

Blood Bank III

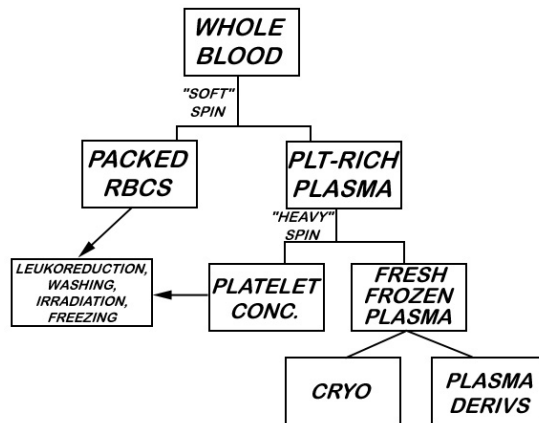
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Blood Components and Component Therapy

I. General

A. Basic concept of “component therapy”

1. Allows for more efficient and effective use of products by giving a patient specifically what he needs and minimizing what he doesn't need.
2. Made possible by advent of plastic bags around 1950.
3. Single unit may be made into numerous components (see figure below representing typical US method).



B. Anticoagulant/preservative solutions

1. Allows blood to be stored for extended periods without drastic effects on most metabolic and therapeutic qualities
2. Red cell storage defined by demonstrating 75% survival of transfused cells at 24 hours after transfusion
3. Traditional anticoagulant/preservatives
 - a. Citrate-phosphate-dextrose (CPD) and citrate-phosphate-dextrose-dextrose (CP2D)
 - 1) Allows 21 days of RBC/whole blood storage
 - 2) Used before additive solutions
 - b. Citrate-phosphate-dextrose-adenine (CPDA-1)
 - 1) Very similar to CPD but with 17.3 mg of adenine (no adenine in CPD)
 - 2) Allows 35 days of RBC/Whole Blood storage
4. Additive solutions (“Adenine Saline” additives)
 - a. Increases shelf life of RBCs to 42 days
 - b. Most common types
 - 1) AS-1 (Adsol®)
 - 2) AS-3 (Nutricel®)
 - 3) AS-5 (Optisol®)
 - c. Specifics vary, but all add more dextrose and adenine to increase blood shelf life.

d. AS-1 and AS-5 also contain mannitol.

5. Know storage details for various products (Table 1)

Product	Storage	Product	Storage
RBCs / Whole blood	35 days (CPDA-1) 42 days (Additives) 1-6 C	WBCs	24 hours; 20-24 C (no agitation)
Frozen RBCs	10 years; -65 C 24 hours after thaw	Fresh Plasma	1 year; -18 C OR 7 years, -65 C 24 hours at 1-6 C after thaw
Washed RBCs	24 hours; 1-6 C	CRYO	1 year at -18 C 6 hours at 20-24 C after thaw (4 hours if pooled)
Platelets	5 days; 20-24 C (gentle agitation)		

C. Quality control of blood products

1. Blood is a controlled product that is tightly regulated by the FDA (with many regulations from the AABB & CAP).
2. Very specific and detailed requirements for process and product acceptability

Product	QC	Product	QC
RBCs	HCT < 80% (all), ≥ 50 g HGB in 95% (apheresis RBCs)	Apheresis platelets	≥ 3.0 x 10 ¹¹ and pH ≥ 6.2 in 90%
RBCs leukoreduced	≤ 5 x 10 ⁶ WBCs in 95%, retain 85% of RBCs	Apheresis platelets leukoreduced	Above + < 5.0 x 10 ⁶ residual WBCs in 95%
Platelets (PC)	≥ 5.5 x 10 ¹⁰ and pH ≥ 6.2 in 90%	CRYO	Factor VIII ≥ 80 IU (all) Fibrinogen ≥ 150 mg (all)
Platelets (PC) leukoreduced	≥ 5.5 x 10 ¹⁰ in 75%, pH ≥ 6.2 in 90%, AND < 8.3 x 10 ⁵ WBCs in 95%	Granulocyte concentrate	≥ 1.0 x 10 ¹⁰ in 75%

II. Blood and Components

A. Whole blood

1. The original blood product!
2. Not stocked in most Blood Banks today
3. Specifics:

Volume:	450-500 ml
Contents:	RBCs (200 ml) Plasma (250 ml) WBCs (10 ⁹) and platelets Anticoagulant (63 or 70 ml)

4. Potential indications:
 - a. Rapid hemorrhage of over 30-40% of blood volume

- 1) Trauma/emergency transfusions most commonly
- 2) Whole blood should be ABO identical, making it tougher to use in emergencies.
- b. Exchange transfusions in neonates (more often “reconstituted” from RBCs and FFP)
- c. Autologous transfusions
5. Contraindications:
 - a. Anything where something more specific to the patient’s needs would be better.
6. Storage Time and Conditions
 - a. Length depends on anticoagulant/preservative used
 - b. 1-6°C.

