
SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA
XXXV
Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)
IV Congreso Ibérico de Medicina Interna
II Congreso de la Sociedad de Medicina Interna de la Región de Murcia
Sociedad Murciana de Medicina Interna
SMI
19-21 de Noviembre de 2014
Auditorio y Centro de Congresos Víctor Villegas. Murcia

Anemia may lead to complications derived to impaired transport of oxygen to tissues.

RBC transfusion adequately restore tissue oxygenation when demand exceeds supply.

WHY SHOULD BE RESTRICTED?

* **Socioeconomic costs**
* **Capacity to adapt**
* **Potential complications**

EN SU OPINIÓN, PUEDE SER PERJUDICIAL LA TRANSFUSIÓN?

a) Nunca

b) Raramente

c) A menudo

d) Siempre

e) No lo se

http://www.congresomovil.com/resultados-votacion.jsp?id_web=1&i=es&id_v=140&id_p=1311&val=1415980304000&pr=si

NONINFECTIOUS COMPLICATIONS OF BLOOD TRANSFUSION

Immune-mediated reactions

Febrile reaction	1/300
Urticaria or other cutaneous reaction	1/50–100
RBC alloimmunisation	1/100
Mistransfusion	1/14000–19000
Hemolytic reaction	1/6000
Fatal hemolysis	$1/10^6$
TRALI	1/5000
TRIM	Unknowm (May be high)
Anaphylaxis	1/20000–50000
GvHD	Uncommon
Immunomodulation	Unknown

Non-immune reactions

TACO	1-10/100
Hypotensive reactions	Unknown
Transfusion-related iron overload	
Michrochimerism	1/5-10000
Posttansfusion purpura	
Metabolic toxicities (hipoCa, hipoK, hipotrermia, coagulopathy)	
RBC storage lesion	Unknown

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TRANSFUSION ASSOCIATED IMMUNOMODULATION

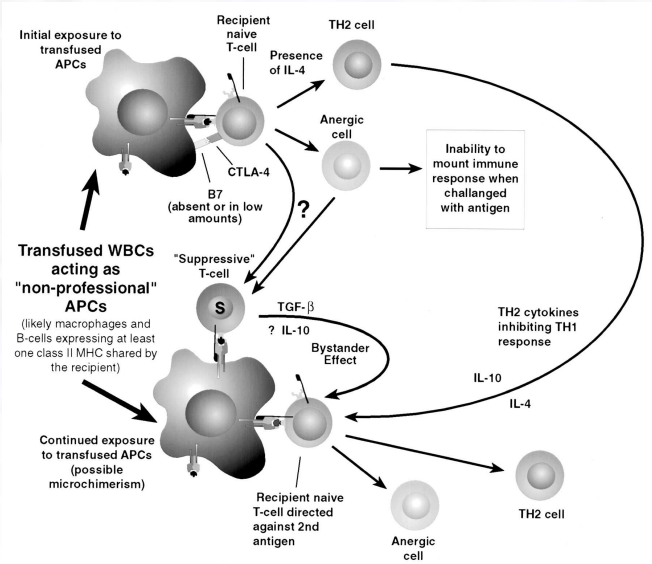
Possible effects of donor WBCs on the host immune system

early antigen-specific immunosuppression and later nonspecific suppression by Th2 suppression of the Th1 response

Immunologically active, intact allogeneic WBCs

Soluble, WBC-derived mediators accumulating in the supernatant fluid of stored RBCs

Soluble HLA peptides circulating in allogeneic plasma



**** Increased risk of bacterial infections***

** <u>Other:</u>*

- Activation of CMV or HIV
- Increased recurrence of malignancies
- Increased risk short-term mortality
- Enhanced survival of renal allografts
- Reduced recurrence of Crohn's disease

HEALTH CARE–ASSOCIATED INFECTION & TRANSFUSION (RESTRICTIVE vs LIBERAL)

Systematic Review & Meta-analysis

* 18 RCT (7593 patients): variable clinical settings

Tf threshold variable: restrictive (most RCT Hb < 7 or 8g/dL) *vs* liberal (most RCT Hb < 10g/dL) .
- Less Patients exposed to blood (27% in restrictive *vs* 67% in liberal groups)
- Fewer Units of blood transfused

Reduced risk serious infections: **12%** *vs* **17%** (RR, 0.82; CI, 0.72-0.95)
NNT: 38 (CI, 24-122)

- MA restricted to 15 RCT with concealed randomization: RR, 0.78; CI, 0.63-0.96
- MA restricted to 8 RCT using leukocyte-reduced RBC: RR, 0.80; CI, 0.67-0.95
- MA according to clinical setting
  - Cardiac patients, 7 RCT: RR, 1.30; CI, 0.85-1.97
  - Critically ill, 2 RCT: RR, 0.83; CI, 0.65-1.04
  - G.I. bleeding, 1 RCT: RR, 0.90; CI, 0.69-1.17
  - Hip/Knee replacement, 6 RCT: RR, 0.70; CI, 0.54-0.91
- MA restricted to 4 RCT with Hb threshold <7 g/dL in the restrictive group: RR, 0.82; CI, 0.70-0.97
  MA restricted to RCT using higher Hb threshold in the restrictive group: RR, 0.92; CI, 0.66-1.28

