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, Charles-Marc Samama, and Sophie Susen


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*


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
Coagulopathy

Massive transfusion

Massive bleeding

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

Mortality
Trauma-induced coagulopathy

- Massive bleeding
- Fluid loading
- Massive RBC transfusion
- Acidosis
- Hypothermia
- Dilution

Coagulopathy

Adapted from Brohi K, Ann Surg 2007*
Trauma-induced coagulopathy

- Tissue Injury
- Acidosis
- Hypothermia
- Fluid loading
- Massive bleeding
- Massive RBC transfusion
- Dilution

Acute traumatic coagulopathy

Trauma-induced coagulopathy

Adapted from Brohi K, *Ann Surg* 2007*
Trauma-induced coagulopathy

- Tissue Injury
- Fibrinolysis
- Systemic anticoagulation
  activated protein C
- Acute traumatic coagulopathy
- Shock
- Acidosis
- Massive bleeding
- Fluid loading
- Massive RBC transfusion
- Hypothermia
- Dilution
- Trauma-induced coagulopathy

Adapted from Brohi K, Ann Surg 2007*
Trauma-induced coagulopathy

- Tissue Injury
- Inflammation
- Shock
- Acidosis
- Massive bleeding
- Fluid loading
- Massive RBC transfusion
- Hypothermia
- Dilution

Fibrinolysis
systemic anticoagulation
activated protein C
Acute traumatic 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

Reduced Coagulation Factor Activity

Jansen JO, J Trauma 2011

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

<table>
<thead>
<tr>
<th></th>
<th>10-15 mL/kg</th>
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<tbody>
<tr>
<td>Fibrinogène g/L</td>
<td>+0.4</td>
<td>+1.0</td>
</tr>
<tr>
<td>II %</td>
<td>+16</td>
<td>+41</td>
</tr>
<tr>
<td>V %</td>
<td>+10</td>
<td>+28</td>
</tr>
<tr>
<td>VII %</td>
<td>+11</td>
<td>+38</td>
</tr>
<tr>
<td>IX %</td>
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<td>+44</td>
</tr>
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Pratima Chowdhury,¹ Anton G. Saayman, Ulrike Paulus,¹ George P. Findlay² and Peter W. Collins¹
Departments of ¹Haematology and ²Intensive Care Medicine, University Hospital of Wales and University of Wales College of Medicine, Heath Park, Cardiff, UK
© 2004 Blackwell Publishing Ltd, British Journal of Haematology, 125, 69–73

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

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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

Increasing plasma:RBC ratio

- Transfusion with high ratio

- Ratio = plasma number / RBC number
The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

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

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)  

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

An FFP:PRBC Transfusion Ratio $\geq 1:1.5$ Is Associated With A Lower Risk Of Mortality After Massive Transfusion

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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events / Total</th>
<th>OR and 95% CI</th>
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<tbody>
<tr>
<td>Borgman, 2007</td>
<td>0.29 (0.16, 0.51)</td>
<td>31 / 162</td>
<td>38 / 84</td>
</tr>
<tr>
<td>Cotton, 2009</td>
<td>0.46 (0.28, 0.75)</td>
<td>54 / 125</td>
<td>88 / 141</td>
</tr>
<tr>
<td>Holcomb, 2008</td>
<td>0.58 (0.40, 0.84)</td>
<td>87 / 252</td>
<td>102 / 214</td>
</tr>
<tr>
<td>Kashuk, 2008</td>
<td>0.44 (0.22, 0.88)</td>
<td>23 / 59</td>
<td>44 / 74</td>
</tr>
<tr>
<td>Maegele, 2008</td>
<td>0.59 (0.42, 0.81)</td>
<td>76 / 229</td>
<td>222 / 484</td>
</tr>
<tr>
<td>Teixeira, 2009</td>
<td>0.18 (0.12, 0.28)</td>
<td>58 / 226</td>
<td>103 / 157</td>
</tr>
<tr>
<td>Scalea, 2008</td>
<td>1.49 (0.63, 3.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snyder, 2009</td>
<td>0.84 (0.47, 1.50)</td>
<td></td>
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</tr>
<tr>
<td>Duchesne, 2008</td>
<td>0.05 (0.02, 0.13)</td>
<td>19 / 71</td>
<td>56 / 64</td>
</tr>
<tr>
<td>Dente, 2009</td>
<td>0.12 (0.02, 0.67)</td>
<td>7 / 50</td>
<td>4 / 7</td>
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Heterogeneity: p=0.01; I²=85%
Quality of evidence: Very low

