Blood and Blood Product Transfusion

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

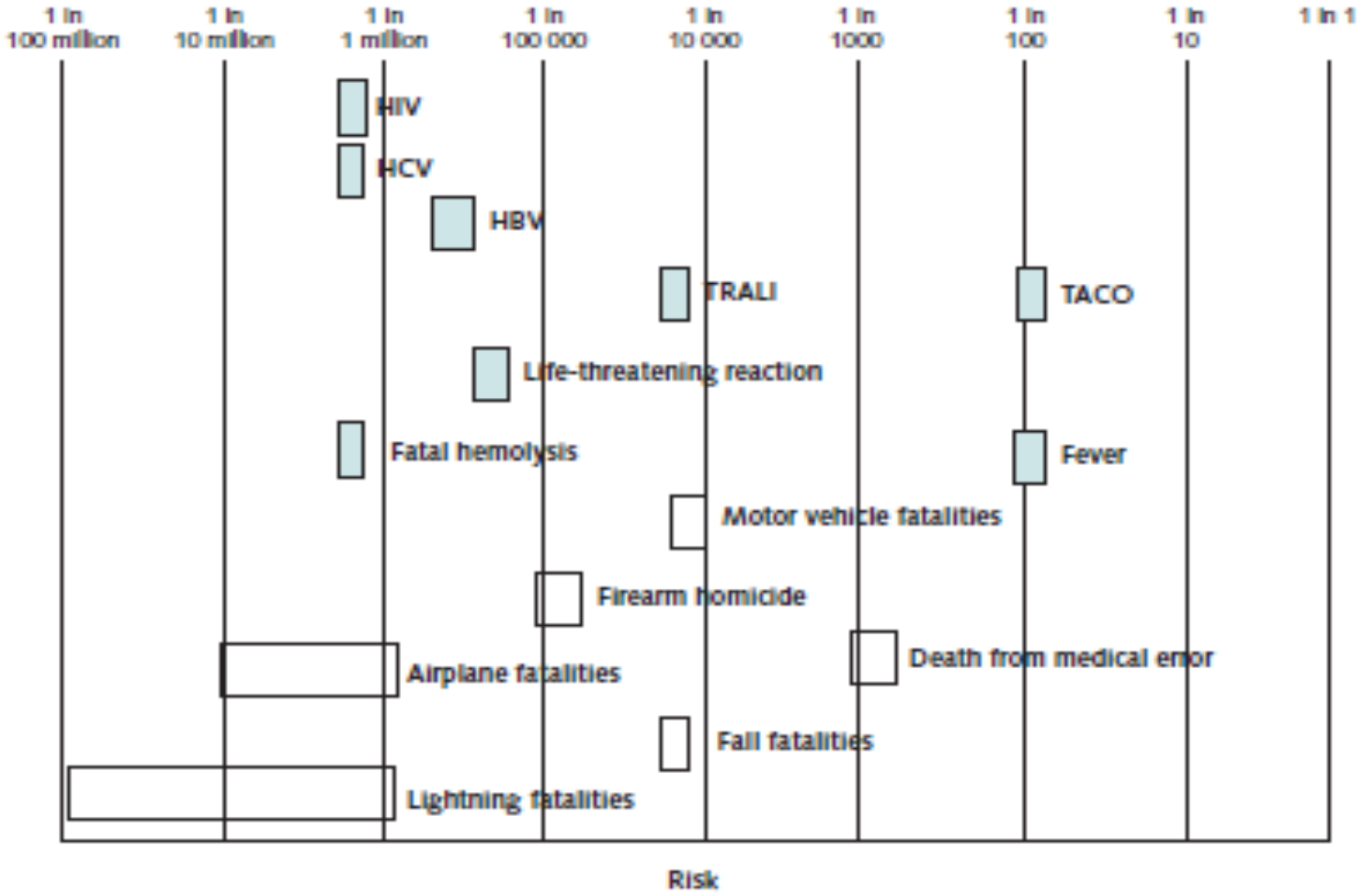
- **Approximately 15 million red blood cell (RBC) units** are transfused annually in the United States (1)

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]

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?

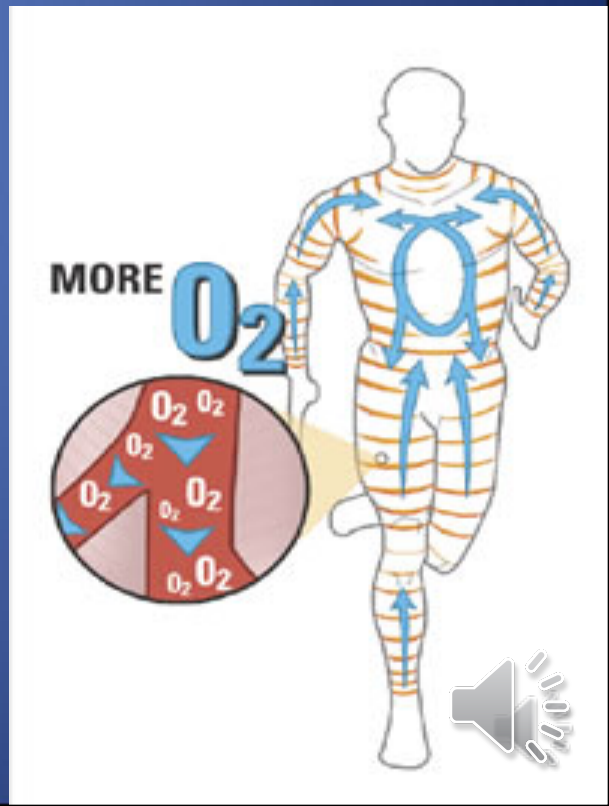
- The body at rest uses approx **250ml O2/L blood**
- O2 delivery can fall with a reduction in any of:
  - Cardiac Output
  - Hb concentration
  - O2 saturation
- Organs most sensitive to hypoxia are Heart and Brain