B. Blood components

1. **Red blood cells/additive solution red blood cells**
2. **Platelets**
 - a. Platelet concentrate
 - b. Apheresis platelets
3. **Modified RBCs and platelets**
 - a. Leukocyte reduced products
 - b. Irradiated products
 - c. Frozen products
 - d. Washed products
4. **Plasma and derivatives**
 - a. Fresh frozen plasma (FFP)
 - b. FFP alternatives (including FP24)
 - c. Cryoprecipitate (“antihemophilic factor”)
 - d. Factor concentrates
 - e. Other plasma derivatives
5. **Miscellaneous products**
 - a. Granulocyte concentrate
 - b. DDAVP
 - c. Recombinant activated factor VII (NovoSeven)
6. **Oxygen therapeutics (“blood substitutes”)**

C. Red blood cells with and without additives

1. Made from whole blood by centrifugation and removal of most of plasma layer, or by apheresis collection (discussed previously).
 - a. May be transfused without modification after preparation or may use additive solution
 - b. Units intended for use with additive solutions are collected into CPD (**NOT** CPDA-1), spun, then mixed with 100 mL of additive solution for 450 mL collections/110 mL for 500 mL collections
 - 1) This gives a product with more volume and less plasma (HCT usually 55-65%)
 - 2) Called “AS RBCs” commonly (“AS” actually stands for “Adenine Saline”, not “additive solution”)

2. Specifics:

Volume:	~250 ml (350 ml with additive solutions)
Contents:	RBCs (~200-250 ml); HCT \leq 80% Plasma (<50 ml) WBCs (10^9) and platelets Anticoagulant Additive solution (if applicable) 200-250 mg iron

3. Indications

a. Need for increased oxygen-carrying capacity

1) How do you decide?

- a) Hemoglobin level is not a very accurate indicator of the need for transfusion
- b) The body has compensatory mechanisms for anemia (hemoglobin dissociation curve shift to right, increased cardiac output, decreased blood viscosity), but these may take time
- c) Cardiac factors and oxygen demand often overlooked
- d) Measuring mixed venous pO₂ and saturation and comparing to arterial levels gives an estimate of current oxygen use
 - Example: 25% extraction (arterial saturation 100%, venous saturation 75%) is normal; extraction may go up to 75% or more when necessary (exercise, etc)
 - Heart muscle, however, has little reserve; extracts close to 75% normally
 - Overall oxygen extraction ratio of 0.5 (50%) or more at rest is deemed “critical.”
- e) All factors (including blood volume, heart function, ability to increase cardiac output, and O₂ requirements) should be addressed when considering transfusion.
 - Because of compensatory mechanisms, chronic anemia is less likely to need transfusion

2) Situations that *may* require red cell transfusion:

- a) Acute hemorrhage (over 30% of blood volume acutely)
- b) Hemolysis
- c) Marrow failure

b. Also indicated in exchange transfusions (often in concert with FFP as “reconstituted whole blood”)

c. General thoughts

- 1) Using a “hard” threshold like HGB of 10 g/dL or HCT 30% is outdated and bad practice

- 2) All specialties have published recommendations that agree with statement above
- 3) In general:
 - If HGB < 6 g/dL, transfusion usually needed
 - If HGB >10 g/dL, transfusion rarely needed
 - If HGB is between 6 and 10, clinical judgment, assessment of situation, etc, is required
4. Contraindications
 - a. Acute hemorrhage < 20% of blood volume
 - 1) Crystalloids are adequate in most of these cases, but many get transfused anyway.
 - b. Chronic and nutritional anemias (folate, B₁₂, iron deficiencies)
 - c. “Almost never” needed for HGB > 10 g/dl
5. Expected effect (per unit)
 - a. Hematocrit increases 3%, hemoglobin 1 g/dl (if not acutely bleeding or hemolyzing).
 - b. Rapid initial effect (can be measured 15-30 minutes after transfusion), maybe ~ 24 hours for full effect.
6. ABO compatibility
 - a. ABO type of transfused RBCs must be compatible with recipient plasma ABO antibodies
 - b. i.e., always protect the transfused cells! (See chart)

		DONOR			
		A	B	AB	O
RECIPIENT	A	✓			✓
	B		✓		✓
	AB	✓	✓	✓	✓
	O				✓

7. Storage and shipping
 - a. Same as for whole blood if CPD, CPDA-1 used
 - b. 42 days at 1-6 C if additive solutions used
 - c. Shipping temperature 1-10 C
8. Compatible fluids
 - a. Normal saline (0.9%)
 - b. ABO compatible plasma
 - c. 5% albumin
 - d. Red cells should not contact lactated Ringer’s solution, D5W, 0.45% NS, antibiotics/other drugs, or TPN
 - 1) The reasons for this are primarily osmotic; hypotonic solutions like 0.45% saline will lead to red cells swelling and bursting, while hypertonic solutions like TPN and antibiotics will lead to shrinkage.
 - 2) LR has enough calcium to counteract the citrate anticoagulant in blood (LR has 3 mEq Ca²⁺/L)
9. Red cell types (most covered in other parts of the handout)
 - a. Red Blood Cells, Low Volume

- 1) Prepared from a low-volume (less than 405 mL) whole blood collection
- b. Red Blood Cells, Adenine Saline Added
- c. Red Blood Cells, Leukocyte-reduced
- d. Red Blood Cells, Frozen
- e. Red Blood Cells, Deglycerolized, and Red Blood Cells, Washed
- f. Red Blood Cells, Irradiated
- g. Red Blood Cells, Apheresis
 - 1) Collected via apheresis, often “double” products
- h. Red Blood Cells, Rejuvenated
 - 1) RBCs in certain preservatives may be “rejuvenated” up to 3 days after expiration (in CPD or CPDA-1), or up to the expiration date (in AS-1) with a solution called “Rejuvesol.”
 - 2) Process restores ATP and 2,3-DPG levels to near-normal levels
 - 3) The rejuvenated product is often then frozen (up to ten years for CPD and CPDA-1 RBCs; up to three years for AS-1 RBCs)
 - 4) Thawed (or immediately transfused) product must be washed prior to transfusion, then transfused within 24 hours.

