Massive Blood Transfusion Protocols

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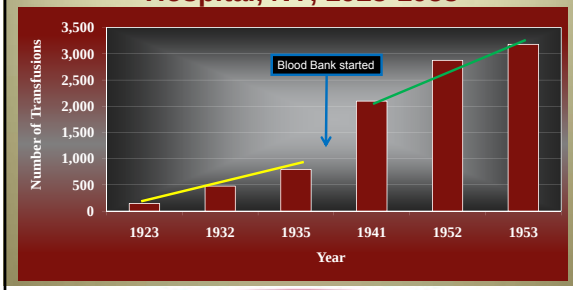
Definitions

- Massive transfusion: Generally defined as transfusion of at least one blood volume (i.e., 10 or more units of blood) within 24 hours
  - Some use 12 hours
  - Some use 6 hours
  - Whole blood units are no longer used, so units of PRBCs is commonly used in definition

Mortality Among Trauma Patients Undergoing Massive Transfusion

Study (1st author)	Year	Average # of PRBC transfusions	Hospital Mortality Rate
Phillips	1987	33 U PRBCs	61%
Wudel	1991	33 U PRBCs	48%
Cosgriff	1997	24 U PRBCs	43%
Velmahos	1998	32 U PRBCs	69.5%
Cinat	1999	63 U PRBCs	71%
Vaslef	2002	33 U PRBCs	57%
Como	2004	25 U PRBCs	39%
Huber-Wagner	2007	20 U PRBCs	35.1%

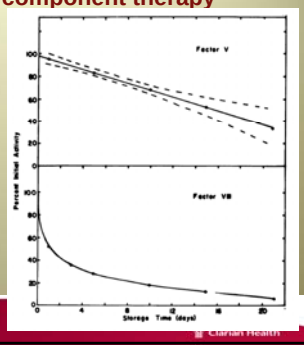
Blood Transfusions at Mount Sinai Hospital, NY, 1923-1953



-Lewisohn R: SG&O 1955; 101:362

Different optimal storage techniques drove the development of component therapy

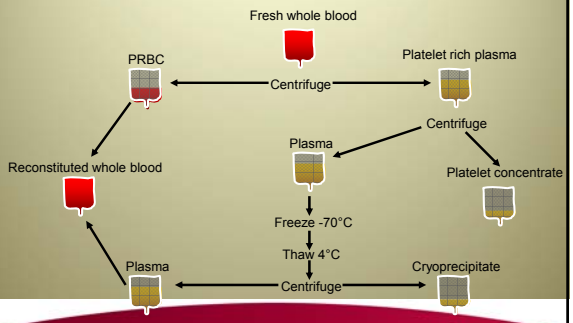
- Techniques for whole blood storage do not preserve components other than RBCs
- Clotting factors
  - Especially Factors V and VIII
  - Can be stored indefinitely in frozen state
- Platelets
  - Dense granules leak out of platelets stored at 4°C, making them nonfunctional
  - Retain 70% or more of their original viability (and clotting factors except FVIII) when stored at room temperature (20-24°C)



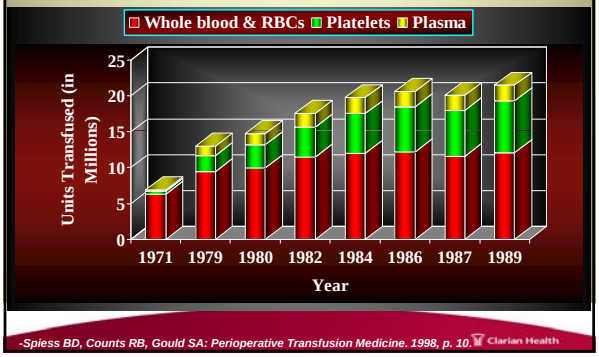
Key Technologies Permitting Component Therapy

- Anticoagulants (1914-1915)
  - Donation process could be separated in time and space from transfusion process
- Plasma fractionation techniques (late 1940s)
- Plastics (1950s)
  - Permitted removal of plasma after separation or centrifugation
- Cryoprecipitate (1965)

Extraction of Blood Components in the 19080s



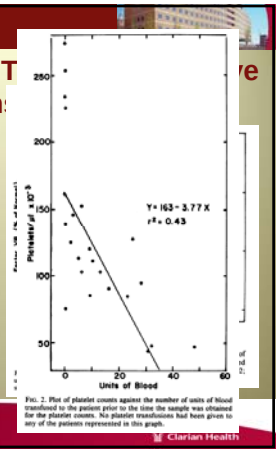
Transfusions in the United States



-Spiess BD, Counts RB, Gould SA: Perioperative Transfusion Medicine. 1998, p. 10.