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

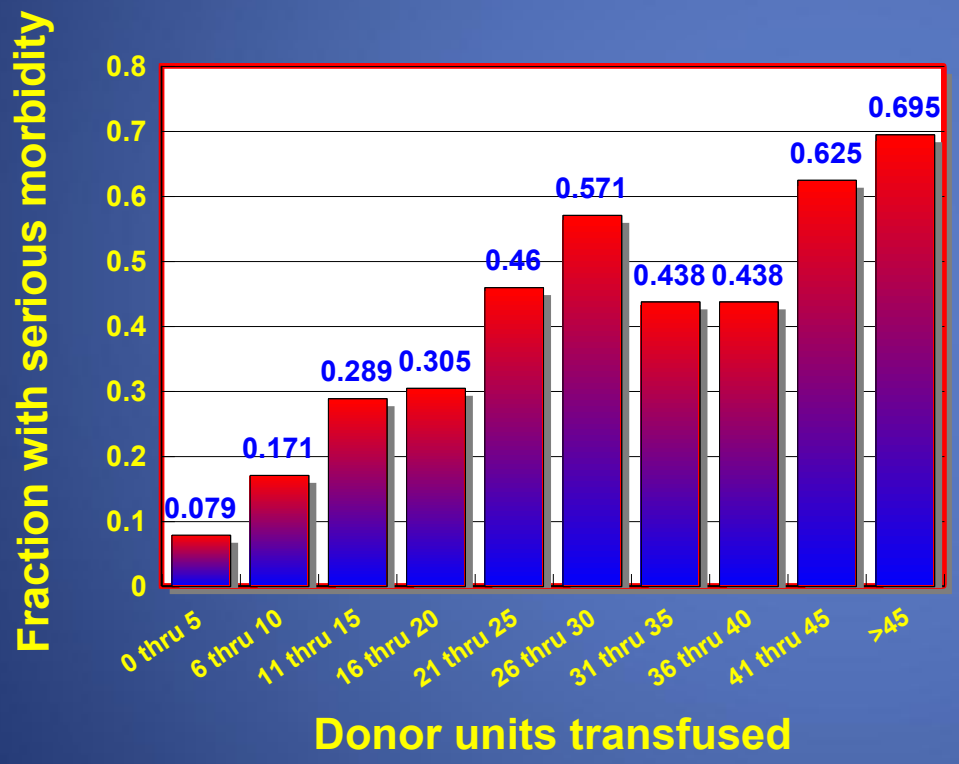
$$Hb \times SaO_2$$



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

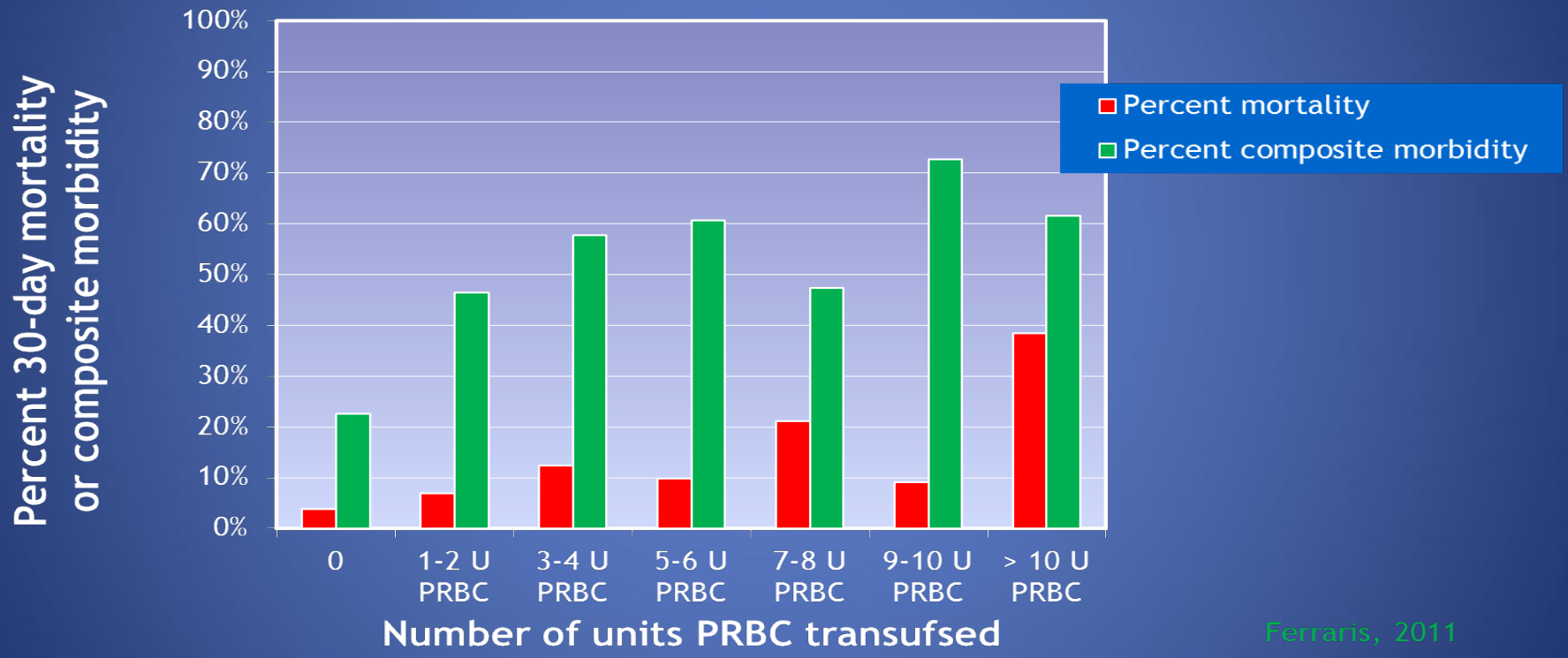
Transfusion & Serious Morbidity in 4,445 Cardiac Surgical Patients



- Serious morbidity and mortality increase with the amount transfused.