D. Platelets

- 1. **Platelet concentrate (PC, “random platelets”)**
 - a. Prepared via centrifugation (“soft” spin then “hard” spin in the US) from a single whole blood unit.
 - b. Minority of US platelets (see apheresis platelets later)
 - c. Specifics

Volume:	40-60 ml
Contents:	Platelets ($\geq 5.5 \times 10^{10}$ in 90% tested) Plasma (including ~80 mg fibrinogen) WBCs (10^7) pH ≥ 6.2 (90% tested)

- d. Indications
 - 1) **Thrombocytopenia**
 - a) Most data supports a threshold of $< 10,000$ in uncomplicated patients (some even suggest 5K).
 - b) Some use a 20K threshold if febrile or septic, 50K if bleeding or undergoing major surgery.
 - c) Near 100K likely necessary for sick neonates and patients with intracranial and pulmonary hemorrhage
 - d) Avoid the prophylactic transfusion if possible!
 - 2) **Thrombocytopeny**
 - a) Congenital defects
 - b) Drugs (ASA, Ticlopidine, Abciximab)
 - c) External agents

- Cardiac bypass machine
- ECMO
- d) Metabolic effects (chronic renal or hepatic failure)
 - Remember, though, that platelets are *not* first-line defense against platelet-related bleeding in renal failure! (Think dialysis, DDAVP, Cryo, conjugated estrogens, etc).
- e. Contraindications
 - 1) **Thrombotic thrombocytopenic purpura** (near absolute)
 - a) Protein deficiency (ADAMTS13) that leads to large von Willebrand's factor multimers and subsequent platelet microthrombi
 - b) More platelets = more thrombi
 - c) Generally accepted contraindication, but some have reported successful transfusions
 - d) Hemolytic-uremic syndrome (HUS) is similar to TTP but lacks neurologic symptoms; similar contraindication
 - 2) **Heparin-induced thrombocytopenia, type II** (near absolute)
 - a) Antibody vs. heparin/platelet factor 4 complex
 - b) Adding platelets may toss more fuel on the fire and lead to more microthrombi.
 - 3) **Immune/idiopathic thrombocytopenic purpura** (relative)
 - a) It usually just doesn't help!
 - 4) **Disseminated intravascular coagulation (DIC)**
 - a) Much discussion and debate about this one, but most will transfuse with very low PLT counts
- f. Dose
 - 1) 1 unit per 10 Kg body weight
 - a) Typically given six to ten bags at a time in adults
 - 2) 10-15 mL/Kg in neonates
- g. Expected effect
 - 1) Current studies lacking (5-10K per bag?)
 - 2) Formulas (CCI, etc.) have some value in determining refractoriness (lack of response); generally used more with apheresis platelets.
 - 3) One-hour post-transfusion count is standard.
- h. Storage and shipping
 - 1) **5 days at 20-24 C** (with gentle agitation)
 - 2) No more than 24 hours without agitation during shipping
- i. ABO and Rh
 - 1) Platelets do not require pretransfusion crossmatches, and ABO-incompatible platelets may be given.

- 2) ABO but not Rh antigens are present on platelets.
 - a) Platelet preparations may contain a few contaminating RBCs with Rh antigens.
 - b) Consider Rh prophylaxis with Rh incompatibility (1 vial RhIG per 30 units Rh+ PC; 1 per 7 Rh+ apheresis units)
- 3) Platelet ABO incompatibilities
 - a) Major = platelet ABO antigens incompatible with recipient plasma (like A plts to O recip)
 - Cleared from circulation faster; less effect
 - b) Minor = donor ABO *antibodies* incompatible with *recipient RBCs* (like O plts to A recipient)
 - More of a concern in children and neonates (“reverse” hemolytic reactions)
 - c) A slight majority have no significant difference in response for ABO incompatible platelet transfusions, but as many as 40% will see some decrease as compared to ABO-identical

2. **Apheresis platelets (“single donor” platelets)**

- a. Made from one donor via apheresis procedure
 - 1) Apheresis = removing whole blood from body, taking what you want, then returning the rest.
 - 2) Roughly 80% of platelets transfused in the US today are apheresis-derived

b. Specifics

Volume:	~ 100 ml
Contents:	Platelets ($\geq 3.0 \times 10^{11}$ in 90% tested) Plasma (incl ~150 mg fibrinogen) WBCs (10^6 - 10^8)

- c. Indications (aside from those listed in the PC section above)

1) **Limiting exposure**

- a) For infectious disease transmission
 - One donor exposure vs at least six for PC decreases risk of viral transmission
 - Also decreases risk of bacterial contamination
- b) For HLA immunization?
 - Traditional thought: fewer donor exposures mean less immunization.
 - Not true! Risk more dependent on number of foreign antigens (not donors) seen; so leukoreduction is more important.
 - “TRAP” study: *NEJM*. 1997;337, No. 26, 1861-9.

2) **Platelet refractoriness (see BB Practical)**

- a) Lack of response to platelet transfusion (immune and nonimmune causes)

- b) May be used as HLA-matched or crossmatched doses for immune refractoriness.
- d. Storage and shipping
 - 1) Same as for PC; 5 days at 20-24 C.
- e. Effect
 - 1) Dose dependent
 - 2) Similar to PC
- f. **Platelet sterility**
 - 1) Since 2004, *AABB Standards* has required that we utilize methods to both *limit* and *detect* bacterial contamination of platelets (both apheresis and platelet concentrate).
 - a) Needed because bacterial contamination is now considered the #1 transfusion infection risk.
 - 2) Limiting contamination
 - a) Careful skin preparation
 - b) Discarding initial 20-30 cc of blood
 - c) Exclusive use of apheresis platelets
 - 3) Detecting contamination
 - a) Culture-based methods
 - Bacterial detection system (Pall)
 - BacT/ALERT (bioMerieux, Inc)
 - b) Less sensitive methods
 - Gram stain, swirling, glucose checks by dipstick

