Blood and Blood Product Transfusion

Amjad Bani Hani, MD

- **Approximately 15 million red blood cell (RBC) units** are transfused annually in the United States (1)

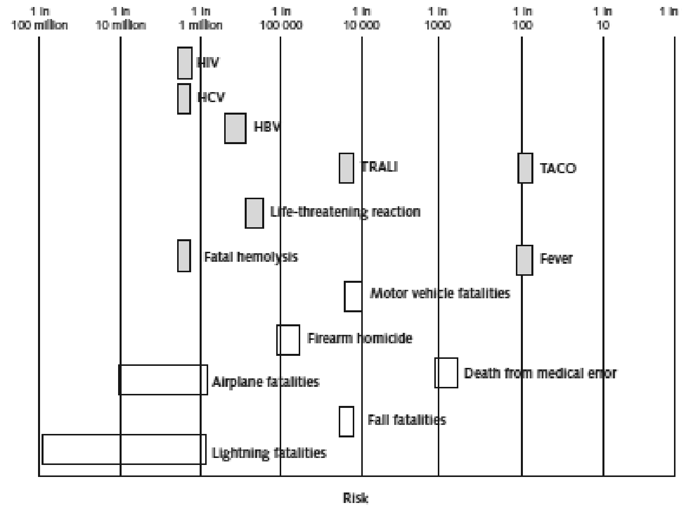
1. U.S. Department of Health and Human Services. The 2009 national blood collection and utilization survey report. Washington, DC: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Health; 2011.

- About 85 million are transfused annually worldwide.

Takei T, Amin NA, Schmid G, Dhingra-Kumar N, Rugg D. Progress in global blood safety for HIV. J Acquir Immune Defic Syndr. 2009;52 Suppl 2:S127-31. [PMID: 19901625]

- Physicians most commonly use hemoglobin concentration to decide when to transfuse.
- However, most guidelines emphasize that transfusion should be given for symptoms of anemia and should not be based on hemoglobin concentration alone.

Figure. Adverse effects of RBC transfusion contrasted with other risks.



"10/30 rule"

RATIONALE FOR TRANSFUSION

- **Role of blood in oxygen delivery**
- **Impact of anemia on morbidity and mortality**

Why?

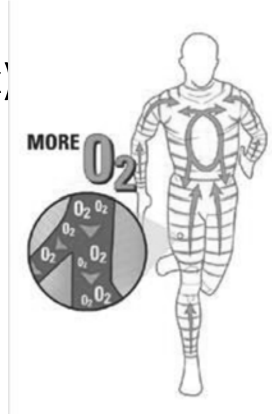
- The body at rest uses approx **250ml O2/L blood**
- O2 delivery can fall with a reduction in any of:
  - Cardiac Output
  - Hb concentration
  - O2 saturation
- Organs most sensitive to hypoxia are Heart and Brain

Why?

- **The purpose of a red cell transfusion is to improve the oxygen carrying capacity of the blood.**
- <u>Oxygen delivery to tissues</u> (O2 Flux)

= Cardiac Output x Oxygen content of blood

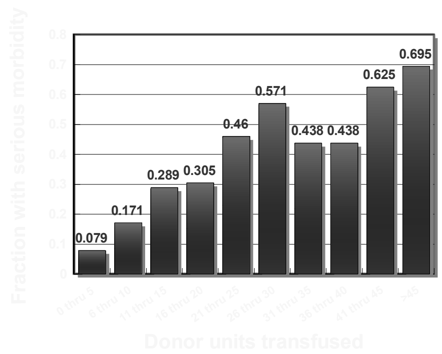
Hb x SaO_2



Blood Transfusion in the Operating Room Is Bad!

- Cardiac Surgery
- Thoracic operations
- Vascular operations
- Cancer procedures
- General Surgery
- Cardiology doesn't get a pass!
  - PCI outcomes worse w/ blood transfusion

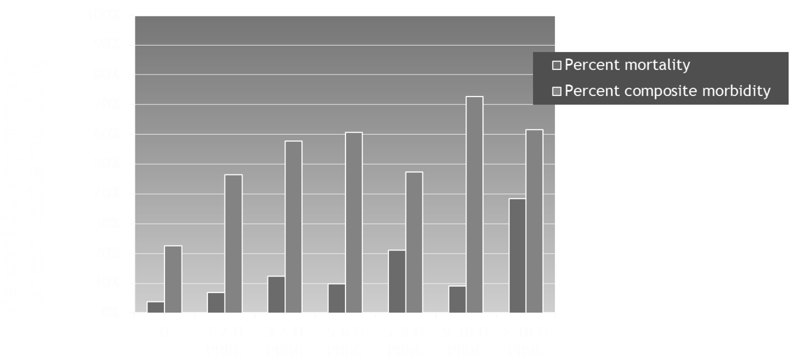
Transfusion & Serious Morbidity in 4,445 Cardiac Surgical Patients



- Serious morbidity and mortality increase with the amount transfused.

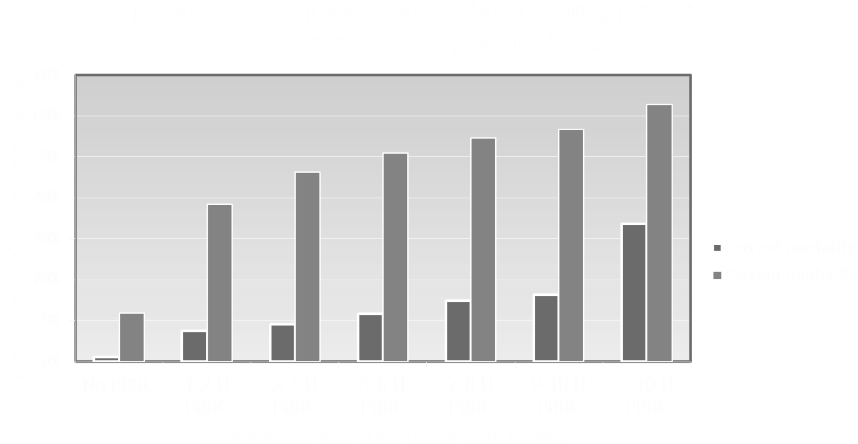
Ferraris, Intl J Angiol, 2006

Intraoperative Blood Transfusion & Lung Surgery



Ferraris, 2011

Blood Transfusion in General Surgical Population



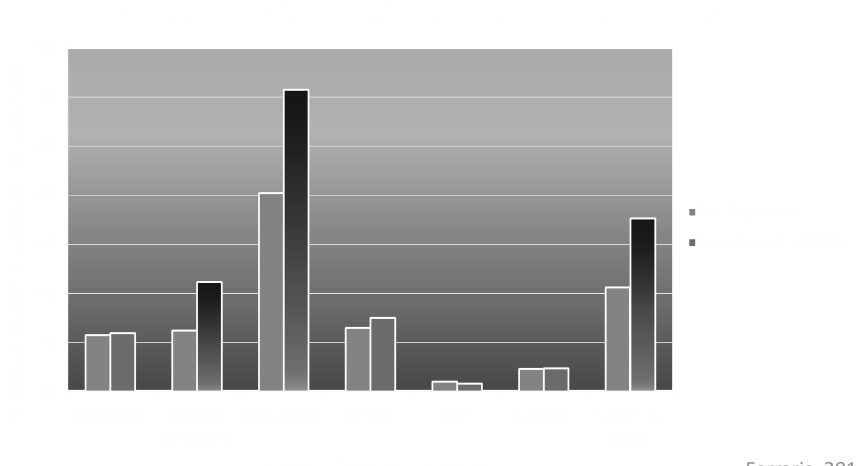
Bleeding After PCI Is a Risk for 1-year Mortality (5,384 patients)

- Independent predictors of 1-year mortality.

Variable	Hazard Ratio (95% CI)
Bleeding w/in 30 days	2.96 (1.96 -4.48)
MI w/in 30 days	2.29 (1.52 - 3.46)
Urgent revascularization w/in 30d	2.49 (1.16 - 5.35)
Age (years)	2.27 (1.78 - 2.89)
Diabetes	1.47 (1.11 - 1.96)
Multivessel CAD	2.72 (1.58 -4.67)
Elevated troponin	1.77 (1.27 -2.47)
LV ejection fraction	0.71 (0.60 - 0.85)
Creatinine	1.10 (1.06 - 1.14)

Ndrepepa, 2008

Why Does Intraoperative Blood Transfusion Lead to Worse Outcomes?



Ferraris, 2011

The High-Risk Patient - Modifiable Risk Factors

2007 & 2011 STS Guidelines

1. Advanced age
2. RBC volume
   a) Small body size
   b) Preoperative anemia
3. Drugs
   a) Anti-platelet drugs
4. Co-morbidities
5. Emergent or complex operations.

