Guidelines for the Appropriate use of Blood Products

James Szymanski, MD
Montefiore Medical Center

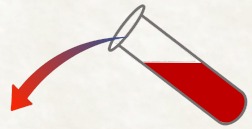
Jamal Carter, MD
Montefiore Medical Center

Monika Paroder, MD, PhD
Montefiore Medical Center
mparoder@montefiore.org

Ronald Walsh, MD
Montefiore Medical Center
Director of Transfusion Medicine

Joan Uehlinger, MD

Speaker(s) and Co-Authors



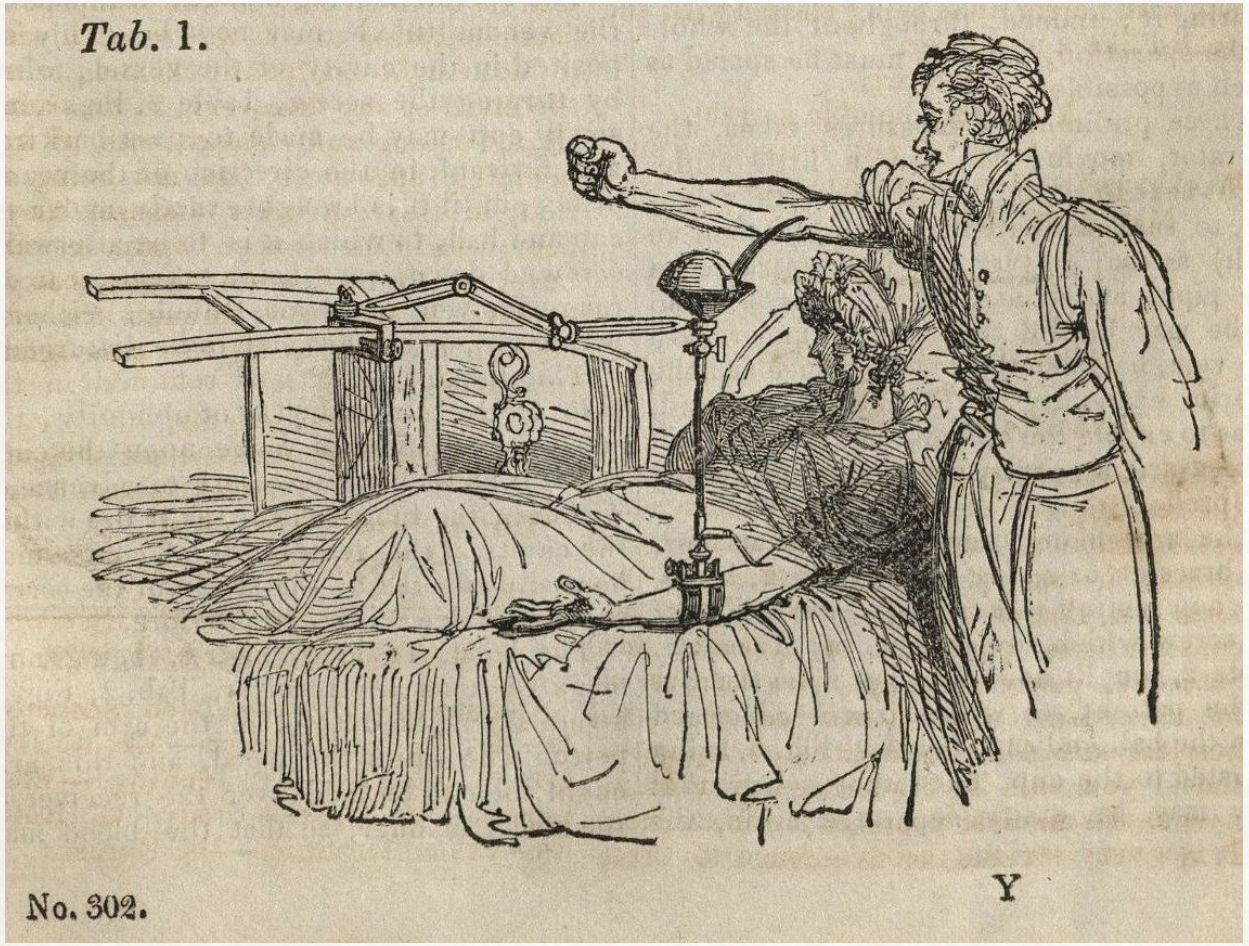
Disclosures

- None

Topics Covered

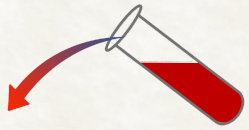
1. Benefits of Component Therapy
2. RBC Transfusion
   - Physiologic basis for RBC transfusion
   - Storage lesion
   - RBC transfusion triggers
3. Platelet Transfusion
   - SDP vs pooled products
   - Prophylactic platelet transfusion triggers
   - Platelet refractoriness
4. Product Modifications
5. Plasma Transfusion
6. Cryoprecipitate Transfusion
7. Granulocytes Transfusion