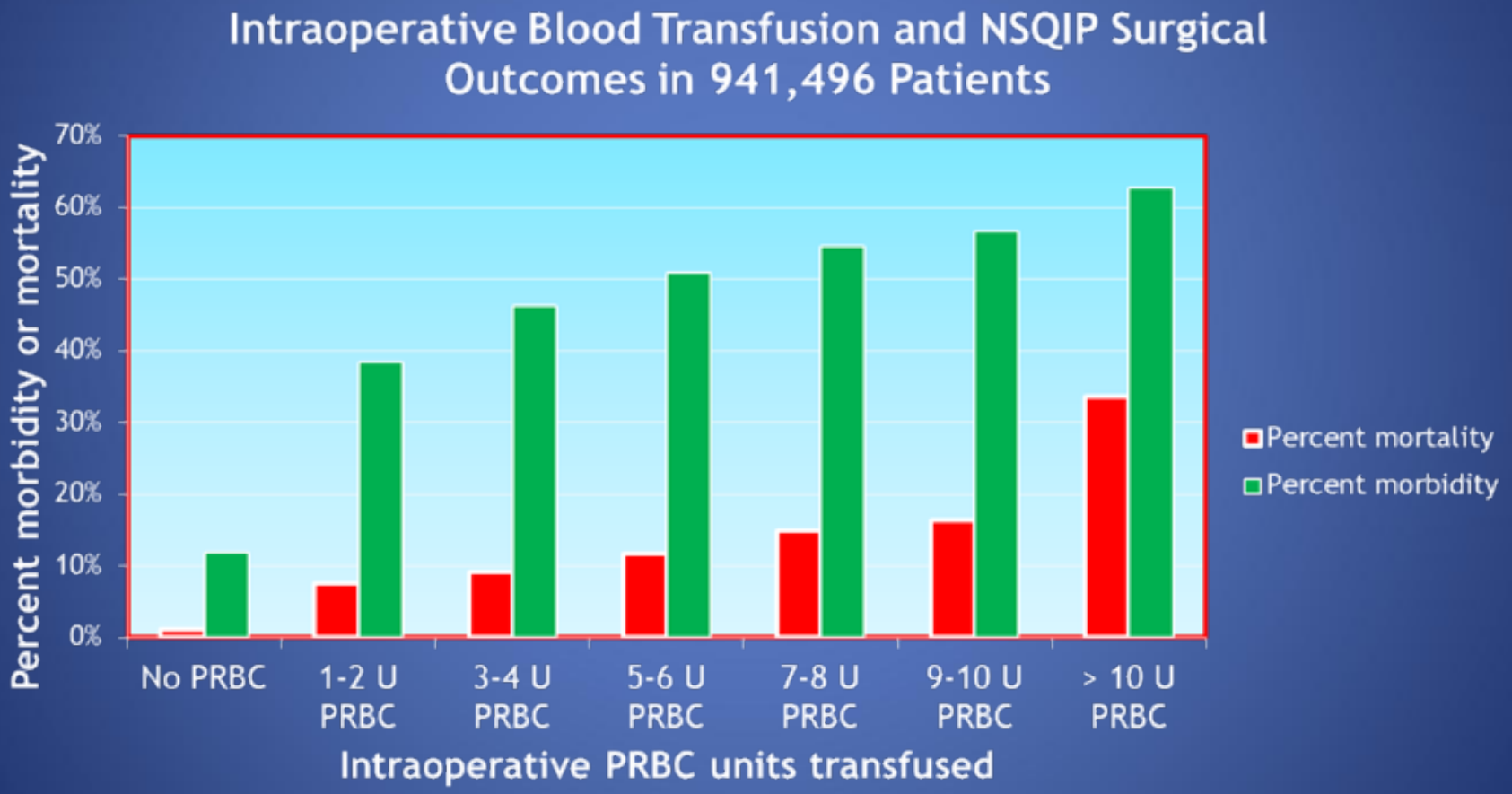
Ferraris, Intl J Angiol, 2006

Intraoperative Blood Transfusion & Lung Surgery



Ferraris, 2011

Blood Transfusion in General Surgical Population

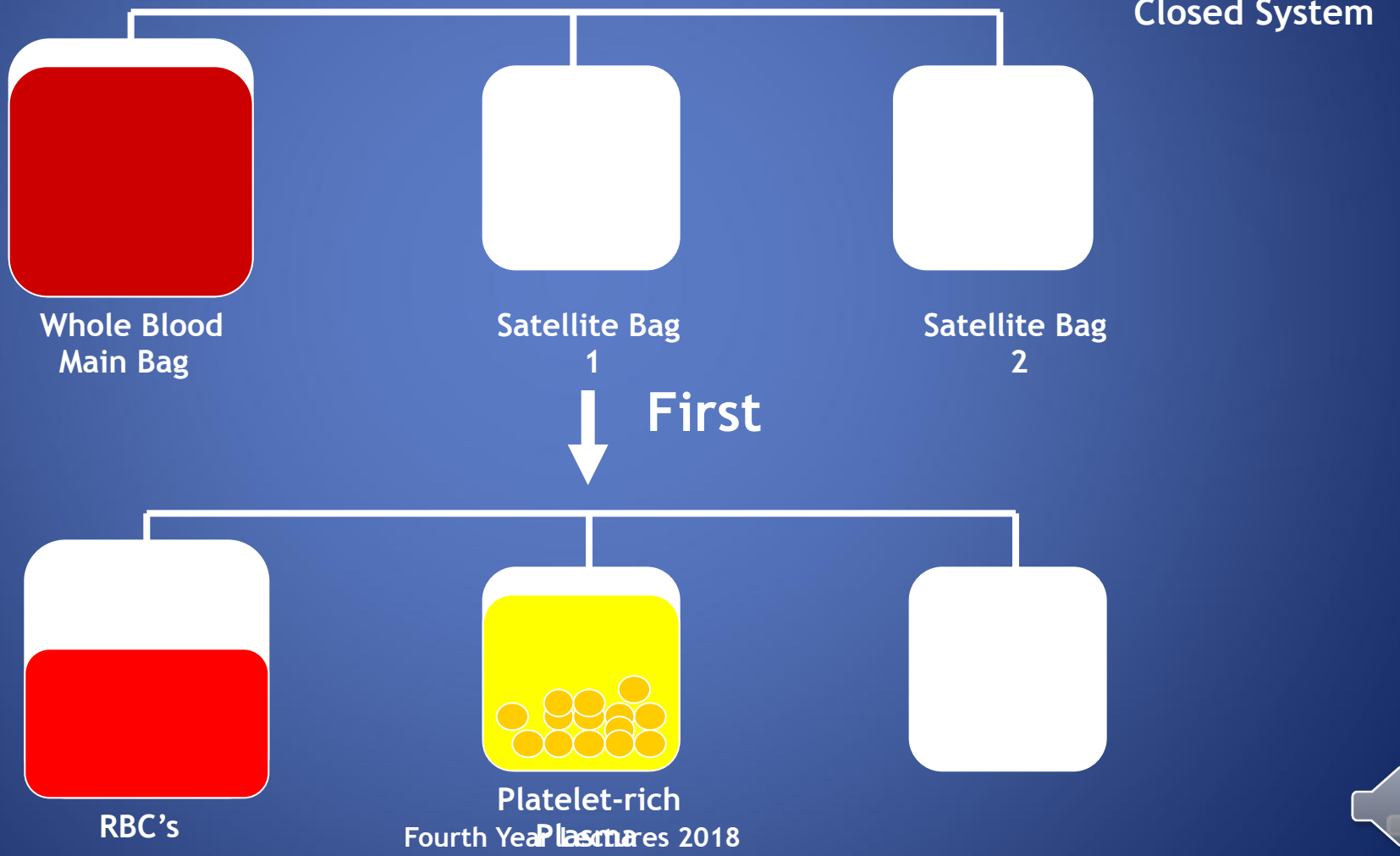


Blood Components

- 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

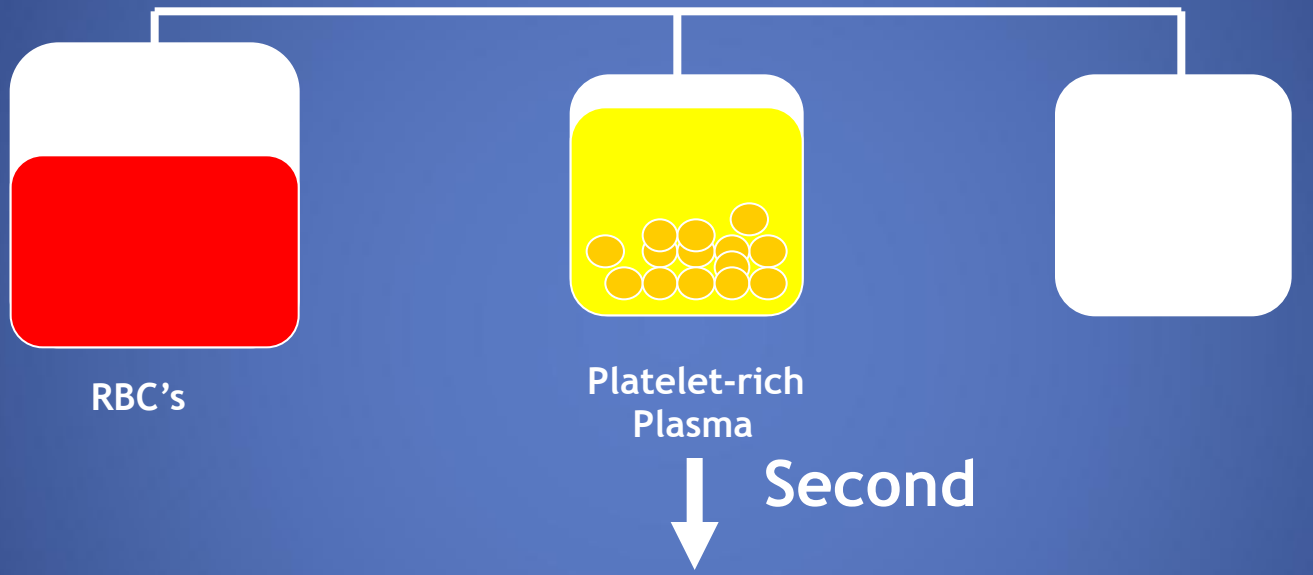
Differential Centrifugation

First Centrifugation



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.

