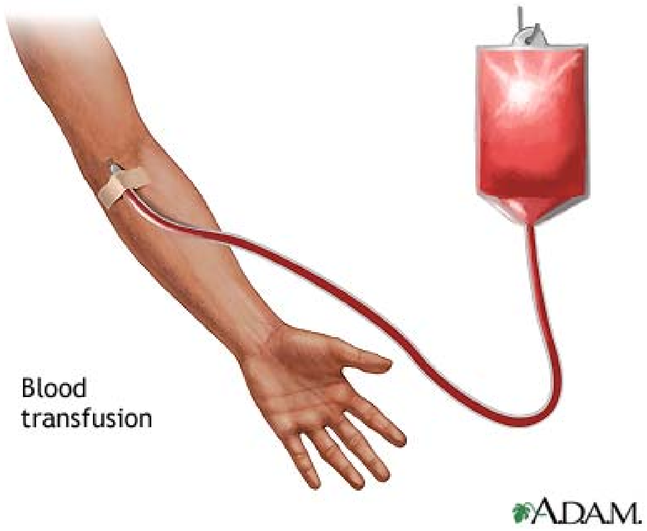
Transfusion Medicine III

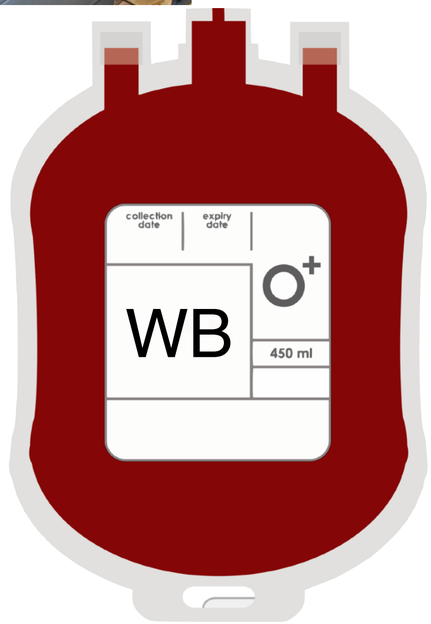
Blood Products from Collection to Use

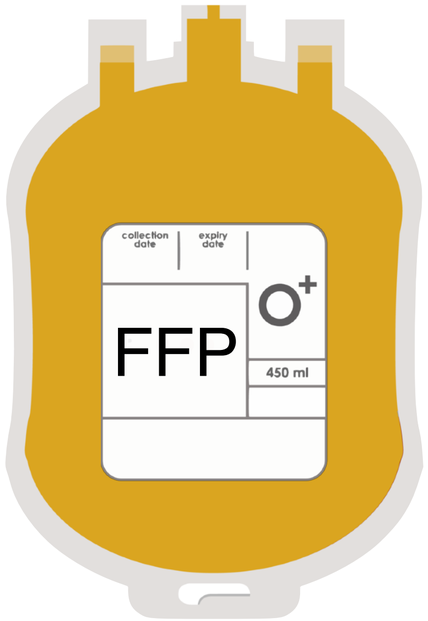
Gimme all your blood...and I want it in little tiny bags.

D. Joe Chaffin, MD
Loma Linda University
3/5/2019

LOMA LINDA UNIVERSITY
TO MAKE MAN WHOLE




collection date
expiry date
WB
O+
450 ml


collection date
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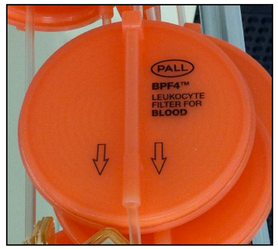
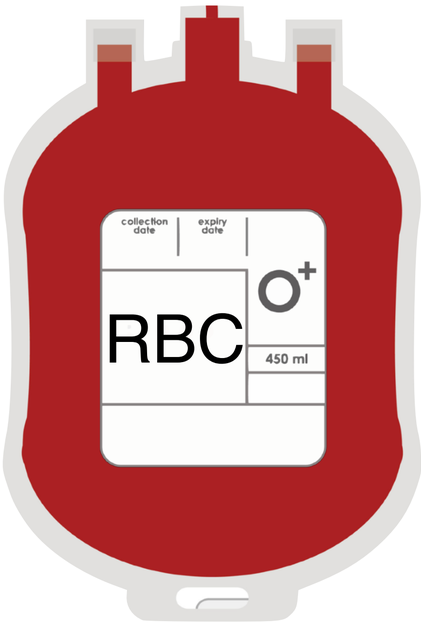
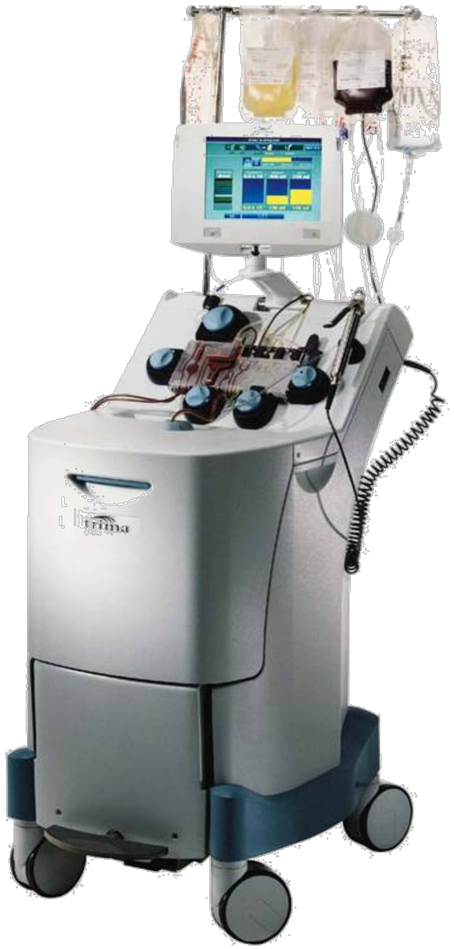
FFP
O+
450 ml


PALL
BPF4™
LEUKOCYTE FILTER FOR BLOOD


collection date
expiry date
RBC
O+
450 ml




TI

Anticoagulant/Preservatives

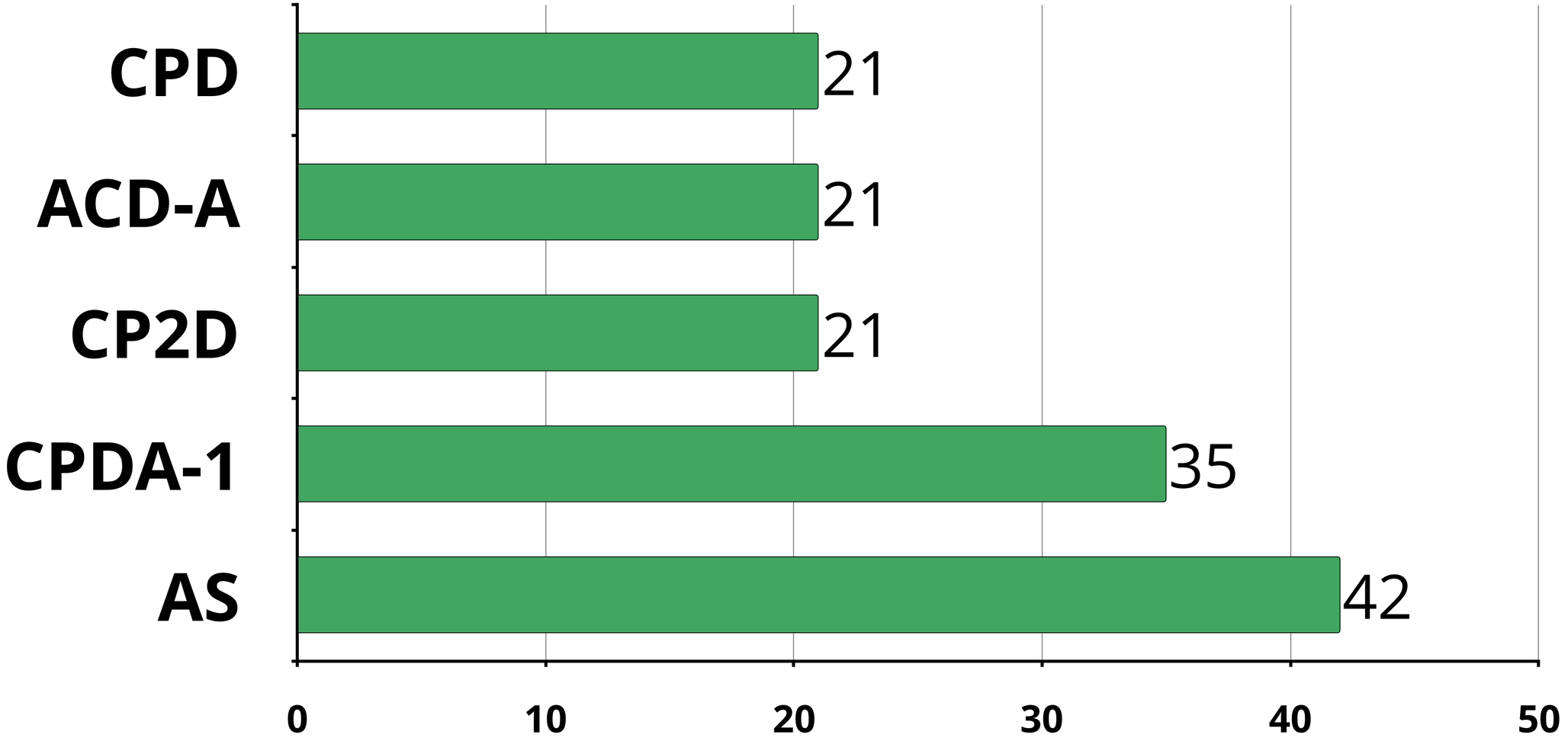
Why we need
- Prevent clotting
- Keep cells fresh

Shelf Life (RBC)
- Labeled RBCs in
- Wait 24 hours
- >75% survival

21 Day Shelf Life

35 Day Shelf Life

RBC Shelf Life



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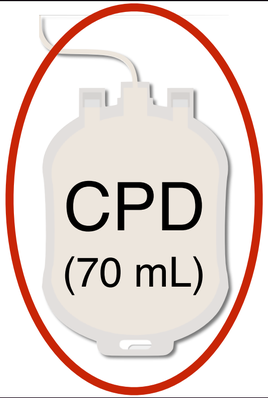
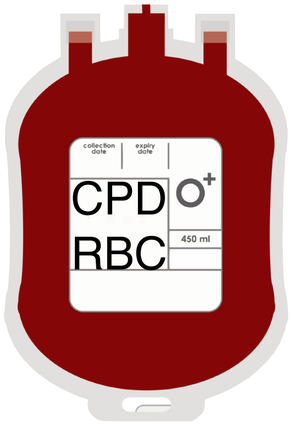
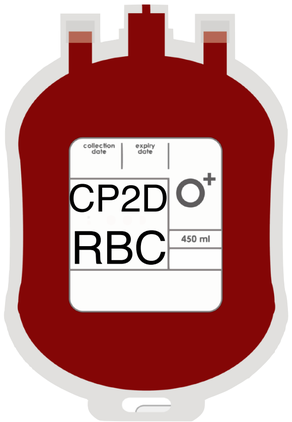


