Apheresis: Basic Principles, Practical Considerations and Clinical Applications

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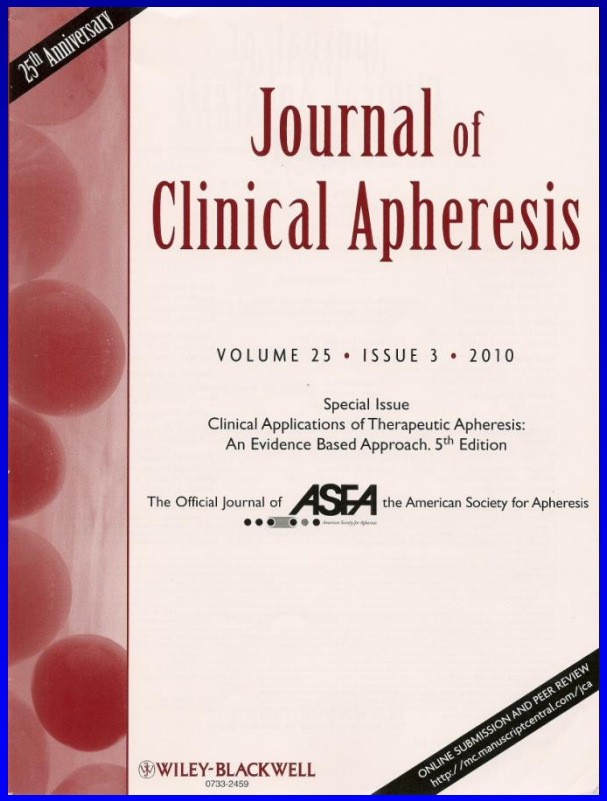
Objectives (Part 1)

- Mechanism of Action
- Definitions
- Technology (ies)
- Use
- Practical Considerations
- Math
- Clinical applications – HPC Collection

Objectives (Part 2)

- Clinical applications: System/ Disease Specific Indications

- ASFA Fact Sheet



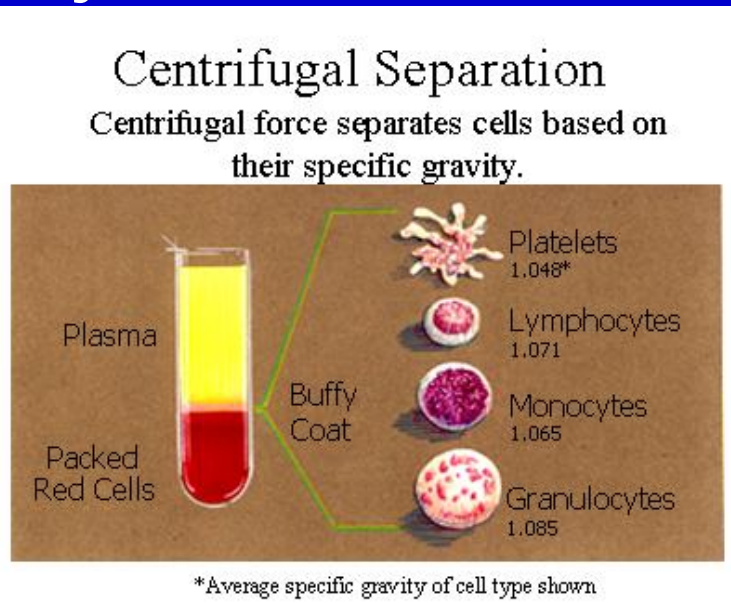

The
Twilight
Zone

Apheresis

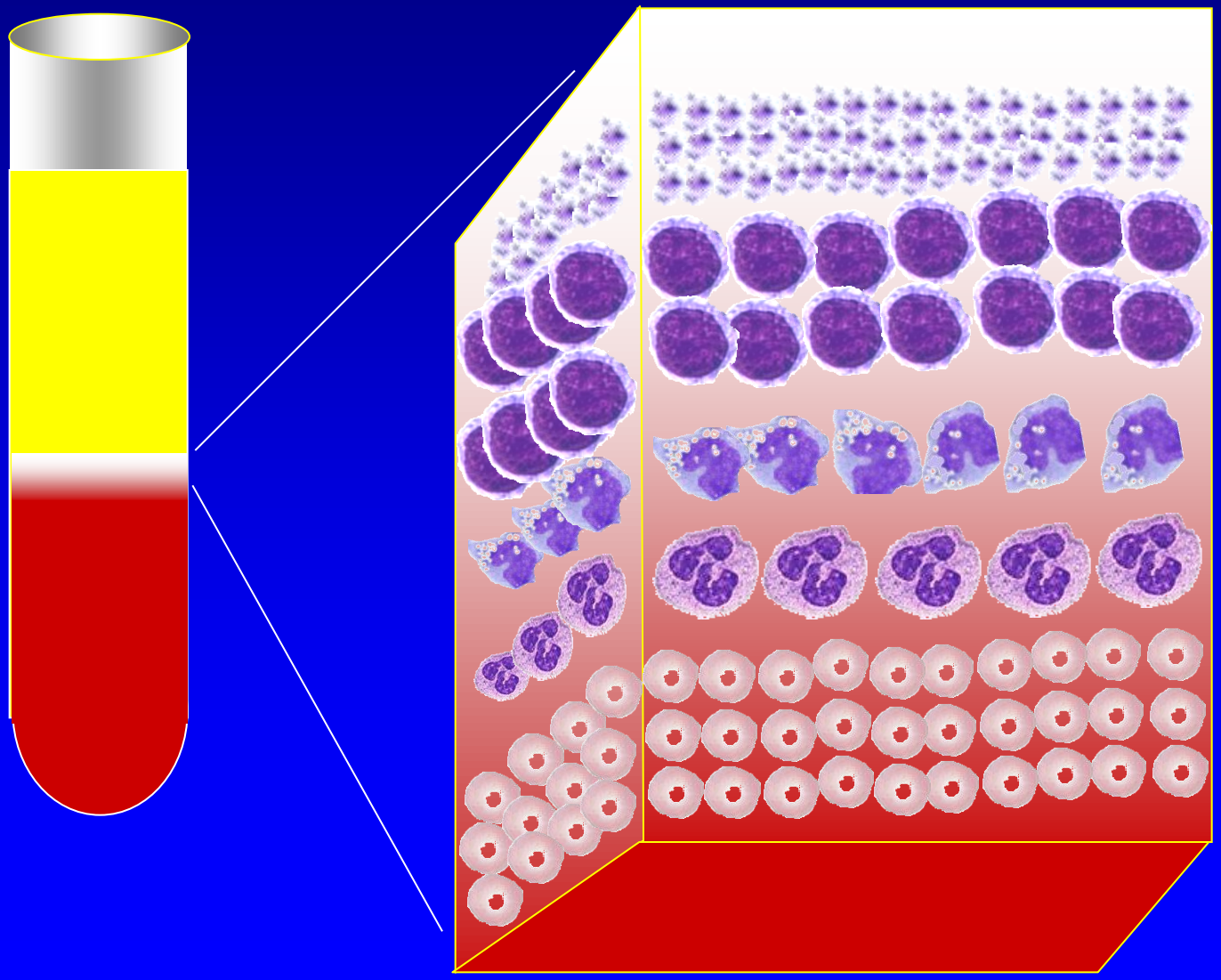
- Derives from Greek, “to carry away”
- A technique in which whole blood is taken and separated extracorporealy, separating the portion desired from the remaining blood.
- This allows the desired portion (e.g., plasma) to be removed and the reminder returned.

Apheresis- Mechanism of Action

- Large-bore intravenous catheter connected to a spinning centrifuge bowl
- Whole blood is drawn from donor/patient into the centrifuge bowl
- The more dense elements, namely the RBC, settle to the bottom with less dense elements such as WBC and platelets overlying the RBC layer and finally, plasma at the very top.



Apheresis: Principles of Separation



Platelets
(1040)

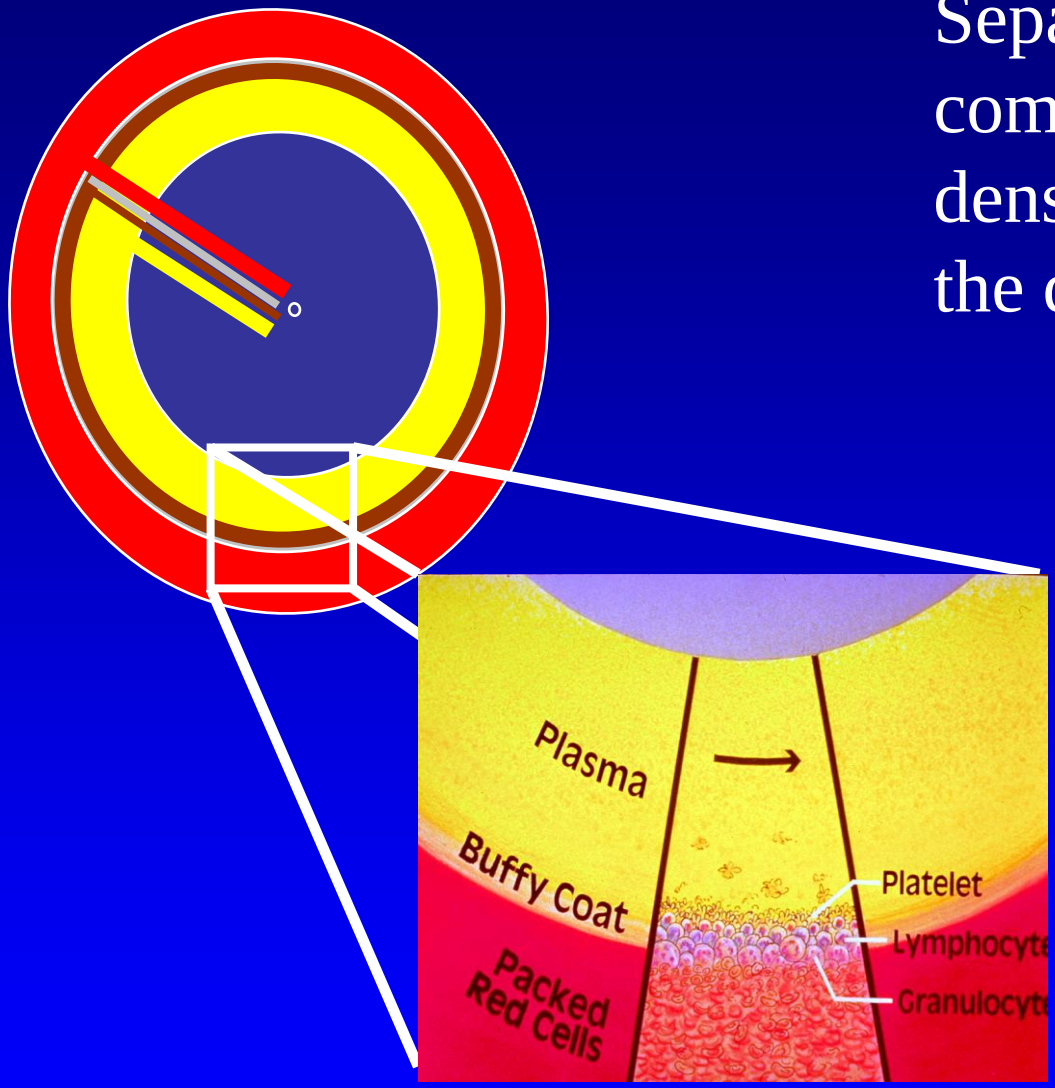
Lymphocytes
(1050-1061)