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

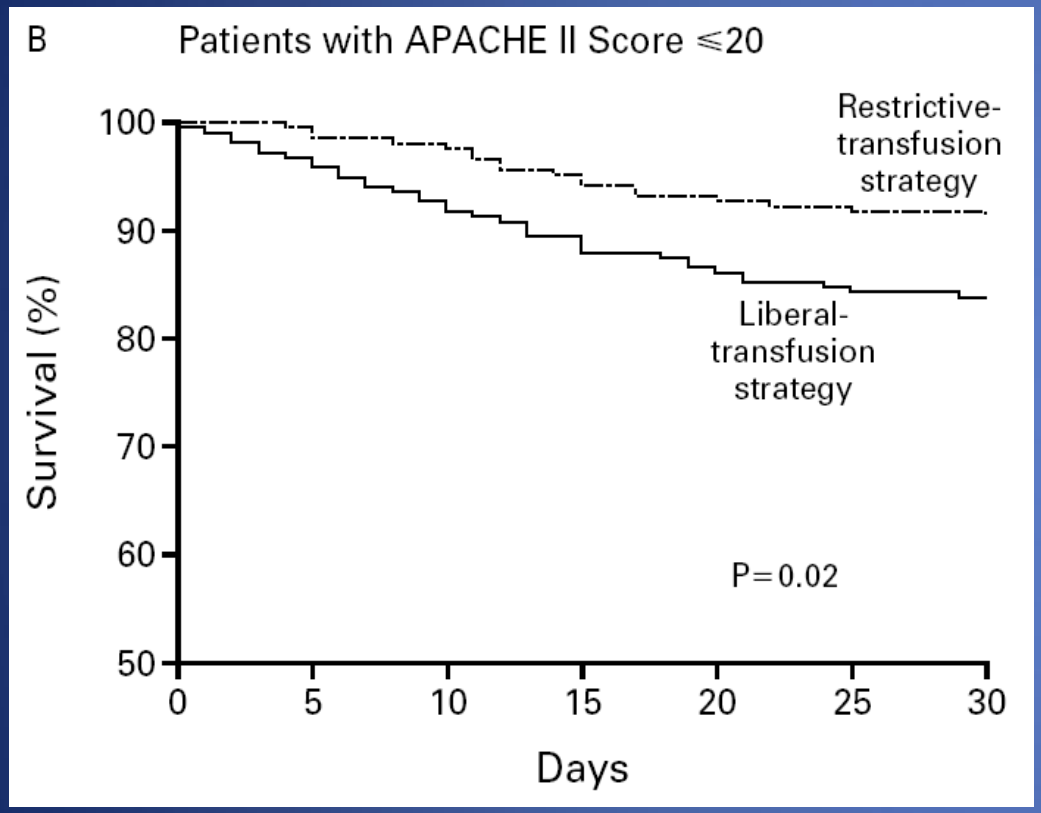
The TRICC Study

No difference 30 day mortality

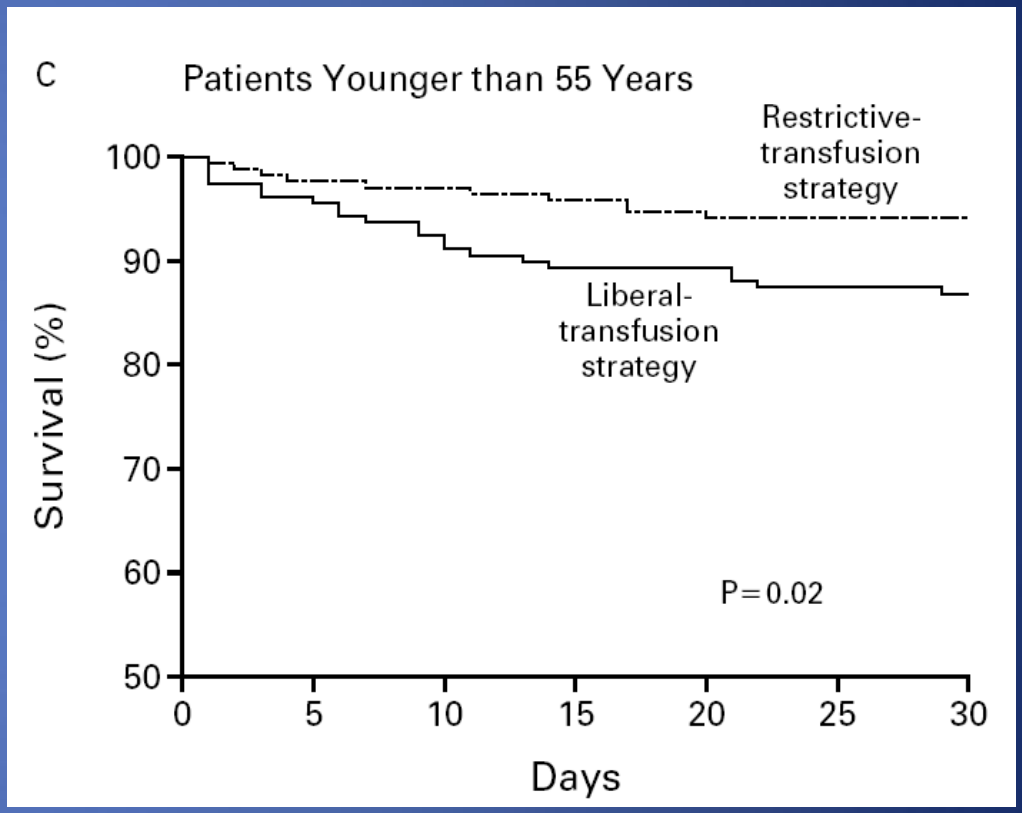
In "healthy" (APACHE II < 20) and young (<55yrs) patients
Transfusion increased mortality

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."