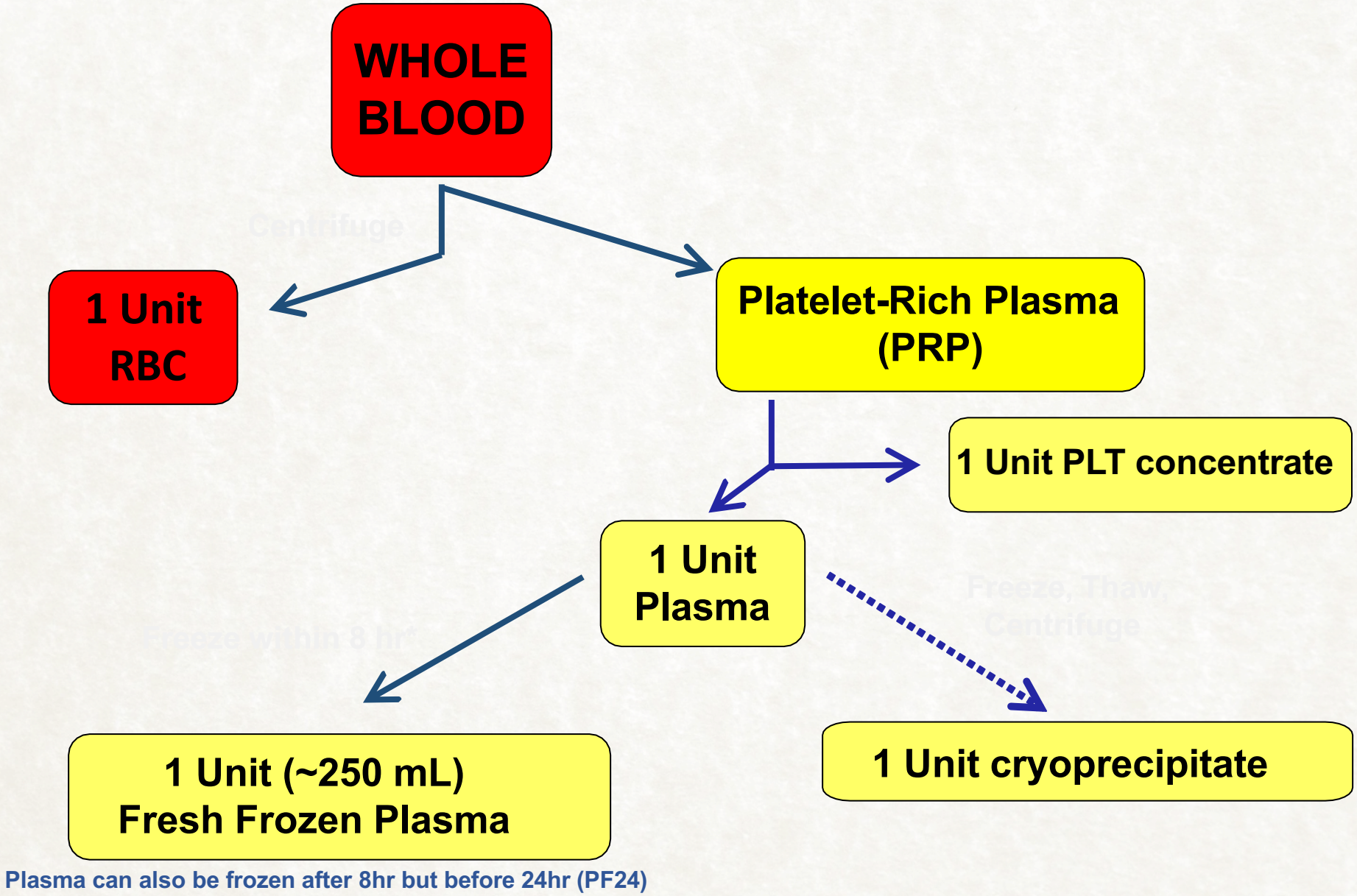
1818: First human-to-human transfusion



Why Transfuse Blood Components?

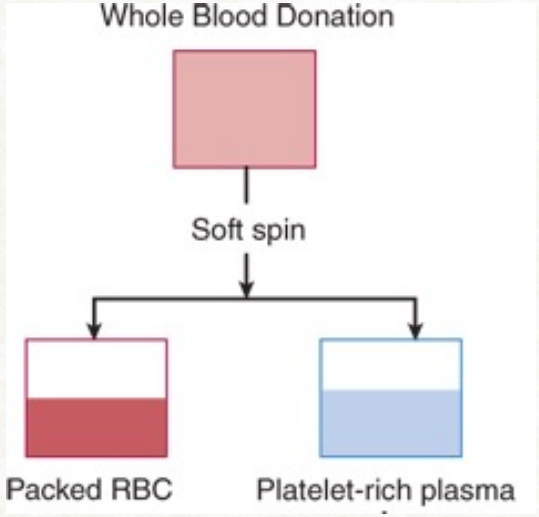
- Whole blood is separated into components
- Advantages of component separation
  - Allow optimum survival of each component
    - ✓ **RBCs** stored at **1-6 C**
    - ✓ **PLTs** stored at **20-24 C** (with constant agitation)
    - ✓ **FFP** stored at **-18 C**
  - Transfuse only specific component needed





Plasma can also be frozen after 8hr but before 24hr (PF24)

Component Preparation: RBCs



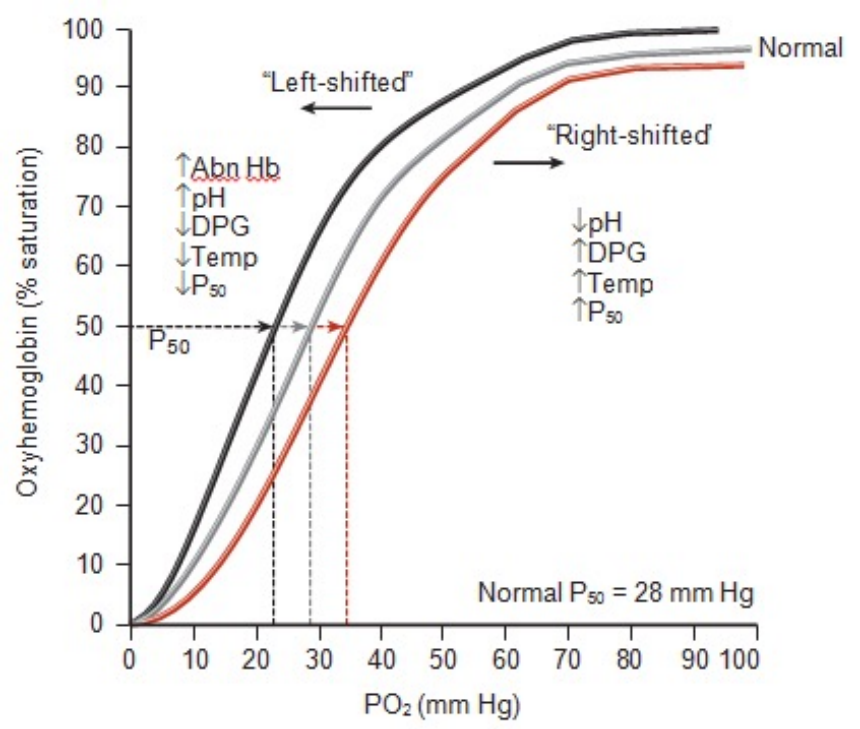
- Volume ~300ml
- Final Hematocrit
  - CPDA-1 ≤ 80%
  - AS **55-65%**
- Storage: **1-6ºC**
- Shelf life
  - CPD or ACD– 21 days
  - CPDA-1 – 35 days
  - AS – **42 days**

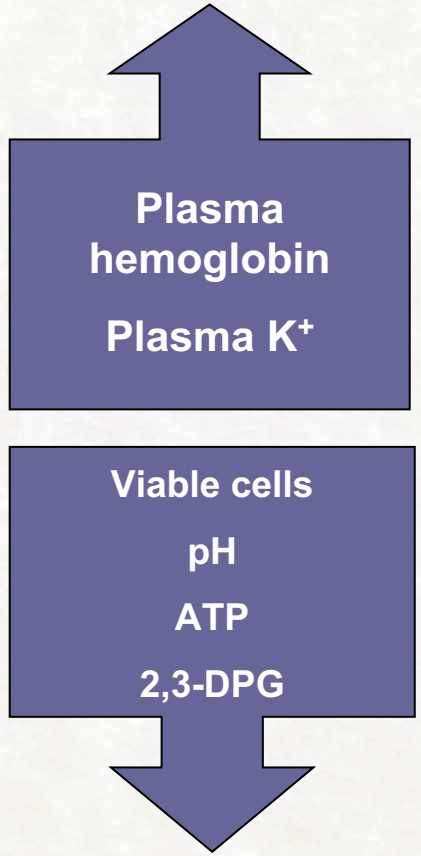
Once transfusion starts it must be completed within 4 hours

CHEMICAL	FUNCTION	PRESENT IN			
		ACD-A	CPD	CP2D	CPDA-1
Citrate (sodium citrate/citric acid)	Chelates calcium; prevents clotting	X	X	X	X
Monobasic sodium phosphate	Maintains pH during storage; necessary for maintenance of adequate levels of 2,3-DPG	X	X	X	X
Dextrose	Substrate for ATP production (cellular energy)	X	X	X	X
Adenine	Production of ATP (extends shelf-life from 21 to 35 days)				X

RBC Storage Lesion

- Preservative solutions help the RBC maintain:
  - -Viability
  - -Function
- During storage, red cells undergo biochemical changes that lead to storage lesion and loss of viability





