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*How do I treat massive bleeding?*

# Red blood cell / plasma / platelet ratio and massive transfusion protocols

**Anne GODIER**
**Service d'Anesthésie-Réanimation**
**Hopital Cochin**
**Paris**

Groupe d'Intérêt en Hémostase Périopératoire

# Conflicts of interest

- LFB
- Octapharma
- CSL-Behring
- Bayer
- BMS-Pfizer
- Boehringer-Ingelheim
- Léo
- Sanofi

# Acknowledgement

- Pr Sophie Susen (Lille)

# 1:1:1 ratio



Increased Platelet:RBC Ratios Are Associated With Improved Survival After Massive Transfusion

*John B. Holcomb, MD, FACS, Lee A. Zarzabal, MS, Joel E. Michalek, PhD, Rosemary A. Kozar, MD, PhD, Phillip C. Spinella, MD, FCCM, Jeremy G. Perkins, MD, Nena Matijevic, PhD, Jing-Fei Dong, MD, PhD, Shibani Pati, MD, PhD, Charles E. Wade, PhD, and the Trauma Outcomes Group*

*J Trauma.* 2011;71: S318–S328

**Plasma/platelets/red blood cell ratio in the management of the bleeding traumatized patient: does it matter?**

*Anne Godier[a], Charles-Marc Samama[a], and Sophie Susen[b,c]*

**Curr Opin Anesthesiol** 2012, 25:242–247

High Ratios of Plasma and Platelets to Packed Red Blood Cells Do Not Affect Mortality in Nonmassively Transfused Patients

*Chitra N. Sambasivan, MD, Nicholas R. Kunio, MD, Prakash V. Nair, MS, Karen A. Zink, MD, Joel E. Michalek, PhD, John B. Holcomb, MD, Martin A. Schreiber, MD, and the Trauma Outcomes Group*

*J Trauma.* 2011;71: S329–S336



Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

*John B. Holcomb, MD,* Charles E. Wade, PhD,* Joel E. Michalek, PhD,† Gary B. Chisholm, PhD,† Lee Ann Zarzabal, MS,† Martin A. Schreiber, MD,‡ Ernest A. Gonzalez, MD,§ Gregory J. Pomper, MD,¶ Jeremy G. Perkins, MD,‖ Phillip C. Spinella, MD,** Kari L. Williams, RN,* and Myung S. Park, MD**

*Ann Surg* 2008;248: 447–458

Effect of High Product Ratio Massive Transfusion on Mortality in Blunt and Penetrating Trauma Patients

*Susan E. Rowell, MD, Ronald R. Barbosa, MD, Brian S. Diggs, PhD, Martin A. Schreiber, MD, and the Trauma Outcomes Group*

*J Trauma.* 2011;71: S353–S357

# Massive bleeding

Severe trauma
Post-partum haemorrhage
Major surgery (cardiac & aortic surgery)
Gastrointestinal bleeding
Liver transplantation