E. Modifications to red cells and platelets

1. Leukocyte reduction

- a. Definitions (as of *AABB Standards*, 26th ed.)
 - 1) Key number in United States to define leukoreduction: $\leq 5 \times 10^6$ residual WBCs
 - a) In Europe, the number is considerably more stringent: $\leq 1 \times 10^6$ residual WBCs
 - 2) Rules
 - a) $\leq 5 \times 10^6$ white cells in 95% of tested units defines leukocyte-reduced:
 - Red blood cells
 - Apheresis platelets
 - Whole blood
 - b) $\leq 8.3 \times 10^5$ WBCs in 95% of tested units defines leukocyte-reduced:
 - Platelet concentrate (note that 8.3×10^5 multiplied by 6 = 5×10^6)
 - c) Each of these products must also retain at least 85% of original component and meet all other QA standards for the component.
- b. Methods
 - 1) Leukocyte reduction filters
 - a) 99.99% of white cells (“4 log” reduction)
 - b) Several manufacturers and types

- 2) Apheresis collection devices
 - a) Most apheresis machines have built-in leukoreduction methods.
 - b) Methods vary by manufacturer.
- c. Types
 - 1) "Prestorage" leukocyte reduction
 - a) Done as early as possible; generally within 72 hours of collection (no set guideline).
 - b) May use inline filters at time of collection or post collection filters for red cells.
 - c) Apheresis machines have filters or other leukoreduction methods built in.
 - 2) "Poststorage" leukocyte reduction
 - a) Done prior to transfusion
 - b) "Bedside" leukoreduction uses product-specific filters at time of transfusion.
 - Probably the least desirable way to leukoreduce using filters
 - Lack of available QC, concern regarding training of transfusionists
 - Many older studies were done with this method, however.
 - c) Better done in transfusion service before issuing
 - Recent FDA memo mandates quality-controlled leukocyte reduction.
- d. Why bother?
 - 1) **Prevention of febrile nonhemolytic transfusion reactions**
 - a) Benign reactions, but mimic early hemolysis
 - b) First type: white cells secrete pyrogenic cytokines in bag *before* transfusion: seen more commonly with platelet transfusions.
 - c) Second type: Patient reacts to transfused white cells, pyrogenic cytokines secreted *after* transfusion.
 - Seen more commonly with red cell transfusions
 - This may be seen with recipient antibodies against transfused WBC antigens or with immune complexes of donor WBCs and coating antibodies binding to macrophages
 - d) Poststorage reduction works fine for second type, prestorage usually necessary to prevent first.
 - 2) **Prevention of HLA immunization**
 - a) Shown to be a very effective means of preventing antibody formation against foreign HLA antigens

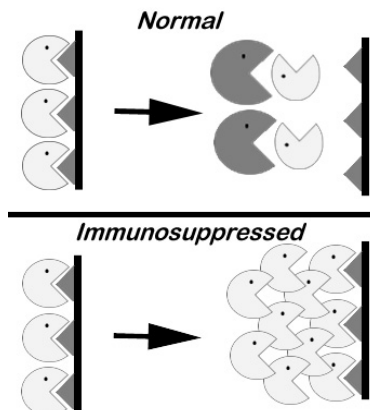
- “TRAP” Study: NEJM 1997, 337; No 26, 1861-9.
 - b) Recommended for all patients who may receive multiple transfusions
 - c) Use of ultraviolet-B treatment also decreases immunization by deactivating lymphocytes, but it is not widely available.
- 3) **Prevention of CMV transmission**
- a) Virus carried only in white cells (probably monocytes).
 - b) *Blood*. 1995;86,3598-3603; “The Bowden Study” – landmark leukoreduction study
 - Suggested filtered products are equivalent to CMV seronegative in preventing CMV seroconversion.
 - *Blood*. 2003;101:4195-4200 study shows performance may not be as good (4% of leukoreduced RBC recipients seroconverted vs. 1.4% of CMV- product recipients)
 - Despite this, in most places, CMV- and leukoreduced products are considered equivalent (“CMV-safe” or CMV-free”).
 - c) Be sure staff is trained in proper use (if used wrong, why bother?).
- 4) **Prevention of immunosuppressive effects of transfusion**
- a) Some consider this the main reason to leukocyte reduce blood products
 - b) Transfusion probably immunosuppresses recipient (“immunomodulation”).
 - Many (but not all) studies show increased post-op infections and increased cancer recurrence in transfused patients
 - c) Donor WBCs are thought to be the cause of the immunosuppression
 - d) Not universally accepted, in fact, quite controversial
- 5) **Reduction of bacterial contamination**
- a) Some studies suggest reduction in bacterial load (especially *Yersinia enterocolitica*) with leukoreduction.
 - b) Probably not reliable enough to depend on!
- 6) **Reduction in the risk of prion disease**
- a) One of the reasons for universal leukoreduction in Europe
 - b) REALLY, REALLY controversial
- e. Leukocyte reduction is NOT indicated for:
- 1) Prevention of graft vs. host disease.