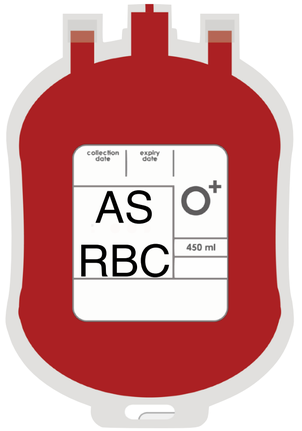
35 Day Shelf Life

21 Day Shelf Life → 42 Day Shelf Life

HCT: 60-80%





→ AS (110 mL) → LR → 

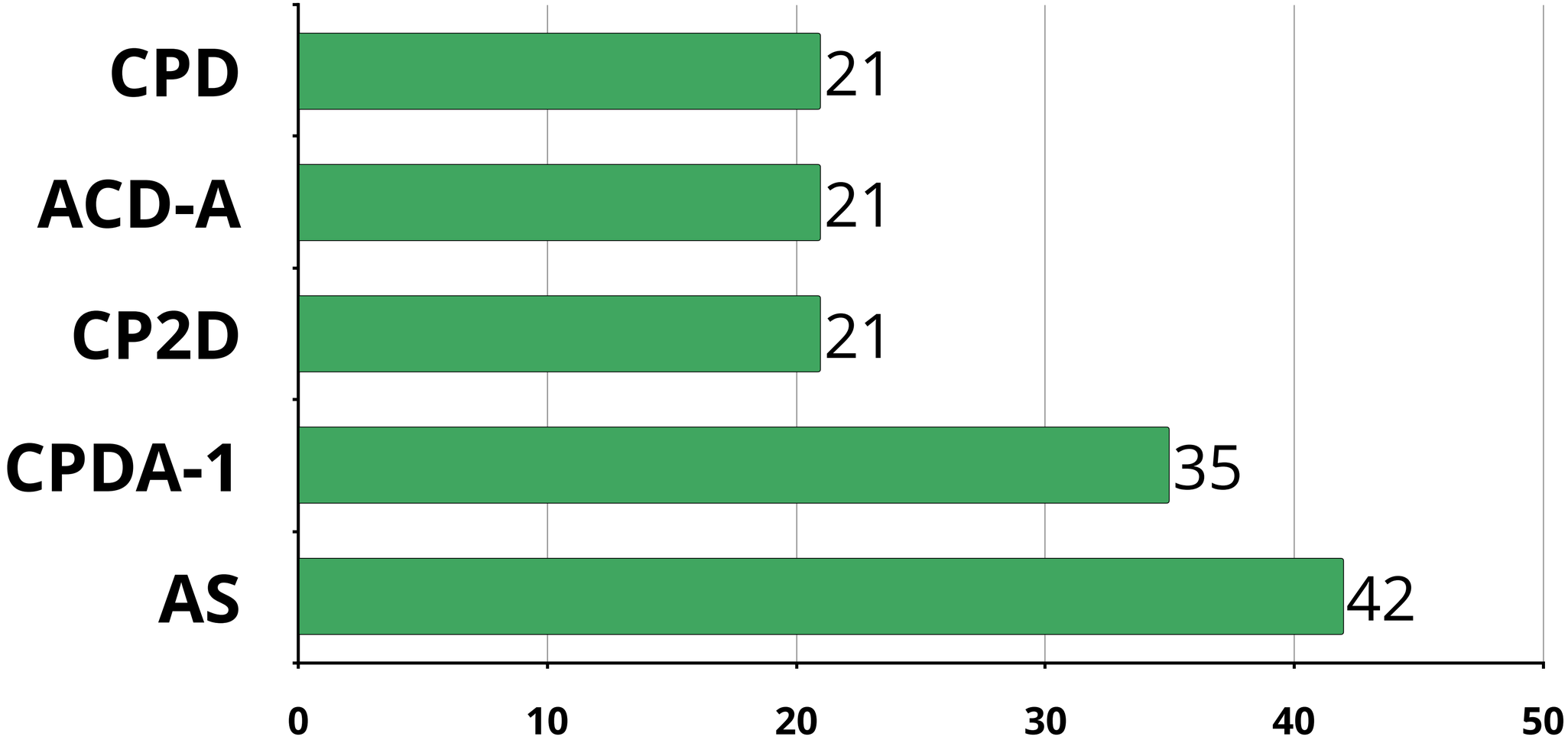
HCT: 50-60%

Types:

- AS-1 (Adsol)*
- AS-3 (Nutricel)
- AS-5 (Optisol)*
- AS-7 (SOLX)*

* = Has mannitol

RBC Shelf Life



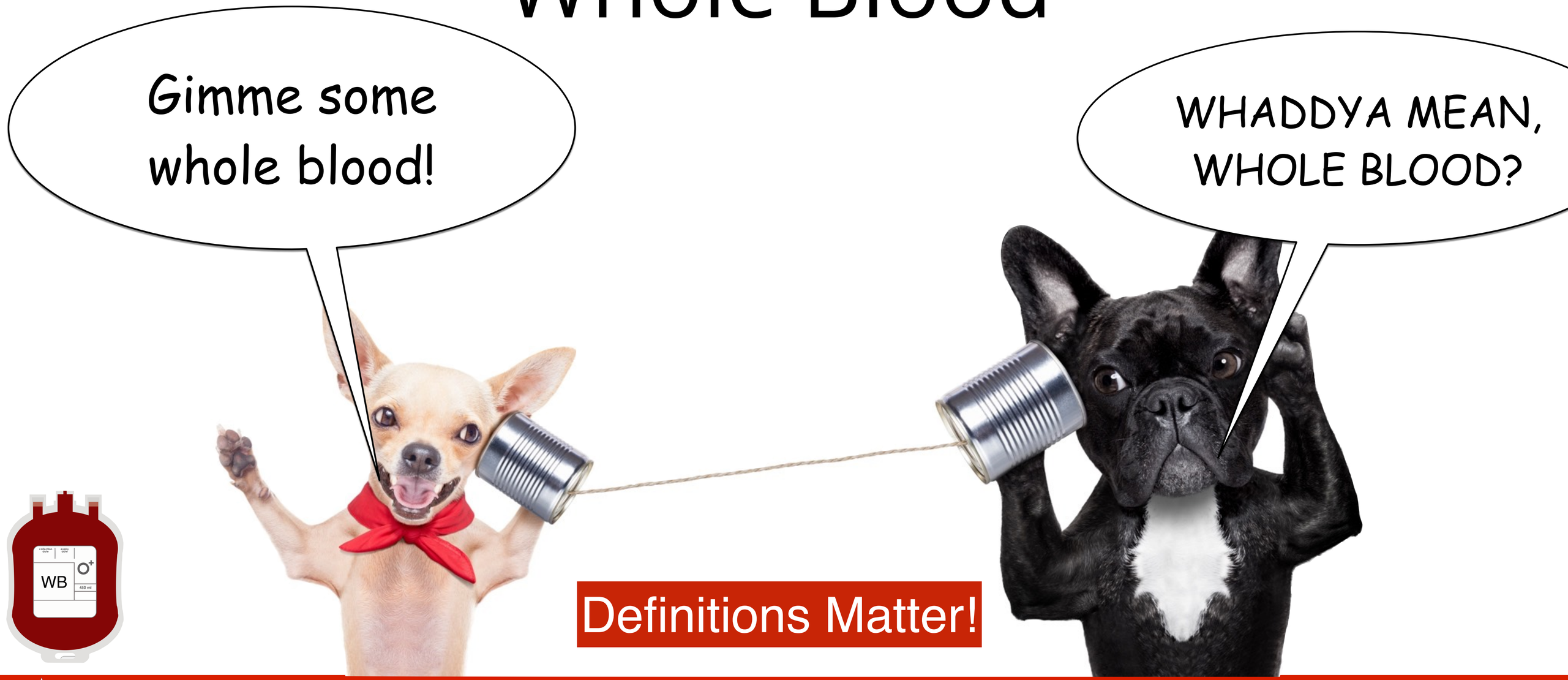
BBGuy.org/LLU

LLUPathology

Table 1: Storage Details for Various Blood Products			
Product	**Storage**	**Product**	**Storage**
RBCs / Whole blood	21 days (CPD/2D) 35 days (CPDA-1) 42 days (AS) All @ 1-6 C	**Granu-locytes**	24 hrs @ 20-24 C (no agitation)
Frozen RBCs	10 years @ –65 C 24 hours @ 1-6 C after thaw	**Frozen Plasma (FFP, PF24 etc.)**	1 year @ –18 C 7 years @ –65 C; 24 hours at 1-6 C after thaw
Washed RBCs	24 hours @ 1-6 C		
Platelets	5 days @ 20-24 C (gentle agitation); 4 hours if pooled in open system	**CRYO**	1 year @ –18 C 6 hours @ 20-24 C after thaw (4 hrs if pooled in open system)

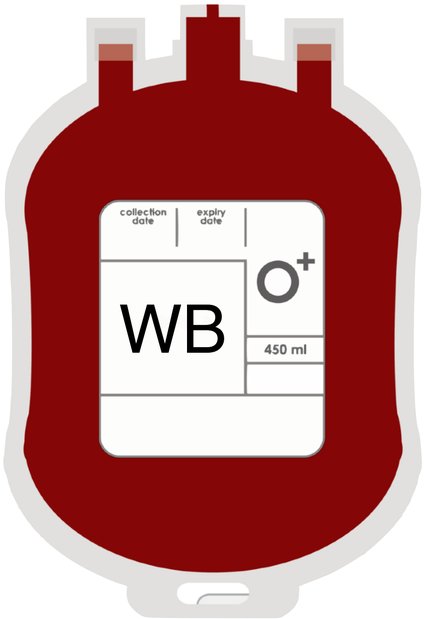
Table 2: Quality Control for Blood Products (US)			
Product	**QC**	**Product**	**QC**
RBCs	HCT < 80% (all), ≥ 50 g HGB in 95% (apheresis RBCs)	**Apheresis platelets**	≥ 3.0×10^{11} and pH ≥ 6.2 in 90%
RBCs leukoreduced	≤ 5×10^{6} WBCs in 95%, retain 85% of RBCs	**Apheresis platelets leukoreduced**	Above + < 5.0×10^{6} residual WBCs in 95%
Platelets (PC)	≥ 5.5×10^{10} and pH ≥ 6.2 in 90%	**CRYO**	Factor VIII ≥ 80 IU (all) Fibrinogen ≥ 150 mg (all)
Platelets (PC) leukoreduced	≥ 5.5×10^{10} in 75%, pH ≥ 6.2 in 90%, AND < 8.3×10^{5} WBCs in 95%	**Granulocyte concentrate**	≥ 1.0×10^{10} in 75%

Whole Blood



Definitions Matter!

