

Blood and Blood Product Use in Trauma Surgery

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Blood Products: Objectives



1. Outline the clinical benefits of transfusion of packed red blood cells, fresh frozen plasma, and platelets
2. Define the potential complications of transfusion of packed red cells, fresh frozen plasma, and platelets
3. List the currently accepted transfusion triggers for packed red cells, fresh frozen plasma, and platelets
4. Understand the mechanisms of action of activated factor VII and activated Protein C
5. Delineate the appropriate clinical uses for activated factor VII and activated Protein C

Blood Products: Summary




Transfusion of packed red blood cells

Transfusion of fresh frozen plasma

Transfusion of platelets

Use of activated factor VII

Use of activated Protein C

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Blood Products: PRBCs



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Blood Products: PRBCs



- Benefits & Side Effects
- Database Studies
- Prospective Studies
- Conclusions

Blood Products: PRBCs



Benefits

- Volume
- O₂ Capacity
- Clotting factors
- Platelets


Adverse Effects

- Transfusion reaction
- Infection
 - Bacterial
 - Viral: HBV, HCV, HIV
- TRALI
- Other

Blood Products: PRBCs



Database Studies

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Blood Products: PRBCs



Blood transfusion: an independent risk factor for postinjury multiple organ failure

- 513 trauma patients
- ISS > 15
- Dose-response relationship between blood transfusion and development of MOF
- **Age of PRBCs**

Moore, *et al.* 1997 Arch Surg 132: 620

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Blood transfusion, independent of shock severity, is associated with worse outcome in trauma

- Shock Trauma, Maryland
- 15,534 patients 1998-2000
- Blood transfusion strong predictor of mortality

Malone, *et al.* 2003 J Trauma 54(5): 898

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Database predictors of transfusion and mortality

- 3 databases: Germany, Miami, Maryland
- Volume of transfusion associated with
 - Mortality and time to death
 - LOS hospital and ICU
 - Results remarkably consistent

Dutton, *et al.* 2006 J Trauma 60(6 Suppl): S70

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Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients

- 277 burn kids > 30% TBSA burn
- > 60% TBSA w/ II
 - Low RBC group; 8% risk of sepsis
 - High RBC group: 58% risk of sepsis

Jeschke, *et al.* 2007 Crit Care Med 35(2): 579

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Effect of blood transfusions on outcome after major burn injury: a multicenter study

- 21 burn centers, 666 patients
- Survivors received a mean of 14 U PRBCs
- Number of transfusions related to:
 - Mortality
 - Infectious complications

Palmieri, *et al.* 2006 Crit Care Med 34(6): 1602


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Blood Products: PRBCs



What is/are the mechanism(s) of the deleterious actions of transfused PRBCs?

- Decreased RBC deformability
- Increased inflammatory response
- Increased free hemoglobin
- Immunosuppression
- **OLD BLOOD**

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Database Studies: Summary


- Dozens in the literature
- Very consistent
- Strong association between transfusion and mortality
- Retrospective
- Cannot draw conclusions re: causation

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Prospective Studies

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Blood Products: PRBCs



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

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CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., Ph.D., IRWIN SCHWEITZER, M.Sc.,
ELIZABETH YETTSIRI, M.Sc., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS
FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

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Blood Products: Hebert



- 25 ICU's in Canada
- 838 patients
- Within 72 hours of admission
- Euvolemic with Hg of ≤ 9.0
- Two strategies
 - Restrictive: Hg 7-9 with 7 as trigger
 - Liberal: Hg 10-12 with 10 as trigger

Hebert, *et al.* 1999 NEJM 340(6): 409

Blood Products: Hebert



TABLE 2. OUTCOMES.*

OUTCOME MEASURE	RESTRICTIVE-TRANSFUSION STRATEGY (N=418)	LIBERAL-TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL	P VALUE
percent					
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	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					
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

Hebert, *et al.* 1999 NEJM 340(6): 409

Blood Products: Hebert



- Decreased transfusion by 54%
- 33% patients received no transfusions
- Cardiac events were less in restrictive group
- **No difference in mortality between restrictive and liberal strategy for patients with coronary artery disease**

Hebert, *et al.* 1999 NEJM 340(6): 409

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Blood Products: Hebert



- Groups with lower mortality with restrictive strategy
 - Younger patients (< 55)
 - Patients with APACHE scores < 20
- Groups with equivalent mortality
 - Older patients (> 55)
 - Patients with APACHE scores > 20

Hebert, *et al.* 1999 NEJM 340(6): 409

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Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients?

