



RBC TRANSFUSION

Science not the
Art of Medicine

Transfusion Camp: September 2022

DISCLOSURE

Research funding from CSL Behring, Octapharma, Defense Research and Development Canada, CIHR, Heart and Stroke, Kidney Foundation, and **Canadian Blood Services**

OUTLINE

Three Cases

- Case 1: Stable patient on the medicine ward
- Case 2: Patient with ischemic heart disease going to the OR
- Case 3: Patient with a gastrointestinal hemorrhage in the ED

RBC Basics

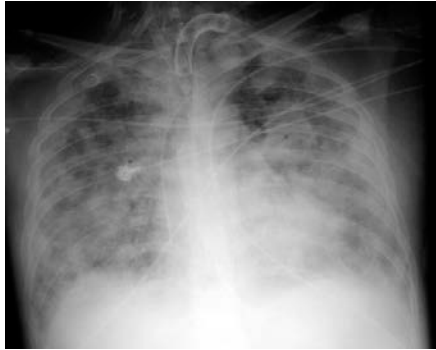
Risks of RBCs

When should you give RBCs?

Back to the three cases

[Note: massive hemorrhage, outpatient transfusions, and pediatric guidelines will be covered later/elsewhere]

WHY IS IT IMPORTANT THAT WE USE RBCS APPROPRIATELY?



Safety

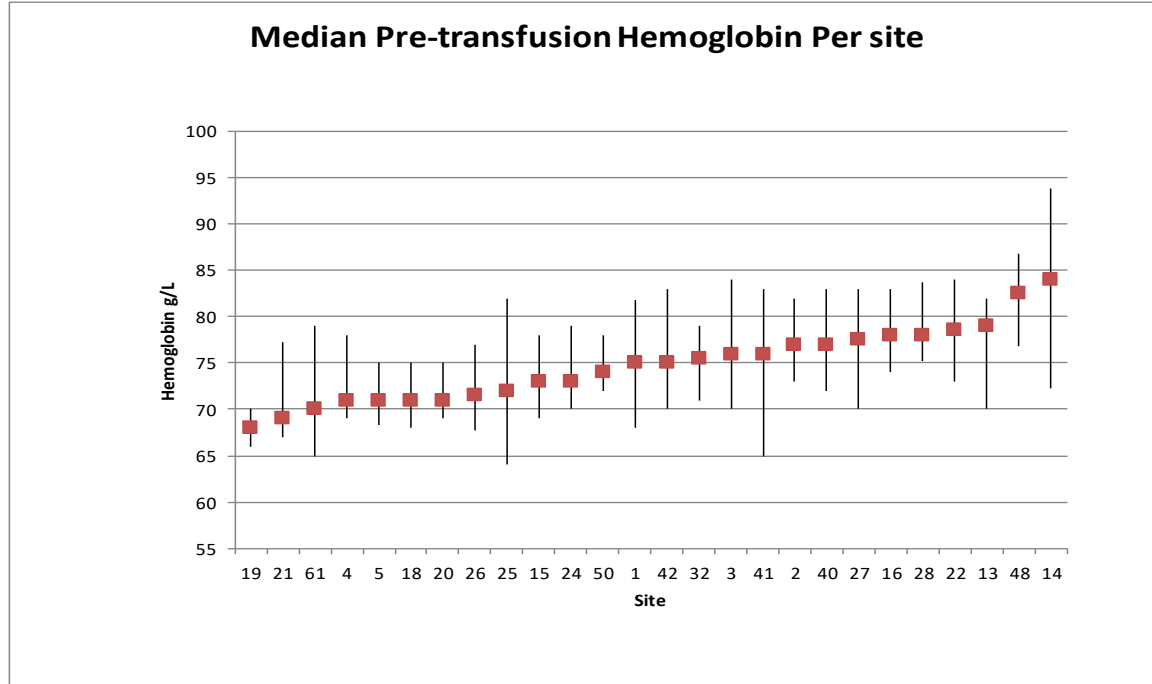


Supply
Donor Fe def



Cost

TRANSFUSION PRACTICE IS HIGHLY VARIABLE





CASES |

CASE 1: STABLE PATIENT ON THE MEDICINE WARD

78 year old man admitted with an exacerbation of heart failure and right leg cellulitis.

During admission the patient has been stabilized with adjustment of cardiac medications, diuretics, and antibiotics and is now day 10 post admission.

The hemoglobin has dropped from 122 g/L on admission to 78 g/L today.

The plan is for discharge home with home care in the next 2-3 days.

CASE 2: PATIENT WITH IHD GOING TO THE OR

86 year old single woman without children with spontaneous hip fracture admitted through the ED.

Past history of ischemic heart disease with CABG 4 years ago.

Increasing difficulties with ADLs but living independently in an apartment.

3 months before admission hemoglobin 113 g/L, MCV 81, ferritin 18.

On list for OR tonight.

CBC shows hemoglobin 89 g/L, MCV 76.

Anemia is asymptomatic.

CASE 3: PATIENT WITH A GI HEMORRHAGE IN THE ED

62 year old man with a suspected upper GI bleed presents to the ED by ambulance with melena, dizziness, and pre-syncope

Past history of hypertension on two agents, including a B-blocker

On a DOAC for atrial fibrillation with last dose 6 hours before admission

HR 89, BP 86/42, in afib

Alert and oriented

2 Liters of crystalloid administered

Hemoglobin 95 g/L (6 months ago hemoglobin was 164 g/L at his routine check up)

HR 81, BP 91/45

We will come back to the cases...but first let's review the evidence

C0556 21 464790 E

5100

O

Rh POSITIVE

Collected on: 02 OCT 2021 12:54

BASICS OF RBC

RBC BASICS

Regular

- Volume 300 mL, hematocrit 50-65%, SAG-M
- Each unit increases hemoglobin by 10 g/L
- Residual plasma – 2-30 mL (2 pack type with different processing)
- Acceptable for transfusion for 42 days from donation

Irradiated

- For immunocompromised patients at risk of TA-GVHD
- More potassium load and free hemoglobin