Rohde JM, et al. JAMA 2014;311:1317-1326

OLD BLOOD: STORAGE LESION

RBC storage lesions: hemolytic propensity

Metabolic & chemical changes
Physical changes (rigidity)

Hemolytic propensity (donor variability)y

Susceptible host

Vascular NO scavenging by free and microparticle-encapsulated Hb

Endothelial dysfunction

NO

NO

Sepsis

Enhanced bacterial growth by heme iron

Vasoconstriction Inflammation

old blood is also associated with
- **Multiorgan dysfunction syndrome**
- **Pneumonia. Sepsis**
- **Renal dysfunction**

INCREASED RISK OF DEATH

Wang D et al. Metaanalysis.Transfusion 2012;52:1184 / Yu B et al. Transfusion 2012;52:1410

Figure adapted from Kanias T & Gladwin M.T. Transfusion 2012;52:1388

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TRANSFUSION REQUIREMENTS
RESTRICTIVE vs LIBERAL

Trial	Comparison	Setting & N	Outcomes
Hébert et al *N Engl J Med*. 1999;340:409	Restrictive Tf: when Hb<70 (to 70-90) Liberal Tf: when Hb<100 (to 100-120)	N=838 (418 vs 420) ICU Patients Exclusion G.I bleeding	30-d **MORTALITY** Similar (18.7% vs 23.3%) Better with restrictive in APACHE ≤20/ Age <55 More Cardiac events (CHF & ACS) with liberal Tf No Tf in 33% vs 0
Lacroix et al *N Engl J Med*. 2007;356:1609	Restrictive Tf: when Hb<70 (to 85-95) Liberal Tf: when Hb<95 (to 110-120)	N=637 (320 vs 317) Pediatric ICU Exclusion G.I bleeding	Similar MODS (Multi-Organ-Dysfunction Synd.) Similar 28-d MORTALITY Similar adverse events No Tf in 54% vs 2%
Carson et al *N Engl J Med*. 2011;365:2453	Restrictive Tf: when Hb<80 (to >80) Liberal Tf: when Hb<100 (to >100)	N=2016 (1009 vs 1007) Hip-fracture surgery & Cardiovasc.dis. (or risk factors) Exclusion G.I bleeding	Similar 60-d DEATH OR INABILITY TO WALK WITHOUT ASSISTANCE Similar 30-d & 60-d MORTALITY Similar acute coronary synd. Similar adverse events No Tf in 59% vs 3%

Lower vs Higher Hb Thresholds for RBC Transfusion

Meta-Analysis

6264 patients from 19 trials in variable clinical settings

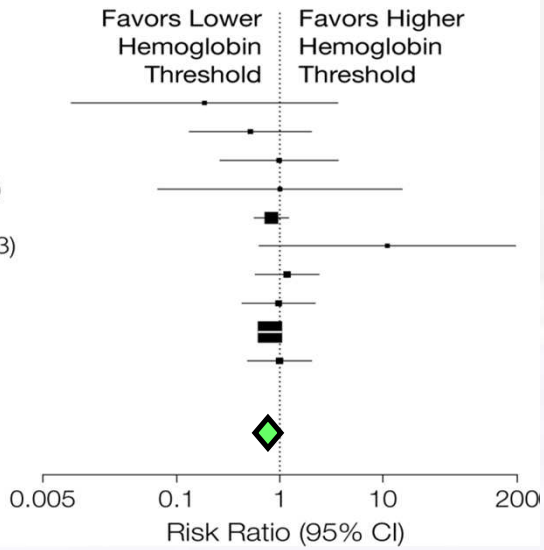
Hb threshold of 7-8 g/dL is associated with fewer transfusion (less patients & RBCunits):

- No differences in cardiac event rates
- Lower hospital mortality
- Similar mortality at 14-day, 30 or 60-day follow-up

Source	Lower Hemoglobin Threshold Events, No.	Lower Hemoglobin Threshold Total, No.	Higher Hemoglobin Threshold Events, No.	Higher Hemoglobin Threshold Total, No.	Risk Ratio (95% CI)
Blair, 1986	0	26	2	24	0.19 (0.01-3.67)
Bracey, 1999	3	215	6	222	0.52 (0.13-2.04)
Bush, 1997	4	50	4	49	0.98 (0.26-3.70)
Carson, 1998	1	42	1	42	1.00 (0.06-15.47)
Carson, 2011	43	1009	52	1007	0.83 (0.56-1.22)
Foss, 2009	5	60	0	60	11.00 (0.62-194.63)
Hajjar, 2010	15	249	13	253	1.17 (0.57-2.41)
Hebert, 1995	8	33	9	36	0.97 (0.42-2.22)
Hebert, 1999	78	418	98	420	0.80 (0.61-1.04)
Lacroix, 2007	14	320	14	317	0.99 (0.48-2.04)
Lotke, 1999	0	62	0	65	NA
Overall random effects model					0.85 (0.70-1.03)