Monocytes
(1065 - 1069)

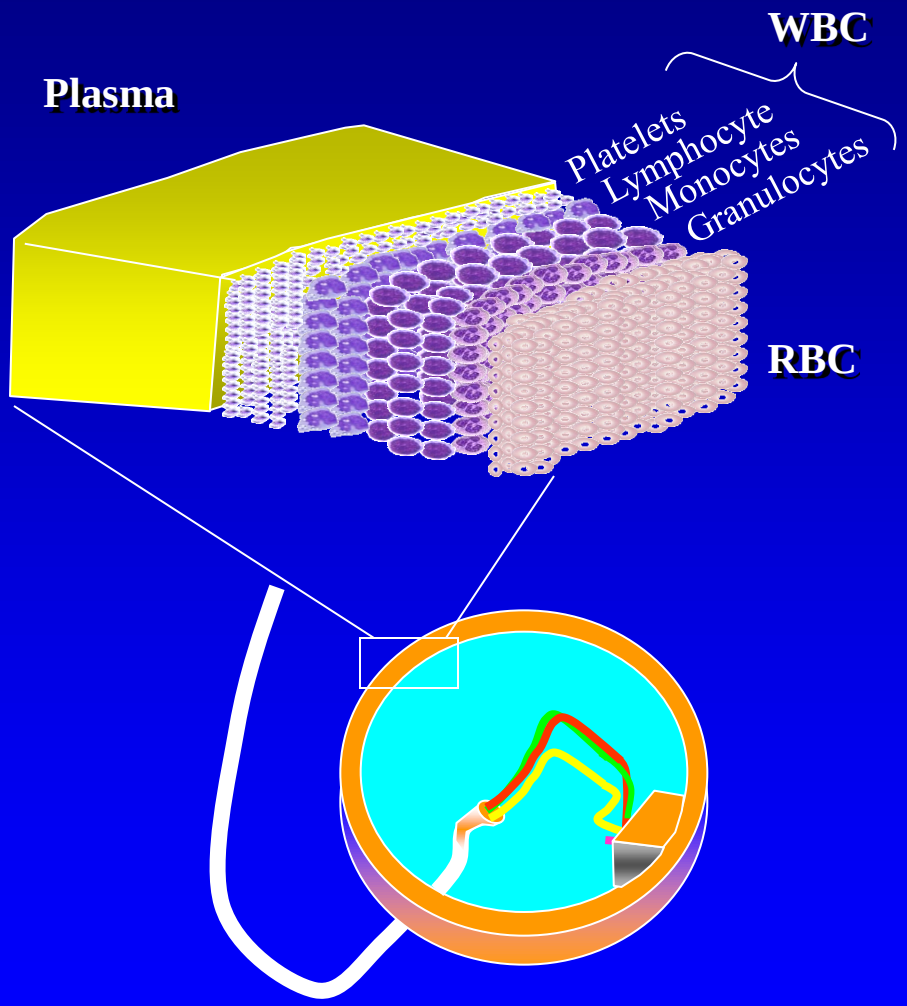
Granulocyte
(1087 - 1092)

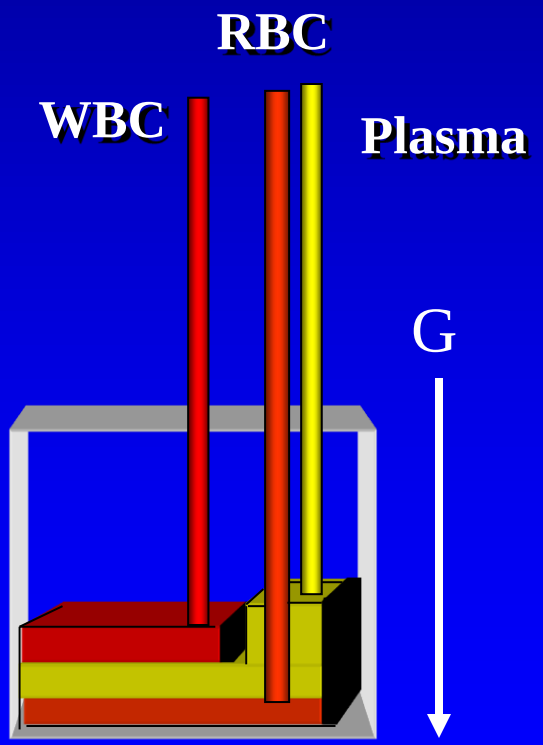
RBC

Separate blood components is based on density with removal of the desired component



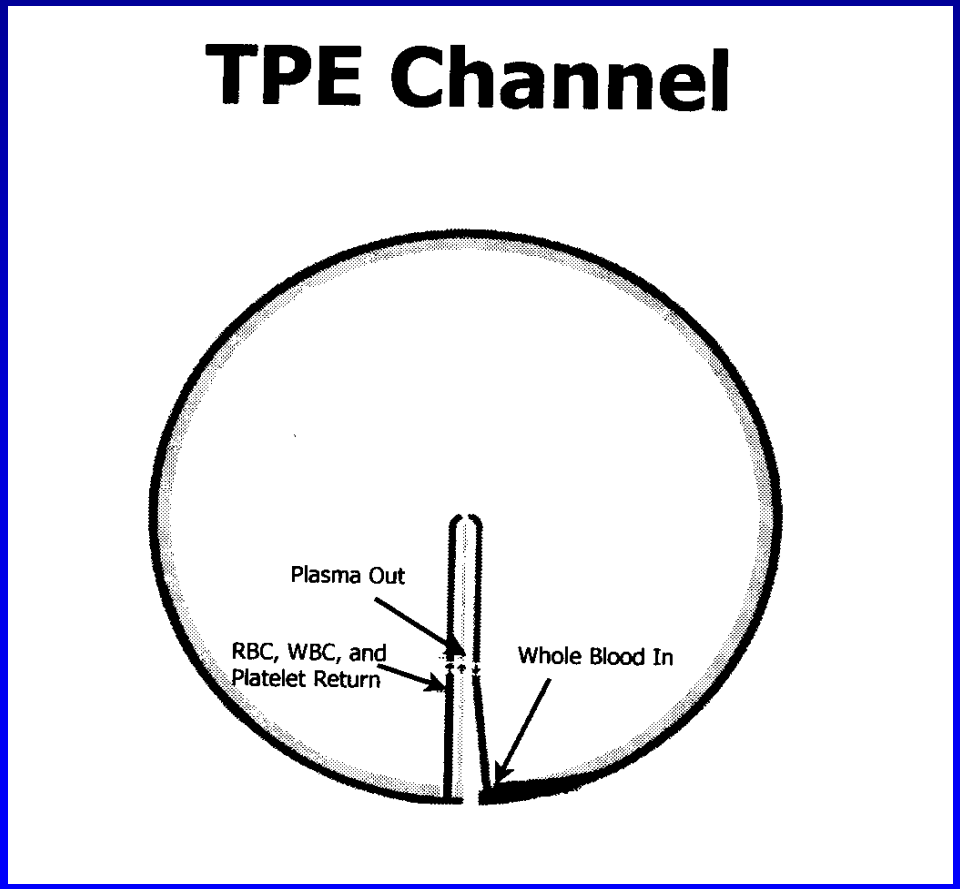
Principals of Apheresis





Cobe Spectra®

Apheresis- Mechanism of Action



Definitions

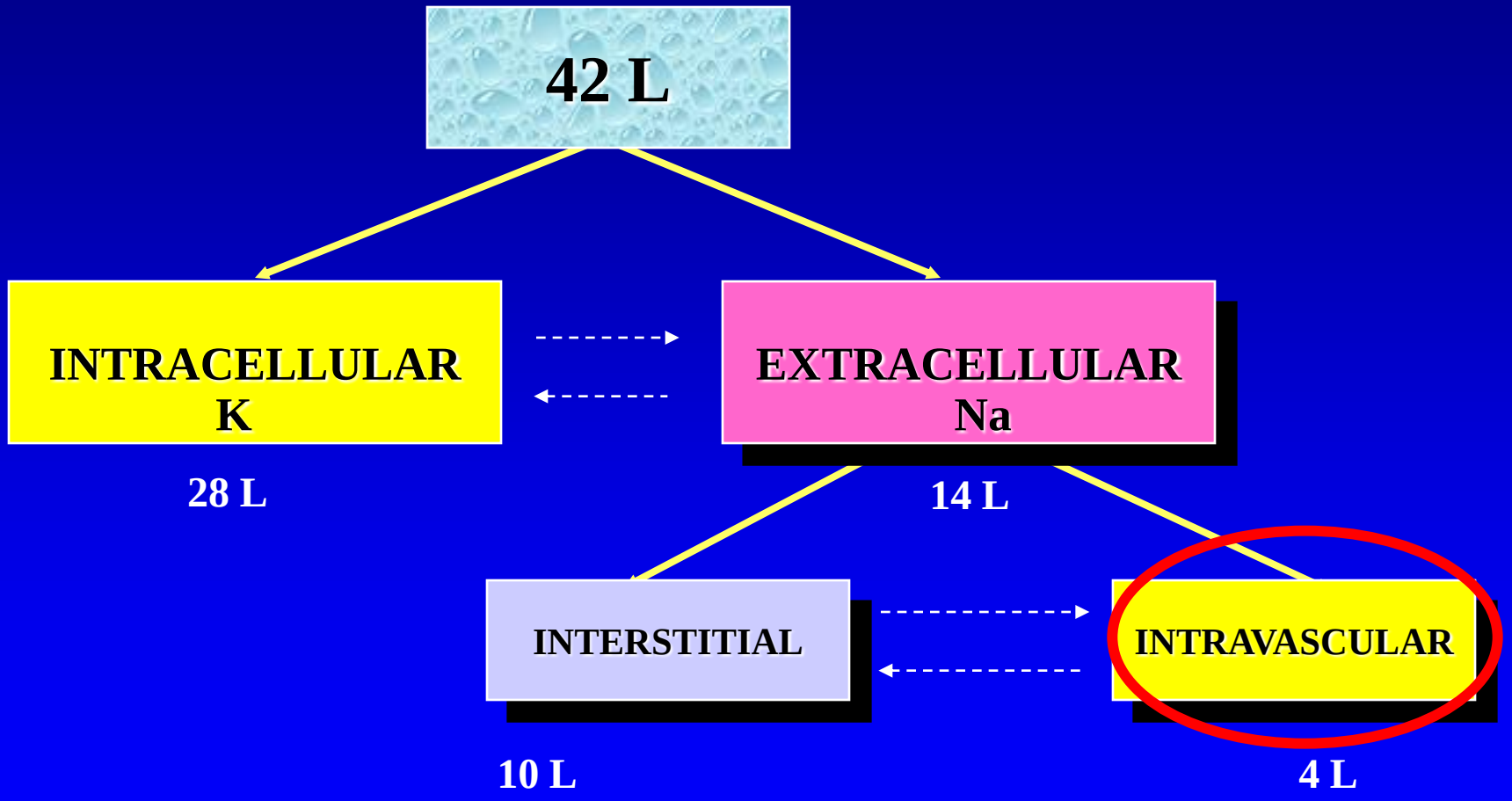
- **Plasmapheresis**: plasma is separated, removed (i.e. less than 15% of total plasma volume) without the use of replacement solution