Favors higher plasma ratio
Favors lower plasma ratio
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
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Heterogeneity: p=0.01; I²=85%
Quality of evidence: Very low

OR and 95% CI

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<th>0.01</th>
<th>0.1</th>
<th>0.25</th>
<th>1</th>
<th>1.5</th>
<th>3.5</th>
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Limitations

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


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

Max V Wohlauer, MD, Ernest E Moore, MD, FACS, Scott Thomas, MD, FACS, Angela Savaia, 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

J Am Coll Surg 2012;214:739–746
Retrospective data regarding platelet transfusion

mortality variation between trauma receiving large amount of platelets compared to small amount

Gunter (N = 259)
Holcomb (N = 466)
Johansson (N = 199)
Cotton (N = 264)
Perkins (N = 462)
Johansson (N = 832)
Zink (N = 460)
Dirks (N = 66)
Retrospective data regarding platelet transfusion

mortality variation between trauma receiving large amount of platelets compared to small amount

- Gunter (N = 239)
- Holcomb (N = 456)
- Johansson (N = 199)
- Cotton (N = 262)
- Perkins (N = 462)
- Zink (N = 832)
- Dirks (N = 65)

mortality

% 70 60 50 40 30 20 10 0

low ratios high ratios

- Gunter 2008
- Holcomb 2008
- Johansson 2008
- Cotton 2009
- Perkins 2009
- Johansson 2009
- Zink 2009
- Dirks 2010
Management of bleeding following major trauma: an updated European guideline


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

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

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

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

Equations:

- Ratio = FFP / RBC
- Deficit = RBC - FFP

Graph:

C. All patients receiving ≥10 units of RBCs in the first 24 hr

Subsequent Mortality Among Those Alive at Given Time Point

Mortality of trauma patients grouped by deficit status

Legend:
- Low Plasma Deficit ≤2
- Moderate Plasma Deficit >2 ≤6
- High Plasma Deficit >6

Time (hours after admission)

1 2 3 6 12 24
Reducing transfusion delay

carefully constructed massive transfusion protocol

- local agreement with the blood bank
- products available as soon as possible
- healthcare professionals
Protocol: 10 RBC
  4 FFP
  2 platelets
→ ratio 1:2.5

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received TEP</td>
<td>0.26 (0.12–0.56)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.998–1.042)</td>
<td>0.071</td>
</tr>
<tr>
<td>Sex</td>
<td>1.040 (0.489–2.214)</td>
<td>0.919</td>
</tr>
<tr>
<td>Penetrating mechanism</td>
<td>1.260 (0.639–2.486)</td>
<td>0.505</td>
</tr>
<tr>
<td>24-h RBC utilization</td>
<td>1.074 (1.028–1.121)</td>
<td>0.001*</td>
</tr>
<tr>
<td>24-h FFP utilization</td>
<td>1.013 (0.963–1.066)</td>
<td>0.612</td>
</tr>
<tr>
<td>24-h PLT utilization</td>
<td>0.914 (0.851–0.981)</td>
<td>0.013*</td>
</tr>
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* Statistically significant at p < 0.05.