Heterogeneity: $I^2 = 0\%$
Test for overall effect: $P = .10$

30-days mortality



Carson JL, Carless PA & Hebert PC. Cochrane Database Syst Rev. 2012;4:CD002042. doi: 10.1002/14651858.CD002042.pub3

TRANSFUSION IN GI BLEEDING

GI bleeding (all causes) accounts for 13.8% of all transfusions

Wallis, Transfusion Med 2006

44% to 55% of all presentations with G.I bleeding receive transfusion of UPRC

Hearnshaw, AP&T 2010
Restellini, AP&T 2013

Lack of evidence on tranfusional policy:

DETRIMENTAL

* Potential complications
* Volume expansion
* May worsen bleeding
* Capacity to adapt

BENEFITIAL

* Improve anemia

Capacity to adapt

QUE NIVEL DE Hb LE PARECE OPTIMO PARA INDICAR TRANSFUSION EN HEMORRAGIA G.I. AGUDA SIN COMORBILIDAD ?

a) Hb ≤ 10

b) Hb ≤ 9

c) Hb ≤ 8

d) Hb ≤ 7

e) Hb ≤ 6

http://www.congresomovil.com/resultados-votacion.jsp?id_web=1&i=es&id_v=140&id_p=1312&val=1415980304000&pr=si

VOLUME RESTITUTION & BLEEDING

Fluid restitution may worsen bleeding due to different mechanisms:

- Mechanical disruption of formed clots

  early clot is fragile and capable of dislodgement if compensatory reduction of vessel pressure/flow is not allowed

  (Interruption of catecholamine-mediated host defense response by rapid increase in plasma volume (pressure/flow) may dislodge early clots & impair formation of new clots)