- **Plasma exchange (TPE):** plasma is separated, removed and replaced with a replacement solution such as colloid (e.g. albumin and/or plasma) or combination of crystalloid/colloid

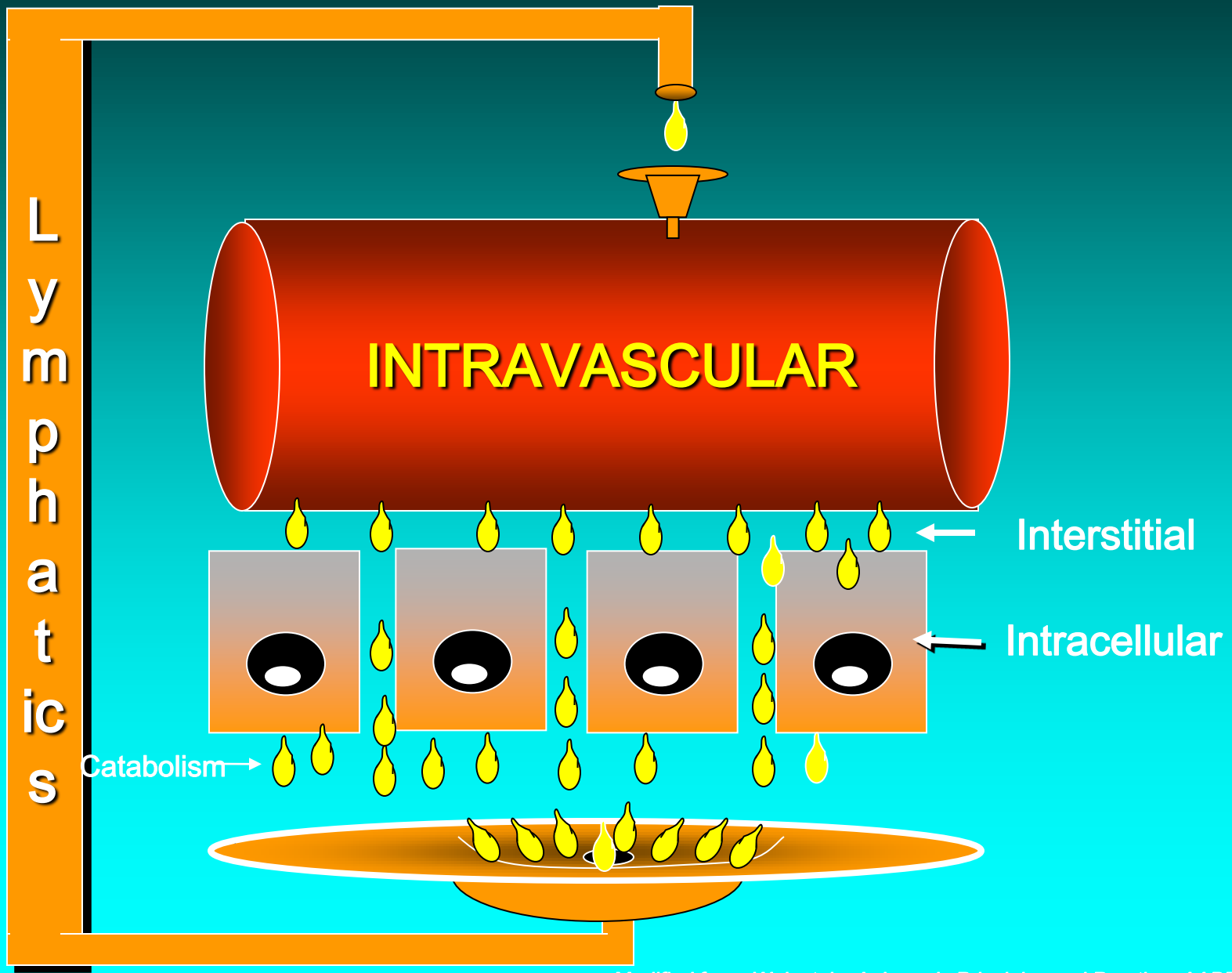
Szczepiorkowski et at, Clinical Applications of Therapeutic Apheresis,

J Clin Apheresis 2007, 22, 104-105.

Plasmapheresis/TPE: Fluid Dynamics



Plasma Exchange : Mathematical Models



Modified from: Weinstein, Apheresis:Principles and Practice- AABB press

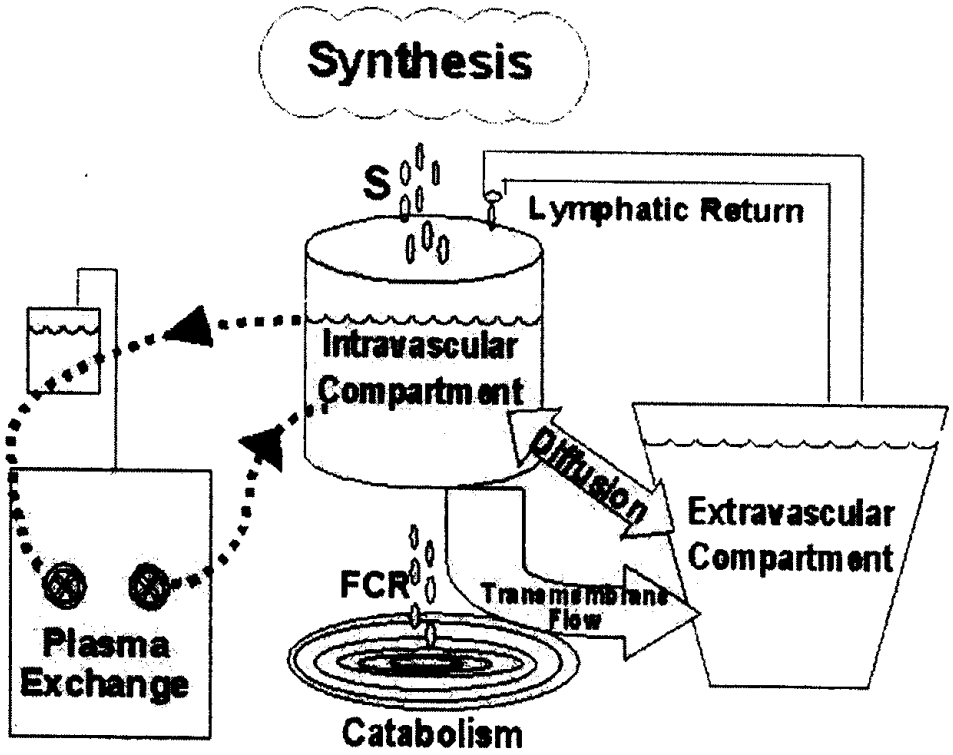


Figure 15-1. A model for the interaction between intravascular and extravascular compartments and the effects of plasma exchange. A soluble substance enters the body through the intravascular compartment at the synthetic rate SR, and is catabolically removed from the body from the intravascular compartment at its fractional catabolic rate (FCR). Movement from the intravascular to the extravascular compartment takes place primarily by diffusion while a smaller component of transmembrane flow occurs by other mechanisms. Soluble substances return from the extravascular compartment back to the intravascular compartment mainly through the lymphatic system, although a small amount of back-diffusion takes place. Plasma exchange directly removes soluble substances only from the intravascular compartment. SR, FCR, and intracompartment movement of each solute are balanced and thus in a steady state so proceed much more slowly than the actual removal of plasma from the intravascular compartment by plasma exchange. Therefore, for the purpose of therapeutic plasma exchange, the intravascular compartment is considered to be an isolated system that can be depleted of its soluble contents by the exchange of plasma for a replacement fluid.

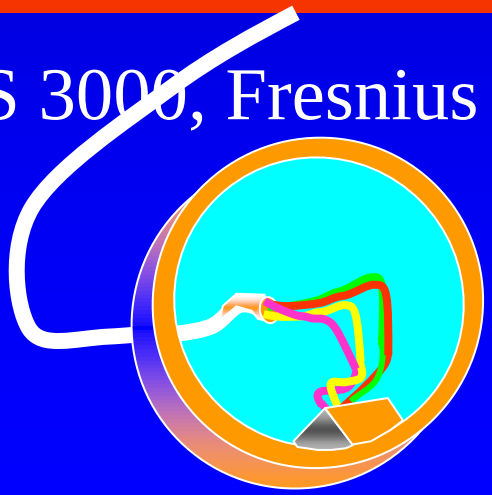
Technology

•Automated centrifugal cell separators allow large of blood to be processed in a short period of time

•Discontinuous flow: Haemonetics MSC

plus, V50, V30

•Continuous flow: Cobe spectra, CS 3000, Fresnius AS 104, Spectra optia



Use of Apheresis

• **Donor** - facilitate collection of a blood component from an allogeneic donor: Platelets, Granulocytes, source plasma, HPC collection

• **Therapy** (therapeutic apheresis):

*removing undesired substances like antibodies, lipids

*reducing excess WBC/Platelets

*automated exchange of sickled RBC

*HPC collection

Use of Apheresis (cont.)

Therapeutic apheresis assures the immediate removal of abnormal substances from the circulation, which are either:

***present in plasma**

***or tightly bound to plasma proteins**

Abnormal Substances Removed From the Circulation by TPE

1) Paraproteins (Waldenstorm's Macroglobulinemia)
2) Autoantibodies (Myasthenia Gravis, Goodpasture's syn.)
3) Lipids (LDL in familial hypercholesterolemia; phynatic acid in refsum's disease
4) Toxins or drugs (that are bound to albumin)
5) Circulating immune complexes (CIC)
6) Soluble mediators of inflammatory response (activated complement component, vasoactive substances)

Apheresis Procedural Elements (+ Practical Considerations):

- **Venous access**
- **Replacement fluid**
- **Normal/abnormal constituents removed**
- **Anticoagulation**
- **Patient history and medications**
- **Frequency and number of procedures**
- **Complications**

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Venous Access

*Apheresis require large bore venous catheters to sustain the flow rates required (50-100 ml/min)

Type of catheters: 17 gauge therumo butterflies

- double lumen dialysis catheters 10-13.5 fr (Shiley, Quinton, Vascath, Permacath)

- Avoid "standard" Hickman or triple-lumen designs: flow rates are inadequate

***Location**: Peripheral: antecubital fossa

central: femoral/subclavian/jugular

arteriovenous shunt/fistula

***Number of lines**: intermittent flow devices (draw and return via the same line): single line

- continuous flow devices : separate lines

Venous Access (cont.)

