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

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: Unknown (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
- Microchimerism: 1/5-10000
- Posttransfusion purpura
- Metabolic toxicities (hipoCa, hipoK, hipotermia, coagulopathy)
- RBC storage lesion: Unknown
### NONINFECTIOUS COMPLICATIONS OF BLOOD TRANSFUSION

#### Immune-mediated reactions

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#### Non-immune reactions

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<td>Unknown</td>
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<tr>
<td>RBC storage lesion</td>
<td>Unknown</td>
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</table>
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
- Soluble HLA peptides circulating in allogeneic plasma
- Soluble, WBC-derived mediators accumulating in the supernatant fluid of stored RBCs
- Immunologically active, intact allogeneic WBCs

* Increased risk of bacterial infections

* Other:
  - 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)

Susceptible host
Endothelial dysfunction

Vascular NO scavenging by free and microparticle-encapsulated Hb

Enhanced bacterial growth by heme iron
Sepsis

Vasoconstriction
Inflammation

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

INCREASED RISK OF DEATH

Figure adapted from Kalias T & Gladwin M.T. Transfusion 2012;52:1388
# TRANSFUSION REQUIREMENTS

## RESTRICTIVE vs LIBERAL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>Setting &amp; N</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Hébert et al           | 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          | 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           | 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 & RBC units):
- No differences in cardiac event rates
- Lower hospital mortality
- Similar mortality at 14-day, 30 or 60-day follow-up

<table>
<thead>
<tr>
<th>Source</th>
<th>Lower Hemoglobin Threshold</th>
<th>Higher Hemoglobin Threshold</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair, 1986</td>
<td>0</td>
<td>2</td>
<td>0.19 (0.01-3.67)</td>
</tr>
<tr>
<td>Bracey, 1999</td>
<td>3</td>
<td>6</td>
<td>0.52 (0.13-2.04)</td>
</tr>
<tr>
<td>Bush, 1997</td>
<td>4</td>
<td>4</td>
<td>0.98 (0.26-3.70)</td>
</tr>
<tr>
<td>Carson, 1998</td>
<td>1</td>
<td>1</td>
<td>1.00 (0.06-15.47)</td>
</tr>
<tr>
<td>Carson, 2011</td>
<td>43</td>
<td>52</td>
<td>0.83 (0.56-1.22)</td>
</tr>
<tr>
<td>Foss, 2009</td>
<td>5</td>
<td>5</td>
<td>11.00 (0.62-194.63)</td>
</tr>
<tr>
<td>Hajjar, 2010</td>
<td>15</td>
<td>13</td>
<td>1.17 (0.57-2.41)</td>
</tr>
<tr>
<td>Hebert, 1995</td>
<td>8</td>
<td>9</td>
<td>0.97 (0.42-2.22)</td>
</tr>
<tr>
<td>Hebert, 1999</td>
<td>78</td>
<td>420</td>
<td>0.80 (0.61-1.04)</td>
</tr>
<tr>
<td>Lacroix, 2007</td>
<td>14</td>
<td>317</td>
<td>0.99 (0.48-2.04)</td>
</tr>
<tr>
<td>Lotke, 1999</td>
<td>0</td>
<td>62</td>
<td>NA</td>
</tr>
</tbody>
</table>

Overall random effects model
Heterogeneity: $I^2 = 0$
Test for overall effect: $P = .10$

30-days mortality
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 transfusional policy:

**BENEFICIAL**
- Improve anemia

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

Capacity to adapt
QUE NIVEL DE Hb LE PARECE OPTIMO PARA INDICAR TRANSFUSION EN HEMORRAGIA G.I. AGUDA SIN COMORBILIDADD?

a) Hb ≤ 10

b) Hb ≤ 9

c) Hb ≤ 8

d) Hb ≤ 7

e) Hb ≤ 6

http://www.congresomovil.com/resultados-votacion.jsp?id_web=b=1&i=es&id_v=140&id_p=1312&val=1415980304000&presi
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
* Stump DC et al. Transfusion 1985;25:349
* Roberts I et al. Lancet 2001;357:385
FACTORS INFLUENCING PORTAL PRESSURE DURING ACUTE BLEEDING

- Variceal bleeding
- Arterial hypotension
- Portocollateral resistance
- Blood in the gut
- Splanchnic hyperemia
- Over-transfusion
- Volume restitution

References:
- Kravetz. Gastroenterology 1989
- Castañeda. Hepatology 2000
- Chen & Groszmann. Gastroenterology 1996
Effects of Blood Volume Restitution Following Bleeding in Portal Hypertension

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

**Effect on Portal Pressure**

Transfusion (1:3 blood expander) as required to maintain MAP 80 mmHg

**Uncontrolled Bleeding**

Mean arterial pressure (mmHg)

**Survival**

Percent of animals surviving

**References**

Kravetz D et al. HEPATOLOGY 1989;9:808-14/
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 (TaO₂) to the tissues. TaO₂ depends on arterial oxygen concentration (CaO₂) and cardiac output (Q).

\[
\text{CaO}_2 = 1.39 \times [\text{Hb}] \times \text{SaO}_2
\]

\[
\text{TaO}_2 = \text{CaO}_2 \times Q = 1.39 \times [\text{Hb}] \times \text{SaO}_2 \times Q
\]