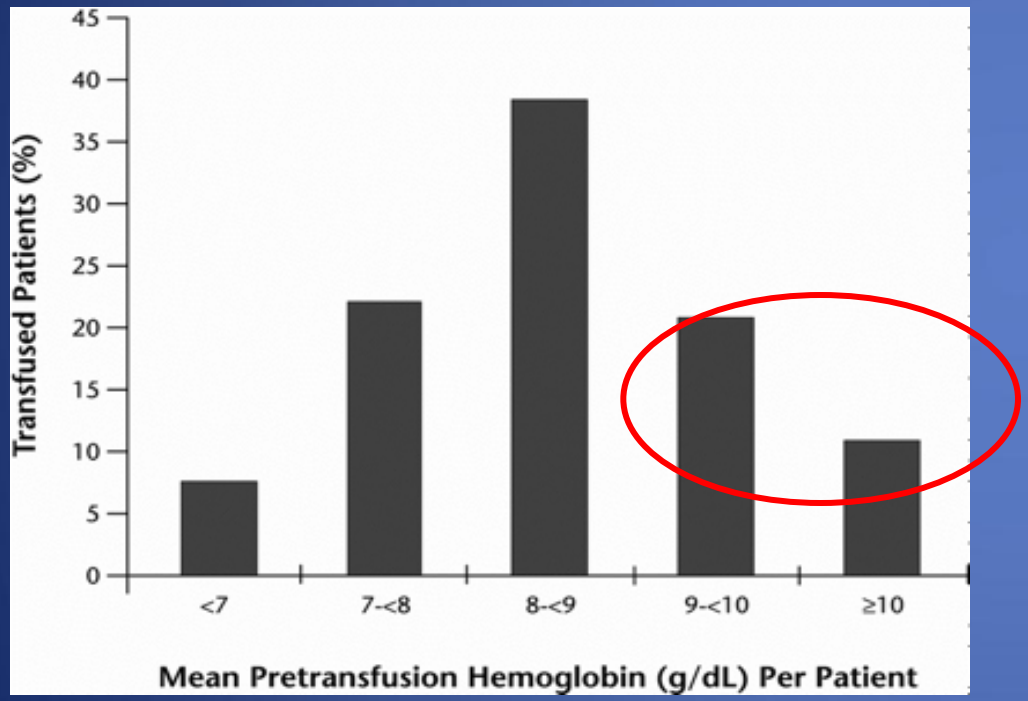
CRIT Study

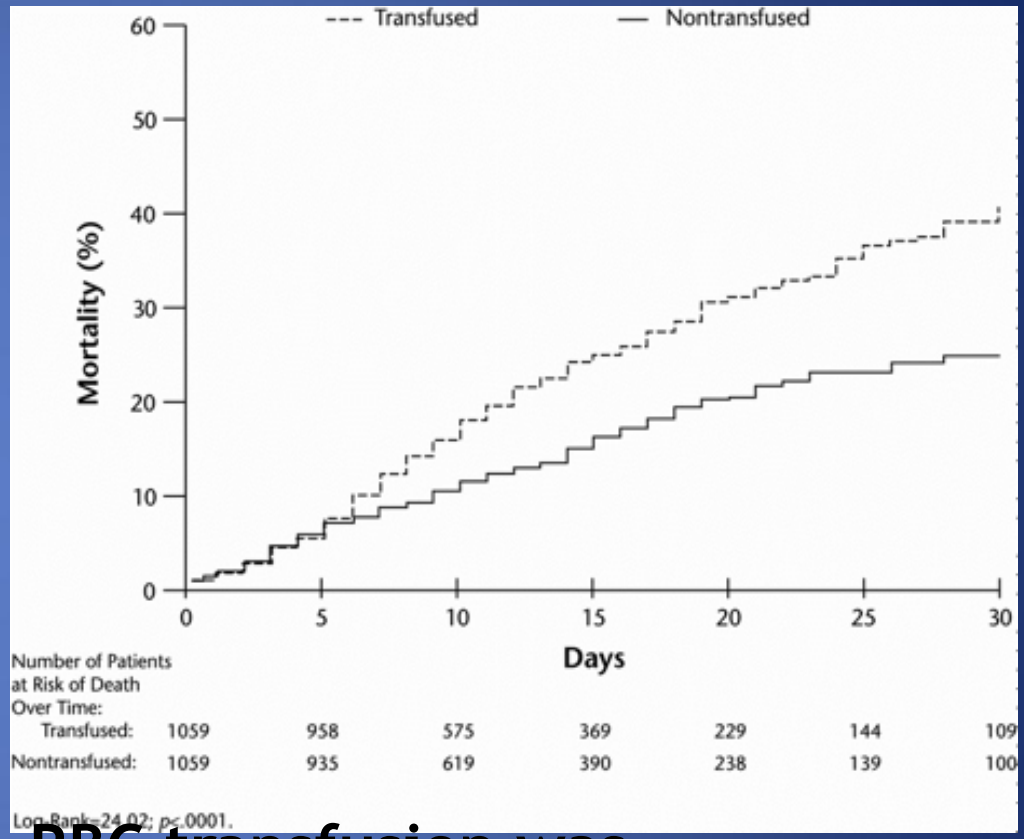
- Prospective, multiple center, observational cohort study of 4,892 ICU pts in the US
- Propensity score matched
- Designed to examine the relationship of anemia and RBC transfusion with clinical outcomes
- Almost 95% of patients admitted to the ICU have a Hb level below “normal” by day 3
- In total, 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 if 3-4 units transfused p < 0.0001

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)

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

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)

