Blood and Blood Product Transfusion

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- Blood and Blood Products
- Indications for transfusion
- Complications of transfusion
- Massive blood transfusion

- **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.

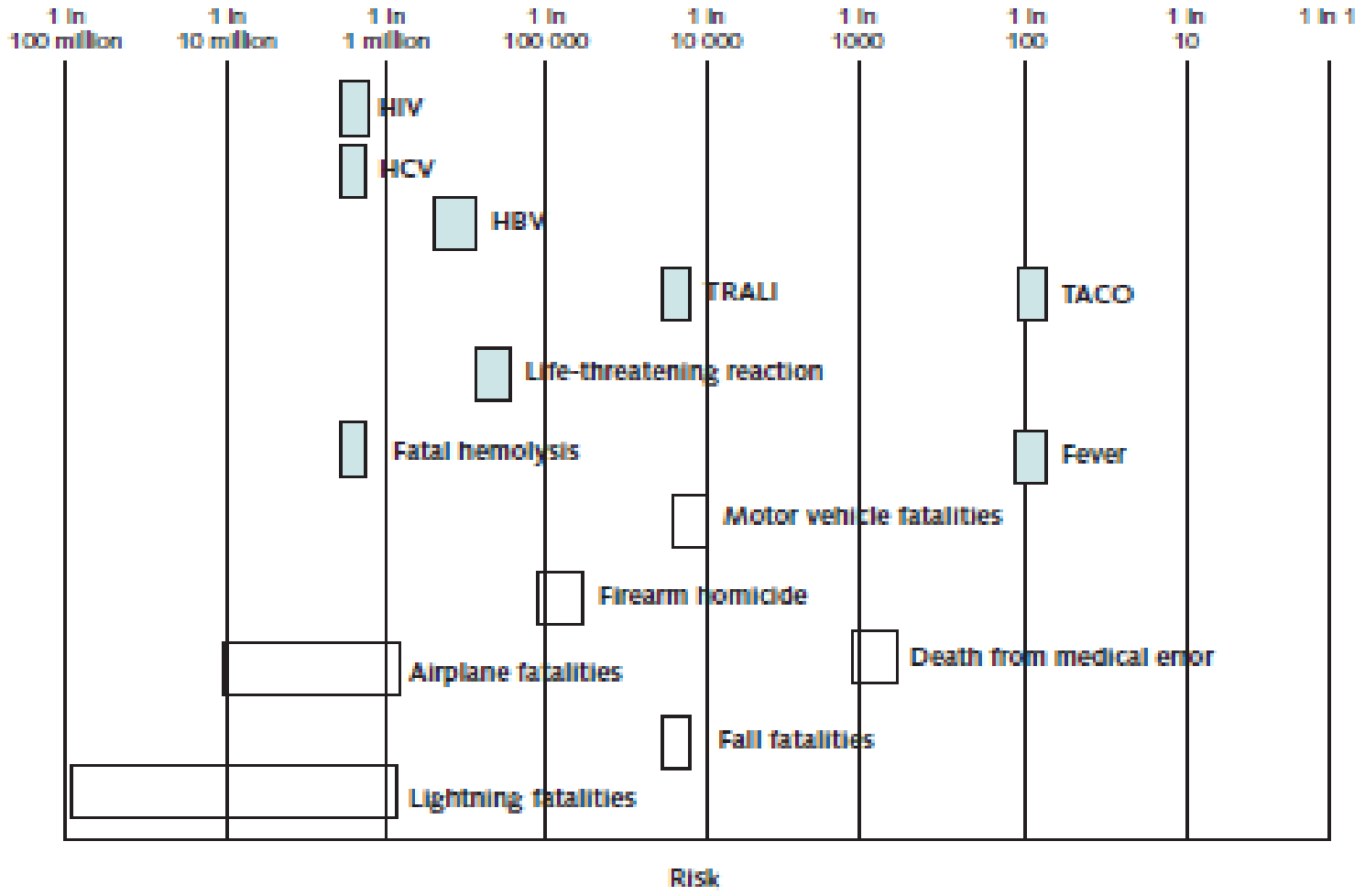
Takei T, Amin NA, Schmid G, Dhingra-Kumar N, Rugg D. Progress in global blood safety for HIV. J Acquir Immune Defic Syndr. 2009;52 Suppl 2:S127-31. [PMID: 19901625]

- Approximately 118 million units of blood are collected worldwide each year.1

World Health Organization. Blood transfusion. June 8, 2022. Accessed February 23, 2023. https://ww.who.int/news-room/facts-in-pictures/detail/blood-transfusion

- Clinicians should offer RBC transfusion to patients only when benefits outweigh harms

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



RATIONALE FOR TRANSFUSION

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

Why ?

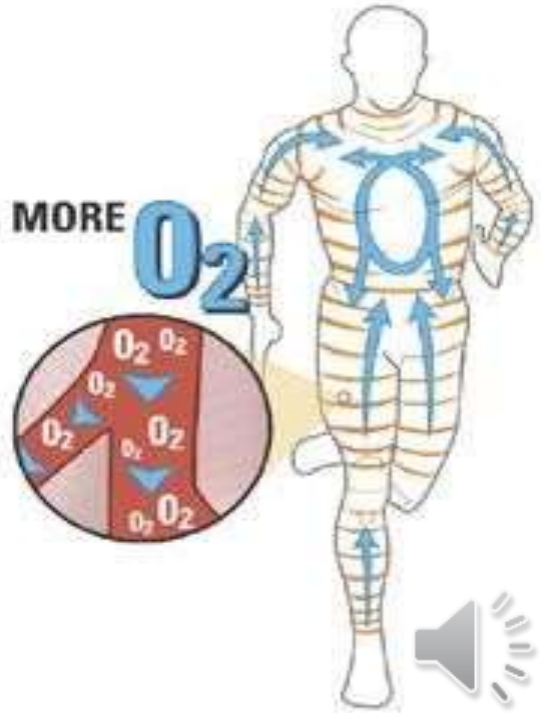
- The body at rest uses approx **250ml O2/L blood**
- O2 delivery can fall with a reduction in any of:
  - Cardiac Output
  - Hb concentration
  - O2 saturation
- Organs most sensitive to hypoxia are Heart and Brain

Why?

