Blood Transfusion and Hemotherapy

Pimpun Kitpoka, M.D.

Associate Professor, Blood Bank
Faculty of medicine, Ramathibodi Hospital,
Mahidol University.

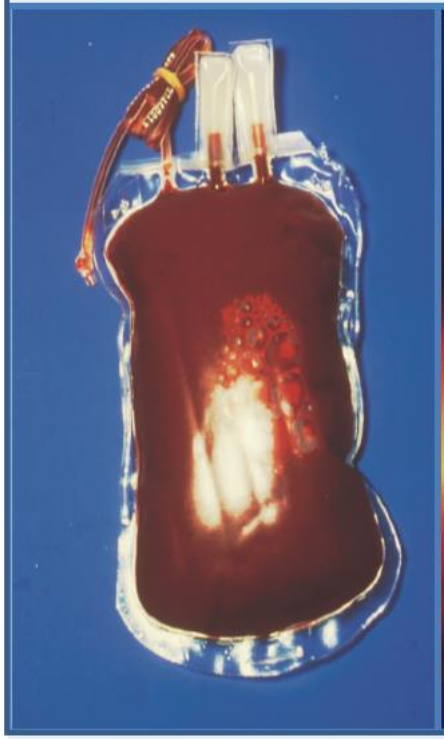
Presentation Outline

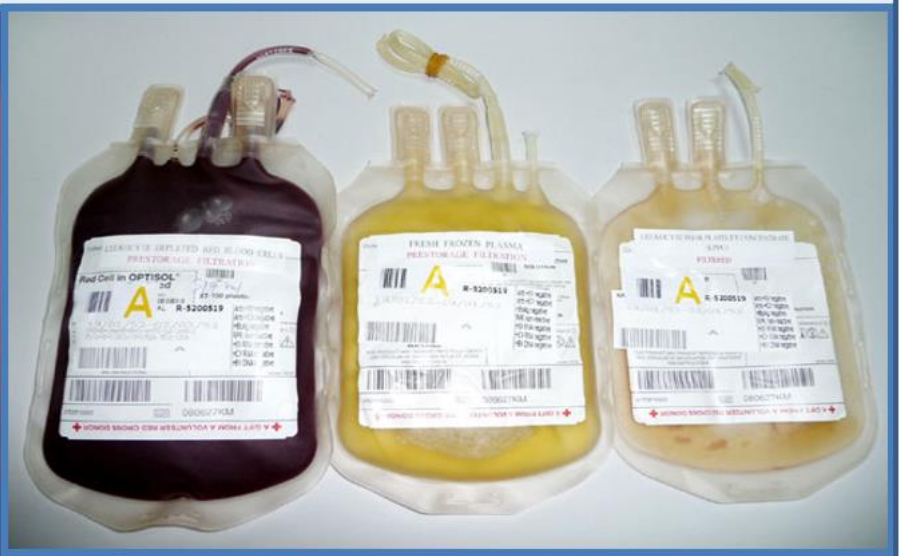
- Type and appropriate use of blood components
- Blood transfusion in special clinical settings
  - ABO-compatible transfusion
  - Platelet refractoriness
  - Transfusion of irradiated blood
  - Transfusion in oncology and transplant patients
  - Emergency blood and transfusion support for trauma
  - Neonatal and pediatric transfusion
  - Transfusion in thalassemic patient
- Transfusion reaction
- Hemotherapy

I Blood Component Therapy

Sources

- **Whole blood donation**





Single unit of whole blood		
RBC	Plasma	Platelet

II Blood Component Therapy

Sources

- Whole blood donation
- Hemapheresis

- Selectively removal of desired component
- Possible to process larger dose of desired component from only one donor

Principle

Donor or patient

Removal of whole blood

Return of the remaining component

RBC, WBC, Plasma

Separation into components

Retention of the desired components

Platelet

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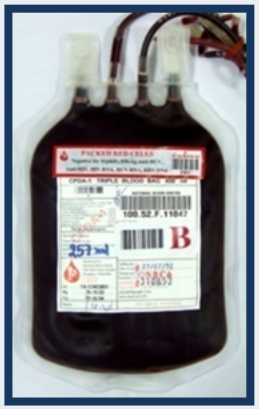
III Blood Component Therapy

- Whole blood derived
  - RBC
  - plasma
  - platelet
- Hemapheresis
  - single donor platelet
  - single donor granulocyte
  - single donor plasma
  - single donor red cell
  - multi-component collection

I Blood Components and Plasma Derivatives

Component / Product	Composition	Volume	Indications
Red Blood Cells 	RBCs approx. Hct 75% reduced plasma, WBCs, platelets	250 mL	Increase red cell mass in symptomatic anemia (WBCs and platelets not functional)

Deleterious Effects of WBC on the Quality of Blood Components

Immunologic effects	Infectious risks
• Degeneration, necrosis, apoptosis o Substances secreted into plasma o Cytokines cause febrile transfusion reactions	• Cell-borne viruses o Cytomegalovirus (CMV) o Epstein-Barr virus (EBV) o Human T-lymphotropic virus types I and II (HTLV-I/II)
• Presentation of foreign HLA antigens to host immune system o Leads to anti-HLA antibodies o Platelet refactoriness o Febrile transfusion reactions o Issues with transplants	• Prions o Variant Creutzfeldt-Jakob disease (vCJD) • Bacteria

Method of Leukoreduction

Method	% WBC Removal	Residual WBC
Centrifugation buffy coat removal	70-80%	10^8
Filtration	>99.9% ($3\log_{10}$)	10^5-10^6
AABB Council of Europe	< 5×10^6 WBC/ product < 1×10^6 WBC/ product	

Potential Benefit from Leukocyte Reduced Blood Component

Indication	Residual WBC	Method
• Prevention of febrile non-hemolytic transfusion reaction	< 5×10^8	Centrifugation Filtration
• Prevention of HLA alloimmunization Platelet refractoriness	< 5×10^6	Filtration
• Prevention of CMV, EBV, HTLV infection	< 5×10^6	Filtration
• Reduction of bacterial contamination	< 5×10^6	Filtration

Febrile nonhemolytic transfusion reaction

Cytokine release	Prevention	
	Prestorage	Poststorage
During transfusion donor WBC recipient WBC	 effective less effective	 effective less effective
During storage from donor WBC (> $3x10^8$ / unit)	effective	less effective

- More common in patients receiving platelets than RBC (18 - 30 % VS 0.2-6.8%)
- Higher prevalence in multitransfused patients

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HLA Alloimmunization

	Prestorage	Poststorage
WBC	effective	effective
Fragmented WBC during storage	effective	ineffective

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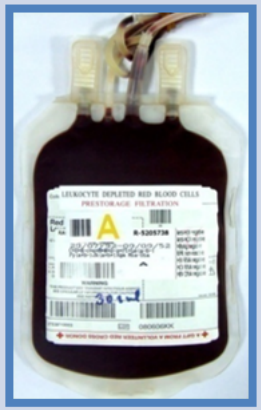
II Blood Components and Plasma Derivatives

Component	Composition	Volume	Indications
RBCs Leukocytes reduced, by filtration or centrifugation 	>85% of RBC volume <5x10^6 WBCs, minimal plasma	250 mL	Increase red cell mass decrease the likelihood of febrile reactions, immunization to HLA, CMV transmission

RBC Transfusion Trigger?

- **There is no standard trigger for RBC transfusion.**

  The trigger should always be evaluated in the context of a multiplicity of factors including rate and amount of blood loss, cardiopulmonary reserve, rate of development of anaemia.

- **Acute blood loss ≥ 15% total blood volume (TBV)**

- **When Hb is < 8 g/dL, RBC transfusion may be beneficial in symptomatic patients or ongoing blood loss.**

- **Pre-operative transfusion is rarely required when Hb > 10 g/dL**

- **One unit of RBC increase the Hb level of an average–sized (70 kg) by 1 g/dL**

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Patient Blood Management in Peri-operative Setting

- **Preoperative evaluation to identify and correct risk factors for bleeding should be done to minimize the need for transfusion.**
  - **Medication that can affect coagulopathy (warfarin, aspirin)**
  - **Congenital or acquired blood disorders such as haemophilia, TTP and liver cirrhosis.**
- **Correction of anemia before surgery with other measures**
  - **Iron replacement**
  - **Erythropoietin**
- **Reduce allogeneic blood usage during surgery**
  - **Preoperative autologous donation**
  - **Intra-operative hemodilution**
  - **Intra-operative cell salvage**

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Surgical Blood Orders

- **Procedures usually require transfusions**
  - **Preoperative** — **crossmatched unit in OR**
  - **Autologous blood** — **autologous unit in OR**

- **Procedures rarely require transfusion**

  Inappropriate for preoperative crossmatch
  - **Type and screen (T/S)**

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Crossmatch to Transfusion Ratio (C:T ratio)

- C : T ratio > 2 : 1 means excessive requests for crossmatches

- How to decrease C : T ratio
  - establishing a guideline for transfusion or a maximal surgical blood order schedule (MSBOS) using data about past blood usuage
  - use of Type and screen (T/S), recommended for surgical procedures which blood usuage is < 0.5 unit

Maximum Surgical Blood Order Schedule (MSBOS)

- **Gynecology**

AP Repair	1 unit
D&C	T/S
Hysterectomy-abdominal	T/S
Hysterectomy-radical	2 units

- **Obstetrics**

C-Section hysterectomy	2 units
C-section	T/S

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I Type and Screen

	Crossmatched	T/S
• ABO typing	done	done
• Antibody screening	done crossmatch ←	done if negative → T/S if positive

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II Type and Screen

	Crossmatched	T/S
• Crossmatch	• done at RT, 37 °C and Coomb' test	• not done
	• release blood to be kept available in OR	• appropriate blood are kept in blood bank and available for immediate release
		• 99.9% assurance of safety

Advantages of Autologous Blood

- Prevents transfusion-transmitted disease
- Prevents red cell alloimmunization
- Supplements the blood supply
- Provides compatible blood for patients with alloantibodies or rare blood groups
- Prevents some adverse transfusion reactions

Predeposit for Scheduled Surgery

- every 3 days
- last phlebotomy : at least 3 days before operation
- usually collect each unit 1 week apart

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Intraoperative Hemodilution

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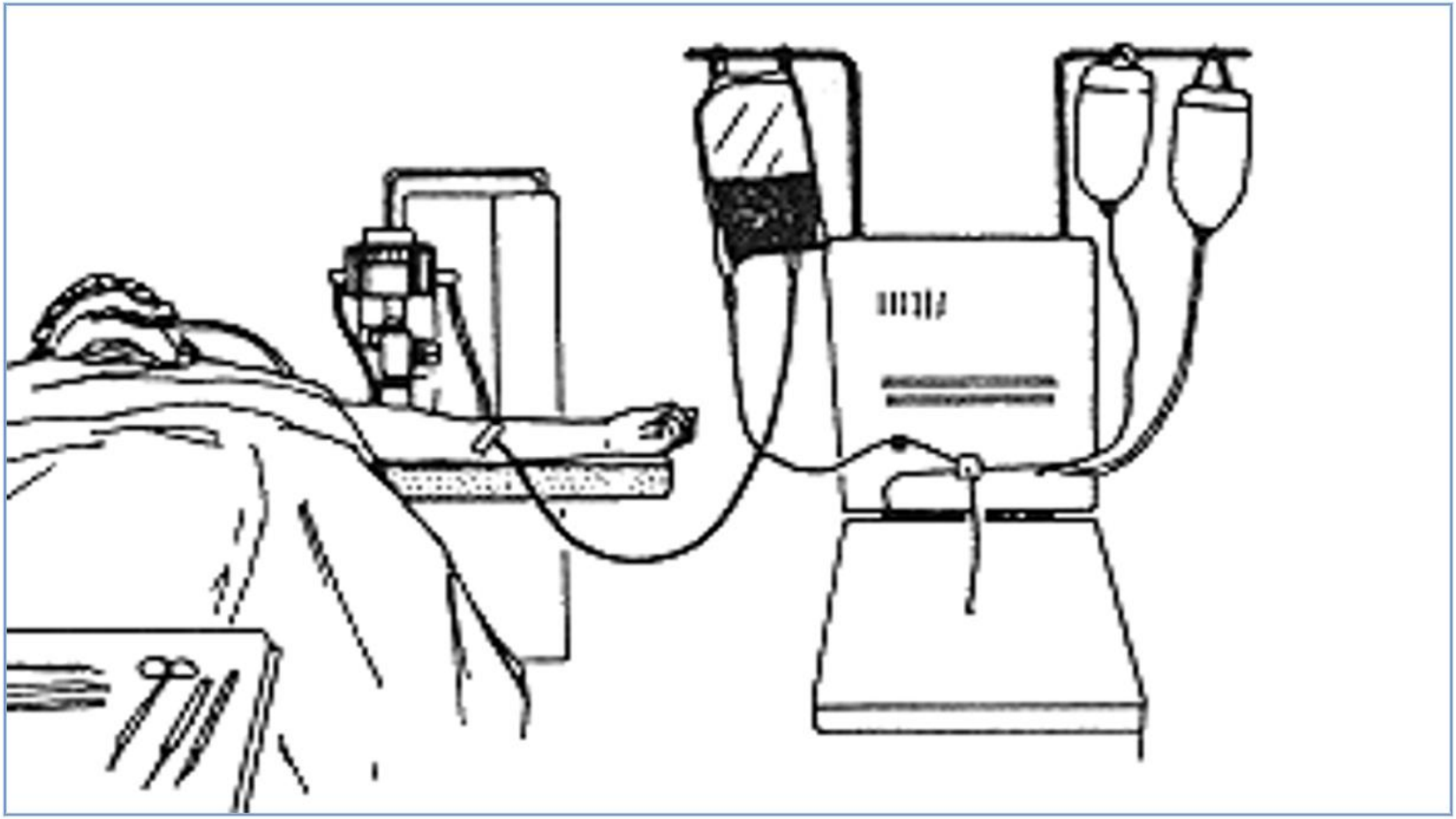
Intraoperative Salvage



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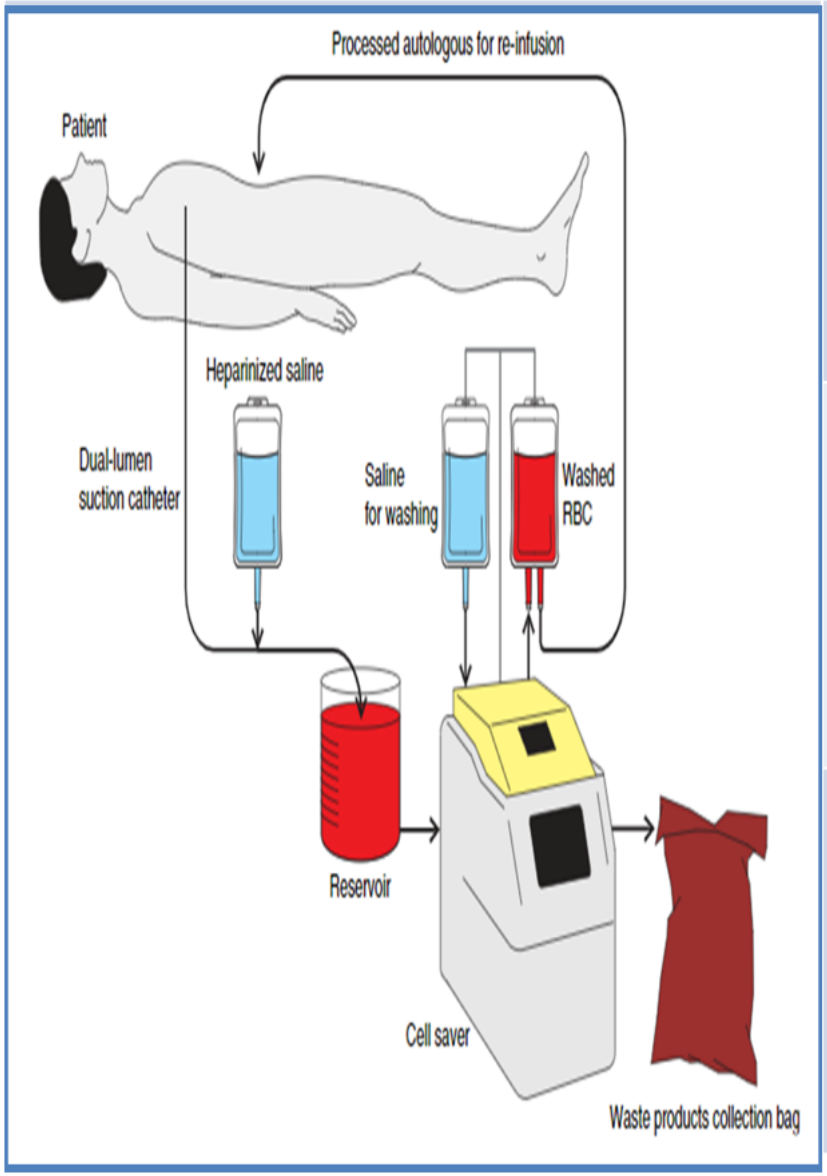
I Perioperative Blood Salvage Program



- **Cell saver work by suctioning blood from the surgical field using low levels of suction to avoid hemolysis, aspirating fat, amniotic fluid, gastric fluid, or bone fragments.**
- **Washing the collected blood to remove debris, and reinfusing the washed RBCs suspended in saline back to the patient either continuously or collected in a bag and reinfused.**
- **It is most useful in cases which a lot of blood is shed, recommended for patients lost at least 20% of blood volume in cardiovascular, orthopedic surgery, liver transplantation.**

II Perioperative Blood Salvage Program Contraindication

- **If the surgical field is grossly contaminated with bacteria (e.g., bowel perforation), washing in conjunction with leukoreduction filters reduced the bacterial load by 99%.**
- **In cases in which malignant cells might be reinfused from tumor resection, the risk of metastasis is theoretical. Malignant cells are typically much larger than blood cells and would be likely to get trapped in the standard blood filter or leukoreduced filters.**
- **The greatest risks have to do with the reinfusion of the collected blood. Blood that is not properly washed may be hemolyzed or contain inflammatory cytokines, which may contribute to DIC in the recipient.**
- **Possibility of introducting an air embolism that can get lodged in lung vessels if the bag is not properly vented.**

Berg M. and Justison G. Transfusion 2013;53:1888-1893

Red Cell Transfusion in Chronic Anemia

- **Most patients are well compensated at their level of anemia and do not required RBC transfusion, especially at Hb >7 g/dl**

- **The cause of anemia should be established before RBC transfusion.**
  - **Specific pharmacological agents (iron, vitamin B12, folate) should be used to correct anemia.**
  - **Erythropoietin should be considered where indicated (e.g., chronic renal failure, anemia of chronic illness)**

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Transfusion of Leucodepleted Blood

- **Patients who have developed febrile non-haemolytic transfusion reactions on two or more occasions**
- **Immuno-compromised CMV-seronegative recipients at risk of CMV transmission, including**
  - **Patients undergoing transplants**
  - **Premature infants**
  - **Infants weighing <1200 g at birth**
- **Patients who are likely to require regular transfusions to reduce the rate of human leucocyte (HLA) alloimmunisation**

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Platelet Product

Individual random donor platelet

Pooled buffy coat removal platelet (4-5 units)

Whole blood derived platelet
Prepared from individual units of whole blood by centrifugation

Apheresis platelet

Single donor platelet from a single donor during 1-2 hour plateletpheresis

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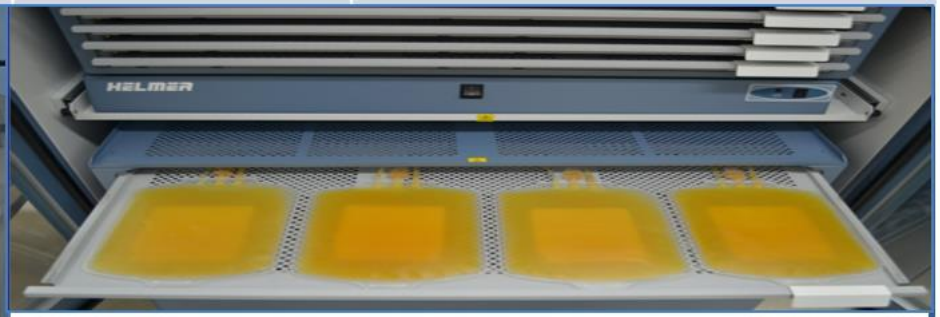
III Blood Components and Plasma Derivatives
Whole Blood Derived Platelet