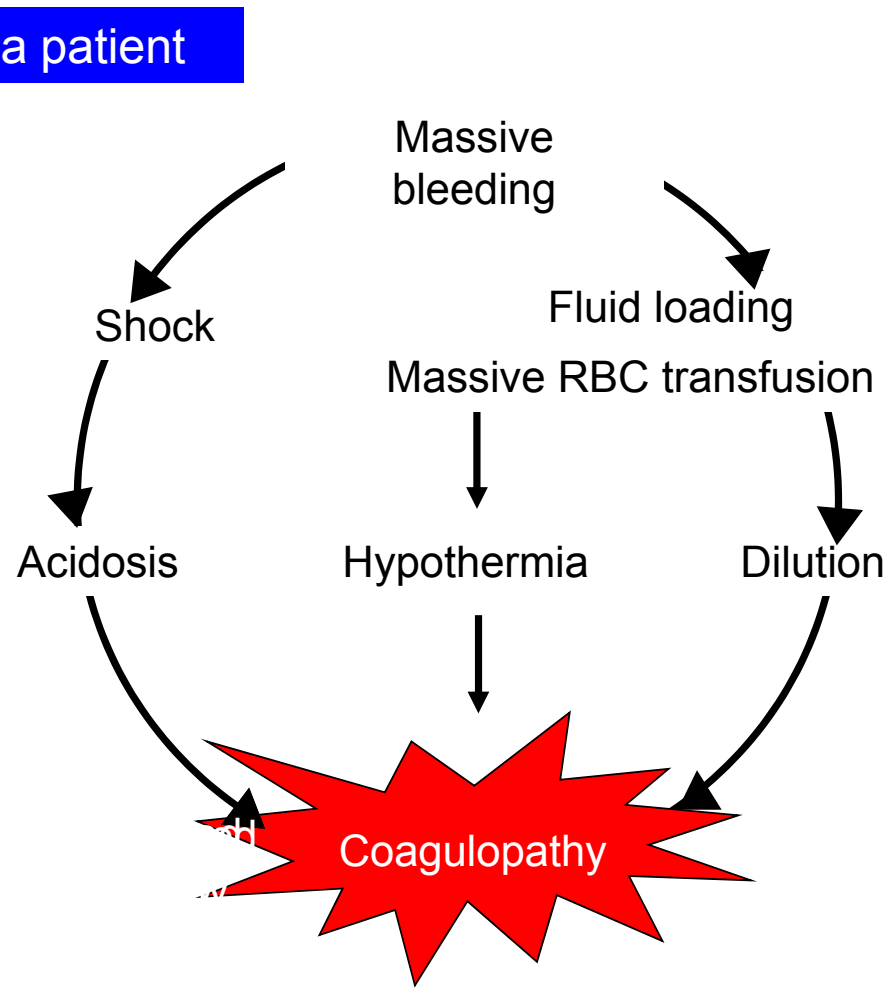
↓

Massive transfusion

↓

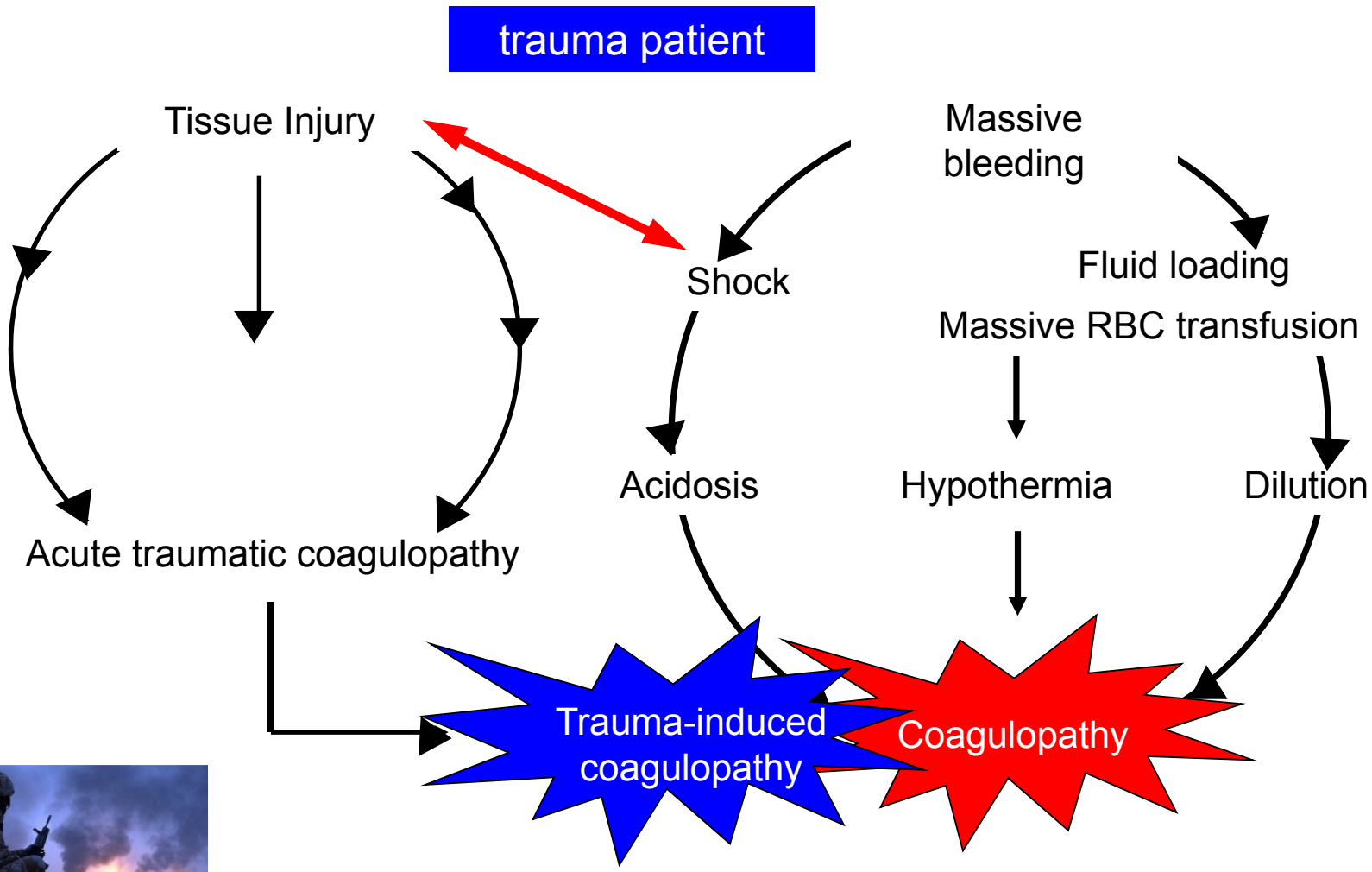
Coagulopathy → Mortality

# Trauma-induced coagulopathy




Adapted from Brohi K, *Ann Surg* 2007*

# Trauma-induced coagulopathy

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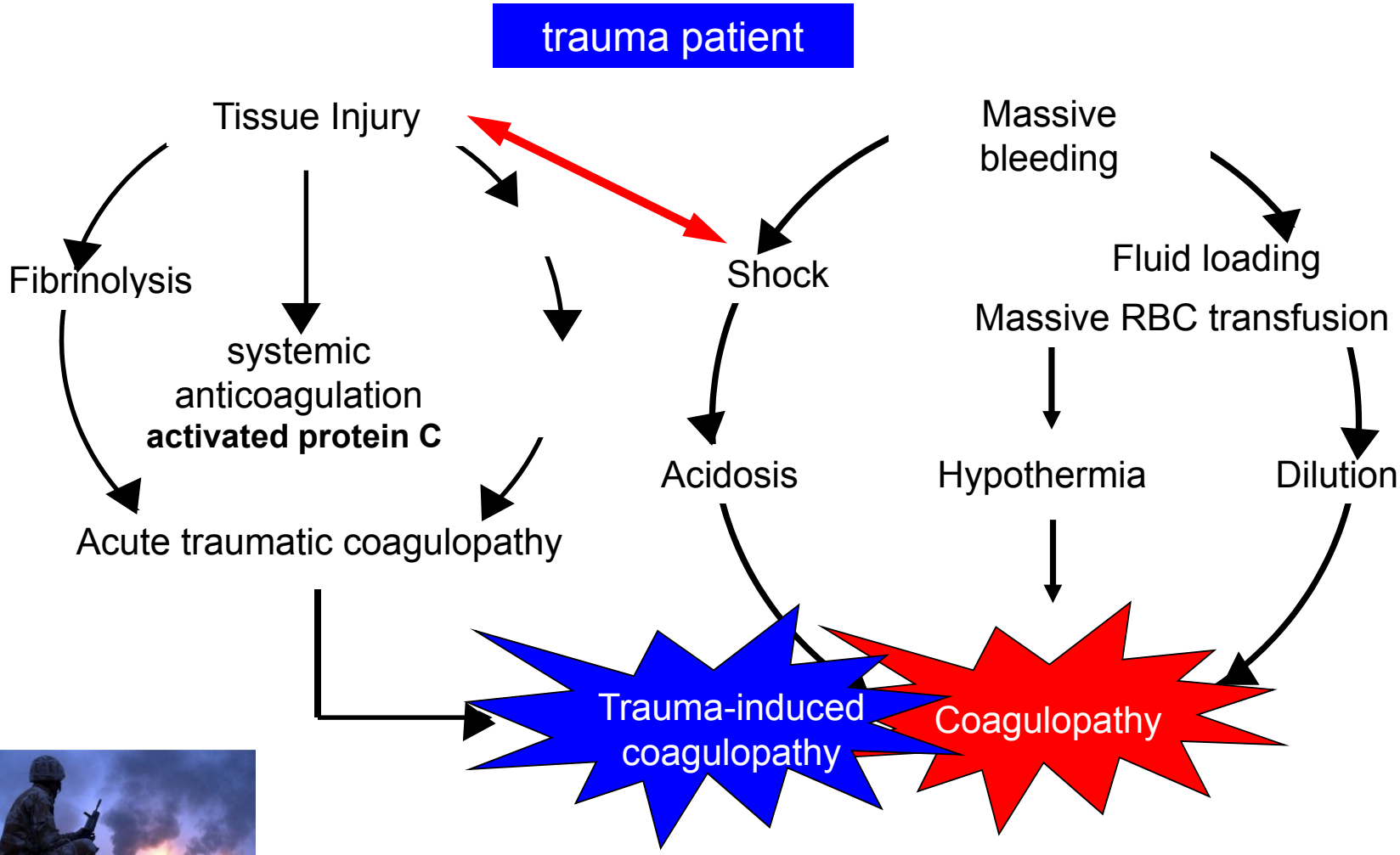
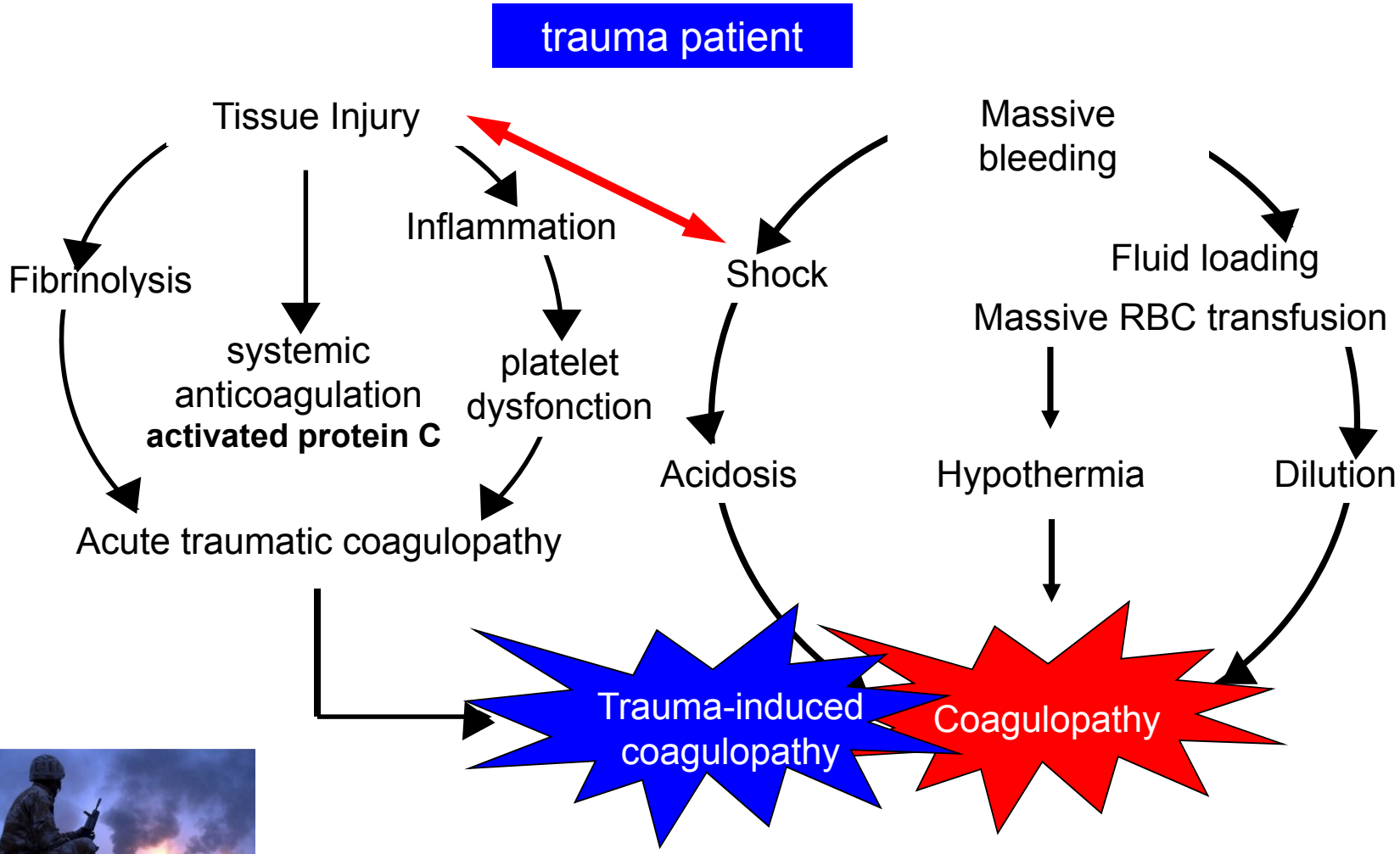