CMV-negative*



* The Canadian National Advisory Committee on Blood–IUT only

PATIENTS REQUIRING IRRADIATED BLOOD ¹⁴⁶

- ◆ First and second degree family members or HLA-selected donors.
- ◆ Intra-uterine or neonatal exchange transfusion.
- ◆ Congenital T-cell immunodeficiency.
- ◆ Autologous stem cell transplant recipients from 7 days prior to stem cell collection to 3 months post-transplant (6 months if total body irradiation is part of the conditioning regimen).
- ◆ Allogeneic stem cell transplant from initiation of conditioning regimen and continued until over 6 months post-transplant and lymphocyte count $>1 \times 10^9/L$ and patient free of chronic GvHD and off all immunosuppressive agents (otherwise continue indefinitely).
- ◆ CAR-T cell infusion from 7 days prior to collection and for 3 months after infusion.
- ◆ All patients with Hodgkin's Disease.
- ◆ Certain therapeutics in select patient populations (see box to right)



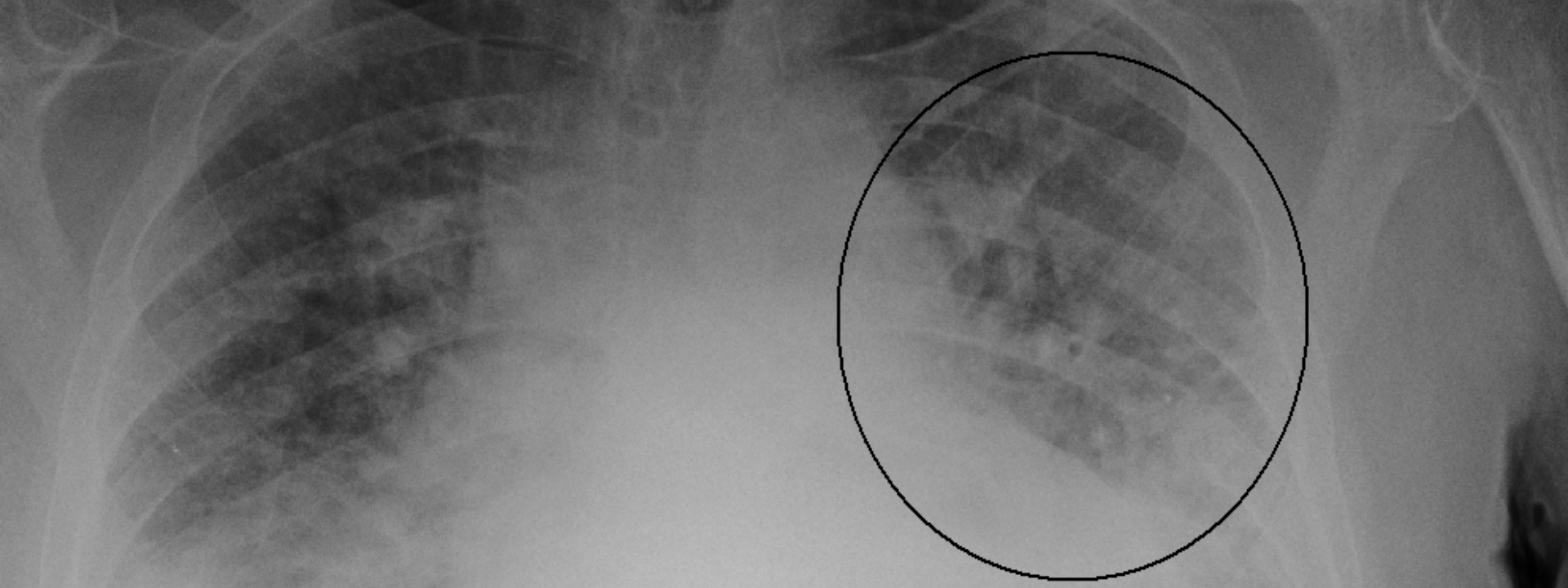
Alemtuzumab (anti-CD52)
Anti-thymocyte globulin (ATG)
Bendamustine
Cladribine (2-CDA)
Clofarabine
Deoxycoformicin
Fludarabine
Nelarabine

Pg. 67

Bloody Easy 5

[More on transfusion complications on day 2]

http://www.bcshguidelines.com/documents/irrad_bcsh_072010.pdf



THE RISKS OF RBCS

There is a
potential risk for
all patients

RISKS OF RBCS

Transfusion associated circulatory overload (TACO) – 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 354,000
- RBC alloantibodies - 1 in 13 (HDFN risk for girls and young women)
- Delayed hemolytic transfusion reactions - 1 in 2500

Anaphylaxis – 1 in 40,000

More bleeding (from GI bleeding trials)

HLA alloimmunization (leading to long waits for organ transplants)

Increased risk of thromboembolic complications

IT'S NOT BECAUSE OF A WORRY ABOUT HIV

<1 in 1,000,000	Transmission of West Nile Virus
1 in 2,000,000	Residual risk of hepatitis B per donation ⁸⁵
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 12,900,000	Residual risk of human immunodeficiency virus (HIV) per donation ⁸⁵
1 in 27,100,000	Residual risk of hepatitis C per donation ⁸⁵
<1 in 1,000,000,000	Transmission of HTLV per unit of component ⁸⁶