Component / Product	Composition	Volume	Indications
Pooled Platelets Leucocytes Reduced (LPPC) 	Platelet yield depend on No. of pooled platelet (4-5) $<5x10^6$ WBCs per final dose of pooled platelets	200 – 300 mL	Bleeding from thrombocytopenia or thrombocytopathy Decrease the likelihood of FNHTR, HLA / HPA alloimmunization and CMV transmission



Platelet Incubator

IV Blood Components and Plasma Derivatives
Single Donor / Apheresis Platelet

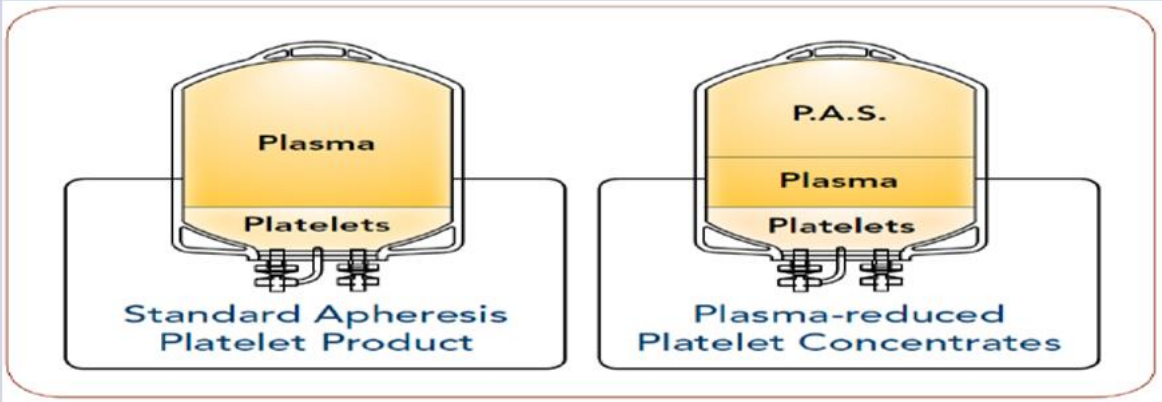
Component / Product	Composition	Volume	Indications
Apheresis Platelets Leukoreduced 	**Platelets ($>3x10^{11}$/unit) plasma $< 1x10^{6}$ WBC**	**200 - 300 mL**	**Same as LPPC HLA / HPA matched platelet IgA-deficiency platelet Rh D negative platelet**

Comparison of Whole Blood Derived and Apheresis Product

	Whole blood derived	Apheresis
Product yield • Platelet Yield • Granulocyte Yield	 $\geq 0.55 \times 10^{11}$ Not available	 $>3 \times 10^{11}$ (x6) $> 0.94 \times 10^{11}$
Donor exposure	Multiple	Single
Risk of alloimmunization and blood transmitted disease	Higher A therapeutic dose is achieved from multiple donors	Lower A therapeutic dose can be achieved from only 1 donor
Cost of production	Lower	More expensive
Ease of leukocyte reduction	Time consuming	Easier
HLA / HPA selection	No	Yes

PAS-Platelet

- A number of crystalloid synthetic solutions known as **Platelet Additive Solutions (PAS)** have been introduced to suspend platelets in the late 1980s, and being used in Europe since 1991.
- The available PAS replace about 65-70% of the plasma volume in a platelet component.



I Potential Advantages of PAS - Platelet

- **Plasma used for platelet storage could directed to other uses such as FFP.**

- **Benefit from plasma reduction in platelet**
  - **Reduction of vasoactive / pyrogenic substances that cause febrile reaction**
  - **Reduction of transfusion reaction from plasma, such as allergic reactions, incompatible plasma.**
  - **Reduced levels of HLA, HNA antibodies, believed to cause transfusion related acute lung injury (TRALI)**

- **Impact on ABO-compatibility practice?**
  - **Reduction of anti-A, anti-B due to dilutional effect of PAS**
  - **? Universal platelet for ABO-incompatible patients (UK : cutoff at 1:128)**

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Transfusion-Related Acute Lung Injury (TRALI)

Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within 6 hours of transfusion, not due to circulatory overload or other likely causes.

HLA antibodies in donor

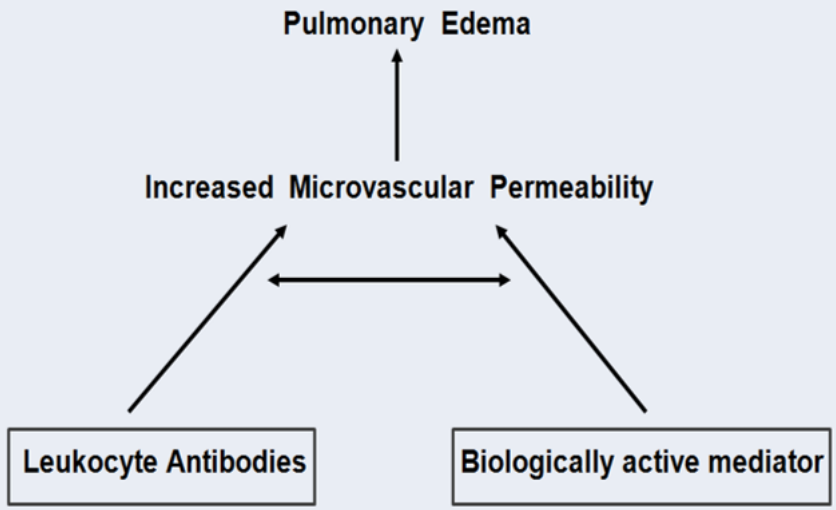
tissue Ag of recipient

Complement

Severe capillary damage

Leakage

Acute non cardiogenic pulmonary edema



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II Potential Advantages of PAS Platelet

- **PAS improves the efficiency of platelet collections**
  - **Additional volume for more plasma component collection / Maximize the capability to collect multiple blood components/ Increase cost effectiveness**
  - **Facilitate pathogen inactivation.**

- **PAS supports 7 day storage of platelets with bacterial detection test.**

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I Platelet Transfusions

- The decision for platelet transfusion should not be based on platelet count alone but should consider the clinical situation and risk factor for bleeding (fever, sepsis, liver disease, renal failure and rapid fall of platelet count).
- The major risk of platelet transfusion is bacterial contamination and life threatening Transfusion related acute lung injury (TRALI)
- Platelet product is available in 2 forms: apheresis platelet and whole blood (WB) derived platelet. Apheresis platelet is prepared from a single donor and contains at least 3.0 x 10^{11} /L platelets suspended in 200-400 mL of plasma.
- Apheresis platelets are recommended to prevent HLA alloimmunisation and platelet refractoriness in patients who require prolonged platelet support

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II Platelet Transfusions

- **ABO antigens are present on platelets, it is preferable to transfuse with ABO compatible platelets**
- **An adult dose of platelet, 1 set of WB derived pooled platelet (4-5 units) or 1 unit of apheresis platelets/10 kg body weight, raise the platelet count by $20x10^9$/L, if there are no other concomitant factors.**
- **Prophylactic platelet transfusion is recommended in patients without risk factors when platelet count is less than 10x109/L and less than 20x109/L with risk factors (sepsis, rapid fall platelet count or coagulation abnormalities)**
- **For dengue fever patients with a rapid fall in platelet count or prolong clotting times, a transfusion trigger at platelet count of 30x109/L is acceptable**
- **For certain procedure at important sites such as intracranial, spinal and eye, the platelet count may need to be kept higher about 80-100$x10^9$/L**

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III Platelet Transfusions

- **Platelet count <50,000 / µL for impending surgery or invasive procedure**
- **Diffuse microvascular bleeding in a patient with documented DIC or transfusion ≥ 1 blood volume and a platelet count <50,000 / µL or laboratory values not yet available**
- **Platelet dysfunction caused by inherited conditions or acquired in renal failure, use of anti-platelet drugs such as aspirin. The platelet count is less useful and the decision to transfusion should be based on clinical circumstances.**

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IV Platelet Transfusions

- **Patients who are refractory to platelet and have class I HLA antibodies should receive class I HLA-matched or crossmatch-selected platelet.**
- **Patients who are refractory to platelet and have HPA antibodies should receive HPA-matched or crossmatch-selected platelet**
- **When leukoreduced WB derived platelet are available, it should be use as equivalent products to apheresis platelets**
- **Female children and females of child-bearing age, who are RhD negative should receive Rh immunoglobulin before, immediately after, or within 72 hours of receiving a RhD-positive platelet component**

Nahirniak et al. Transfus Med Rev 2015; 29:3-13.

Rh Matching

- Platelets do not express Rh antigens, but contaminated Rh-D positive RBC may lead to alloimmunization in Rh-D negative recipients.
- A small but immunogenic dose of RBC can be contained in a platelet unit.
  - 0.036 mL in whole blood derived platelet
  - 0.00043 mL in apheresis platelet
- Rh D negative apheresis platelet / double dose platelets if available.
- Rh IG should be given to D-negative females of childbearing potential and to children if Rh D positive platelet is given. The formation of anti-D could have impact on her future pregnancies.
- A 300-µg dose is sufficient to protect against the immunizing effect of the D-positive RBC contained in platelet products.
- Given the 3-week half-life of IgG, an IV single dose should provide prophylaxis for multiple platelet transfusion over 2 - 4 week period.

Contraindications to Platelet Transfusion

- **Autoimmune idiopathic thrombocytopenia purpura***
- **Thrombotic thrombocytopenia purpura***
- **Heparin-induced thrombocytopenia***

***Consider platelet transfusion with life-threatening bleeding**

- **Bleeding due to coagulopathy only**
- **Bleeding controllable with direct / local pressure**

Transfusion Therapy : Clinical Principles and Practice 2nd Edition, AABB Press Bethesda, Maryland 2005

V Blood Components and Plasma Derivatives

Component / Product	Composition	Indications
Fresh frozen plasma or FFP (200-250 mL)	plasma, all coagulation factors	multiple factor deficiencies , DIC, dilutional coagulopathy, severe liver disease, F V deficiency

* Contraindications of plasma transfusion include blood volume expansion, source of protein for nutritionally deficient patients.

I Fresh Frozen Plasma

- FFP is produced from whole blood or by plasmapheresis, frozen within 8 hours
- FFP contains adequate levels of all soluble coagulation factors (≥70 % fibrinogen, factors VIII , II , VII , V , IX , X , XI , XII and XIII), albumin, immunoglobulin and naturally occurring anticoagulants (protein C, protein S, antithrombin, plasminogen)
- The therapeutic dose is usually 10-20 mL/Kg
- Tests for coagulopathy such as PT, aPPT, INR, platelet counts and fibrinogen level should be obtained to guide decisions on plasma transfusion
- All attempts must be made to identify the underlying cause of coagulopathy

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II Fresh Frozen Plasma

- **FFP is recommended for massive blood transfusion, especially with evidence of microvascular bleeding and associated with significant (>1.5 x of normal range) abnormalities in PT and aPPT.**

- **FFP is indicated in acute DIC associated with microvascular bleeding and bleeding due to coagulopathy associated with chronic liver disease**

- **FFP is indicated for replacement for plasma exchange in thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS),**

- **FFP is indicated for treatment of anticoagulant deficiencies such as protein C, protein S or antithrombin when specific treatment is not available**

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Cryoprecipitate

Coagulation Factor	Per Bag	Half – Life (hours)
Fibrinogen	150 – 250 mg	100 – 150
Factor VIII	80 – 150 U	12
von Willebrand factor	100 – 150 U	24
Factor XIII	50 – 75	150 -300

Lood It Up! (A Quick Reference in Transfusion Medicine) AABB Press Bethesda,Maryland 2006

VI Blood Components and Plasma Derivatives

Component / Product	Composition	Volume	Indications
Cryoprecipitated AHF 	Fibrinogen Factors VIII XIII vWF	15 mL	Deficiency of Fibrinogen, F XIII Second choice in treatment of hemophilia A, vWF disease Fibrin sealant

Cryoprecipitate Transfusion

Cryoprecipitate

Thaw

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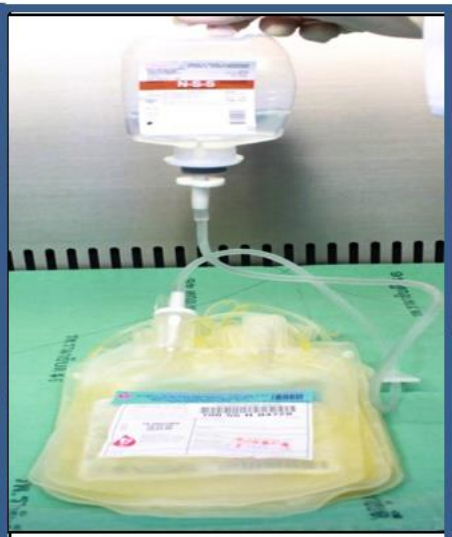
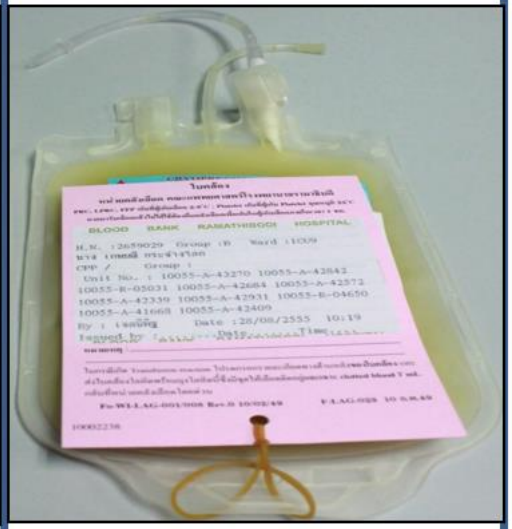


Add 0.9% NSS

Pooling

Pooled Cryoprecipitate



Issue

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Guidelines for the Use of Cryoprecipitate

- **Hypofibrinogenemia (fibrinogen < 100 mg/dl) or dysfibrinogenemia with active bleeding or undergoing an invasive procedure. 1 unit / 5 Kg BW equivalent to 10 units for an average size adult should be administered.**
- **Factor XIII deficiency with active bleeding or undergoing an invasive procedure**
- **von Willebrand disease**
  - **when demopressin is contraindicated or not available**
  - **when Factor VIII conc, which contains vWF, is not available**
  - **when the patient is unresponsive to therapy**
- **Hemophilia A**

Pediatric Transfusion A Physician's Handbook, 2nd (2006).

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IX Blood Components and Plasma Derivatives

Component (Volume)	Composition	Indications
Cryoprecipitate *removed plasma CRP (200 mL)	plasma, reduced FV, VIII, XIII, vWF, fibrinogen	Haemophilia B, Prothrombin complex deficiency

* Contraindications of plasma transfusion include blood volume expansion, source of protein for nutritionally deficient patients

l Products for Treatment of Coagulopathies

Deficiency	Therapeutic products
Fibrinogen	Fibrinogen concentrate Cryoprecipitate
Prothrombin	Fresh frozen plasma
Factor V	Fresh frozen plasma
Factor VII	Factor VII concentrate Recombinant VIIa Fresh frozen plasma
Factor VIII	Factor VIII concentrate Cryoprecipitate
vWF	vWF concentrate Cryoprecipitate

D. Veljkovic, ISBT Science Series 2011;6: 198–205.

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II Products for Treatment of Coagulopathies

Deficiency	Therapeutic products
Factor IX	Factor IX concentrate Prothrombin complex concentrate Fresh frozen plasma
Factor X	Fresh frozen plasma
Factor XI	Fresh frozen plasma
Factor XIII	Factor XIII concentrate Cryoprecipitate Fresh frozen plasma
Vitamin K (II, VII, IX, X)	Fresh frozen plasma (neonates, infants)
Warfarin overdose (II, VII, IX, X)	Prothrombin complex concentrate (older infants, adolescents)
Multiple factor	Fresh frozen plasma Cryoprecipitate Recombinant VIIa

D. Veljkovic, ISBT Science Series 2011;6: 198–205.

I Recombinant Factor VIIa

- **Action : By pass the need for F VIII and IX by enhancing the thrombin generation on activated platelets via direct activation of F X**
- **Clinical Indication**
  - **Food and Drug Administration (FDA) - approved indications**
  - **Off - label indications**
- **Theoretical risk : r VIIa may bind to exposed tissue factor and initiate local thrombosis**

II Recombinant Factor VIIa
FDA Indications

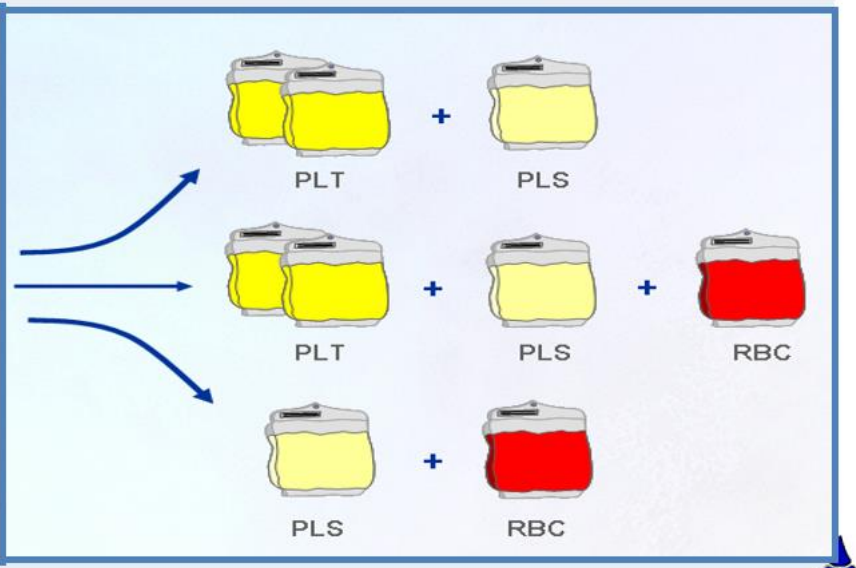
- The treatment of bleeding episodes or prevention of bleeding in
  - Invasive surgery in hemophilia A or B patient with inhibitors to Factor VIII or IX
  - Congenital F VII deficiency
- Dose of 60-120 µg/kg given every 2-3 hours because of its relatively short half-life
- The decision to use should generally be made in consultation with a hematologist

III Recombinant Factor VIIa
Off-label indications

- **Qualitative and quantitative platelets disorders and life threatening bleeding unresponsive to platelet transfusion**
- **Prolonged international normalized ratio (INR) which require rapid reversal**
- **Uncontrollable hemorrhage associated with trauma and liver failure**

Apheresis

• Single collection Single dose platelet Plasma Peripheral stem cell	1 component collection from a single donor during one apheresis session
• Multicomponent collection Double / Triple dose platelet Double RBC Plasma / platelet	Collection of more than one identical or different component from a single donor during one apheresis



Advantages of Multicomponent Collection
Maximal Utilization of Resources

Donor	Multicomponent collection
Male / female / large / high Hb Group O in particular Rare blood type RBC phenotyping	DDRBC  2 units of filtered SDR
Male / high platelet count Group AB in particular HLA / HPA matched	Plasma Double / Triple dose platelet
Female / Male / not large	Whole blood donation

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Minimal Requirement for Single, Double and Triple Dose Platelet

Platelet yield ($x10^{11}$ /L)	Plateletpheresis	
	European Union	USA
Single dose platelet	≥ 2	≥ 3
Double dose platelet	≥ 5	≥ 6.5
Triple dose platelet	≥ 7.5	≥ 9.5