History of Component T ve Blood Tran

- Deficiency of Factors V & VIII in stored whole blood did not translate into serious deficiencies in MT patients [Counts, et al.: Ann Surg 1979; 190(1):91-99]:
  - Factor VIII levels actually higher than normal
    - Potentially due to its role as an acute phase reactant
- However, dilutional thrombocytopenia was observed



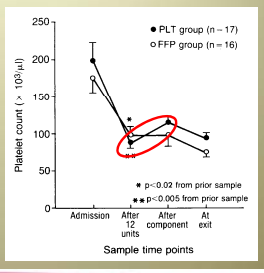
Prophylactic platelet administration in massive transfusion (Reed et al: Ann Surg 1986; 203:40-48)

- Prospective, randomized, controlled clinical trial of patients undergoing massive transfusion comparing:
  - 6 U platelet concentrates (420 ml) Q12 RBC units

  VS.
  - 2 U FFP (440 ml) Q12 RBC units
- Only functional difference was the addition of platelets in the study group

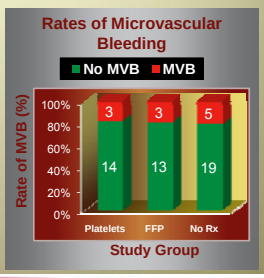
Prophylactic platelet administration in massive transfusion (Reed et al: Ann Surg 1986; 203:40-48)

- Both groups showed equivalent drops in platelet counts
- Platelet group showed slight increase after prophylactic component administered

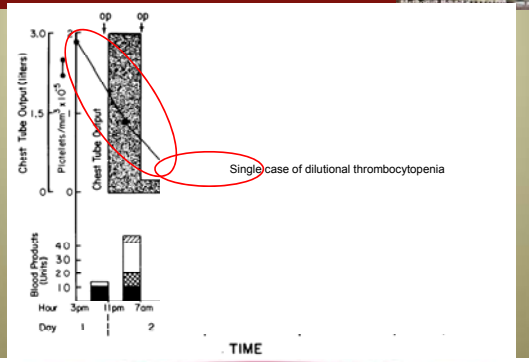


Prophylactic platelet administration in massive transfusion (Reed et al: Ann Surg 1986; 203:40-48)

- Rates of microvascular bleeding
  - No different between platelet and FFP groups
  - No different from previous study from same group [Counts, et al.: Ann Surg 1979; 190(1):91-99]:



How bad is dilutional thrombocytopenia?



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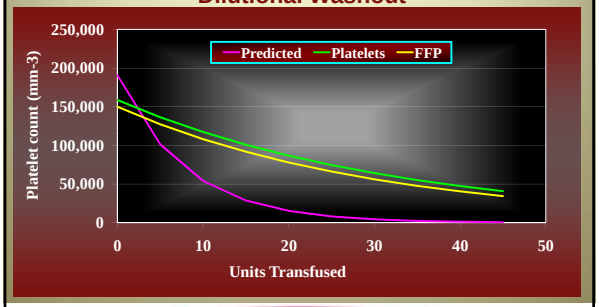
Prophylactic Platelet & FFP Transfusion vs. Dilutional Washout



-Reed, et al: Ann Surg, 1986; 203:40-48

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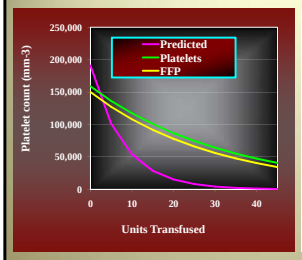

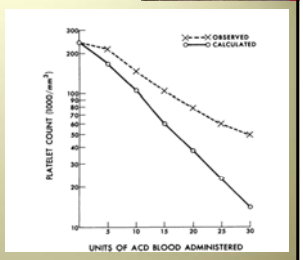

Reed, et al.: Ann Surg 1986; 203:40-48 **Miller, et al.: Ann Surg 1971; 174:794-801**