- Planned/occasional procedure - peripheral line and removal after the procedure
- Few days/ bed rest- femoral line (risk of infection/thrombosis)
- Multiple procedures for a long period of time - neck central vein or artriovenous shunt/fistula
- Do not forget:

*Dressing change

*Flush

Apheresis Procedural Elements (+ Practical Considerations):

- **Venous access**
- **Replacement fluid**
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- **Anticoagulation**
- **Patient History and Medications**
- **Extracorporeal Volume**
- **Frequency and number of procedures**

Replacement Fluid

- Must be FDA approved to use w/blood products [get mixed w/rbc before the return phase]
- Replacement solutions:
  - ***Crystalloids** – **normal saline 0.9%***
  - ***Colloids** – **5% albumin; plasma***

Replacement Fluid

*__The primary function of the replacement fluid is to maintain intravascular volume__

**additional features:

- Restoration of important plasma proteins
- Maintenance of colloid osmotic pressure
- Maintenance of electrolyte balance

Replacement Fluids

TTP/HUS	**FFP** **Cryodepleted FFP** **Mixtures : Albumin /FFP** **Albumin /FFP**
Neurological **GBS, MG, Stiff-man** **CIDP**	**5% Human Albumin** **Albumin/Saline (70% /30%)**
Renal **(RPGN, FSGS)**	**5% Human Albumin** **Albumin/Saline (70% /30%)**
Post Transplant	**5% Human Albumin** **Albumin/Saline (70% /30%)** **Consider adding FFP at the end if post op**

Patients with hepatic failure, coagulopathy, pre-op or post-op use FFP or finish with FFP

Comparison of Replacement Fluids

Replacement Fluid	Advantage	Disadvantage
Crystalloid	Low cost Hypoallergenic No infectious risk	Hypo-oncotic No coagulation factors No immunoglobulins 2-3 volumes required
Albumin	Iso-oncotic No infectious risk	Higher cost No coagulation factors No immunoglobulins
Plasma	Immunoglobulins Coagulation factors Iso-oncotic	Infectious risk Citrate Allergic reactions ABO compatibility

Replacement Fluid and Balance

3 choices of fluid balance (FB):

1) 100% FB – isovolemic –volume replaced=volume removed
2) <100% FB – hypovolemic (“dry”) - volume replaced < volume removed
3) >100% FB – hypervolemic (“wet”) - volume replaced > volume removed

Apheresis Procedural Elements (+ Practical Considerations):

- **Venous access**
- **Replacement fluid**
- **Normal/abnormal constituents removed**
- **Anticoagulation**
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- **Frequency and number of procedures**
- **Complications**

Normal/abnormal Constituents Removed

TPE:

- **One volume exchange removes about 63%- 65% of most plasma constituents**
- **A single two-volume exchange removes about 86% of plasma constituents**

⇒Increasing the volume beyond 1-1.5 volumes has very little impact on removal of plasma constituents

Volume of Patient Plasma Exchanged (PEX)

1pv= 63%↓, 2 vol=86% ↓, 3 vol=95%

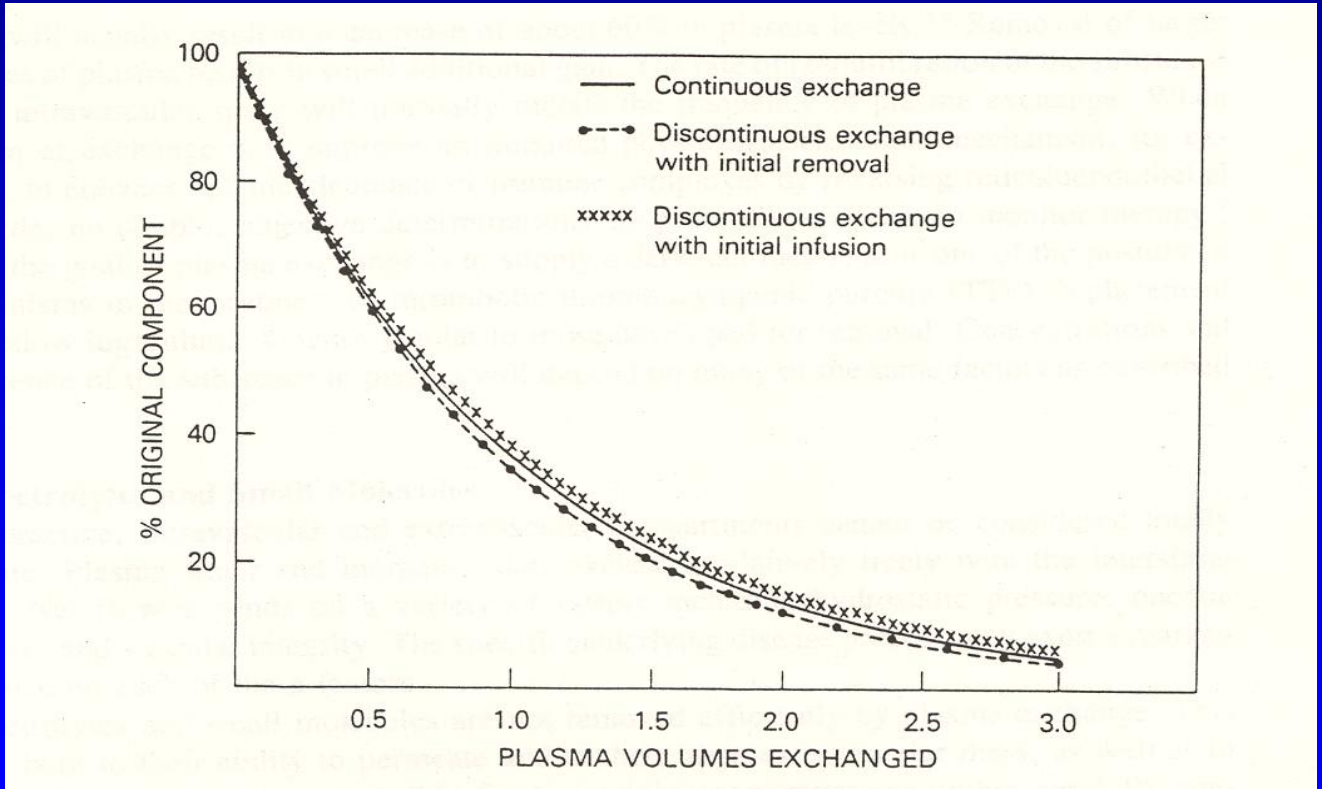

FIGURE 1. Relationship between volume exchanged and concentration of plasma components. Discontinuous exchange assumes removal of 0.1 plasma volumes per pass. (Modified from McCullough, J. and Chopek, M., *Lab. Med.*, 12, 745, 1981. With permission.)

Volume of Patient Plasma Exchanged (PEX)

- **Little advantage beyond 1.0-1.5 volumes**

1pv= 63%↓, 2 pv=86% ↓, 3 pv=95%

- **Removal of IgG and IgM by plasma exchange:**

measure	IgG	IgM
intravascular amount	45%	76%
"total body" removal		
1.0 PEX vol.	28%	48%
1.5 PEX vol.	35%	59%
2.0 PEX vol.	39%	65%

Normal/abnormal Constituents Removed

TPE:

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Normal Constituents Removed

Coagulation factors:

- Most coagulation factors are lost at the same rate
- Rapidly synthesized;replacement usually is 2-3 days following exchange
- Practical: measure PT/PTT/Fibrinogen every 2-3 days (rather then daily)

Platelets:

- ↓ 25-30% per procedure
- Endogenous synthesis replaces lost platelets within 2-4 days (except hypoplastic/aplastic marrow)
- Lab work (esp. chemistry): not immediate post-procedure; allow equilibrium intra/ extravascular space

Apheresis Procedural Elements (+ Practical Considerations):

- **Venous access**
- **Replacement fluid**
- **Normal/abnormal constituents removed**
- **Anticoagulation**
- **Patient history and medications**
- **Frequency and number of procedures**
- **Complications**

Anticoagulation

Anticoagulation citrate Dextrose (ACD):

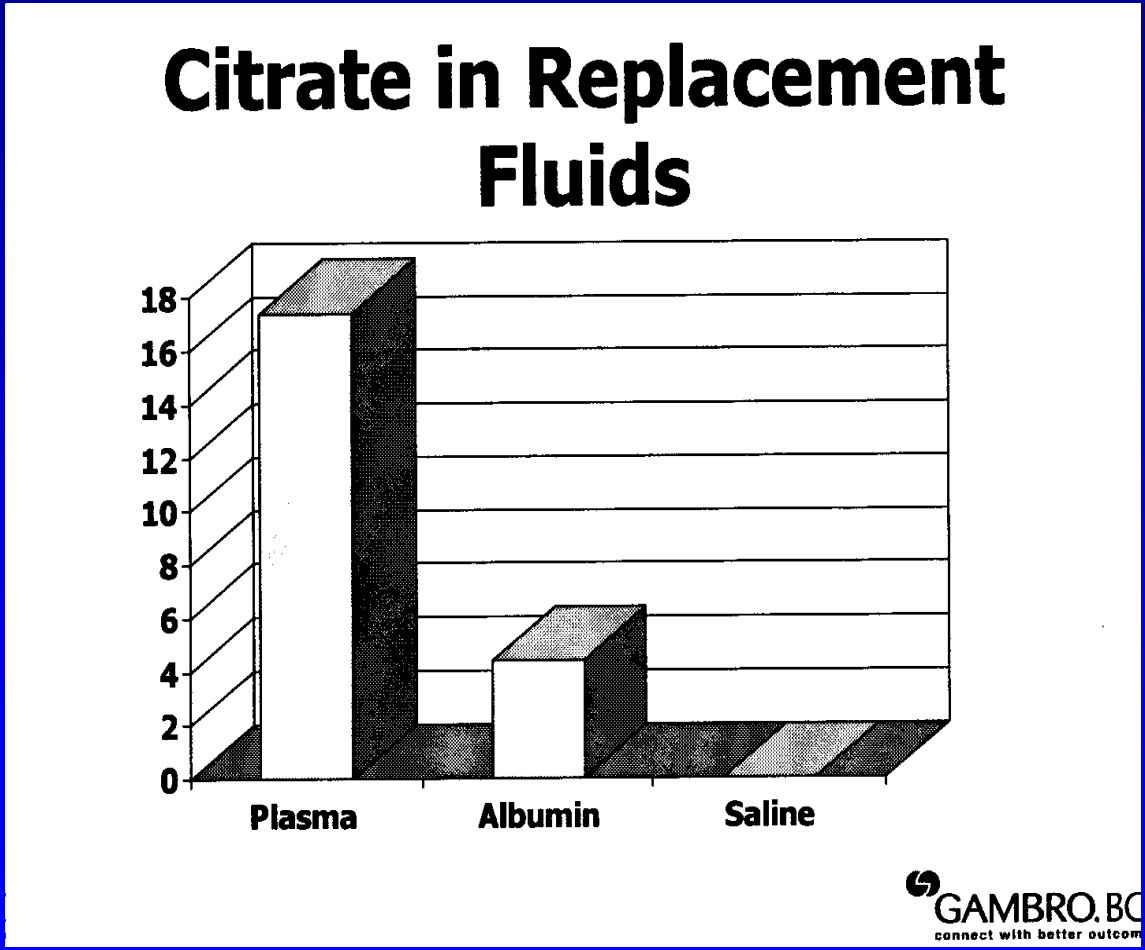
- Found in human cells, plant cells, and citrus fruits
- Chelates positively charged calcium ions (ionized calcium) and blocks calcium-dependent clotting factor reactions
- Works extracorporeally
- Metabolized in the liver almost immediately upon return
- Side effects: hypocalcemia.