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

= Cardiac Output x Oxygen content of blood

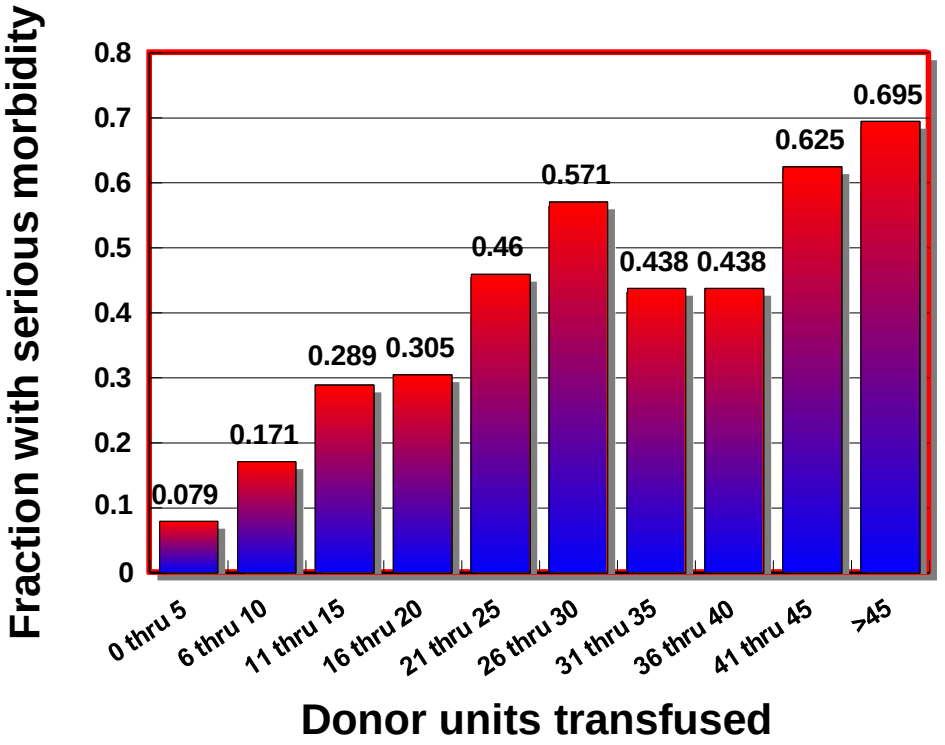
$$Hb \times SaO_2$$



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

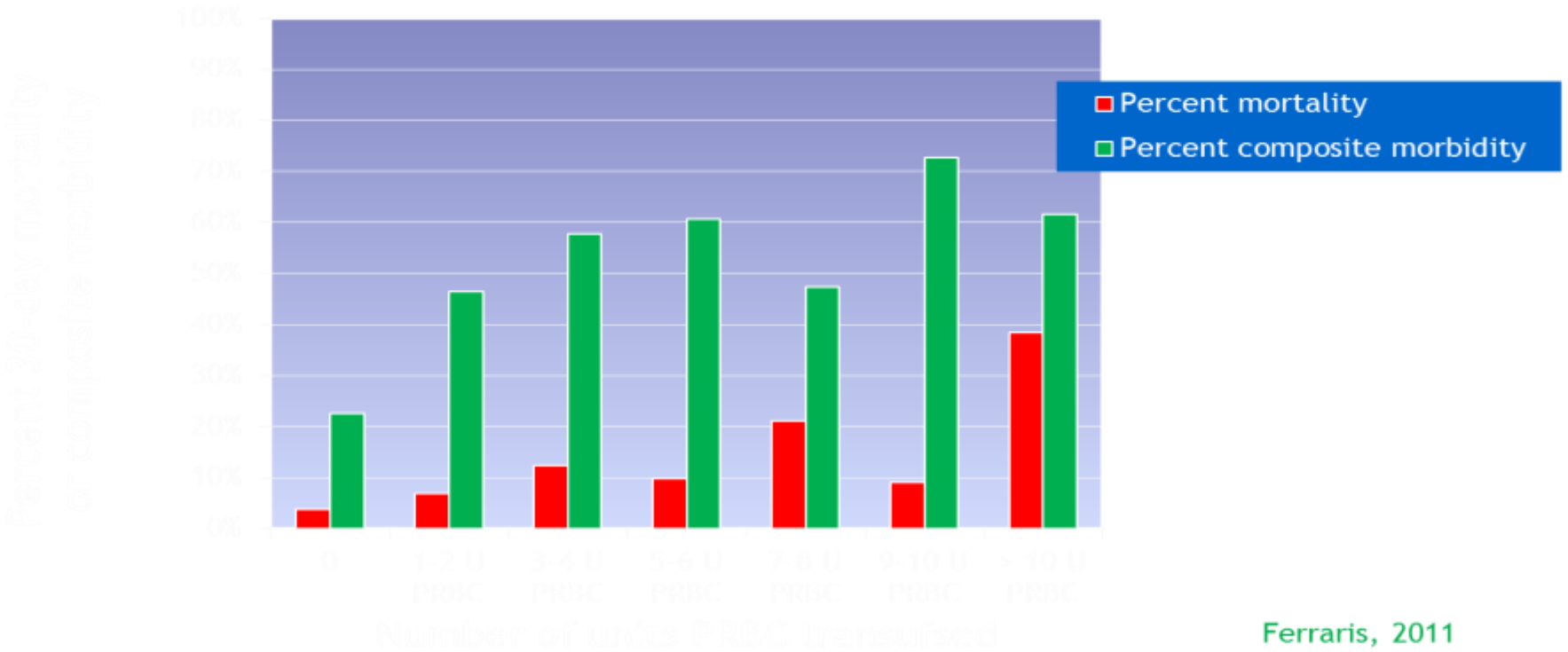
Transfusion & Serious Morbidity in 4,445 Cardiac Surgical Patients



- Serious morbidity and mortality increase with the amount transfused.

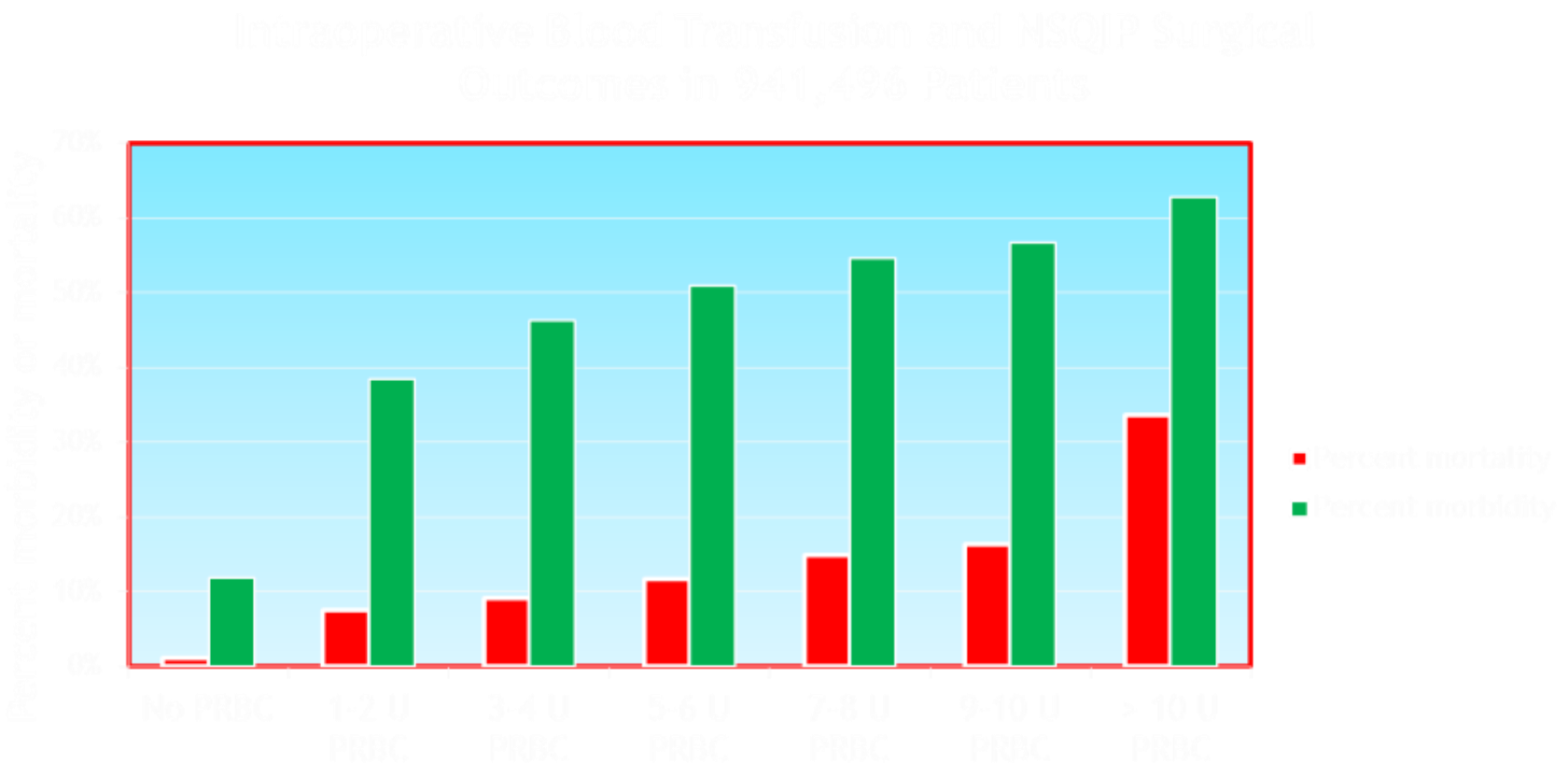
Ferraris, Intl J Angiol, 2006

Intraoperative Blood Transfusion & Lung Surgery



Ferraris, 2011

Blood Transfusion in General Surgical Population



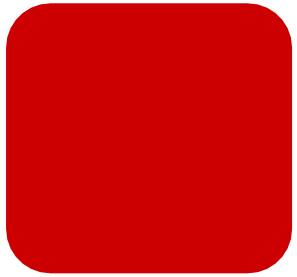
Blood Components

- 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

Closed System



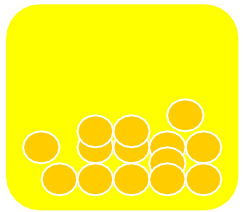
Whole Blood
Main Bag

Satellite Bag
1

Satellite Bag
2

First

RBC's

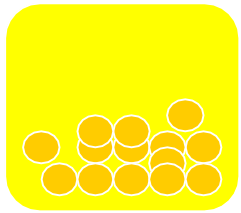


Platelet-rich
Plasma

Differential Centrifugation

Second Centrifugation

RBC's



Platelet-rich Plasma

Second

RBC's

Platelet Concentrate

Plasma

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.