- Altering coagulation cascade

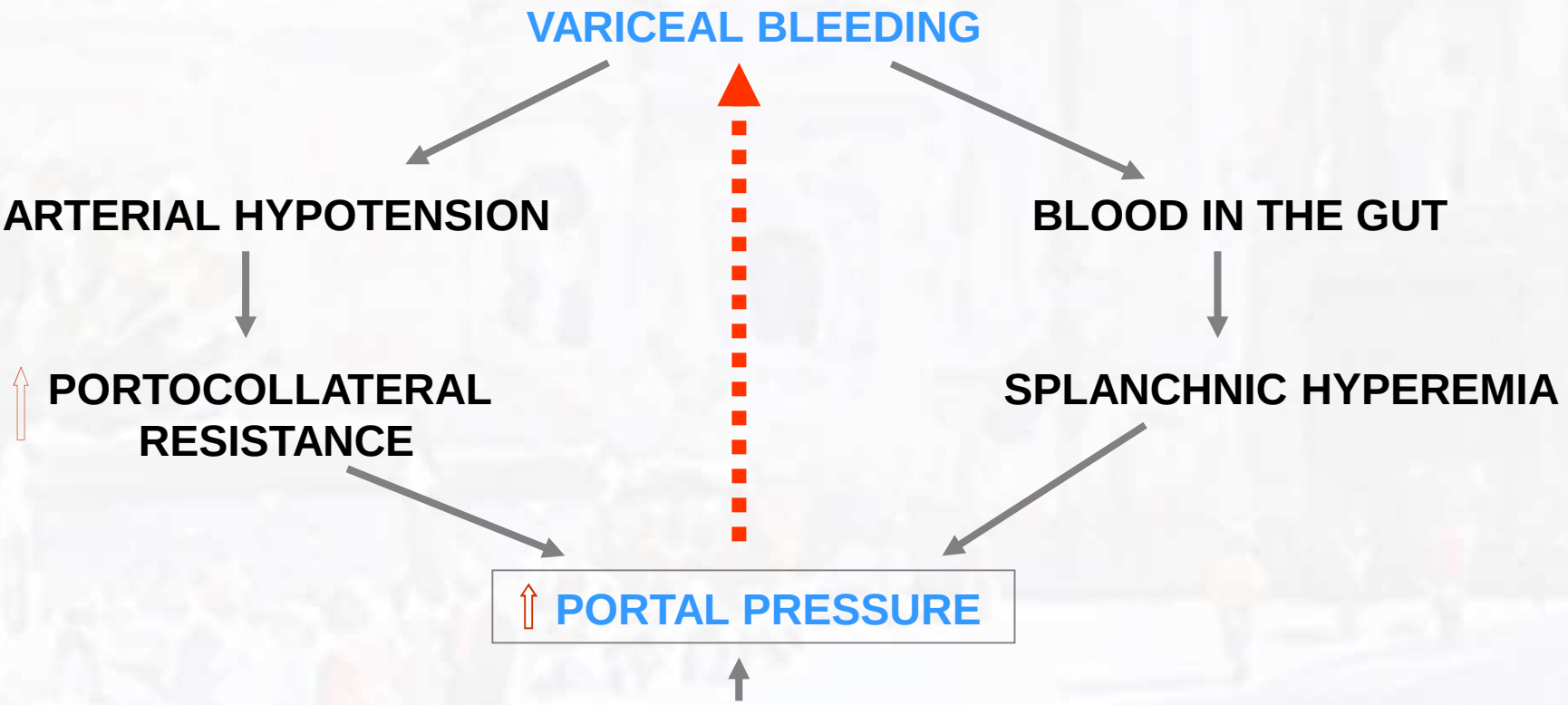
  * Diluting clotting factors

  * Disturbing platelet aggregation

  * Altering coagulation cascade

* Jorgensen et al. Throm Res 1980:17:13
* Stibbe & Kirby. BMJ 10975;2:750
* Evans PA et al. Br J Anaesth 1998;81:198
* Treib J et al. Haemostasis 1996;26:210
* Stump DC et al. Trasnfusion 1985;25:349
* Mardel SN et al. Lancet 1996;347:825
* Roberts I et al. Lancet 2001;357:385

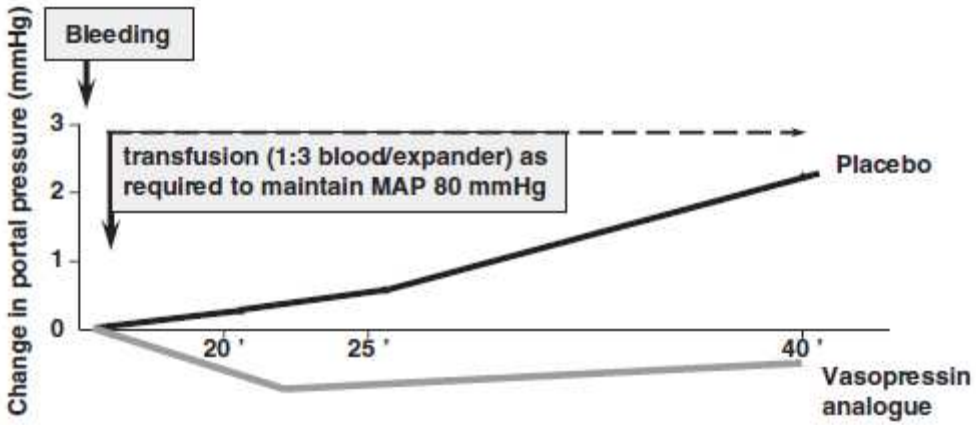
FACTORS INFLUENCING PORTAL PRESSURE DURING ACUTE BLEEDING



* McCormick. Gut 1995;36:100.
* Kravetz. Gastroenterology 1989
* Castañeda. Hepatology 2000
* Chen & Groszmann. Gastroenterology 1996

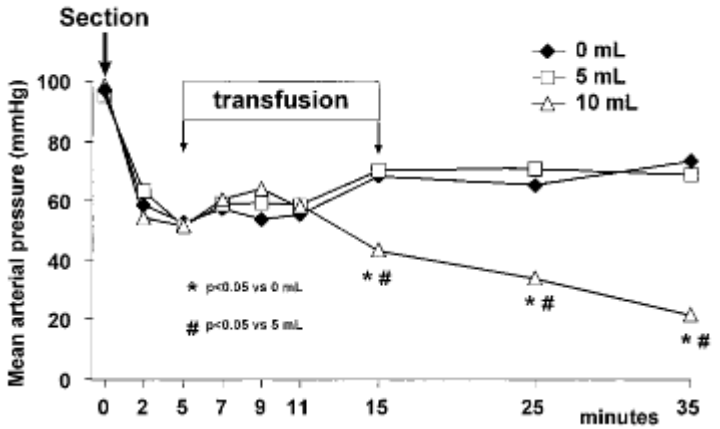
Effects of Blood Volume Restitution Following Bleeding in Portal Hyertension

EFFEC ON PORTAL PRESSURE

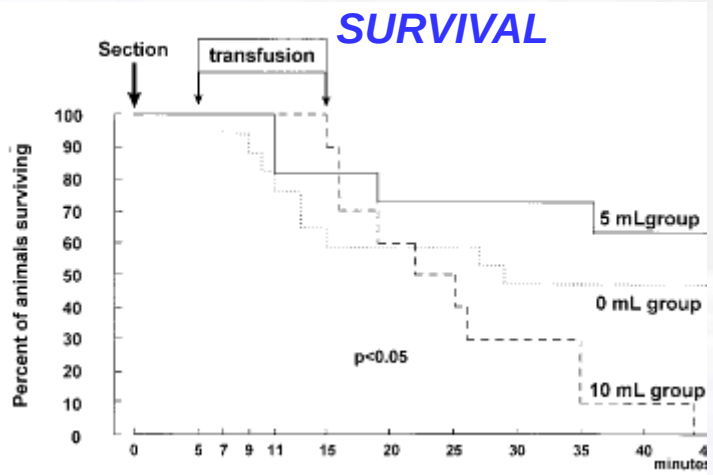


Even using a conservative target (MAP= 80 mmHg) volume replacement induced a rebound increase in portal pressure

UNCONTROLLED BLEEDING



SURVIVAL



Boyer Jlet al. N Eng J Med 1966;275:750-4/ Kravetz D et al. Gastroenterology 1986;90:1232-40/ Kravetz D et al. HEPATOLOGY 1989;9:808-14/ Koshy A et al. Clin Sci 1990;78:193-7/ Castañeda B et al. HEPATOLOGY 2000;31:581-6/ Castañeda B et al. HEPATOLOGY 2001;33:821-5.