- a) Irradiation is only proven method (cases of TA-GVHD with leukoreduced blood reported)
 - 2) Transfusion of previously frozen products (FFP, cryo, etc)
 - 3) Transfusion of granulocyte concentrate
 - f. Potential complications of leukoreduction
 - 1) Anaphylactoid reactions
 - a) Seen in patients taking ACE inhibitors (captopril, enalapril, etc), which block breakdown of bradykinin induced by interaction with the filter surface
 - b) More in transfusion reaction section
2. **Washing**
- a. 1-2 L of saline removes about 99% of plasma.
 - b. Generally takes one to several hours (automated)
 - c. Shelf life
 - 1) Red cells: 24 hours post-wash
 - 2) Platelets: 4 hours post-wash
 - d. Why bother?
 - 1) **Removal of plasma proteins (RBCs and platelets)**
 - a) Classic example: IgA deficiency
 - Few IgA deficient patients develop anti-IgA; exposure leads to anaphylaxis.
 - Requires more washing (3L or so)
 - IgA-deficient donors are alternative.
 - b) Removal of unwanted antibodies
 - ABO antibodies (neonatal transfusions)
 - Other antibodies (white cell and platelet)
 - 2) **Neonatal alloimmune thrombocytopenic purpura (platelets)**
 - a) Severe congenital thrombocytopenia usually due to maternal anti-PL^{A1} (HPA-1A); analogous to HDN
 - Mom exposed through pregnancy or transfusion
 - Re-exposure leads to antibody re-activation.
 - Antibody crosses placenta and trashes baby's platelets.
 - b) Washed maternal platelets are treatment of choice (lack the offending antigen and antibody).
 - 3) **Repeated febrile nonhemolytic reactions (RBCs and platelets)**
 - a) Removes cytokines and WBCs
 - b) It works, but seems like overkill
 - e. NOT adequate to prevent graft vs host disease
3. **Freezing**
- a. Cryopreservative agents protect component while freezing and thawing.

- 1) Glycerol used for red cells in either 40% or 20% concentrations (40% most common).
- 2) Dimethyl sulfoxide (DMSO) used for platelets, but recovery isn't great.
- b. Why bother?
 - 1) **Storage of rare or autologous units**
 - 2) **Plasma hypersensitivities (as with washed)**
 - 3) **Repeated febrile reactions (as with washed)**
- c. Storage
 - 1) Red Cells
 - a) 10 years at -65 C (40% glycerol) or -120 C (20% glycerol)
 - b) 24 hours at 1-6 C after thawing/deglycerolizing
 - 2) Platelets
 - a) No defined storage times (probably 4 hours post-removal of DMSO, though)

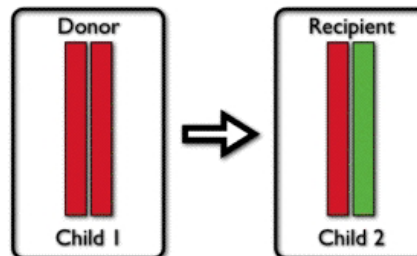
4. Irradiation

- a. Irradiation is effective in deactivating lymphocytes without significantly damaging anything else.
- b. We use irradiation as a means to prevent *transfusion-associated graft vs. host disease*
- c. TA-GVHD sequence/requirements:
 - 1) Viable, active lymphocytes are transfused.
 - a) Exact minimum number needed to cause TA-GVHD unknown.
 - 2) Donor and recipient are not HLA-identical.
 - 3) Recipient is unable to respond to neutralize the effect of the transfused WBCs.
- d. The normal response:
 - 1) Transfused lymphocytes (CD4 and CD8) mount an immune response against HLA incompatible host tissues.
 - 2) Normally, host lymphs (most believe just CD8) counterattack and neutralize the response (see top of figure below).



- e. Lack of host neutralization (bottom of figure above) may lead to TA-GVHD.

- 1) Almost uniformly fatal
- 2) Patients present with:
 - a) Fever 7-10 days post-transfusion
 - b) Characteristic face/trunk rash that spreads to extremities
 - c) Diffuse mucositis with nausea/vomiting, watery diarrhea
 - d) Hepatitis
 - e) **Pancytopenia and subsequent marrow aplasia**
- f. Radiation dose
 - 1) 2500 cGy (“rad”) dose required targeted to center of bag, with at least 1500 cGy in all parts of the bag
- g. Risk factors
 - 1) **Immunosuppression**
 - a) Congenital T-cell deficiencies (DiGeorge’s, SCID, Wiskott-Aldrich)
 - b) Stem cell or marrow transplant recipients
 - c) Patients taking *Fludarabine*
 - 2) **Intrauterine and premature neonate transfusions**
 - 3) **Hodgkin’s disease**
 - a) Patients with other hematologic malignancies often get irradiated blood, too.
 - 4) **Receiving blood from a first-degree relative donor or receiving HLA-“matched” units**
 - a) HLA-heterozygous recipient getting blood from an HLA-homozygous donor
 - Child 2 gets blood from child 1 in picture below (child 1 is HLA homozygous, while child 2 shares one haplotype with child 1)
 - Child 2 does not see child 1 as foreign, but child 1 does see child 2 as having a foreign HLA type (because of the non-shared HLA genes).
 - b) Recipient doesn’t recognize transfused cells as foreign, so no counterattack.