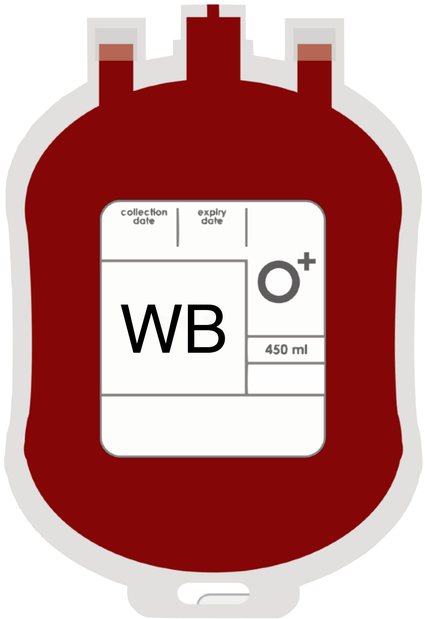
Whole Blood



Warm, fresh

Unmodified

Untested



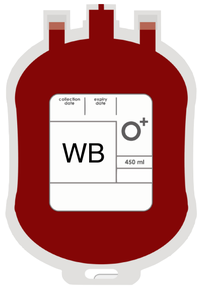
Cold, stored

Low-titer ABO abs

Leukoreduced but platelet-rich

Whole Blood

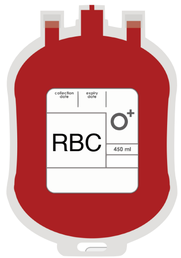
- Indication for Group O, low-titer, cold whole blood:
  - **Trauma massive transfusion (universal)**
    - ✓ Appears safe so far
    - ✓ Cold PLTs may have better immediate activity
- Other forms
  - Reconstituted: Exchange transfusions (neonates)
- Storage length depends on anticoagulant
  - Always at 1-6 C



Red Blood Cells

- 5.9 M units/yr as of 2014 (declining)

Volume:	350 mL (incl. additive)
Contents:	RBCs (200-250 mL)
	Plasma (< 50 mL)
	WBCs (10^9) and PLTs
	Anticoagulant/preservative
	Additive solution (110 mL)
	200-250 mg iron



Consumption/Delivery

DO_2: Oxygen delivery (supply)

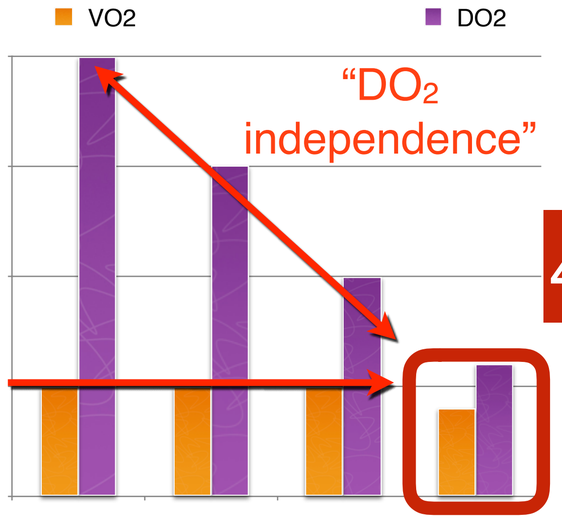
$DO_2 = CO \times CaO_2$

Cardiac Output

HR x SV

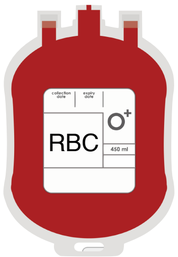
Arterial O_2

Hgb O_2 + plasma O_2



4-5 g/dL?

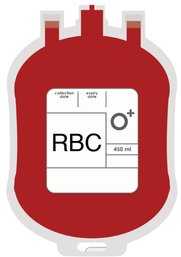
Unless below critical DO_2, RBCs have minimal effect!



VO_2 = Oxygen consumption
DO_2 = Oxygen delivery

Why Use?

- Insufficient O_2 delivery due to carrying capacity
  - Acute hemorrhage (>30% of BV)
  - Hemolysis
  - Marrow failure
- Replace malformed RBCs in Sickle Cell Disease
- Exchange coated RBCs in neonates with HDFN



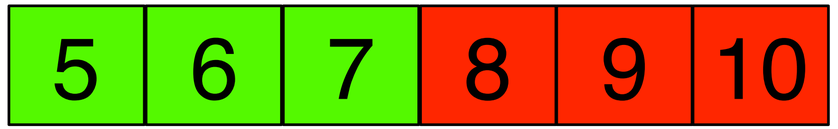
JAMA | Special Communication

Clinical Practice Guidelines From the AABB
Red Blood Cell Transfusion Thresholds and Storage

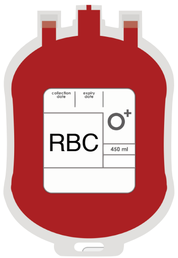
Jeffrey L. Carson, MD; Gordon Guyatt, MD; Nancy M. Heddle, MSc; Brenda J. Grossman, MD, MPH; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Terry Gernsheimer, MD; John B. Holcomb, MD; Lewis J. Kaplan, MD; Louis M. Katz, MD; Nikki Peterson, BA; Glenn Ramsey, MD; Sunil V. Rao, MD; John D. Roback, MD, PhD; Aryeh Shander, MD; Aaron A. R. Tobian, MD, PhD

- Stable hospitalized patients: 7 g/dL

- Ortho/Cardiac surg: 8 g/dL or symptoms
- Chronic CV disease: 8 g/dL



- Others with no recommendation:
  - Acute coronary syndrome
  - Marked thrombocytopenia
  - Chronic anemias

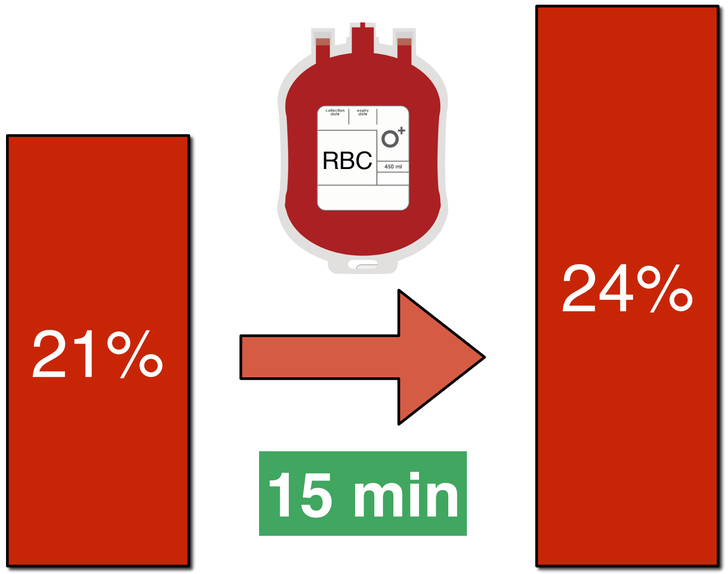


Source: Carson JL et al, JAMA 2016

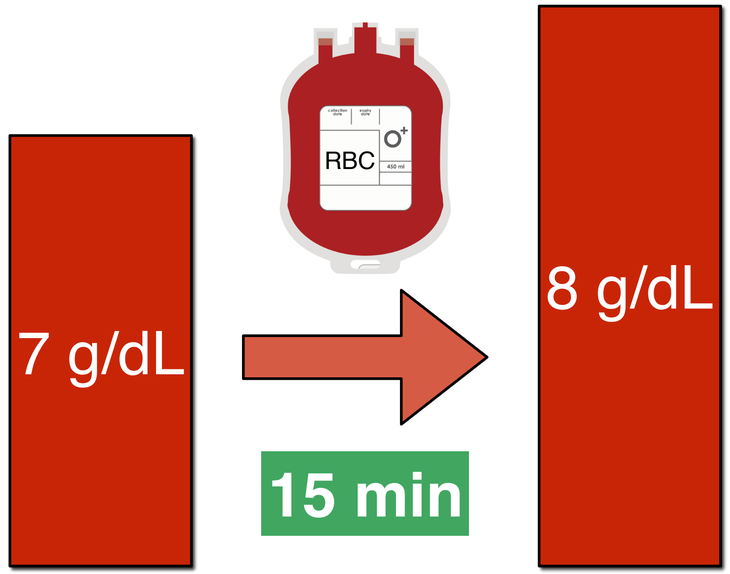
Why NOT to Use

- Smaller acute hemorrhages
  - 1L (20%) OK with saline
- Nutritional anemias
  - Folate, B12, iron

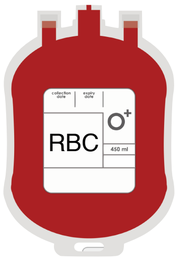
Effect in non-bleeding Pts



Hematocrit

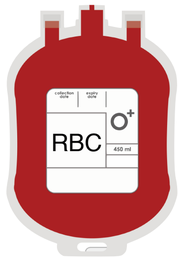


Hemoglobin



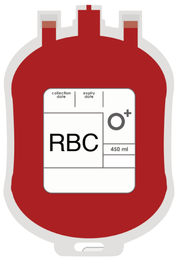
Storage

- Depends on anticoagulant
  - 42 days with additives
- Always at 1-6 C
- Shipping
  - Temperature range 1-10 C

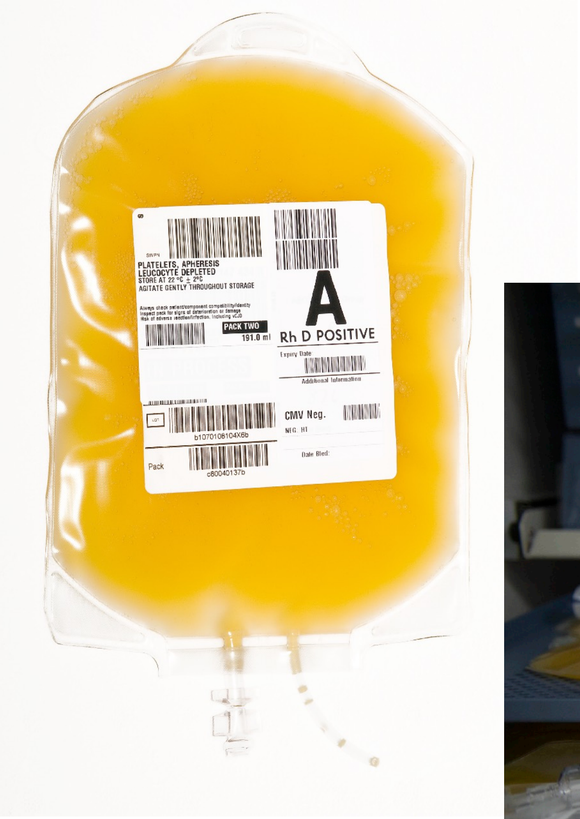


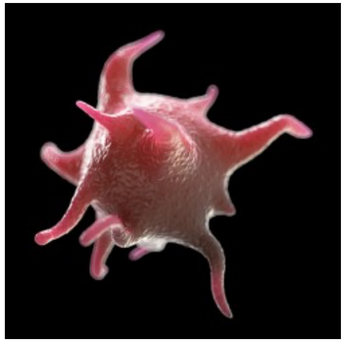
Compatible Fluids

- NaCl (0.9%, not 0.45%)
- ABO compatible plasma
- 5% albumin
- Plasma-Lyte 148, Plasma-Lyte-A, Normosol-R ph 7.4
- NOT:
  - LR (3 mEq Ca2+/L), antibiotics, other meds, TPN