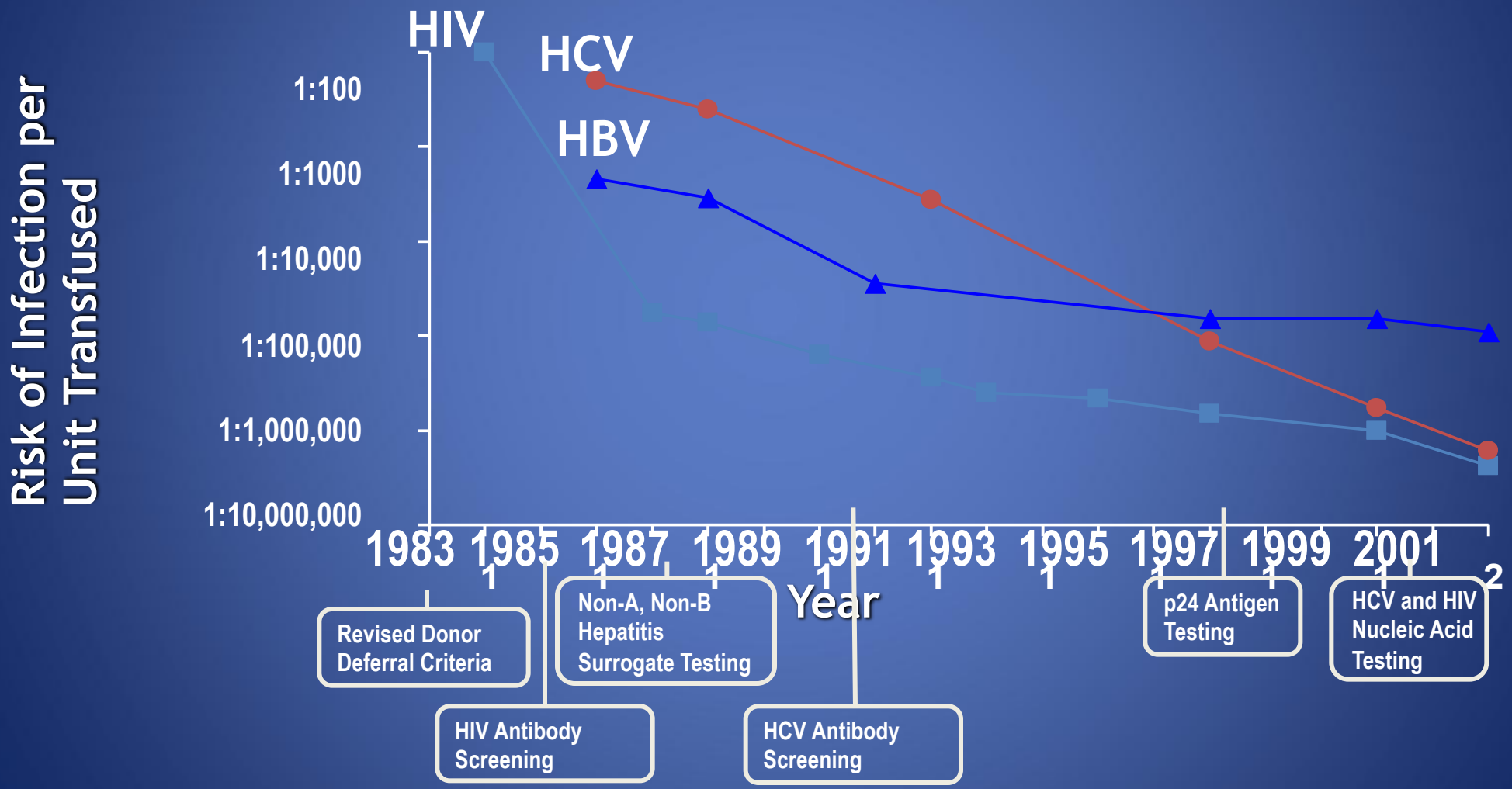
Chronic Transfusion Reactions

- 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

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



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

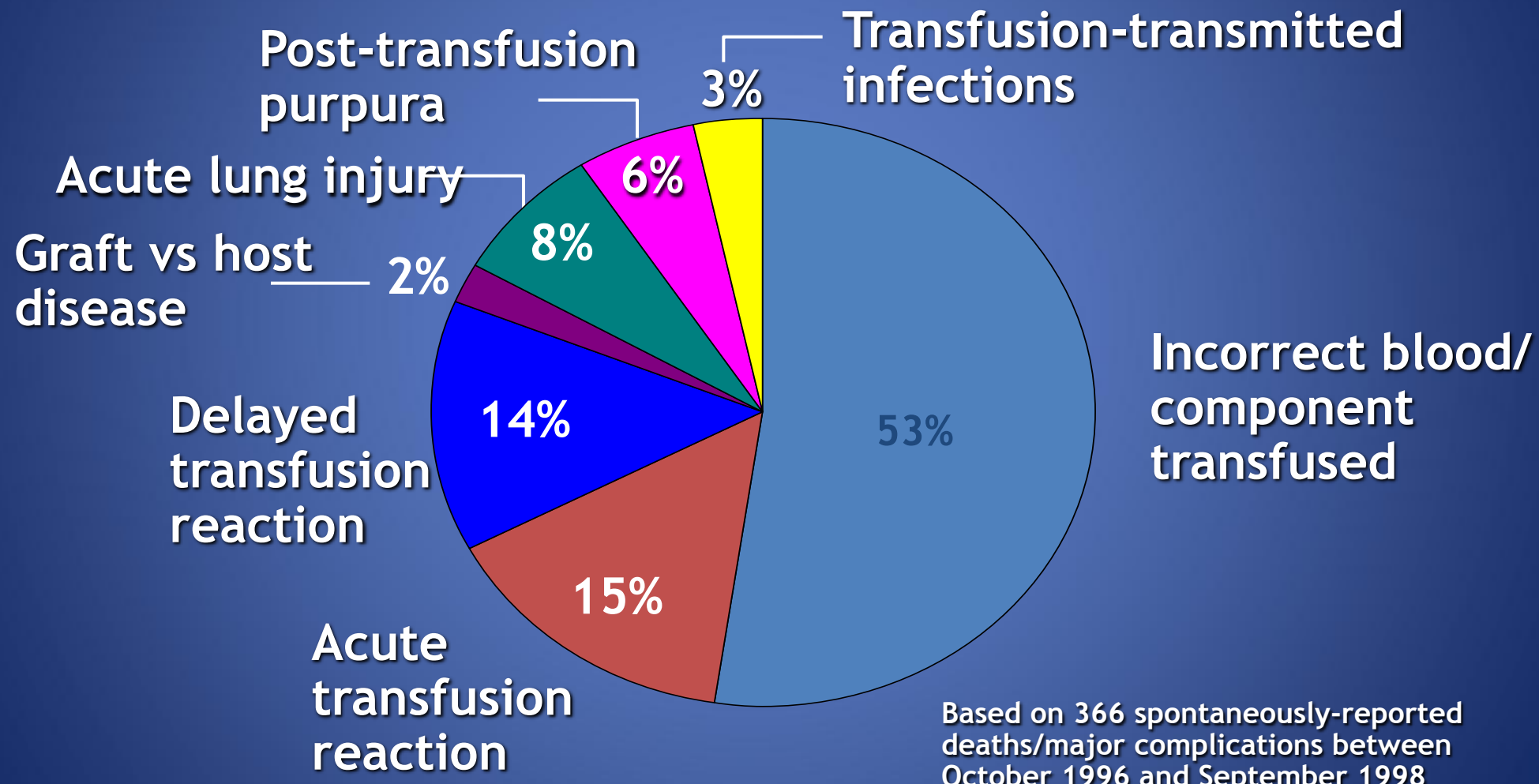
Risks of Transfusion: Infectious Disease

- ✓ 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.

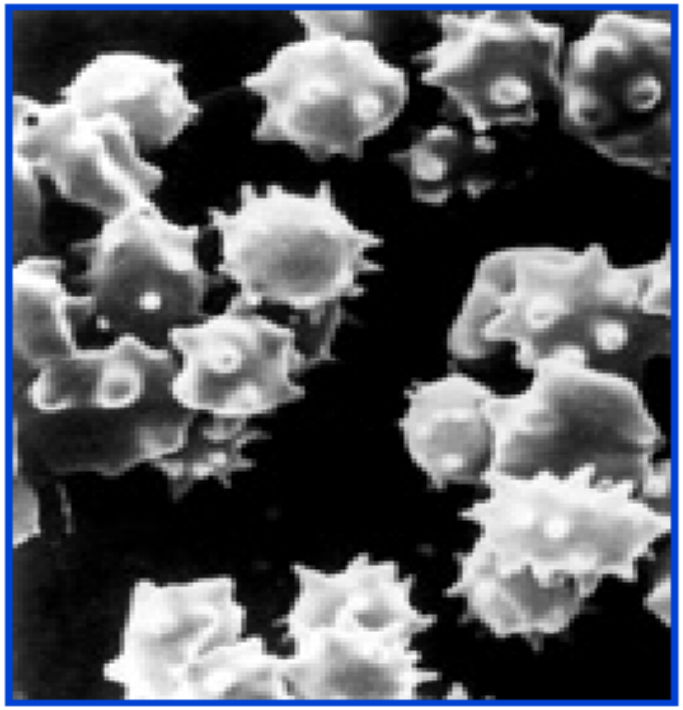
Why is blood transfusion NOT associated with improved outcome?

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

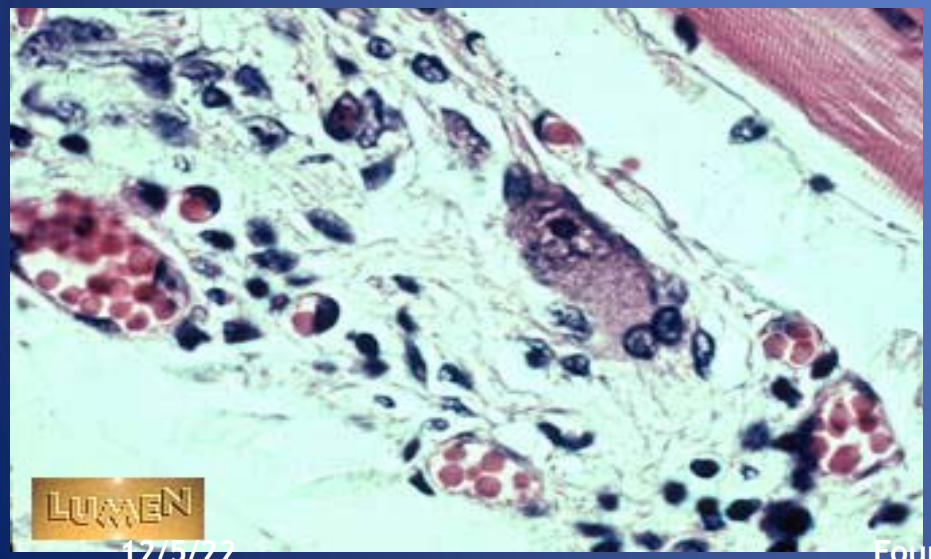
Day 35

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).