Physiologic basis for transfusing Red cells

Goal is to avoid: O_2 delivery not meeting O_2 demand

Oxygen delivery (DO_2) = arterial oxygen content(CaO_2) x Cardiac output(CO)

=(1.34 x Hb x O_2sat) + (0.003 x PaO_2)

Hemoglobin Changes

- Increase oxygen extraction ratio
- Changes in O_2-Hb affinity

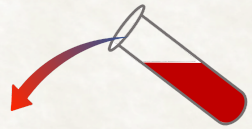
Increased HR + Contractility

Redistribution to vital organs

- Vasoconstriction of venous reservoir
- Arterioles constriction

Summary of Major RBC Threshold Trials

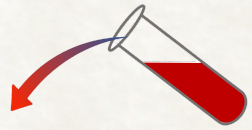
Trial	Population	Participants (n)	Thresholds (hemoglobin)	Primary outcome
TRICC	Critical care	838	7 g/dL vs 10 g/dL	30d mortality 18.7% vs 23.3%, P=0.1
FOCUS	Hip fracture	2016	8 g/dL vs 10 g/dL	Death or inability to walk across room at 60d, 35% vs 34.7%, P=0.9
Villanueva et al.	Upper GI Hemorrhage	921	7 g/dL vs 9 g/dL	Mortality at 45d, 5% vs 9% P=0.02
TRISS	Septic Shock	998	7 g/dL vs 9 g/dL	90d mortality, 43% vs 45% P=0.4
TITRE2	Post-cardiac surgery	2003	7.5 g/dL vs 9 g/dL	Infection or ischemic event in 3mo, 35% vs 33% P=0.3



Liberal vs Restrictive Hemoglobin Triggers

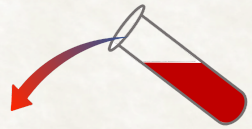
- Systematic review, 31 trials, N=12587
- Range of clinical scenarios
- Restrictive thresholds
  - 43% reduction in transfusions
  - No difference in 30-day mortality or morbidity
  - No difference in pneumonia, wound infection, or bacteremia
  - Insufficient data for: ACS/MI, brain injury, stroke, thrombocytopenia, cancer/heme malignancy, bone marrow failure

Carson et al. Cochrane Database Syst Rev. 2016.



Society Guidelines – RBC Triggers

Year	Society	Hemoglobin
2009	American College of Critical Care Medicine	7g/dL
2009	Society for Critical Care Medicine	7g/dL
2011	Society for Advancement of Blood Management	8g/dL
2011	Society of Thoracic Surgeons	7-8g/dL
2012	National Cancer Care Network	7-9g/dL
2012	British Committee for Standards in Hematology	7-8g/dL
2013	American Society of Hematologists	7-8g/dL
2016	AABB	7-8g/dL



RBC Transfusion

Indications: Increase O_2 carrying capacity

- AVOID Transfusion based on Lab Values alone

Assess tolerance of low Hgb

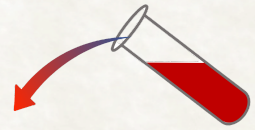
- **Acute anemia** (rapid onset) vs **Chronic anemia** (gradual onset, +/- physiologic adjustment)
- **Increased risk of ischemia** - pulmonary disease, coronary artery disease, cerebral vascular disease, etc.

Hemoglobin threshold < **7** g/dL

- Stable non-bleeding adults

Hemoglobin threshold < **8** g/dL

- Patients with preexisting cardiovascular disease



Product Modifications: Freezing/Deglycerolization of RBCs

Freezing/Deglycerolization of RBCs: used for "**rare**" blood (i.e U neg)

- Can store RBC for up to 10 years at -65C or below.
- Cold temps will generally freeze RBCs thus lyse them
  - ✓ **Hypertonic glycerol** solution is used to draw water out of cells.
- To prepare glycerolized RBCs units for use
  - ✓ Wash +"Rehydrate" the RBC cells by using by using progressively dilute saline
    - 12% -> 1.6% -> 0.9%
- Deglycerolized units can be used only for **24 hours**

Sickle Cell Disease Prophylactic Antigen Matching

CLINICAL GUIDELINES

blood advances

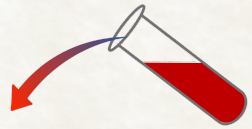
American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

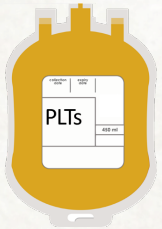
Stella T. Chou,[1] Mouaz Alsawas,[2] Ross M. Fasano,[3] Joshua J. Field,[4] Jeanne E. Hendrickson,[5,6] Jo Howard,[7,8] Michelle Kameka,[9] Janet L. Kwiatkowski,[1] France Pirenne,[10] Patricia A. Shi,[11] Sean R. Stowell,[3] Swee Lay Thein,[12] Connie M. Westhoff,[13] Trisha E. Wong,[14] and Elie A. Akl[15]

[1]Division of Hematology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [2]Mayo Clinic Evidence-Based Practice Research Program, Mayo Clinic, Rochester, MN; [3]Center for Transfusion and Cellular Therapy, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA; [4]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [5]Department of Laboratory Medicine and [6]Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [7]Department of Haematological Medicine, King's College London, London, United Kingdom; [8]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [9]Nicole Wertheim College of Nursing and Health Sciences, Florida International University, Miami, FL; [10]INSERM-U955, Laboratory of Excellence, French Blood Establishment, Créteil, France; [11]New York Blood Center, New York, NY; [12]Sickle Cell Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; [13]Laboratory of Immunohematology and Genomics, New York Blood Center, New York, NY; [14]Division of Hematology/Oncology, Department of Pediatrics, Oregon Health and Science University, Portland, OR; and [15]Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

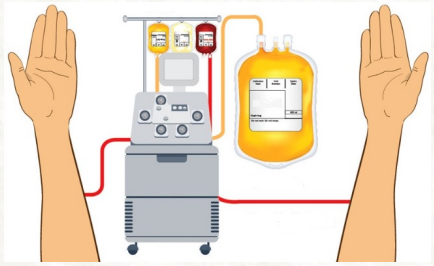
Prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions

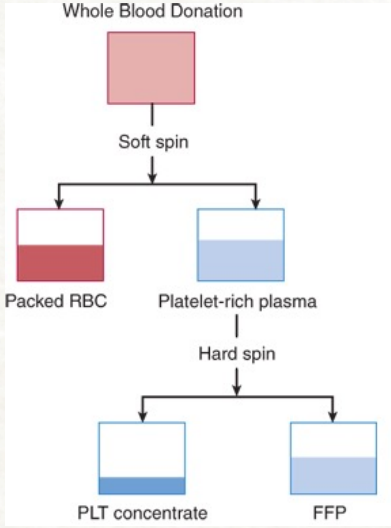
(strong recommendation, moderate certainty in the evidence about effects)





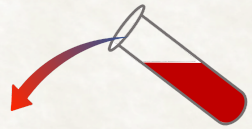
Component Preparation: Platelets





	Apheresis	Whole Blood-derived
Volume (mostly plasma)	200-300 ml	50-70 ml
# Platelets	≥ 3.0×10^{11}	≥ 5.5×10^{10}
# RBCs	>0.0002 ml	0.2-0.6 ml
Storage	20-24°C w/ gentle agitation x 5d (up to 7d) → highest risk component for bacterial contamination	
Dose	1 apheresis unit	Pooled "6-pack"
Administration	As volume tolerated	
1hr PLT increment	20,000-50,000 /μl per unit	~10,000 /μl per unit

RhD Neg Patients with childbearing potential should consider receiving anti-D immunoprophylaxis



When to transfuse?