  ↑ small pts, large vol. of citrated blood, liver dysfunction

Heparin:

- Prevents conversion of fibrinogen to fibrin and prothrombin to thrombin
- Systemic anticoagulation
- Metabolized slowly 1-2 hours
- Individual sensitivity and elimination rates

Anticoagulation



Apheresis Procedural Elements (+ Practical Considerations):

- **Venous Access**
- **Replacement Fluid**
- **Normal/abnormal Constituents Removed**
- **Anticoagulation**
- **Patient History and Medications**
- **Frequency and Number of Procedures**
- **Complications**

Patient History and Medications

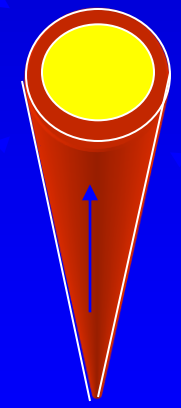
- **Does patient have a disease which is amenable to treatment by the requested apheresis procedure**
- **Does the patient/donor capable of sustaining the fluid shifts associated with apheresis**
- **Certain medications, most notably antibiotics and anticoagulant can be removed by apheresis - should be given *immediately after* the procedure**
- **Angiotensin-converting enzymes (ACE) inhibitors**

ACE inhibitors

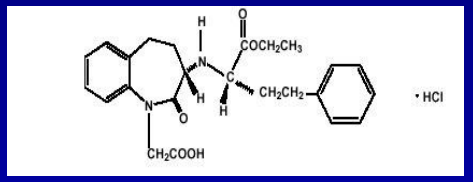
A.C.E.

Angiotensin I → Angiotensin II

Vasoconstriction →

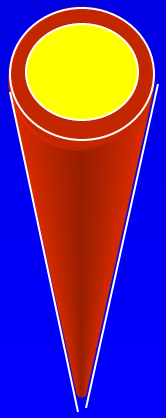


ACE inhibitors



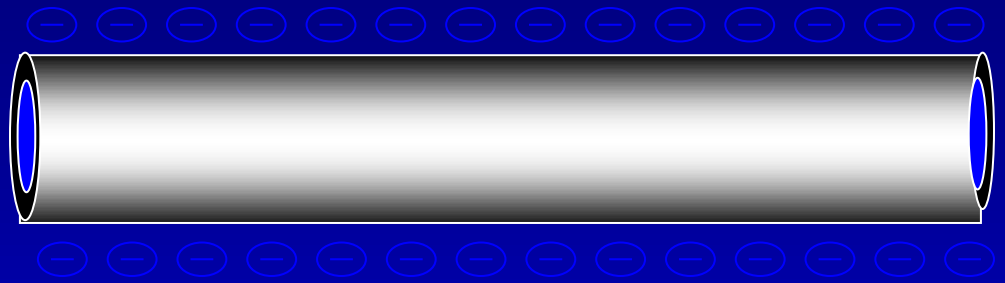
A.C.E. Inhibitor

Angiotensin I → X → **Angiotensin II**



No vasoconstrictive effect

ACE inhibitors and Apheresis



ACE Inhibitor

Kinase I & II

X

Breaks down Bradykinin

XII

XII a

Prekalikrein

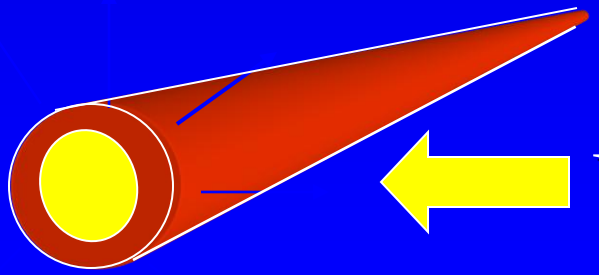
Kallikrein

H.M.W.K

Bradykinin

1- Activation of XII

2- Inhibition of Kinase II



Vasodilatation

Apheresis Procedural Elements (+ Practical Considerations):

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- **Patient history and medications**
- **Frequency and number of procedures**
- **Complications**

Frequency and Number of Procedures

Depends on: Disease being treated, Patient signs and symptoms, Lab values

Substance	Volume Treated (ml/kg)	Treatment Interval (hours)	Number of Treatments
Autoantibodies	40 – 60	24 – 48	4 – 6
Immune complexes	40 – 60	24 – 48	treat to response
Paraproteins	40 – 60	24	treat to response
Cryoproteins	40 – 60	24 – 48	treat to response
Toxins	40 – 60	24 – 72	treat to response
TTP / HUS	40	24	to remission

Modified from : Weinstein, in McLeod, Apheresis, Principles and Practice, 3rd edition, AABB press, 2010

Interval between Exchanges : Why we do what we do...

Alteration in Blood Constituents by a 1- PV Exchange

Constituent	% decrease	% recovery 48 hrs post exchange
Clotting factors	25 – 50	80 – 100
Fibrinogen	63	65
Immuneglobulins	63	45
Paraproteins	20 – 30	Variable
Liver Enzymes	55 – 60	100
Bilirubin	45	100
C3	63	60 – 100
Platelets	25 – 30	75 – 100

Modified from : Weinstein, in McLeod, Apheresis, Principles and Practice, 3rd edition, AABB press, 2010

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Complications

1) Hypotension

S/S: lightheadedness **↑ pulse rate**

dizziness **shallow breaths**

faintness **perspiration**

Treatment: ↓ head of bed, ↑ foot of bed, Give NS, Monitor VS,

Look for drugs (ACE inhibitors)

2) **Vasovagal syncope**

S/S: ↓B/P **↓ pulse rate**

feeling of apprehension, distress, doom

nausea, Pallor, sweating, syncope, convulsions

Treatment: same as hypotention

Complications - 2

3) **Hypocalcemia**

S/S: Parasthesia, perioral tingling

Chills/vibrations of chest wall

Severe citrate toxicity - tetany, heart rhythm disturbances

Treatment:

↓AC flow rate to the patient
Decrease blood flow rate
Give Ca tables (Tums)

Give dairy products

For severe citrate toxicity – stop procedure, IV Calcium

Complications - 3

4) **Allergic reaction:**

Etiology: blood products/ ethylene oxide/ACE inhibitors

S/S: hives
swelling (eyes,lips, tongue)
rash
breathing difficulties
flushing, hypotension (m/p ACE inhibitors)
burning eyes, periorbital edema (m/p ethylene oxide)

Treatment:

Pause procedure

Give medication per order: Antihistamines, corticosteroids, epinephrine

Discontinue procedure if no improvement

Complications – 4

5) **Other side effects:**

***Vascular access: hematoma, phlebitis, infection**

***Air embolism**

***Loss of blood components: → bleeding**

***Thrombocytopenia (30% decrease)**

***Hypofibrinogenemia (50% decrease)**

TABLE II. Adverse Reactions of Therapeutic Apheresis

Reaction	% of procedures
ACD Toxicity	3.0
Vasovagal Reactions	0.5
Vascular Access Complications	0.15
FFP Related Reactions	0.12
Hepatitis B (from FFP)	0.06
Arrhythmias	0.01
Hemolysis	0.01
Single death (from underlying disease)	0.006
Total	3.856

TABLE III. Severity of Adverse Reactions (%)

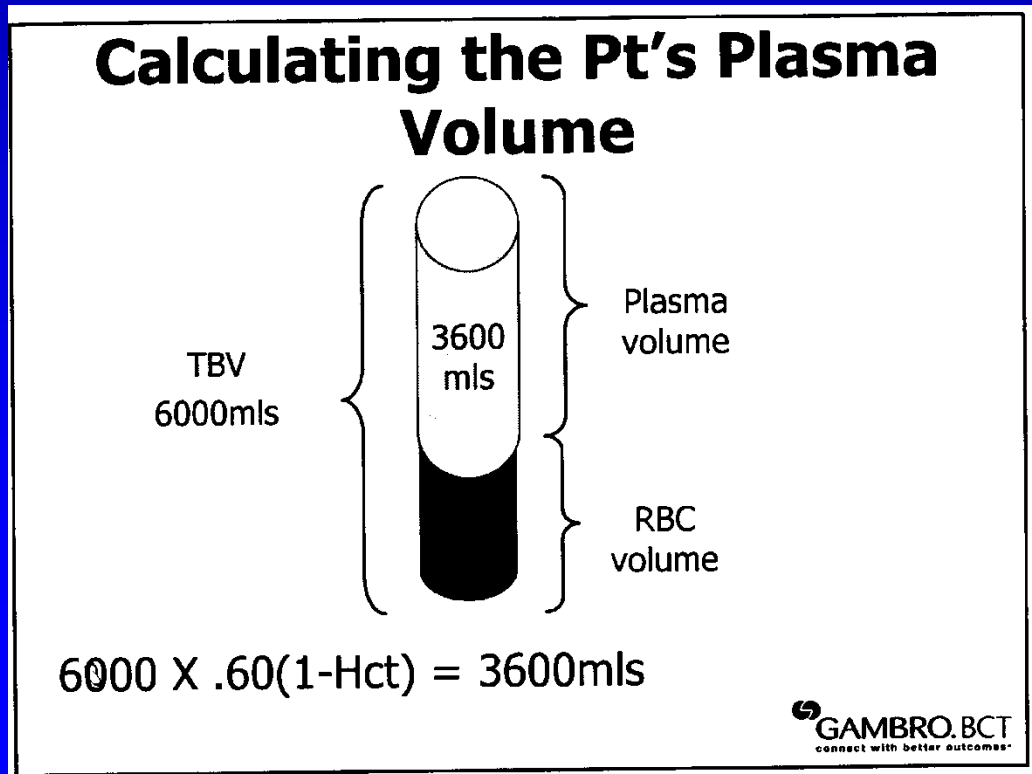
Reaction	Mild	Moderate	Severe	Fatal
ACD toxicity	85	12	3	0
Vasovagal reactions	1	73	26	0
Vascular access complications	39	49	12	0
FFP related reactions	36	53	11	0

Journal of Clinical Apheresis 16:3, 130

Therapeutic Apheresis Math

Blood/Plasma Volume

- Total Blood Volume (TBV):
  - -Height
  - -Weight
  - -Sex
- Plasma Volume
  - -TBV x (1-Hct)



Blood/Plasma Volume Calculations

- **Calculate treatment dose**
  - **TPE and RBC Exchange replacement fluid volumes**
  - **Cytoreduction and PBSC collections**

- **Determine patient tolerance/safety**

  Calculating % of extracorpreal volume

  - The amount of blood outside the patient's body at any given time
  - Should not exceed 15% of patient's total estimated blood volume
  - Depend on the technology/procedure, it varies between 131-284 ml

Blood Volume Calculations

Total Blood Volume (TBV)

- **Three Methods:**
  - Gilcher's rule of Five for adults
  - Nadler's formula for adults
  - Pediatrics: ml/Kg
- **Volume Adjustment:**
  - Pregnancy, Muscularity, Obesity

TBV - Nadler's Formula

Nadler's Formula

- Males:

0.006012 X height^3 (inches)
+ 14.6 X weight (pounds)
+ 640

= TBV in mLs

Nadler's Formula (cont.)

- Females:

0.005835 X height^3 (inches)
+ 15 X weight (pounds)
+ 183

= TBV in mLs

Nadler's Formula (cont.)