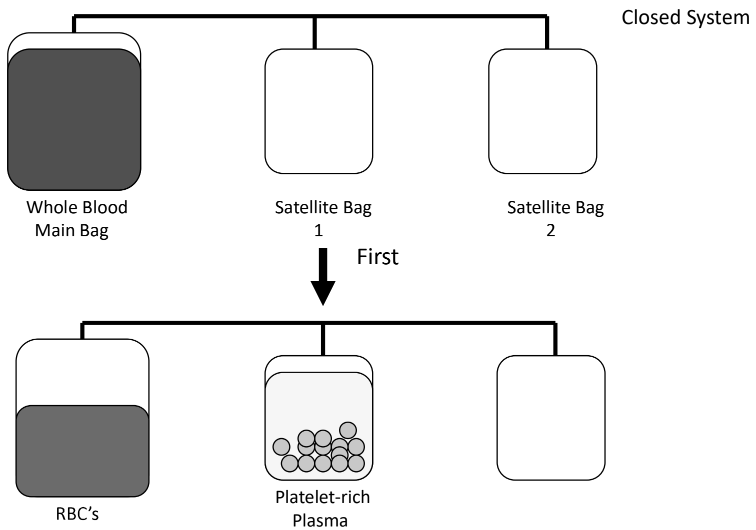
* Ferraris, et al. STS Guidelines. Ann Thorac Surg. 2011

Blood Components

- Prepared from Whole blood collection or apheresis
- Whole blood is separated by differential centrifugation
  - Red Blood Cells (RBC's)
  - Platelets
  - Plasma
    - Cryoprecipitate
    - Others
- Others include Plasma proteins—IVIg, Coagulation Factors, albumin, Anti-D, Growth Factors, Colloid volume expanders
- Apheresis may also used to collect blood components

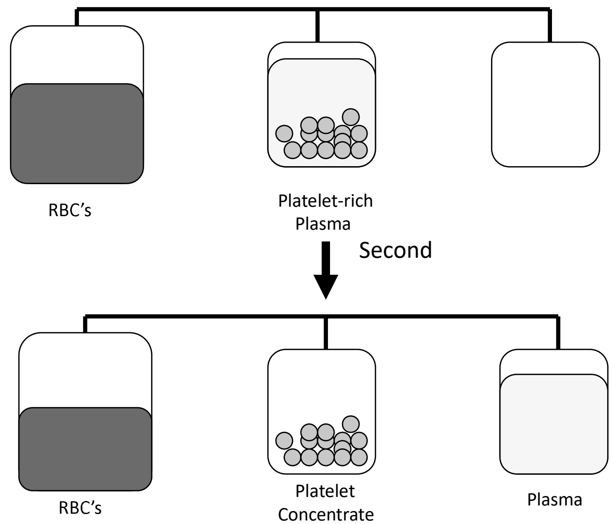
Differential Centrifugation

First Centrifugation



Differential Centrifugation

Second Centrifugation



Whole Blood

- Storage
  - 4° for up to 35 days
- Indications
  - Massive Blood Loss/Trauma
- Considerations
  - Use filter as platelets and coagulation factors will not be active after 3-5 days
  - Donor and recipient must be ABO identical

RBC Concentrate

- Storage
  - 4° for up to 42 days, can be frozen
- Indications
  - Many indications—ie anemia, hypoxia, etc.
- Considerations
  - Recipient must not have antibodies to donor RBC's (note: patients can develop antibodies over time)
  - Usual dose 10 cc/kg (will increase Hgb by 2.5 gm/dl)
  - Usually transfuse over 2-4 hours (slower for chronic anemia

Platelets

- Storage
  - Up to 5 days at 20-24°
- Considerations
  - Contain Leukocytes and cytokines
  - 1 unit/10 kg of body weight increases Plt count by 50,000
  - Donor and Recipient must be ABO identical

- Indications
- 10,000/mm3 in stable, non-bleeding patients,
- 20,000/mm3 in unstable non-bleeding patients
- 50,000/mm3 in patients undergoing invasive procedures or actively bleeding.

Prophylactic preoperative transfusion

1. is rarely required counts >100,000/mm3,
2. is usually required for counts <50,000/mm3
3. guided by risk factors for intermediate counts.

- Neurologic or ophthalmologic or Cardiac procedures require a
- platelet count near 100,000/mm3.

Plasma and FFP

- Contents—Coagulation Factors (1 unit/ml)
- Storage
  - FFP--12 months at –18 degrees or colder
- Indications
  - Coagulation Factor deficiency, fibrinogen replacement, DIC, liver disease, exchange transfusion, massive transfusion

- Considerations
  - Plasma should be recipient RBC ABO compatible
  - Usual dose is 20 cc/kg to raise coagulation factors approx 20%

Cryoprecipitate

- Description
  - Precipitate formed/collected when FFP is thawed at 4°
- Storage
  - After collection, refrozen and stored up to 1 year at -18°
- Indication
  - Fibrinogen deficiency or dysfibrinogenemia
  - vonWillebrands Disease
  - Factor VIII or XIII deficiency
  - DIC (not used alone)

- Considerations
  - ABO compatible preferred (but not limiting)
  - Usual dose is 1 unit/5-10 kg of recipient body weight

Leukocyte Reduction Filters

- Used for prevention of transfusion reactions
- Filter used with RBC's, Platelets, FFP, Cryoprecipitate
- May reduce RBC's by 5-10%
- Does not prevent Graft Verses Host Disease (GVHD)

Background

- Carson et al. "Mortality and morbidity in patients with very low **postoperative** Hb levels who decline blood transfusion." Transfusion 2002
  - Mortality
    - Hgb 7.1 to 8.0 (n = 99) — zero percent
    - Hgb 5.1 to 7.0 (n = 110) — 9 percent
    - Hgb 3.1 to 5.0 (n = 60) — 30 percent
    - Hgb ≤3.0 (n = 31) — 64 percent

The TRICC Study

- Enrolled 838 euvolemic, anemic, critically ill pts who were admitted to 1 of 25 Canadian ICUs
- Patients were stratified according to center and disease severity (APACHE II) and placed into one of two groups
  - **Restrictive group**: Transfuse if Hb < 7 and maintain between 7 and 9
  - **Liberal group**: Transfuse if Hb < 10 and maintain between 10 and 12
- The primary outcome measure was death from all causes in the 30 days after randomization

Herbert PC, et al. NEJM 1999

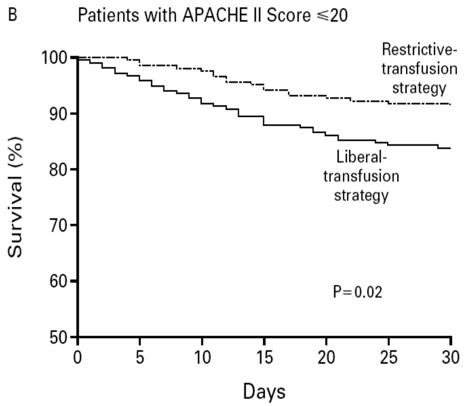
The TRICC Study

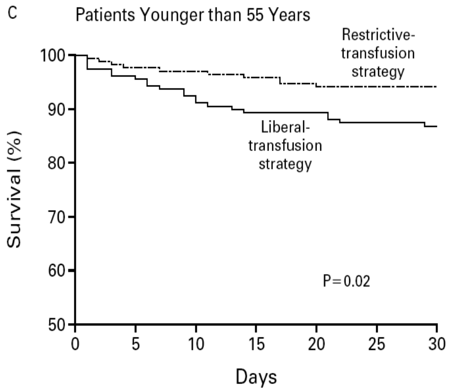
No difference 30 day mortality

In "healthy" (APACHE II < 20) and young (<55yrs) patients
Transfusion increased mortality

Herbert PC, et al. NEJM 1999

The TRICC Study





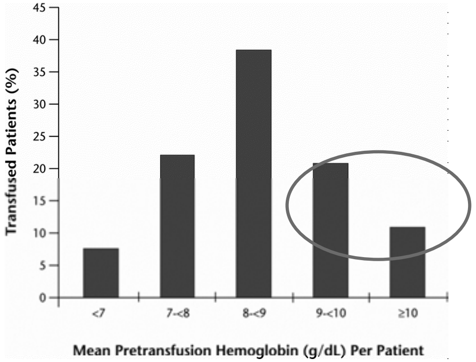
8.7% vs 16.1%

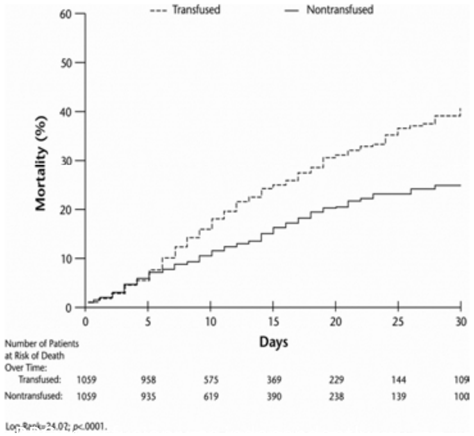
5.7% vs 13.0%

Herbert PC, et al. NEJM 1999

"A restrictive red blood cell transfusion strategy generally appears to be safe in most critically ill patients with cardiovascular disease…
with the possible exception of
patients with acute myocardial infarction and unstable angina."