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

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

- 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)

When to transfuse

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

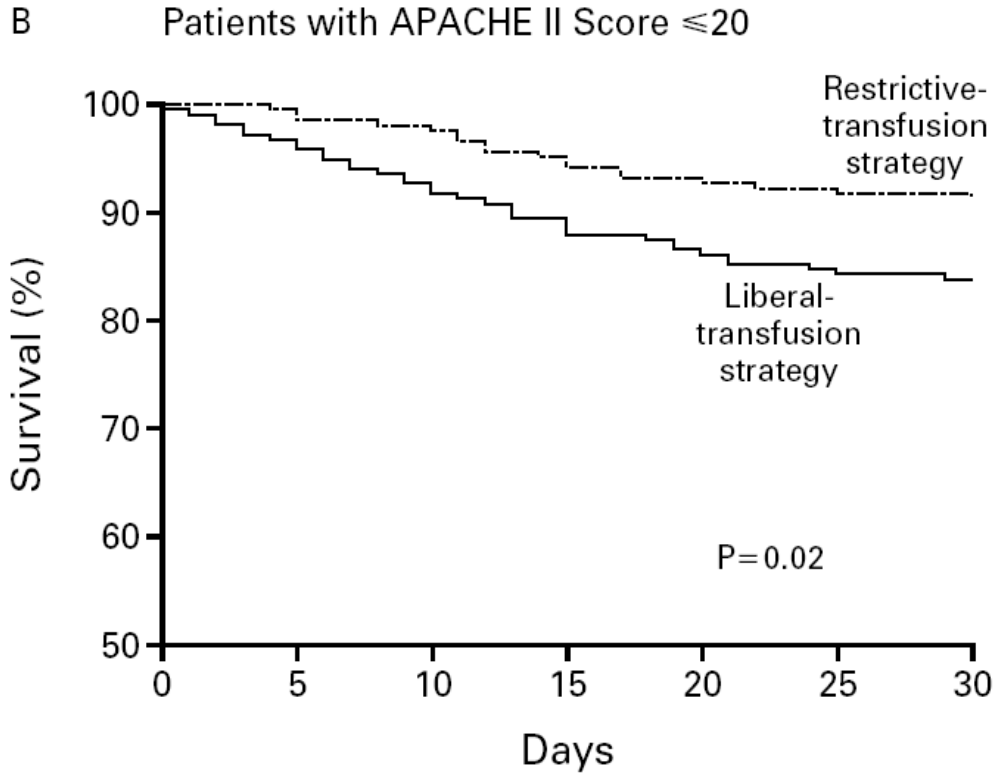
The TRICC Study

No difference 30 day mortality

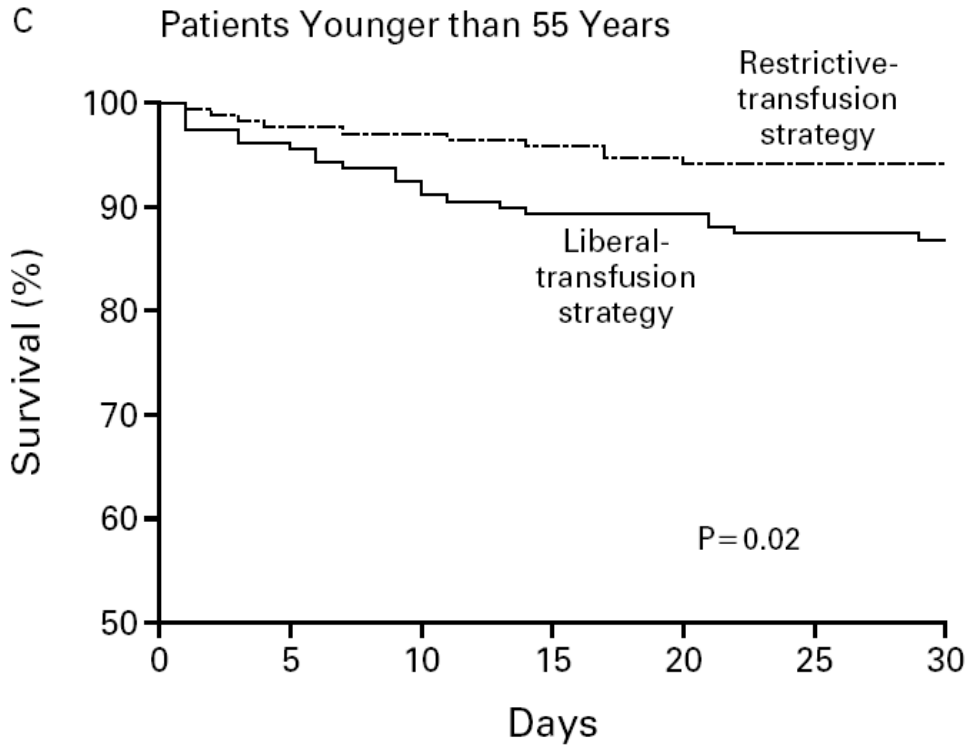
In “healthy” (APACHE II < 20) and young (<55yrs) patients
Transfusion increased mortality

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."