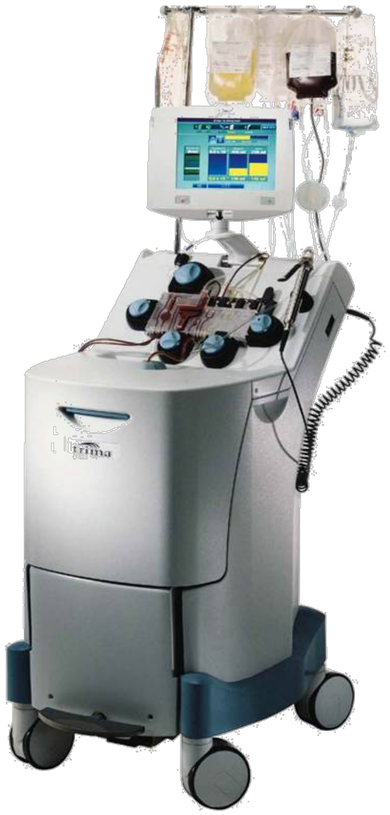


Platelets


PLATELETS, APHERESIS
LEUCOCYTE DEPLETED
STORE AT 22 °C ± 2°C
AGITATE GENTLY THROUGHOUT STORAGE
A
Rh D POSITIVE
PACK TWO
191.0 ml
CMV Neg.
Pack



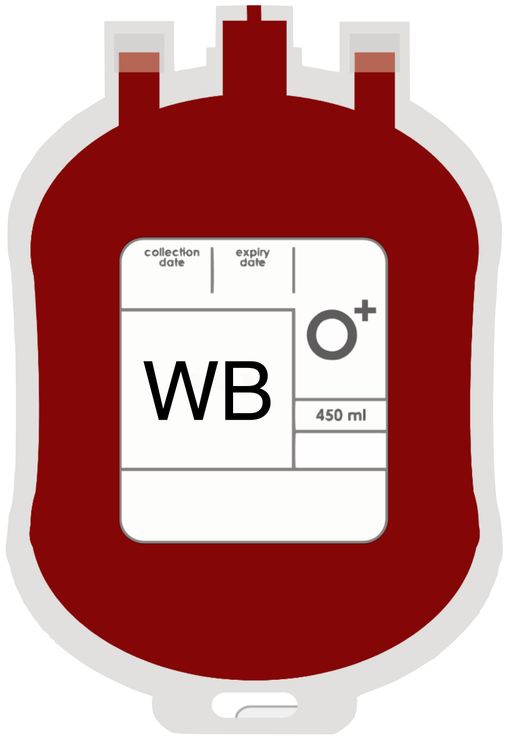
Platelets: Two Options



>90%

Multiple products

Limits exposure



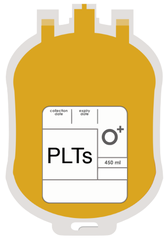
<10%

Pooled product

Trauma

Apheresis Platelets

Volume:	150-300 mL (or more)
Contents:	PLTs ($\geq 3.0 \times 10^{11}$ in 90%)
	Plasma (100-150 mL)
	WBCs ($\leq 5.0 \times 10^{6}$)
	pH $\geq$ 6.2 (90%)



WBD-Platelets

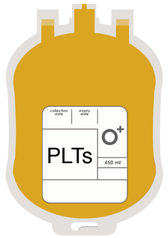
Volume: 40-60 mL each

Contents: PLTs ($\geq 5.5 \times 10^{10}$ in 90%)

Plasma (40-60 mL)

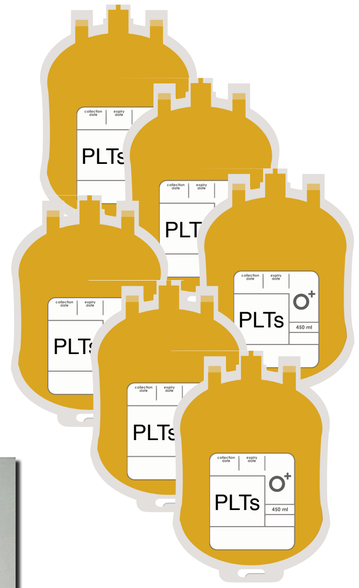
WBCs ($\sim 10^{7}$)

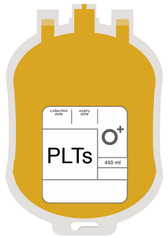
pH $\geq$ 6.2 (90%)



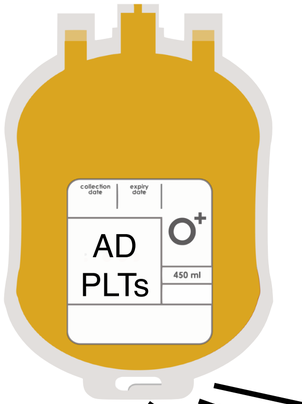
Typical Conversions

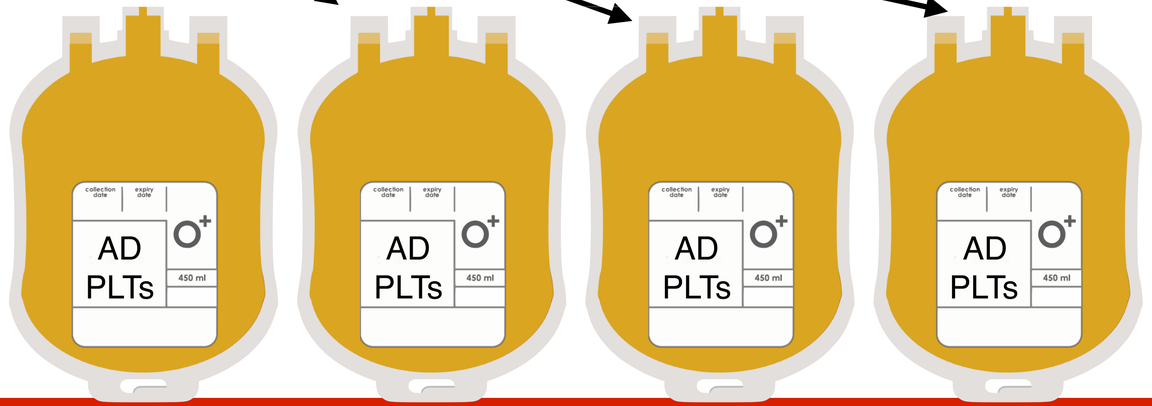
4-6 of these (Whole blood)





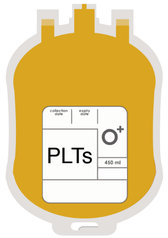
One of these (Apheresis)

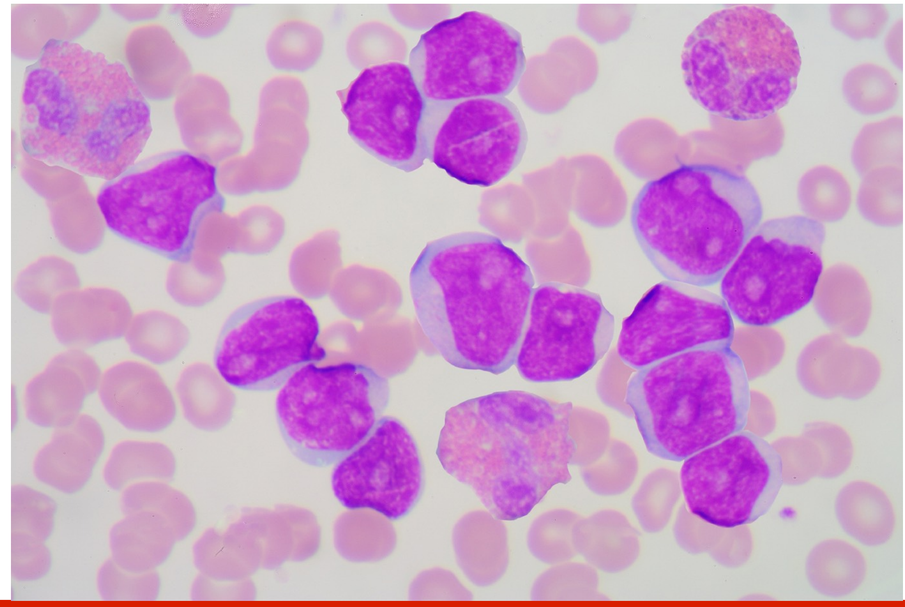




Thrombocytopenia

- “Might bleed" vs. “IS bleeding” debate
  - Answered in Heme/Onc (prophylactic helps)
- Increased risks (? higher threshold):
  - Fever
  - Sepsis
  - Thrombocytopathy
  - Splenomegaly?
  - Coagulopathy?





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

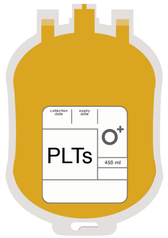
No bleeding or risk factors: <10K

Elective CVC placement: <20K

Elective lumbar puncture: <50K

Major non-neuraxial surgery: <50K

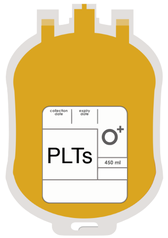
No prophylaxis for CPB



Source: Kaufman RM et al, Ann Int Med 2015

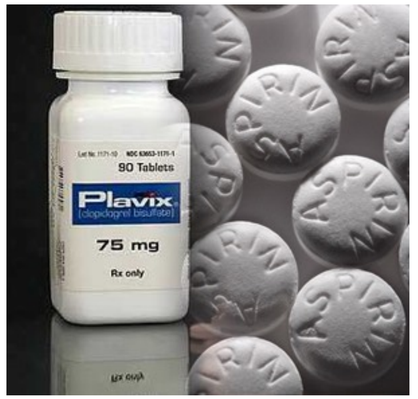
Controversial

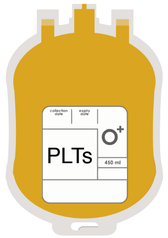
- <u>Liver biopsy/endoscopy/regional anesthesia?</u>
  - 50K common (sometimes 100K!)
  - Count is not predictive of bleeding
  - Skill of operator IS predictive!
- <u>Cranial bleed?</u>
  - Data suggesting worse if on anti-PLT
- <u>Cranial surg/Pulm or eye hemorrhage?</u>
  - No rec; typically 100K used



Thrombocytopathy

- Prophylactic not indicated!
- Congenital defects
- Drugs (ASA, clopidogrel)
- Cardiopulmonary bypass, ECMO
- Metabolic effects
  - Renal failure



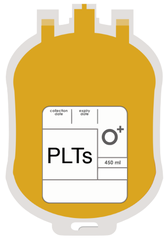


When NOT to Give

- Thrombotic Thrombocytopenic Purpura/HUS
- Heparin-induced thrombocytopenia, type II
- Immune Thrombocytopenic Purpura (ITP)
- Post-transfusion Purpura (PTP)

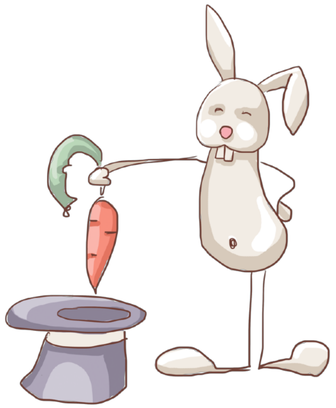
How Much?