- h. Patients probably NOT at risk (but often get irradiated products anyway).
 - 1) Organ transplant recipients
 - 2) Term neonates
 - 3) Aplastic anemia

- 4) AIDS patients (CD8 lymphs that defend from foreign WBCs have preserved function until late in disease).
- 5) Patients receiving previously frozen blood products (FFP, cryoprecipitate)
 - a) Note that frozen/thawed/deglycerolized red cells MUST be irradiated; because they were cryopreserved, viable cells may remain.
- i. Don't use irradiation for:
 - 1) Preventing CMV transmission
 - 2) Peripheral progenitor cell infusions
- j. Maximum storage: 28 days after irradiation or regular expiration date, whichever comes first
 - 1) K+ and free hemoglobin increase in red cells
 - 2) Doesn't change shelf life for platelets, since platelets are stored for only five days anyway
 - 3) May change red cell shelf-life depending on what day in the lifespan the product is irradiated

F. Plasma Group

1. Fresh frozen plasma (FFP)

- a. Use (and abuse) greatly increased in recent years.
- b. Specifics:

Volume:	200-250 ml
Contents:	All coagulation factors <ul style="list-style-type: none"> • 400 mg fibrinogen • 1 IU/ml of all others Almost no <u>viable</u> cells Anticoagulant

- c. Basic notes about coagulation
 - 1) 100% levels of coagulation factors are not required for adequate hemostasis.
 - a) 20-30% levels are enough in most cases.
 - 2) However, factor levels at which someone will clot don't necessarily give normal PT/PTT.
 - 3) Factor VII in vivo half-life is only about 4 hours.
- d. Indications
 - 1) **Coagulopathy due to multiple factor deficiencies**
 - a) Liver disease
 - Decreased production of all hepatic factors; seen first with F VII (increased PT).
 - 2) **Urgent reversal of vitamin K deficiency from dietary factors or warfarin use (or overdose)**
 - a) Warfarin affects factors II, VII, IX, X
 - b) IV or SQ vitamin K takes hours (between 6 and 12) to replenish these factors.
 - c) For non-bleeding patients, most can be corrected without plasma administration (hold dose and give vitamin K)

- d) Prothrombin Complex Concentrate (PCC) or recombinant Factor VII (NovoSeven) may be better choices than FFP in bleeding patients (smaller volume)
 - e) In general, need at least 4-6 units initial dose of FFP to attain hemostasis in someone who is acutely bleeding and on warfarin (usually more).
 - f) “Normal” PT/PTT not necessary
- 3) **Trauma transfusion**
- a) Recent literature showing that trauma patients given plasma in close to 1:1 ratio with RBCs have better survival (first discovered in military)
 - b) Much current study going on, with majority of literature supporting principle
 - c) Many trauma centers have established “trauma/massive transfusion protocols” that attempt to make 1:1 ratio automatic
 - d) Concerns about plasma transfusion complications (TRALI) and plasma wastage
- 4) **Dilutional coagulopathy**
- a) Transfusion of multiple coag factor poor products (RBCs and crystalloids in massive transfusion) dilutes coag factors.
 - b) Usually not apparent until after at least 10-15 or more units of RBCs (with accompanying fluid) in a 24 hour time span
 - c) May become less of an issue with massive transfusion protocols and 1:1 ratios mentioned above
- 5) **Transfusion or plasma exchange for TTP/HUS**
- a) FFP has normal amounts of ADAMTS13, the protein lacking in TTP
 - b) If nonresponsive, consider “cryo-reduced” plasma (FFP with cryo removed), or solvent/detergent-treated plasma (no longer on market).
- 6) **Other factor-specific coagulopathies that do not have a factor concentrate available**
- 7) **Rare circumstances**
- a) Protein C or S deficiency if no factor concentrate is available.
 - b) C1 esterase inhibitor deficiency
 - c) Factor XIII deficiency
- e. Not indicated for:
- 1) Volume expansion
 - a) Alternatives (albumin, plasma protein fraction, crystalloids) are safer.
 - 2) Heparin reversal
 - a) Supplies antithrombin, which potentiates heparin!

- b) Use protamine sulfate or just stop the heparin.
- 3) Factor deficiencies with specific concentrates available (like factor VIII and IX)
- 4) Prophylactic or pre-procedure treatment of mild elevations of PT/PTT
 - a) Generally become significant at about 1.5 times midpoint of normal or more
 - b) Many retrospective studies in this setting show:
 - (1) It doesn't work (no change in bleeding from transfused vs. non-transfused patients)
 - (2) The lab values are rarely "corrected" by the transfusion anyway!
- 5) "Nutrition," "Wound healing," or "patient well-being"
- f. Preparation/storage
 - 1) **Pre-storage**
 - a) Made from a single whole blood donation.
 - b) Centrifuged, separated, and frozen at -18 C within 8 hours (kept for up to one year)
 - c) May also be kept at -65 C for up to 7 years
 - 2) **Pre-transfusion**
 - a) Thawed at 30-37 C.
 - b) Stored at 1-6 C for 24 hours.
- g. Dosage
 - 1) Most often given two bags at a time in adults, but this dose is often inadequate.
 - 2) 10-20 mL/Kg is more appropriate dosage
 - 3) 10-15 mL/Kg is an appropriate dose in neonates.
- h. Effect
 - 1) A two-unit dose increases factor levels by about 20-30% in a 70 Kg person.
 - 2) Transient due to short half-lives (especially factor VII)
 - 3) Greatly elevated PT/PTT more affected than mildly elevated.
- i. ABO and Rh
 - 1) Donor plasma antibodies must be compatible with recipient RBCs.
 - 2) Can give without regard to Rh.