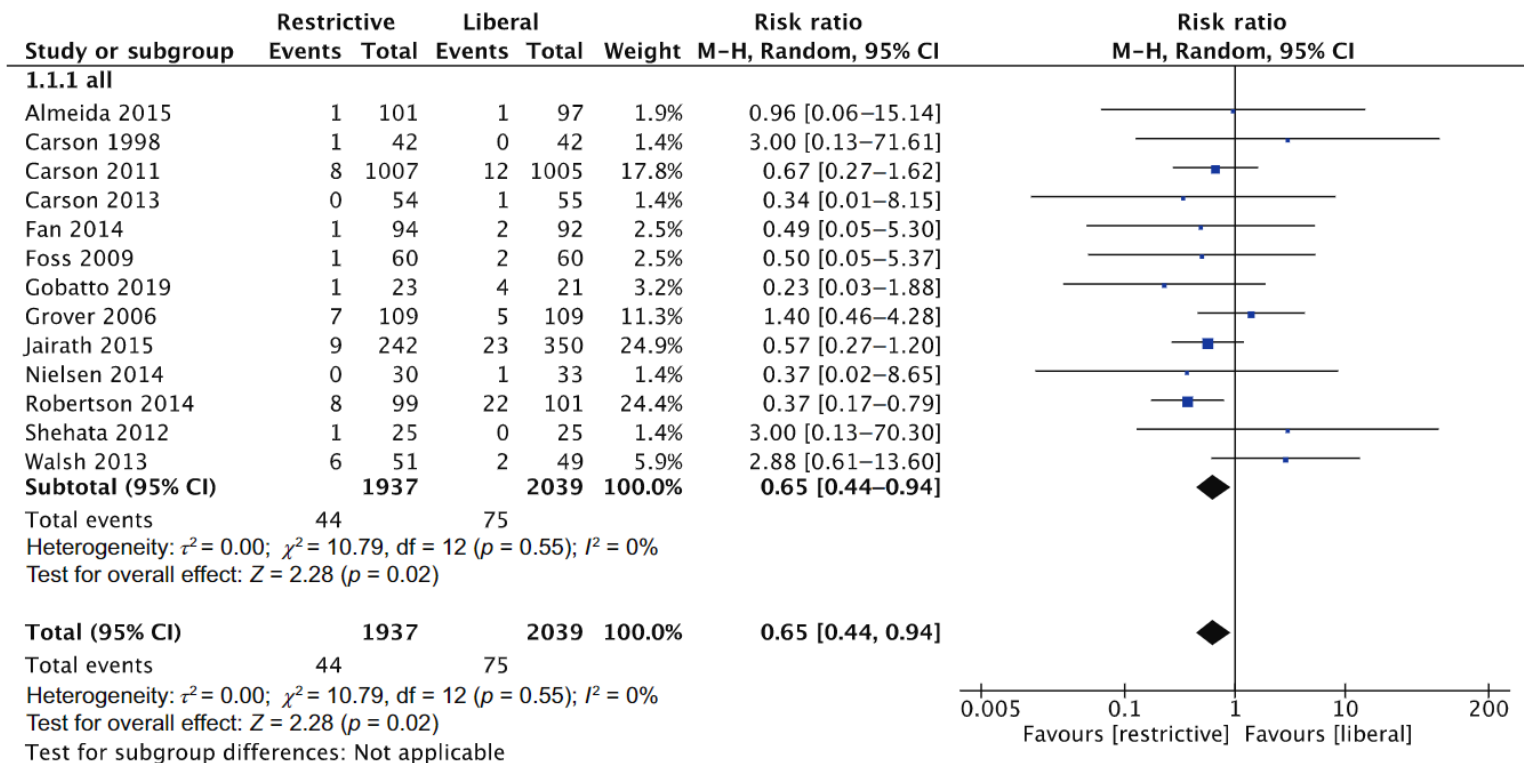
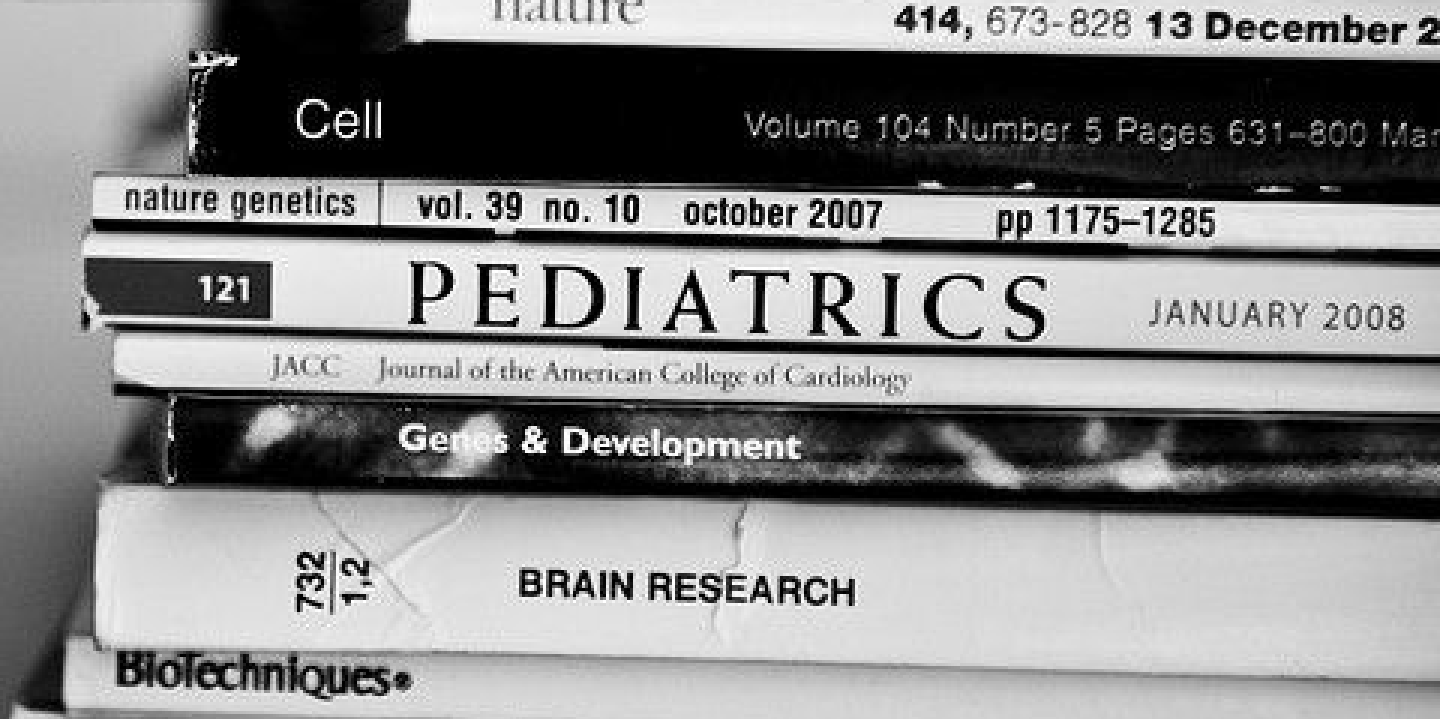


FIGURE 1 Comparison of thromboembolic events between restrictive and liberal transfusion strategies in randomized controlled trials (RCTs). Size of squares for risk ratio reflects weight of RCT in pooled analysis. Horizontal bars represent 95% confidence intervals (CIs). Risk ratio >1.0 favours liberal transfusion strategy. df, degrees of freedom; M-H, Mantel-Haenszel; Random, random-effects model