Example: Male height: 62 inches
weight: 190 lb

	0.006012 X 238328	(1458)
+	14.6 X 190	(2774)
+	604	(604)
=		4836 mL

TBV - Gilcher's Rule of Five

Gilcher's Rule of Fives

Blood Volume (mL/kg of body weight)

Donor	Fat	Thin	Normal	Muscular
Male	60	65	70	75
Female	55	60	65	70
Infant/child	-	-	70/80	-

Estimated Blood Volume

Table 16-2. Estimated Blood Volume

Patient	Estimated Blood Volume
Adult (not pregnant)	70 mL/kg (Estimated plasma volume: 40 mL/kg)
Pregnant female	80 mL /kg
Child	80 mL/kg
Full-term neonate	85 mL/kg
Preterm neonate	100 mL/kg

TBV Adjustments

- **Fat** has 11-22 ml of blood per kg
  - Obese: may use lean body weight plus 20%
- **Muscle** has 92 ml of blood per kg
  - Body builders: increase TBV

- **Pregnancy**
  - **Plasma and RBC Volume Increases:**
    - **Amount of increase is dependent on the number of fetuses, number of previous pregnancies, and gestation. Plasma volume increase plateaus at 32 weeks and RBC increase plateaus at 34 weeks.**
    - **Plasma volume increase is greater than the RBC volume increase**
      - **Anemia of pregnancy!**

Treatment Dosage

A "typical" order for TPE:

- **Remove 3L of plasma (based on 1PV exchange; regular size 70kg patient; PV ~40 mg/kg)**
- **Replacement fluid per disease : for example**

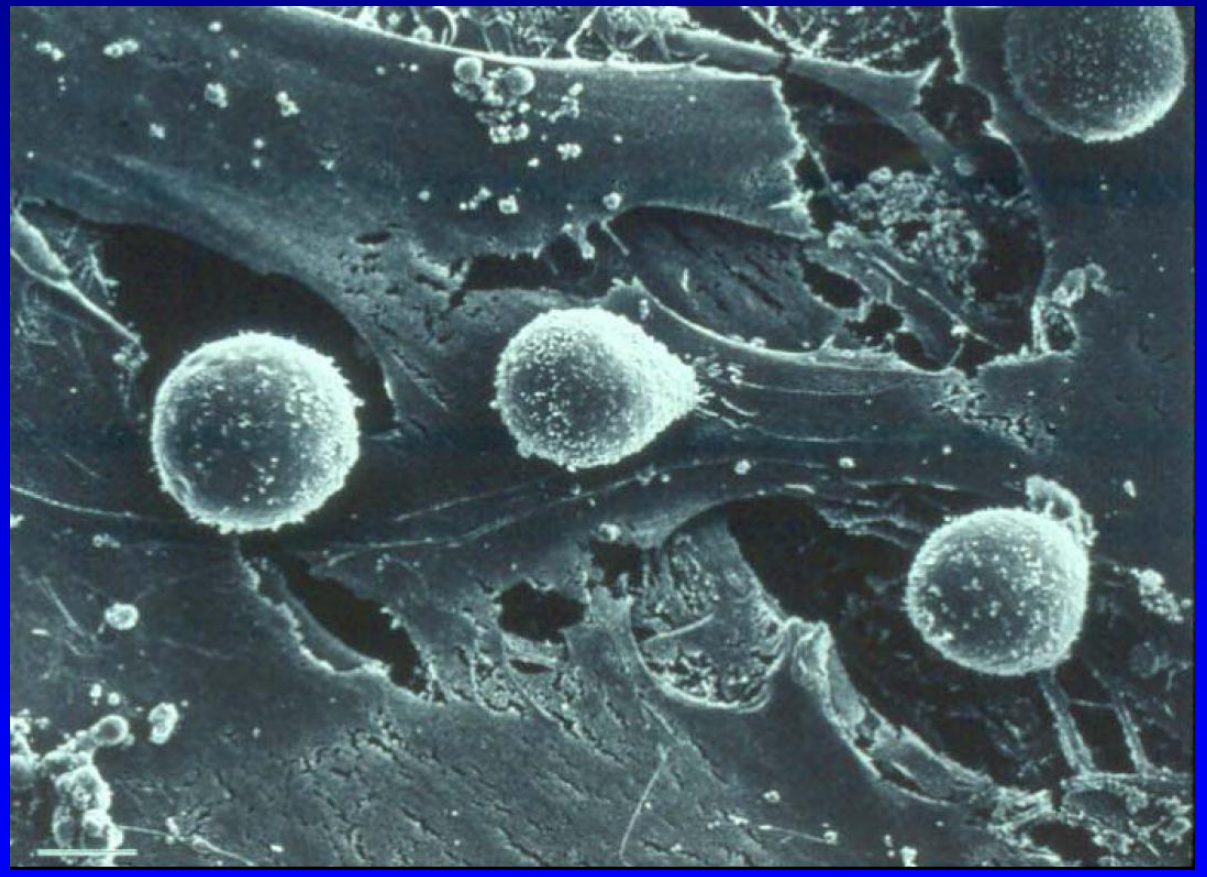
TTP: Replace 100% with 3L FFP (~ 12 units , 250cc each)

Or GBS: replace 100% with 3L 5% albumin (each alb. 250cc =12 bottles)

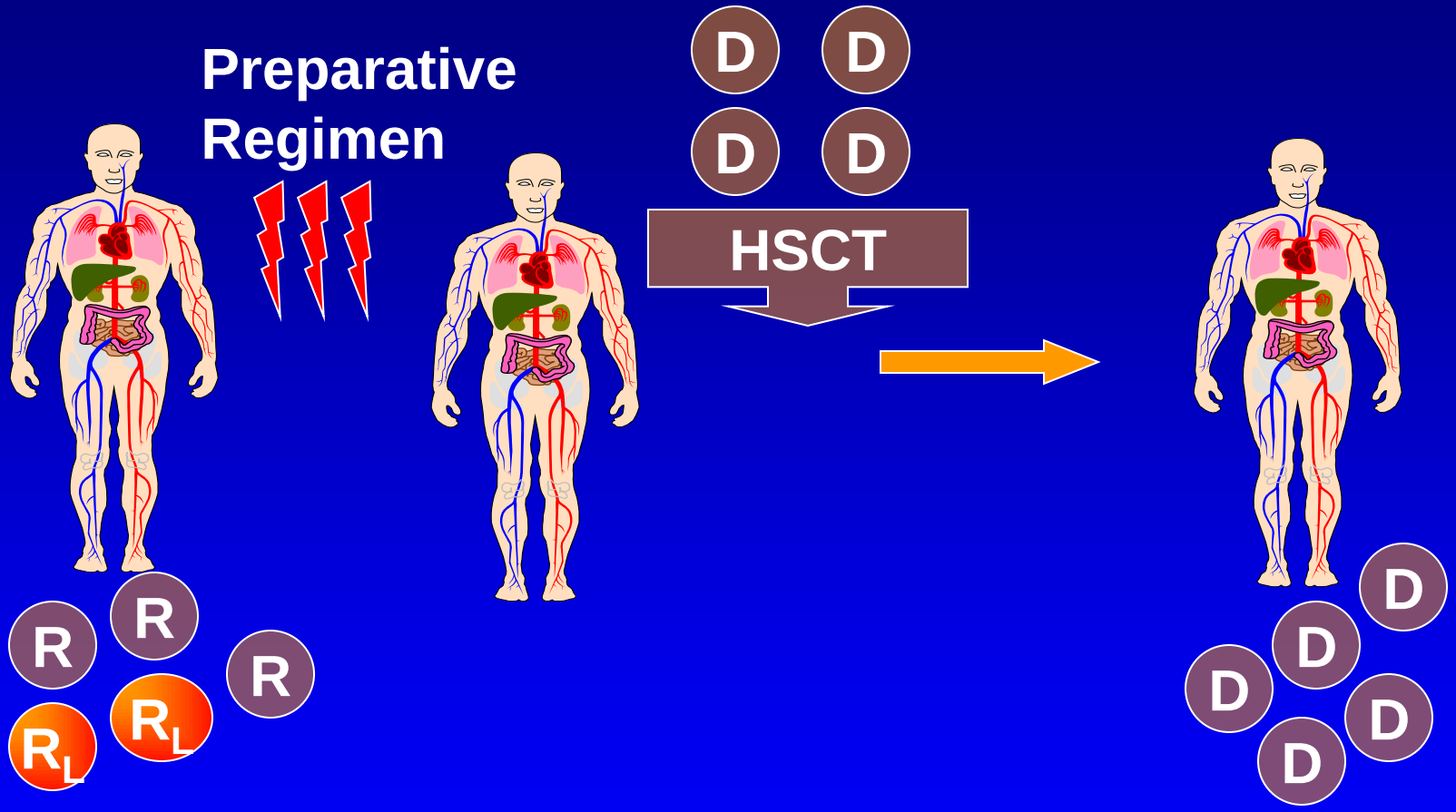
- **Frequency : per disease: for example**

TTP: daily; GBS: QOD x 5 treatments

Peripheral Blood Stem Cell (PBSC) Collections: **Why, What, When**

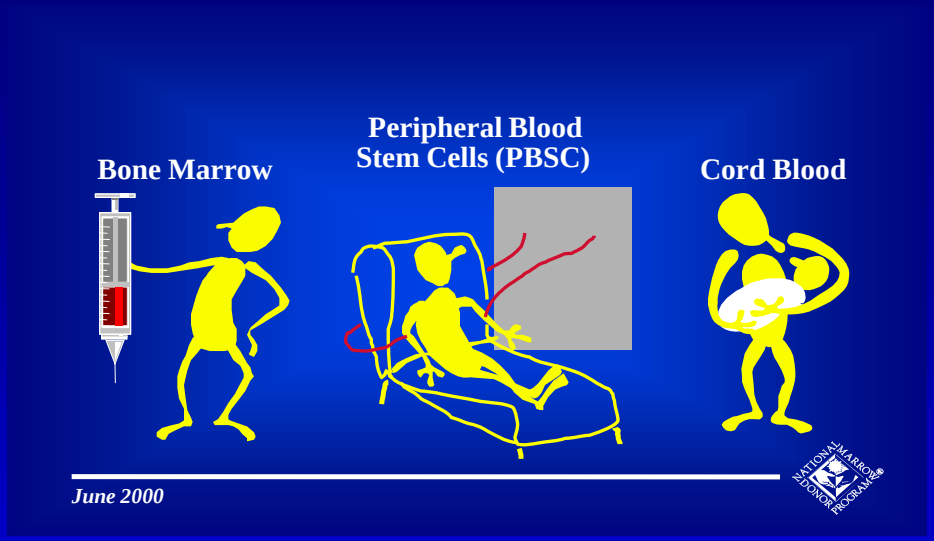


Hematopoietic Stem Cells Transplant



Preparative Regimen: TBI, Chemo
Role: eradicate cancer, immunosuppression to allow engraftment (allotransplant)