- 100/103 patients
- Hg 8.2 vs 10.4
- Transfusion 2.3 units vs 4.3 units
- **NO DIFFERENCE IN OUTCOME MEASURES**

McIntyre, Hebert, *et al.* 2004 J Trauma 57(3): 563

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Blood Products: PRBCs



Anemia management program reduces transfusion volumes, incidence of ventilator associated pneumonia, and cost in trauma patients

- Restrictive and liberal strategies, non-randomized
- Trigger in restrictive strategy : Hg of 7
- Mean transfusion 23.1 vs 17.1 U PRBCS (22.5%)
- **VAP: 8.1% vs 0.8 %**
- **COST: \$503,000 vs \$397,000**
- **NO DIFFERENCE IN OTHER OUTCOMES**

Early, *et al.* 2004 J Trauma 61(1): 1

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Blood Products: PRBCs



Evidence based red cell transfusion in the critically ill: Quality improvement using computerized physician order entry

- Restrictive and “no” strategies, non-randomized
- Trigger in restrictive strategy : Hg of 7
- Mean transfusion 1.08 vs 0.86 U PRBCS
- Reduced inappropriate transfusions 17.7% to 4.5%
- Reduced transfusion complications
- **NO DIFFERENCE IN MORTALITY**

Rana, *et al.* 2006 Crit Care Med 34(7): 1892

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Blood Products: Conclusions



Increased O₂ carrying capacity as a result of RBC transfusion is questionable

There are many mechanisms by which RBC transfusions adversely affect patients

Retrospective studies demonstrate a consistent and strong association between transfusion and poor outcome

Prospective studies do not support this association

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Blood Products: Conclusions



The “10/30” rule for RBC transfusion is likely obsolete

The trigger of 7 is as safe as the trigger of 10 for most patient populations

The trigger of 10 does not seem to be more harmful than 7 *in trauma and/or sick patients*

Much research into the pathophysiology of transfusion remains to be performed

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Blood Products: FFP



The use of FFP in massive transfusion

Transfusion-related acute lung injury (TRALI)

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Blood Products: FFP



Fresh frozen plasma should be given to patients requiring massive transfusion

- Database review
- 97 patients requiring massive transfusion
- Coagulopathy present at admission, persisted during ICU stay. INR 1.8 to 1.6 to 1.4
- Coagulopathy associated with mortality
- Give FFP in 1:1 ratio with blood

Gonzalez,, *et al.* 2007 J Trauma 62(1): 112

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Blood Products: TRALI



- Acute respiratory insufficiency following transfusion of blood products
 - Common with FFP, platelet use
 - Most common with whole blood?
- Hypoxemia, hypotension, tachycardia, fever
- HLA + donor antibodies; 2-hit hypothesis
- Dx is by exclusion; send blood to lab
- Treatment is supportive
- #1 cause of transfusion related mortality

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Blood Products: Platelets



Indications for Early Fresh Frozen Plasma, Cryoprecipitate, and Platelet Transfusion in Trauma

- Platelets may be depleted early in acute injury
- Likely contributes to coagulopathy
- Minimum platelet count in trauma patients: 50,000
- Begin platelet transfusions early in massive resuscitation
- Ratio of 0.8 U platelets to 1 U PRBC

Ketchum, *et al.* 2006 J Trauma 60(6): S51

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Platelets and FFP: Summary



- Platelets and clotting factors are depleted early in severe traumatic injury
- This contributes to coagulopathy seen in trauma patients, and potentiates the lethal triad of acidosis, hypothermia, and coagulopathy
- This possibly contributes to early and late mortality in trauma patients
- Platelets and clotting factors should be repleted aggressively and early in injured patients
- **1:1 Ratio**

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Blood Products: Factor VII



- rFVIIa approved for hemophilia patients
- Binds to exposed tissue factor (TF)
- Active only in presence of TF
- Activates the extrinsic clotting pathway
- Does not cause systemic hypercoagulability
- Rapid onset; short duration of action
- May bind to platelets and activate FX on platelet surface