Adapted from Brohi K, *Ann Surg* 2007*

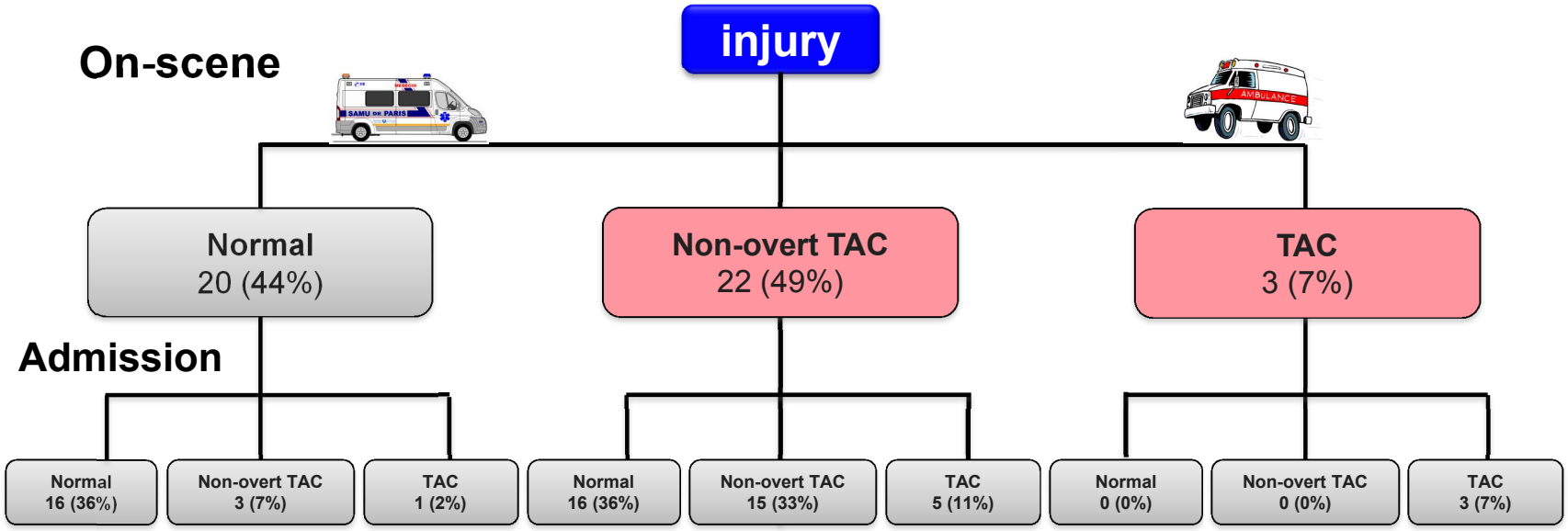
# Trauma-induced coagulopathy




Adapted from Brohi K, *Ann Surg* 2007*

# Early onset of coagulopathy in trauma

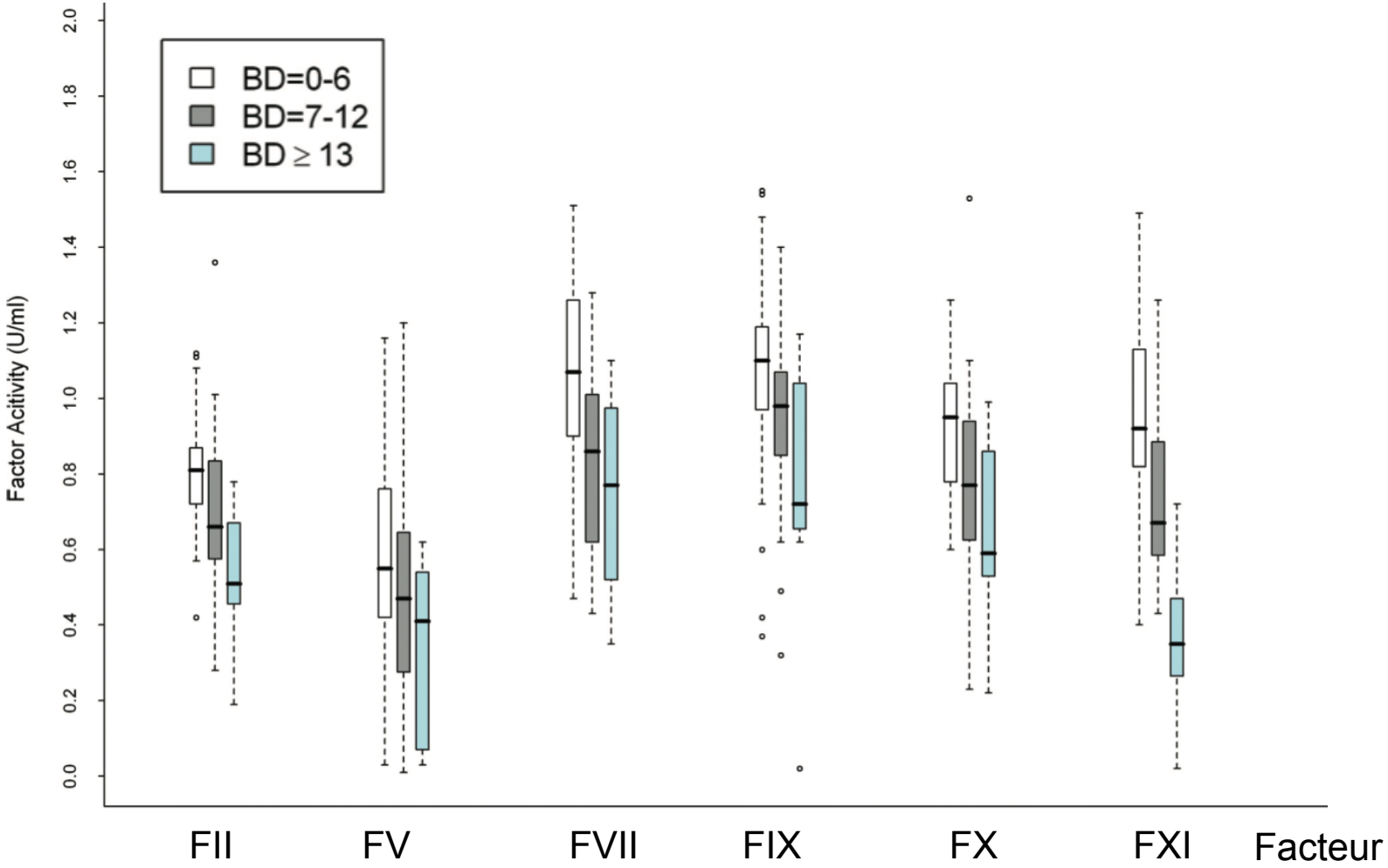
- On-scene: TAC = trauma-associated coagulopathy