PHYSIOPATHOLOGY OF RBC TRANSFUSION

The aim of RBC transfusion is the need to increase arterial oxygen transport (TaO_2) to the tissues. TaO_2 depends on arterial oxygen concentration (CaO_2) and cardiac output (Q).

$$\mathbf{CaO_2} = 1.39 \times [Hb] \times SaO_2$$

$$\mathbf{TaO_2} = CaO_2 \times Q = 1.39 \times [Hb] \times SaO_2 \times Q$$

⇓ **Hb**
Consider *transfusion UPRC*

⇓ **Q**
- non-compensated *volemic loss*
- reduced *ejection fraction*
(due to myocardial hypoxia..)

⇓ **SaO_2**
changes in ventilatory function and gas exchange.

⇓ TaO_2 ⟺ **CaO2** = 1.39 x [Hb] x SaO_2

TaO2 = CaO_2 x Q

VO_2 (O_2 consumption)= TaO_2 x ERO_2

ERO_2 (peripheral O_2 extraction)= CaO_2-CvO_2

Increase Q

(Increased systolic ejection volume)

- increased venous return (enhanced venous tonus)
- increased ventricular performance (neuro-adrenergic stimulation)
- reduced left ventricular afterload (by reduction of blood viscosity)

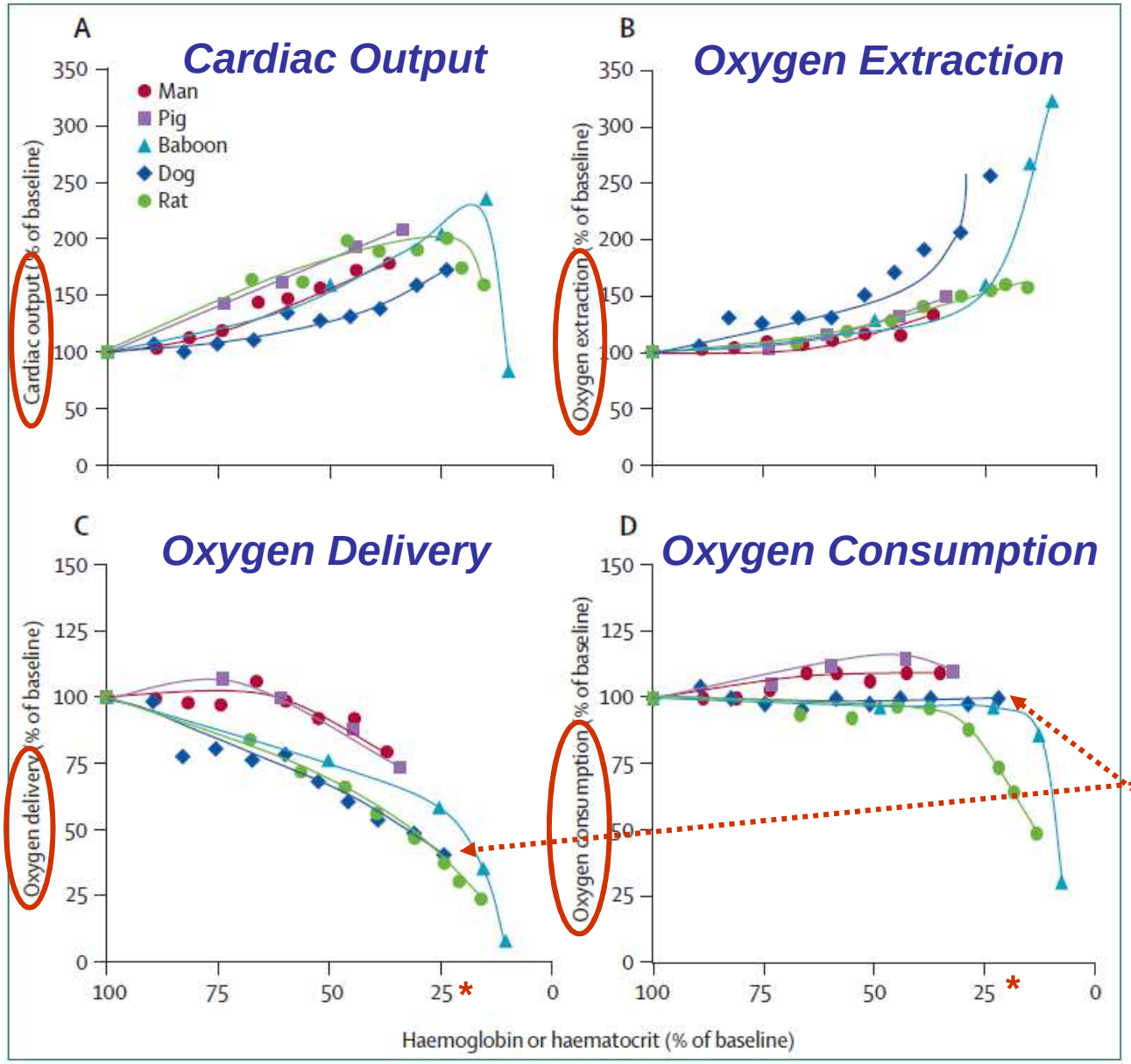
Reposition of volemia: essential to increase Q and tolerate acute anaemia

