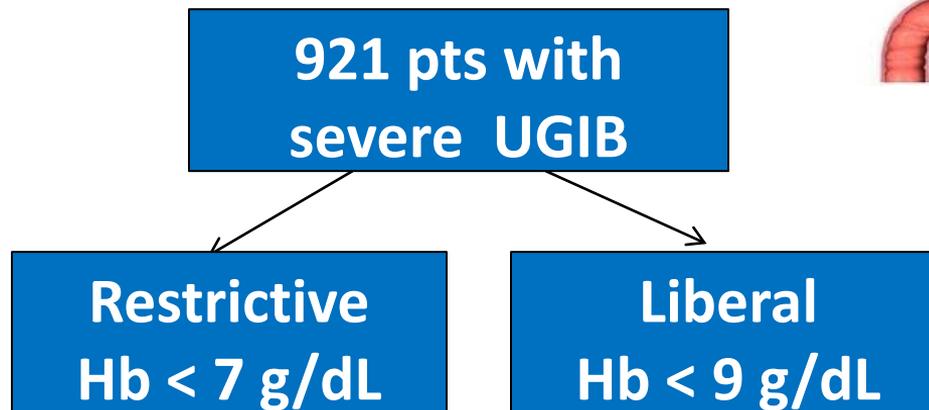
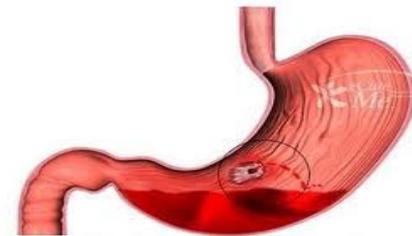
Table 3. Primary and Secondary Outcomes at 30 Days Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Outcome	No. (%)		Difference (95% CI), %	Relative risk (1-sided 97.5% CI)
	Restrictive	Liberal		
Primary (major adverse cardiovascular events), No./total No. (%) [95% CI]^a				
As-treated population	36/327 (11.0) [7.5 to 14.6]	45/322 (14.0) [10.0 to 17.9]	-3.0 (-8.4 to 2.4)	0.79 (0.00 to 1.19)
As-randomized population	38/342 (11.1) [7.6 to 14.6]	46/324 (14.2) [10.2 to 18.2]	-3.1 (-8.4 to 2.3)	0.78 (0.00 to 1.17)

ACP Clinical Practice recommendations

- ▶ Patients: Adults with CHF/CHD and anemia
- ▶ RBC: No benefit to a liberal transfusion strategy
- ▶ Recommendation: ACP recommends a restrictive transfusion strategy (7-8 g/dL) for patients with CHD

Acute UGI Bleeding



6 week survival	95%	91%	P=0.02
Further bleeding	10%	16%	P=0.05
Adverse events	40%	48%	P=0.02
RBC transfusion	1.5 units	3.7 units	P<0.001
No RBC transfusion	51%	15%	P<0.001

PPH – WOMB Trial

- ▶ 37 Dutch hospitals, 521 women randomized
- ▶ PPH with >1000 ml, Hb drop of 19+ points, and hemoglobin between 4.8-7.9 g/L, no severe symptoms of anemia (dyspnea, syncope, HR>100)
- ▶ Randomized to transfusion or no transfusion

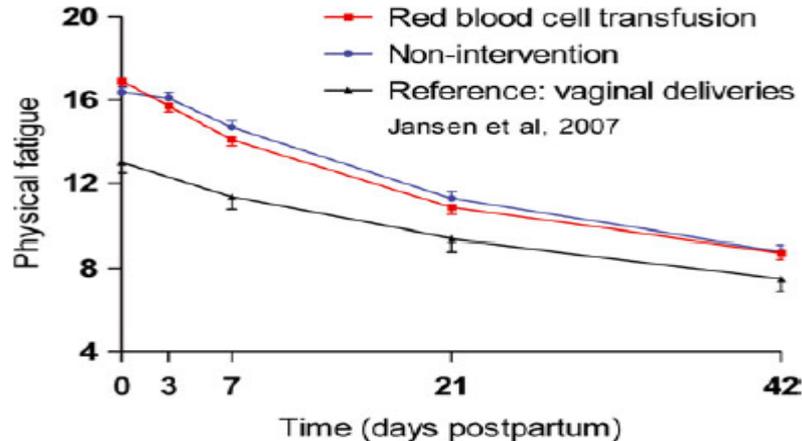


Table 2. Blood loss, haemoglobin concentration, and RBC transfusion

Variable	Transfusion (n = 258)	Non-intervention (n = 261)	P
RBC transfusion			
Units per woman	2 (2–2)	0 (0–0)	<0.001
Total units*	517	88	<0.001
Hb concentration after transfusion, g/dl**	9.0 (8.5–9.6)	8.9 (8.2–9.7)	0.56
Hb concentration at discharge (g/dl)***	9.0 (8.5–9.5)	7.4 (6.8–7.7)	<0.001
Hb concentration at 6 weeks (g/dl)****	12.1 (11.3–12.6)	11.9 (10.9–12.6)	0.18