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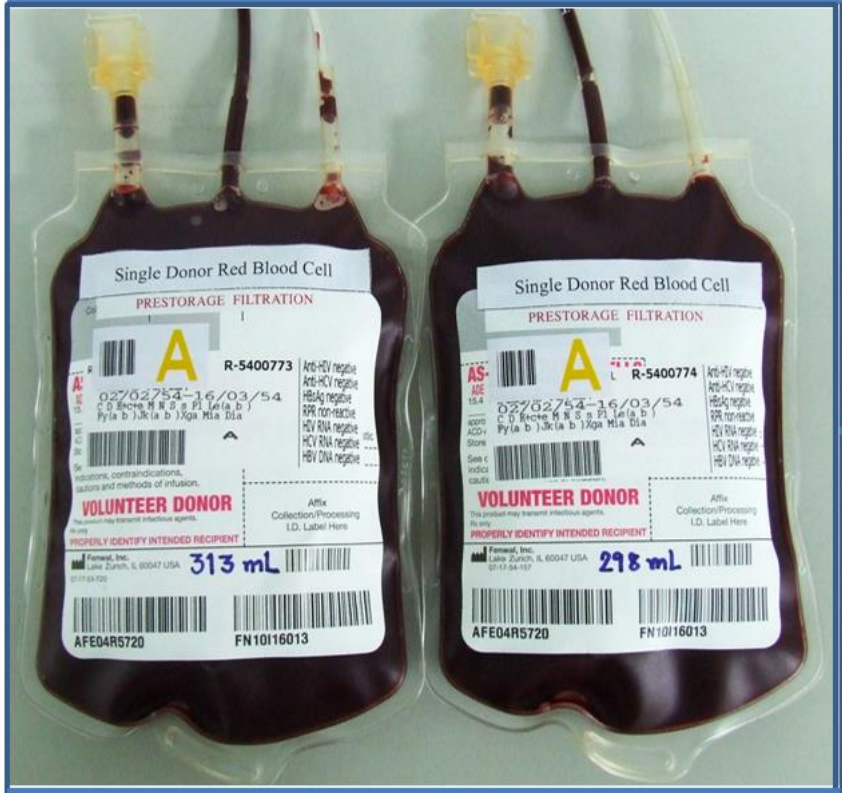
RBC Collection



Filtered Double RBC

- Standard 1 unit whole blood donation
  - ≤ 13 % whole blood volume
  - up to 525 mL / 10 – 15 min
- Double RBC apheresis

Intermittent Flow
Haemonetics® MCS+

Continuous Flow
Alyx™

US Recommendation for Donor Selection for DDRBC Apheresis

		Male	Female
Hematocrit		≥ 40%	≥ 40%
Hemoglobin		≥ 13.3 g/dL	≥ 13.3 g/dL
Height		≥ 155 cm	≥ 165 cm
Absolute Red Cell Volume by Donor Weight	360 mL	59 kg	68 kg
	400 mL	68 kg	≥ 79 kg
	420 mL	≥ 79 kg	

Harrison JF et al. Transfusion Medicine 2006 (16); 155-164

Advantages of DRBC

- Reduce risk of transfusion transmitted disease from donor exposure when 2 units RBC from 1 donor are transfused to the same patient
- The expected rise in Hb should be more predictable, because apheresis RBC contain a defined amount of RBC per unit, rather than the variable Hb contents amount from WB derived RBC
- Minimal lesion of collection
  - Anticoagulant is continually added at a constant ratio.
  - At the beginning of WB collection, the WB is drawn onto anticoagulant, instantly damaged upon contact because acid is available in large excess
- DRBC had less storage lesion when compared with WB donation based on reduced hemolysis, reduced K+, reduced glycolytic activity and LDH

Popovsky, M.A. (2006). Safety of 2-RBC donation: Donor and recipient considerations. *Transfus Apher Sci*, 35, 3-4.

ABO Identical
Compatible / Incompatible

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Suggested ABO Group Selection for Transfusion of Compatible RBC

Recipient ABO Group	Component ABO Group			
	1st Choice	2nd Choice	3rd Choice	4th Choice
AB	AB	A or	B	O
A	A	O		
B	B	O		
O	O			

* From Brecher ME, ed. Technical manual. 15th ed. Bethesda, MD: AABB, 2005:486.

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Suggested ABO Group Selection for Transfusion of Compatible Plasma and Platelet

Recipient ABO Group	Component ABO Group			
	1st Choice	2nd Choice	3rd Choice	4th Choice
AB	AB			
A	A	AB		
B	B	AB		
O	O	A or	B	AB

•From Brecher ME, ed. Technical manual. 15th ed. Bethesda, MD: AABB, 2005:498.

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Platelet Refractoriness

- Platelet antigens and antibodies overview
- Platelet transfusion
  - Platelet products
  - Guideline
- Platelet refractoriness
  - Causes
  - Laboratory investigation
  - Management

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I Platelet Refractoriness

- **An inability to achieve an expected incremental response to platelet transfusion.**
- **A diagnosis of refractoriness should be made only after**
  - **At least 2 consecutive ABO-compatible platelet transfusions**
  - **Stored platelet less than 72 hours**

  Resulting in poor platelet increments.
- **20-70% of multitransfused patients**

II Platelet Refractoriness

- **Transfusion service factors**
  - **Storage of platelet**
  - **Blood irradiation**
- **Immune cause**

  1 - hour posttransfusion platelet count increment
- **Nonimmune cause**

  18 - 24 hour posttransfusion platelet count increment

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Transfusion Service Factors
Platelet Quality

- **Platelet quality decline by day 5 of storage**
- **Platelet age affects CCI**
- **Gamma-irradiation does not seem to affect either markers of platelet quality in vitro or platelet recovery in vivo**

Immune Cause of Platelet Refactoriness

Platelet Antigens

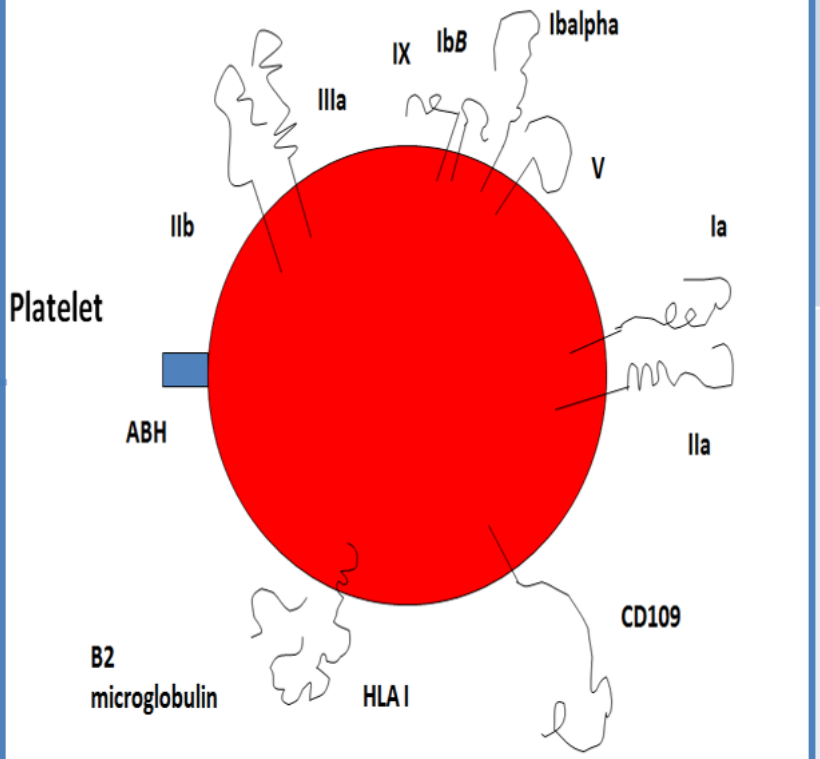
- Non - specific platelet antigen
  - Red cell antigens

    ABO, Lea, Leb, Ii , P, Cr
  - HLA Class I antigen
- Human platelet antigen

Platelet Antibodies

- ABO antibodies
- HLA antibodies, most common
- Human Platelet (HPA) alloantibodies
- Platelet autoantibodies

Pathophysiology



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I Posttransfusion platelet count increment (CI)

$$CI = \frac{(\text{Post-tx plt ct}) - (\text{Pre-tx plt ct})}{\text{Platelets transfused } x10^{11}} \times BSA$$

- where
  - tx = transfusion
  - plt = platelet
  - ct = count
  - BSA = body surface area in square meters
- Post-tx sample should be drawn 1 hour and 18-24 hours post-tx

II Posttransfusion platelet count increment (CI)

- The corrected count increment (CCI) is determined using the formula.

$$CCI = \frac{[\text{Posttransfusion count /µl} - \text{Pretransfusion count/µl}] \times \text{Body surface area}}{\text{Number of platelet } (x10^{11})}$$

- If $4x10^{11}$ platelets or approximately 6 pooled platelet concentrates to a patient with a $2m^2$ body surface area (calculated from height and weight charts) and the patient's posttransfusion minus pretransfusion count is 40,000/µl

Then the $CCI = \frac{40{,}000 \times 2}{4} = 20{,}000$

Causes of Platelet Refractoriness

Nonimmune	Immune
Fever	ABO incompatibility
Sepsis	HLA antibodies
Splenomegaly / Sequestration	Human platelet antigen (HPA) antibodies
Disseminated intravascular coagulation	Drug associated autoantibodies
Hemorrhage	
Microangiopathic hemolytic syndrome • Thrombotic thrombocytopenic purpura • Hemolytic uremic syndrome	
Medication (eg, amphotericin, vancomycin)	

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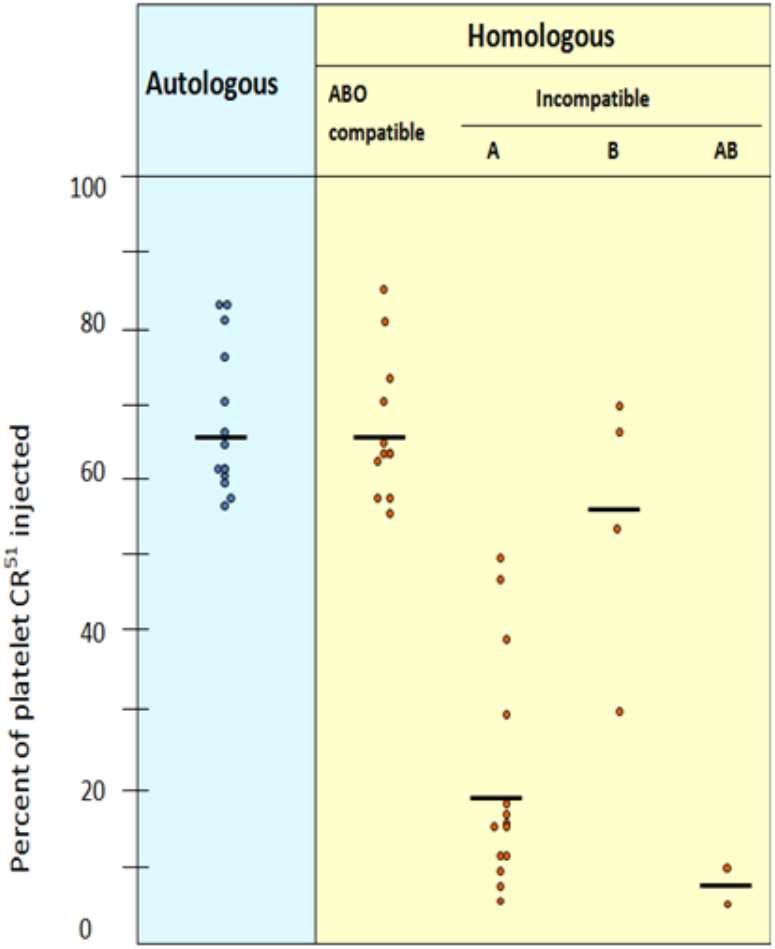
Posttransfusion platelet count increment (CI)

	1 hour CI	18-24 hour CI
Acceptable CCI	> 7.5 x 10^9 /L	> 4.5 x 10^9 /L
Indicative information	Patients who repeatedly have poor 1 hour CCI response are more likely to be immune refractory • Platelet antibodies • Splenomegaly	Poor response at 18-24 hour CCI are commonly caused by non-immune cause • Fever • Infection • Sepsis • DIC

ABO Compatibility



- **Platelet express ABH antigen, passively adsorbed from plasma (A, B substances)**
- **ABO-incompatible platelet transfusion are associated with a reduced posttransfusion CCI and patients with a lower CCI also have higher anti-A/B titers.**

Refractoriness and Alloimmunization Rates After Transfusing ABO-Matched Versus Mismatched Platelets

Platelet Transfusions	Enrolled	Female patients	Possible Prior sensitization*	Platelet Transfusions Median (range)	Platelet refractoriness † P=.001	New antibodies		
						Anti-A/B ‡	Anti-HLA	Platelet specific
ABO Matched	13	10 (77%)	9 (69%)	7 (5-19)	1 (8%)	0	1 (8%)	1 (8%)
ABO Mismatched	13	2 (15%)	4 (31%)	9 (4-30)	9 (69%)	7 (54%)	5 (38%)	4 (31%)

* Possible prior sensitization after pregnancy / transfusion.

† 1-hour post- transfusion corrected count increment less than 4500

‡ ≥ three doubling dilution increase over their baseline

From Carr R et al. Br J Haematol. 1990;75:408-413.34

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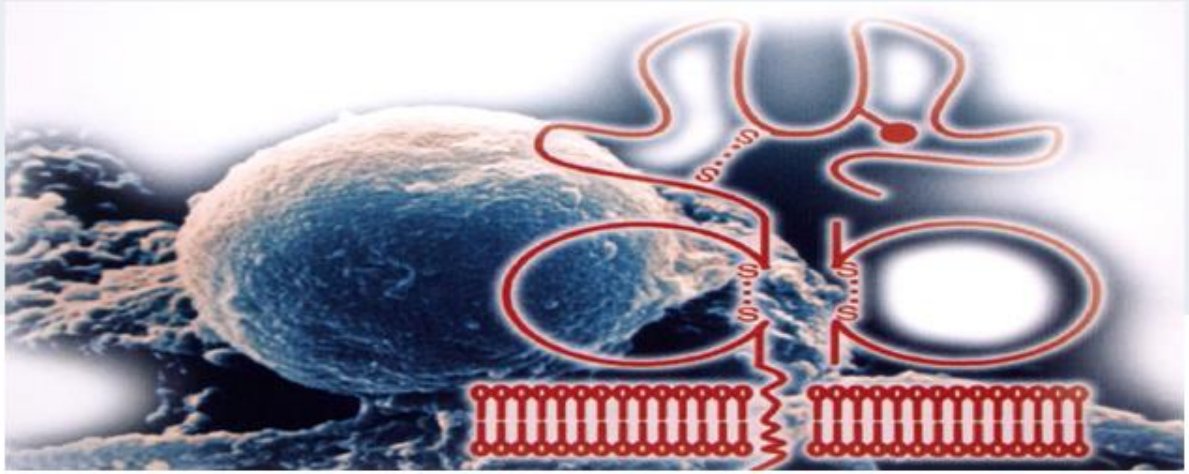
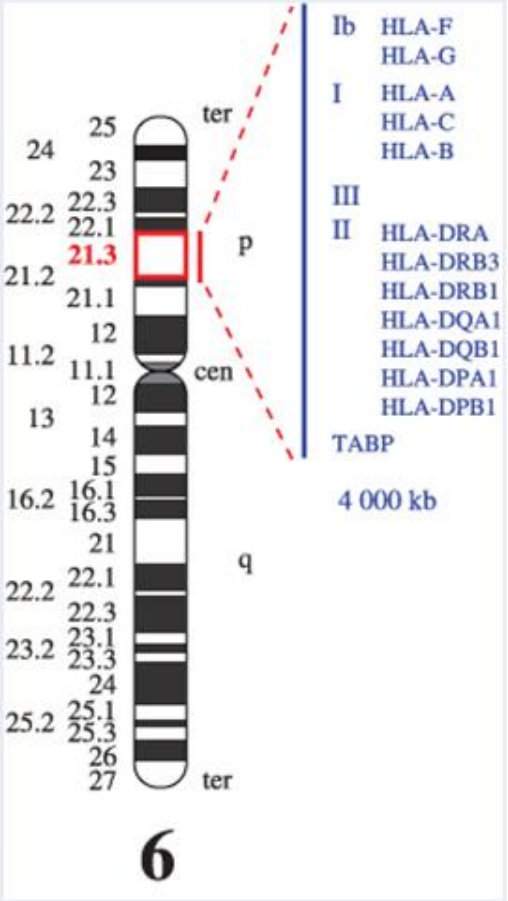
Major Histocompatibility Complex (MHC)

- Complex of genes on chromosome 6
- 4 million base pairs in length
- Named for role in tissue transplant
- 30% of 150 expressed genes* involved in immune response (complement, antigen processing, cytokines)
- Most famous members control tissue compatibility – MHC (HLA) class I and class II genes





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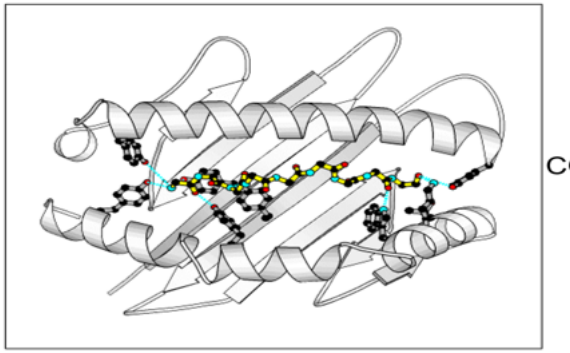
HLA Expression

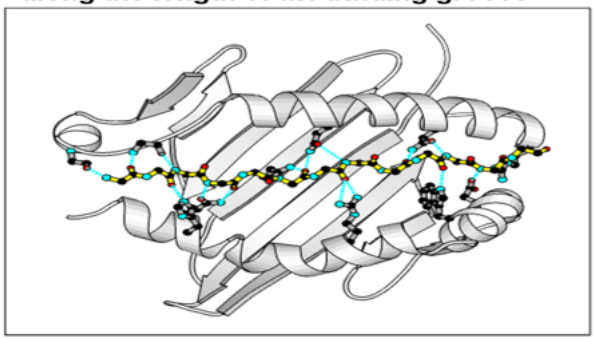
- **Tissue distribution**
  - **Class I - most cells**
  - **Class II – Professional antigen presenting cells**
  - **Monocytes & activated T express DR**
- **Density on cell (~105 molecules / cell)**
  - **Class II > Class I; DRB1>DRB3, DRB4**
- **Alleles at locus co-dominantly expressed**

Peptides are bound to MHC class I molecules by their ends.