The decision to perform transfusion should therefore depend on the body's capacity to increase cardiac output

Increase ERO_2

- Redistribution of blood flow from organs with a high ERO2 reserve (kidney, liver) to organs with limited ERO2 reserve (heart, brain). Driven by an increase in neuro-adrenergic stimulation
- Recruitment of capillaries
- Reduction in haemoglobin affinity for oxygen

Changes in cardiac output and oxygen extraction, delivery and consumption with decrease of Hb concentration in humans, pigs, baboons, dogs, and rats



"critical Hb≤ 5 g/dL"

Figure adapted from Klein HG, Spahn DR, & Carson JL. Lancet 2007;370:415.

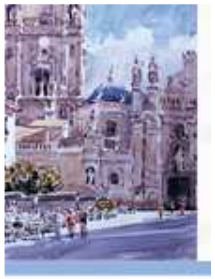
Weiskopf RB et al. jAMA 1998;279:217–21/ van Woerkens EC et al. J Appl Physiol 1992;72:760–69/ Moss GS et al. Surg Gynecol Obstet 1976;142:357–62/ van der Linden P et al. Anesthesiology 2003;99:97–104/ Jamnicki M et al. J Cardiothorac Vasc Anesth 2003;17:747–54.

TRANSFUSION REQUIREMENTS In Gastrointestinal Bleeding

Trial	Comparison	Setting & N	Outcomes
Blair et al *Br J Surg*. 1986;73:783-785	Tf ≥ 2 UPRBC vs No Tf during first 24-h unless Hb <80 (or persistent shock)	N=50 (24 vs 26) Acute G.I. bleeding (no-variceal)	REBLEEDING (Tf vs No): 37% vs 4% (p <0.01) Death (Tf vs No): 8% vs 0 Tf reverse the hypercoagulable response to bleeding (shortened cloting times with bleeding corrected with Tf)
Villarejo et al *Acta Gastroenterol Latinoam 1999;29:261*	Tf if HTc <28% vs Tf if HTc <21%	N=60 (30 vs 30) Final N=27 Acute G.I. bleeding (no-variceal)	Similar rate of organ failure Similar hospital stay No mortality

TRANSFUSION REQUIREMENTS In Gastrointestinal Bleeding

Trial	Comparison	Setting & N	Outcomes
Hearnshaw et al *Aliment Pharmacol & Ther* 2010;32:215	Prospective Observational U.K. Multicenter Early (<12h.) Tf vs No Groups inhomogeneous	N=4441(1974 Tf, 44%) Acute G.I. bleeding (variceal & no-variceal) Endoscopy in all	**Higher rebleeding in Early-Tf** (24% vs 7%) (23% vs 15%, for group with Hb ≤80) (24% vs 7%, for group with Hb >80) Higher after adjustment: OR= 2.26, 95%CI= 1.76-2.90 **Higher Mortality in Early-Tf** (12% vs 5%) Higher mortality adjusted by Rockall (not by Rockall+Hb)
Taha et al *Frontline Gastroenterol* 2011;2:218	Observational Scotland.UK. Single center Tf (<24h.) vs No Tf Groups inhomogeneous	N=1340 (564 Tf, 42%) Acute G.I. bleeding (no-variceal) Endoscopy in all	**Higher 30-d Mortality in Tf** (8% vs 3%) (7% vs 1%, for group with Hb <100) (12% vs 4%, for group with Hb ≥100) Higher mortality with Tf after adjustment for age, Rockall, Charlson & Hb (OR= 1.9, 95%CI= 1.0-1.3) **Higher 2-yr Mortality in Tf** (35% vs 19%) Higher mortality adjusted for age, Rockall, Charlson & Hb (OR= 1.7, 95%CI= 1.3-2.3)
Restellini et al *Aliment Pharmacol & Ther* 2013;37:316	Observational Study Canadian Registry (RUGBE). Multicenter Early (<24h.) Tf vs No Tf Groups inhomogeneous	N=1677 (900 Tf, 54%) Acute G.I. bleeding (no-variceal) Endoscopy in all	**Higher rebleeding in Early-Tf** (23% vs 11%) Higher rebleeding with Tf after adjustment for confounders: OR= 1.8, 95%CI= 1.2-2.8 **Higher Mortality in Early-Tf** (7% vs 4%) No significance after adjustment for confounders: OR= 1.0, 95%CI= 0.6-1.8