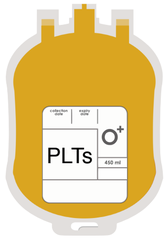
- WBD-PLTs 1 per 10 Kg
  - Usually 4-6 at a time
  - Pooled at blood center or hospital
- AD-PLTs 1 bag per dose
- Smaller doses may be ok
- 10-15 mL/Kg in neonates



Expected Effect

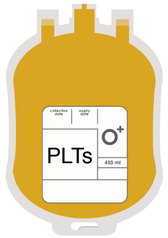
- > 20-30,000 is “eyeball ok”
- Corrected Count Increment for standard eval
- One hour post count is standard
  - But 10 minute counts can be magical!
    - ✓ No bump at 10 min usually = antibodies
    - ✓ Bump at 10 min but not at 1 hr = nonimmune



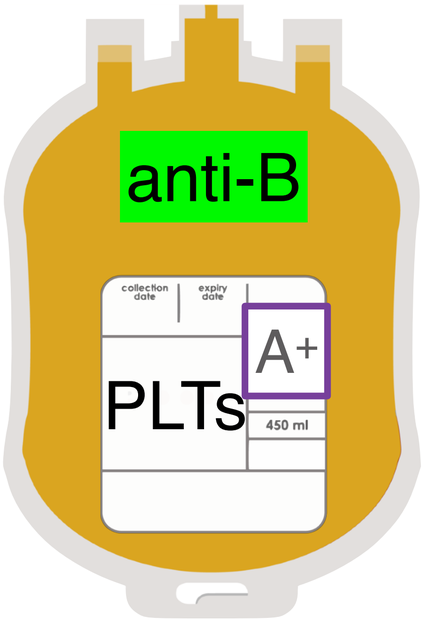


Platelet Storage

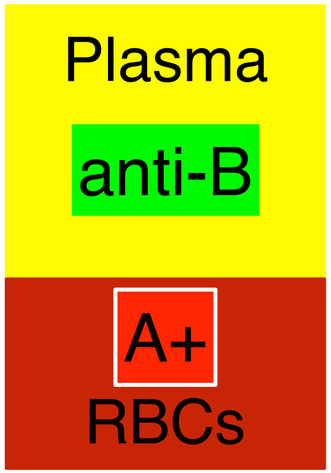
- **5 days, 20-24C, gentle agitation**
  - AD, WBD (unpooled)
  - WBD (pooled by blood center)
  - 7 day option with Verax (later)
- 4 hours: Transfusion service pooling
- Shipping:
  - 20-24 C, < 24 hours without agitation



ABO-Identical PLT Transfusion

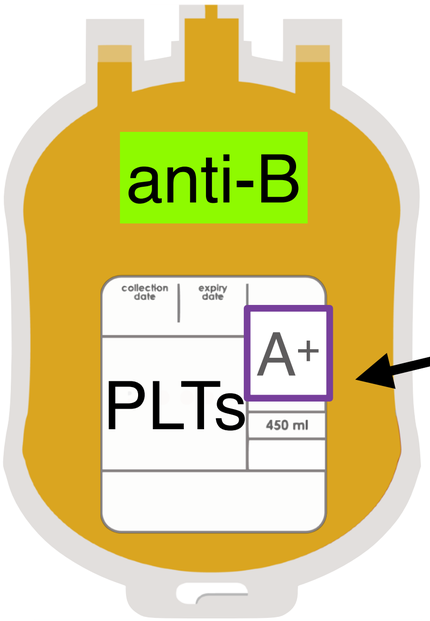


A Pos Donor

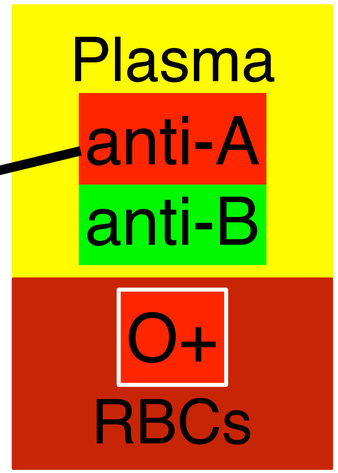


A Pos Recipient

Major-incompatible PLT Transfusion



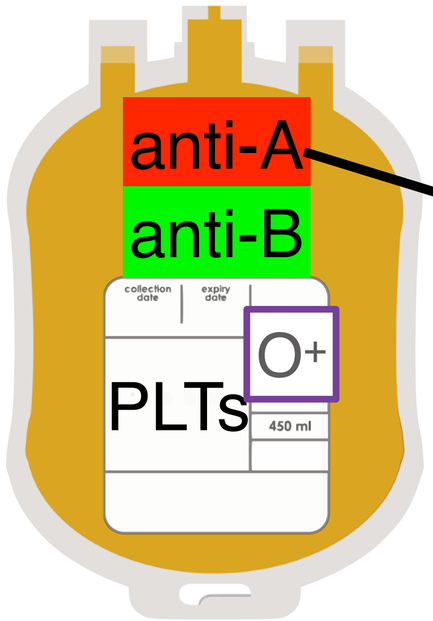
A Pos Donor



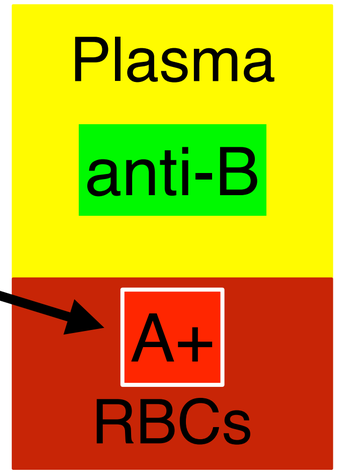
O Pos Recipient

Risk: Decreased response

Minor-incompatible PLT Transfusion



O Pos Donor



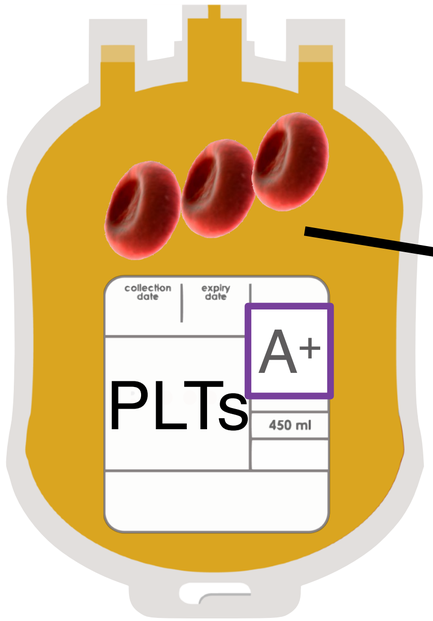
A Pos Recipient

Risk:
Patient RBC hemolysis

Consider titers for anti-A, -B

ABO-Identical, Rh incompatible PLT Transfusion

AD PLTs: 0.0004 mL of RBCs!



A Pos Donor

Plasma

A-
RBCs

A NEG Recipient

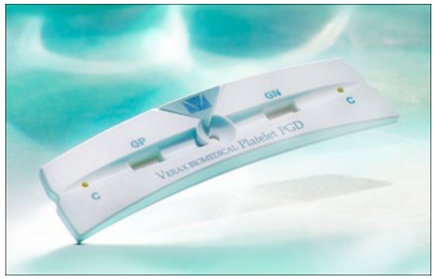
Risk: Patient anti-D

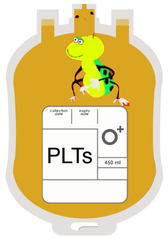
Risk ~1%

Consider RhIg for child-bearing aged females

Sterility Testing

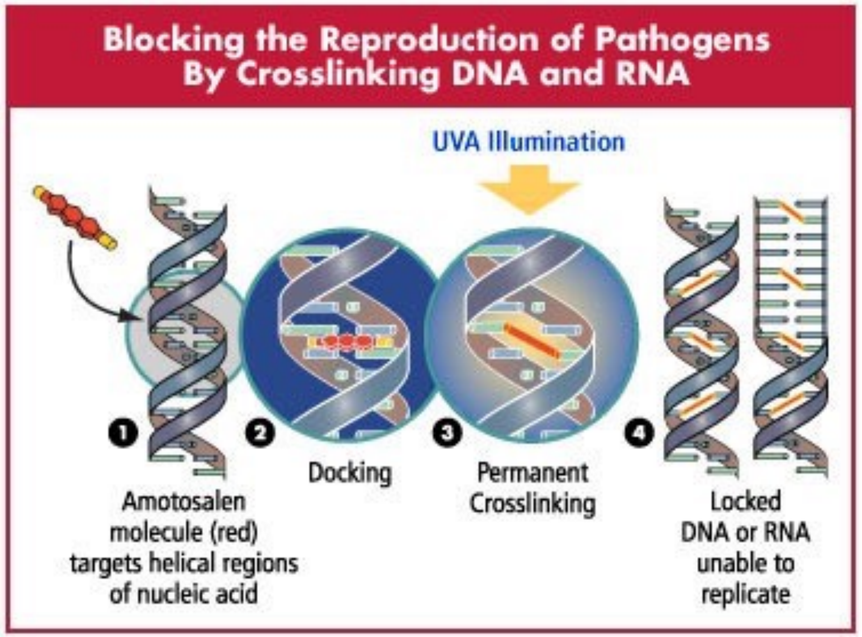
- ALL Platelets must have!
- Culture-based (AD, pooled WBD)
  - 24 hour wait required
  - BacT/ALERT
- Pre-issue (Verax PGD pre-issue)
- Gram stain, swirling, etc no good!
- Pathogen reduced platelets (next)

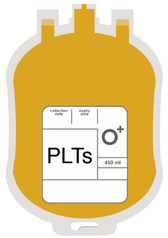




The Future

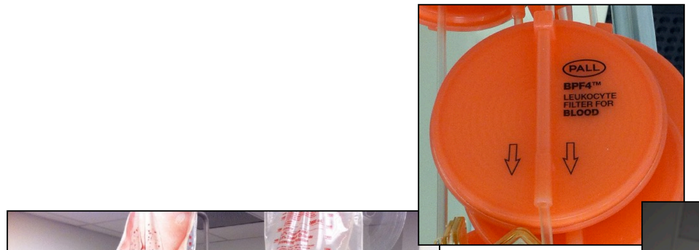
- Pathogen-reduced platelets

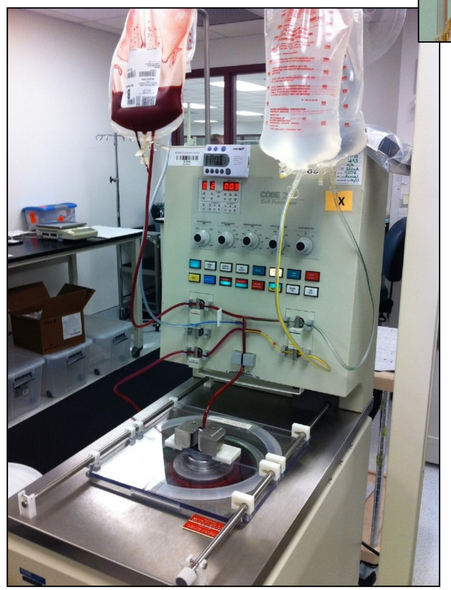




Modified Products

- Leukocyte Reduced Products
- Irradiated products
- Frozen products
- Washed products