CRIT Results





Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes

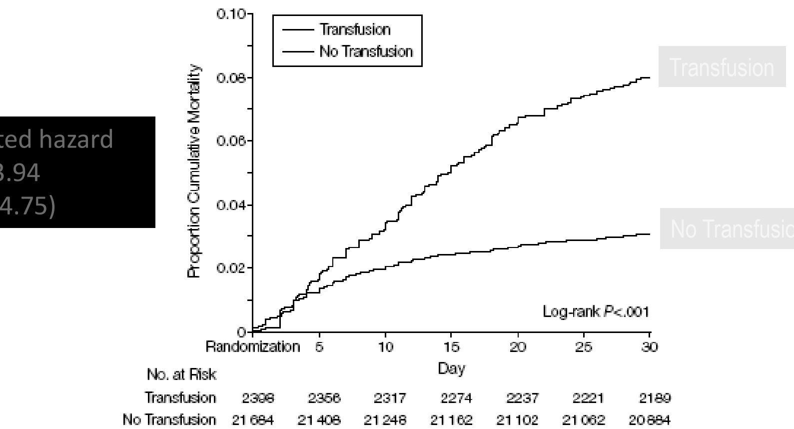
- Analysis of 24,112 enrollees in 3 large international trials of patients with acute coronary syndromes
- Association between transfusion and outcome
- Cox proportional hazards modeling
- Main outcome = 30 day mortality

Rao SV et al. *JAMA. 2004;292:1555-1562*

Blood Transfusion and Clinical Outcome in Acute Coronary Syndrome

Figure 1. Kaplan-Meier Estimates of 30-Day Mortality Among Patients Who Did and Did Not Receive Blood Transfusion

Adjusted hazard ratio 3.94 (3.26-4.75)



Survival data were missing for 3 patients who received tranfusion and for 27 patients who did not receive transfusion.

Rao SV et al. *JAMA. 2004;292:1555-1562*

Background

- Villanueva et al. "Transfusion strategies for acute upper gastrointestinal bleeding." NEJM Jan 2013.
  - 2 Arms. Patients w/o significant comorbid illnesses.
    - Restrictive transfusion strategy: Tx only for Hg<7
    - Liberal transfusion strategy: Tx when Hg <9.
  - **Patients receiving a restrictive transfusion strategy had significantly less rebleeding and adverse events.**
  - Restrictive transfusion also w/ trend toward lower mortality for Peptic ulcer bleeding (not significant) and pt's w/ Cirrhosis Child Pugh classes A and B (significantly less).

When to Pull the "transfusion Trigger?"

- **Should not be based solely on hemoglobin number.**
- Decision should consider clinical scenario, patient characteristics, and symptoms.

When to Pull the "transfusion Trigger?"

- American Association of Blood Banks Guidelines
  - Hgb <6 – Transfusion recommended
  - Hgb 6-7 – Transfusion likely recommended
  - Hgb 7-8 – **Restrictive Transfusion Strategy** for stable patients (Strong recommendation). Consider transfusion only if post-operative or symptomatic (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).
  - Hgb 8 – 10 – TRANSFUSION GENERALLY NOT INDICATED
    - Can consider Tx in special circumstances (ie ACS w/ active ischemia, symptomatic anemia, active bleeding, critical ill septic shock with ScVO2<70).
  - Hgb >10 – TRANSFUSION NOT INDICATED

Transfusion Complications

- Acute Transfusion Reactions (ATR's)
- Chronic Transfusion Reactions
- Transfusion related infections

Acute Transfusion Reactions

- Hemolytic Reactions (AHTR)
- Febrile Reactions (FNHTR)
- Allergic Reactions
- TRALI
- Coagulopathy with Massive transfusions
- Bacteremia

Acute Hemolytic Transfusion Reactions (AHTR)

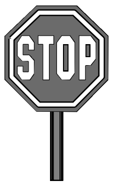
- Occurs when incompatible RBC's are transfused into a recipient who has pre-formed antibodies (usually ABO or Rh)
- Antibodies activate the complement system, causing intravascular hemolysis
- Symptoms occur within minutes of starting the transfusion
- This hemolytic reaction can occur with as little as 1-2 cc of RBC's
- Labeling error is most common problem
- **<u>Can be fatal</u>**

Symptoms of AHTR

- High fever/chills
- Hypotension
- Back/abdominal pain
- Oliguria
- Dyspnea
- Dark urine
- Pallor

What to do?

If an AHTR occurs



- **STOP TRANSFUSION**
- **ABC's**
- Maintain IV access and run IVF (NS or LR)
- Monitor and maintain BP/pulse
- Give diuretic
- Obtain blood and urine for transfusion reaction workup
- Send remaining blood back to Blood Bank

Blood Bank Work-up of AHTR

- Check paperwork to assure no errors
- Check plasma for hemoglobin
- DAT
- Repeat crossmatch
- Repeat Blood group typing
- Blood culture

Labs found with AHTR

- Hemoglobinemia
- Hemoglobinuria
- Positive DAT
- Hyperbilirubinemia
- Abnormal DIC panel

Monitoring in AHTR

- Monitor patient clinical status and vital signs
- Monitor renal status (BUN, creatinine)
- Monitor coagulation status (DIC panel– PT/PTT, fibrinogen, D-dimer/FDP, Plt, Antithrombin-III)
- Monitor for signs of hemolysis (LDH, bili, haptoglobin)

Febrile Nonhemolytic Transfusion Reactions (FNHTR)

- Definition--Rise in patient temperature >1°C (associated with transfusion without other fever precipitating factors)
- Occurs with approx 1% of PRBC transfusions and approx 20% of Plt transfusions
- FNHTR caused by alloantibodies directed against HLA antigens
- Need to evaluate for AHTR and infection

What to do?

If an FNHTR occurs

- STOP TRANSFUSION
- Use of Antipyretics
- Use of Corticosteroids for severe reactions
- Use of Narcotics for shaking chills
- Future considerations
  - May prevent reaction with leukocyte filter
  - Use single donor platelets
  - Washed RBC’s or platelets

Allergic Nonhemolytic Transfusion Reactions

- Etiology
  - May be due to plasma proteins or blood preservative/anticoagulant
  - Best characterized with IgA given to an IgA deficient patients with anti-IgA antibodies
- Presents with urticaria and wheezing
- Treatment
  - Mild reactions—Can be continued
  - Severe reactions—Must STOP transfusion and may require steroids or epinephrine
- Prevention—Premedication (Antihistamines)

TRALI

Transfusion Related Acute Lung Injury

- Clinical syndrome similar to ARDS
- Occurs 1-6 hours after receiving plasma-containing blood products
- Caused by WBC antibodies present in donor blood that result in pulmonary leukostasis
- Treatment is supportive
- High mortality

Massive Transfusions

- Coagulopathy may occur after transfusion of massive amounts of blood (trauma/surgery)
- Coagulopathy is caused by failure to replace plasma
- See electrolyte abnormalities
  - Due to citrate binding of Calcium
  - Also due to breakdown of stored RBC's

Bacterial Contamination

- More common and more severe with platelet transfusion (platelets are stored at room temperature)
- Organisms
  - Platelets—Gram (+) organisms, ie Staph/Strep
  - RBC's—Yersinia, enterobacter
- Risk increases as blood products age (use fresh products for immunocompromised)

Chronic Transfusion Reactions

- Alloimmunization
- Transfusion Associated Graft Verses Host Disease (GVHD)
- Iron Overload
- Transfusion Transmitted Infection

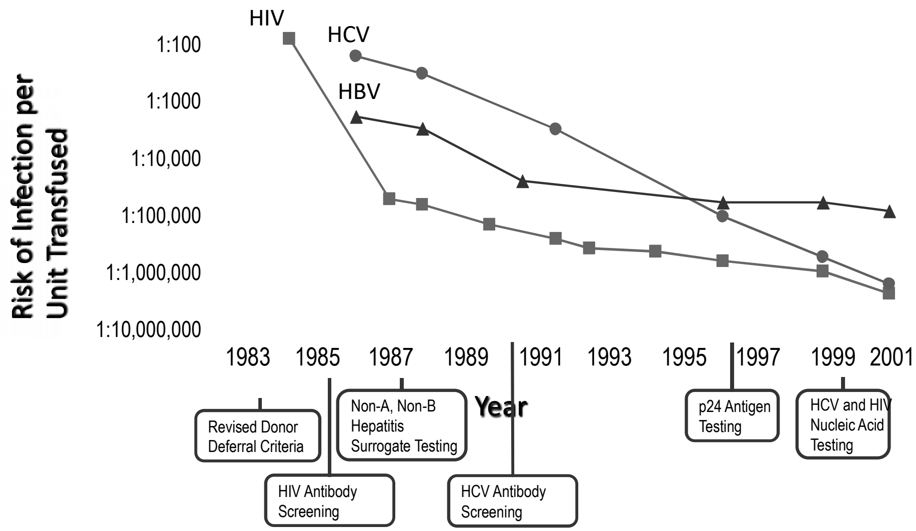
Transfusion Associated GVHD

- Mainly seen in infants, BMT patients, SCID
- Etiology—Results from engraftment of donor lymphocytes of an immunocompetent donor into an immunocompromised host
- Symptoms—Diarrhea, skin rash, pancytopenia
- Usually fatal—no treatment
- Prevention—Irradiation of donor cells

Transfusion Associated Infections

- Hepatitis C
- Hepatitis B
- HIV
- CMV
  - CMV can be diminished by leukoreduction, which is indicated for immunocompromised patients

Decline in HIV, HBV, HCV Risks of Transmission via Blood Tx



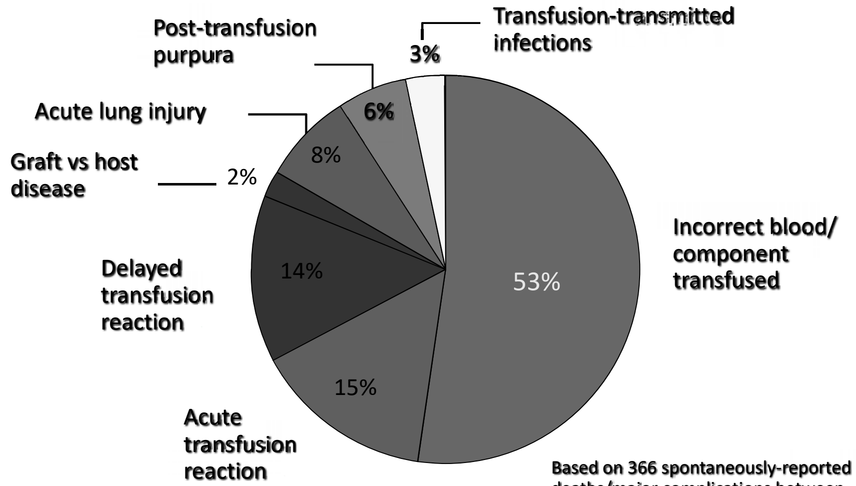
Busch MP, et al. *JAMA.* 2003;289:959-62.