Hydrogen bonds and ionic interactions (dotted blue lines)

Peptides bind to MHC class II molecules by interactions along the length of the binding groove



Hydrogen bonds (dotted blue lines)

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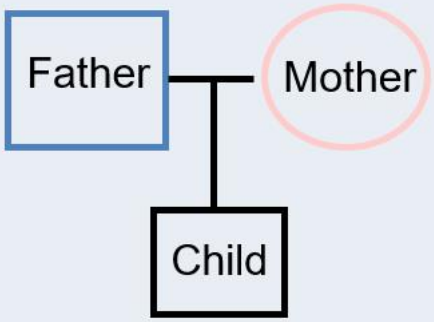
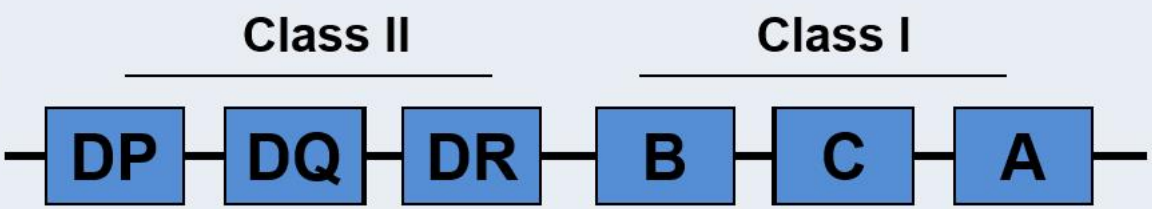
Haplotypes

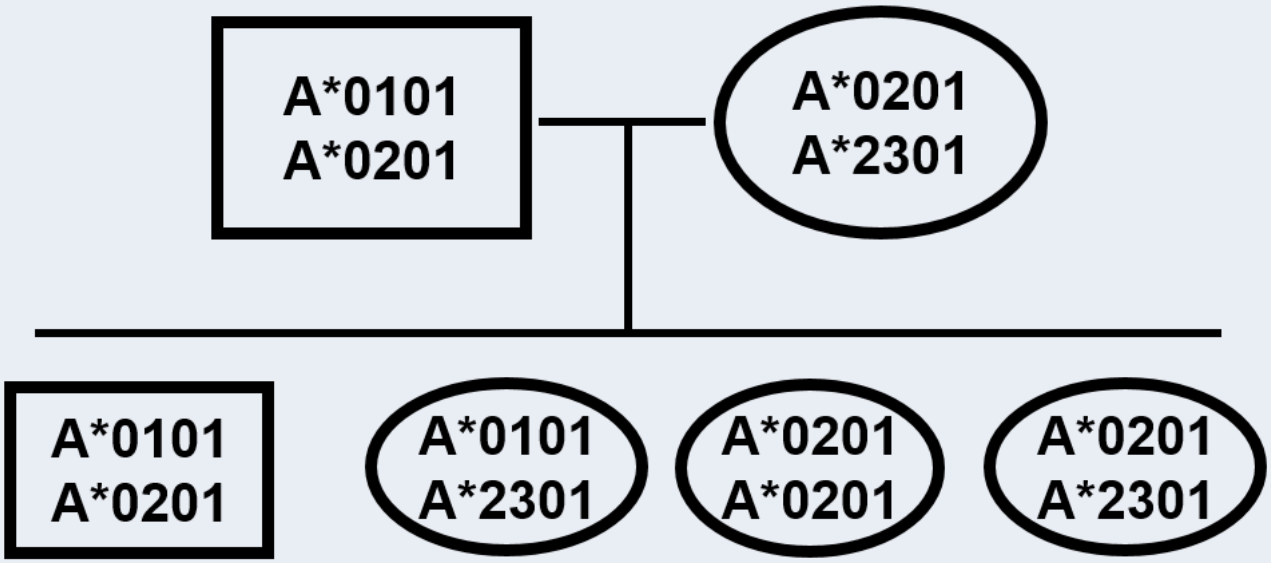
- **HLA Inherit as a haplotype**
- **Several loci with codominant expression**





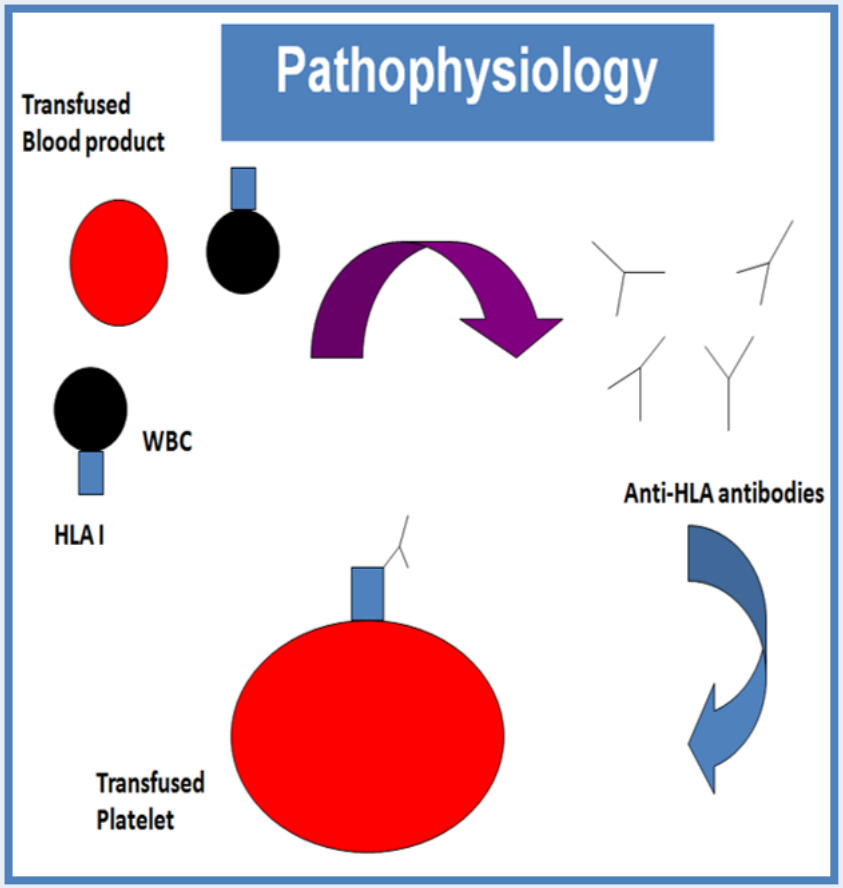
HLA genes linked on chromsome 6 in MHC

Inheritance of HLA-A Locus Alleles in a Family



- 4 possible genotypes in children
- Heterozygous vs homozygous
- 1 in 4 chance that two sibs inherit same two alleles

I Immune Cause
Antibodies to HLA Class I antigen



- Platelet can absorb soluble HLA antigen class I from plasma on their surfaces
- Patients produce IgG antibodies against specific and common epitopes
- Leukoreduction dropped the incidence of alloimmunization, but there is no difference in the rate of alloimmunization between leukoreduced, pooled whole blood derived and single donor platelet

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II Immune Cause
Antibodies to Human platelet antigen (HPA)

System	Antigen	Alternative Names
HPA-1	HPA-1a	Zw^a, PI^{A1}
	HPA-1b	Zw^b, PI^{A2}
HPA-2	HPA-2a	Ko^b
	HPA-2b	Ko^a, Sib^a
HPA-3	HPA-3a	Bak^a, Lek^a
	HPA-3b	Bak^b
HPA-4	HPA-4a	Yuk^b, Pen^a
	HPA-4b	Yuk^a, Pen^b
HPA-5	HPA-5a	Br^b, Zav^b
	HPA-5b	Br^a, Zav^a, Hc^a
HPA-6	HPA-6a	Ca^b, Tu^b
	HPA-6b	Ca^a, Tu^a
HPA-7	HPA-7a	Mo^b
	HPA-7b	Mo^a
HPA-8	HPA-8a	Sr^b
	HPA-8b	Sr^a
HPA-9	HPA-9a	Max^b
	HPA-9b	Max^a
HPA-10	HPA-10a	La^b
	HPA-10b	La^a
HPA-11W	HPA-11bw	Gro^a
HPA-12W	HPA-12bw	Ly^a
HPA-13W	HPA-13bw	Sit^a

- HPA polymorphism are due to single amino acid changes in glycoprotein on platelet surface
- The incidence of anti-HPA varies from 2-11% and leukoreduction does not affect this incidence
- Anti-HPA are generally infrequent.

III Immune Cause
Drug – Related Immune Destruction

- Initial coating of platelet
- Adsorption of the drug-antibody complex to the surface of platelets

List of medications with drug-induced thrombocytopenia or with the formation of drug-dependent platelet antibodies

Antibiotic

Ampicillin
Amoxicillin
Cephalosporins
Ciprofloxacin / levofloxacin
Nafcillin
Metronidazole
Penicillin
Rifampin
Sulfonamides
Vancomycin
Amphotericin

Histamine-receptor antagonists

Cimetidine
Famotidine
Ranitidine

Analgesics

Acetaminophen
Diclofenac
Fentanyl
Ibuprofen
Naproxen
Salicylates

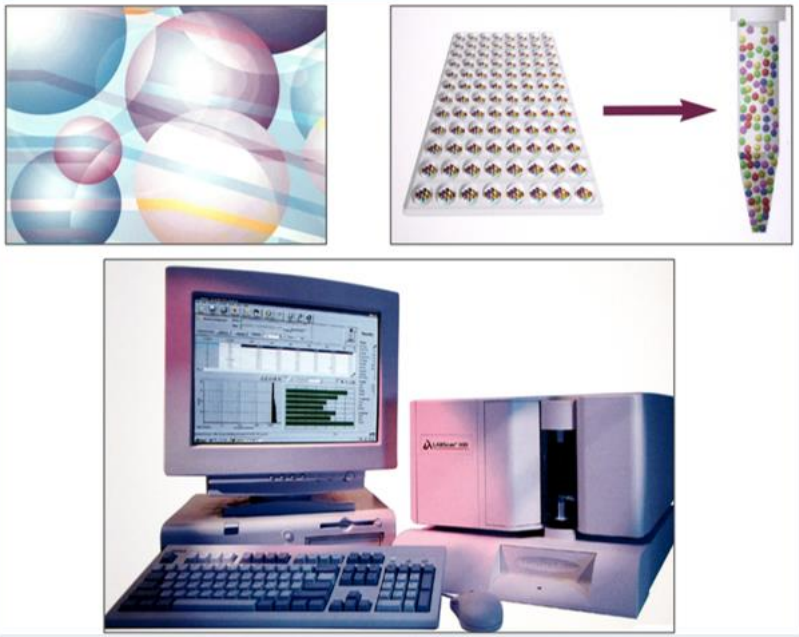
Chemotherapeutics immunosuppressants

Bleomycin
Ciclosporin
Oxaliplatin
Fludarabine
Rituximab

Antithrombotics

Clopidogrel/ticlopidine
GPIIb/IIIa antagonists
Heparin

Laboratory Test and Management of Platelet Refractoriness



- HLA-matching
- HLA-crossmatching
- Detection of antibody specificities

HLA Testing

Serological test

- **Microlymphocytotoxicity test**

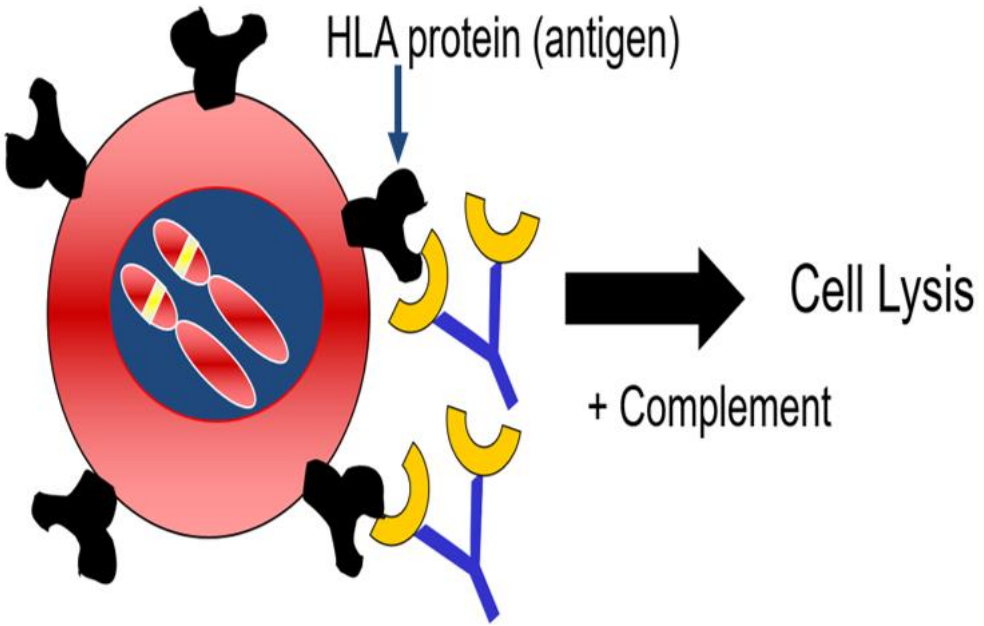
  T cell ⟶ HLA-A, B, C

  enriched B cell ⟶ HLA-DR, DQ

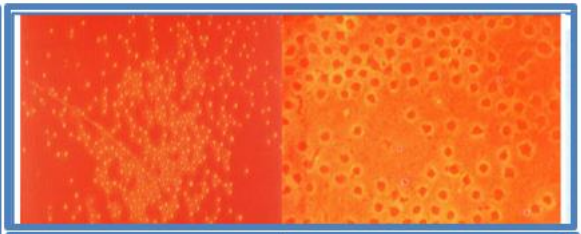
- **2 color Immunofluorescense test**

DNA typing

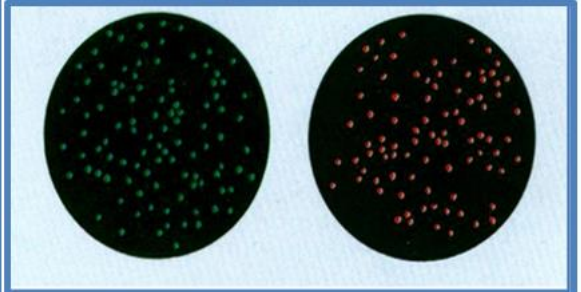
Serologic HLA Typing



Lymphocytotoxicity test



Negative	Positive



Read the HLA typing result with a fluorescence microscope for dual assessment of positive (red) and negative (green) reactions

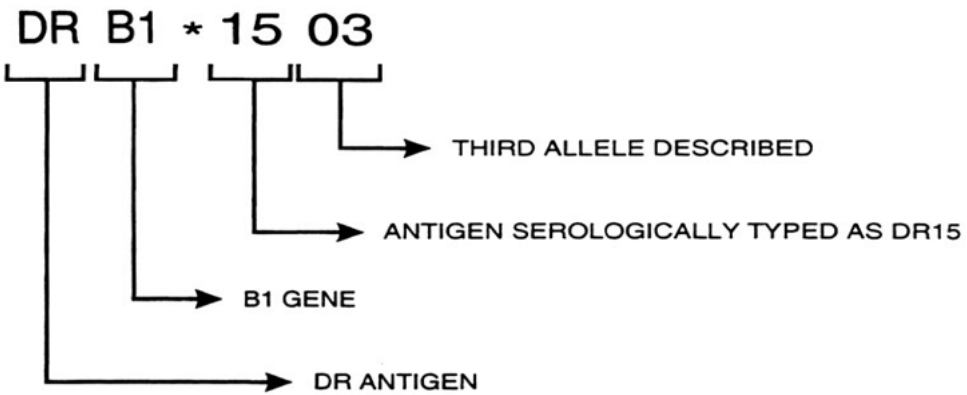
Possible data-coding strategy for HLA typing

Score	% dead cells	interpretation*
1	up to 10	negative
2 = +	10 - 20	questionably negative
4 = + +	20 - 40	questionably positive
6 = + + +	40 - 80	positive
8 = + + + +	80 - 100	strongly positive

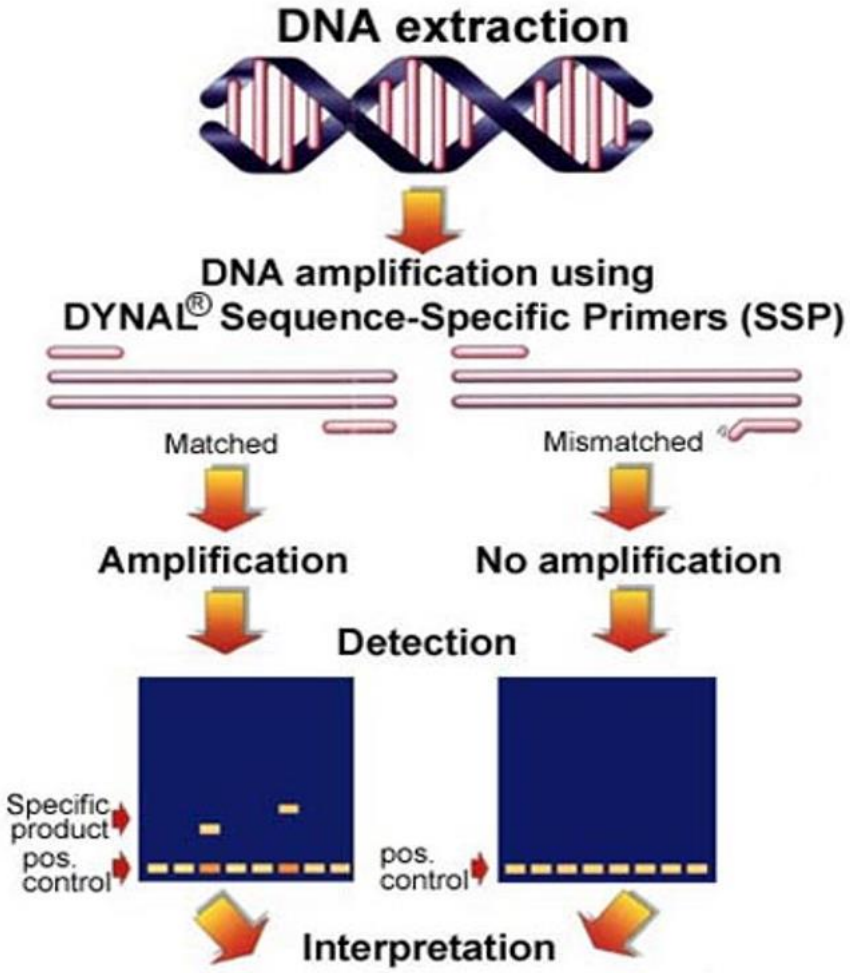
* Taking the control into account

DNA Typing Methods

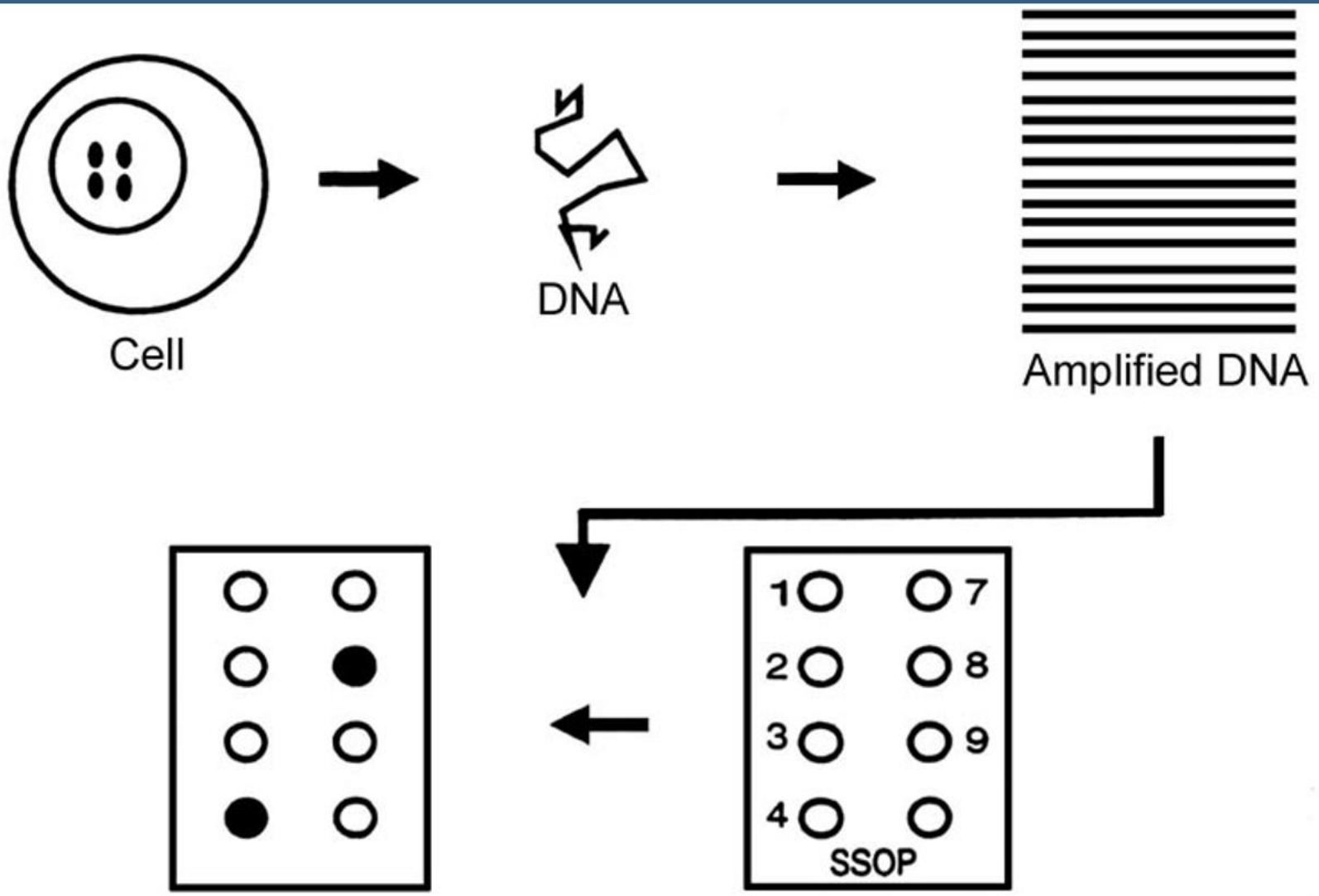
- Polymerase chain reaction (PCR) amplification of genes
- Methods
  - Sequence specific priming (SSP)
  - Sequence specific oligonucleotide probes (SSOP)
  - Sequence based typing (SBT)