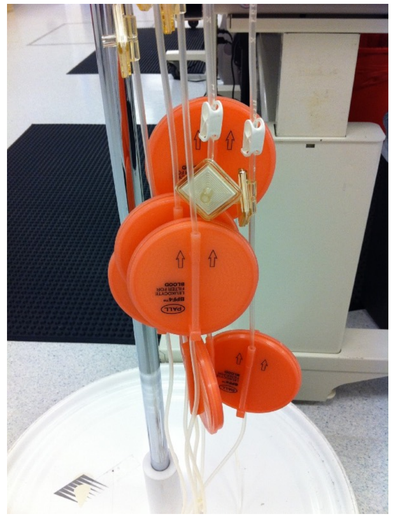
Leukocyte Reduced Products

$\leq 5.0 \times 10^6$ WBC	$\leq 8.3 \times 10^5$ WBC
(95% of tested)	(95% of tested)
LR-RBCs	LR-PLTs
LR-AD-PLTs	

5×10^6 / 6 bags = $\underline{8.3 \times 10^5}$ per "bag"

Leukocyte Reduced Products

- “Prestorage”
  - < 3 days after collection
  - Various methods
- “Pretransfusion”
  - “Bedside”; rarely done now
  - Old studies often included



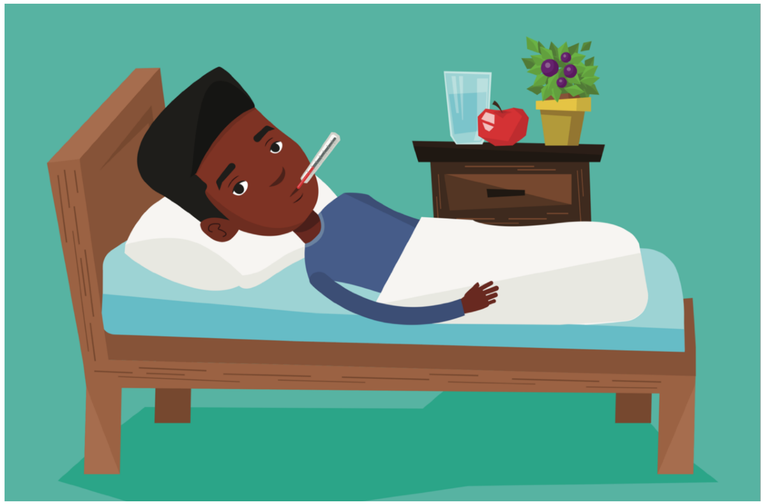
Leukocyte Reduced Products

- Established benefits:
  - Febrile transfusion reactions
  - HLA immunization
  - CMV transmission

Leukocyte Reduced Products

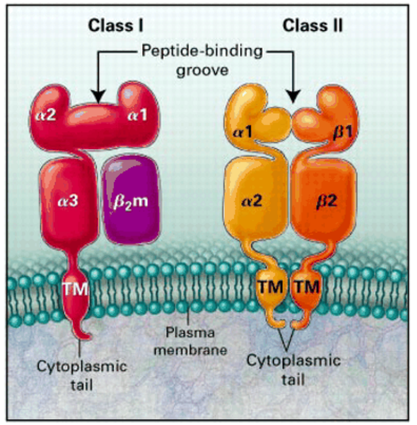
- **Reduce Febrile Transfusion Reactions**

  - Removes WBC that can either:
    - ✓ Secrete cytokines in bag
    - ✓ Interact with recipient WBCs



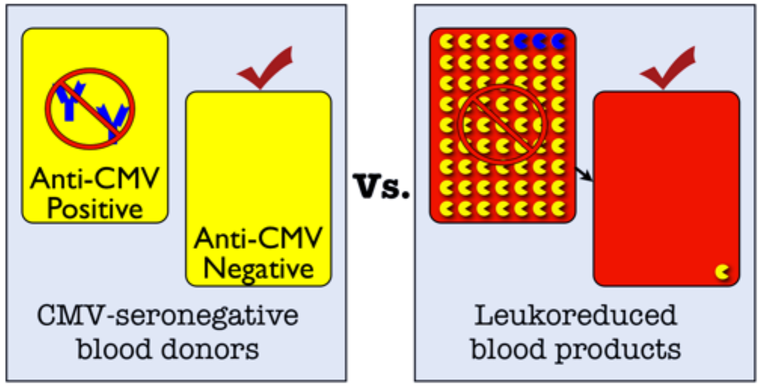
Leukocyte Reduced Products

- **Reduce HLA immunization risk** 
  - Foreign HLA antigens require donor lymphocytes for processing
  - Leukoreduction prevents this interaction



Leukocyte Reduced Products

- **Reduce CMV transmission** 
  - CMV only in WBCs (monocytes)
  - Removal of WBCs = reduction of CMV risk
  - About 1-4% risk with LR or CMV– products
  - See podcast (BBGuy.org/047)



Leukocyte Reduced Products

- It also works to prevent:
  - Reperfusion injury after cardiac bypass
- It *might* work to prevent:
  - Immunosuppression (TRIM)
  - Septic transfusion reactions
  - Prion disease (vCJD)

Washed Blood Products

- Remove plasma from cellular products
- 1-2 L saline / 99% of plasma
- 1 to several hours
- Shelf life
  - RBCs: 24 hours
  - Platelets: 4 hours

Why Wash Blood?

- **Remove harmful plasma proteins**
  - Pt with IgA deficiency with anti-IgA
  - Pt with haptoglobin deficiency
  - Antibodies
    - ✓ ABO antibodies in minor PLT incompatibility
    - ✓ Neonatal alloimmune thrombocytopenia

- **Remove unwanted plasma electrolytes (K+)**

Frozen Red Cells

- Long-term storage of valuable RBCs
- Protect with glycerol (40% most common)
  - ✓ Remove before transfusion
    - ➡ Hemolysis is risk if not removed
- Why?
  - Patients with high-frequency antibodies
  - Donors with rare phenotypes
  - Autologous units for later use

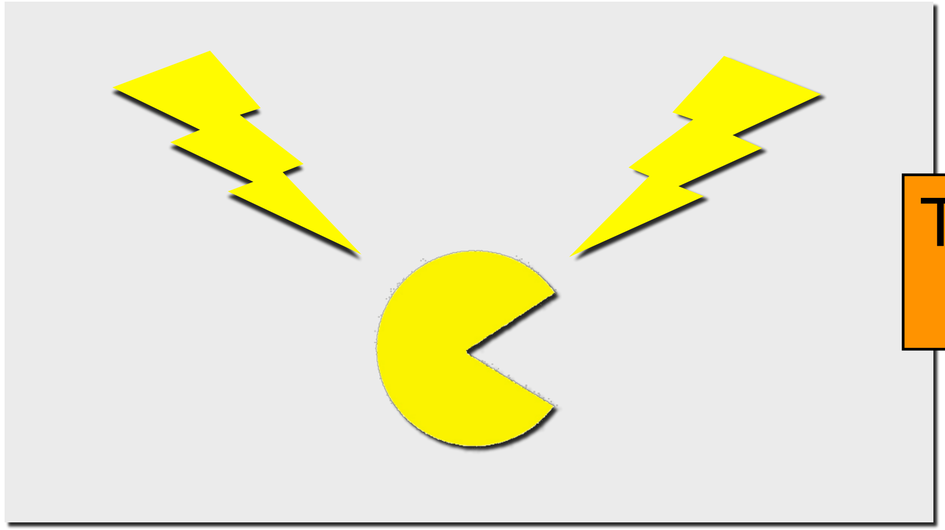
Frozen Blood Products

- Red cells
  - 10 years at –65 C
  - 24 hours at 1-6 C after deglycerolizing
- Platelets (in DMSO)
  - At least 2 years at –80 C
  - Not FDA-licensed

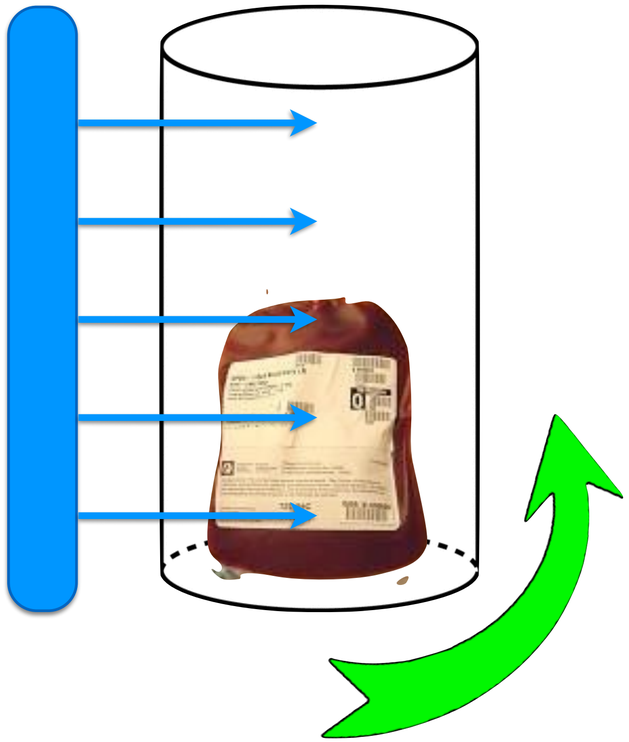
Photo courtesy LifeStream Blood Bank

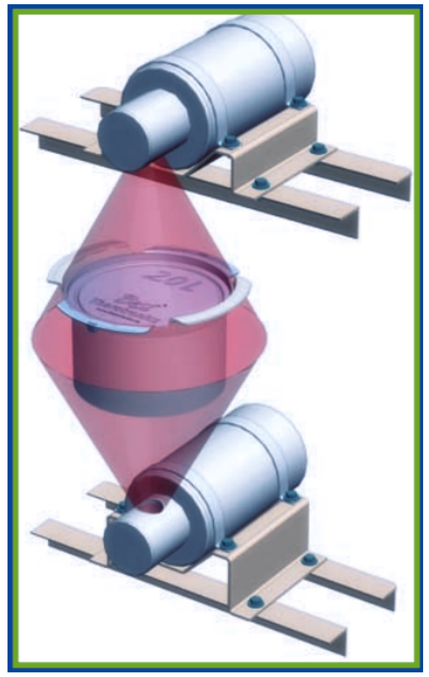
Irradiation

2500 cGy targeted to center of bag,
1500 cGy to all parts



Targets T-lymphocytes to prevent TA-GVHD





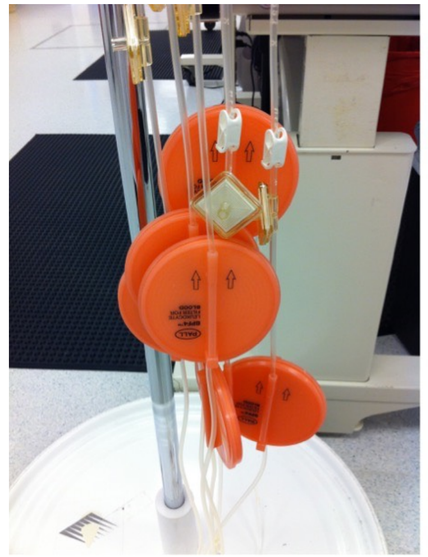
Maximum 28 day
shelf life after irradiation

Who Needs Irradiated Products?