Risks of Transfusion: Infectious Disease

- ✓ HIV = 1 in 1.8 million
- ✓ HCV = 1 in 1.6 million
- ✓ HBV = 1 in 220,000

HIV = human immunodeficiency virus.
HCV = hepatitis C virus.
HBV = hepatitis B virus.
Busch MP, et al. *JAMA*. 2003;289:959-62.

Serious Hazards of Transfusion



Based on 366 spontaneously-reported deaths/major complications between October 1996 and September 1998 in the UK and Ireland.

Williamson LM, et al. *BMJ*. 1999;319:16-9.

Risks of Blood Transfusion

Minor allergic reactions	1:100
Bacterial infection (platelets)	1:2,500
Viral hepatitis	1:5,000
Hemolytic transfusion reaction	1:6,000
HTLV I/II infection	1:200,000
Acute lung inj TRALI 1:5,000	1:500,000
Anaphylactic shock	1:500,000
Fatal hemolytic reaction	1:600,000
Graft-vs-host disease	Rare
Immunosuppression	Unknown

HTLV = human T-cell leukemia-lymphoma virus.
Klein HG. *Am J Surg*. 1995. 170;6A(suppl):21S-26S.

Immune Effects of Blood

- **Immunologic effects of autologous and allogenic blood transfusions:**
  - Decreased T-cell proliferation
  - Decreased CD3, CD4, CD8 T-cells
  - Increased Soluble cytokine receptor
    - sTNF-R, sIL-2R
  - Increased Serum neopterin
  - Increased Cell-mediated lympholysis
  - Increased TNF-alpha
    Increased suppressor T-cell activity
    Reduced natural killer cell activity

TRIM – Transfusion-associated Immunomodulation

McAlister FA, et al, British Journal of Surgery 1998; 85: 171-178
Innerhofer et al. Transfusion 1999 Oct;39(10):1089

Blood Tx Increases Risk of Postoperative Bacterial Infection

- 20 peer-reviewed studies, 1986-2000
- N = 13,152 (Tx 5215, No-Tx 7937)
- **Association of Blood Tx to Infection**
  - **Common OR 3.45** (range 1.43-15.15)
  - 17 of 20 studies with $p < 0.05$
- **Trauma subgroup**
  - **Common OR 5.26** (range 5.03-5.43)
  - All studies with $p < 0.05$ (0.005 – 0.0001)
  - Blood Tx associated with greater risk in trauma pts

Hill GE, Minei JP et al. *J Trauma 2003;54:908-914*

Transfusion Increases the Risk of Postoperative Infection after Cardiovascular Surgery

Michael K Banbury, MD, FACS, Mariano E Brizzio, MD, Jeevanantham Rajeswaran, MSc, Bruce W Lytle, MD, FACS, Eugene H Blackstone, MD

- 15,592 Cardiovascular operations
- Infection endpoints bacteremia, SSI
- 55% of pts received PRBCs, 21% plts, 13% FFP, 3% cryoprecipitate
- Increased RBC tx associated with increased infection ($p < 0.0001$), confirmed by logistic regression analysis.

J Am Coll Surg 2006;202:131-138

Red blood cell transfusions and nosocomial infections in critically ill patients*

- Prospective cohort study, n=2085
- Project Impact
- Nosocomial Infections: 14.3% vs. 5.8%, $p < 0.001$

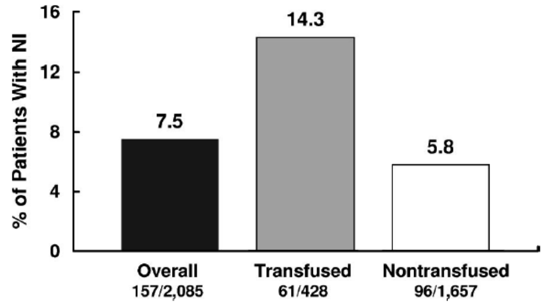


Table 4. Analyses of Predictive Factors for Nosocomial Infection

	Odds Ratio	95% Confidence Interval	*p* Value
Multivariate (n = 428)			
Patient age	0.996	0.980–1.012	.64
Maximum age of RBC units transfused	1.012	0.981–1.045	.44
No. of RBC units transfused	1.097	1.028–1.171	.005
Univariate (n = 399)			
POS based on MPM-0 score	.382	0.099–1.474	.16

RBC, red blood cell; POS, probability of survival; MPM-0, Mortality Prediction Model score.

Taylor RW et al.
Crit Care Med 2006; 34:2302–2308

Transfusion-Associated Microchimerism: A New Complication of Blood Transfusions in Severely Injured Patients

William Reed,[a,b] Tzong-Hae Lee,[a] Philip J. Norris[a,b,c] Garth H. Utter,[d] and Michael P. Busch[a,b]

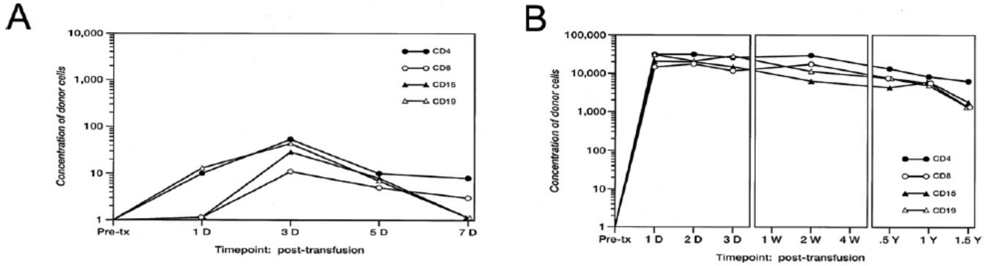


Figure 1 Representative survival kinetics of donor leukocyte subpopulations (including CD4, CD8, CD15, and CD19) following transfusion of female elective surgery (A) and severe trauma (B) patients. Frozen whole-blood samples were subjected to the enrichment of $CD4^+$, $CD8^+$, $CD15^+$, and $CD19^+$ leukocyte subpopulations, followed by amplification, hybridization, and quantitation using human Y-chromosome–specific primers and probe. Y-axis: concentration of donor cells per milliliter of recipient blood. X-axis: time points when recipient blood samples were collected. Reprinted from Lee et al, Blood, 1999.

Leukoreduction does not diminish tx-associated Microchimerism

Reed W, et al. Semin Hematol 2007:44:24-31
Utter G et al. Transfusion 2006 Nov;46(11):1863-9

Transfusion Reaction Summary

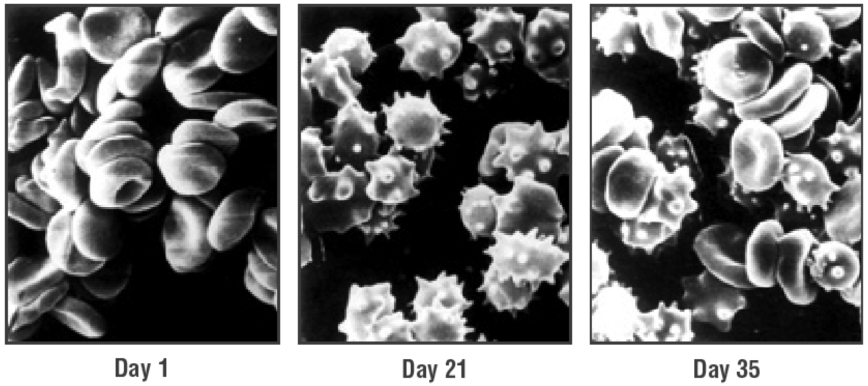
- AHTR can be fatal
- **Stop the Transfusion**
- Monitor for symptoms and complete evaluation
- FNHTR is a diagnosis of exclusion
- TRALI (ARDS-like reaction)
- Prevention methods – using filters, irradiation and premedication

Why is blood transfusion NOT associated with improved outcome?

Stored RBCs

- Decreased RBC deformability
- Decreased 2,3, DPG
- Metabolic acidosis
- Altered oxygen carrying capacity
- Increased red cell death with increased age of blood (~30% dead)
- No improvement in oxygen utilization at the tissue level

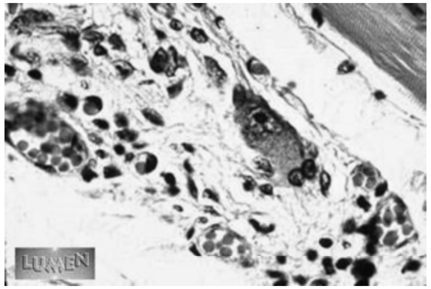
Age of Blood

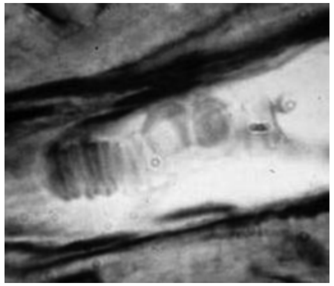


Scanning electron micrographs of red blood cells isolated from stored blood on Day 1, Day 21, and Day 35. During storage, the shape of RBCs changed gradually from normal discoid to echinocytes (dented or shriveled red cells).
Reproduced with permission from: Hovav et al. *Transfusion.* 1999;39:277-281.