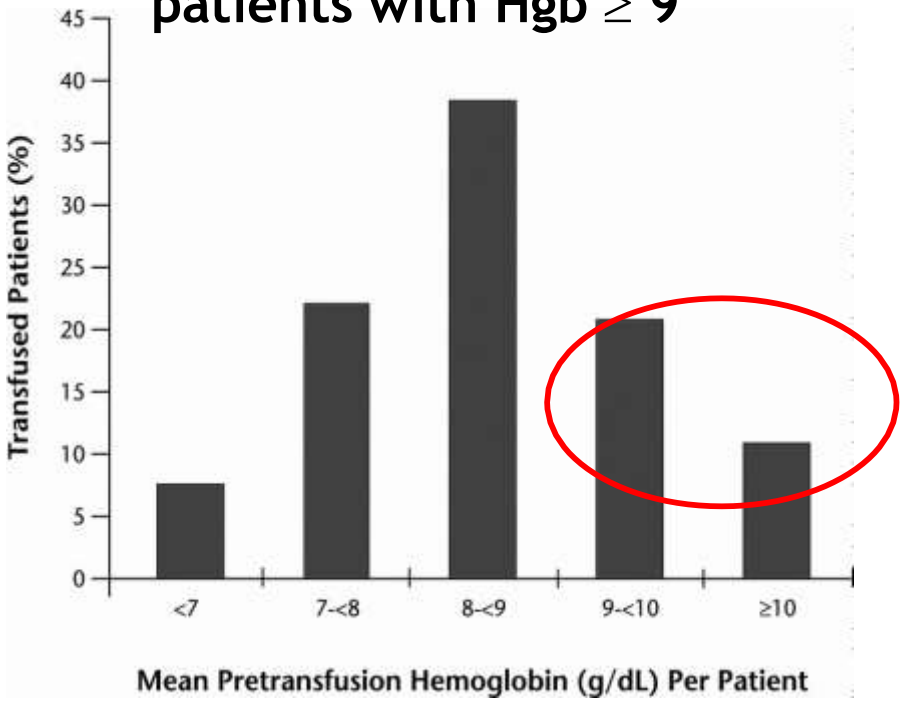
CRIT Study

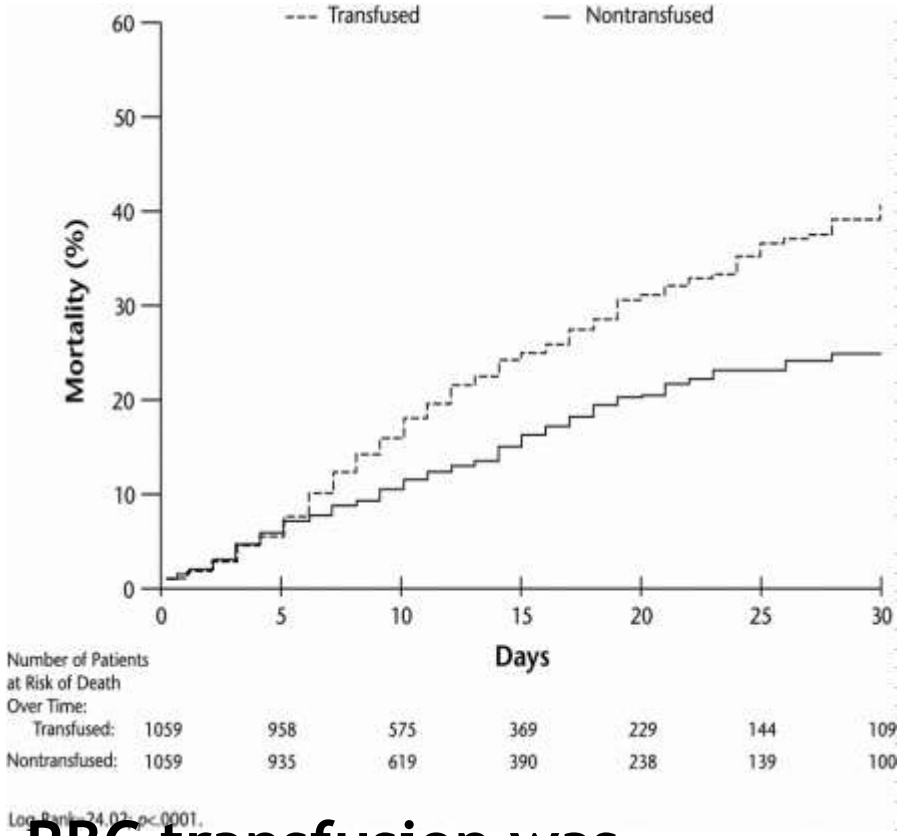
- Prospective, multiple center, observational cohort study of 4,892 ICU pts in the US
- Propensity score matched
- Designed to examine the relationship of anemia and RBC transfusion with clinical outcomes
- Almost 95% of patients admitted to the ICU have a Hb level below “normal” by day 3
- In total, 11,391 RBC units were transfused.
- Overall, 44% of pts admitted to the ICU received one or more RBC units while in the ICU

Crit Care Med. 2004 Jan;32(1):39-52

CRIT Results

35% of Blood transfused in patients with Hgb ≥ 9





The mean pre-transfusion Hb was
8.6 ± 1.7 g/dL

RBC transfusion was independently associated with higher mortality (OR 1.65 CI 1.35-2.03). OR 2.62 transfused p <

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 <7
- Hgb 7-8

- Transfusion recommended
- **Restrictive Transfusion Strategy** for stable patients

  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).

– 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)

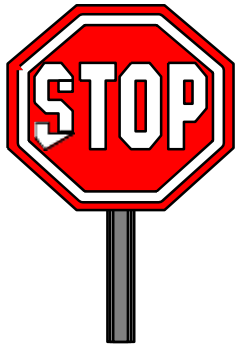
- Occurs when incompatible RBC's are transfused into a recipient who has pre-formed antibodies (usually ABO or Rh)
- Antibodies activate the complement system, causing intravascular hemolysis
- Symptoms occur within minutes of starting the transfusion
- This hemolytic reaction can occur with as little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

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 (Direct AntiglobulinTest)
- Repeat crossmatch
- Repeat Blood group typing
- Blood culture

Labs found with AHTR

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

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

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)

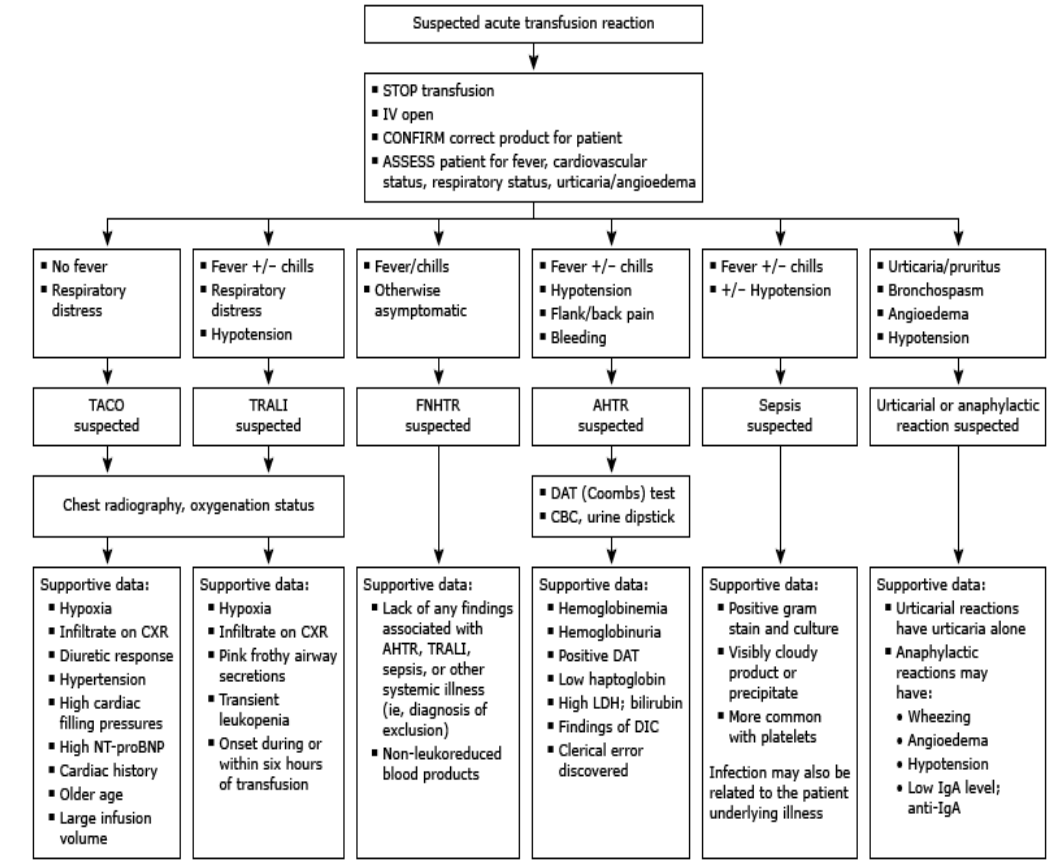
TRAL

I

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

Initial approach to a suspected acute transfusion reaction



This graphic includes some of the most common and life-threatening reactions; other reactions are also possible and should be pursued if the clinical picture seems inconsistent with one of these. The transfusion service should be notified of any severe transfusion reaction and may request samples of the transfused product and patient blood; the transfused product should not be discarded until discussion with the transfusion service has taken place. In cases of suspected AHTR, the transfusion service must be contacted immediately because another patient may be at risk of receiving the incorrect blood product. Refer to UpToDate topics on transfusion reactions for further details of the evaluation and management of these conditions.

TACO: transfusion-associated circulatory overload; TRALI: transfusion-related acute lung injury; FNHTR: febrile nonhemolytic transfusion reaction; AHTR: acute hemolytic transfusion reaction; ALI/ARDS: acute lung injury/adult respiratory distress syndrome; DAT: direct antiglobulin test (Coombs test); CBC: complete blood count; CXR: chest x-ray; LDH: lactate dehydrogenase; DIC: disseminated intravascular coagulation.