Annals of Internal Medicine CLINICAL GUIDELINE

Platelet Transfusion: A Clinical Practice Guideline From the AABB

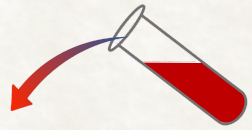
Richard M. Kaufman, MD; Benjamin Djulbegovic, MD, PhD; Terry Gernsheimer, MD; Steven Kleinman, MD; Alan T. Tinmouth, MD; Kelley E. Capocelli, MD; Mark D. Cipolle, MD, PhD; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Brenda J. Grossman, MD, MPH; Paul D. Mintz, MD; Barbara A. O'Malley, MD; Deborah A. Sesok-Pizzini, MD; Aryeh Shander, MD; Gary E. Stack, MD, PhD; Kathryn E. Webert, MD, MSc; Robert Weinstein, MD; Babu G. Welch, MD; Glenn J. Whitman, MD; Edward C. Wong, MD; and Aaron A.R. Tobian, MD, PhD

Ann Intern Med. 2015;162(3):205-13

Prophylactic transfusion

No bleeding or risk factors: <10K
Elective CVC placement: <20K
Elective lumbar puncture: <50K
Major non-neuraxial surgery: <50K

Major neuraxial surgery: <100K



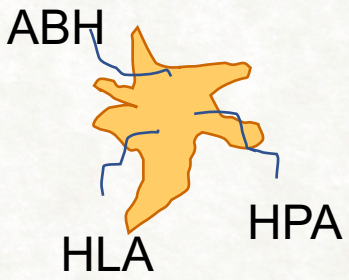
What to Transfuse?

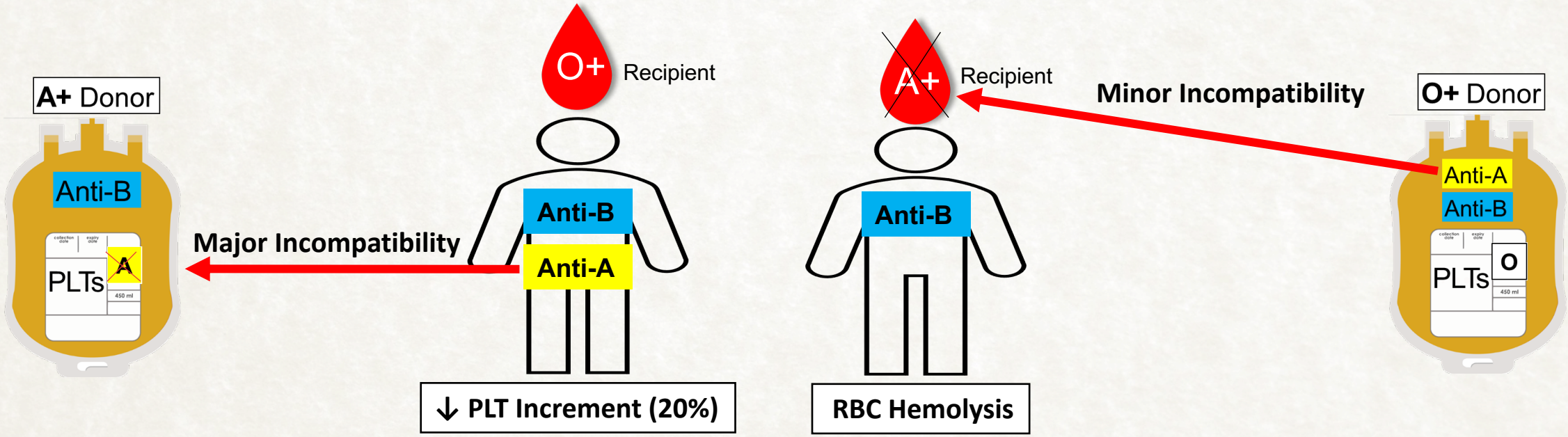
Platelet Surface

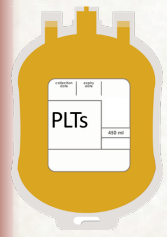
-ABO antigens but *not Rh*

-Class 1: HLA- A and HLA-B

-HPA (human platelet antigens)







Platelet Transfusion in Cancer Patients

VOLUME 36 · NUMBER 3 · JANUARY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Charles A. Schiffer, Kari Bohlke, Meghan Delaney, Heather Hume, Anthony J. Magdalinski, Jeffrey J. McCullough, James L. Omel, John M. Rainey, Paolo Rebulla, Scott D. Rowley, Michael B. Troner, and Kenneth C. Anderson

-Preparation of Platelet Products

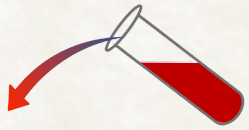
Pooled platelet concentrates and apheresis **single donor platelets** can be **used interchangeably**. Comparative studies have shown that the post-transfusion **increments**, **hemostatic benefit**, and **adverse effects** are **similar among these platelet products**.

(**Type of recommendation**: evidence based; **Evidence quality**: high; **Strength of recommendation**: strong)

-Preparation of Leukoreduced Products

The incidence of alloantibody-mediated **refractoriness to platelet transfusion** can be **decreased** in patients with cancer when both **platelet** and **RBC** products are **leukoreduced** before transfusion**.**

(**Type of recommendation**: evidence based; **Evidence quality**: high; **Strength of recommendation**: strong)



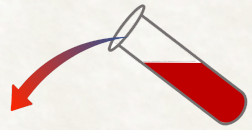
Assessing Responses to Platelet Transfusions

Therapeutic: Cessation of bleeding
Prophylactic: Observation of increments

Poor responses (increment < 10,000/µL) to 2-3 transfusions should prompt further investigation

Expected count increment

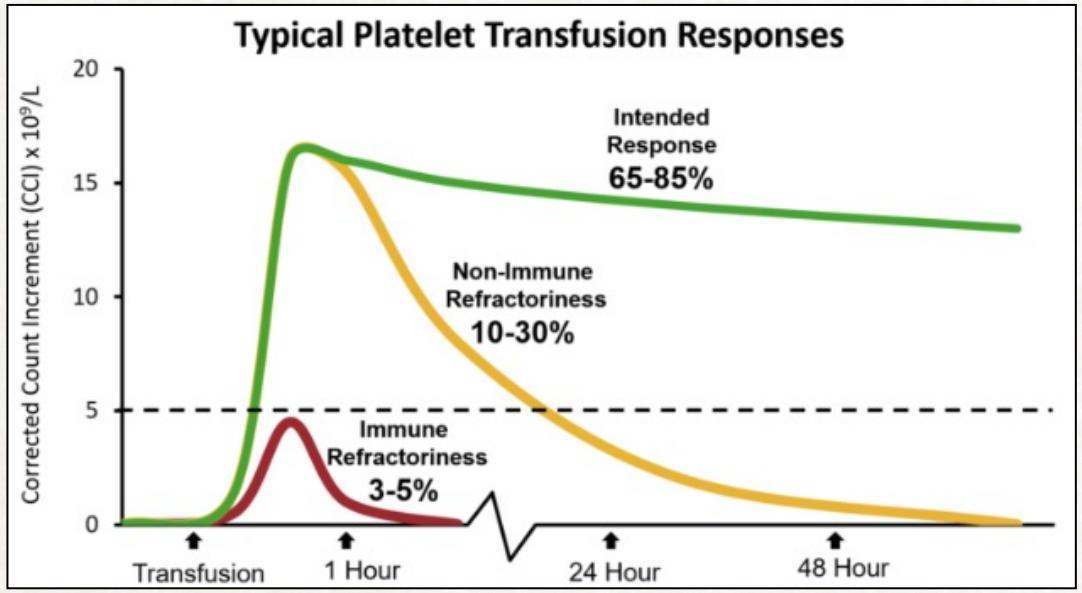
	1 concentrate 1.0×10^{11}	1 Pheresis unit 4.0×10^{11}
50 lb/ 23 kg	22,000/µl	88,000/µl
100 lb/ 45 kg	11,000	45,000
150 lb/ 68 kg	7,400	30,000
200 lb/ 91 kg	5,500	22,000