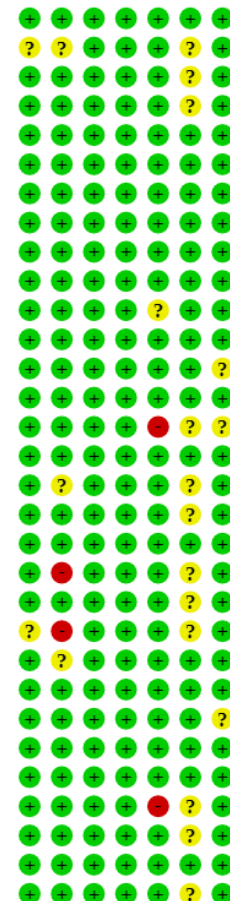
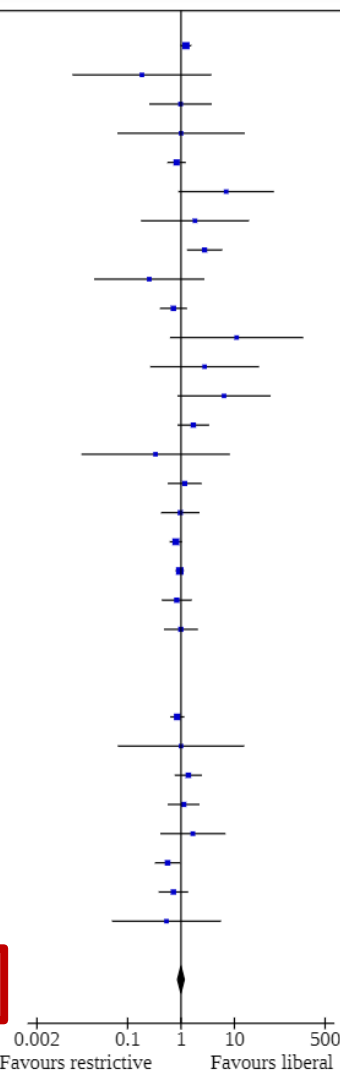


47 RCTS WITH 20,967 PATIENTS

restrictive (70-75-80)
vs. liberal (90-95-100)

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

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]



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

MORTALITY

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)				

Restrictive thresholds:

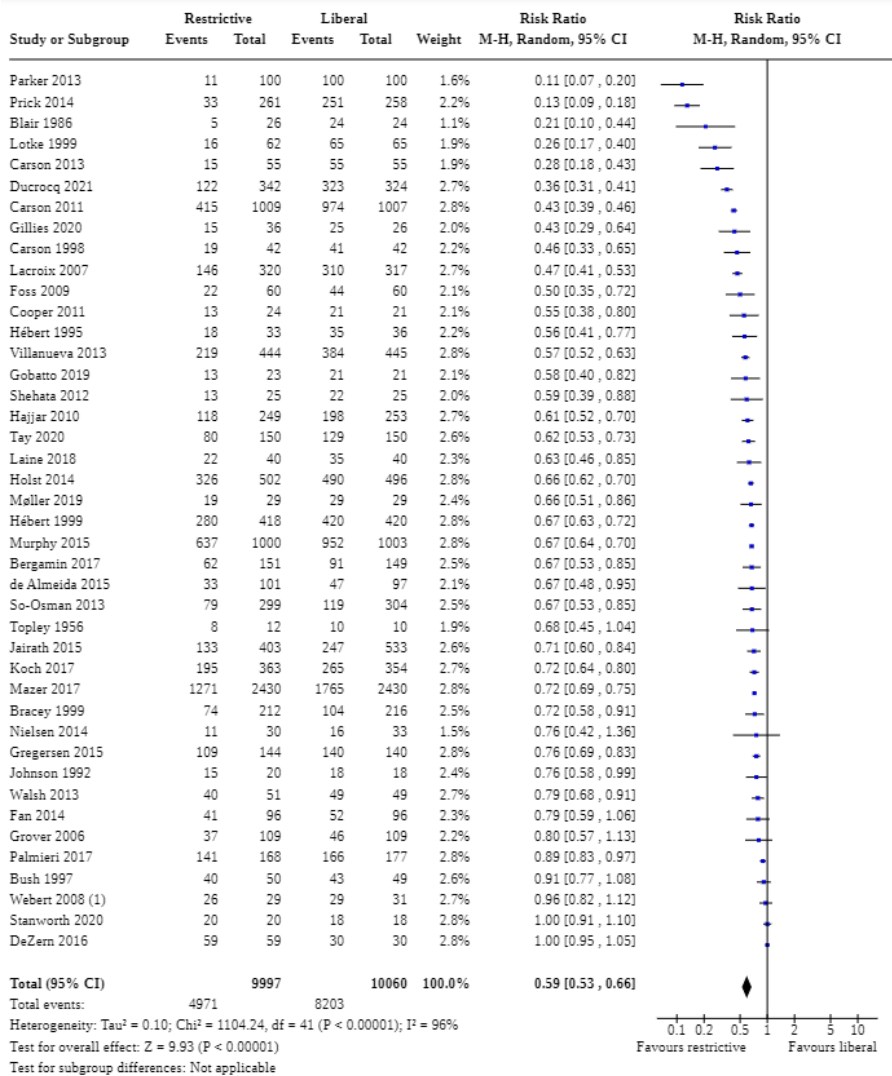
Reduce the risk of transfusion

Relative Risk = 0.59 (0.53-0.66)