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

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.
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

<table>
<thead>
<tr>
<th>Sequence of pack</th>
<th>RBCs</th>
<th>Plasma unit</th>
<th>Platelet eq. unit (n × 0.5 $10^{11}$)</th>
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<tr>
<td></td>
<td>Second</td>
<td>6</td>
<td>4</td>
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<td>First</td>
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Godier A, Samama M, Susen S. Curr Opin Anesthesiol 2012
## Packs

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<td>4</td>
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<td></td>
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<td><strong>Shaz et al. 2010 [24]</strong></td>
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<td>6</td>
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<tr>
<td><strong>Chambers et al. 2011 [3]</strong></td>
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<td>Second</td>
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Immediate availability of plasma in the 1\textsuperscript{st} 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

<table>
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<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Events</th>
<th>Total Plasma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedstrand, 1987</td>
<td>3.83 (0.42, 34.68)</td>
<td>0.42</td>
<td>34.68</td>
<td>4/142</td>
<td>1/133</td>
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<tr>
<td>Swisher, 1996</td>
<td>1.14 (0.93, 1.40)</td>
<td>0.93</td>
<td>1.40</td>
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<tr>
<td>Gajic, 2004</td>
<td>2.15 (0.97, 4.76)</td>
<td>0.97</td>
<td>4.76</td>
<td>13/35</td>
<td>30/139</td>
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<tr>
<td>Massicotte, 2005</td>
<td>3.54 (1.31, 9.61)</td>
<td>1.31</td>
<td>9.61</td>
<td>30/135</td>
<td>5/67</td>
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<tr>
<td>Scalea, 2008</td>
<td>0.57 (0.19, 1.68)</td>
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<tr>
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<td>0.50 (0.25, 1.00)</td>
<td>0.25</td>
<td>1.00</td>
<td>14/118</td>
<td>28/132</td>
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<td>Kaibori, 2008</td>
<td>1.02 (0.17, 6.26)</td>
<td>0.17</td>
<td>6.26</td>
<td>2/11</td>
<td>5/28</td>
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**OR and 95% CI**

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<th>Lower Limit</th>
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<th>Events</th>
<th>Total Plasma</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedstrand, 1987</td>
<td>3.83 (0.42, 34.68)</td>
<td>0.42</td>
<td>34.68</td>
<td>4/142</td>
<td>1/133</td>
<td></td>
</tr>
<tr>
<td>Swisher, 1996</td>
<td>1.14 (0.93, 1.40)</td>
<td>0.93</td>
<td>1.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gajic, 2004</td>
<td>2.15 (0.97, 4.76)</td>
<td>0.97</td>
<td>4.76</td>
<td>13/35</td>
<td>30/139</td>
<td></td>
</tr>
<tr>
<td>Massicotte, 2005</td>
<td>3.54 (1.31, 9.61)</td>
<td>1.31</td>
<td>9.61</td>
<td>30/135</td>
<td>5/67</td>
<td></td>
</tr>
<tr>
<td>Scalea, 2008</td>
<td>0.57 (0.19, 1.68)</td>
<td>0.19</td>
<td>1.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchesne, 2008</td>
<td>0.50 (0.25, 1.00)</td>
<td>0.25</td>
<td>1.00</td>
<td>14/118</td>
<td>28/132</td>
<td></td>
</tr>
<tr>
<td>Kaibori, 2008</td>
<td>1.02 (0.17, 6.26)</td>
<td>0.17</td>
<td>6.26</td>
<td>2/11</td>
<td>5/28</td>
<td></td>
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**Heterogeneity**: p=0.02; I²=61%

**Quality of evidence**: Very low ⊕⊕⊕

Favors plasma Favors control
Impact of Plasma Transfusion in Trauma Patients Who Do Not Require Massive Transfusion

Kenji Inaba, MD, FRCSC, FACS, Bernardino C Branco, MD, Peter Rhee, MD, FACS, 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

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<tr>
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<th>Total (n = 568)</th>
<th>Plasma in 12 h (n = 284)</th>
<th>No plasma in 12 h (n = 284)</th>
<th>Odds ratio (95% CI)</th>
<th>p Value*</th>
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<tr>
<td>Mortality, %</td>
<td>15.7</td>
<td>17.3</td>
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<td>ARDS, %</td>
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<td>3.5</td>
<td>3.0 (1.4–6.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- increase in complications
- no improvement in survival
- ➤ increase in complications
- ➤ volumes of plasma

Overall complications

number of units of plasma transfused in 12 hours
increase in complications

no improvement in survival

► in complications
► volumes of plasma
Impact of Plasma Transfusion in Trauma Patients Who Do Not Require Massive Transfusion

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