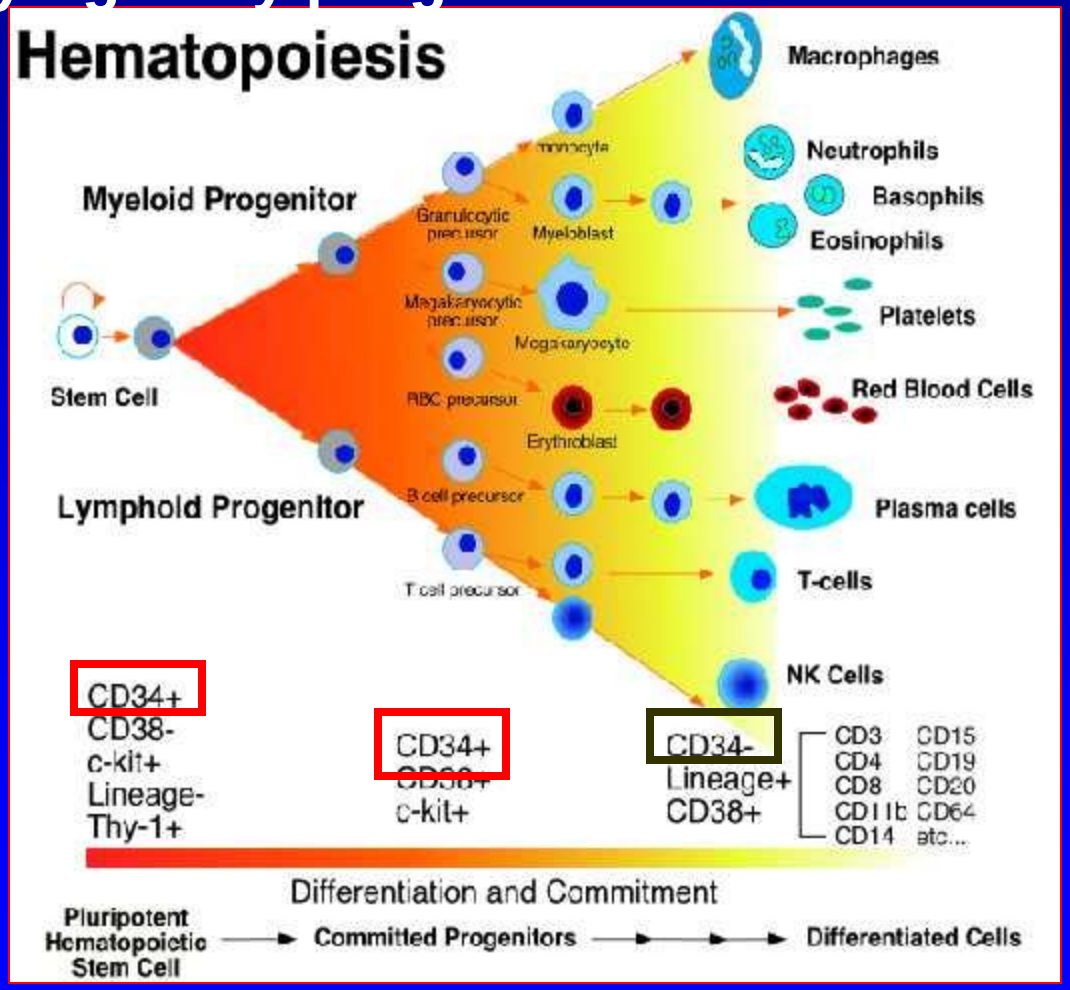
Sources of Hematopoietic Progenitors Cells



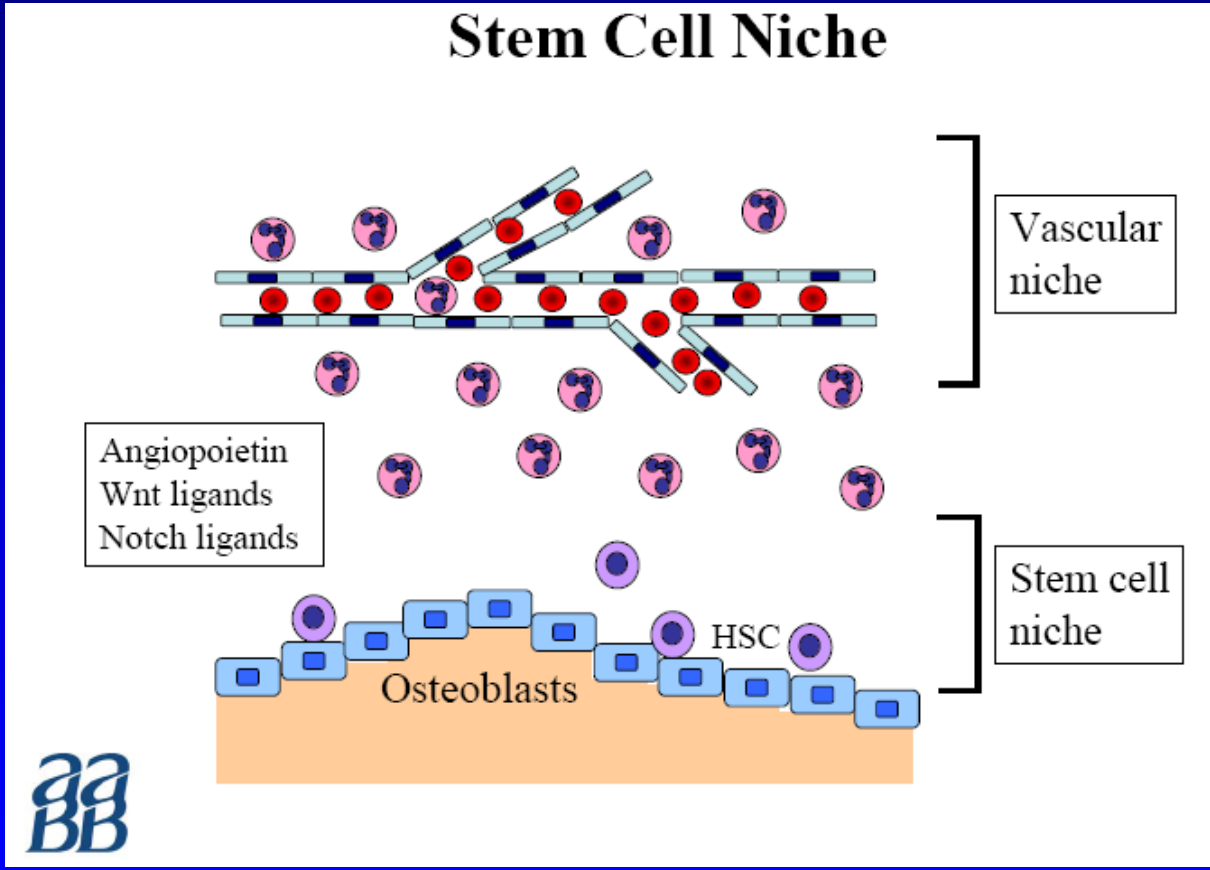
	Bone Marrow	Peripheral Blood	Cord Blood
Advantage	• Large number of cells • Lower number of mature T-cells	• Easy to collect • Multiple collection	• Collection has no risks • Readily available
Disadvantage	• Surgical procedure • General anesthesia	• Treatment with G-CSF • Bone pain • May require central venous access	• Low cell dose • No multiple collection

HSCs Quantification: Why CD34

CD34 remains the major surface marker for identifying early progenitors



So, we know “who and what” we need…



How do we collect the dose we need ?

In Steady State

- HPCs circulating in very low concentration:

  CD34 is present on ~1.5% (1-3%) of the BM Cells & <0.1% of WBC in PB .
- CD34 concentration in PB is 2-5X10^6/L
- For transplant recipient 70kg - you will need

  2-5X10^6/kg =140-350X10^6 CD34
- 140-350X10^6 CD34: you need to collect

  2-5X10^6/L 28-175 L blood
- Apheresis machines collect 50-70% CD34 cells from the blood ⇒ 56-350 L blood would have to be processed
- Impractical, expensive and probably not possible – something has to be done…

Increase the Yield of Collection

- Increase number of CD34 cells - mobilization
- Increase volume of blood processed each collection
- Increase number of collections

Mobilization of PBSCs

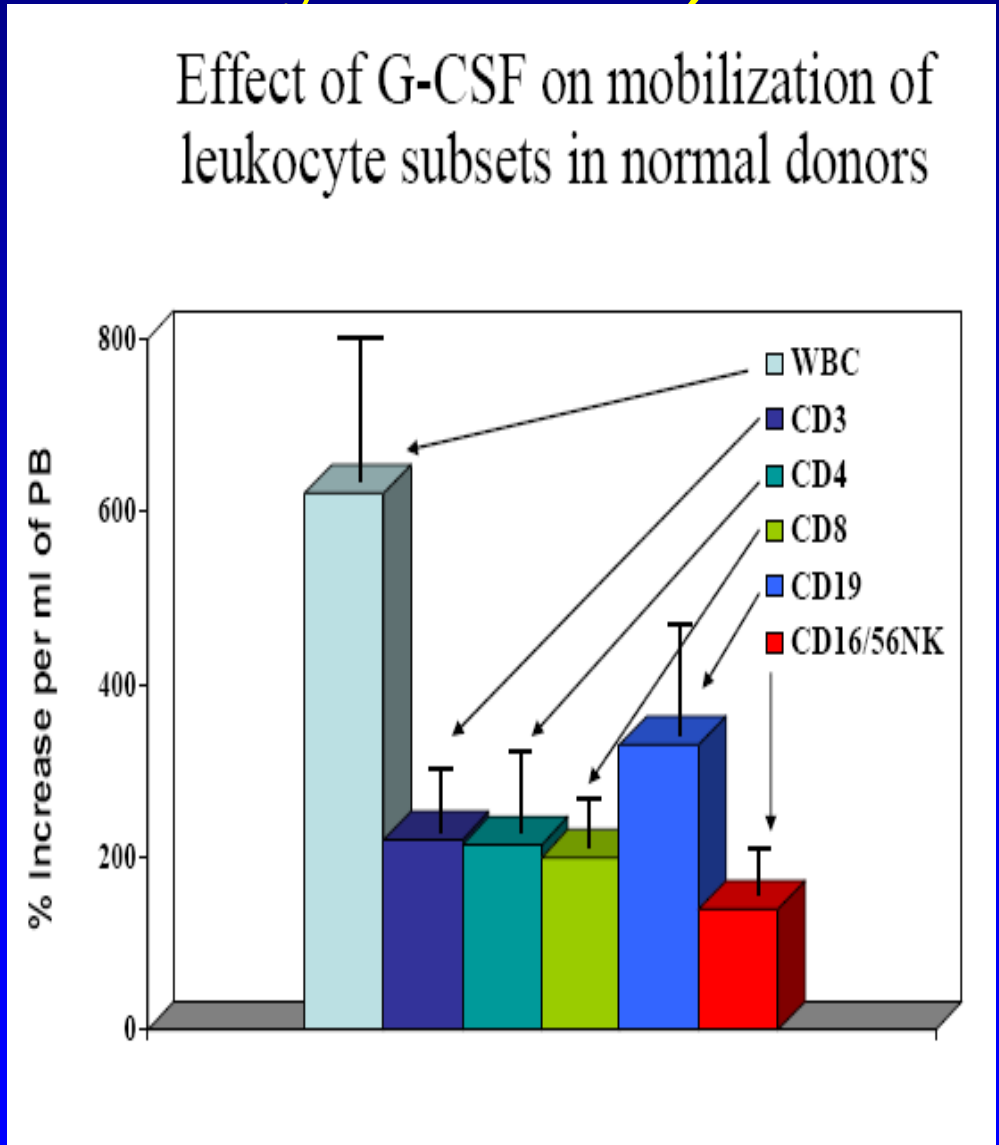
- **Hematopoietic Growth Factors:**

  FDA approved: Granulocyte colony stimulating factor (G-CSF), Granulocyte/macrophage stimulating factor (GM-CSF)

- **Chemotherapy (not for allogeneic donors)**
  - **HPCs ↑↑ (X20-25) during early hem. Recovery phase after chemotherapy-induced-marrow-aplasia**
- **AMD3100 (Mozobil™, plerixafor)**
  - **Potent and selective inhibitor of CXCR4**
  - **Reversible inhibition of the binding of stroma-derived factor (SDF-1α) to its receptor CXCR4**