By -1.21 (-1.67 to -0.75) units

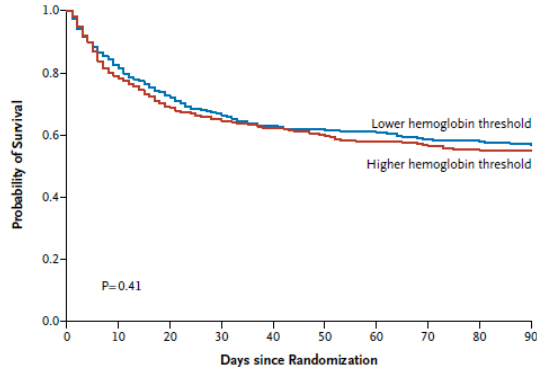
Each unit about \$1000

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

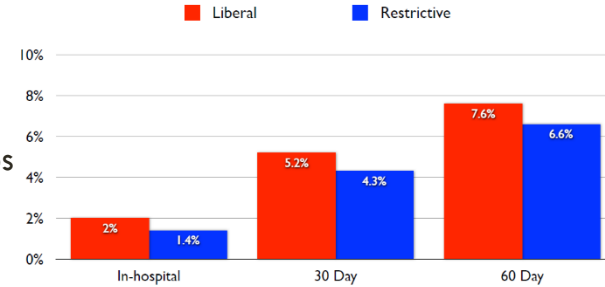


KEY RBC TRIALS

TRISS
Holst
NEJM 2014
Septic Shock
n=998
70 vs 90 g/L
No subgroups



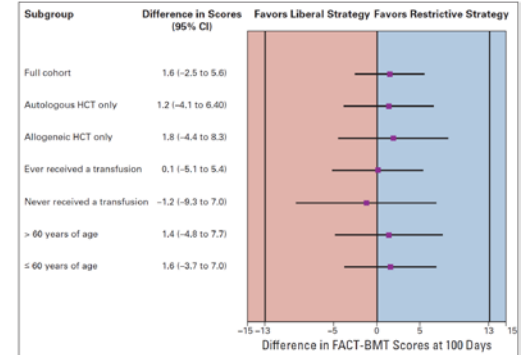
FOCUS
Carson
NEJM 2011
Fractured hips
Periop
n=2016
80 vs 100



TRICS III
Mazer
NEJM 2017
CVSx
n=5035
75 vs 95 g/L
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
70 vs 90



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

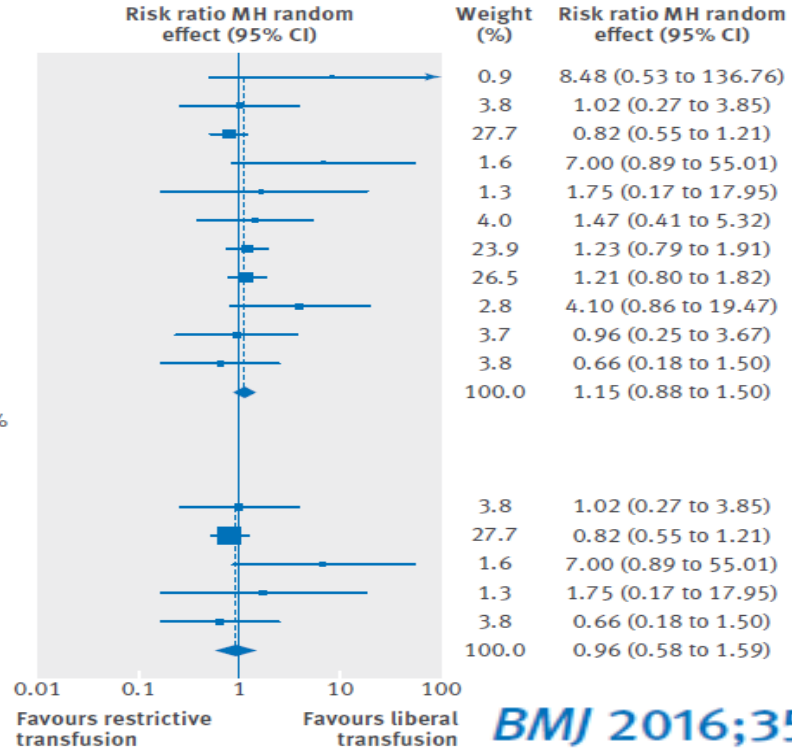
Test for overall effect: $z=1.04$, $P=0.30$