On-scene and trauma resuscitation room coagulation status

Floccard B, *et al. Injury* 2012;43:26–32

# Reduced Coagulation Factor Activity




Severe trauma patients

Jansen JO, J Trauma 2011

bjh research paper

# Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients

Pratima Chowdhury,[1] Anton G. Saayman, Ulrike Paulus,[1] George P. Findlay[2] and Peter W. Collins[1]
*Departments of [1]Haematology and [2]Intensive Care Medicine, University Hospital of Wales an University of Wales College of Medicine, Heath Park, Cardiff, UK*
 *British Journa of Haematology*, **125**, 69–73

| | 10-15 mL/kg | 30 mL/kg |
|---|---|---|
| Fibrinogène g/L | +0.4 | +1.0 |
| II % | +16 | +41 |
| V % | +10 | +28 |
| VII % | +11 | +38 |
| IX % | +8 | +28 |
| X % | +15 | +37 |
| XI % | +9 | +23 |
| XII % | +30 | +44 |

Br J Haematol 2004;125:69-73

bjh research paper

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Br J Haematol 2004;125:69-73

# Plasma


- coagulation factors
- fibrinogen
  - 1 FFP = 400 mg of fibrinogen
- proteins, including immunoglobulins and albumin
- volume expansion with high oncotic pressure
- Preclinical studies
  - less pro-inflammatory than artificial colloids
  - protective effects on endothelial permeability and vascular stability

Pati S. J Trauma 2010; 69 Suppl 1:S55-63.

# Increasing plasma:RBC ratio

- Transfusion with high ratio

- Ratio = plasma number / RBC number

The Journal of TRAUMA® Injury, Infection, and Critical Care

# The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

J Trauma. 2007;63:805–813.

*Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD*

246 trauma patients with massive transfusion (>10 RBC) → FFP:RBC → 1:1.4 / 1:2.5 / 1:8 → mortality

The Journal of TRAUMA® Injury, Infection, and Critical Care

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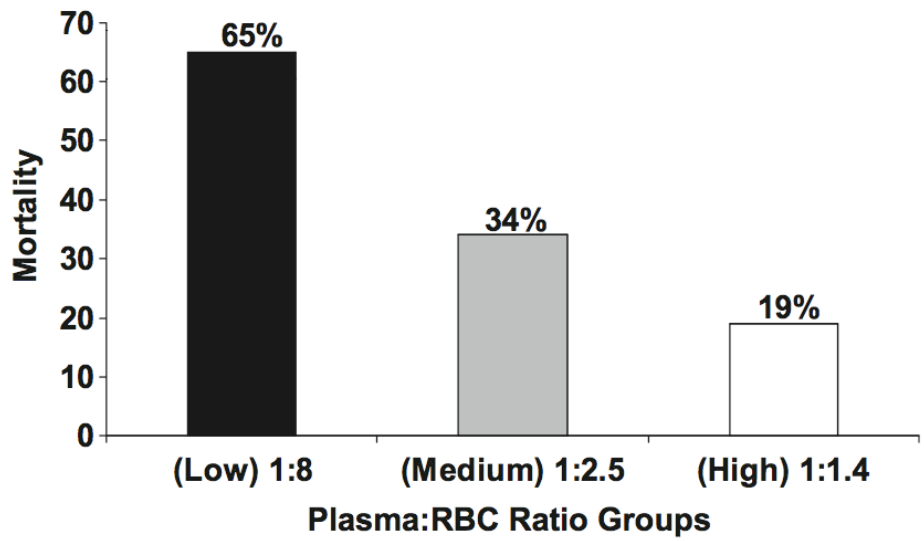



**Fig. 1.** *Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.*

# Military trauma studies: beneficial effect of high FFP:RBC ratio


*The Journal of* **TRAUMA**® *Injury, Infection, and Critical Care*

## An FFP:PRBC Transfusion Ratio ≥1:1.5 Is Associated With A Lower Risk Of Mortality After Massive Transfusion

*Jason L. Sperry, MD, MPH, Juan B. Ochoa, MD, Scott R. Gunn, MD, Louis H. Alarcon, MD, Joseph P. Minei, MD, Joseph Cuschieri, MD, Matthew R. Rosengart, MD, MPH, Ronald V. Maier, MD, Timothy R. Billiar, MD, Andrew B. Peitzman, MD, Ernest E. Moore, MD, and The Inflammation the Host Response to Injury Investigators*

*J Trauma.* 2008;65:986–993.

*The Journal of* **TRAUMA**® *Injury, Infection, and Critical Care*

## Damage Control Resuscitation for Vascular Surgery in a Combat Support Hospital

*Charles J. Fox, MD, David L. Gillespie, MD, E. Darrin Cox, MD, John F. Kragh, Jr., MD, Sumeru G. Mehta, MD, Jose Salinas, PhD, and John B. Holcomb, MD*

*J Trauma.* 2008;65:1–9.

*The Journal of* **TRAUMA**® *Injury, Infection, and Critical Care*

## Effect of Plasma and Red Blood Cell Transfusions on Survival in Patients With Combat Related Traumatic Injuries

*Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Alec C. Beekley, MD, Sarah E. Niles, MD, MPH, Daniel F. McLaughlin, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC*

*J Trauma.* 2008;64:S69–S78.

**military** ⟷ **civilian trauma studies**

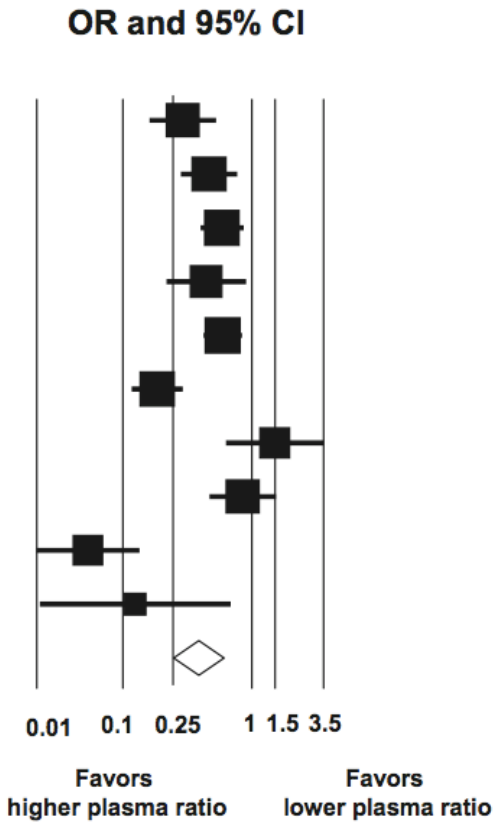
# The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis

*Mohammad Hassan Murad, James R. Stubbs, Manish J. Gandhi, Amy T. Wang, Anu Paul, Patricia J. Erwin, Victor M. Montori, and John D. Roback*

**TRANSFUSION** 2010.

**Mortality in patients undergoing massive transfusion**
n=3400

| | OR | Lower limit | Upper limit | Events / Total Plasma | Events / Total Control |
|---|---|---|---|---|---|
| Borgman, 2007 | 0.29 | 0.16 | 0.51 | 31 / 162 | 38 / 84 |
| Cotton, 2009 | 0.46 | 0.28 | 0.75 | 54 / 125 | 88 / 141 |
| Holcomb, 2008 | 0.58 | 0.40 | 0.84 | 87 / 252 | 102 / 214 |
| Kashuk, 2008 | 0.44 | 0.22 | 0.88 | 23 / 59 | 44 / 74 |
| Maegele, 2008 | 0.59 | 0.42 | 0.81 | 76 / 229 | 222 / 484 |
| Teixeira, 2009 | 0.18 | 0.12 | 0.28 | 58 / 226 | 103 / 157 |
| Scalea, 2008 | 1.49 | 0.63 | 3.53 | | |
| Snyder, 2009 | 0.84 | 0.47 | 1.50 | | |
| Duchesne, 2008 | 0.05 | 0.02 | 0.13 | 19 / 71 | 56 / 64 |
| Dente, 2009 | 0.12 | 0.02 | 0.67 | 7 / 50 | 4 / 7 |
| | **0.38** | **0.24** | **0.60** | | |




**Heterogeneity : p=0.01; $I^2$=85%**
**Quality of evidence: Very low ⊕OOO**

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# Limitations

- retrospective studies (or cohort studies)
- missing data
- analytical bias
- survival bias

RESEARCH Open Access

# Management of bleeding following major trauma: an updated European guideline

CRITICAL CARE
april 2013

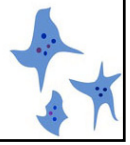
Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R.