Poor Efficacy of Blood Tx

- RBCs stored > 15 days lose deformability and ATP
- Altered capillary lumen size (decreased cross-sectional diameter) in critically ill patients
- Increased "stickiness" (adherence) of RBCs to altered endothelium in the microcirculation of critically ill pts.





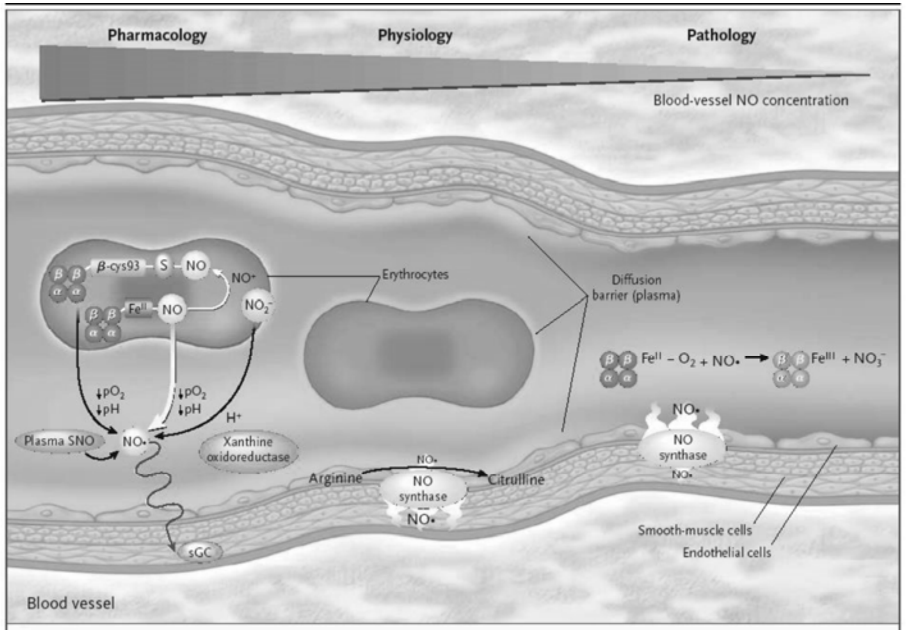
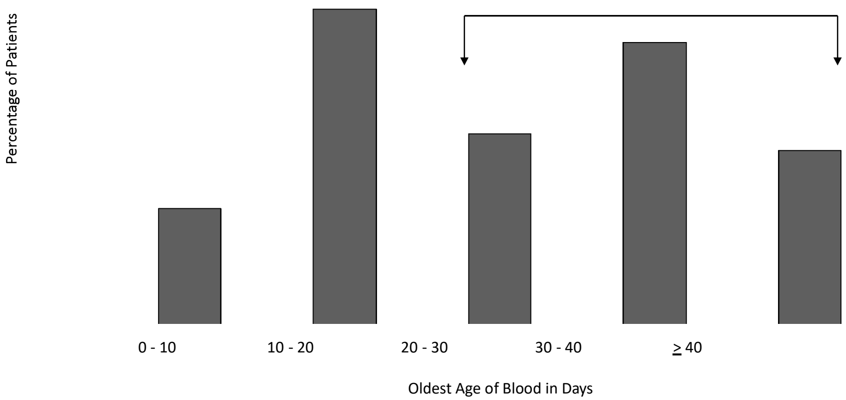


Figure 1. A Model of the Interactions of Nitric Oxide (NO) with Erythrocytes and Cell-free Hemoglobin in an Arterial Blood Vessel.

Schechter, Gladwin, NEJM April 10, 2003

Distribution of Transfused Units by Age of Blood – CRIT Study

60% of Blood transfused is > 20 days old



In Trauma Subset, 68% of blood is > 20 days old

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Duration of Red-Cell Storage and Complications after Cardiac Surgery

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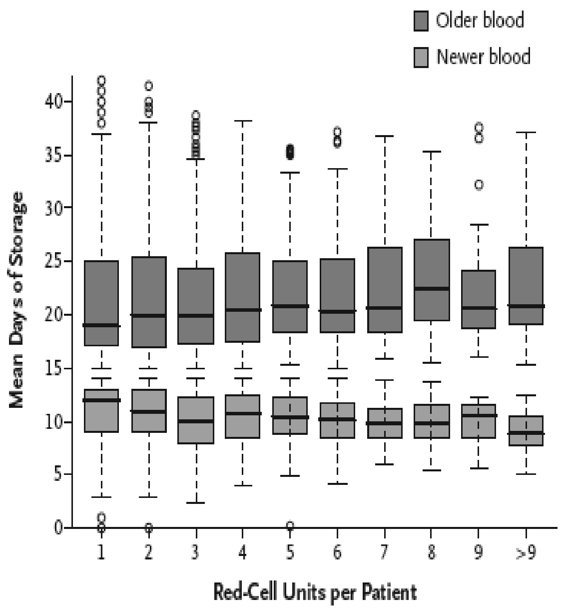
March 20, 2008

N Engl J Med 2008;358:1229-39.

- The median duration of storage was 11 days for newer blood and 20 days for older blood.
- Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, P = 0.004), intubation beyond 72 hours (9.7% vs. 5.6%, P<0.001), renal failure (2.7% vs. 1.6%, P = 0.003), and sepsis or septicemia (4.0% vs. 2.8%, P = 0.01).
- A composite of complications was more common in patients given older blood (25.9% vs. 22.4%, P = 0.001).
- Similarly, older blood was associated with an increase in the risk-adjusted rate of the composite outcome (P = 0.03).
- At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, P<0.001).



N Engl J Med 2008;358:1229-39.

Massive Transfusion

Definitions

- Replacement of one blood volume in a 24 hour period
- Transfusion of >10 units RCC in 24 hours
- Transfusion of 4 or more RCC within 1 hour when ongoing need is foreseeable
- Replacement of >50% of the total blood volume within 3-4 hours

Case Scenario

- A 27-year-old male was involved in a high speed RTA. Ambulance services brought him to our ER.
- Primary survey revealed :
  - A: Clear airway, central trachea
  - B: Respiratory rate 20, Pulse oximetry reading 95% on high flow oxygen
  - C: Heart rate 125, Arterial blood pressure 90 ⁄ 60 mmHg
  - D: Glasgow Coma Scale (GCS) 10 ⁄ 15 (E4, V2, M4), Symmetrical reactive pupils.
  - E: Exposure showed ....

A trauma series of X-rays: showed evidence of pelvic fracture with widening of the pubic symphysis and the sacroiliac joints.

fracture of the shaft of right femur.

- 20 min after arrival:
  - The patient became hemodynamically unstable with marked hypotension (BP 60 / 30) , tachycardia (HR 167)
  - Fall in hemoglobin (Hb) level from 11 $g.dl^{-1}$ to 5 $g.dl^{-1}$.

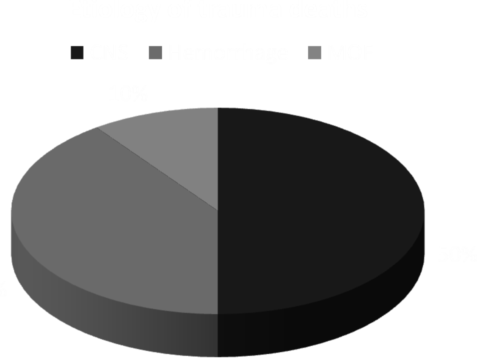
Classification of Hemorrhage

American College of Surgeons Committee on Trauma
Advanced Trauma Life Support Program

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (ml)	Up to 750	750-1,500	1,500-2,000	≥ 2,000
Blood loss (% blood volume)	Up to 15%	15%-30%	30%-40%	≥40%
Pulse rate	<100	>100	>120	≥140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiratory rate	14-20	20-30	30-40	>35
Urine output (ml/hr)	≥30	20-30	5-15	Negligible
CNS — mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Causes of death following multiple trauma

- Uncontrolled bleeding in Trauma represents 40% of multiple trauma-related deaths.