- Dilutional coagulopathy previously noted by Miller, et al., in Vietnam
- Also noted that observed platelet counts exceeded those predicted by exponential washout equation

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Historical Perspective on Massive Transfusion

- Whole blood fractionation
- Component therapy became primary mode of blood delivery
  - Improved resource utilization
  - Improved safety
  - Regulatory approval focused on RBC membrane viability & ATP concentrations
- Regulatory approval not based on
  - Oxygen delivery capability by stored RBCs
  - Impact of stored RBCs on inflammation & immune function

Component Therapy Established in 1980s

- Red blood cells
  - Addressed by NIH Consensus Development Conference Statement, June 27-29, 1988
- Platelets
  - Addressed by NIH Consensus Development Conference Statement, October 6-8, 1986
- Plasma
  - Addressed by NIH Consensus Development Conference Statement, Sept. 24-26, 1984

Problems with Component Therapy in Massive Transfusion

- No evidence documenting equivalent clinical outcomes in trauma patients between whole blood & component therapy
- Previous studies of prophylaxis indicated dilutional impact occurred early
  - Resuscitation protocols that initiated clotting factor & platelet administration after dilutional effect weren't effective
  - Only whole blood transfusion would effectively prevent dilutional coagulopathy

Problems with Component Therapy in Massive Transfusion

- Storage age of PRBCs has been prolonged to 42 days
  - Transfusion of older stored PRBCs to critically ill adults is independently associated with
    - Increased infection risk
    - Multi-organ failure
    - Death
  - Transfusion of fresh blood should prevent such problems
    - "Replace what they're losing"

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Warm Fresh Whole Blood (WFWB) vs. Component Therapy (CT)

Spinella PC, et al.: J Trauma 2009;66:S69-S76

- WFWB has been used out of necessity in US combat hospitals in Afghanistan & Iraq
  - >6,000 units transfused
- Retrospective analysis of
  - 100 WFWB MT pts. (WFWB w/PRBCs & FFP but no aPlts vs.
  - 254 CT MT pts. (PRBCs, FFP, & aPlts, but no WFWB)
- Similar demographics and injury severity

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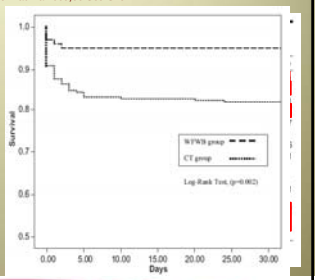
Warm Fresh Whole Blood (WFWB) vs. Component Therapy (CT)

Spinella PC, et al.: J Trauma 2009;66:S69-S76

- WFWB pts. received
  - Fewer PRBC units
  - Fewer FFP units
  - Median of 5 units WFWB
- There were more massive transfusion cases in the WFWB patients
- Overall survival was improved in WFWB patients



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Feasibility of Warm Fresh Whole Blood

- WFWB logistically more feasible in military operations
  - Thousands of available donors in disciplined environment
- Civilian setting has no such capability
  - Component therapy developed to deal with more efficient use of scarce resources
- Giving all components at the initiation of MT could mimic WFWB except for
  - Storage lesion
  - Inflammatory stimulus

Retrospective Studies of FFP:RBC Ratios in Massive Transfusion

Author	Year	# MT Pts	FFP:RBC Ratio	% Mortality
Borgman	2007	246	1:8 vs 1:2.5 vs 1:1.4	65 vs 34 vs 19
Maegele	2008	713	<1:1 vs 1:1 vs >1:1	46 vs 35 vs 24
Holcomb	2008	466	< 1:2 vs ≥1:2	60 vs 40
Sperry	2008	415	< 1:1.5 vs ≥1:1.5	35 vs 28
Gunter	2008	259	< 2:3 vs ≥2.3	62 vs 41
Duchesne	2008	135	1:4 vs 1:1	88 vs 26
Zink	2009	452	1:4 vs 1:4-1:1 vs ≥1:1	55 vs 41 vs 26
Kashuk	2008	133	≤1:5 vs 1:4 vs 1:3 vs ≥1:2	77 vs 58 vs 39 vs 40
Scalea	2008	81	No differences observed	
Snyder	2009	134	1:3.7 vs 1:1.3	58 vs 40
Teixeira	2009	383	≤1:8 vs >1:8-≤1:3 vs >1:3-≤1:2 vs >1:2	90 vs 49 vs 25 vs 26