*Recommendation 26*

**We recommend the initial administration of plasma [fresh frozen plasma (FFP) or pathogen-inactivated plasma] (Grade 1B) or fibrinogen (Grade 1C) in patients with massive bleeding.**

**If further plasma is administered, we suggest an optimal plasma:red blood cell ratio of at least 1:2. (Grade 2C)**

# Platelet : RBC ratio?

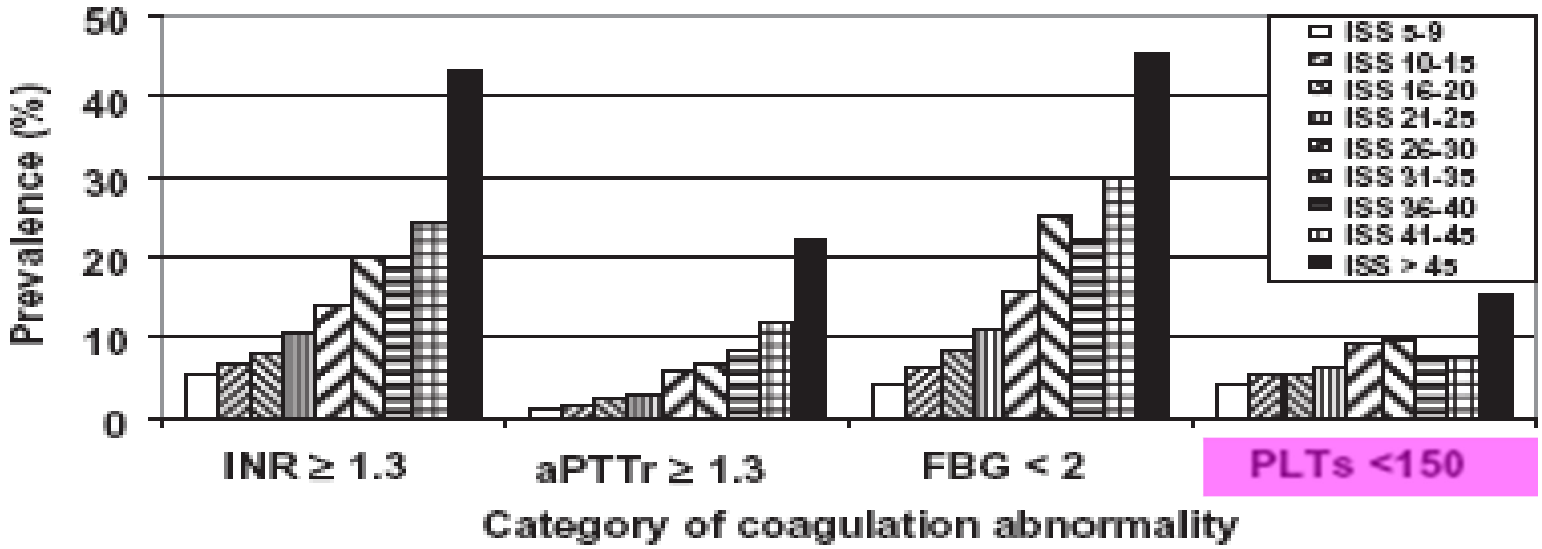


# The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center

*Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM.Transfusion. 2009;49:34-9*

Records of all patients admitted to a large urban trauma center during 2000 through 2006