4.8



AABB RBC Guideline 2016

- ▶ Transfusion is not indicated until the hemoglobin is 7 g/dL for hospitalized, hemodynamically stable patients (including ICU patients) – strong recommendation, moderate quality evidence
- ▶ For orthopedic and cardiac surgery and those with pre-existing cardiovascular disease, the AABB recommends 8 g/dL (strong recommendation, moderate quality evidence)
 - ▶ 8 g/dL likely comparable to 7 g/dL but RCT evidence not available for all groups
- ▶ Acute coronary syndrome – no recommendation

2018 Frankfurt Guidelines

- ▶ **Newer but same as AABB plus:**
 - ▶ The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiovascular surgery
 - ▶ The panel recommended a restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding

Reasonable approach for inpatients

Remember not to transfuse for pallor/fatigue!

Patient scenario	Hemoglobin threshold	Transfusion approach
Young patient with severe iron or B12 deficiency anemia with only fatigue and pallor	Any	Iv iron (or B12 im/po)
Young patient with reversible asymptomatic anemia (eg. Postpartum, recovering young trauma)	<5 g/dL	1 unit
Average patient without symptoms or cardiac history (eg. ICU, CVICU, hem-onc)	<7 g/dL	1 unit
Cardiac history without symptoms	<7-8 g/dL	1 unit
Hemodynamic symptoms (tachycardia, pre-syncope, etc)	<9 g/dL	1 unit
Myocardial infarction with only fatigue and pallor	<8 g/dL	1 unit GO SLOW
Slow bleeding and asymptomatic anemia	<7 g/dL	1-2 units
Rapid hemorrhage (eg. Stabbing, gunshot, varices)	Keep 6-11 g/dL	As many as you need! Don't forget to use the term uncrossmatched!



Rwanda Oncology Doctor: Global Community Must "Reduce the Disparities in Cancer Care" - Partners In Health Canada (pihcanada.org)

Case 1

- ▶ 27 year old female, 2 days post C-section complicated by moderate post-partum hemorrhage
- ▶ Pre-delivery hemoglobin was 10.5 g/dL
- ▶ Hemoglobin this morning is 5.7 g/dL
- ▶ Heart rate 87. blood pressure 102/56.
- ▶ She is pale and tired but no pre-syncope or lightheadedness
- ▶ You have ordered a dose of intravenous iron
- ▶ Plan is for discharge today
- ▶ Should you transfuse 1 unit of RBCs before sending her home?



Case 2

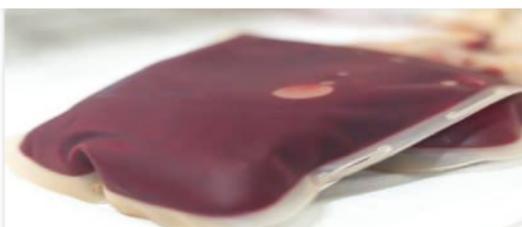
- ▶ 76 year old woman 4 days post-op from hip fracture surgery (after fracture from a fall)
- ▶ Plan to discharge tomorrow
- ▶ Hemoglobin 7.1 g/dL
- ▶ Asymptomatic, vitals stable
- ▶ No cardiac history
- ▶ Should you transfuse red blood cells?



Summary

- ▶ Use these trials to help set your 'general' transfusion trigger where you might **consider** a transfusion
- ▶ Don't be overly prescriptive – just because the hemoglobin is 6.9 g/dL you have to transfuse...or 7.1 g/dL and you hold off
- ▶ Look at your patient – Are they symptomatic? Adjust the trigger to your patient's co-morbidities
- ▶ Unless rapid bleeding 1 unit at a time
- ▶ Write a rate
- ▶ Anticipate and prevent TACO





023: RBC Transfusion Guidelines with Jeff Carson

Whither RBCs? There's no one better than lead author Dr. Jeff Carson to discuss the 2016 AABB RBC transfusion threshold recommendations!



035: Why Give Platelets? with Rick Kaufman

Platelets are tiny, but they can be a big issue! Dr. Rick Kaufman magnifies what the evidence shows about platelet transfusion.

[Listen to This Episode!](#)



016: Plasma Transfusion with Jeannie Callum

As many as 50% of plasma transfusions are unnecessary or inappropriate! You need to know why, and Dr. Jeannie Callum explains it SO well!