Calculate Corrected Count Increment

$$CCI = \frac{(\text{post-platelet count} - \text{pre-platelet count})(BSA)}{(3.5\ [\text{approximate \# platelets transfused} \times 10^{11}])}$$

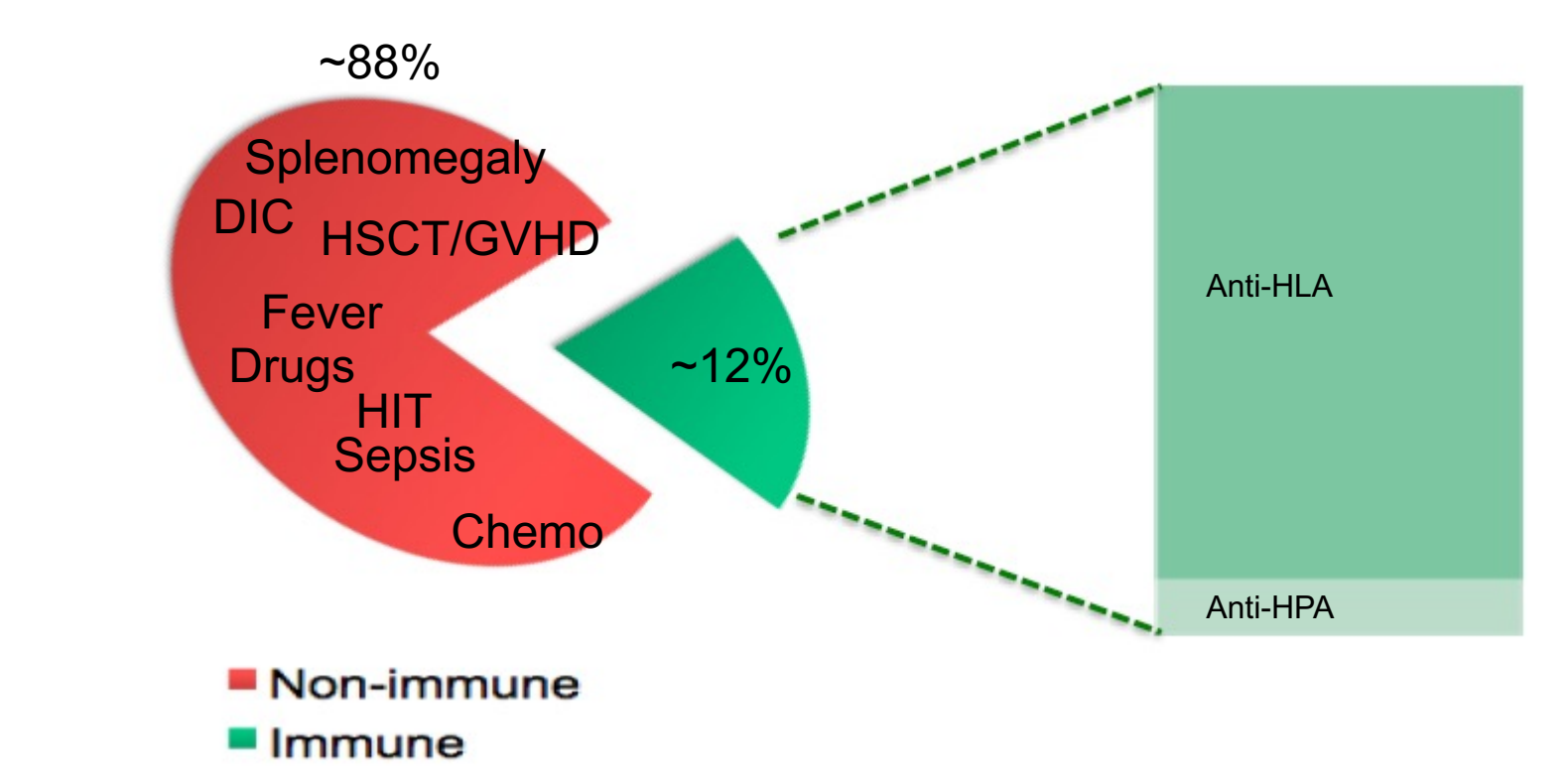
CCI > 7.5 Good Response at 1 hr and >5 at 24 hr

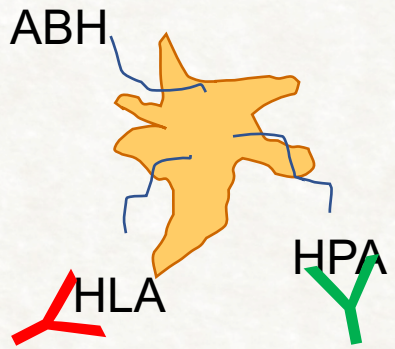


Example: Patient (1.7 M^z) transfused with 1 apheresis platelet unit. Initial platelet count=2. At 1 hr, plts=30K.

CCI=(30-2)(1.7)/3.5=13

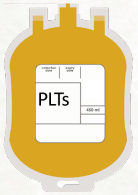
Platelet Refractoriness



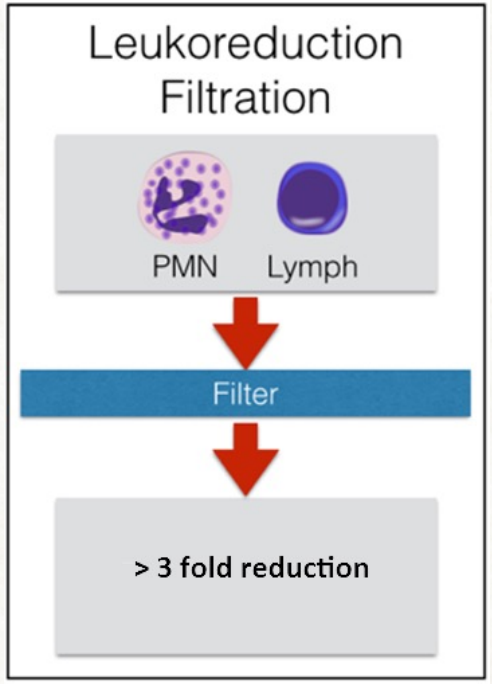


Delaflor-Weiss, E et al. *Transfus Med Rev.* 2000, Vol. 14, pp. 180-96.
Doughty, HA et al. *Vox Sang.* 1994, Vol. 66, pp. 200-5.