Massive Transfusions

- Coagulopathy may occur after transfusion of massive amounts of blood (trauma/surgery)
- Coagulopathy is caused by failure to replace plasma
- 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 Infections

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

Transfusion: Infectious Disease

- ✓ HIV = 1 in 1.8 million
- ✓ HCV = 1 in 1.6 million

HIV = human immunodeficiency virus.
HCV = hepatitis C virus.
HBV = hepatitis B virus.

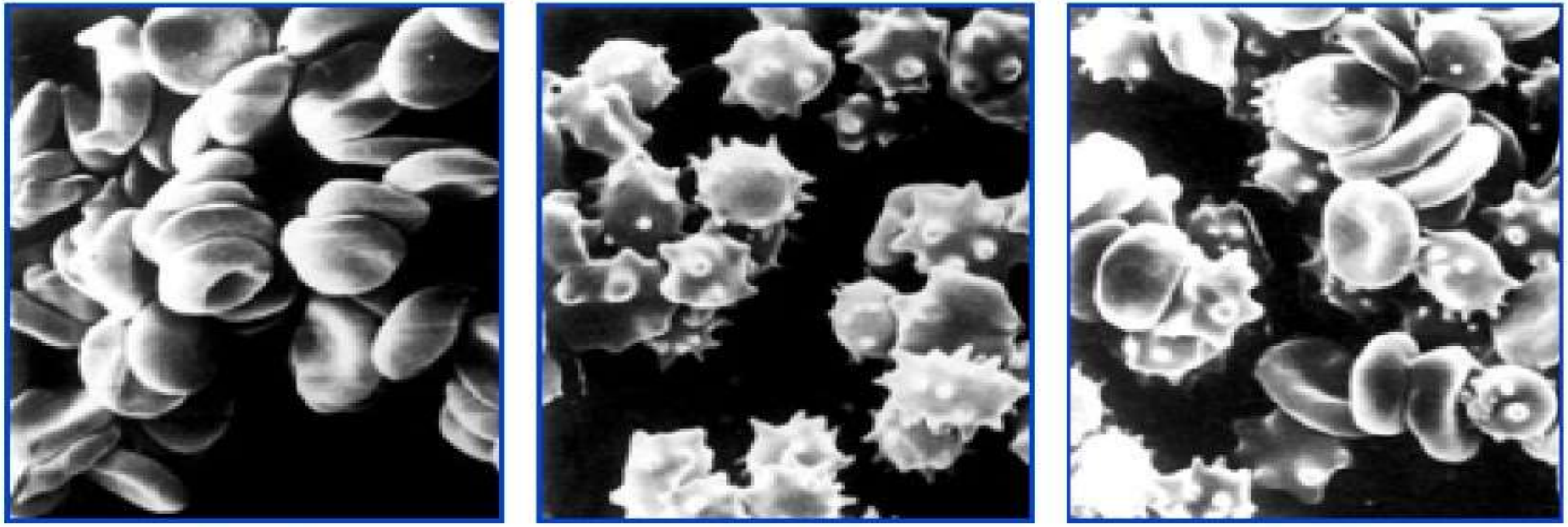
usch MP, et al. *JAMA*. 2003;289:959-62.

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



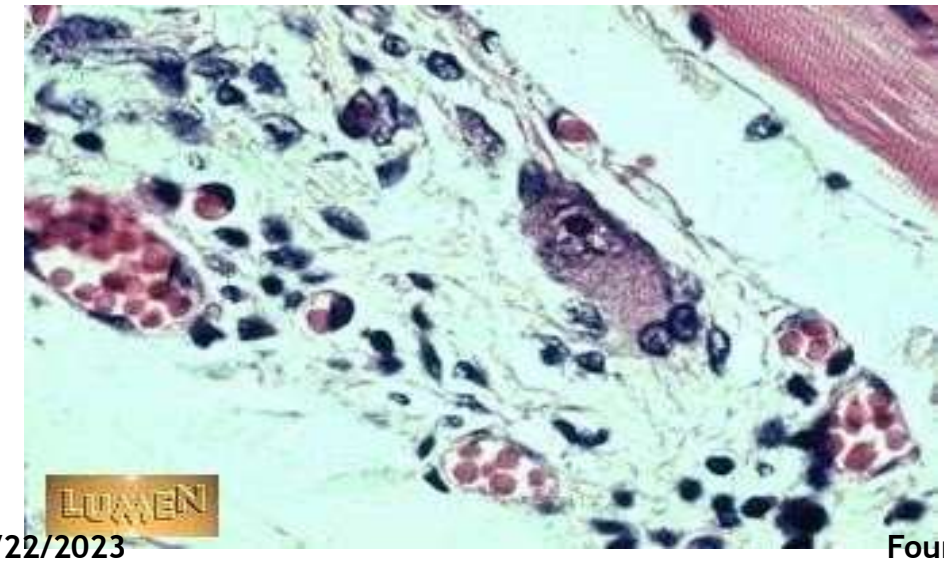
Day 1 Day 21 Day 35

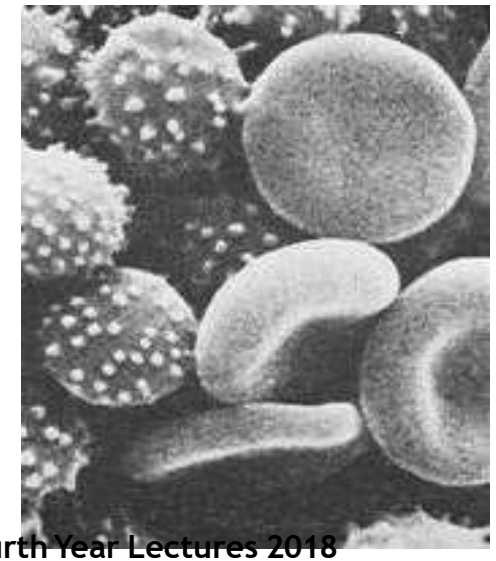
Scanning electron micrographs of red blood cells isolated from stored blood on Day 1, Day 21, and Day 35. During storage, the shape of RBCs changed gradually from normal discoid to echinocytes (dented or shriveled red cells).

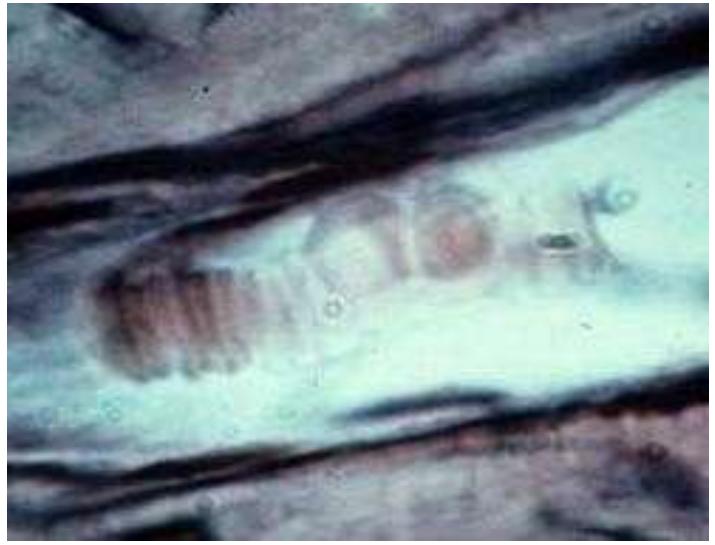
Reproduced with permission from: Hovav et al. *Transfusion*. 1999;39:277-281.

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.