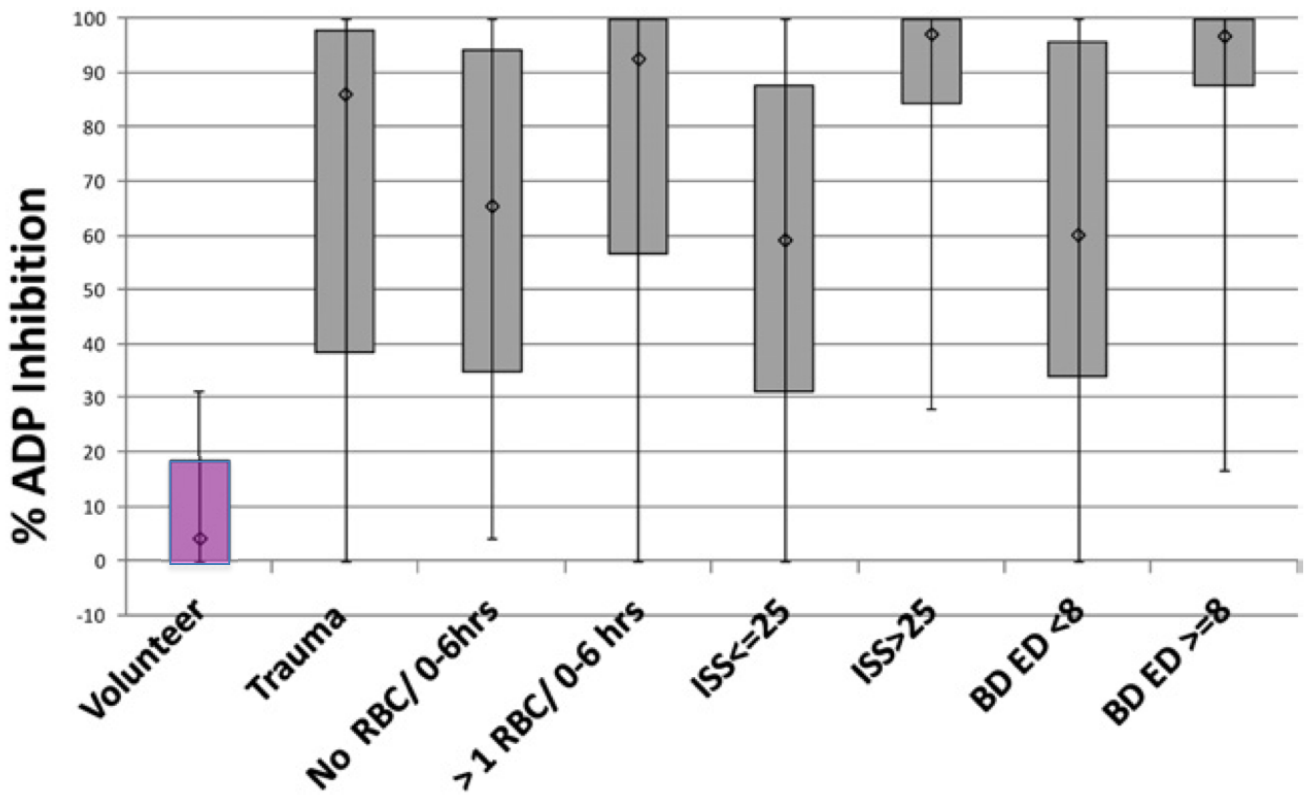
N=23 000



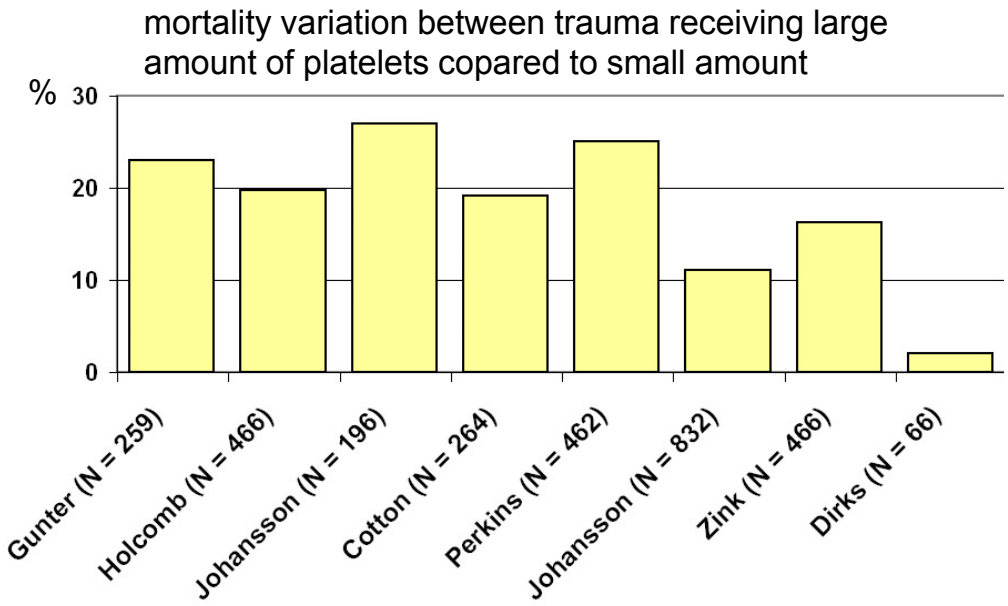
# Early Platelet Dysfunction: An Unrecognized Role in the Acute Coagulopathy of Trauma

*J Am Coll Surg*
2012;214:739–746

Max V Wohlauer, MD, Ernest E Moore, MD, FACS, Scott Thomas, MD, FACS, Angela Sauaia, MD, PhD, Ed Evans, BA, CCP, Jeffrey Harr, MD, MPH, Christopher C Silliman, MD, PhD, Victoria Ploplis, PhD, Francis J Castellino, PhD, Mark Walsh, MD



# Retrospective data regarding platelet transfusion



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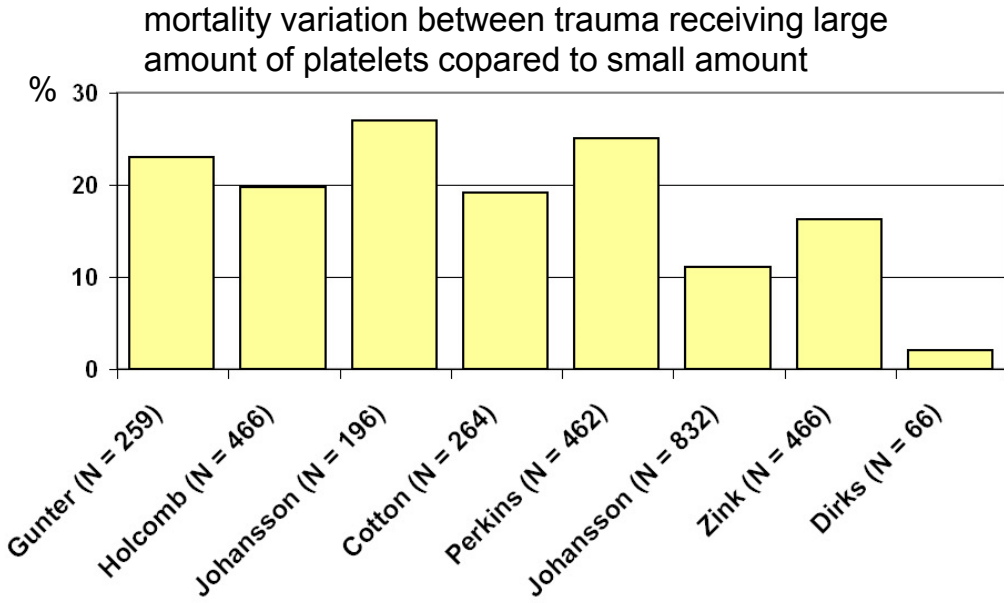
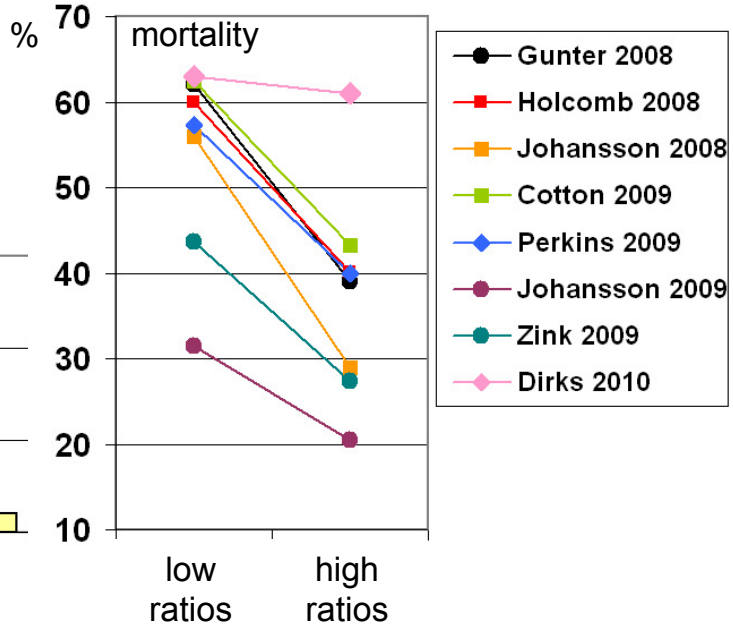


RESEARCH Open Access

# Management of bleeding following major trauma: an updated European guideline

CRITICAL CARE
april 2013

Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R.

**We recommend that platelets be administered to maintain a platelet count above 50 × $10^9$/l. (Grade 1C)**

**We suggest maintenance of a platelet count above 100 × $10^9$/l in patients with ongoing bleeding and/or TBI. (Grade 2C)**

**TRANSFUSION DE PLAQUETTES :**

**PRODUITS, INDICATIONS**

**UPDATED GUIDELINES**

**TEMPORARY VERSION**

afssaps

Increasing platelet:RBC ratio is associated with a mortality decrease

For massive transfusion platelet units must be part of the second transfusion package

Platelets must be transfused with a platelet:RBC ratio between 1:5 and 1:1.
This ratio may be close to 1:1

# Increasing ratios is not enough

**1:1:1**

**Ratio : a time-dependent variable**

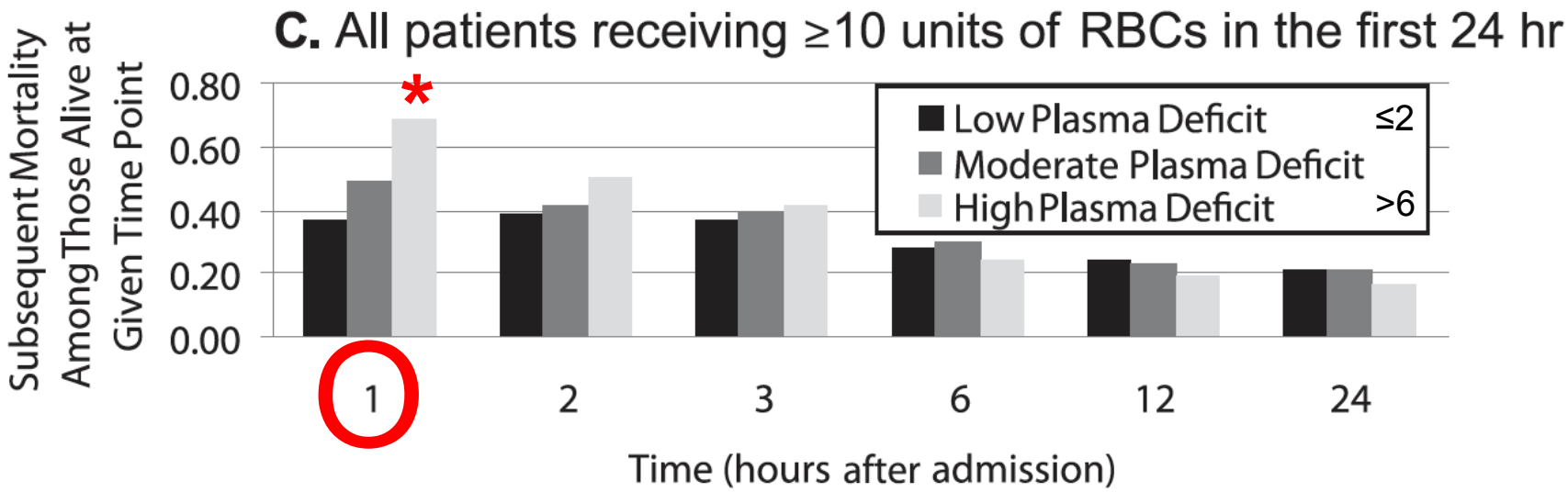
t

# Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma

TRANSFUSION
2011;51:1925-1932.