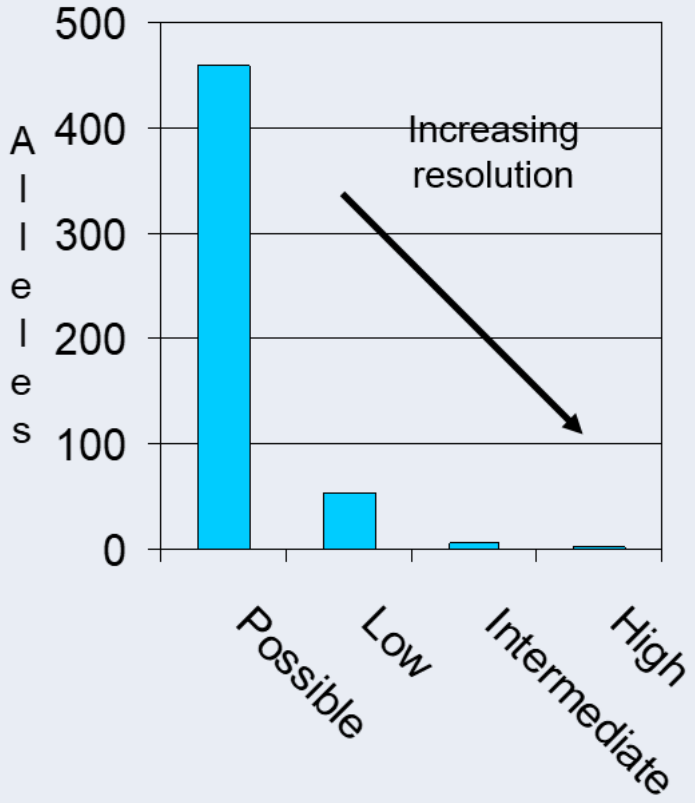
Sequence-Specific Primers DNA Typing



PCR/SSOP – REVERSE DOT BLOT



DNA Typing Results



- **Low**
  - **DRB1*04 (over 50 possibilities)**
- **Intermediate**
  - **DRB1*0401 or *0403 or *0404 or *0405 or *0406 or *0408**
- **Allele**
  - **DRB1*0405 (1 possibility)**

HLA Antibody Detection

- **Overall assessment by measuring recipient serum for PRA**

  PRA = % panel reactivity

  Positive 24 cells in 60 cells.

  PRA = 24/60 X 100 = 40 %

- **PRA Class I and Class II**
- **Single antigen Class I and Class II**

ELISA

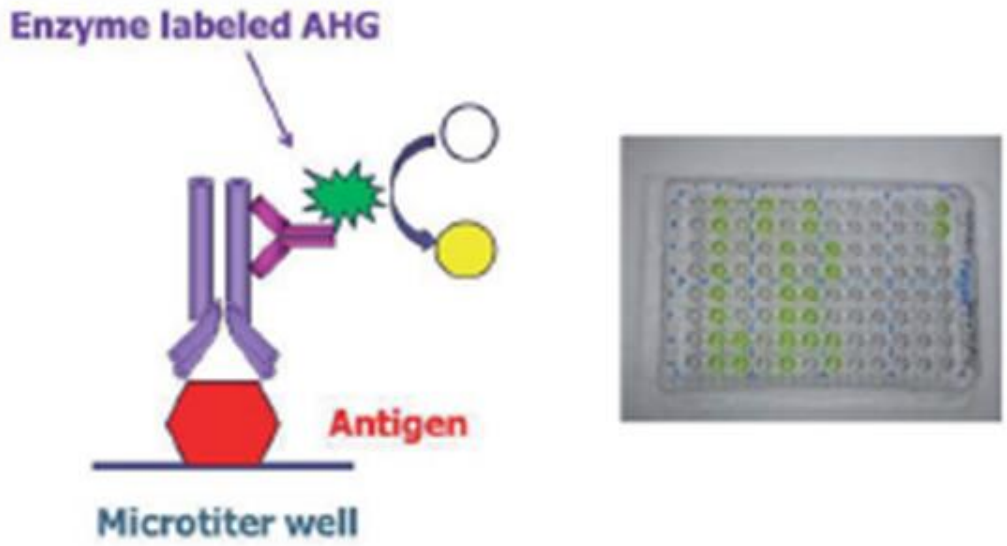
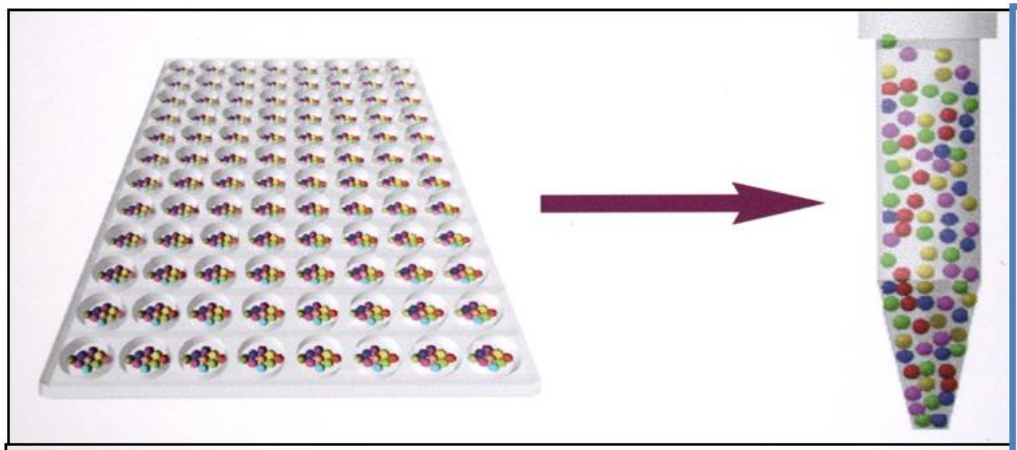
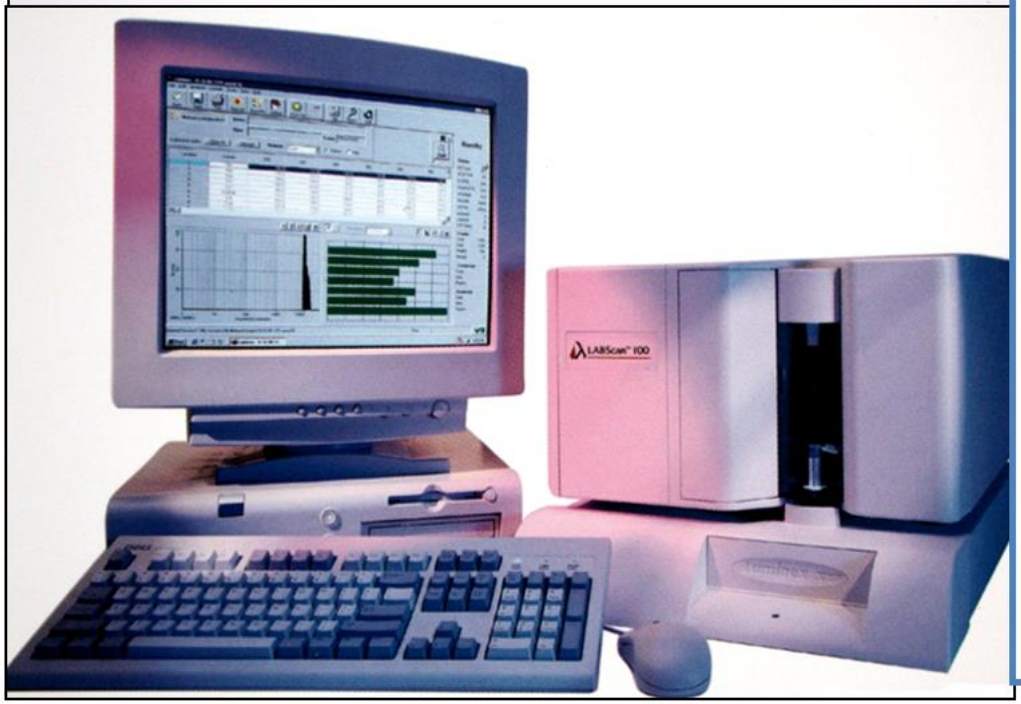


Fig. 1. (A) HLA antigen is bound to the microtiter well. Enzyme attached to AHG acts on a substrate to produce a color change. (B) Microtiter plate with positive (yellow) and negative (no color) wells.

Kopko PM. Transfusion 2015;55,235-244.

Multiplex Flow Cytometric Bead Assay





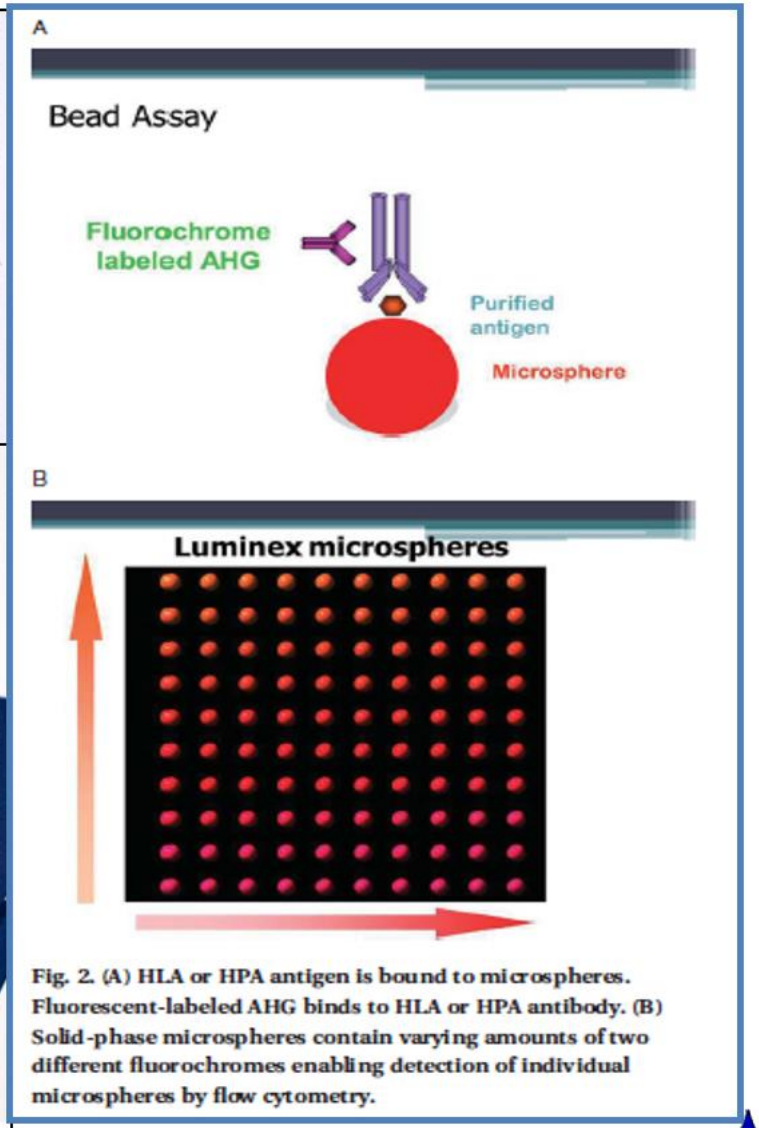
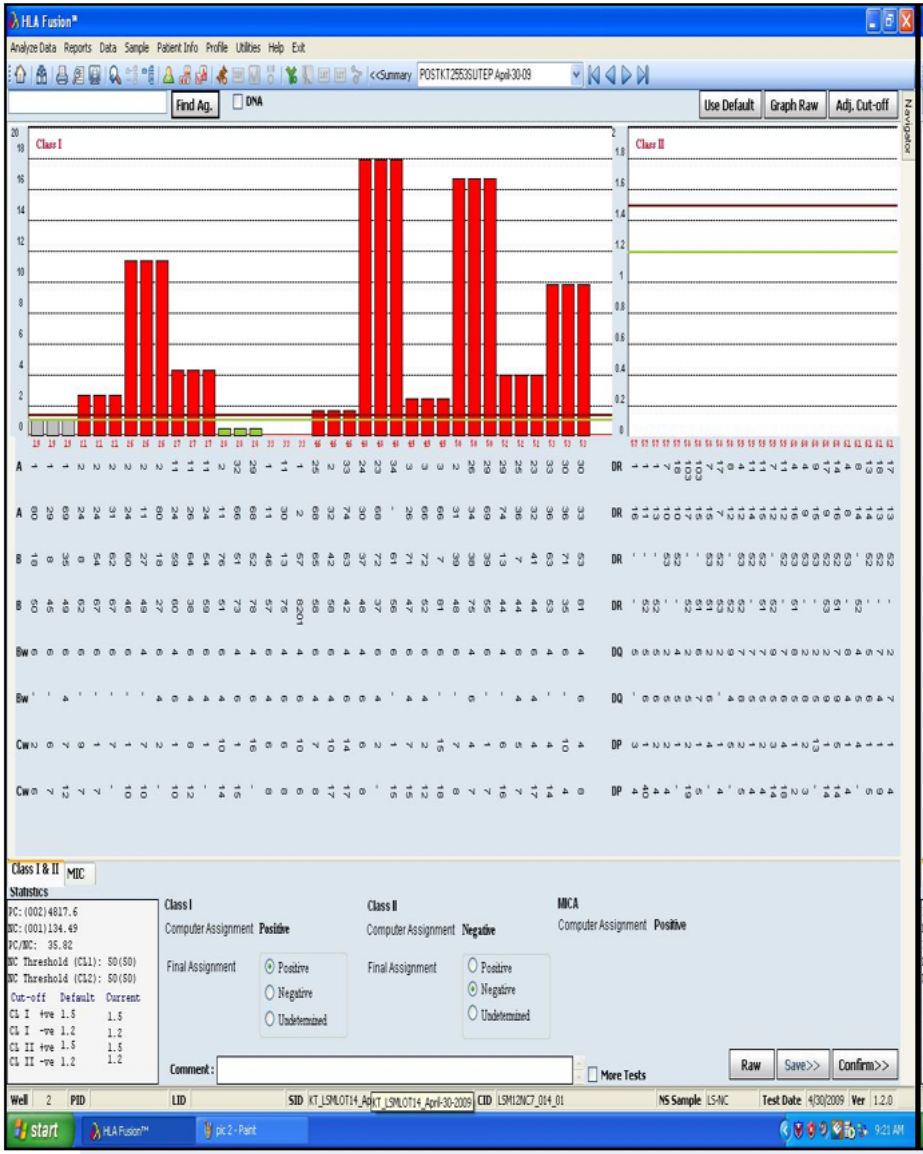
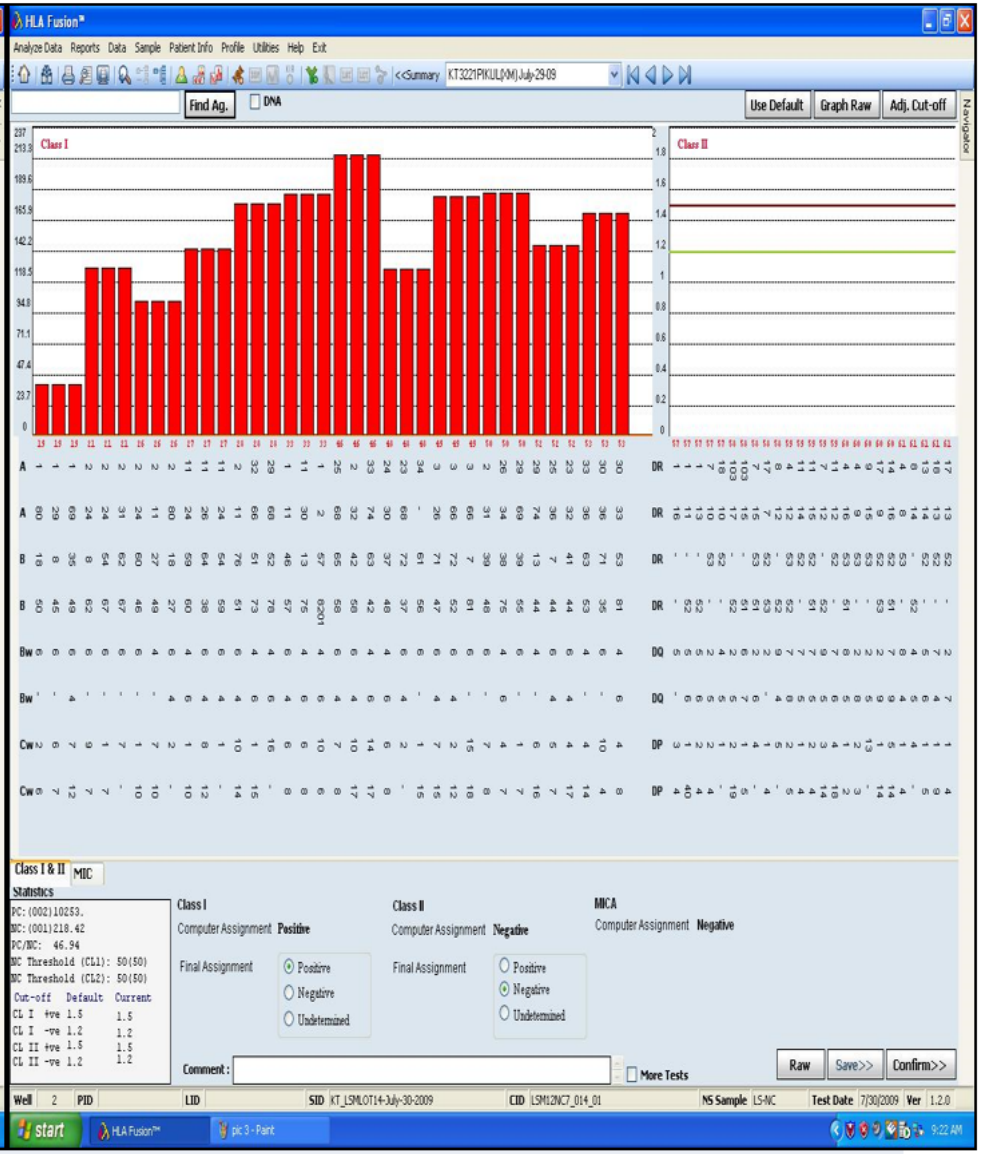


Fig. 2. (A) HLA or HPA antigen is bound to microspheres. Fluorescent-labeled AHG binds to HLA or HPA antibody. (B) Solid-phase microspheres contain varying amounts of two different fluorochromes enabling detection of individual microspheres by flow cytometry.