Retrospective Studies of Platelet:RBC Ratios in Massive Transfusion

Author	Year	# MT Pts	FFP:RBC Ratio	% Mortality
Holcomb	2008	466	< 1:2 vs ≥1:2	60 vs 40
Perkins	2009	462	<1:16 vs 1:16-<1:8 vs ≥ 1:8	57 vs 40 vs 25
Zink	2009	452	1:4 vs 1:4-1:1 vs ≥1:1	44 vs 47 vs 27
Johansson	2009	832	1:1.6 vs 1:1.3	32 vs 24

Summary of Recent Studies of Massive Transfusion

- Nearly all studies indicate that higher FFP:RBC ratios and higher Platelet:RBC ratios are associated with lower 24-hour & 30-day mortalities
- It is difficult to glean which ratios are optimum
- Current consensus is that 1:1: 1 ratios are likely ideal, although definitive evidence is lacking

Problems with Recent Massive Transfusion Studies

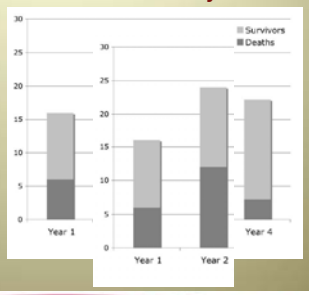
- All are retrospective
  - Different methods of stratification by injury severity and/or degree of shock
  - No consistency in FFP:PRBC or Plt:PRBC ratios evaluated
- Potential survivor bias involved
  - i.e., patients with more severe injuries die more rapidly before FFP & Platelets are administered
  - So low FFP:PRBC & Plt:PRBC ratios have higher mortalities
  - Some studies excluded patients who died in the first hour
- No control on timing of component transfusions
  - Some were administered within 24 hours, some within just a few hours

Is Mortality Improved Due to Different Ratios or Better Supply Routes?

- Riskin, et al. (J Am Coll Surg 2009;209:198–205.) reviewed MTP protocol implementation at Stanford
- In 2005, started a protocol supporting
  - 1:1.5 FFP:PRBC ratio
  - improved communications
  - enhanced systems flow to optimize rapid blood product availability

Massive Transfusion Protocols: The Role of Aggressive Resuscitation Versus Product Ratio in Mortality Reduction

- Mortality was significantly reduced after protocol initiation
  - 45% before
  - 19% after



Riskin, et al.: J Am Coll Surg 2009;209:198–205.

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Massive Transfusion Protocols: The Role of Aggressive Resuscitation Versus Product Ratio in Mortality Reduction

- Despite the protocol change, the FFP:PRBC ratio did not change
  - 1:1.8 before & after
- The Plt:PRBC ratio did change
  - 1:1.7 before
  - 1:1.3 after

Table 2. Mean Units and Ratios of Product Used, Pre- and Postmassive Transfusion Protocol 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*

*Statistically significant; $p \leq 0.05$.
FFP, fresh frozen plasma; MTP, massive transfusion protocol; Plt, platelets; PRBCs, packed red blood cells.

Riskin, et al.: J Am Coll Surg 2009;209:198–205.

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What did change was the efficiency of blood delivery

Table 3. Mean Minutes to First Transfusion of Type-Specific Blood Products Before and after Implementation of Massive Transfusion Protocol

Product	Pre-MTP, mean (95% CI)	Post-MTP, mean (95% CI)	Average time savings:
PRBCs	115 (85–146)	71 (49–93)	44 minutes
FFP	254 (185–323)	169 (130–209)	85 minutes
Platelets	418 (316–519)	241 (169–311)	177 minutes

*Statistically significant; $p \leq 0.05$.
FFP, fresh frozen plasma; MTP, massive transfusion protocol; PRBCs, packed red blood cells.

Riskin, et al.: J Am Coll Surg 2009;209:198–205.