- Immunosuppressed patients
  - *Stem cell/marrow transplant recipients*
  - T-cell defects (including drugs)
  - Aplastic anemia
- Fetuses or premature neonates
- Patients with Hodgkins Disease
- Granulocyte recipients
- 1st-degree relatives or HLA-matched

Miscellaneous

- Not for CMV prevention
- Not for stem cell infusions (duh!)
- LR is NOT interchangeable!
  - We don't know minimum threshold



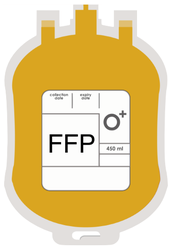
Not Good Enough!

Fresh Frozen Plasma

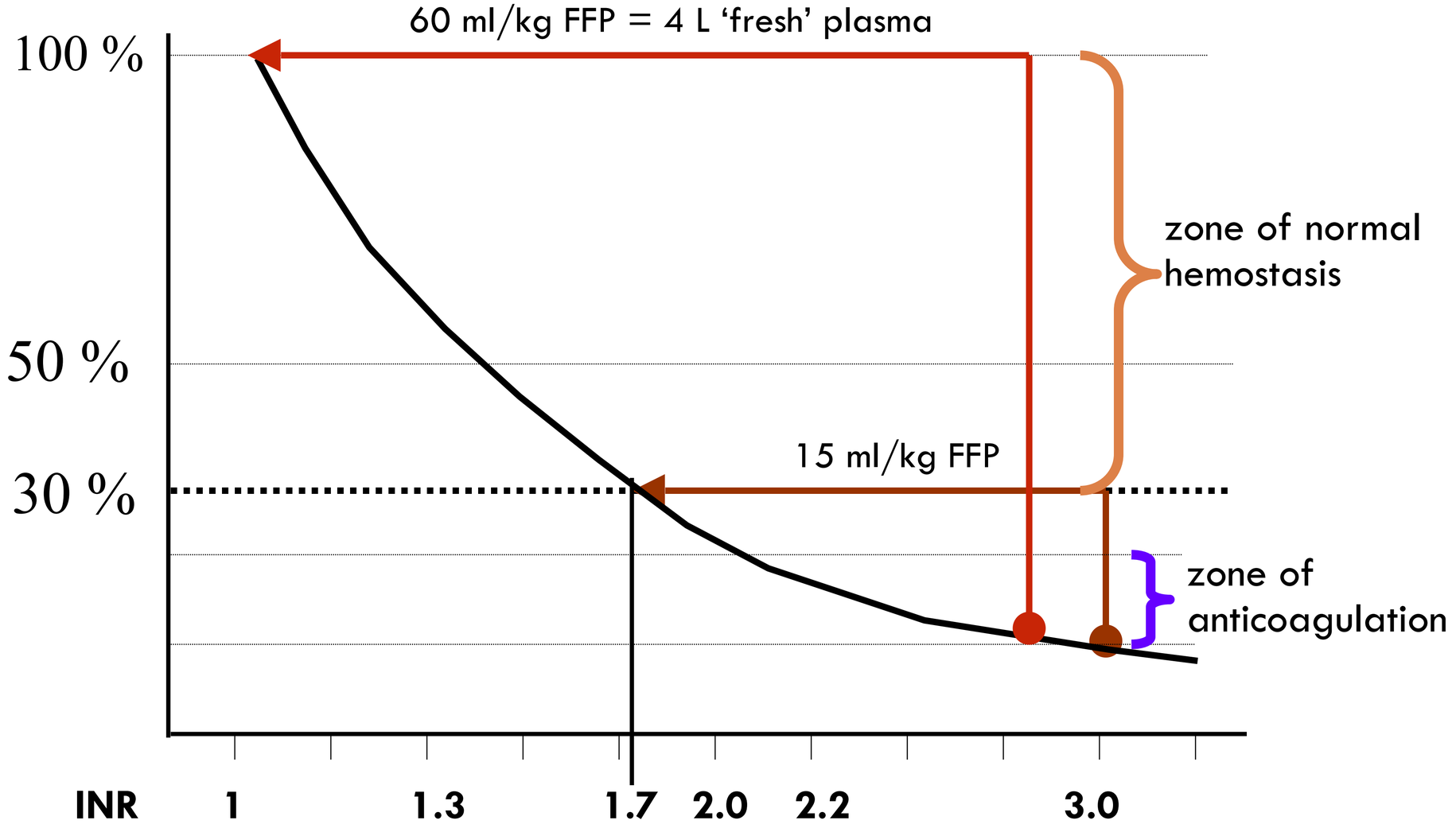
- Whole blood-derived
- Apheresis-derived
  - 1^{o} collection or concurrent

Fresh Frozen Plasma

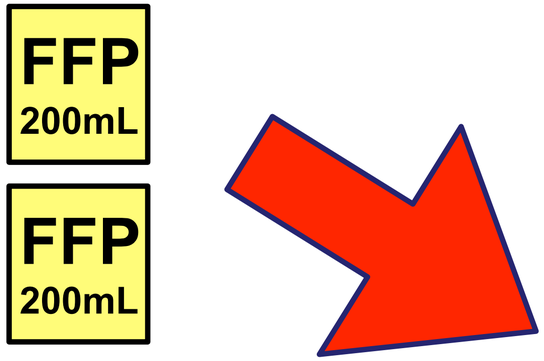
Volume:	200-300 mL
Contents:	All coagulation factors
	>500 mg fibrinogen
	1 IU/mL of all others
	Lysed RBCs and WBCs
	No QC required



Relationship between INR and coagulation factors



Slide courtesy Dr. Jeannie Callum



INR 1.1-1.5!

Each unit is about 7% of total PV

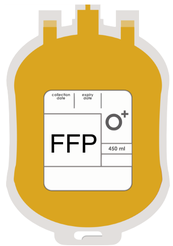
Plasma Volume

3 L

INR 1.7

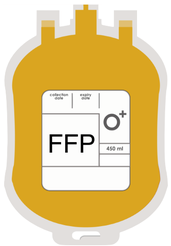
FFP “Indications”

- Bleeding/operative patients with coagulopathy from multiple factor deficiencies
  - Hepatic failure (avoid prophyaxis)
  - Dilution, consumption
- Bleeding patients needing urgent reversal of warfarin effect
  - 4 factor PCC may be better choice ($$)



FFP Indications

- Trauma massive transfusion
  - 1:1 RBC:FFP ratio
  - PROPPR study published 2015 (no difference in mortality, less exsanguination)
- Transfusion/exchange in TTP
- Factor-specific coagulopathies without a factor concentrate (V, XI)



FFP Contraindications

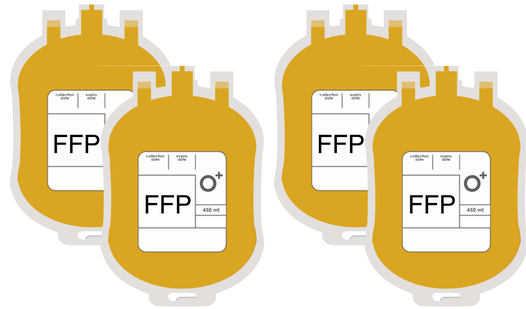
- Volume expansion
- Heparin reversal
- Specific concentrate available
- Prophylaxis with mild INR elevations
- Nutrition, wound healing, etc.

FFP Preparation

- Pre-storage
  - Plasma at –18 C within 8 hours
    - WHY? To preserve Factors V and VIII
  - 1 year at -18 C, 7 years at -65 C
- Pre-transfusion
  - Thaw at 30-37 C
  - Keep at 1-6 C for 24 hours

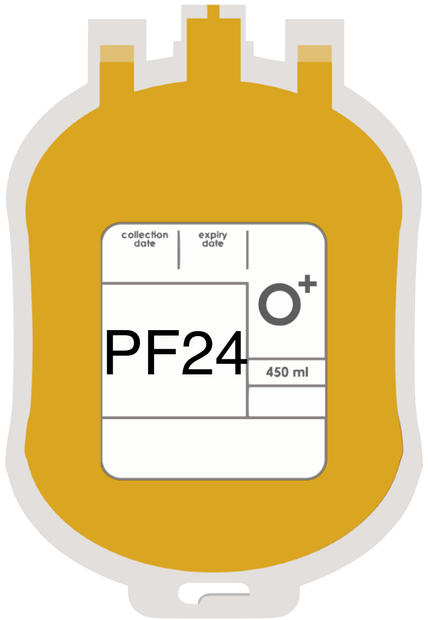
Dosage and Effect

- Two at a time common (inadequate!)
  - 10-20 mL/Kg is appropriate
- 20-30% factor increase per dose
- Transient effect (FVII $t^{1/2}$ = 4 hrs!)
- ABO compatible (no crossmatch)
- Rh doesn't matter