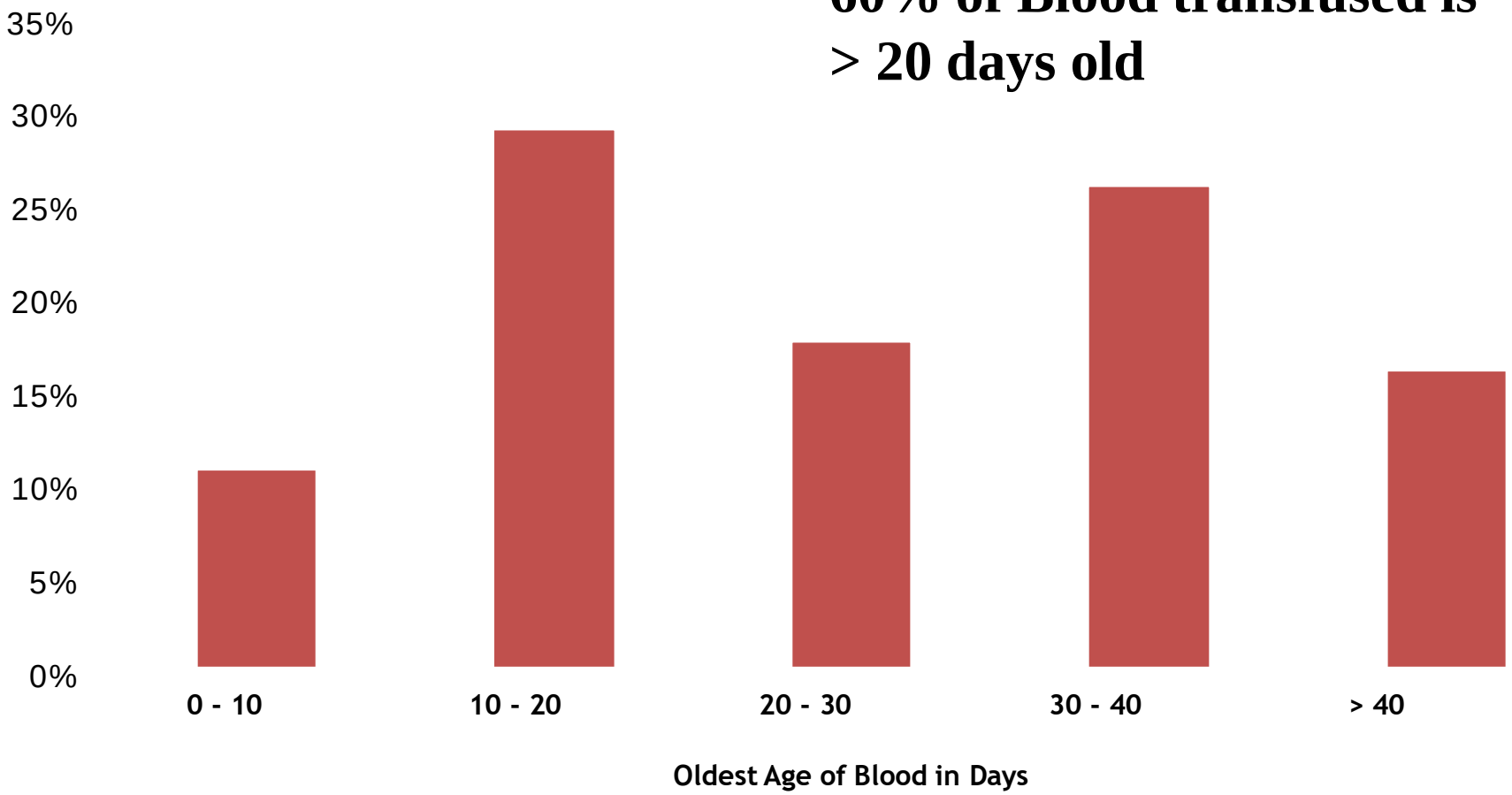






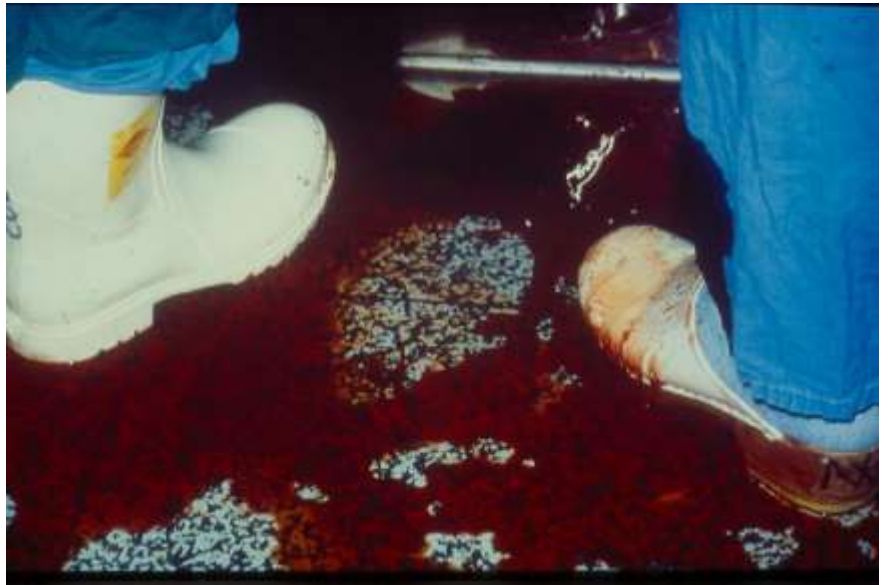
Distribution of Transfused Units by Age of Blood - CRIT Study

60% of Blood transfused is > 20 days old

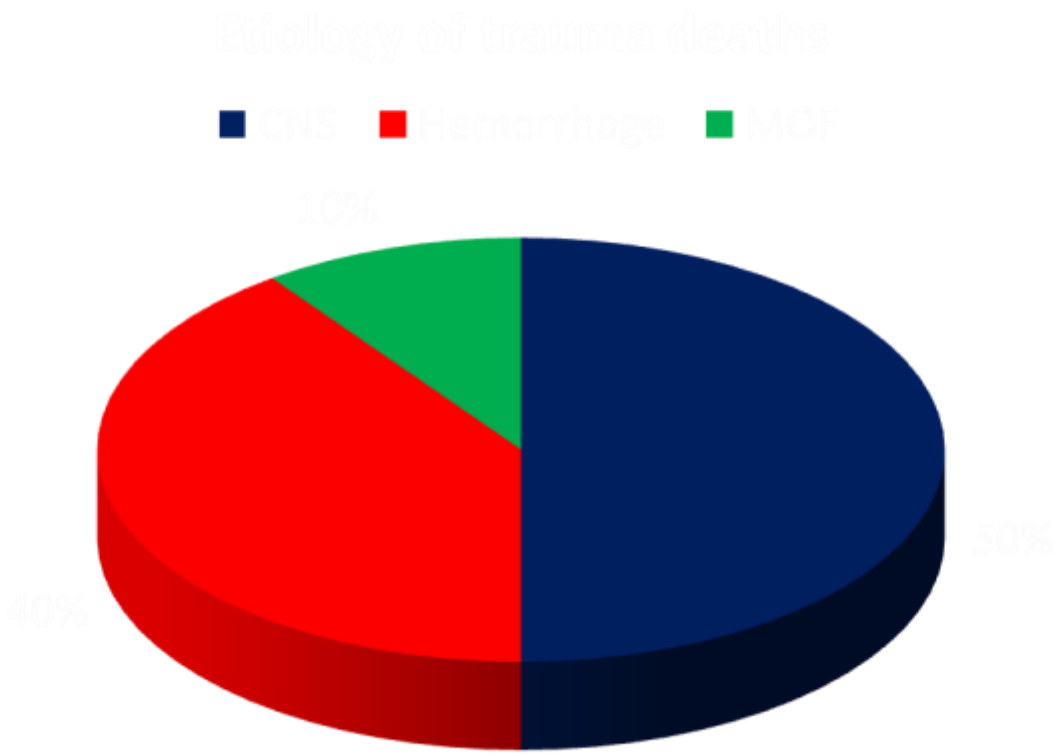


In Trauma Subset, 68% of blood is > 20 days old

Massive blood Transfusion



Causes of death following multiple trauma



Current Orthopaedics (2004) 18, 304-310

Classification of Hemorrhage

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

	CLASS III	CLASS IV
	1,500-2,000	≥ 2,000
	30%-40%	≥40%
	>120	≥140
	Decreased	Decreased
		Negligible

What is Massive transfusion?