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Massive Transfusion Coagulopathy's Relationship to Shock

Table 1. Clinical data (mean ± SD)

	Group I	Group II	Group III	Group IV	Group V
Patients	8	7	7	7	7
Shock period, min	0	23 ± 8	65 ± 18	150 ± 13	299 ± 58
Blood substitution, liters	1.5 ± 2.2	12.6 ± 3.5	10.9 ± 1.7	12.8 ± 2.1	13.7 ± 2.5
Storage time, days	7.1 ± 2.8	10.5 ± 1.8	8.0 ± 2.5	8.1 ± 2.4	8.7 ± 2.1

- Older small study out of Germany
- Categorized massively transfused patients by their duration of shock
- Volume of transfusion was not significantly different between the groups

Harke & Rahman: Massive Transfusion in Surgery and Trauma. New York: Alan R Liss, 1982, pp 213-224.

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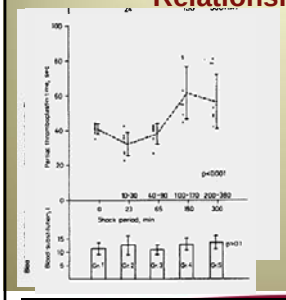
Massive Transfusion Coagulopathy's Relationship to Shock



- Platelet counts fell proportional to the duration of shock (and not the volume of transfusion)
- Clotting times (PTT) appeared to prolong as the duration of shock worsened
- Duration of shock appeared to have a direct relationship to mortality
- Given that resuscitation volumes were similar in all 5 groups, dilution may not play as much of a role as do shock and underresuscitation

Harke & Rahman: Massive Transfusion in Surgery and Trauma. New York: Alan R Liss, 1982, pp 213-224.

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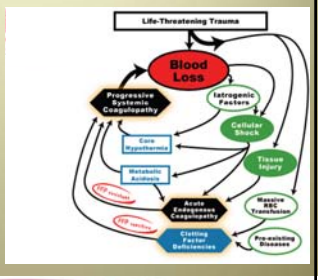
General Sense of the Current Knowledge

- Massively transfused patients have a high mortality and frequently develop the lethal triad
  - Coagulopathy
  - Acidosis
  - Hypothermia
- Damage control surgery & resuscitation help to correct the problem
- Most of the coagulopathy is probably consumptive in nature, although dilution, hypothermia, and acidosis contribute



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Clarian Methodist MBTP

- Developed by multidisciplinary group over 6 months
  - Goal is1:1:1 transfusion of components
  - Will track
    - Adherence to protocol
    - Component consumption
    - Timing of administration
    - FFP:PRBC & Plt:PRBC ratios
    - Patient outcomes
- Went live on January 12,2010
  - Used on 40 patients through July 17, 2010
  - Analysis is underway

Who will need massive transfusion?

- Variables used in identification of potential massive transfusion patients
  - Heart rate > 120
  - Systolic blood pressure < 90
  - Unstable pelvis on physical examination
  - Free fluid on abdominal ultrasound
  - pH < 7.25
  - Base excess < -2
  - Hematocrit < 32%
  - Hemoglobin ≤ 11
- No rapid accurate predictive model yet exists

Massive Transfusion: Current State of the Art in Trauma

- Trauma patients in severe shock with signs of ongoing hemorrhage
  - ATLS: ABCs
  - C: Volume resuscitation with
    - Crystalloid
    - PRBCs:FFP:Plt in a 1:1:1 or 1:1:0.5 ratio
    - Determination & control of bleeding sources
      - Embolization
      - Damage control laparotomy
      - Aggressive ICU resuscitation
      - Later definitive repairs

Summary

- "Prophylactic" transfusions after the initiation of massive transfusion are ineffective
  - Dilution has already occurred
- Recent data suggests that 1:1:1 transfusion protocols are associated with lower 30-day mortalities
  - Could potentially be due to more efficient delivery of components and shorter duration of shock
- Immediate repletion and continued resuscitation with warm fresh whole blood has the greatest likelihood of providing fresh effective blood to bleeding victims.

Future Directions

- Better prediction of who needs massive transfusion
  - Encourages earlier initiation of effective resuscitation
- Ideally, point of care testing of coagulation status
  - Rapid turnaround would permit more rapid correction of deficiencies
- Simpler systems for rewarming and resuscitation

Questions and Answers

(You may need to turn up the volume.)