LSM – Low PRA

LSM – High PRA

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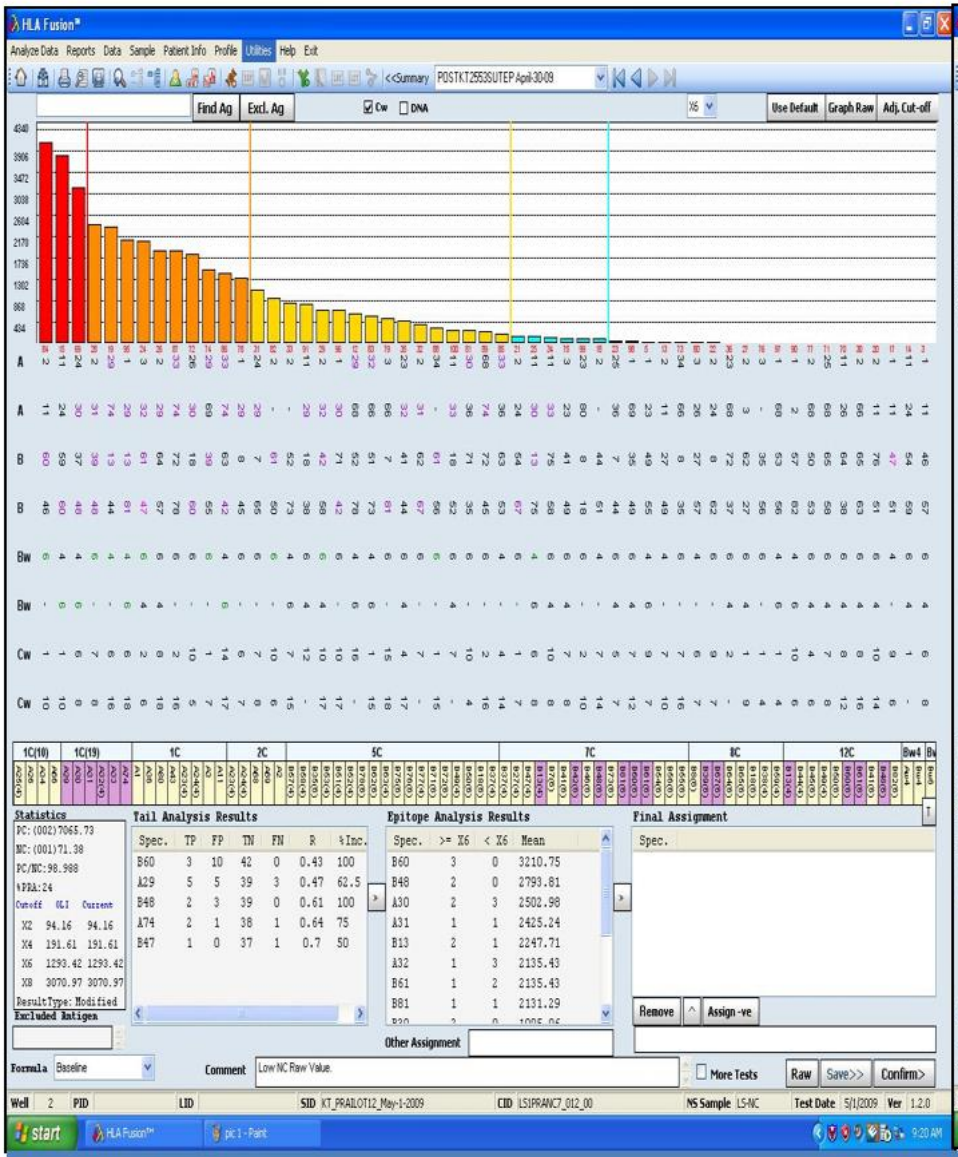
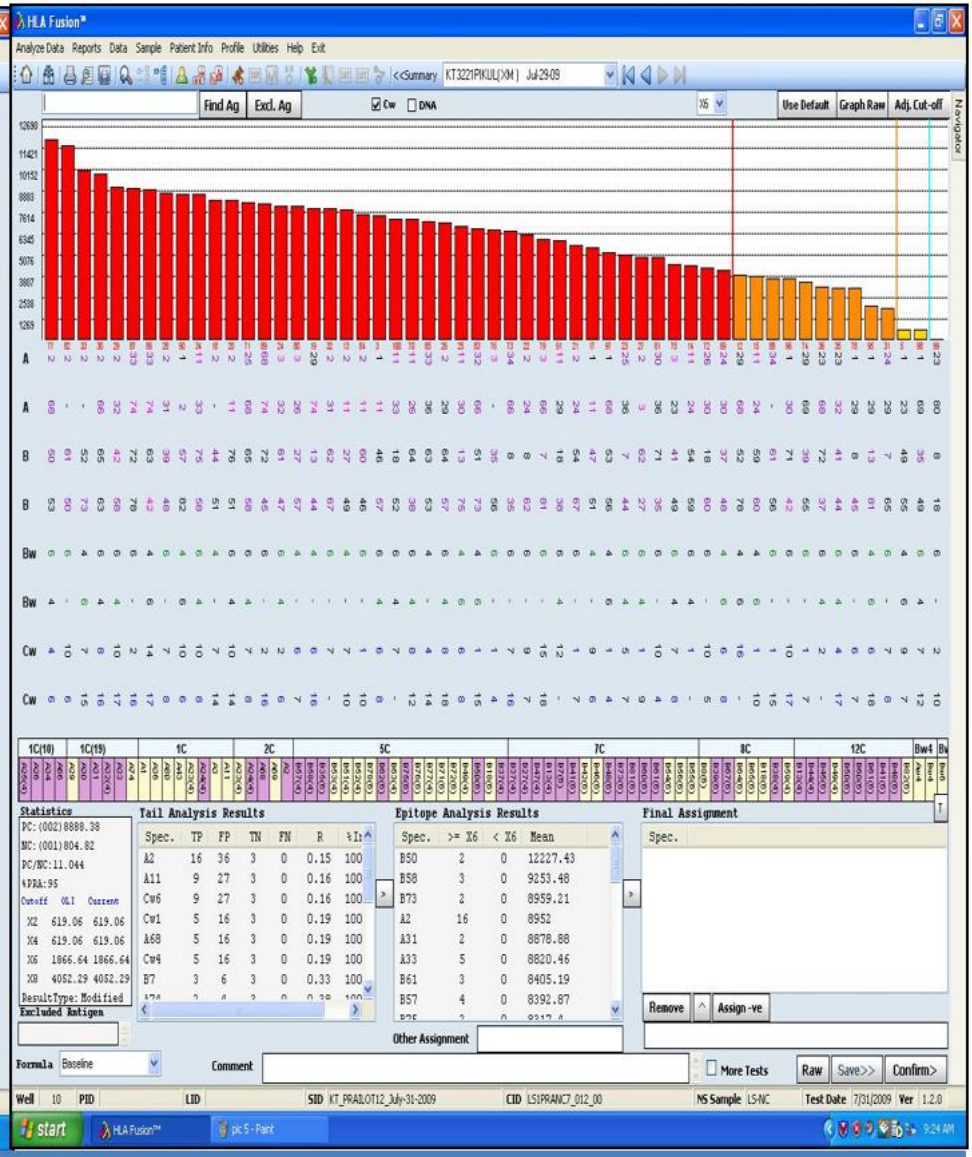


PRA Class I



High PRA Class I

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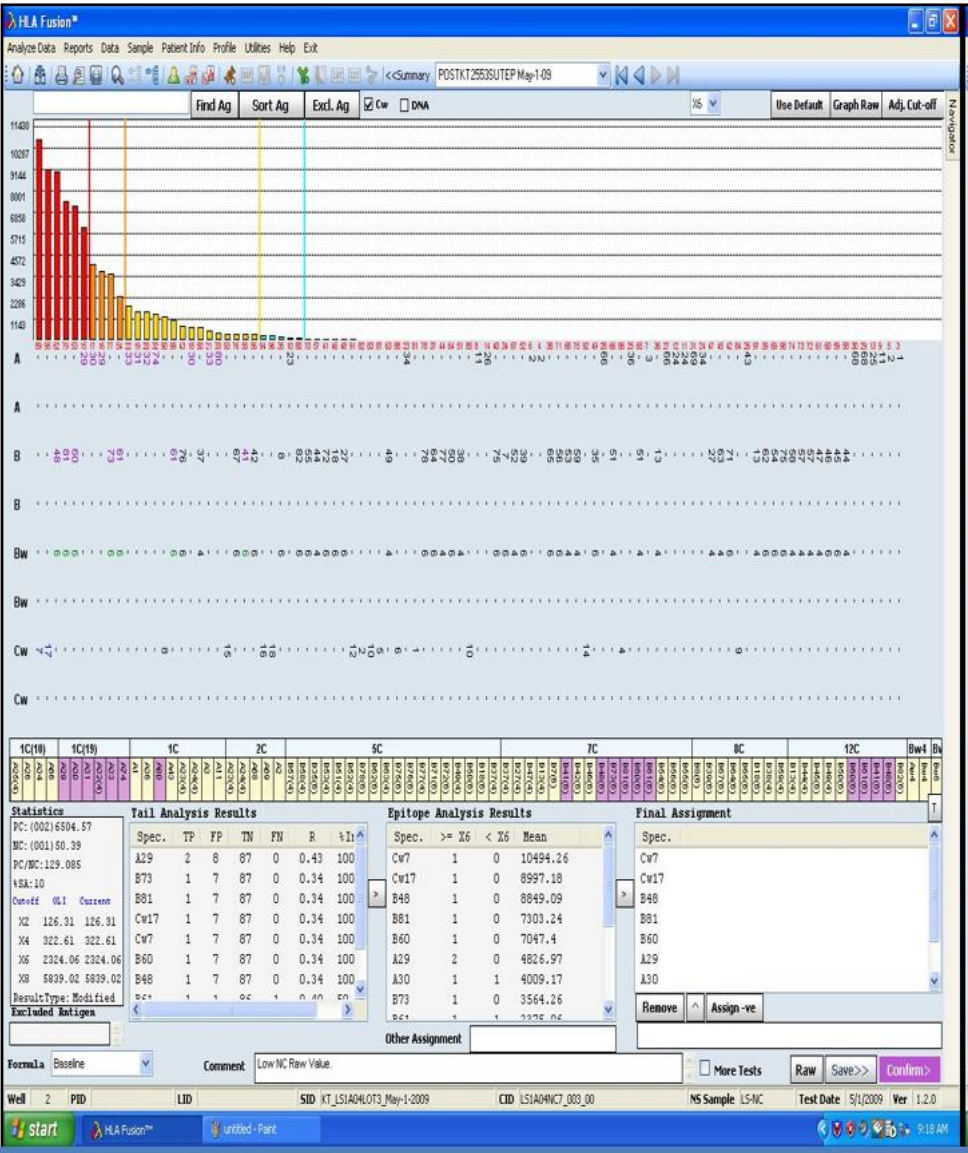
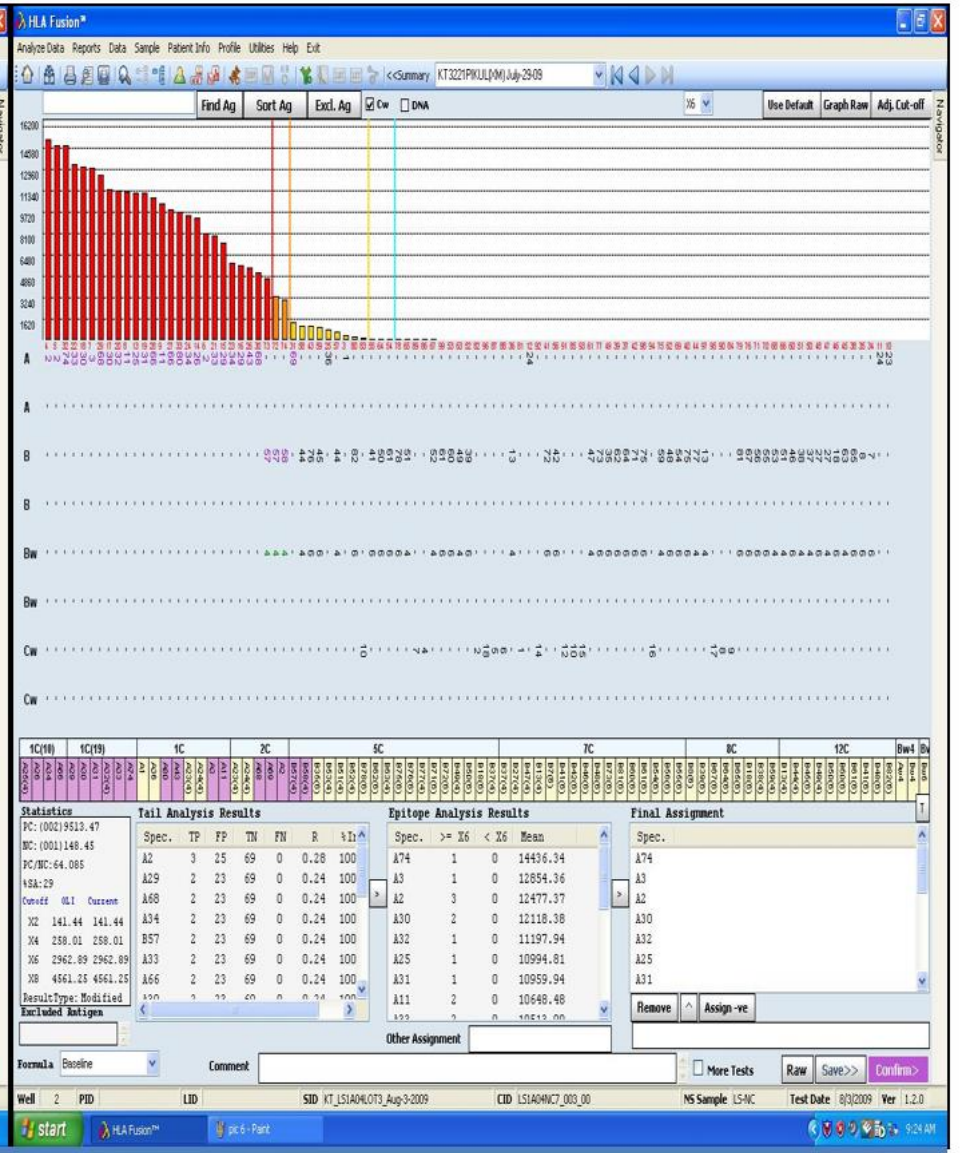


Single Antigen Class I



Single Antigen Class I

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I Management

- **Non-immune causes**

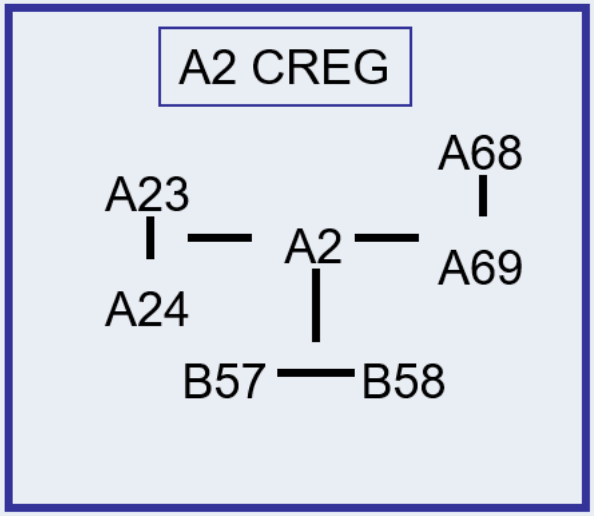
  mainly depends on treating the underlying illness

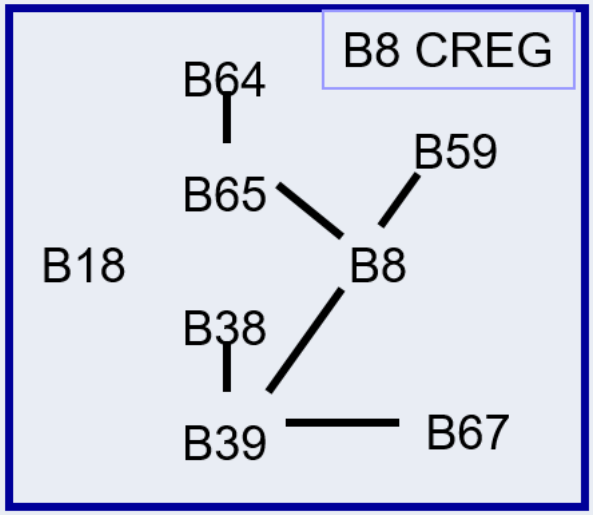
- **Immune case**
  - **HLA antibody Screening**
  - **HLA matching**
  - **HLA crossmatching**
  - **Antibody specificity prediction**
  - **HPA antibody**

- **Alternative Management Strategies**

II Management

- **HLA typing should be done before chemotherapy**
- **HLA – matched platelets , based on Cross reactive epitope groups (CREG)**
  - **Antigen with common epitopes**
  - **Antibody that react with these antigens that shared determinants. They often cause cross reaction in serology**





SOME MAJOR HLA CLASS I CREGS

Major CREG	Occurrence on HLA Molecules	Approximate Frequency (%)
1C	A1, w36, 3, 9, 10, 11, 28, w19	79
2C	A2, 28, 9	66
5C	B5, 17, 17, 18, 35, w53, w70	50
7C	B7, w22, 27, w42, 40, w41, 13, w47, w48	54
8C	B8, 14, 16, 18	38
12C	B12, 21, 13, 40, w41	44
4C	B9, 25, 32, Bw4	79
6C	B11, Cw1, 3, 7, Bw6	87

Pimpun Kitpoka,M.D.

I Platelets Selection for Alloimmunized Patients
HLA Matched Platelet

- Determine HLA phenotype and ABO type of the recipient
- Screen patient's serum for HLA antibody

- Select from the donor pool with the most compatible HLA and, if possible, ABO systems.
  - Matching of donor HLA-A and -B antigens.
  - Providing platelets that lack antigens against patient's antibodies
  - If HLA-identical platelets are unavailable, platelets from donor whose mismatched HLA types are serologically cross-reactive with the recipient's may be substituted.
  - Although ABO is expressed on platelets, ABO matching is usually not critical, but should be considered if HLA-matched platelets are not effective.

II Platelets Selection for Alloimmunized Patients HLA Matched Platelet

- In alloimmune refractory patients, the best increments occur in the success of Grade A and B1U or B2U HLA-matched transfusions.
- Platelets mismatched for some antigens (eg, B44, B45) that are poorly expressed on platelets may also be adequate

Match Grade	Description	Examples of Donor Phenotypes for a Recipient Who Is A(1,3); B(8,27)
A	4-antigen match	A1,3;B8,27
B1U	1 antigen unknown or blank	A1,-; B8,27
B1X	1 cross-reactive group	A1,3;B8,7
B2UX	1 antigen blank and 1 cross-reactive	A1,-; B8,7
C	1 mismatched antigen present	A1,3;B8,35
D	2 or more mismatched antigens present	A1,32;B8,35
R	Random	A2,28;B7,35

Concise guide to transfusion medicine. AABB Press.2017.

Pimpun Kitpoka,M.D.

III Platelets Selection for Alloimmunized Patients
HLA Crossmatched Platelet

- **Each potential platelet is tested against a current patient serum using a solid-phase red cell adherence test. The more heavily alloimmunized a patient is, the less likely it will be to find a crossmatch-compatible platelet.**

- **Compared with HLA matched, crossmatching can be more convenient and avoids exclusion of HLA-mismatched but compatible donors, and facilitates selection of compatible platelet when non-HLA antibodies are present**

Pimpun Kitpoka,M.D.