- 10 units of red cells in 24 hours
- Total blood volume is replaced within 24 hours
- Three units over one hour with ongoing bleeding
- 50% of total blood volume is replaced within 3 hours

- The replacement of blood loss with red cells and a crystalloid volume expander will result in gradual dilution of plasma clotting proteins, leading to prolongation of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT)

- A similar dilutional effect on the platelet concentration can be seen with massive transfusion

Massive transfusion protocol (MTPs)

- Established to provide rapid blood replacement in a setting of severe haemorrhage

- Early optimal blood transfusion is essential to sustain organ perfusion and oxygenation

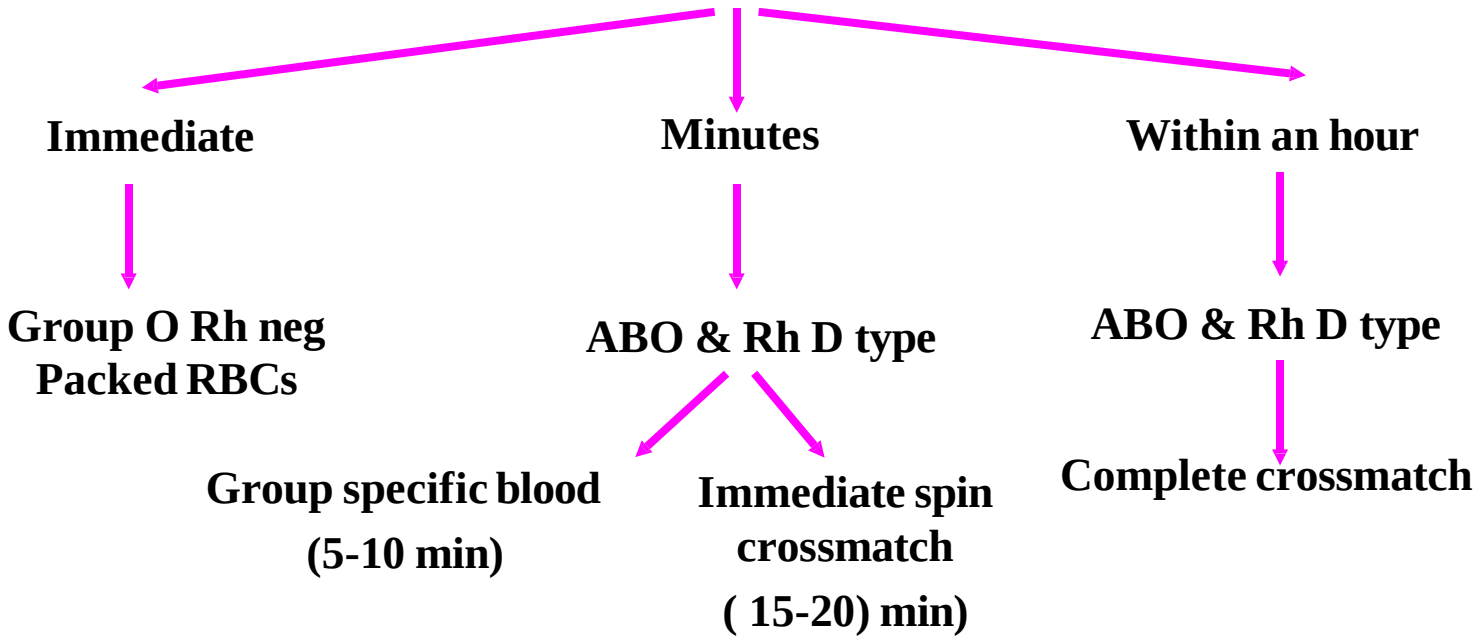
Massive Transfusion-Clinical Settings

- Trauma
- Surgery (e.g. Liver, Cardiovascular)
- Less frequent
  - abdominal aortic aneurysm
  - liver transplant
  - obstetric catastrophes
  - GI bleeding

Challenges

- Types of components to be administered
- Selection of the appropriate amounts
- TIME

Emergency blood issue



If units are issued without X match – written consent of physician to be taken,
– complete X match protocols followed after issue

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.

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.

Recommendations

- “Damage control” approach
- Improved survival when the ratio of transfused Fresh Frozen Plasma (FFP, in units) to platelets (in units) to red blood cells (RBCs, in units) approaches 1:1:1

Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007; 62:307.

Patients who have sustained severe traumatic injuries and/or who are likely to require massive transfusion should receive a 1:1:1 ratio of FFP to platelets to RBCs at the outset of their resuscitation and transfusion therapy

- *Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007; 63:805.*
- *Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248:447.*
- *Cotton BA, Au BK, Nunez TC, et al. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 2009; 66:41.*
- *Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010; 50:493.*
- *Inaba K, Lustenberger T, Rhee P, et al. The impact of platelet transfusion in massively transfused trauma patients. J Am Coll Surg 2010; 211:573.*
- *de Biasi AR, Stansbury LG, Dutton RP, et al. Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma (CME). Transfusion 2011; 51:1925.*

Fibrinogen concentrate

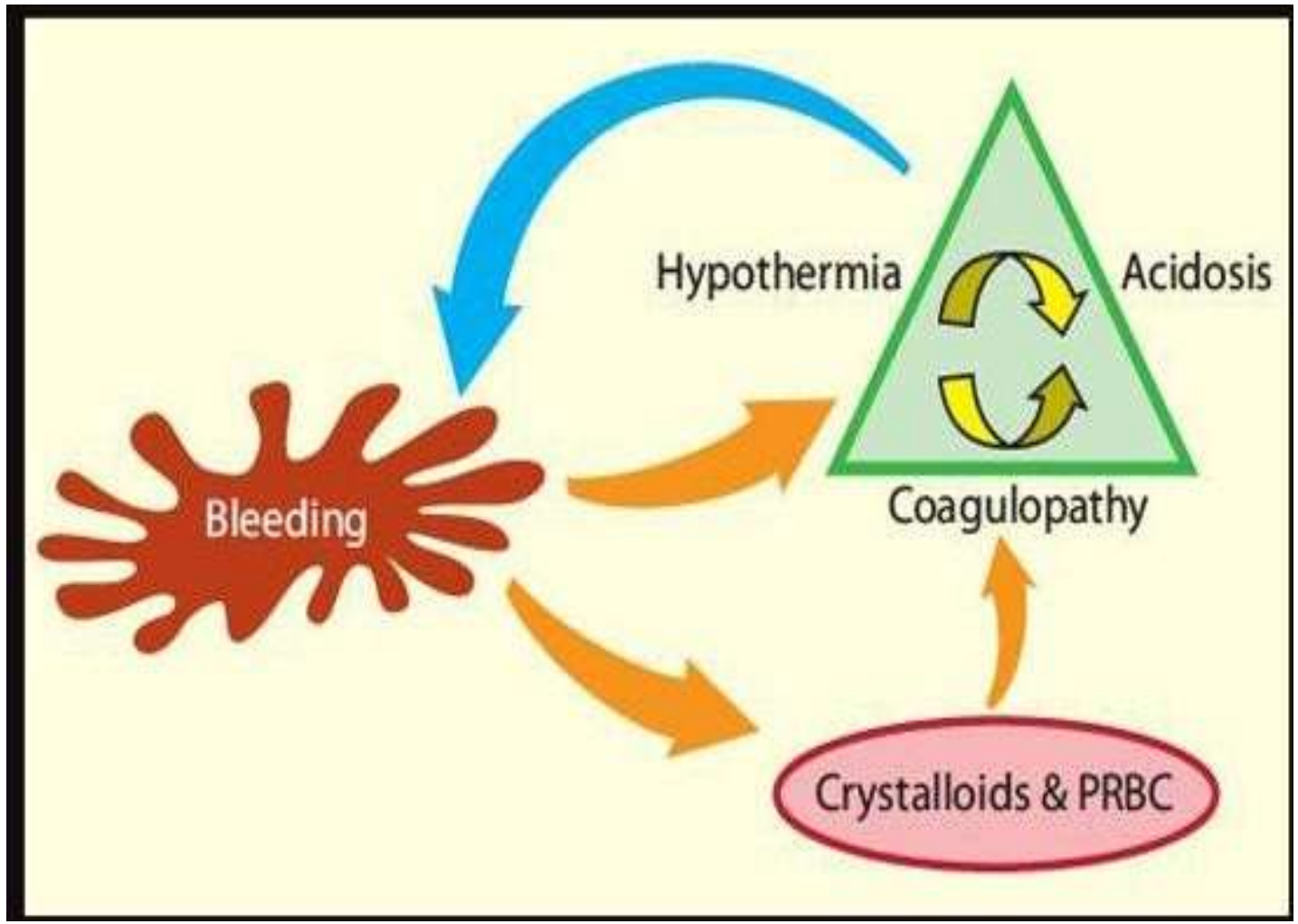
- European guidelines recommend fibrinogen concentrate when the level falls below 1.5g
- Cost of fibrinogen concentrate is much more than cryoprecipitate
- Availability