DESIGN OF THE STUDY

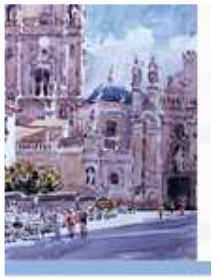
INCLUSION CRITERIA:

- Severe acute G.I. Bleeding
- Age >18ys

EXCLUSION CRITERIA:

- **Massive exsanguinating bleeding**
- **Clinical Rockall score of 0 plus Hb >12 g/dl**
- **Other criteria:**

- declined blood transfusion
- Acute coronary syndrome
- symptomatic peripheral vasculopathy
- stroke and transient ischemic attack
- recent trauma or surgery
- transfusion within the previous 90 days
- lower gastrointestinal bleeding
- refusal to participate in the study
- previous decision to avoid specific medical therapy



DESIGN OF THE STUDY

Severe acute G.I. Bleeding + Age >18ys.
& No-exclusion criteria

↓

Randomization
Immediately after admission
Stratified according to PHT

↙ ↘

Restrictive strategy group
Hb threshold for transfusion of RBC= 7 g/dL
Target: 7-9 g/dL
(N= 444)

Liberal strategy group
Hb threshold for transfusion of RBC= 9 g/dL
Target: 9-11 g/dL
(N= 445)

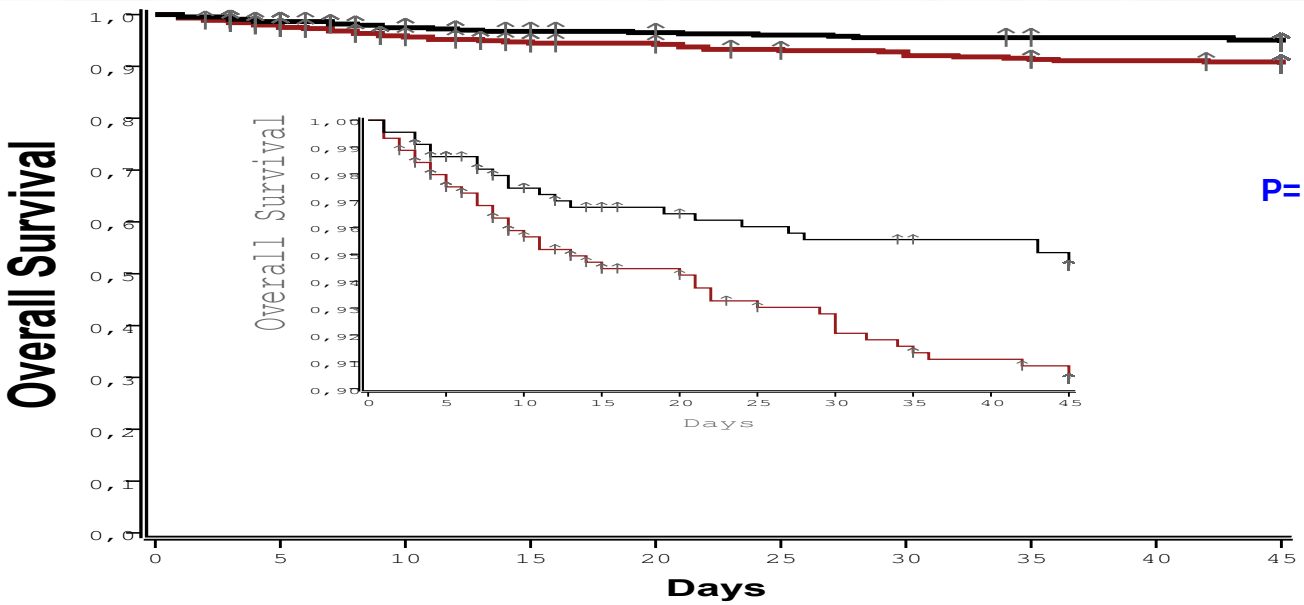
UPRBC transfused one at a time. Hb measured after transfusion to decide further Tf.
Transfusion was allowed at any time when:

* symptoms or signs related with anemia
* massive bleeding
* surgical intervention was required.

Transfusion & Survival in G.I. bleeding

Transfusion in 219 patients (49%) with restrictive strategy vs 384 (86%) with liberal
Mean nº of RBC units of 1.5±1.3 vs 3.7±3.8 (P< 0.001)

SURVIVAL ACCORDING TO TRANSFUSION STRATEGY



Restrictive Strategy

Liberal Strategy

P= 0.02

Restrictive Strategy

Liberal Strategy

Patients at Risk

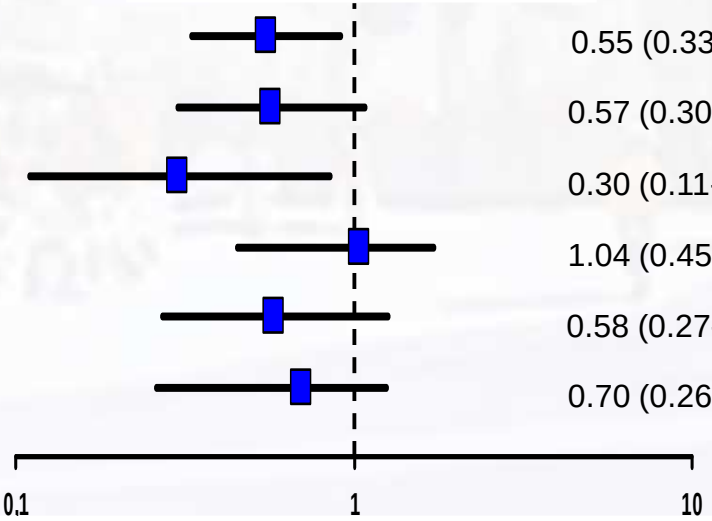
Restrictive Strategy	444	429	412	404	401	399	397	395	394	392
Liberal Strategy	445	428	407	397	393	386	383	378	375	372