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

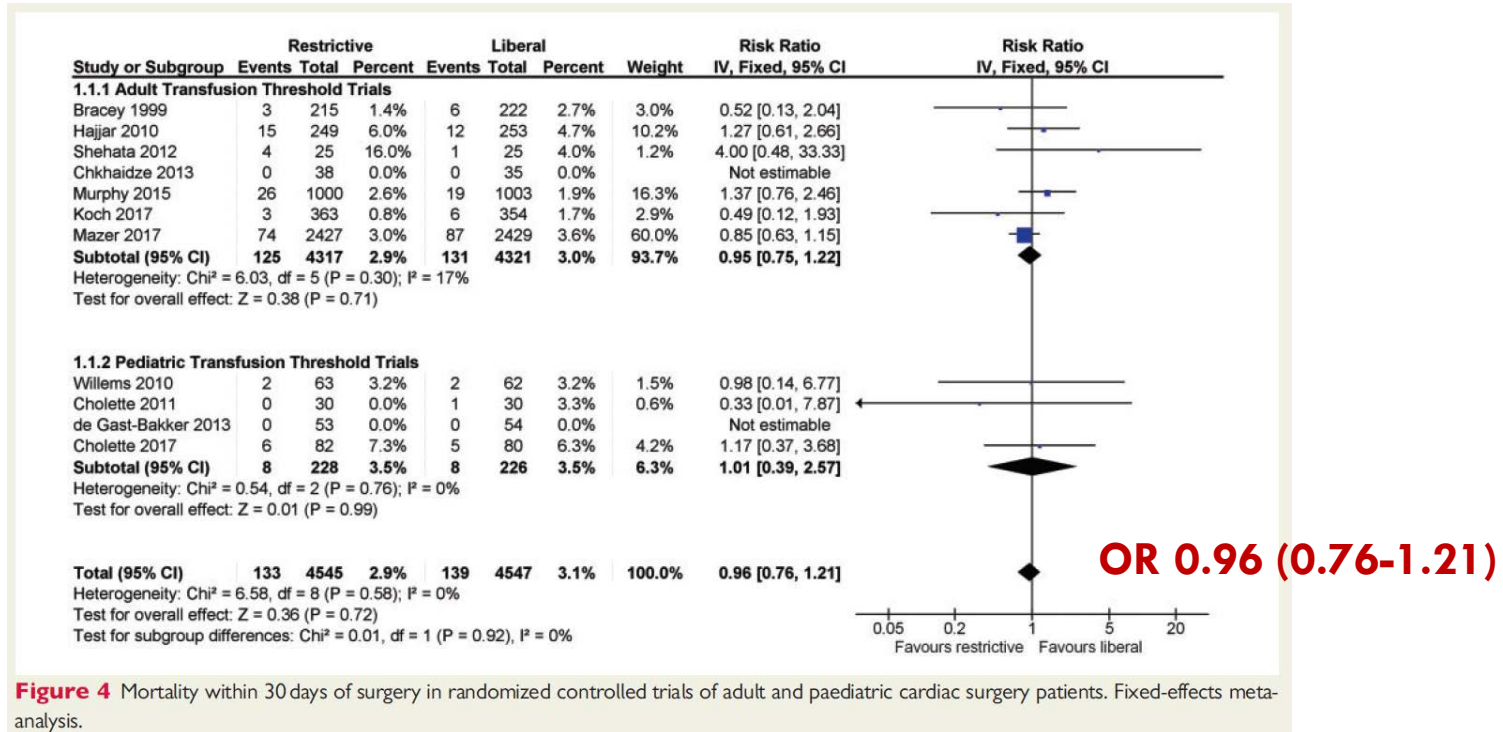


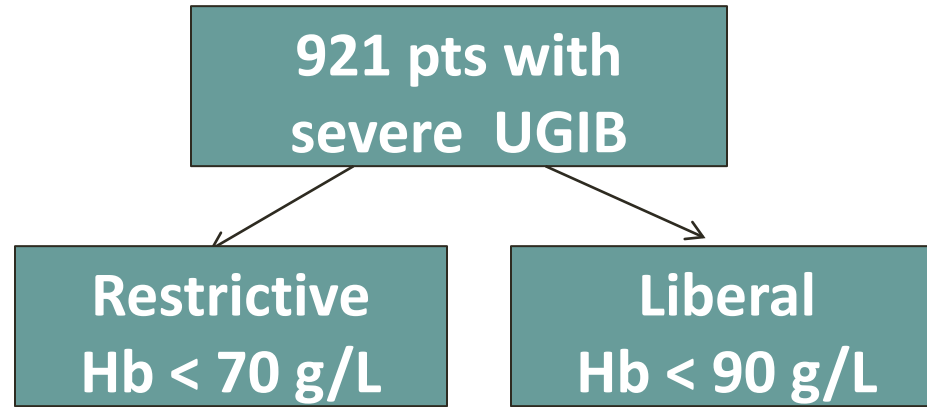
Figure 4 Mortality within 30 days of surgery in randomized controlled trials of adult and paediatric cardiac surgery patients. Fixed-effects meta-analysis.

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)

GI 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 48-79 g/L, no severe symptoms of anemia (dyspnea, syncope, HR>100)

Randomized to transfusion or no transfusion

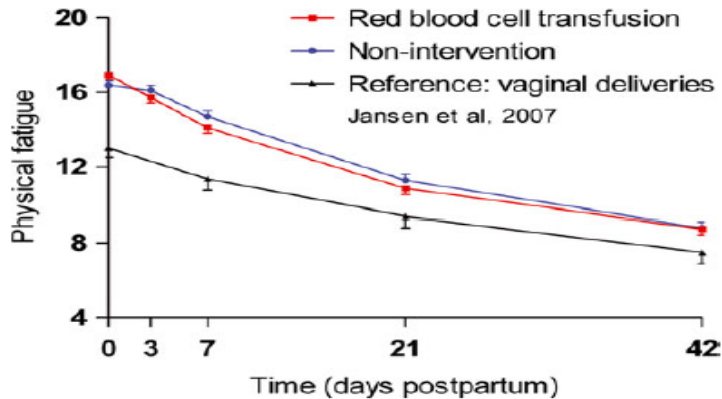


Table 2. Blood loss, haemoglobin concentration, and RBC transfusion

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

AABB RBC GUIDELINE 2016

Transfusion is not indicated until the hemoglobin is 70 g/L 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 80 g/L (strong recommendation, moderate quality evidence)

- 80 g/L likely comparable to 70 g/L but RCT evidence not available for all groups

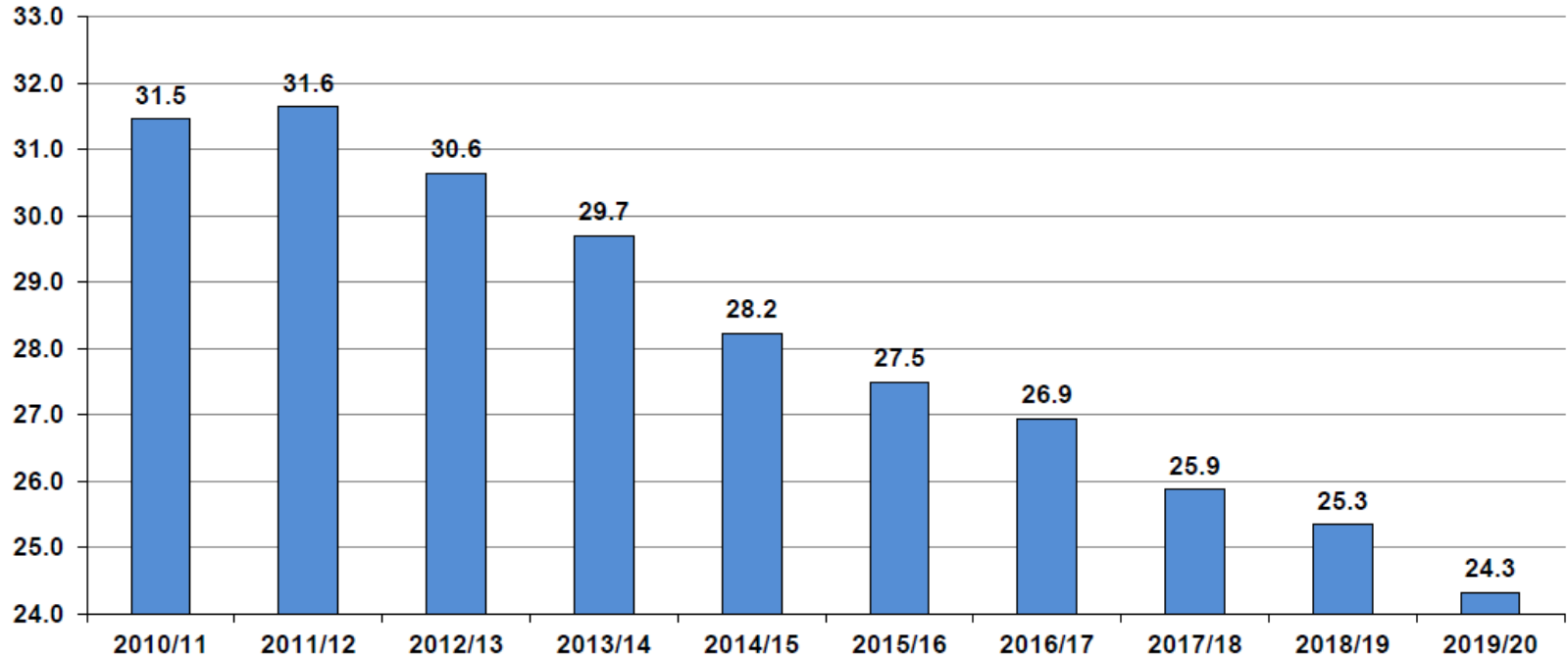
Acute coronary syndrome – no recommendation