		<i>DONOR</i>			
		A	B	AB	O
RECIPIENT	A	✓		✓	
	B		✓	✓	
	AB			✓	
	O	✓	✓	✓	✓

- 2. Plasma variants
 - a. **Plasma frozen within 24 hours of phlebotomy (FP24)**

- 1) Plasma that is not frozen in 8 hours like FFP, but within 24 hours
 - 2) Factor V levels are essentially equal to those in FFP, while factor VIII levels reportedly decline by about 20-25% in comparison to FFP
 - 3) Stored up to 12 months frozen, like FFP
 - 4) After thaw, has 24 hour shelf life, but may be relabeled as “thawed plasma” (see below)
 - 5) In most situations, can be used identically to FFP (very few coagulopathic patients have low factors V and/or VIII).
 - a) DIC and other consumptive coagulopathies are notable exceptions, as these patients may have very low factor VIII levels.
- b. **Thawed plasma**
- 1) FFP/FP24, once thawed, is only good for 24 hours.
 - 2) After 24 hours, can be relabeled as “thawed plasma” and kept at 1-6 C for up to 5 days.
 - a) Note: This process is not recognized by the FDA
 - 3) Indications, like PF24, are essentially identical to FFP.
- c. **Liquid plasma/plasma**
- 1) Plasma separated from whole blood at any point up to 5 days after expiration
 - 2) Liquid plasma: stored at 1-6 C, not frozen
 - a) Can be transfused up to 5 days after whole blood expiration date.
 - 3) Plasma: stored at -18 C or below
- d. **Plasma, cryoprecipitate reduced (“cryo-reduced plasma”, “cryosupernatant”)**
- 1) Residual plasma that remains after cryoprecipitate removed from FFP (see below).
 - 2) Product contains less von Willebrand’s factor (especially larger multimers), so may be useful in TTP plasma exchanges if regular FFP doesn’t work (literature shows mixed results on this).
 - 3) Storage and transfusion just like FFPa.
- e. **Donor-retested FFP**
- 1) Tries to eliminate window-period transmissions by holding plasma at least 112 days (two possible 56-day donor cycles) for re-testing of the donor
 - 2) Not widely used due to administrative headaches and increased cost
- f. **Solvent/detergent-treated plasma (SDP, PLAS+[®]SD)**
- 1) Available in Europe; removed from US market by Red Cross in 2002

- 2) Pooled ABO-identical plasma from as many as 2500 donors treated to deactivate enveloped viruses (HIV, HTLV, HBV, HCV).
- 3) Why it wasn't widely embraced
 - a) Pooled product; fear of undiscovered pathogens.
 - b) Nonenveloped viruses (Parvo, HAV) unaffected
 - c) Higher cost than FFP when introduced
- g. **Linked plasma**
 - 1) Ensuring that patient receives plasma and red cells from same donor
 - 2) Saves donor exposures
 - 3) Adds much complexity to process; not widely used
3. **Cryoprecipitate**
 - a. Also has seen increased use in recent years.
 - b. Specifics:

Volume:	Approximately 15 mL
Contents:	<p>≥ 150 mg fibrinogen (us. ~250 mg)</p> <p>≥ 80 IU factor VIII</p> <p>80-120 IU von Willebrand's factor</p> <p>40-60 IU factor XIII</p> <p>Fibronectin</p>

- c. ABO and Rh
 - 1) Same as for FFP
- d. Indications
 - 1) **Fibrinogen deficiency (congenital or acquired)**
 - a) General threshold: 100 mg/dl for adequate hemostasis post-surgery.
 - b) Calculation in BB Practical section
 - c) Many use 10-20 bags per dose in adults, more if fibrinogen is less than 50 mg/dl.
 - d) 10 bags deliver about 2500 mg of fibrinogen in about 150 ml of volume
 - > 1 liter FFP needed for same amount!
 - 2) **Treatment of von Willebrand's disease**
 - a) Second-line therapy; should be used only if factor VIII concentrates are not available.
 - Some factor VIII concentrates (eg, "Humate-P") contain vWF.
 - b) Cryo may be used for severe forms.
 - Dose 1 bag per 10 Kg body weight q 8 hr
 - c) DDAVP can be used for milder forms.
 - 3) **Treatment of uremic thrombocytopenia**
 - a) Acquired adhesion defect (probably) which may respond to vWF supplementation
 - b) Generally seen with creatinine levels > 3 mg/dL
 - c) Cryo is second line of defense (after DDAVP, dialysis)

- d) Also consider conjugated estrogens, increasing HCT to ~30%
- e) *Am J Med.* 1994;96:168-79 describes treatment of uremic thrombocytopenia.
- 4) **Factor XIII deficiency**
- 5) **Topical “glue”**
 - a) Formerly mixed with bovine thrombin and applied directly to raw surfaces
 - b) Currently available fibrin sealants (treated, virus-free) have made this obsolete.
- 6) **Treatment of hemophilia A**
 - a) Absolutely second-line therapy; use only if emergency and no factor VIII concentrate available.
 - b) Calculation in BB Practical section for exams
 - c) General targets:
 - For hemarthrosis, GI hemorrhage, trauma without bleeding: 50% F VIII level
 - For surgery, trauma with bleeding, intracranial hemorrhage: 100% F VIII level
- e. Manufacture
 - 1) Made from a single unit of FFP.
 - 2) Thaw FFP at 1-6 C, spin and remove liquid, re-freeze slushy precipitate within 24 hours.
- f. Storage and preparation for transfusion
 - 1) **-18 C for 1 year**
 - 2) After thawing (at 30-37 C, like FFP), store up to 6 hours at 20-24 C (unlike FFP)
 - 3) If units are pooled, transfuse within 4 hours.
 - 4) No compatibility testing required, though ABO-compatible is preferred.
 - 5) Can give without regard to Rh status
- 4. **Factor concentrates**
 - a. **Factor VIII concentrate**
 - 1) Used for moderate to severe hemophilia A
 - 2) Virus inactivated or recombinant
 - 3) Dosage: discussed in BB Practical
 - 4) Target levels: as above
 - 5) May contain vWF and be used in vWD.
 - b. **Factor IX concentrate**
 - 1) Used for hemophilia B
 - 2) Old Factor IX complex concentrate not often used anymore (risk of thrombosis).
- 5. **Albumin and plasma protein fraction**
 - a. Volume expanders
 - b. Virus inactivated
 - c. Ridiculously expensive!
 - d. Differ only in composition
 - 1) Albumin: 96% albumin, 4% globulins/others

2) PPF: 83% albumin, 17% globulins/others.