Transfusion & Survival in G.I. Bleeding According to Source of Bleeding

Source of bleeding: Peptic ulcer in 437 patients (49%)
Varices in 210 patients (24%) (esophageal in 190 (21%))
277 patients (31%) had cirrhosis

DEATH BY 6-WEEKS ACCORDING TO SUBGROUP

Subgroup	Restrictive Strategy nº of patients / total nº (%)	Liberal Strategy nº of patients / total nº (%)	Hazard Ratio (95% CI)	P value
Overall	23/444 (5)	41/445 (9)	0.55 (0.33-0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30-1.08)	0.08
Child-Pugh class A/B	5/108 (4)	13/109 (12)	0.30 (0.11-0.85)	0.02
Child-Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45-2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (17)	0.58 (0.27-1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26-1.25)	0.26



MORTALITY & Tf STRATEGIES

(RESTRICTIVE VS LIBERAL)

Systematic Review & Meta-analysis

Tf threshold of 7 or 8 g/d vs Higher, results in fewer:

- Patients exposed to blood Tf (RR, 0.61; CI, 0.52-0.72) / (RR, 0.57; CI, 0.46-0.70)
- Units of blood transfused Mean Difference (-1.19; CI, -1.85 to -0.53) / (-1.98; CI, -3.22 to -0.74)

Carson JL, et al. Cochrane Database Syst Rev. 2012;4:CD002042 / Salpeter SR, et al. Am J Med 2014;127:124-1312

* ***2012 Meta-analysis***

19 RCT (6264 patients): variable clinical settings

Tf threshold: Hb 7 or 8 g/dL vs Higher

30-days mortality 7% vs 9% (RR, 0.85; CI, 0.70-1.03)

60-days mortality 11% vs 14% (RR, 0.88; CI, 0.72-1.06)

Carson JL, et al. Cochrane Database Syst Rev. 2012;4:CD002042

* ***2014 Meta-analysis***

3 RCT (2364 patients): ICU patients (adult & pediatric), G.I.bleeding

Tf threshold: Hb 7-g/dL vs 9-10 g/dL

Total mortality 11% *vs* **14%** (RR, 0.80; CI, 0.65-0.98)

-16 RCT (4572 patients): Hb 7.5-10 g/dL vs Higher treshold Tf strategy

Total mortality (RR, 1.03; CI, 0.81-1.31)

Salpeter SR, et al. Am J Med 2014;127:124-1312

TRANSFUSION THRESHOLD IN CARDIOVASCULAR DISEASE

* Higher risk of death with transfusion in patients with cardiovascular disease:
  - myocardial infarction and anemia (Meta-analysis of Observational studies)

Chatterjee S et al. JAMA Intern Med 2013;173:132

  - percutaneous coronary intervention (large cohort study with 31885 death events)

Sherwood MW, et al. JAMA 2014;311:836

* In patients with risk factors for cardiovascular events or with stable disease:
Restrictive Tf as safe as Liberal Tf (after hip surgery)

Carson JL et al. NEJM 2011;365:2453

Restrictive Tf as safe as Liberal Tf (after cardiac surgery)

Hajjar LA, et al. JAMA 2010;304:1559

* RCTs show Higher risk of death with restrictive transfusion than with liberal Tf in patients with acute myocardial infarction:
  2 RCT (N=151 patients); Death 2.7% with liberal Tf vs 11.7% with restrictive Tf)

Cooper HA, et al. Am J Cardiol 2011;108:1108
Carson JL et al. Am Heart J 2013;165:964

TRANSFUSION POLICY IN ACUTE G.I. BLEEDING

Severe acute G.I. Bleeding

↓

HDK & hematologic Assessment
Blood Pressure & Heart Rate
Hemoglobin / Coagulation

↘ ***Hypovolemia***
Cautious Volume Restitution

↙ ***Anemia***

Hb threshold for transfusion of UPRBC

- **General:** ⇢ **trigger: 7 g/dL ⇨ target: 7-9 g/dL**

- **Cardivascular disease**
  Age
  Symptoms
  Ongoing bleeding
  Surgery

⇢ **trigger: 8-9 g/dL ⇨ target: 9-10 g/dL**

* Transfuse Units RBC one at a time. Measure Hb after transfusion to decide further Tf.
* Final decision of transfusion on the basis of the individual patient

XXXV
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