2018 FRANKFURT GUIDELINES

Newer but same as AABB plus:

- The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <75 g/L) in patients undergoing cardiovascular surgery
- The panel recommended a restrictive transfusion threshold (hemoglobin concentration 70-80 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding

RBC UNITS PER 1,000 POPULATION



Canadian
Blood
Services

BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

COMPARISON TO THE REST OF THE WORLD

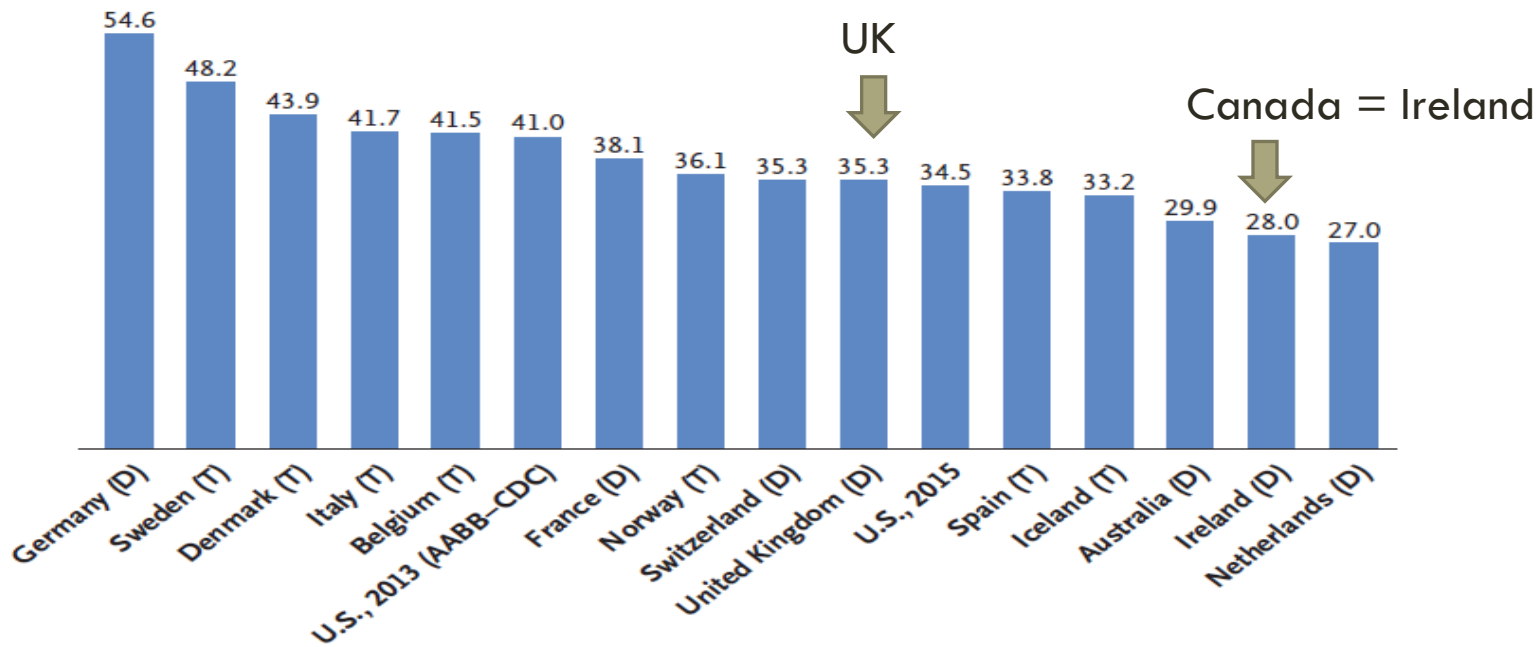
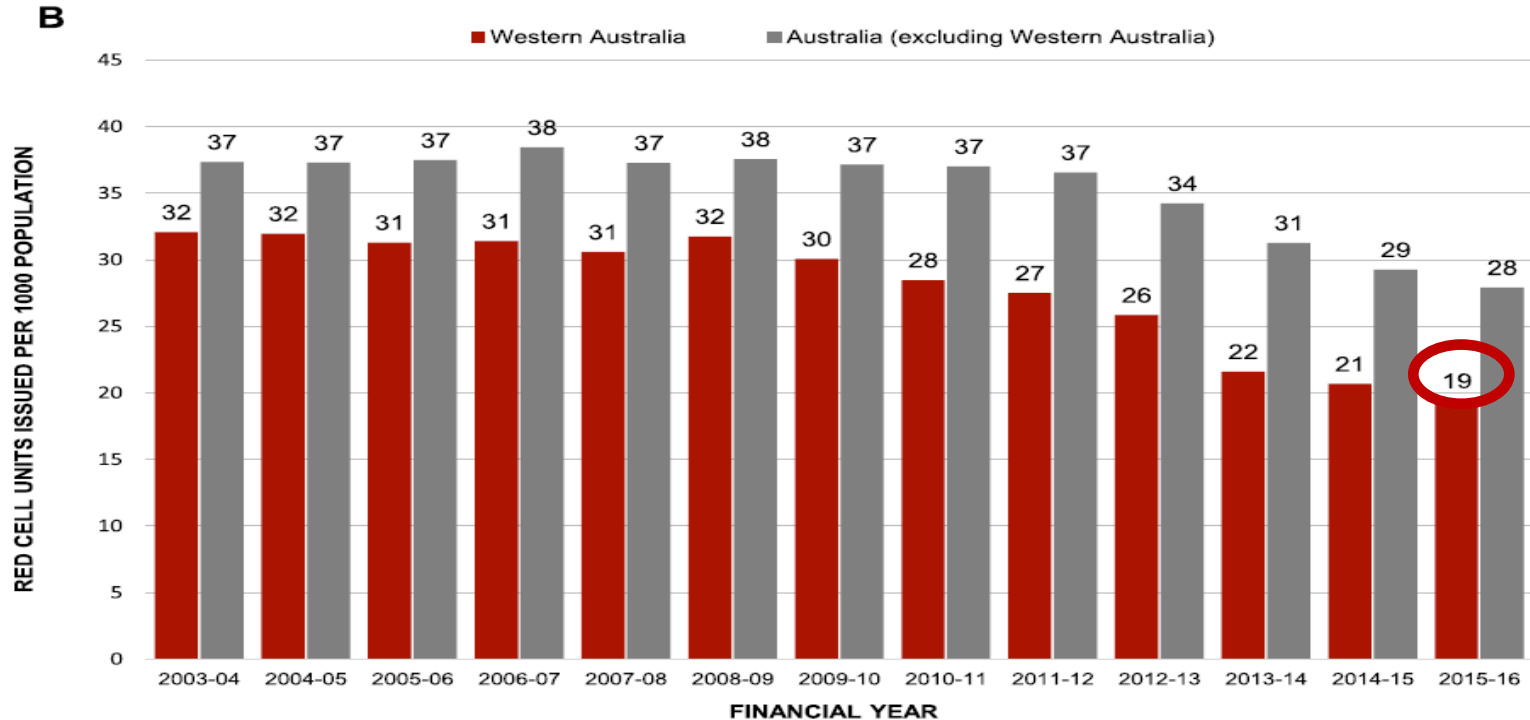