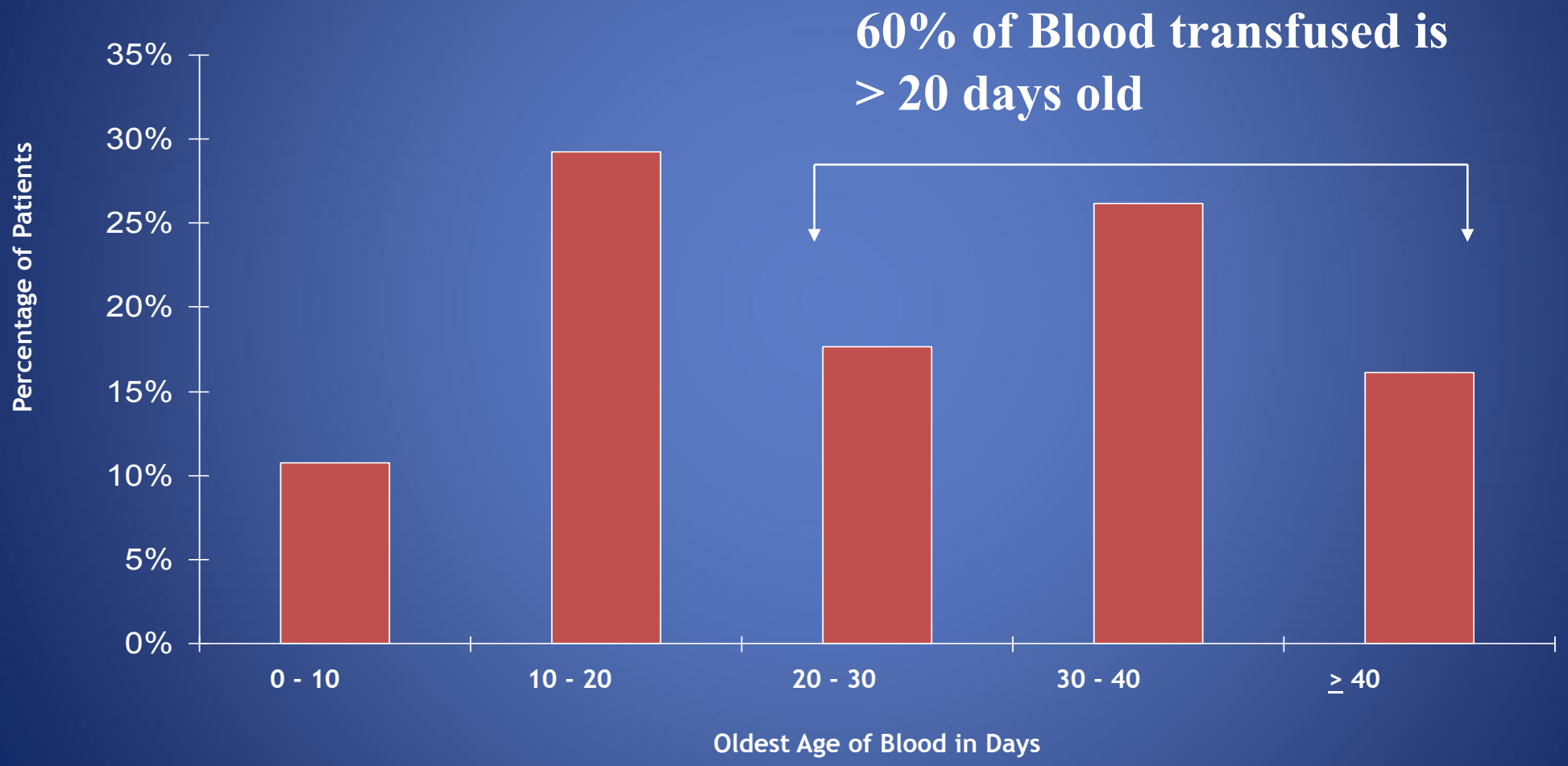
Reproduced with permission from: Hovav et al. *Transfusion*. 1999;39:277-281.

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



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

Massive Transfusion

Massive Transfusion

Definitions

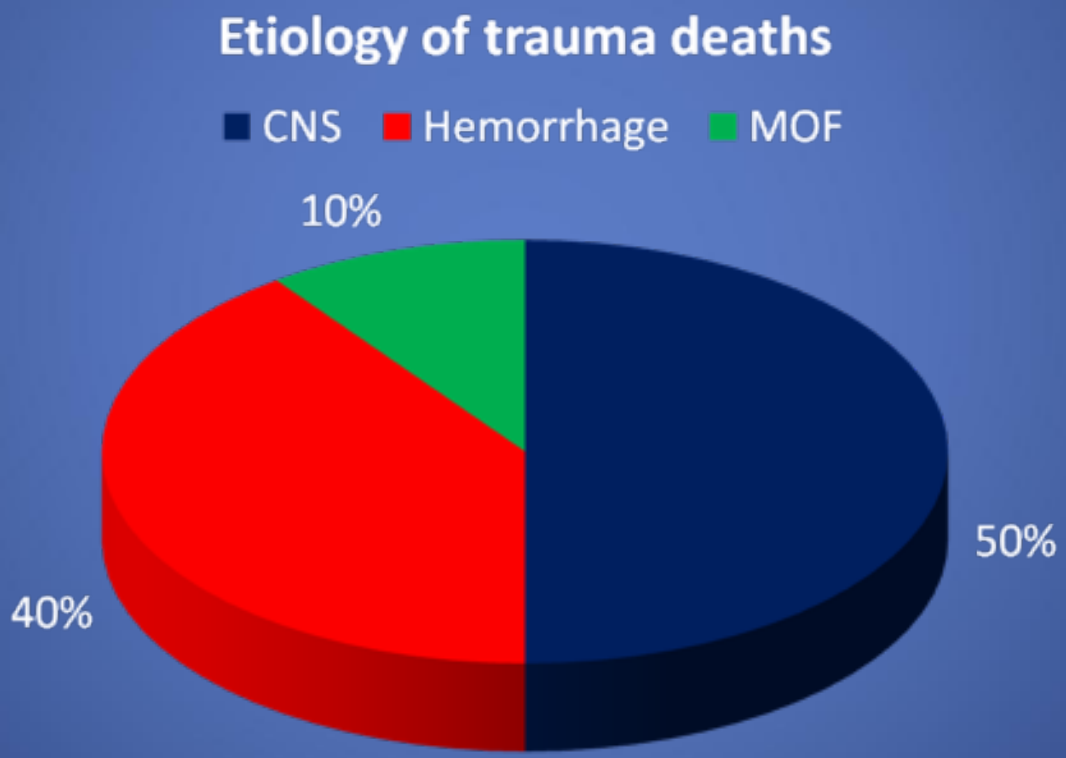
- Replacement of one blood volume in a 24 hour period
- Replacement of >50% of the total blood volume within 3-4 hours
- Transfusion of 3 or more RCC within 1 hour or 4 blood component units in 30 min. when ongoing need is foreseeable