*Andreas R. de Biasi, Lynn G. Stansbury, Richard P. Dutton, Deborah M. Stein, Thomas M. Scalea, John R. Hess*

Ratio = FFP / RBC → Deficit = RBC - FFP




Mortality of trauma patients grouped by deficit status

# Reducing transfusion delay

carefully constructed massive transfusion protocol

- local agreement with the blood bank
- products available as soon as possible
- healthcare professionals

The Journal of TRAUMA® Injury, Infection, and Critical Care

# Damage Control Hematology: The Impact of a Trauma Exsanguination Protocol on Survival and Blood Product Utilization

*J Trauma.* 2008;64:1177–1183.

*Bryan A. Cotton, MD, Oliver L. Gunter, MD, James Isbell, MD, Brigham K. Au, BS, Amy M. Robertson, MD, John A. Morris, Jr., MD, Paul St. Jacques, MD, and Pampee P. Young, MD, PhD*

**Protocol : 10 RBC**
**4 FFP**
**2 platelets**
**→ ratio 1:2.5**

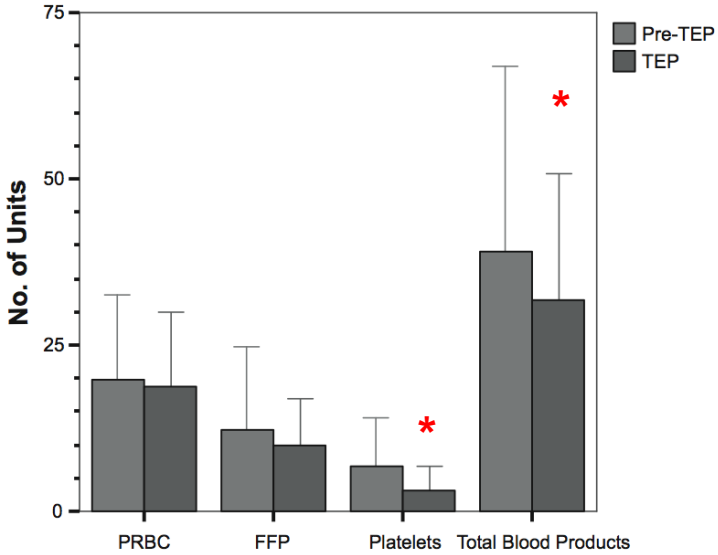



**Fig. 1.** *Unadjusted initial 24-hour blood product utilization before and after implementation of TEP. Each bar corresponds to the mean number of units transfused + standard deviation.*

**Table 3** Odds Ratios for 30 Days Mortality in Study Groups

| Variable | Odds Ratio (95% CI) | *p* |
|---|---|---|
| Received TEP | 0.26 (0.12–0.56) | 0.001* |
| Age | 1.02 (0.998–1.042) | 0.071 |
| Sex | 1.040 (0.489–2.214) | 0.919 |
| Penetrating mechanism | 1.260 (0.639–2.486) | 0.505 |
| 24-h RBC utilization | 1.074 (1.028–1.121) | 0.001* |
| 24-h FFP utilization | 1.013 (0.963–1.066) | 0.612 |
| 24-h PLT utilization | 0.914 (0.851–0.981) | 0.013* |

* Statistically significant at $p < 0.05$.

CI, confidence interval; TEP, trauma exsanguination protocol; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelets.

# Reducing transfusion delay

carefully constructed massive transfusion protocol

- local agreement with the blood bank
- products available as soon as possible
- healthcare professionals

↓

- which blood products?
- number?
- sequence?

↓

- transfusion package

# Packs

| | Sequence of pack | RBCs | Plasma unit | Platelet eq. unit ($n \times 0.5\ 10^{11}$) |
|---|---|---|---|---|
| Cotton *et al.* 2009 [21] | First | 10 | 4 | 10 |
| | Second | 6 | 4 | 10 |
| Dirks *et al.* 2010 [14] | First | 5 | 5 | 8 |
| | Second | 5 | 5 | 8 |
| Duchesne *et al.* 2010 [2 | First | 6 | 6 | 0 |
| Shaz *et al.* 2010 [24] | Second | 6 | 6 | 6 |
| Chambers *et al.* 2011 [3 | First | 4 | 4 | 6 |
| | Second | 4 | 4 | 6 |

Godier A, Samama M, Susen S. Curr Opin Anesthesiol 2012

# Packs

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Godier A, Samama M, Susen S. Curr Opin Anesthesiol 2012

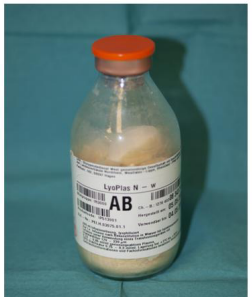
# Immediate availability of plasma in the 1st pack


Thawing plasma



**thawed AB group plasma**
stored for immediate availability together with O group RBC

**radio wave-based thawing technology**




**Freeze-dried plasma**

**1:1:1 ratio in blood transfusion:**
**many argues in massive transfusion**

↓

**non massively transfused patients?**

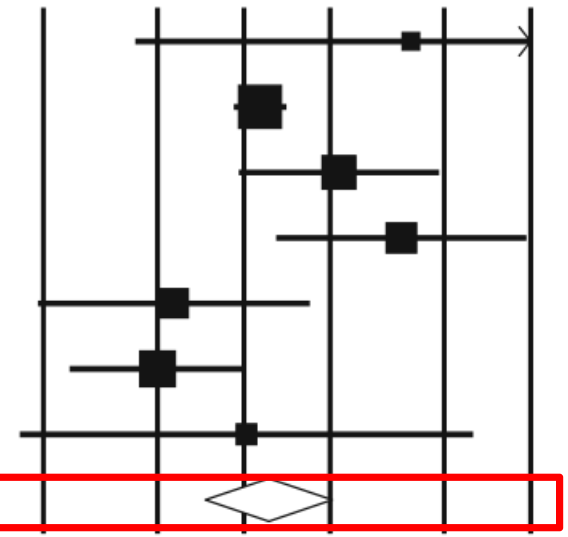
# The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis

*Mohammad Hassan Murad, James R. Stubbs, Manish J. Gandhi, Amy T. Wang, Anu Paul, Patricia J. Erwin, Victor M. Montori, and John D. Roback*

**TRANSFUSION** 2010.

**Mortality in patients undergoing surgery without massive transfusion**

| | OR | Lower limit | Upper limit | Events / Total Plasma | Events / Total Control |
|---|---|---|---|---|---|
| Hedstrand, 1987 | 3.83 | 0.42 | 34.68 | 4 / 142 | 1 / 133 |
| Swisher, 1996 | 1.14 | 0.93 | 1.40 | | |
| Gajic, 2004 | 2.15 | 0.97 | 4.76 | 13 / 35 | 30 / 139 |
| Massicotte, 2005 | 3.54 | 1.31 | 9.61 | 30 / 135 | 5 / 67 |
| Scalea, 2008 | 0.57 | 0.19 | 1.68 | | |
| Duchesne, 2008 | 0.50 | 0.25 | 1.00 | 14 / 118 | 28 / 132 |
| Kaibori, 2008 | 1.02 | 0.17 | 6.26 | 2 / 11 | 5 / 28 |
| | **1.22** | **0.73** | **2.03** | | |




**Heterogeneity : p=0.02; $I^2$=61%**

**Quality of evidence: Very low ⊕OOO**

# Impact of Plasma Transfusion in Trauma Patients Who Do Not Require Massive Transfusion

J Am Coll Surg
2010;210:957–965.