Hematopoietic Growth Factors – WBC Effects (Healthy Donors)

- **WBC, gran. ↑ within 12-18H post first dose**
- **Usually WBC ↑ to 30-40 x10^9/L**
- **Gran. will stay ↑as long as daily dose is continued**
- **Lymphocyte , monocyte count ↑ slightly**



Hematopoietic Growth Factors – CD34 Effects (Healthy Donors)

- **Do not ↑ until 3-4 daily doses are given**
- **Maximum ↑ after 4-5 doses**
- **After that- ↓ even if continue G-CSF**

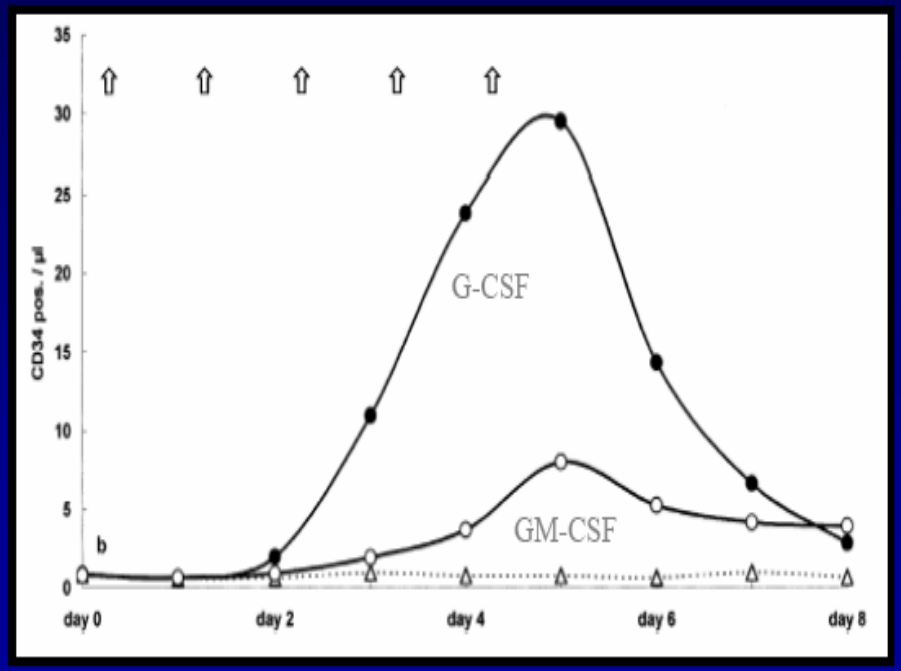
⇒Window of collection is very narrow

⇒Most centers will start collections 12-24h post 3-5 days of G-CSF injection

Hematopoietic Growth Factors – CD34 Effects – Cont.

- **Therapeutic dose for 5 days: CD34 ↑ 10-30 fold (w/chemo – 50-200)**
- **Peak CD34 cell count on D4-5: 20-100/μL**
- **Wide interindividual variability**

Kinetics of CD34 mobilization: G-CSF and GM-CSF



Fischmeister et al, Ann Hematol, 1999

Hematopoietic Growth Factors – CD34 Effects - Cont.

- **Preharvest CD34 cell concentration in the donor's blood is predictive of the total yield of progenitor cells**
- **In general, a peripheral blood CD34 cell concentration of 10 /μL can be expected to result in a yield of at least $1X10^6$/kg**

- **Other factors: gender (M>F), age (<65 better yield) , prior chemo/radiation**

So, When to start the collection ?

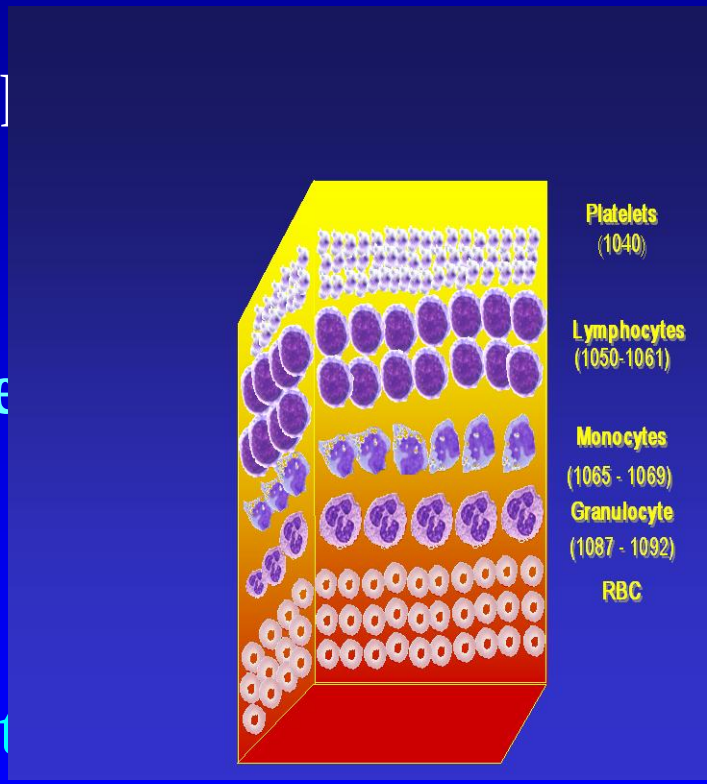
- **At least 4-5 days of G-CSF injection**
- **↑ WBC: 30-40 x10^9/L; 5-10 after chemo,**

  Peds lower
- **Preharvest peripheral blood CD34 cell concentration of at least 10 /μL**

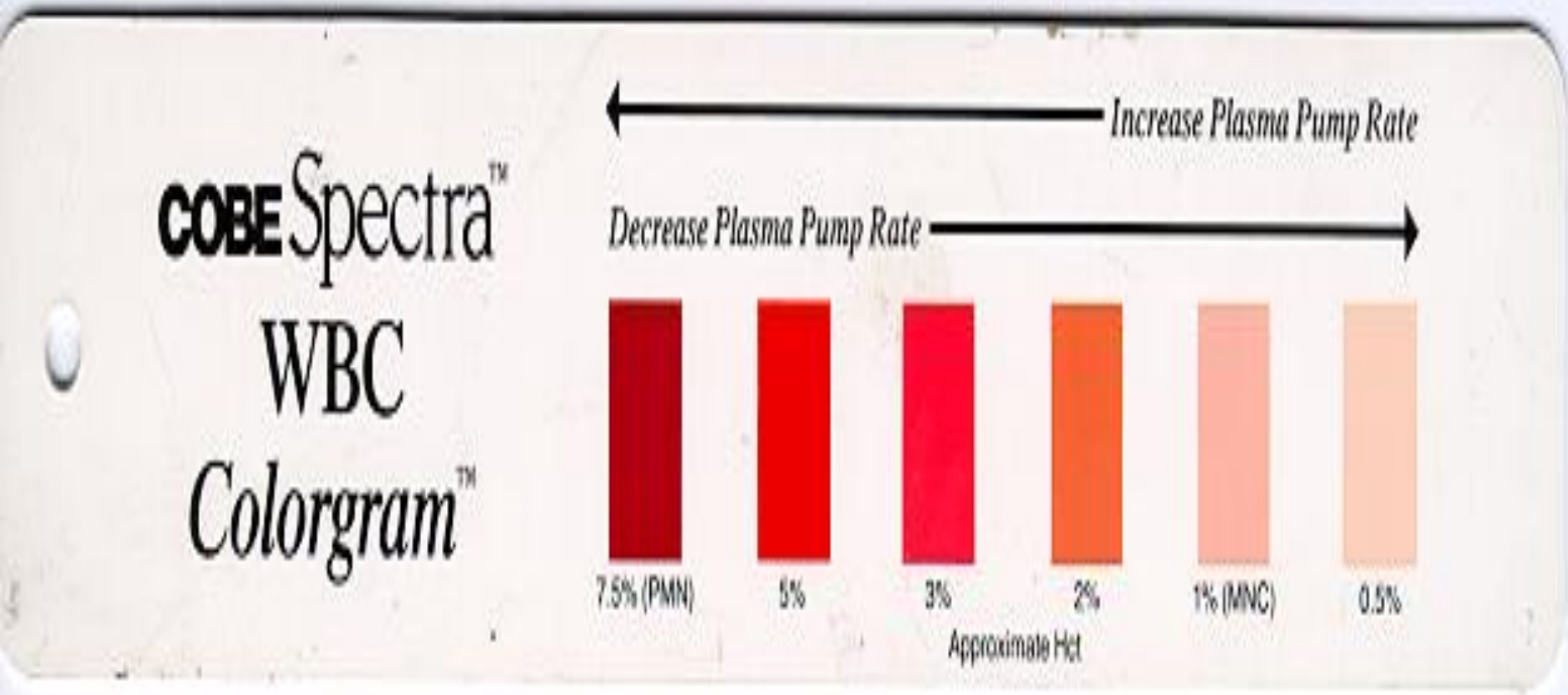
  (allo higher; auto- lower …the important thing is to set a threshold!!!)
- **Range of reported triggers: 5-20 CD34+ cells/ μL**

HPC Collections –Technical Aspects

- **Long procedures**
- **Extracorporeal Volume (ECV):** high with MNC sets; Should not exceed 15% of patient's total estimated blood volume
  → **Pediatrics (<20kg) – RBC prime**
- HPCs are similar in size and density to lymphocytes and monocytes
  → **HPCs are collected with large number of lymphocytes and platelet**



HPC Collection Technichal Aspects-Guide



Post Collection Donor Issues

- **Platelets**
  - **Each collection, a donor loses ~$4x10^{11}$ plt**
  - **Plt count ↓ 30% (in product + G-CSF suppression)**
  - **After 2 collections, plt <100,000 in 20-23% of donors**
  - **Delayed plt recovery (as oppose to immediate in plateletpheresis donors):**

    start to rise only ≥2 days

    return to normal 7-10 days post collection

    pre-donation baseline by 1 year post donation
  - **Donors with low platelet counts are at potential risk from bleeding and remain at risk for up to 1 week**

Miller, BBMT 2008; Tassi BMT 2005

Collection Donor Issues
Side Effects of Mobilizing Agents

Agent	*Common toxicities*	*Uncommon toxicities*
G-CSF	**Bone pain**	**Splenic rupture**
	Low grade fever	**Thrombosis (CVA, MI)**
	Headache	**Flare of autoimmune disease**
	Injection site reaction	**Precipitation of sickle cell crisis**
	Splenic enlargement	
GM-CSF	**Bone pain**	**High fever**
	Low grade fever	**Hypotension**
	Headache	**Dizziness**
	Injection site reaction	
	Fluid retention	
AMD3100	**Bloating, Flatulence**	**Premature ventricular contractions**
	Injection site reaction	
	Paresthesias	

Post Collection Donor Issues

G-CSF long term safety

- Available reports from single institutions with f/u for as long as 7 years have not revealed an increased risk of developing leukemia or myelodysplasia after HPC mobilization

Cavallaro, BMT 2000; anderlini BMT 2002, Tassi BMT 2005

- F/u of 3928 unrelated donors in a single center demonstrated incidence of leukemia among donors that was similar to the expected rate in an age-adjusted control population

Holig blood 2009

- Prospective trial of 2408 unrelated donors from NMDP – no cases of AML of myelodysplasia

Pulsipher Blood 2009