Classification of Hemorrhage

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

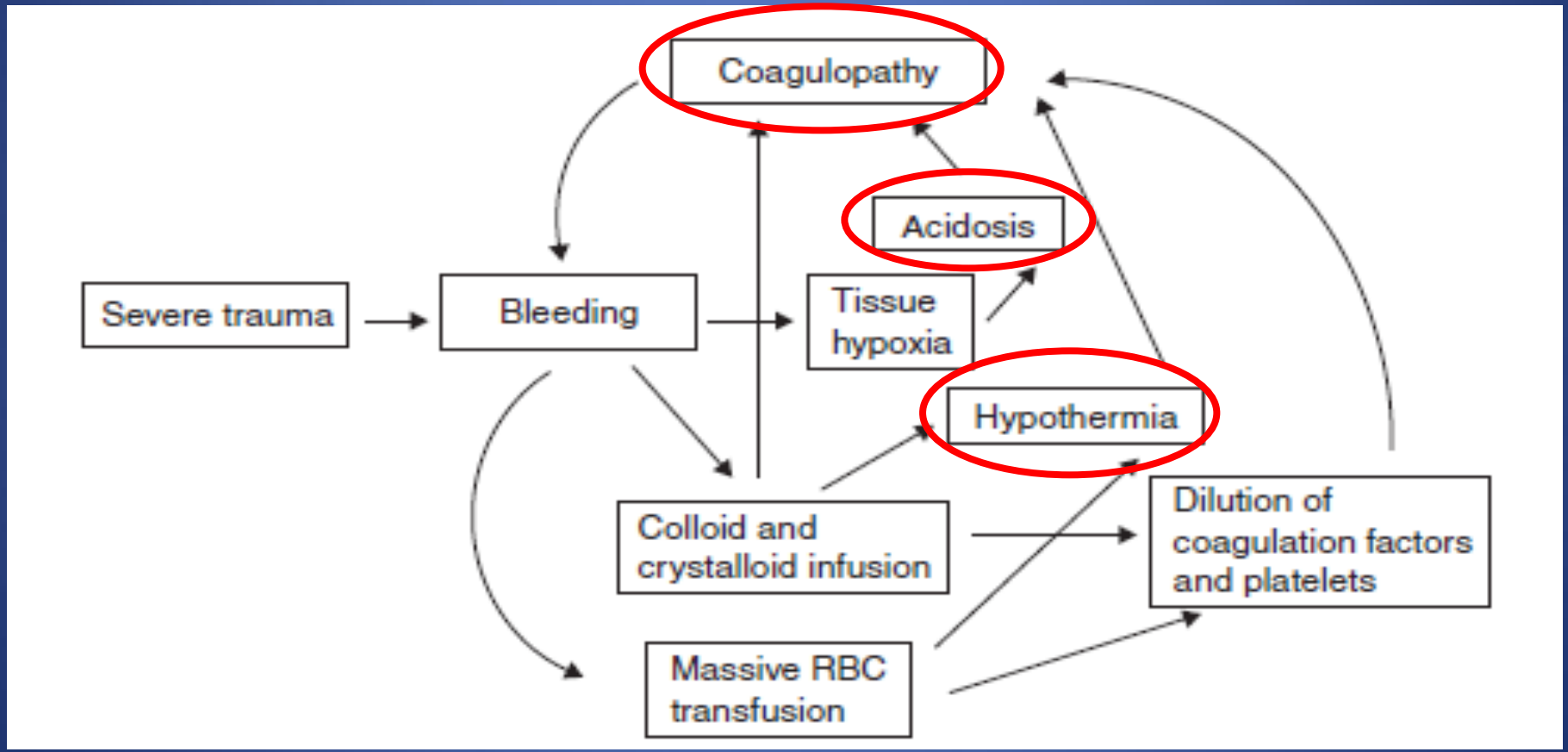
	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (ml)	Up to 750	750-1,500	**1,500-2,000**	**≥ 2,000**
Blood loss (% blood volume)	Up to 15%	15%-30%	**30%-40%**	**≥40%**
Pulse rate	<100	>100	**>120**	**≥140**
Blood pressure	Normal	Normal	**Decreased**	**Decreased**
Pulse pressure (mmHg)	Normal or increased	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



Current Orthopaedics (2004) 18, 304-310

The Lethal Triad in Trauma


Coagulopathy
Acidosis
Severe trauma
Bleeding
Tissue hypoxia
Hypothermia
Colloid and crystalloid infusion
Dilution of coagulation factors and platelets
Massive RBC transfusion

Coagulopathy

- Activation and consumption of coagulation factors secondary to tissue trauma
- reduced activity of coagulation factors from prolonged shock, hypoxia, hypothermia, or failure to clear activation peptides that act as competitive inhibitors
- acute disseminated intravascular coagulation (acute DIC)

- coagulation abnormalities may be induced by the dilutional effects of blood replacement on coagulation proteins and the platelet count
- consumption of coagulant proteins, and fibrinolysis
- extensive blood loss
- Dilutional effects of physiologic vascular refill

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

- 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

- Hypothermia reduces the enzymatic activity of plasma coagulation proteins, but has a greater effect by preventing the activation of platelets via traction on the glycoprotein Ib/IX/V complex by von Willebrand

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)

- Acidosis (ie, excess protons) specifically interferes with the assembly of coagulation factor complexes involving calcium and negatively-charged phospholipids. As a result, the activity of the factor Xa/Va prothrombinase complex is reduced by 50, 70, and 80 percent at pHs of 7.2, 7.0, and 6.8, respectively [20]. The resulting delayed production and reduced concentrations of generated thrombin lead to delayed fibrin production, altered fibrin structure, and increased susceptibility to fibrinolysis [21]. The interaction of acidosis with coagulopathy

Massive Blood Transfusion complications

- Coagulopathy
- 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

- Metabolic Acidosis
- Hyperkalemie (especially in Renal impairment)
- Citrate Toxicity (Metabolic Alkalosis and Hypocacemia)
- Hypomagnesiemia

Massive Blood Transfusion Management

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

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+

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 10^9/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^{0}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

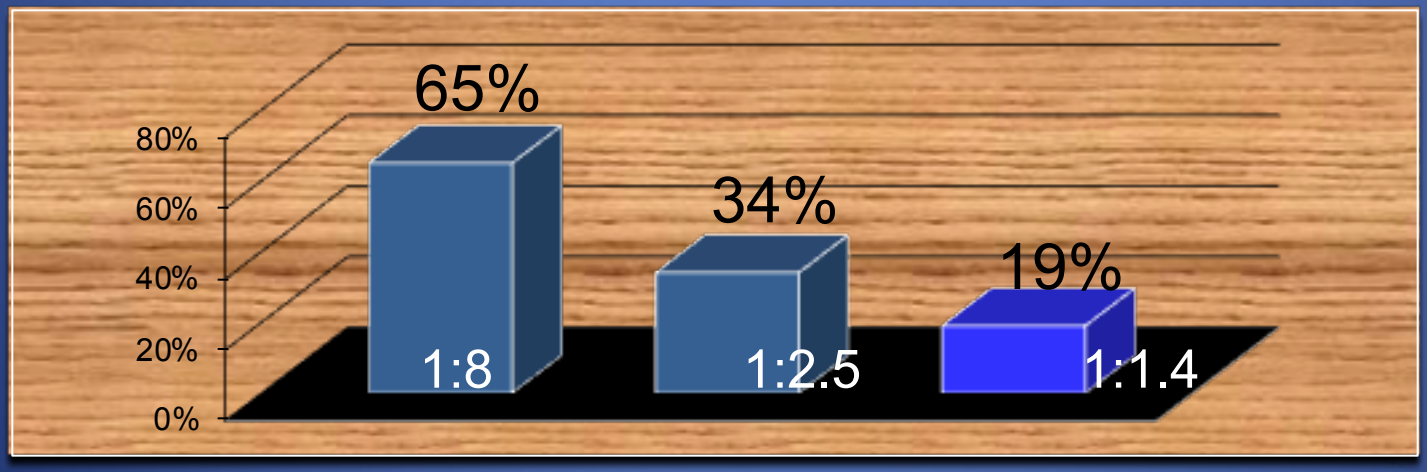
- Meta-analysis from 2012 reports of reduced mortality in trauma patients treated with the highest FFP or PLT to RBC ratios.

- 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.

What is the optimal ratio of blood products ?

Thank You