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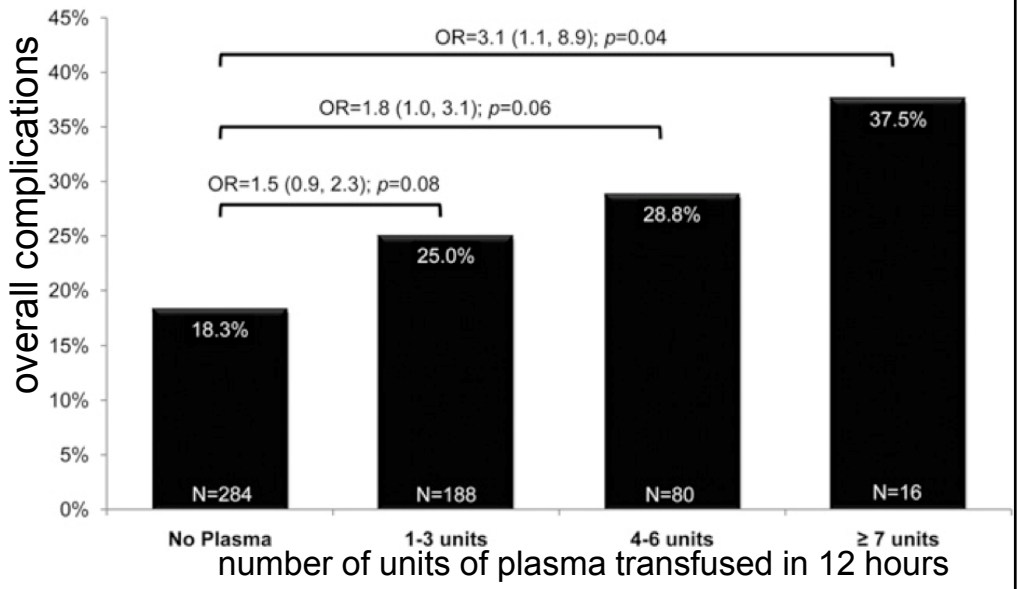
Lorne H Blackbourne, MD, FACS, John B Holcomb, MD, FACS, Pedro GR Teixeira, MD, Ira Shulman, MD,
Janice Nelson, MD, Demetrios Demetriades, MD, PhD, FACS

**Table 3.** Outcomes between Patient Groups

| | Total (n = 568) | Plasma in 12 h (n = 284) | No plasma in 12 h (n = 284) | Odds ratio (95% CI) | p Value* |
|---|---|---|---|---|---|
| Mortality, % | 15.7 | 17.3 | 14.1 | 1.3 (0.8–2.0) | 0.30 |
| Overall complication, % | 22.5 | 26.8 | 18.3 | 1.7 (1.1–2.4) | 0.016 |
| ARDS, % | 6.7 | 9.9 | 3.5 | 3.0 (1.4–6.2) | 0.004 |

- increase in complications
- no improvement in survival
- ↗ in complications as ↗ volumes of plasma



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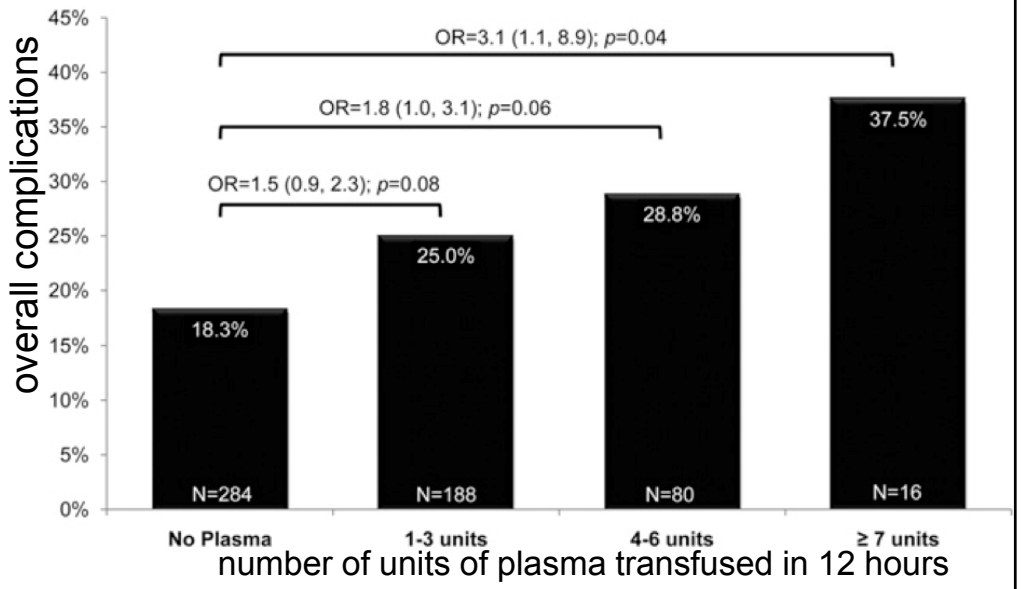

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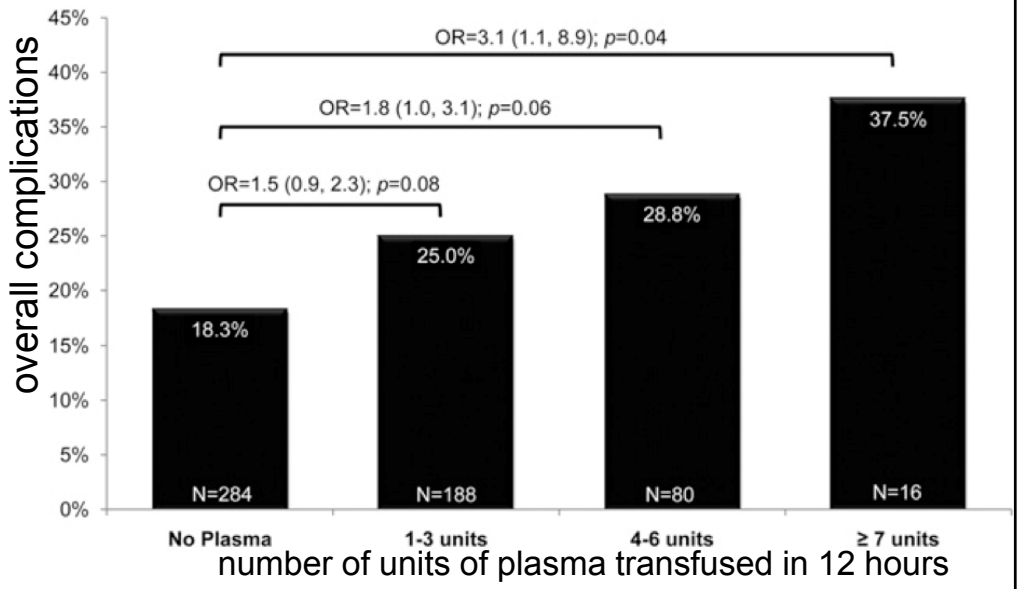

# Conclusion: Management of massive bleeding

- A growing body of evidence supports that high ratios improve outcome
- Only in massive bleeding
- → minority of patients
- Only a small aspect of massive bleeding management
  - immediate delivery of blood products
  - through pre-established protocols
- FFP/PLT/RBC ratios matter to define the content of packs immediately available within the golden hour.