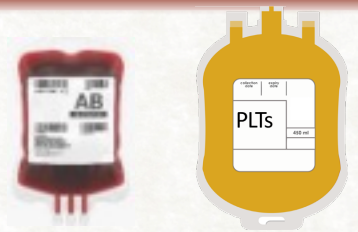
Product Modifications: Leukocyte Reduction



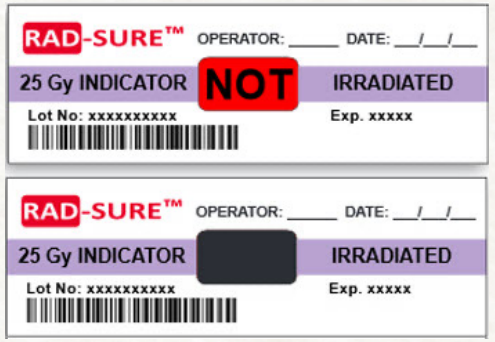
- ↓ CMV transmission
  - CMV virus reside within Monocytes
  - Equivalent to products collected from CMV seronegative donors
- ↓ Febrile Non-hemolytic Reactions
  - WBCs removed before they can leak cytokines
- ↓HLA alloimmunization
  - Decreased incidence of Platelet refractoriness *(TRAP Trial)*

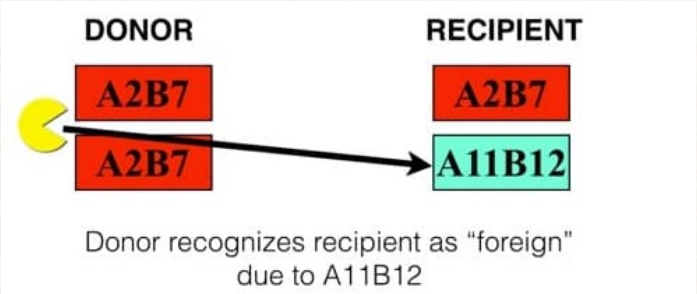


Product Modifications: Irradiation

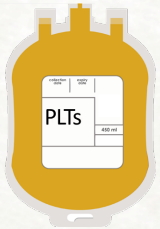


- Prevents transfusion associated GVHD (Mortality >90%)
  - induces DNA crosslinks, prevents (dividing) lymphocyte proliferation
  - Minimum dose to center **25 Gy**, minimum to rest **15 Gy**
- Indications to irradiate:
  - T cell deficits (acquired/congenital)
  - Stem cell transplant patients
  - Intrauterine/neonatal transfusions
  - Patients with Hematologic malignancies
  - Infants up to the age where congenital cellular deficiencies can be identified
  - Transfusions from relatives or HLA-matched products



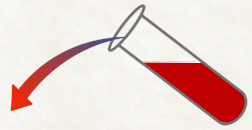


Product Modifications: Washed Blood Products



Washed Products: anaphylaxis prevention

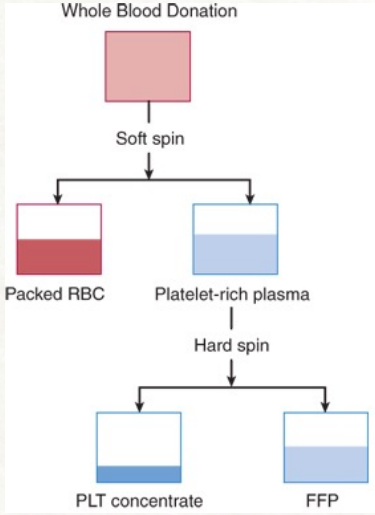
- Indicated:
  - **IgA deficiency** with **IgA antibody**;
  - History of **Anaphylactic reaction** to blood products
- Mechanism: Removes the "allergen" in the plasma/supernatant of RBC/platelet products
- Drawbacks:
  - Washed RBCs expire in **24 hrs**, Platelets in **4 hrs**
  - 20% loss of product due to washing

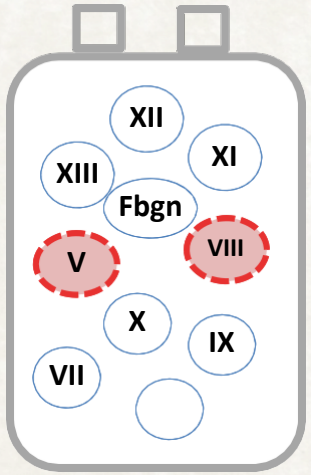


Component Preparation: Plasma

Fresh Frozen Plasma (FFP)
-Separated and frozen within 8 hrs of collection

Plasma Frozen within 24 hrs (PF24)
-Separated and frozen within 24 hrs
-Slight decrease in labile coagulation factors (Factor 5, Factor 8)





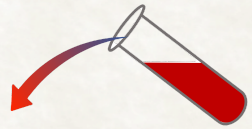
-General FFP: ~250 mL per unit
- 1 unit/mL of activity of each coagulation factor per mL of plasma
- **ABO group matching**

-Storage & Expiration
≤ **-18ºC** for 1 year
≤ -65ºC for 7 years

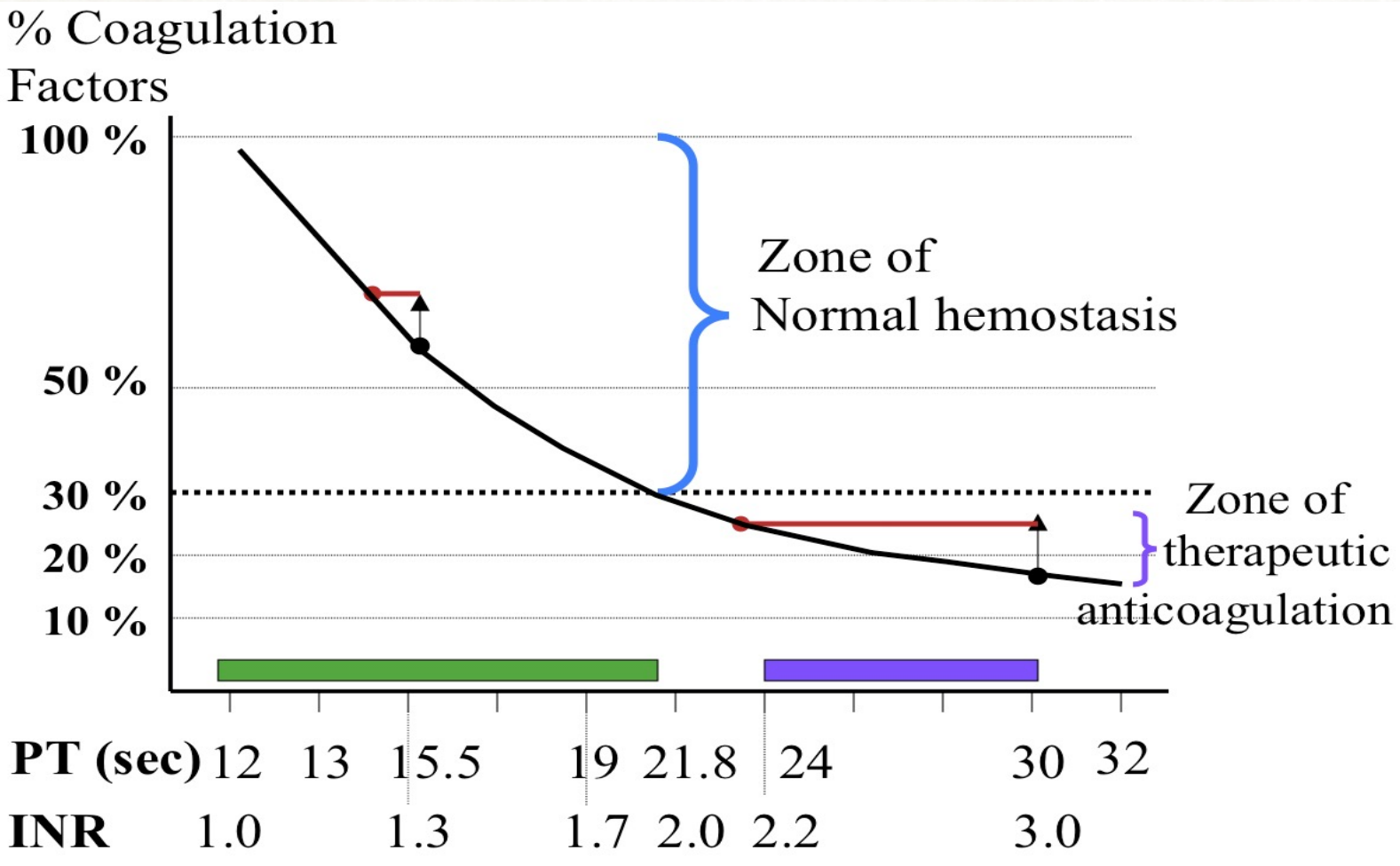
When to transfuse Plasma?