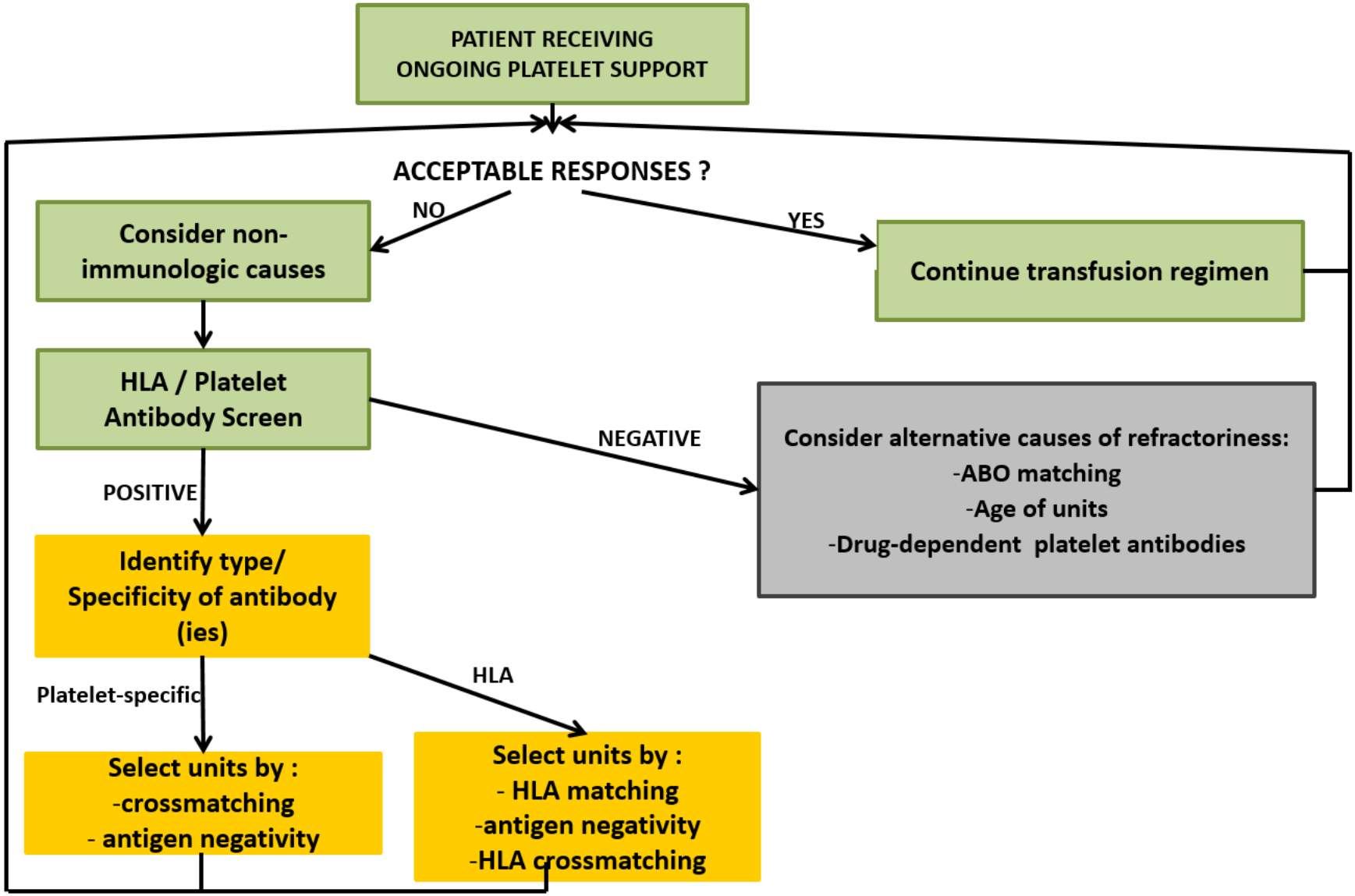
IV Platelets Selection for Alloimmunized Patients HPA Crossmatched Platelet

- **Screen patient serum for anti-HPA, HPA antigen (if there is a history of poor response to HLA-identical, matched, crossmatched platelets).**

- **Crossmatch available platelet units without regard to patient or donor HLA type when only antibodies to human platelet antigens are present.**

Pimpun Kitpoka,M.D.

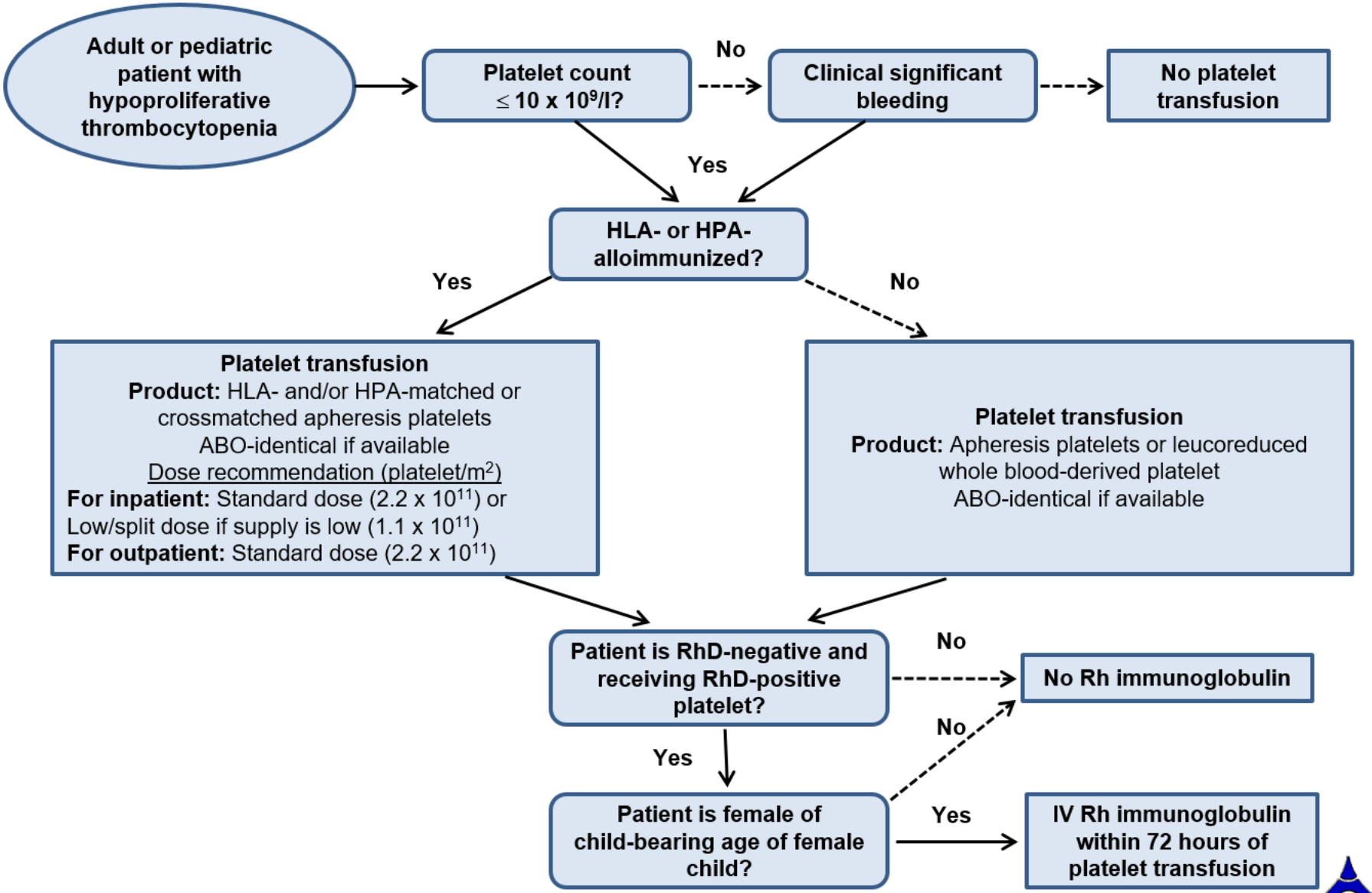
Approach to management of patients with platelet refractoriness



AABB technical Manual : 18th edition, 2014

Pimpun Kitpoka,M.D.

Guidance on platelet transfusion for patients with thrombocytopenia



Nahirniak et al. Transfus Med Rev 2015; 29:3-13.

Pimpun Kitpoka,M.D.

IV Alternative Managements

- IVIG
- Antifibrinolytic, epsilon aminocaproic acid
- Recombinant activated FVII
- Small-dose frequent platelet transfusion
- Prevention of platelet refractoriness

I Alternative Management Strategies

Treatment	Findings	Reference	Summary
IVIG	Consensus recommendations for off-label use of intravenous IVIG states that, for patients with thrombocytopenia and refractoriness to platelet transfusions, evidence does not support routine use of IVIG. It may have some role in patients with severe thrombocytopenia of documented immune basis for whom other modalities are unsuccessful or contraindicated	47–49	This expensive treatment should not be used or considered as replacement for HLA-compatible platelets for alloimmunized patients

Forest SK. Hematol Oncol Clin N AM.2016,655-677.

II Alternative Management Strategies

Treatment	Findings	Reference	Summary
Protein A column	Small study using 10 refractory patients. Protein A column therapy was effective in improving platelet response in 6 patients; no follow-up study	52	Unclear evidence. Protein A columns unavailable at many institutions and have potential side effects
Massive platelet dose transfusion	In animal studies and 2 alloimmunized humans, infusion of a massive dose of platelets to absorb the alloantibodies led to significant improvement in subsequent platelet transfusions and in bleeding symptoms	53	Anecdotal evidence May be considered for arresting hemorrhage in emergency situations when compatible platelets are unavailable

Forest SK. Hematol Oncol Clin N AM.2016,655-677.

III Alternative Management Strategies

Treatment	Findings	Reference	Summary
Continuous slow platelet transfusion	Anecdotal success in 3 patients with AML and platelet refractoriness when platelet concentrate was infused slowly over 6 h	54	Anecdotal evidence. Small-dose frequent platelet transfusions may be helpful in maintaining vascular integrity despite lack of increase in posttransfusion platelet count
Activated factor VII	Anecdotal success in controlling bleeding in platelet refractory patients	55,56	Anecdotal evidence. There is concern for prothrombotic risk. May be considered for arresting hemorrhage in emergency situations

Forest SK. Hematol Oncol Clin N AM.2016,655-677.

Prevention

- Leucodepleted blood component
- Avoid unnecessary and overdose platelet transfusions

Potential patient benefits	Prestorage	Poststorage
HLA alloimmunization		
• WBC	effective	effective
• Fragmented WBC during storage	effective	ineffective
Platelet refractoriness		
• HLA	effective	ineffective
• HPA	ineffective	ineffective

Pimpun Kitpoka,M.D.

Comparison of Leukoreduced Whole Blood Derived and Apheresis Platelet

	Controls: untreated pooled random donor platelets	Leukoreduced pooled random donor platelets	Leukoreduced single-donor apheresis platelets
Number of patients	131	137	132
Alloimmunization	45%	18% ($P < 0.001$)*	17% ($P < 0.001$)*
Refractoriness	16%	7% ($P = 0.03$)*	8% ($P = 0.06$)*
Alloimmunization and refractoriness	13%	3% ($P = 0.004$)*	4% ($P = 0.01$)*

Adapted from reference 40.
*as compared to control group.

Pavenski K. Tissue antigen 2012;79,237-245.

Pimpun Kitpoka,M.D.

Transfusion in Oncology and Transplant Patients

Pimpun Kitpoka, M.D.

I Transfusion Requirements for Transplant Patients Pretransplant Phase

- All cellular components should be prestorage leukoreduced by filtration to reduce HLA alloimmunization, platelet refractoriness, CMV transmission and febrile reaction

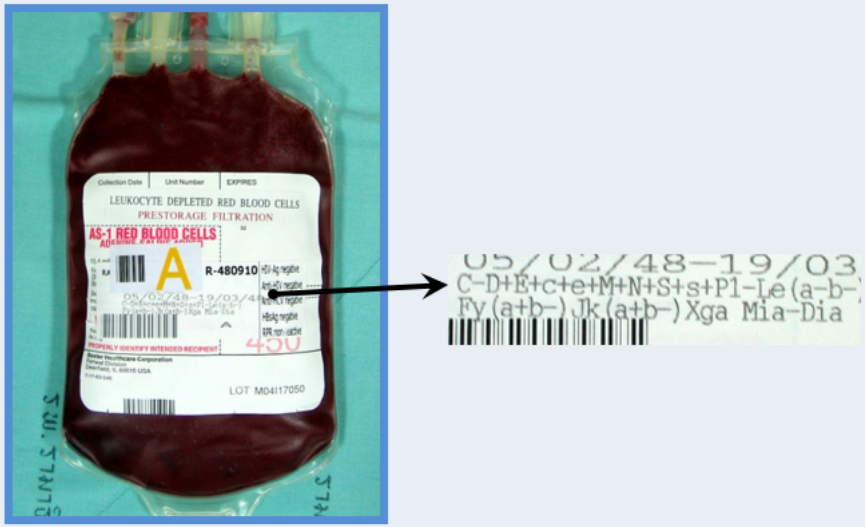
- Prestorage leukoreduced blood is as efficacious in the prevention of CMV as units collected from CMV – seronegative donors.

- The use of single donor instead of WB derived pooled donor platelet concentrate should be considered

- Family members should not be blood donors to prevent alloimmunization against minor histocompatibility and private antigen

II Transfusion Requirements for Transplant Patients

Recipients RBC Typing



RBC Phenotyping

Phenotyped RBC in patients with RBC alloantibodies / autoantibodies to provide most-compatible blood and predict the specificity of antibodies.

III Transfusion Requirements for Transplant Patients Posttransplant Phase

- **Use of irradiated cellular blood to prevent transfusion graft versus host disease (GVHD) due to transfusion of viable T lymphocytes in blood by inhibiting lymphocyte engraftment and proliferation**

- **The most commonly used source is Cesium (Cs-137). A midplane dose of 25 Gy with the minimum dose of 15 Gy to any point within the canister**

Blood irradiation

Irradiated Blood

Pimpun Kitpoka,M.D.

I Transfusion Associated Graft-versus-Host Disease TA-GVHD

- Engraftment of immunocompetent donor T-lymphocyte into immunocompromised recipients
- Rare event but high mortality rate
- Clinical Manifestations and Diagnosis
  - Acute syndrome within 4-30 days following blood transfusion
  - Dysfunction of skin, liver, GI, bone marrow

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II TA-GVHD

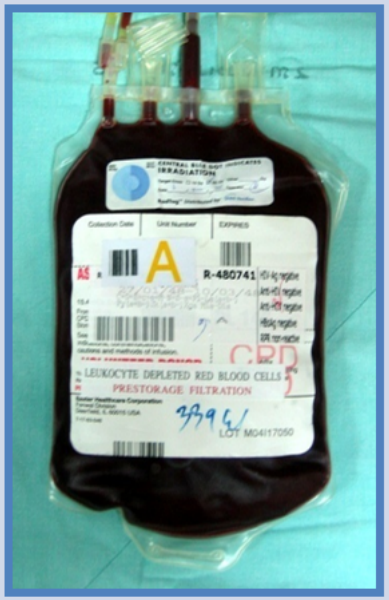
- **Immune and pathophysiologic mechanisms**
  - **Different HLA antigens are presented to donor T-cells by host macrophages**
  - **Donor T-cell activation, blast transformation, clonal proliferation and differentiation**
  - **Donor effector cells damage recipient target tissues**
- **Blood component implicated in TA-GVHD**
  - **All cellular components**

    RBCs, leukocytes, platelets
  - **There is no report from plasma components**

III TA-GVHD / Prevention

- **Remove T-lymphocyte by filtration cannot guarantee removal of sufficient lymphocytes to prevent GVHD**
- **Inactivation of transfused lymphocytes by gamma irradiation of components do not reduce immunogenicity**
- **Granulocyte retain normal antibacterial and chemotactic function**

I Administration of Blood Components
Irradiated RBC



- RBC become damaged by irradiation upon prolonged storage. Increased levels of potassium in supernatant has been noted to double within 1-2 days.
- Expired on their original outdate or 28 days from the date of irradiation, whichever come first
- Some hospitals elected not to store irradiated RBC > 48 hours for neonatal or infant transfusion
- For patients susceptible to hyperkalemia , irradiation just prior to transfusion or removal of the supernatant plasma

II Administration of Blood Components Irradiated Platelet

- **Significant changes in cell function have not been shown in platelets kept for 5 days**
- **No change in storage time**

Indications for Transfusion of Irradiated Cellular Components

- Haematopoietic stem cell transplant recipients (autologous or allogenic) from the time of conditioning chemotherapy onwards
- Immunologic immaturity (fetus/premature infant)
  - Intrauterine transfusion
  - Exchange transfusion
- Acquired T-cell defects
  - BM / PBSC transplant recipients (allogeneic / autologous)
  - Hodgkin's disease
- Haplotype sharing between donor and recipient

  Transfusion from blood relatives

Pimpun Kitpoka,M.D.

Emergency Blood and Transfusion Support for Trauma

Pimpun Kitpoka, M.D.

I Massive Transfusion

Table 2 TBV estimation: TBV for paediatrics (in ml kg^{-1} body weight)

Patient	Estimation of TBV (ml kg^{-1} body weight)
Neonate (0–4 kg)	85
Infant (5–9 kg)	85
Young child (10–24 kg)	75
Older child (25–49 kg)	70
Young adult (≥50 kg)	Use Gilcher's rule in Table 1

Table 1 TBV estimation: TBV for adults based on Gilcher's rule of five for blood volume (in ml kg^{-1} body weight)

Patient	Fat	Thin	Normal	Muscular
Male	60	65	70	75
Female	55	60	65	70

The 3 most common definitions of massive transfusion in adult patients are

- **Transfusion of ≥ 10 RBC units, which approximates the total blood volume (TBV) of an average adult patient, within 24 hours**
- **Transfusion of > 4 RBC units in 1 hour with anticipation of continued need for blood product support**
- **Replacement of > 50% of the TBV by blood products within 3 hours**

Total Blood Volume Estimation

Pham H.P. and Shaz B.H. British Journal of Anaesthesia. 2013; 111(S1): i71-i82

Pimpun Kitpoka,M.D.

II Massive Transfusion

- **Trauma patients were typically treated with RBC plus crystalloid, with hemostatic products such as platelets, plasma, and cryoprecipitate based on laboratory test.**

- **More aggressive approach, focused on early transfusion with plasma, platelets, and RBCs in fixed ratio (eg, 1:1:1). For platelets, the "1" refers to a single whole blood derived platelet concentrate and not 1 apheresis platelet unit)**

- **Massive transfusion protocols (MTPs) are designed to rapidly provide blood components in a balanced ratio of plasma and platelets to RBCs, particularly when laboratory testing is not rapid enough.**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

Comparison of Crystalloid and Colloid Solutions

	Crystalloid	Colloid
Intravascular retention	Poor	Good
Peripheral edema	Common	Possible
Pulmonary edema	Possible	Possible
Easily excreted	Yes	No
Allergic reactions	Absent	Rare
Cost	Inexpensive	Expensive

Transfusion Medicine. 2nd edition. 2005.