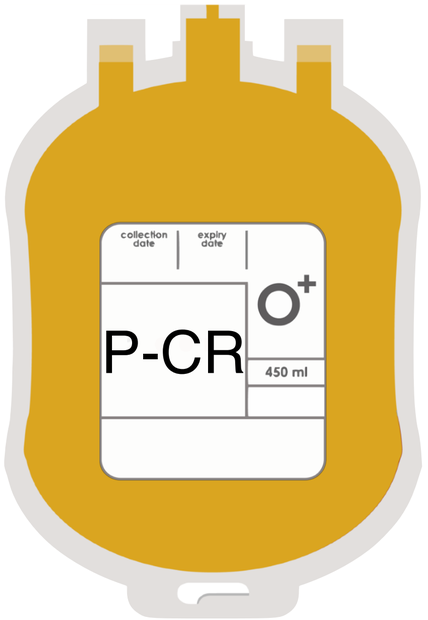
Plasma Variants-Frozen

Plasma frozen within 24 hours



-Majority of “FFP”
-Use just like FFP
-Store/thaw = FFP
-Can’t make CRYO

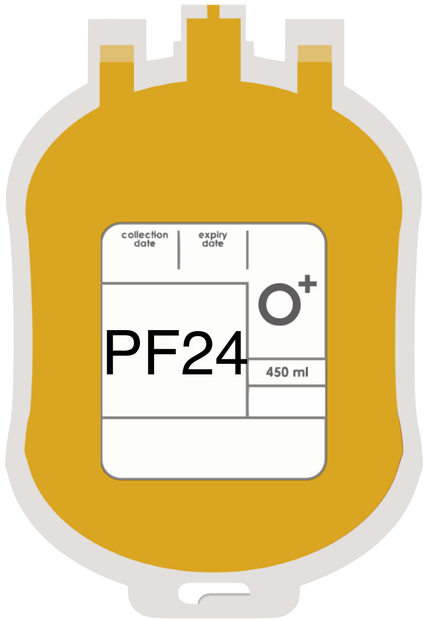
Plasma Cryoprecipitate-reduced



-FFP after CRYO
-↓FVIII, FBG, vWF
-Refractory TTP
-Store/thaw = FFP

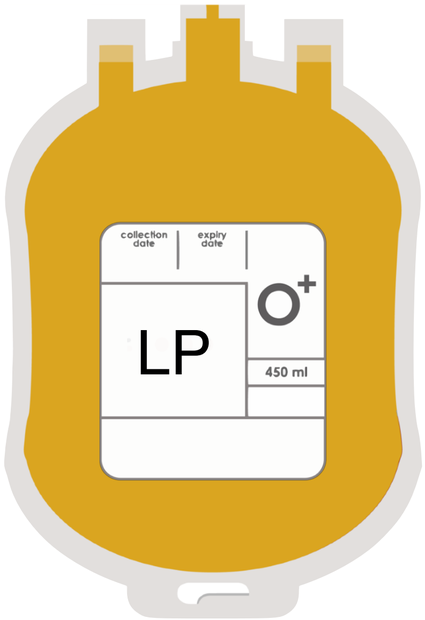
Plasma Variants-Liquid

Thawed Plasma



-FFP/PF24 >24 hrs
-1-6C up to 5 days
-Use = FFP

Liquid Plasma



-Never Frozen
-Use in trauma/MT
-Expires 26 days
-Store 1-6C

Cryoprecipitate

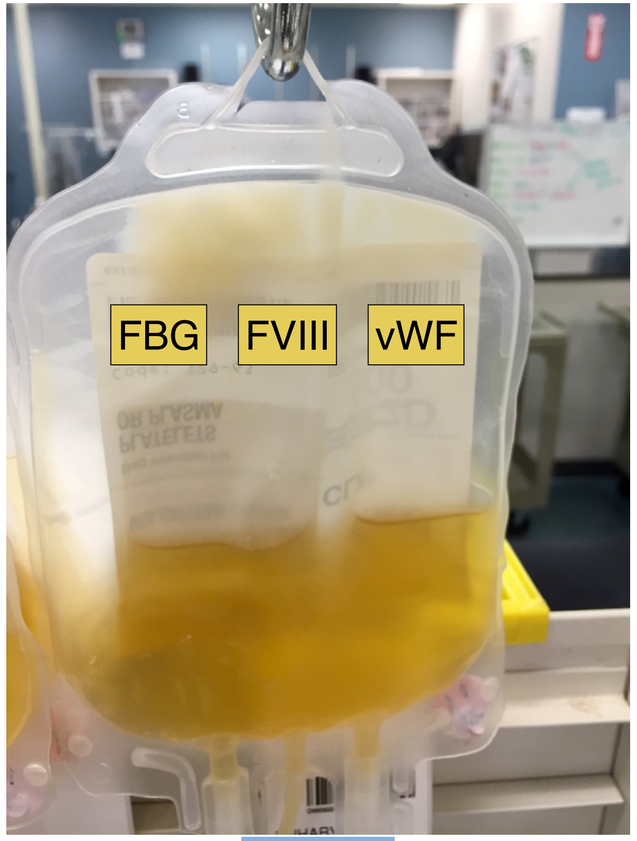
Volume:	~15 mL each
Contents:	≥ 150 mg fibrinogen
	≥ 80 IU Factor VIII
	80-120 IU vWF
	40-60 IU Factor XIII
	Fibronectin

Easy!
Us. > 250 mg

CRYO Preparation

Thaw overnight 1-6C

Spin



Drain

Pool and Freeze –18C

Cryoprecipitate Uses

- **Fibrinogen deficiency**
  - Target at least 150 mg/dL
  - Approx. 2500 mg in 10 bags
- Thrombocytopathy in renal failure (2nd line-DDAVP)
- Topical “glue” (infrequent now)
- vWD treatment (2nd line after Humate-P)
  - 1 bag per 10 Kg q 8 hours

Cryoprecipitate

- Store like FFP (–18 C for 1 year)
- Thaw like FFP (30-37 C)
- **Keep UNLIKE FFP**
  - 6 hours at 20-24 C
  - 4 hours if pooled with open system

- ABO, Rh compatibility irrelevant (but many match ABO)

Myths

- “CRYO = small volume FFP”
  - No FVII
  - Can’t replace FFP in vol-sensitive
- “More fibrinogen in CRYO than FFP”
  - Not possible
  - Just more concentrated

Granulocyte Concentrate

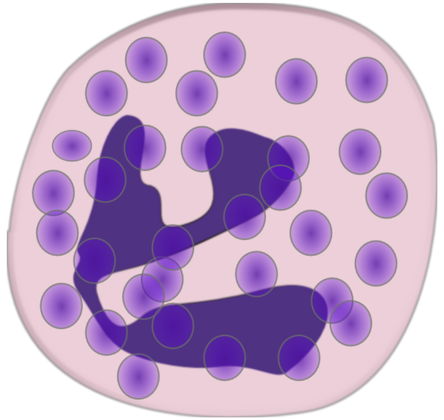
Volume:	200-300 mL
Contents:	≥ 1 x 10^{10} neutrophils
	20-50 mL RBCs (needs XM)
	~1 x 10^{11} platelets
	Plasma

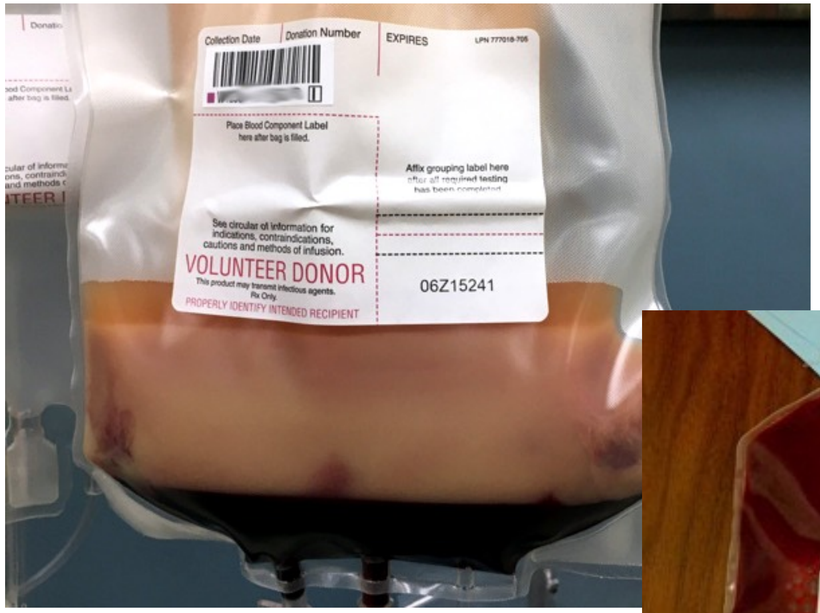
Granulocyte Concentrate

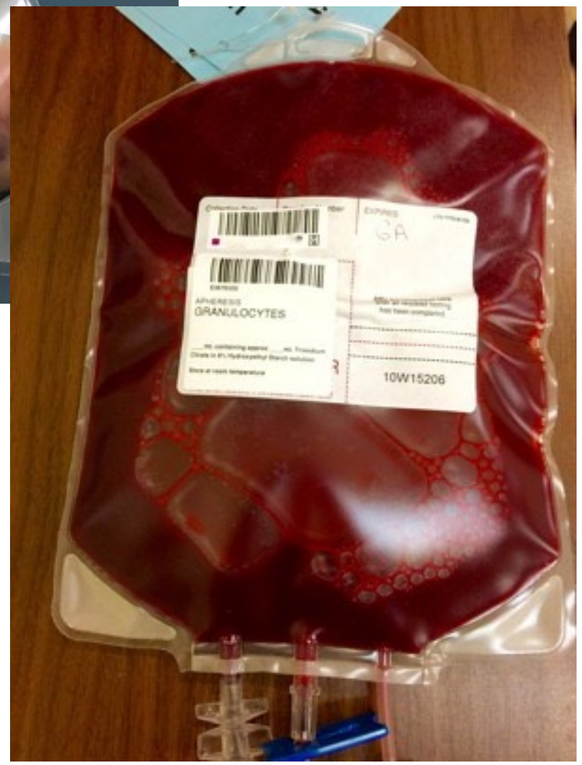
- Large studies show no proven effect
- RING suggests at least 4.0 x 10^{10} for effect
- Potential recipients:
  - Preemies with sepsis/infections
  - Transplant patients with infections
  - CGD/LAD patients
- Stimulate donors (G-CSF +/- steroids)

Granulocyte Concentrate

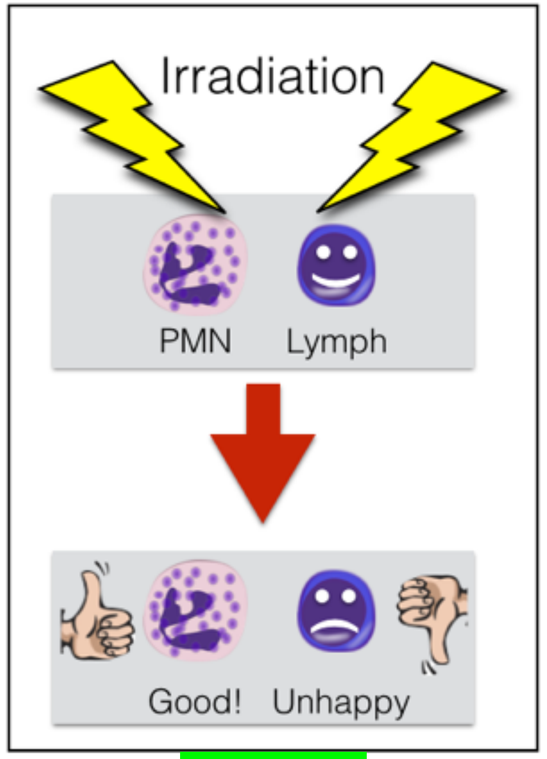
- Indications:
  - Neutropenia (<500/uL), reversible
  - Fever 24-48 hrs
  - Proven bacterial/fungal infx
  - Unresponsive to antibiotics
- 24 hours at 20-24 C, no agitation



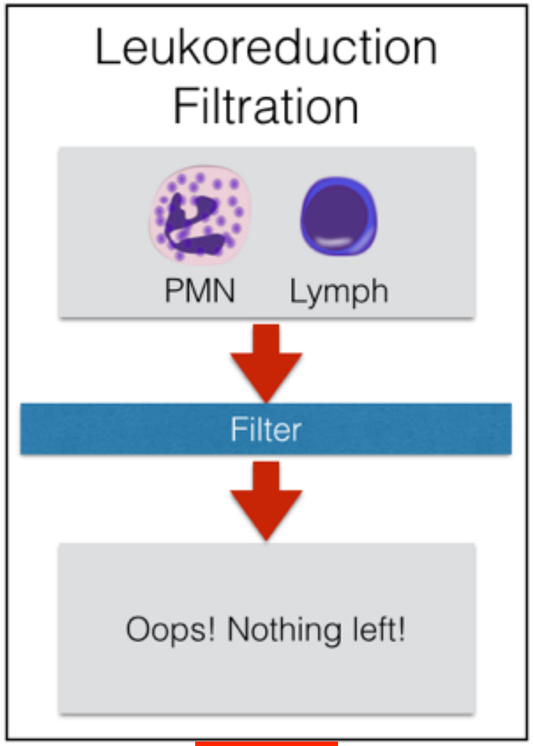




XM
ABO/Rh
Antibodies



YES



NO

DDAVP

- Treats vWF deficiency and may help:
  - Uremic thrombocytopathy
  - vWD
  - Mild Hemophilia A
  - Hepatic thrombocytopathy

Prothrombin Complex Concentrate

- Pharmaceutical concentrate of Vitamin-K factors
  - II, **VII**, IX, X
  - Current form (“K-centra”) contains all 4 factors
- Indicated to reverse VKA (warfarin) effect in:
  - Acute major bleeding
  - Urgent surgical procedure
- Cost: Up to ~$6000/dose


B-NEGATIVE, AND MAKE IT A DOUBLE!
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