- ↓ Hb
  - Consider transfusion UPRC

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

- ↓ SaO₂
  changes in ventilatory function and gas exchange.
**TaO\textsubscript{2}**

Increase Q

- 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\textsubscript{2}

- Redistribution of blood flow from organs with a high ERO\textsubscript{2} reserve (kidney, liver) to organs with limited ERO\textsubscript{2} reserve (heart, brain). Driven by an increase in neuro-adrenergic stimulation
- Recruitment of capillaries
- Reduction in haemoglobin affinity for oxygen

\[
\text{VO}_2 \text{ (O}_2\text{ consumption)} = \text{TaO}_2 \times \text{ERO}_2 \\
\text{ERO}_2 \text{ (peripheral O}_2\text{ extraction)} = \text{CaO}_2 - \text{CvO}_2
\]

\[
\text{TaO}_2 = \text{CaO}_2 \times Q
\]

\[
\text{CaO}_2 = 1.39 \times [\text{Hb}] \times \text{SaO}_2
\]
Changes in cardiac output and oxygen extraction, delivery and consumption with decrease of Hb concentration in humans, pigs, baboons, dogs, and rats

# TRANSFUSION REQUIREMENTS In Gastrointestinal Bleeding

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<tr>
<td>Blair et al</td>
<td>Tf ≥ 2 UPRBC vs No Tf during first 24-h unless Hb &lt;80 (or persistent shock)</td>
<td>N=50 (24 vs 26) Acute G.I. bleeding (no-variceal)</td>
<td>REBLEEDING (Tf vs No): 37% vs 4% (p &lt;0.01) Death (Tf vs No): 8% vs 0 Tf reverse the hypercoagulable response to bleeding (shortened clotting times with bleeding corrected with Tf)</td>
</tr>
<tr>
<td>Villarejo et al</td>
<td>Tf if HTc &lt;28% vs Tf if HTc &lt;21%</td>
<td>N=60 (30 vs 30) Final N=27 Acute G.I. bleeding (no-variceal)</td>
<td>Similar rate of organ failure Similar hospital stay No mortality</td>
</tr>
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Tf: Transferrin
UPRBC: Unit of Packed Red Blood Cells
# TRANSFUSION REQUIREMENTS
## In Gastrointestinal Bleeding

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<th><strong>Outcomes</strong></th>
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| Hearnshaw et al  
*Aliment Pharmacol & Ther*  
2010;32:215 | Prospective Observational U.K. Multicenter Early (<12h.) Tf vs No Tf | 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 |
| Taha et al  
*Frontline Gastroenterol*  
2011;2:218 | Observational Scotland.UK. Single center Tf (<24h.) vs No Tf | N=1340 (564 Tf, 42%) 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 |
| Restellini et al  
*Aliment Pharmacol & Ther*  
2013;37:316 | Observational Study Canadian Registry (RUGBE). Multicenter Early (<24h.) Tf vs No Tf | N=1677 (900 Tf, 54%) Acute G.I. bleeding (no-variceal) Endoscopy in all | Higher mortality in Early-Tf (12% vs 5%) Higher mortality adjusted by Rockall (not by Rockall+Hb) |
| | | | 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) |

**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
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
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 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

Patients at Risk

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<thead>
<tr>
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<th>Liberal Strategy</th>
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<tr>
<td></td>
<td>444</td>
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<td>375</td>
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<td>392</td>
<td>372</td>
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## 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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Restrictive Strategy n° of patients / total n° (%)</th>
<th>Liberal Strategy n° of patients / total n° (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>23/444 (5)</td>
<td>41/445 (9)</td>
<td>0.55 (0.33-0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients with cirrhosis</td>
<td>15/139 (11)</td>
<td>25/138 (18)</td>
<td>0.57 (0.30-1.08)</td>
<td>0.08</td>
</tr>
<tr>
<td>Child-Pugh class A/B</td>
<td>5/108 (4)</td>
<td>13/109 (12)</td>
<td>0.30 (0.11-0.85)</td>
<td>0.02</td>
</tr>
<tr>
<td>Child-Pugh class C</td>
<td>10/26 (38)</td>
<td>12/29 (41)</td>
<td>1.04 (0.45-2.37)</td>
<td>0.91</td>
</tr>
<tr>
<td>Bleeding from varices</td>
<td>10/93 (11)</td>
<td>17/97 (17)</td>
<td>0.58 (0.27-1.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>Bleeding from peptic ulcer</td>
<td>7/228 (3)</td>
<td>11/209 (5)</td>
<td>0.70 (0.26-1.25)</td>
<td>0.26</td>
</tr>
</tbody>
</table>
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)


* 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)


* 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)

* Higher risk of death with transfusion in patients with cardiovascular disease:
  - myocardial infarction and anemia (Meta-analysis of Observational studies)
  - percutaneous coronary intervention (large cohort study with 31,885 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)
  Carson JL et al. Am Heart J 2013;165:964
**Severe acute G.I. Bleeding**

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

**Anemia**
- **Hb threshold for transfusion of UPRBC**
  - **General:**
    - *trigger:* 7 g/dL  \(\Rightarrow\) *target:* 7-9 g/dL
  - **Cardiovascular disease**
    - **Age**
    - **Symptoms**
    - **Ongoing bleeding**
    - **Surgery**
      - *trigger:* 8-9 g/dL  \(\Rightarrow\) *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.
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