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Blood Products: Factor VII



- Six animal trials demonstrate efficacy and safety
- Multiple case reports and case series in the USA
- Ongoing clinical trial in the US
 - Prospective, randomized, blinded
 - High dose, ? thrombotic complications
- Military Use

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Blood Products: Factor VII



Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

- Drug (200,100,100 ug/kg) vs placebo p 8th U RBC
- 301 patients: blunt 143, penetrating 134
- Blunt trauma group
 - Transfusion reduced 2.6 U PRBC
 - Massive transfusion reduced 33% to 14%

Boffard, *et al.* 2005 J Trauma 59(1): 8

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Blood Products: Factor VII



Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

- Penetrating trauma group
 - Similar trends
 - Not statistically significant
- Trend toward decreased mortality
- Adverse events equivalent
- **NO INCREASE IN THROMBOEMBOLIC EVENTS**

Boffard, *et al.* 2005 J Trauma 59(1): 8

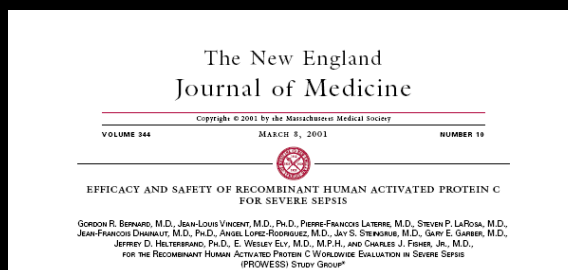
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Blood Products: Factor VII



- Efficacy in trauma patients demonstrated
- Patient selection remains an issue
- Timing and dosing also remain issues
- Thromboembolic complications are concerning
- Results from the ongoing clinical trial will be helpful


Blood Products: Xigris



Blood Products: Xigris



- Natural anticoagulant
- Vitamin K dependent
- Activated by thrombin
- Destroys Va and VIIIa
- Limits clot by facilitating fibrinolysis
- Deficiency leads to hypercoaguability

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Blood Products: Xigris



- Inflammation→activated protein C
- Decreases thrombin
- Inhibits cytokine production
 - TNF, IL-1, IL-6
- Inhibits binding and rolling of PMN's
 - Binds selectins
- Decreased levels in septic patients

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Blood Products: Xigris



- Randomized, double-blind, placebo-controlled, multicenter trial
- Septic patients: APC vs placebo
 - ≥ 3 signs of systemic inflammation
 - ≥ 1 organ or system dysfunction < 24 h
- Outcome: death

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Blood Products: Xigris



- 1690 patients
- Mortality
 - APC: 24.7%
 - Placebo: 30.8%
- Bleeding complications
 - APC: 3.5%
 - Placebo: 2.0%

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Blood Products: Xigris




THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death


Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Brückmann, M.D., Alvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*

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Blood Products: Xigris




- 2613 patients
- Same protocol except low risk of death
 - APACHE < 25
 - Single organ failure
- No difference in outcome
- Study terminated early

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Blood Products: Xigris



- Careful patient selection
- Bleeding
 - Should not use during surgery
 - Can't use in kids, pregnant women
- Expensive
- Use in trauma remains to be defined

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Blood Products: Conclusions




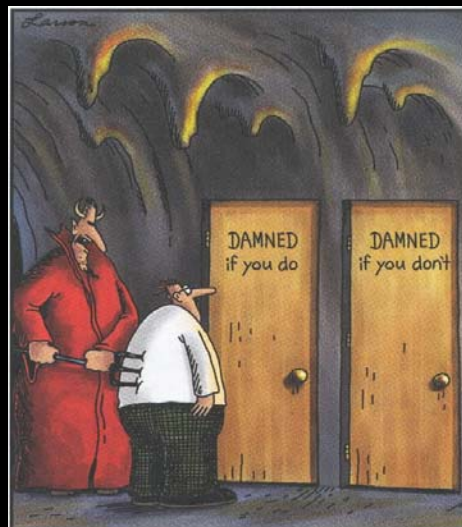
- A transfusion trigger of 7 appears to be safe for stable trauma patients
- FFP and platelets should be given early and aggressively in trauma patients
- aFVII demonstrates efficacy in reducing transfusion in trauma patients
- Activated Protein C use in trauma patients remains to be elucidated

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"C'mon, c'mon—it's either one or the other."