Cryoprecipitate

- Most common blood product used to replace fibrinogen
- Contains approximately 200–250 mg of fibrinogen per unit
- Standard dose of two 5-unit pools should be administered **early** in major **obstetric haemorrhage**.
- Subsequent **cryoprecipitate** transfusion should be guided by fibrinogen results, aiming to keep levels above 1.5 g/l.

Complications of Massive Transfusion

- Hypothermia
- Acid/base derangements
- Coagulopathy
- Citrate toxicity
- Electrolyte abnormalities
  - hypocalcemia
  - hypomagnesemia
  - hypokalemia
  - hyperkalemia
- Transfusion-associated acute lung injury


Hypothermia
Acidosis
Coagulopathy
Bleeding
Crystalloids & PRBC

Acidosis and hypothermia

- Acidosis
  - Interferes with formation of coagulation factor complexes
- Hypothermia
  - Reduces enzymatic activity of coagulation factors
  - Prevents activation of platelets

Hypothermia

10 units of cold blood products and an hour of surgery can lead to a 3°C drop in core temperature and hypothermic coagulopathy

RBCs that are stored at 4C are transfused rapidly

Lowers the recipient's core temperature and further impairs haemostasis.

Reduces the metabolism of citrate and lactate

Increases the likelihood of hypocalcaemia, metabolic acidosis and cardiac arrhythmias.

Shifts the oxyhaemoglobin dissociation curve to the left, reducing tissue oxygen delivery

Prevention of hypothermia

- A high capacity commercial blood warmer should be used to warm blood components

Coagulopathy

- Dilutional coagulopathy
- Disseminated intravascular coagulation.
- Consumption of platelets and coagulation factors

ALTERATIONS IN HEMOSTASIS

- Acute DIC
  - microvascular oozing
  - prolongation of the PT and aPTT in excess of that expected by dilution
  - significant thrombocytopenia
  - low fibrinogen levels
  - increased levels of D-dimer

Hypocalcaemia

- Citrate binds calcium
- Results in hypotension, small pulse pressure, flat ST-segments and prolonged QT intervals on the ECG.
- Slow i.v. injection of calcium gluconate 10%

Hyperkalaemia

- The potassium concentration of blood increases during storage, by as much as 5–10 mmol u1 .

Hyperkalaemia rarely occurs during massive transfusions unless the patient is also hypothermic and acidotic

Monitoring recommendations

- PT, aPTT
- Platelet count
- Fibrinogen
- Electrolytes
- Viscoelastic test
  - after the administration of every five to seven units of red cells.

Goals

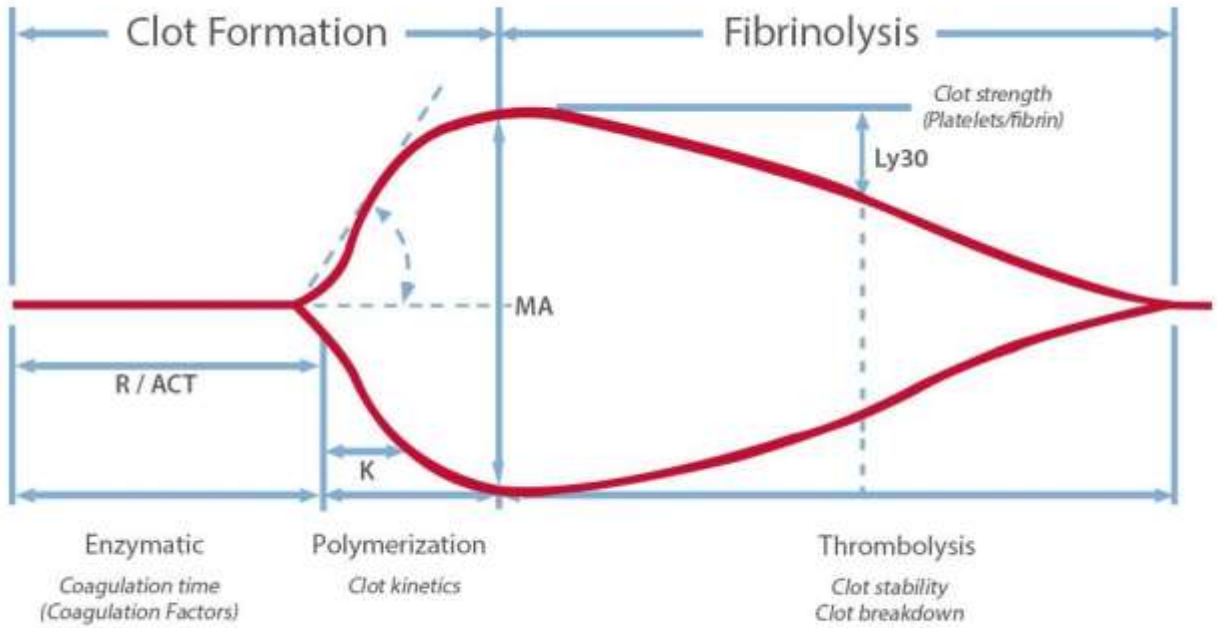
Massive Blood Transfusion Management

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

Viscoelastic whole-blood assays

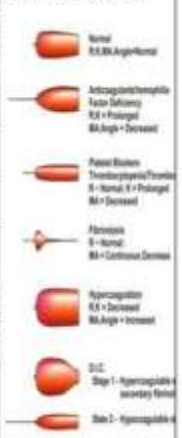
- TEG® and ROTEM®
- provide information on the coagulation process through the graphic display of clot initiation, propagation and lysis.
- used to guide transfusion of blood components

Measure all phases of hemostasis in whole blood.



The TEG® hemostasis system continuously measures all phases of hemostasis as a net product of whole blood components

- Costeffective -since it reduces inappropriate transfusions, thus improving transfusion management and patients' clinical outcome

Laboratory Value	Interpretation	Blood Product Transfusion	QUALITATIVE INTERPRETATION — PATTERN RECOGNITION
R less than 4 min	Enzymatic Hypercoagulability	No treatment if bleeding	
R between 11-14 min	Low clotting factors	Plasma and RBC's	
R greater than 14 min	Very low clotting factors	Plasma and RBC's	
a-angle<45 degrees	Low fibrinogen level	Cryoprecipitate/ Fibrinogen/Platelets	
MA between 46-54 mm	Low platelet function	Platelets / Cryoprecipitate/ Fibrinogen	
MA between 41-45 mm	Very low platelet function	Platelets / Cryoprecipitate/ Fibrinogen	
MA at 40 mm or less	Extremely very low platelet function	Platelets/ Cryoprecipitate/ Fibrinogen	
MA greater than 73 mm	Platelet Hypercoagulability	No treatment if bleeding	
LY30 greater than 3% , CI less than 1.0	Primary fibrinolysis	**Tranexamic acid** 1g IV over 10 minutes followed by 1g in 250cc NS infused over 8 hours	

- Refer to TEG analysis tree for values outside these ranges

Thank You