- Transfused to patients requiring massive transfusion
- Patients with multiple clotting factor deficiencies (INR ≥ 1.5) and
  - Acute or chronic liver disease with active or expected bleeding
  - Active bleeding with DIC
  - Prevention of intra-operative bleeding in patients with DIC or liver disease
- Single clotting factor deficiencies without a factor concentrate (Factor 5, Factor 11)
- Thrombotic microangiopathies (TTP, HUS, etc.)

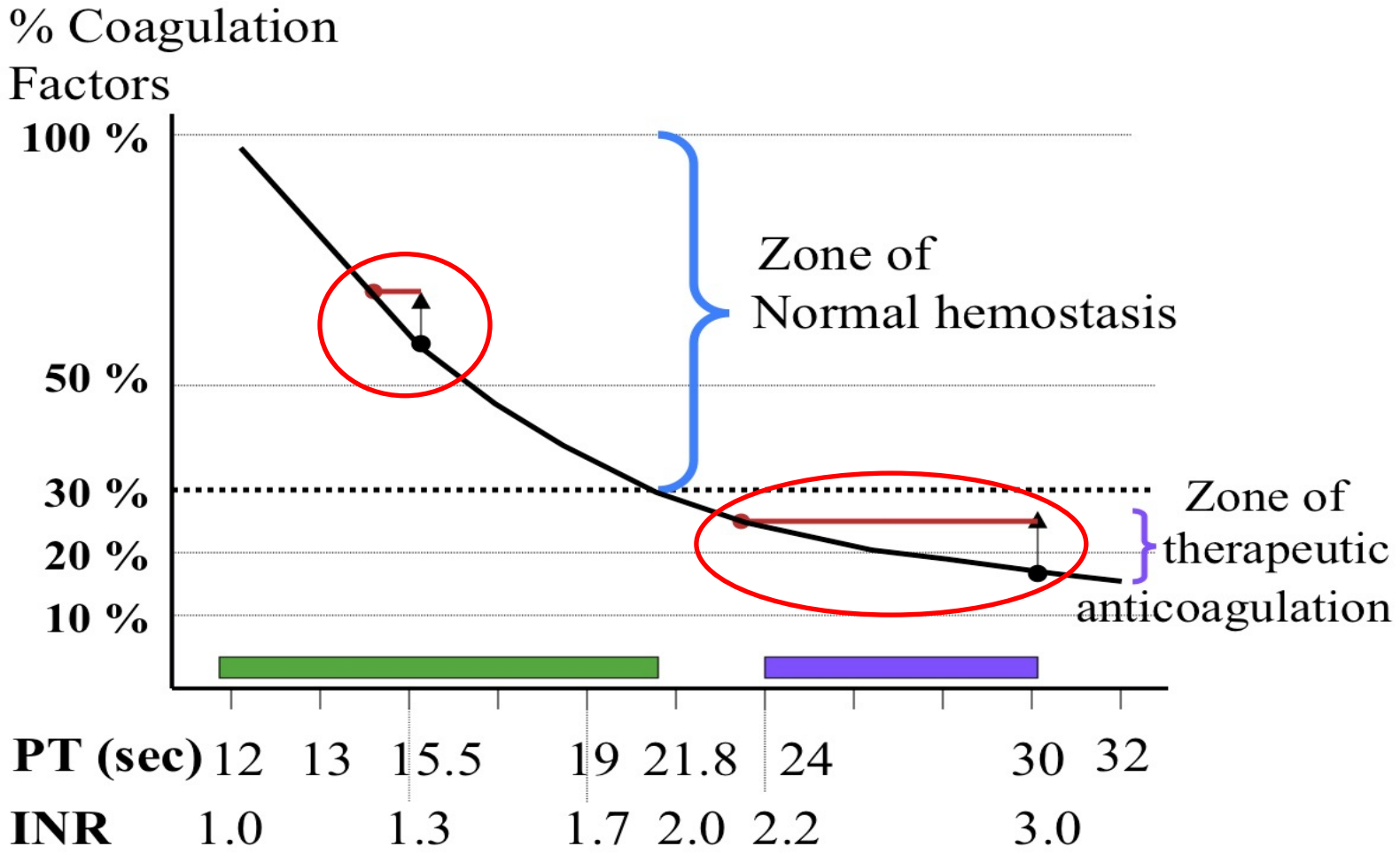
- Usual dose is **10-15 mL/kg** – expected to increase factor levels about 20-30%
- 1 unit/mL of activity of each coagulation factor per mL of plasma
- Must consider half-life of the deficient factor that you are correcting