Current Orthopaedics (2004) 18, 304–310

…All bleeding eventually stops

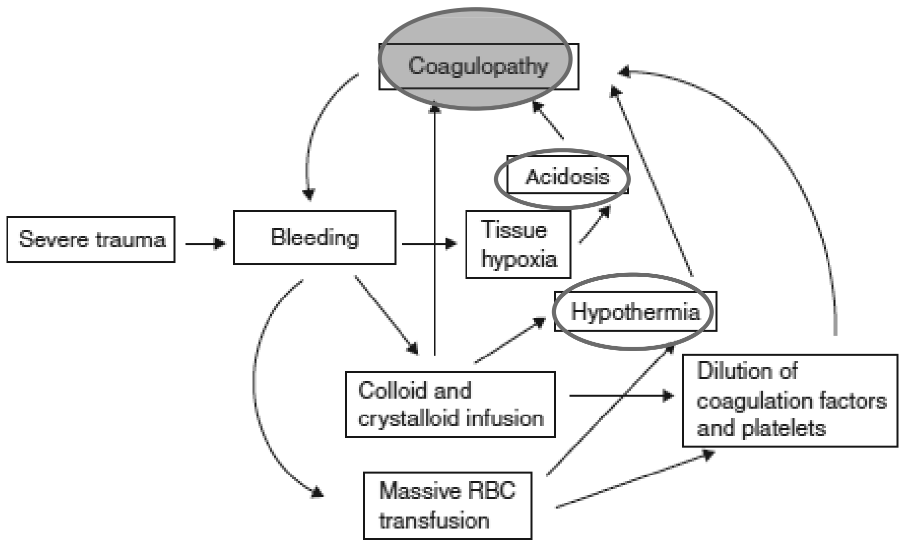
Epidemiology of Massive Transfusion

- Massive transfusion accounts for 3-5% of civilian and 8-10% of military trauma, but has a 30-60% mortality
  - Uncontrolled hemorrhage = most common cause of preventable early death
- Resuscitation with crystalloids/colloids or plasma-poor red cell concentrates causes dilutional coagulopathy
- Conducting a massive transfusion is a COMPLEX medical procedure
  - Health care professionals and hospitals remain ill-prepared for such an event

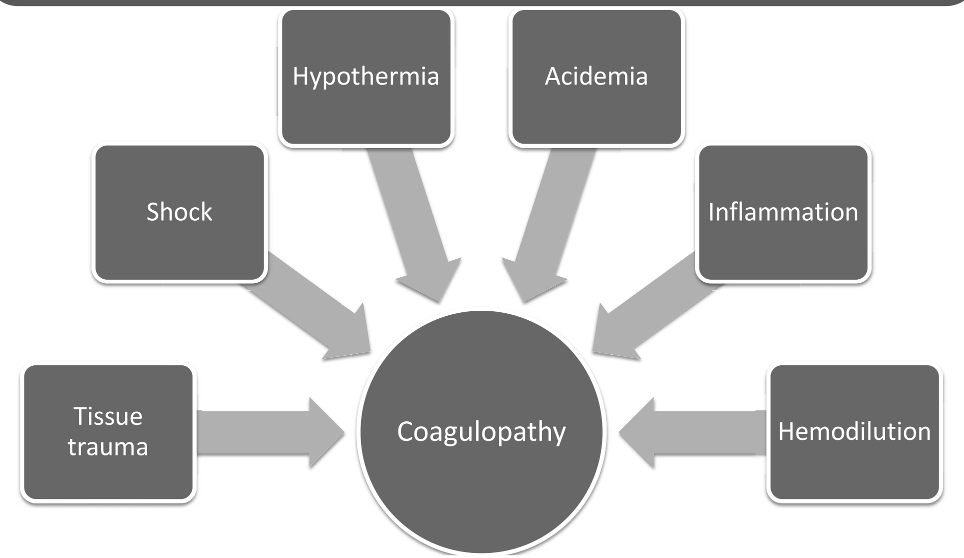
Winnipeg Regional Health Authority Caring for Health

University of Manitoba

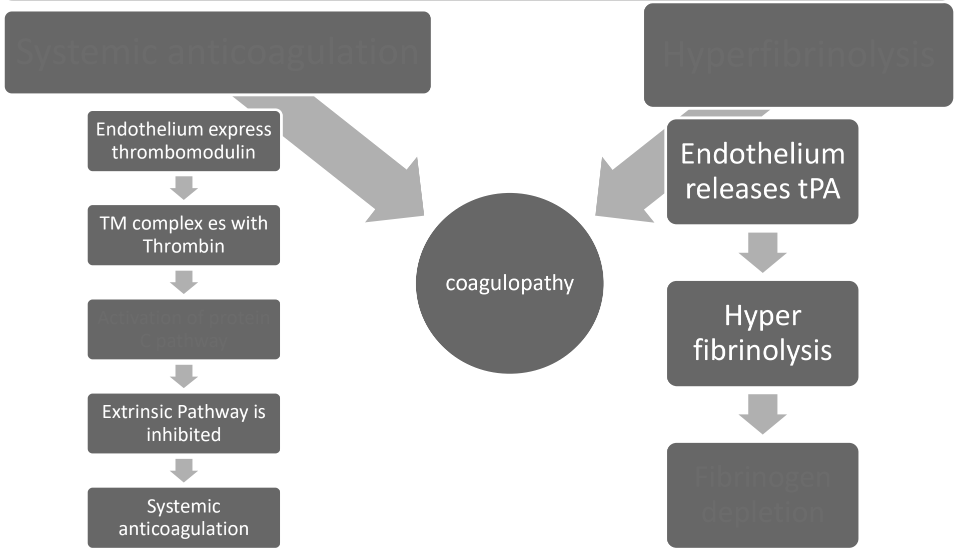
The Lethal Triad in Trauma



Mechanism of Coagulopathy in trauma



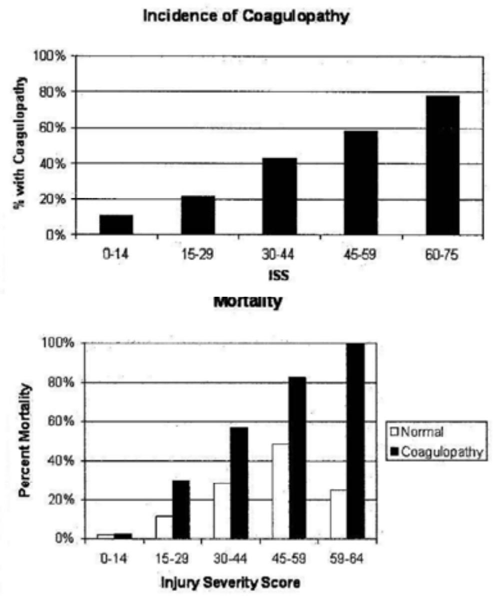
Mechanism of Coagulopathy in trauma

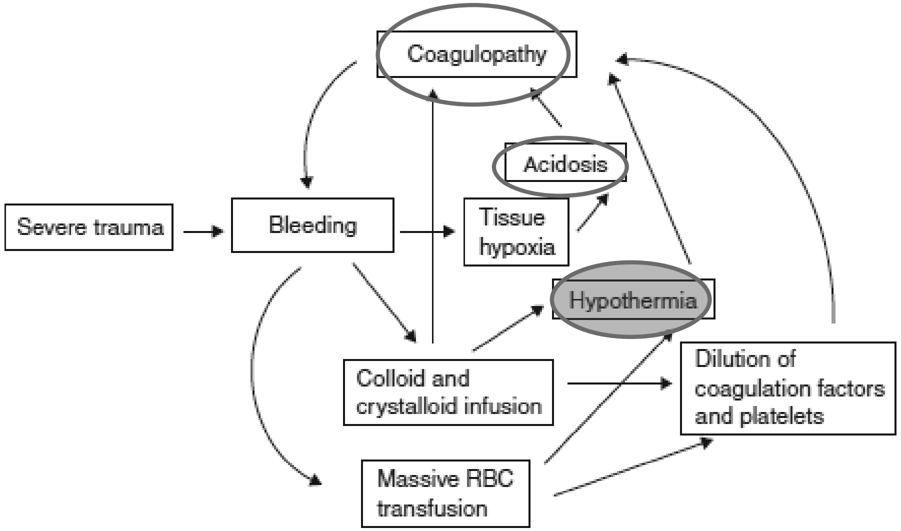


Acute Traumatic Coagulopathy

Karim Brohi, BSc, FRCS, FRCA, Jasmin Singh, MB, BS, BSc, Mischa Heron, MRCP, FFAEM, and Timothy Coats, MD, FRCS, FFAEM

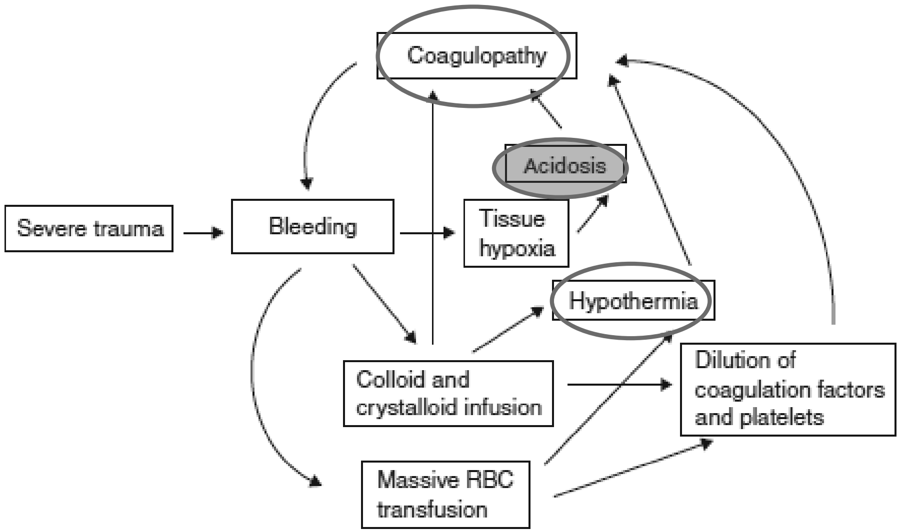
J Trauma. 2003;54:1127–1130.