Figure 3. Transfusion Rates in the United States in 2013 and 2015, as Compared with Rates in Other Developed Countries.

WHAT PATIENT BLOOD MANAGEMENT ADDS TO RESTRICTIVE TRANSFUSION THRESHOLDS



REASONABLE APPROACH FOR INPATIENTS

Patient scenario	Hemoglobin	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)	<50 g/L	1 unit
Average patient without symptoms or cardiac history (eg. ICU, CVICU, hem-onc)	<70 g/L	1 unit
Cardiac history without symptoms	<70-80 g/L	1 unit
Hemodynamic symptoms (tachycardia, pre-syncope, etc)	<90 g/L	1 unit
Myocardial infarction with only fatigue and pallor	<80 g/L	1 unit GO SLOW
Slow bleeding and asymptomatic anemia	<70 g/L	1-2 units
Rapid hemorrhage (eg. Stabbing, gunshot, varices)	Keep 60-110 g/L	As many as you need! Order uncrossmatched!

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CASE 1: STABLE PATIENT ON THE MEDICINE WARD

78 year old man admitted with an exacerbation of heart failure and right leg cellulitis.

During admission the patient has been stabilized with adjustment of cardiac medications, diuretics, and antibiotics and is now day 10 post admission.

The hemoglobin has dropped from 122 g/L on admission to 78 g/L today.

The plan is for discharge home with home care in the next 2-3 days.

What could be causing his slow drop in hemoglobin?

When would you think of a blood transfusion?

How many units would you transfuse?

How slow?

Does a blood transfusion improve heart failure or post-discharge outcomes?

CASE 2: PATIENT WITH ISCHEMIC HEART DISEASE GOING TO THE OR

86 year old single woman without children with spontaneous hip fracture admitted through the ED.

Past history of ischemic heart disease with CABG 4 years ago.

Increasing difficulties with ADLs but living independently in an apartment.

3 months before admission hemoglobin 113 g/L, MCV 81, ferritin 18.

On list for OR tonight.

CBC shows hemoglobin 89 g/L, MCV 76.

Anemia is asymptomatic.

What is the cause of the anemia?

What is the first-line treatment of this type of anemia?

What is role of transfusion for this patient?

How many units would you transfuse at a time?

How slow?

What blood bank testing should be done pre-OR?

CASE 3: PATIENT WITH A GI HEMORRHAGE IN THE ED

62 year old man with a suspected upper GI bleed presents to the ED by ambulance with melena, dizziness, and pre-syncope

Past history of hypertension on two agents, including a B-blocker

On a DOAC for atrial fibrillation with last dose 6 hours before admission

HR 89, BP 86/42, in afib

Alert and oriented

2 Liters of crystalloid administered

Hemoglobin 95 g/L (6 months ago hemoglobin was 164 g/L at his routine check up)

HR 81, BP 91/45

What is the role of red cell transfusion in GI bleeds?

How many units would you transfuse at a time?

Should you activate the massive hemorrhage protocol?

What is the consequence of liberal transfusion strategy in GI bleeding?

SUMMARY

RBCs are expensive and associated with adverse events

Adhere to a restrictive transfusion strategy – 70 g/L and 1 unit at a time = default strategy unless brisk hemorrhage

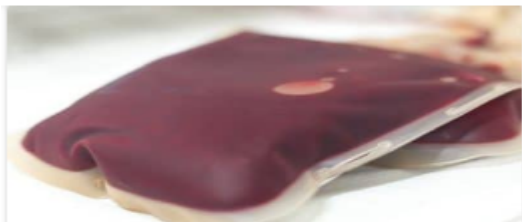
The largest risk is TACO – be thoughtful with onboarding

We have an extensive literature base to support a restrictive transfusion strategy

Guidelines support a restrictive approach

5 THINGS I HOPE YOU WILL DO IN 2022-2023

1. Give iron deficient patients iron instead of blood unless clear hemodynamic instability
2. Make extra efforts for young patients of childbearing potential to prevent transfusion and alloimmunization risk
3. Adopt a restrictive transfusion approach for most patients
4. **Transfuse one at a time** (even in the operating room) unless brisk bleeding – check hemoglobin after every unit
5. Thoughtfully onboard red cells in patients at higher risk of 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!



THANK YOU FOR YOUR ATTENTION
HAPPY TO TAKE QUESTIONS |