G. Granulocyte concentrate

1. Uncommonly used today.
2. Specifics

Volume:	Usually 200-300 mL
Contents:	WBCs ($\geq 1.0 \times 10^{10}$) Platelets ($> 3 \times 10^{11}$) RBCs (> 2 ml) Plasma Anticoagulant

3. Indications
 - a. May be considered in premature neonates with infections, transplant patients with infections, patients with chronic granulomatous disease
 - b. Aside from above, a clinical situation including:
 - 1) Fever for 24-48 hours,
 - 2) Culture-proven bacterial or fungal infection
 - 3) No response to antibiotic therapy
 - 4) Neutropenia ($< 500/\mu\text{L}$)
 - 5) *Reversible* bone marrow hypoplasia
4. Not indicated for:
 - a. Prophylactic use
 - b. Patients with no hope of marrow recovery
5. Cans and Can'ts!
 - a. **Can irradiate** granulocytes to prevent TA-GVHD.
 - 1) Irradiation harms lymphocytes but doesn't really affect granulocytes greatly.
 - b. **Can't filter** granulocytes to prevent CMV transmission.
 - 1) This seems obvious, doesn't it? Filters remove white cells, right? Are you with me? Hello?
 - 2) To protect against CMV transmission, need CMV-negative donor.
6. Storage conditions
 - a. 24 hours at 20-24 C *without* agitation
7. Caution
 - a. Granulocyte concentrate has abundant red cells, so must be ABO and Rh compatible.
 - b. Crossmatch required before transfusion, also.

H. DDAVP

1. Synthetic form of ADH used initially for treatment of diabetes insipidus.
2. As a fortunate side effect, causes release of vWF from endothelial cell storage; seems to functionally increase factor VIII, as well.
3. Potential indications:
 - a. Uremic thrombocytopenia

- 1) 0.3 µg/Kg IV
- 2) Generally should be considered before platelets or cryoprecipitate.
- b. Mild hemophilia A
- c. von Willebrand's disease
 - 1) Works in types without marked deficiency
 - 2) Don't use in type IIB or III
 - a) IIB: may cause clotting.
 - b) III: ineffective
- d. Hepatic failure (for improved platelet function)
4. Effect diminishes/vanishes with repeat doses ("tachyphylaxis").

I. Recombinant activated factor VII (NovoSeven)

1. Non-human-plasma-derived activated factor VII that is currently FDA-approved for use in:
 - a. Hemophiliacs (A or B) with inhibitors (bleeding prevention and bleeding treatment)
 - b. Patients with congenital factor VII deficiency (bleeding prevention and bleeding treatment)
2. Widespread "off-label" use has occurred in past few years, as NovoSeven gained reputation as a "magical" hemostatic agent!
3. Shouldn't be used without care, as there is an estimated 1-2% risk of thrombosis
 - a. *JAMA*. 2006;295:293-298 (O'Connell, et al) article reported that most serious thromboembolic complications from NovoSeven followed off-label use.
 - b. Serious complications included thrombotic stroke, acute MI, and pulmonary emboli; NOTE that these were not definitely *caused* by NovoSeven, just *associated* with its use.
4. Best evidence suggests off-label use may be most appropriate for:
 - a. Treat/prevent surgical bleeding in trauma patients
 - b. Reversal of anticoagulant therapy (warfarin and factor Xa inhibitors)
 - c. Treat/prevent surgical bleeding in advanced liver failure patients.
 - d. Perioperative blood loss prevention (after failed clotting factor replacement therapy) in cardiac surgery, neurosurgery, OB/GYN surgery, and urologic surgery
5. Many other off-label uses are being studied, including use in hemorrhagic strokes and use in platelet-related bleeding.
6. Not indicated for routine pre-procedure bleeding prophylaxis.
7. Typical doses: 20 to 40 mcg/Kg in non-emergencies, 41 to 90 mcg/Kg otherwise
 - a. Roughly 2-hour half-life, so dose must be repeated often

J. “Blood substitutes”

1. Popular with the press
2. Probably better termed “blood supplements” or “oxygen therapeutics” because none can do everything that blood can do.
3. Various, competing technologies
 - a. Hemoglobin-based oxygen carriers (HBOC’s)
 - 1) Hemopure (Biopure); polymerized bovine hemoglobin
 - 2) PolyHeme (Northfield Labs); polymerized human hemoglobin
 - 3) Hemospan aka “MP4” (Sangart); conjugated human hemoglobin
 - 4) HemAssist (Baxter); cross-linked human hemoglobin removed in 1998 due to concerning results in phase III trials
 - b. Perfluorocarbon solutions
 - 1) Oxygent (Alliance)
4. Products in trials or approved:
 - a. Hemopure approved in South Africa for acutely anemic patients.
 - 1) Currently under study for similar use in US, but not approved for phase III trials
 - b. PolyHeme completed phase III trials in US in 2006.
 - c. Hemospan in phase III trials in Europe
5. Potential advantages
 - a. Universal compatibility
 - b. Less stringent storage (many are stored at room temperature).
 - c. Infectious disease risk “eliminated”
6. Problems
 - a. Short half-life (less than 24 hours)
 - b. Free hemoglobin may cause vasoconstriction by reducing nitric oxide (NO) levels.
7. Uses
 - a. Trauma or other massive transfusion setting
 - b. Military settings
 - c. Orthopedic surgeries