Hypothermia

- A temperature < 35°C is associated with an increase in mortality.
- Trauma patients that are hypothermic are not perfusing their tissue
- The coagulation cascade is an enzymatic pathway that degrades with temperature and ceases at 33.3C
  - Reduces activity of clotting factors by 50% at 34 C
  - Platelet activation almost eliminated at 30 C



Acidosis

Base deficit (BD) ≥ 6 identifies patients that
- require early transfusion,
- increased ICU days and
- risk for ARDS and MOF

- BD of ≥ 6 is strongly associated with the need for MT and mortality.
- Patients have an elevated BD before their blood pressure drops to classic "hypotension" levels.
- Acidosis contributes more to coagulopathy more than hypothermia (not reversible)

Massive Blood Transfusion complications

- Fluid overload
- Thrombocytopnea
- Hypocalcemia
- Decreased oxygen release by transfused red cells due to 2,3-bisphosphoglycerate (2,3-BPG) levels (left shift in Hg-O2 curve).
- Hypothermia

Massive Blood Transfusion Management

- Haemostatic Resuscitation
- Fluid management
- Metabolic acid base correction
- Normal temperature
- Calcium management

Maintain Hb> 8 g.dl

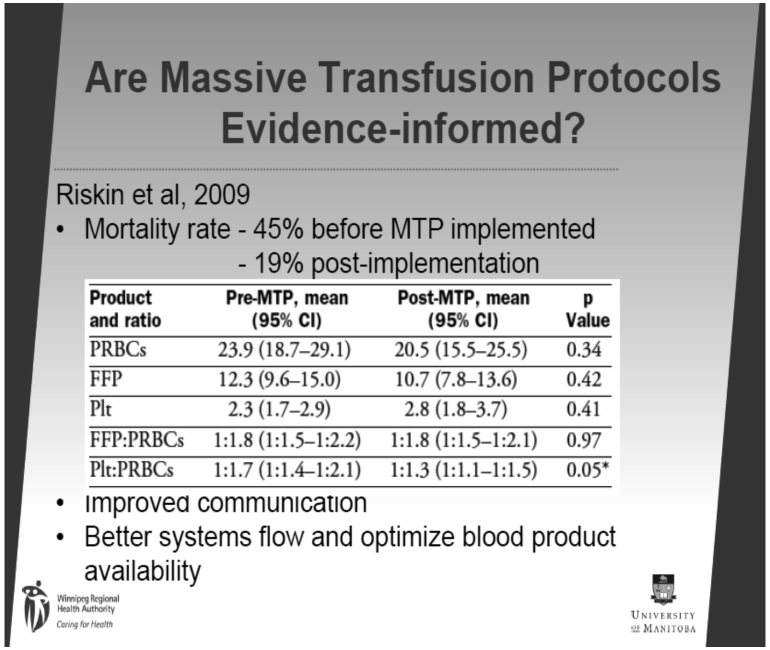
- Assess degree of urgency
- Employ blood salvage to minimize allogeneic blood use
- Give red cells
- Group O Rh D negative In extreme emergency Until ABO and Rh D groups known
- Use blood warmer and/or rapid infusion device if flow rate >50 ml/kg/h in adult

Maintain adequate coagualtion

- Anticipate platelet count <50 after 2 blood volume replacement.
- Maintain PT & APTT < 1.5 · mean control
- Give FFP 12–15 ml/kg guided by tests
- Anticipate need for FFP after 1–1.5 blood volume replacement
- Allow for 30 min thawing time

Maintain adequate coagulation

- Maintain Fibrinogen > 1.0 g/l
- If not corrected by FFP give cryoprecipitate (Two packs of pooled cryoprecipitate for an adult)
- Allow for 30 min thawing time
- Keep ionised Ca2+ > 1Æ13 mmol/l



Are Massive Transfusion Protocols Evidence-informed?

Riskin et al, 2009

- Mortality rate - 45% before MTP implemented
  - 19% post-implementation

Product and ratio	Pre-MTP, mean (95% CI)	Post-MTP, mean (95% CI)	p Value
PRBCs	23.9 (18.7–29.1)	20.5 (15.5–25.5)	0.34
FFP	12.3 (9.6–15.0)	10.7 (7.8–13.6)	0.42
Plt	2.3 (1.7–2.9)	2.8 (1.8–3.7)	0.41
FFP:PRBCs	1:1.8 (1:1.5–1:2.2)	1:1.8 (1:1.5–1:2.1)	0.97
Plt:PRBCs	1:1.7 (1:1.4–1:2.1)	1:1.3 (1:1.1–1:1.5)	0.05*

- Improved communication
- Better systems flow and optimize blood product availability

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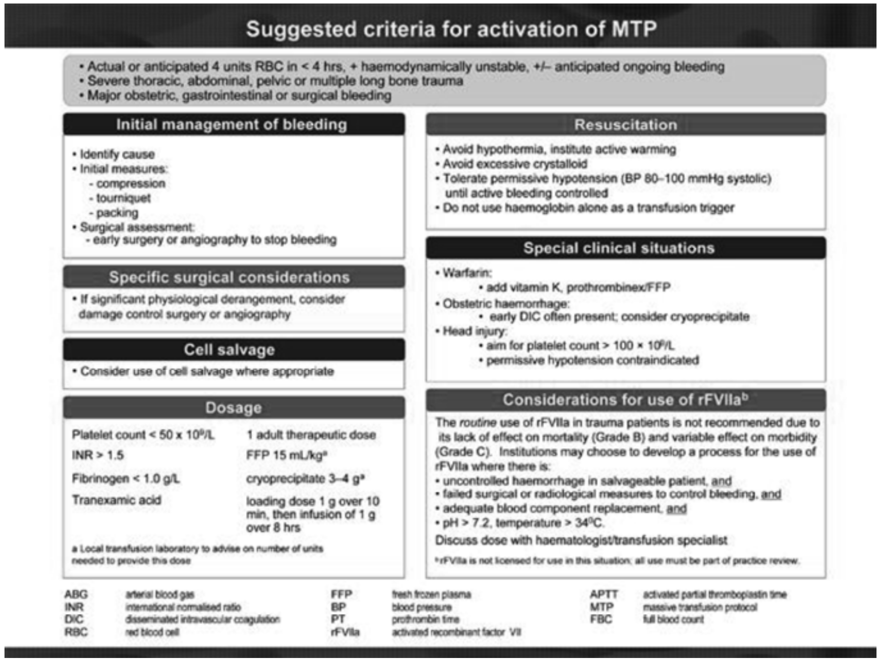


Suggested criteria for activation of MTP

- Actual or anticipated 4 units RBC in < 4 hrs, + haemodynamically unstable, +/– anticipated ongoing bleeding
- Severe thoracic, abdominal, pelvic or multiple long bone trauma
- Major obstetric, gastrointestinal or surgical bleeding

Initial management of bleeding

- Identify cause
- Initial measures:
  - compression
  - tourniquet
  - packing
- Surgical assessment:
  - early surgery or angiography to stop bleeding

Specific surgical considerations

- If significant physiological derangement, consider damage control surgery or angiography

Cell salvage

- Consider use of cell salvage where appropriate

Dosage

Platelet count < 50 x 10⁹/L	1 adult therapeutic dose
INR > 1.5	FFP 15 mL/kg[a]
Fibrinogen < 1.0 g/L	cryoprecipitate 3–4 g[a]
Tranexamic acid	loading dose 1 g over 10 min, then infusion of 1 g over 8 hrs

a Local transfusion laboratory to advise on number of units needed to provide this dose

Resuscitation

- Avoid hypothermia, institute active warming
- Avoid excessive crystalloid
- Tolerate permissive hypotension (BP 80–100 mmHg systolic) until active bleeding controlled
- Do not use haemoglobin alone as a transfusion trigger

Special clinical situations

- Warfarin:
  - add vitamin K, prothrombinex/FFP
- Obstetric haemorrhage:
  - early DIC often present; consider cryoprecipitate
- Head injury:
  - aim for platelet count > 100 × 10^9/L
  - permissive hypotension contraindicated

Considerations for use of rFVIIa[b]

The *routine* use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C). Institutions may choose to develop a process for the use of rFVIIa where there is:

- uncontrolled haemorrhage in salvageable patient, and
- failed surgical or radiological measures to control bleeding, and
- adequate blood component replacement, and
- pH > 7.2, temperature > 34°C.

Discuss dose with haematologist/transfusion specialist

b rFVIIa is not licensed for use in this situation; all use must be part of practice review.

ABG	arterial blood gas	FFP	fresh frozen plasma	APTT	activated partial thromboplastin time
INR	international normalised ratio	BP	blood pressure	MTP	massive transfusion protocol
DIC	disseminated intravascular coagulation	PT	prothrombin time	FBC	full blood count
RBC	red blood cell	rFVIIa	activated recombinant factor VII		

Haemostatic Resuscitation: FFP

- Meta-analysis from 2010-2012: Patients undergoing massive transfusion, high FFP to RBC ratios was associated with a significant reduction in the risk of death (odds ratio (OR) 0.38 (95%CI 0.24-0.60) and multiorgan failure (OR 0.40 (95%CI 0.26-0.60).