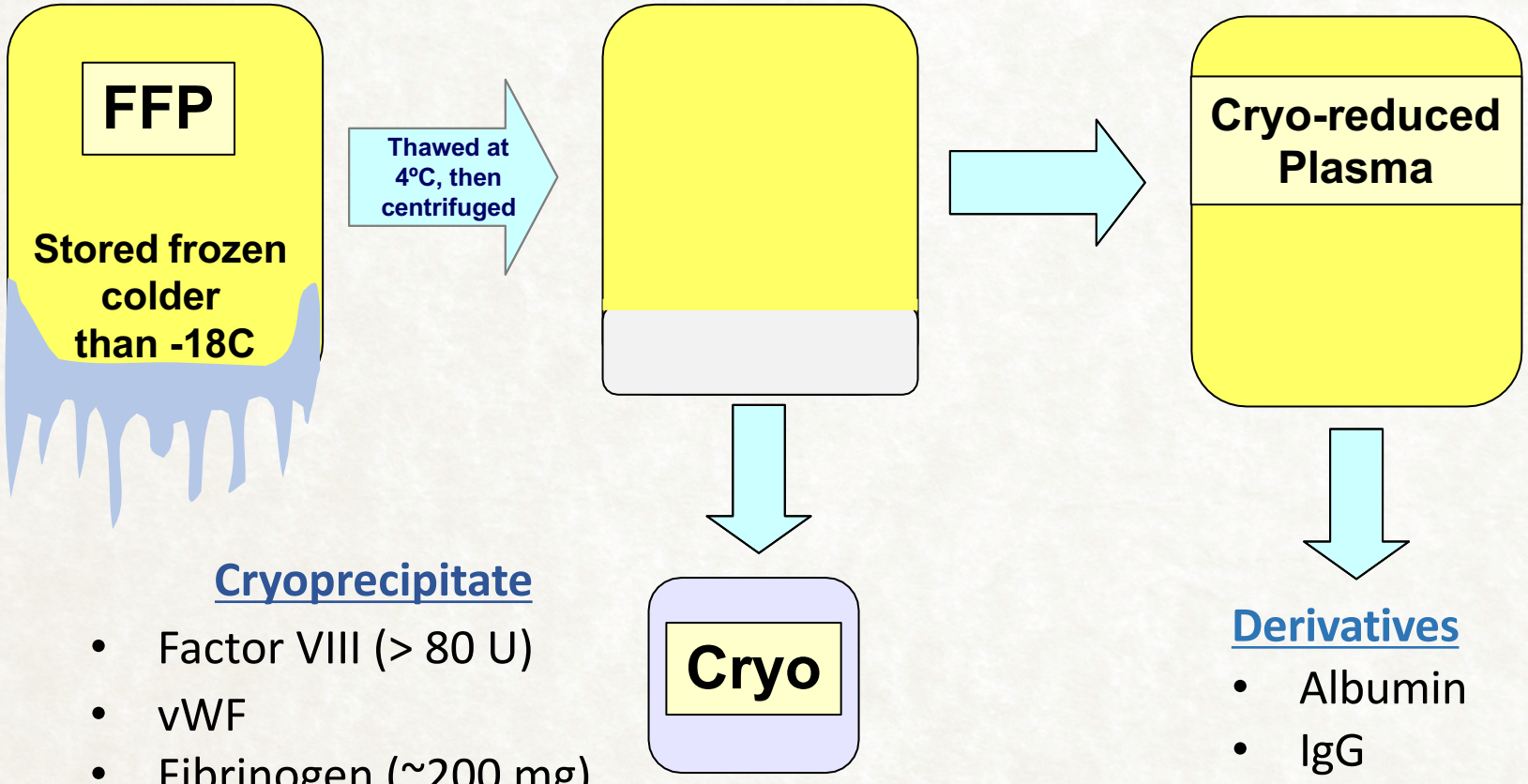
INR and Coagulation factor levels



Effect of FFP depends on initial INR



Component Preparation: Cryoprecipitate



- Volume ~15ml
- Storage & Expiration
  - -Frozen ≤-18ºC for 1 year
  - -Thawed 20-24 ºC for 6 hours
  - -Pooled 20-24 ºC for 4 hours

Cryoprecipitate

- Factor VIII (> 80 U)
- vWF
- Fibrinogen (~200 mg)
- Factor XIII

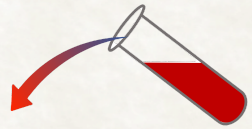
Derivatives

- Albumin
- IgG

When to transfuse Cryoprecipitate?

- **Hypofibrinogenemia** (< 150 mg/dL)
  - Associated with consumptive coagulopathies (DIC)
  - Isolated fibrinogen deficiency with active bleeding or in patients at risk
  - Postpartum hemorrhage >200 mg/dL
- Dysfibrinogenemia
- Uremic bleeding unresponsive to DDAVP
- Von Willebrand Disease or Hemophilia A (**only** when factor concentrates are unavailable)
- Hemorrhagic stroke or intracranial bleeding in patients receiving systemic TPA
- Isolated Factor XIII deficiency

- 1 unit of Cryo per 10 kg TBW, ↑ Fibrinogen 50 mg/dL
- 1 pool of cryoprecipitate = 5 units (approx. 75 mL)



Granulocyte Transfusion

TRANSFUSION MEDICINE

BLOOD, 29 OCTOBER 2015 • VOLUME 126, NUMBER 18

Efficacy of transfusion with granulocytes from G-CSF/dexamethasone–treated donors in neutropenic patients with infection

Thomas H. Price,[1,2] Michael Boeckh,[1,3] Ryan W. Harrison,[4] Jeffrey McCullough,[5] Paul M. Ness,[6] Ronald G. Strauss,[7] W. Garrett Nichols,[3,8] Taye H. Hamza,[4] Melissa M. Cushing,[9] Karen E. King,[6] Jo-Anne H. Young,[5] Eliot Williams,[10] Janice McFarland,[11] Jennifer Holter Chakrabarty,[12] Steven R. Sloan,[13] David Friedman,[14] Samir Parekh,[15] Bruce S. Sachais,[16,17] Joseph E. Kiss,[18,19] and Susan F. Assmann[4]

Key Points

- Overall, no benefit of granulocyte transfusion therapy was observed, but the power of the study was reduced due to low accrual.
- Post hoc secondary analysis suggested that patients receiving higher doses tended to have better outcomes than those receiving lower ones.

Indications:

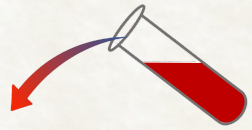
- Neutropenia (<500/uL) with
- Severe Bacterial/fungal infection unresponsive to appropriate antibiotics
- Expectation of marrow recovery

Collection:

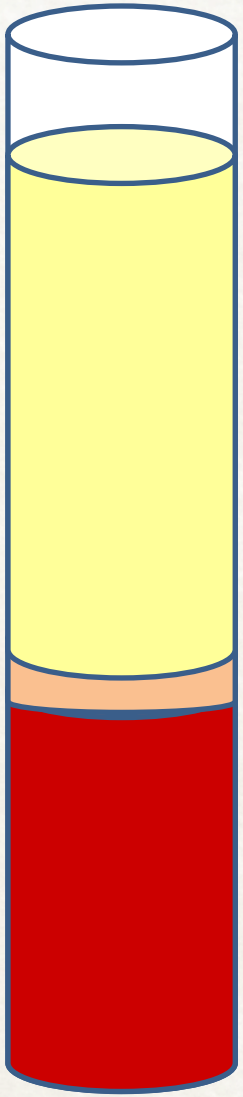
- Pre-treatment of donors with corticosteroids and G-CSF significantly increases collection yield

Product:

- Granulocytes **expire in 24 hrs**
  - viral testing on the product won't be completed prior to issuing; needs Emergency release
- Must be ABO + Crossmatch compatible
- Irradiate to prevent GVHD
- **Don't Leukoreduce the product**



Review: Blood Components & Indications



Plasma

Bleeding w/INR >1.5 (multiple factor deficiencies)
Massive hemorrhage
Factor deficiency w/o concentrate

Cryoprecipitate

Low fibrinogen

Platelets

<10K -prophylactic
<20K –prophylactic (CVC placement)
<50K -major surgery/LP
<100K CNS/eye injury/surgery
Massive hemorrhage

RBCs

Decreased tissue oxygenation
Symptomatic anemia
Massive hemorrhage