- Murad MH, Stubbs JR, Gandhi MJ, Wang AT, Paul A, Erwin PJ, Montori VM, Roback JD: The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. *Transfusion* 2010, 50:1370-1383

Haemostatic Resuscitation: FFP

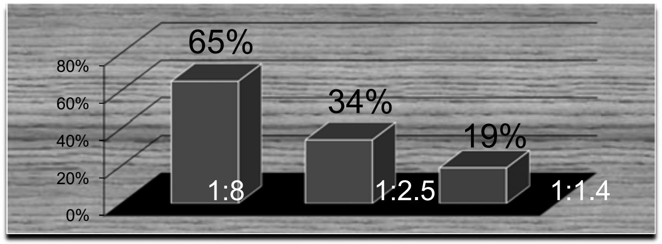
- Meta-analysis from 2012 reports of reduced mortality in trauma patients treated with the highest FFP or PLT to RBC ratios.

- Johansson PI, Oliveri R, Ostrowski SR: Hemostatic resuscitation with plasma and platelets in trauma. *A meta-analysis. J Emerg Trauma Shock* 2012, 5:120-125.

Coagulopathy of Massive Transfusion

Mortality Vs FFP/RBC ratio

- Retrospective review of 246 patients receiving a massive transfusion (> 10 units of blood)



Borgman MA. et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital J trauma, 2007. 66:805-813

Haemostatic Resuscitation: Plts

- Platelets are also pivotal for hemostasis: low Plts increases mortality.
- The highest survival was established in patients who received both a high PLT:RBC and a high FFP:RBC ratio.

- Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, Williams KL, Park MS: Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg* 2008, 248:447-458.

Haemostatic Resuscitation: plt

- Retrospective study of massively transfused patients: As apharesis platelet to RBC ratio increased, a stepwise improvement in survival was seen and a high apheresis PLT:RBC ratio was independently associated with improved survival.

- Zink KA, Sambasivan CN, et al: **A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study.** *Am J Surg* 2009, **197:**565-570.

What is the optimal ratio of blood products ?

TRANSFUSION

Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients

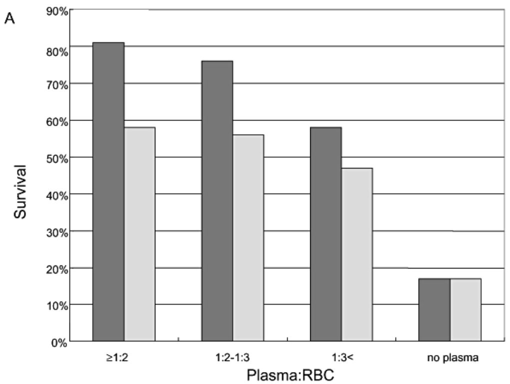
Beth H. Shaz, Christopher J. Dente, Jeffrey Nicholas, Jana B. MacLeod, Andrew N. Young, Kirk Easley, Qiang Ling, Robert S. Harris, Christopher D. Hillyer

Article first published online: 5 OCT 2009
DOI: 10.1111/j.1537-2995.2009.02414.x

Issue

Transfusion
Volume 50, Issue 2, pages 493–500, February 2010

A



B

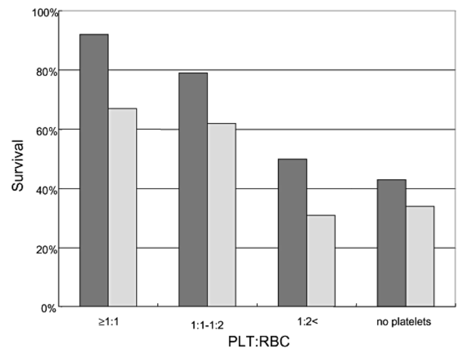
Plasma:RBC	≥1:2	1:2-1:3	1:3<	no plasma
n	86	66	38	24
24-hour survival	81%	76%	58%	17%
30-day survival	58%	56%	47%	17%
ISS(ave)	30	26	27	27
Penetrating	47%	44%	47%	50%
MTP	81%	56%	47%	29%

C

Plasma:RBC	n	MTP	24-hour survival	30-day survival	ISS (ave±SD)	Penetrating
high	100	79%	80%	59%	29 ±12	49%
low	114	46%	58%	44%	27 ±14	44%
		p<0.01	p<0.01	p=0.03	p=0.46	p=0.45

Figure 1. Plasma:RBC product transfusion ratios effect on patient survival. (A) Survival versus ratio. () 24-hour survival; () 30-day survival. (B) Patient characteristics in each ratio group. (C) Patient outcome and characteristics in high (one or more plasma per two RBC products) versus low (less than one plasma per two RBC products) transfusion group. Ave = average.

A



B

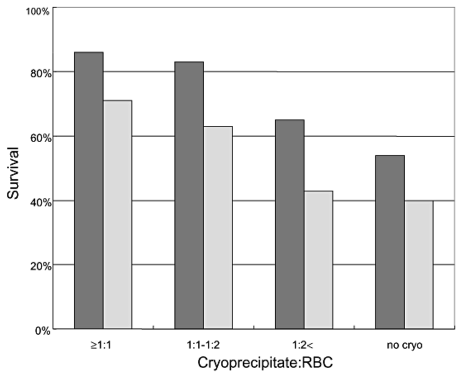
PLT:RBC	≥1:1	1:1-1:2	1:2<	no PLTs
n	48	78	32	56
24-hour survival	92%	79%	50%	43%
30-day survival	67%	62%	31%	34%
ISS(ave)	32	26	28	28
Penetrating	38%	51%	50%	45%
MTP	58%	69%	53%	59%

C

PLT:RBC	n	MTP	24-hour survival	30-day survival	ISS (ave±SD)	Penetrating
high	126	65%	84%	63%	28 ±12	46%
low	88	57%	45%	33%	28 ±14	47%
		p=0.22	p<0.01	p<0.01	p=0.97	p=0.93

Figure 2. PLT-to-RBC product transfusion ratios effects on patient survival. (A) Survival versus ratio. () 24-hour survival; () 30-day survival. (B) Patient characteristics in each ratio group. (C) Patient outcome and characteristics in high (one or more apheresis PLTs per 20 RBC products) versus low (less than one apheresis PLTs per 20 RBC products) transfusion group. Ave = average.

A



B

Cryoprecipitate:RBC	≥1:1	1:1-1:2	1:2<	no cryoprecipitate
n	28	59	37	90
24-hour survival	86%	83%	65%	54%
30-day survival	71%	63%	43%	40%
ISS(ave)	29	30	28	26
Penetrating	50%	37%	46%	51%
MTP	64%	54%	57%	68%

C

Cryoprecipitate:RBC	n	MTP	24-hour survival	30-day survival	ISS (ave±SD)	Penetrating
high	87	57%	84%	66%	30 ±14	41%
low	127	65%	57%	41%	27 ±12	50%
		p=0.29	p<0.01	p<0.01	p=0.09	p=0.24

Figure 3. Cryoprecipitate-to-RBC product transfusion ratios effects on patient survival. (A) Survival versus ratio. () 24-hour survival; () 30-day survival. (B) Patient characteristics in each ratio group. (C) Patient outcome and characteristics in high (one or more unit of cryoprecipitate per two RBC products) versus low (less than 1 unit of cryoprecipitate per two RBC products) transfusion group. Ave = average.

- Pre-defined Massive Transfusion Protocols are associated with REDUCTION of organ failure and post injury complication J Trauma 2009 Jan ; 66(1) 41-48

Ratio 10-4-2: RBC-FFP-PLts

	Pre-MMT (n-141)	MMT (n=129)	P-values
24hr survival (%)	61	69	0.185
30d survival (%)	**37.6**	**56.8**	**0.001**
Hospital length of stay d (+/-SD)	16.4(+/-12.1)	12 (+/-12.1)	0.049
ICU stay, (days)	6.6(+/-9.4)	5.0 (+/- 8.3)	0.239
Ventilator (days)	8.2 (+/-9.7)	5.7 (+/-7.2)	0.017
IO crystalloid, Litres	7L	4.8L	<0.001
IO blood products units	11U	14.7U	0.001
24hr blood products	38.7U	31.2U	0.05

Complications comparison

	Pre-MMT (n-141)	MMT (n=129)	P-values
Systemic inflammatory response syndrome SIRS (%)	55.3	52.8	0.682
Severe sepsis/septic shock (%)	19.8	10	0.019
Ventilator-dependent respiratory failure(%)	62.4	60.8	0.787
VAP(%)	39	27.2	0.041
Abdominal compartment syndrome(%)	9.9	0	<0.001
Open abdomen(%)	30.5	6.4	<0.001
Need of Renal replacement therapy(%)	2.8	3.2	0.826

- Pre-defined Massive Transfusion Protocols are associated with REDUCTION of organ failure and post injury complication J Trauma 2009 Jan ; 66(1) 41-48

Ratio 10-4-2: RBC-FFP-PLts

Fresh Whole Blood:

- Routine use of fresh whole blood (FWB) for resuscitation of bleeding patients was abandoned in the civilian setting.
- In the combat setting, however, FWB has been used.
- In a report of US military patients in Iraq and Afghanistan from January 2004 to October 2007, those with hemorrhagic shock, a resuscitation strategy that included FWB was associated with improved 30-day survival (95% vs. 82%, p=0.002).

- Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB: Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma* 2009, 66:S69-S76.

Haemostatic Agents:

- Antifibrinolytis: Shakur H, et al: CRASH-2 Trial collaborators: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet* 2010, 376:23-32.
- Recombinant factor VII: Hauser CJ at al: Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *J Trauma* 2010, 69:489-500.
- Fibrinogen concentrate
- Prothrombin complex concentrate

- Questions?