III Massive Transfusion

- **Typical ratios of plasma and platelets to RBCs range from 1:1:1 to 1:1:2. There is no statistically significant difference in recipient survival in these trauma setting.**
- **It is common to incorporate fixed ratios (ie, 1:1:1 or 1:1:2) into local MTPs to improve the speed and simplicity of the initial response.**
- **Issue uncrossmatched RBC group O if the recipient's ABO group is unknown. Indicate on the tag or label attached to the unit that compatibility testing was not completed**
- **Begin compatibility tests promptly. If incompatibility is detected, the recipient's physician should be notified as soon as possible.**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

IV Massive Transfusion / Emergent Transfusion

- **Blood administration after nongroup-specific transfusion**
  - **Group O RBC units in additive solution contain minimal residual plasma, which minimized passive transfusion of anti-A and anti-B. Therefore, switching to ABO identical RBC can be done safely.**
  - **Once a sample is received and the recipient's ABO and Rh type are determined, the recipient can begin receiving group-specific components, as the consumption of type O cells by one patient will deplete inventory needs for other patients.**
  - **An occasional recipient may exhibit a transient positive direct antiglobulin test (DAT) result.**

- **If possible, an abbreviated crossmatch, such as immediate spin (IS) crossmatch, should be performed to confirm the ABO compatibility of the units administered.**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

Red Blood Cell Component Availability for Emergency

Component	Availability	Principle Immunohematologic Risks
Group O RBCs*	0 – 5 minutes	Hemolytic transfusion reaction resulting from patient's red cell alloantibody
ABO and Rh-type identical uncrossmatched RBCs	10 – 15 minutes	Hemolytic transfusion reaction resulting from ABO-incompatible transfusion or other alloantibody present in the patient
Crossmatched RBCs	40 – 60 minutes	Hemolytic transfusion reaction

*** D-negative for females of childbearing potential**

Transfusion Therapy Clinical Principles and Practice. 2nd ed. 2005

Pimpun Kitpoka,M.D.

I Complications of Massive Transfusion
Citrate Toxicity

- **Rapidly transfused large volumes of citrated blood, particularly in liver disease, citrate levels may rise, binding calcium, resulting in hypocalcemia..**
- **Hypocalcemia leads to symptoms of perioral and peripheral tingling, shivering, and light-headedness, followed by a diffuse sense of vibration, neuronal excitability, muscle cramps, fasciculations, spasm, and nausea.**
- **In the CNS, hypocalcemia increase the respiratory center sensitivity to carbon dioxide, causing hyperventilation. Hypocalcemia decreased myocardial contractility and systemic vascular resistance because myocardial contraction is dependent on intracellular movement of ionized calcium.**
- **Hypocalcemia can be treated by slowing the blood infusion and Intravenous replacements with calcium gluconate or calcium chloride**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

Pimpun Kitpoka,M.D.

II Complications of Massive Transfusion
Hyperkalemia

- **When RBC are stored at 1-6°C, the intracellular potassium gradually leaks into supernatant. The total extracellular potassium is < 0.5 mEq for fresh RBC and only 5-7 mEq for expired units. These rarely cause problems in the recipient because of rapid dilution.**

- **However, hyperkalemia can be a problem in patients with renal failure, premature infants, and newborns receiving large transfusions, such as in cardiac surgery or exchange transfusion.**

- **No treatment or preventive strategy for hyperkalemia is usually necessary.**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

Pimpun Kitpoka,M.D.

III Complications of Massive Transfusion
Hemostatic Abnormalities

- **When the lost blood is initially replaced with RBCs and crystalloids, coagulopathy is frequently ascribed to the dilution of platelets and clotting factors.**

- **Studies demonstrated a progressive increase in the incidence of microvascular bleeding (MVB), after replacement of 2 to 3 blood volumes (20 to 30 units).**

- **There is frequently discordance between the laboratory assessment and the clinical evidence of bleeding. Low fibrinogen (<100) and platelet counts (≤50,000) are better predictors of hemostatic failure than elevations of PT and PTT.**

Fung MK, ed. AABB Technical Manual, 19th , 2017.

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IV Complications of Massive Transfusion
Hemostatic Abnormalities

- **Transfusion of the equivalent of 1 whole blood–derived platelet unit per 10 kg for the patient whose platelet count is less than 50,000/μL**
- **Transfusion of FFP if the INR is over 1.5**
- **Transfusion of cryoprecipitate if the fibrinogen concentration is ≤ 1 g/L. Distinguishing between a dilutional coagulopathy and DIC in a massively transfused patient depends on the D-dimer level.**
- **Antifibrinolytics may have a role. Tranexamic acid should be given as early as possible.**

Hui et al,Blood component therapy and massive transfusion inCritical Care Obstetrics,6th ed.2019.

Pimpun Kitpoka,M.D.

Common Blood Component Alternatives

Content (s)	Common dosage	Blood component substitute
Fibrinogen	70 mg/kg	Cryoprecipitates
Factor VIIa	40 – 90 mcg/kg	FFP, plasma
VWF, FVIII	40 – 60 units/kg	Cryopecipitates
FII, FVII, FIX, FX, Proteins C and S	30 units/kg	FFP, plasma

Hui et al,Blood component therapy and massive transfusion inCritical Care Obstetrics,6th ed.2019.

Pimpun Kitpoka,M.D.

Practice Guidelines for Blood Component Therapy in Surgery and Trauma

Blood Component	Indications	
Platelet concentrates	Massive transfusion Cardiopulmonary bypass surgery Neurologic surgery Ophthalmologic surgery	Platelet count < 80-100,000/μL
	Other surgery	Platelet count < 50-80,000/μL
Fresh Frozen Plasma	PT INR > 1.5 (>1.3 for neurologic, ophthalmologic surgery) and / or aPTT > 1.5 times the top of the reference range	
Cryoprecipitate	Fibrinogen < 100 mg/dL	

PT = prothrombin time; aPTT = activated partial thromboplastin time ; INR = international normalized ratio.

Transfusion Therapy Clinical Principles and Practice. 2nd ed. 2005

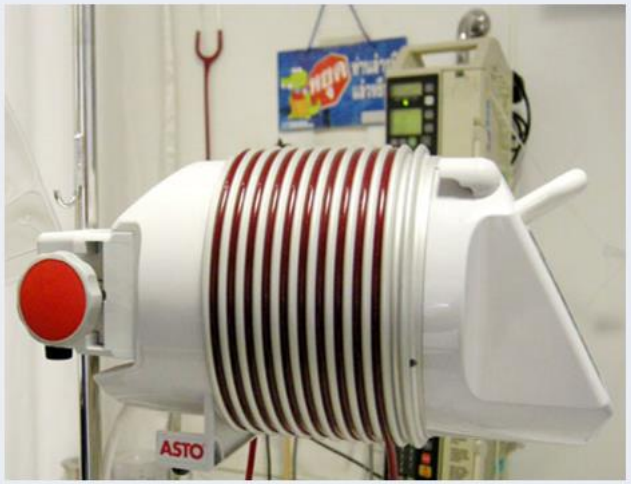
V Complications of Massive Transfusion
Hypothermia

- **Hypothermia below 30 °C may result in ventricular arrhythmias and worsened coagulopathy. Massively transfused blood should pass through blood warmers that do not cause thermal injury to RBCs.**

- **Use only the temperature-monitored blood warmer to avoid hemolysis.**

  Indications for blood warming:

  - **Adults receiving blood > 50 mL/Kg/hr**
  - **Children receiving blood > 15 mL/Kg/hr**
  - **Patients with clinically active cold agglutinin**
  - **Rapid infusion of blood through central lines (cold blood may induce arrhythmias)**



Fung MK, ed. AABB Technical Manual, 19th , 2017
Look It Up! (A Quick Reference in Transfusion Medicine) AABB Press Bethesda,Maryland 2006.

Pimpun Kitpoka,M.D.

Potential Complications of Massive Transfusion

- Dilutional thrombocytopenia
- Dilutional coagulopathy
- Hypothermia
- Hypocalcemia
- Hyperkalemia
- Adult respiratory distress syndrome due to microaggregates

Transfusion Medicine. 2nd edition. 2005.

Pimpun Kitpoka,M.D.

Massive Transfusion Protocols

When developing an MTP, it should have the following components :

- **When and who should initiate MTP**
  Bleeding is unexpected and blood loss is large.
- **Notification of the transfusion service regarding start and stop of MTP.**
- **Blood product preparation and delivery (predetermined composition packages eg. 1:1:1, 1:1:2)**

Fung MK, ed. AABB Technical Manual, 19th , 2017.
Hui et al,Blood component therapy and massive transfusion inCritical Care Obstetrics,6th ed.2019.

Pimpun Kitpoka,M.D.

I Massive Transfusion Protocol / Ramathibodi Hospital

Package	Blood Product	Remark	Laboratory Turn Around Time (min)		
			Initial Crossmatch	Group specific Uncrossmatch	Group O Uncrossmatch
1	1.1 RBC gr. O ที่คลังเลือดเก็บ Stand by ไว้ให้ในตู้เก็บเลือดที่ ER และ OR	ต้องเจาะเลือดผู้ป่วยก่อนให้ PRC gr. O จำนวน 2 tube EDTA + Clotted Blood (6 mL)			5
	1.2 RBC 3 units	ต้องเจาะเลือดผู้ป่วยก่อนให้ PRC gr. O			5
	1.3 RBC 3 units	มีประวัติ ABO blood group จากประวัติเดิมอย่างน้อย 2 ครั้ง สามารถเลือกเป็น group specific ได้ แต่ต้องเจาะเลือดผู้ป่วยเพื่อทดสอบความเข้ากันได้	15	10	

II Massive Transfusion Protocol / Ramathibodi Hospital

Package	Blood Product	Remark	Laboratory Turn Around Time (min)		
			Initial Crossmatch	Group specific Uncrossmatch	Group O Uncrossmatch
2	RBC 6 units	ต้องเจาะเลือดผู้ป่วยเพื่อทดสอบความเข้ากันได้	15	10	
	FFP 2 units		30		
	LPPC 1 set (~6 unit of PC) or SDP 1 unit	ในภาวะขาดแคลน อาจไม่ได้ตามที่กำหนดไว้	10		
3	RBC 6 units	ต้องเจาะเลือดผู้ป่วยเพื่อทดสอบความเข้ากันได้	15	10	
	FFP 2 units		30		
	LPPC 1 set (6 unit of PC) or SDP 1 unit	ในภาวะขาดแคลน อาจไม่ได้ตามที่กำหนดไว้	10		
	CPP 10 units		30		

III Massive Transfusion Protocol / Ramathibodi Hospital

Package	Blood Product	Remark	Laboratory Turn Around Time (min)		
			Initial Crossmatch	Group specific Uncrossmatch	Group O Uncrossmatch
4	RBC 10 units	ต้องเจาะเลือดผู้ป่วยเพื่อทดสอบความเข้ากันได้	15	10	
	FFP 10 units		30		
	LPPC 2 set (~12 unit of PC) or SDP 2 units	ในภาวะขาดแคลน อาจไม่ได้ตามที่กำหนดไว้	10		

BLOOD BANK DEPARTMENT OF PATHOLOGY,

RAMATHIBODI HOSPITAL

Accreditation No. 4033/50

โปรดเขียนด้วยบรรจงให้อ่านได้ชัดเจนทั้ง 4 แผ่น

CLINICAL INDICATION.....

Date..... Age ..... Yrs.

Name..... Sex □ Male □ Female

H.N. ..... Clinic/Ward .....

Name of Blood Drawer .....

TYPE OF BLOOD REQUESTED

			Unit
□ 1.	* PRC	Packed Red Cell	
□ 2.	* LPB	Leukocyte poor red blood cell	
□ 3.	* LPBF	Leukocyte poor red blood cell, filtration	
□ 4.	* LPBI	Leukocyte poor red blood cell, filtration & irradiation	
□ 5.	* SDRF	Single donor red cell, filtration	
□ 6.	* SDFI	Single donor red cell, filtration & irradiation	
□ 7.	* LPPC	Pooled leukocyte poor platelet concentrate 4 u	
□ 8.	* LPPF	Pooled leukocyte poor platelet concentrate, filtration 4 u	
□ 9.	* LPPI	Pooled leukocyte poor platelet concentrate, filtration & irradiation 4 u	
□ 10.	* SDP	Single donor platelet, closed system	
□ 11.	* SDPF	Single donor platelet, filtration	
□ 12.	* SDPI	Single donor platelet, filtration & irradiation	
□ 13.	* SDG	Single donor granulocyte	
□ 14.	* FFP	Fresh Frozen Plasma	
□ 15.	CRP	Cryo Removed Plasma	
□ 16.	CPP	Cryoprecipitate	
□ 17.	Fibrin Glue 100 IU/2 ml +set		
□ 18.	Fibrin Glue 250 IU/2 ml +set		
□ 19.	Fibrin Glue 250 IU/5 ml +set		
□	Other preparation		

□ 20 * **AUTOLOGOUS BLOOD**.....

Previous Tx □ No □ Yes When .....

Type of request □ Stat □ Today

□ Preoperative □ Type & screen (T/S)

Time & Date of Blood to be used .....

LAB. REQUEST

□ 21.* ABO group .....

□ 22.* Rh (D) ..... □ * Rh (Complete typing) .....

□ 23.* DCT Direct Coombs test .....

□ 24.* ICT Indirect Coombs test .....

□ 25.* Ab. Identification .....

DONOR : unit number Group

Massive Blood Transfusion Package 1

Massive Blood Transfusion Package 2

Massive Blood Transfusion Package 3

EMERGENCY REQUEST. I certify that the urgency of the medical condition of my patient is sufficiently grave to warrant the use of :

□ Initial crossmatched blood (15 min)

□ Group specific uncrossmatched blood (5 min)

□ Group O packed red cell uncrossmatched blood (promptly issue) and direct that the blood bank personnel provides the blood immediately.

I accept full responsibility for this request.

Sign.....**M.D.**

Order by : .....**M.D.** **Examined by :** .....

หมายเหตุ * เป็นการทดสอบที่ได้รับการรับรอง ISO 15189 จากสำนักมาตรฐาน ห้องปฏิบัติการ ศูนย์วิทยาศาสตร์การแพทย์ กระทรวงสาธารณสุข

10000269

Fo-WI-LAG-001/006 Rev.1 01/05/52 F-LAG-017 1 พ.ค. 52

ใบรับเลือด หน่วยคลังเลือด คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

วันที่.....H.N. .....

ชื่อ.....Ward .....

รหัส	ชนิดของเลือด	จำนวนยูนิต
600020	□ Packed red cell (PRC)	
600013	□ Leukocyte poor red blood cell (LPRC) โดยวิธี centrifugation	
600014	□ Leukocyte depleted red blood cell โดยวิธี Filtration	
600021	□ Leukocyte depleted red blood cell, Filtration and irradiation	
600032	□ Single donor red cell, filtration (SDRF)	
600033	□ Single donor red cell, filtration and irradiation (SDFI)	
600015	□ Autologous blood	
600001	□ Platelet concentrate	
600023	□ Pooled leukocyte poor platelet concentrate (LPPC) 4 unit	
600044	□ Leukocyte depleted platelet concentrate 4 units (Filtration method)	
600045	□ Leukocyte depleted platelet concentrate 4 units (Filtration and irradiation)	
600026	□ Single donor platelet closed system	
600027	□ Single donor platelet closed system, filtration	
600028	□ Single donor platelet closed system, filtration and irradiation	
600025	□ Single donor granulocyte	
600002	□ Fresh frozen plasma	
600034	□ Fresh frozen plasma, filtration	
600035	□ Fresh frozen plasma, filtration and irradiation	
600030	□ Cryoprecipitate-removed plasma (CRP)	
600003	□ Cryoprecipitate	
600048	□ Fibrin Glue 100 IU/ 2 mL (No Set)	
600051	□ Fibrin Glue 100 IU/ 2 mL (With Set)	
600049	□ Fibrin Glue 250 IU/ 2 mL (No Set)	
600052	□ Fibrin Glue 250 IU/ 2 mL (With Set)	
600050	□ Fibrin Glue 250 IU/ 5 mL (No Set)	
600053	□ Fibrin Glue 250 IU/ 5 mL (With Set)	

Massive Blood Transfusion Package 1

Massive Blood Transfusion Package 2

Massive Blood Transfusion Package 3

รหัส	ค่าบริการอื่นๆ	จำนวน
600029	□ ค่าบริการฉายแสงเลือด	
600091	□ Double bag 450 mL	
600092	□ Transfer bag 300 mL	
600093	□ Transfer bag 600 mL	
600094	□ Transfer bag, Aliquot	
600054	□ เชื่อมถุงโลหิตด้วยเครื่องอัตโนมัติ	
600095	□ Single bag CPD-A1 450 mL	
600099	□ Leukocyte removal from RBC by filtration	
600100	□ Leukocyte removal from platelet by filtration	
600096	□ Plasma transfer set	
600097	□ Blood warmer set	
600098	□ Normal saline solution (NSS) 100 mL	
600089	□ การเตรียม ABO incompatible Bone Marrow	
600090	□ การปั่นแยก Bone Marrow	
.....	□ Other Preparation.....	

ผู้ขอรับเลือด : .....

Fo-WI-LAG-001/009 Rev.1 01/03/54 F-LAG-024 1 มี.ค. 54 10000141

Pimpun Kitpoka,M.D.

Neonatal and pediatric Transfusion

Pimpun Kitpoka, M.D.

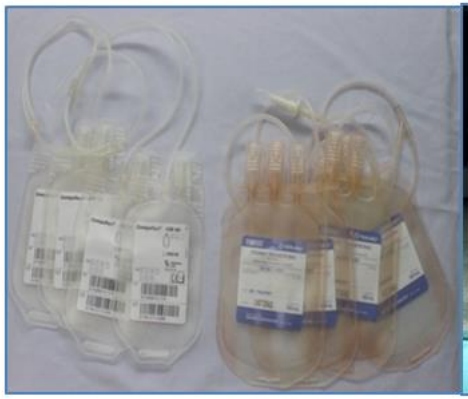
I Neonatal and Pediatric Transfusion Practice
Transfusion Administration

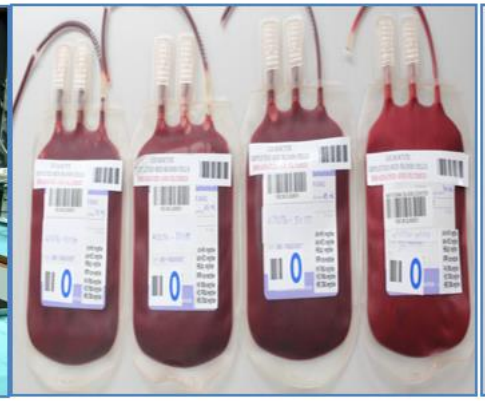
Partial unit for pediatrics patients

- on request : RBC
- Inventory : plasma

RBC Additive Solution

- Theory concern - large volumes of adenine and mannitol associated with renal toxicity
- Mannitol , an osmotic diuretic associated with fluid shifts, may affect cerebral blood flow in infants. Small-volume (5-15 mL/kg) transfusions are safe. However, for infants with renal or hepatic insufficiency, it is recommended that AS should be removed from RBC units, particularly in multiple transfusion.






II Neonatal and Pediatric Transfusion Practice
Transfusion Administration

CMV

- May be transmitted to neonates transplacentally, during birth process, via breast milk, or a postpartum because of close contact.
- Multitransfused neonates born to seronegative mothers may benefit from CMV-reduced-risk (filtered blood or units collected from CMV-seronegative donors).

Volume Reduction and Washing

- Volume reduction, reduces the platelet count in the unit, is reserved for infants with fluid restrictions.
- Washing is performed to remove harmful maternal antibodies.

I Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

- **FNAIT is the platelet-specific version of HDFN; in contrast to HDFN that affects the subsequent pregnancies, FNAIT affects the first involved pregnancy**
- **A mother is homozygous negative for that particular paternal HPA antigen. Maternal immune globulin IgG alloantibodies directed against the paternally derived HPA cross the placenta, binding to the antigen expressed on the fetal platelets.**
- **Maternal antibody can be detected as early as 17 weeks' gestation, and the fetus may develop thrombocytopenia as early as 20 weeks' gestation.**
- **The most commonly implicated antigen is HPA-1a**

Concise guide to transfusion medicine. AABB Press.2017.

Pimpun Kitpoka,M.D.

II Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

Diagnosis

- **Testing maternal serum for platelet antibodies using assays that can differentiate platelet-specific from non-platelet-specific reactivity**
- **Performing platelet genotyping on parental DNA**
- **Demonstration of both a HPA antibody in the maternal serum and the corresponding incompatibility for the antigen in the parental platelet types confirms the diagnosis.**

Concise guide to transfusion medicine. AABB Press.2017.

Pimpun Kitpoka,M.D.

III Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) Treatment and Prevention

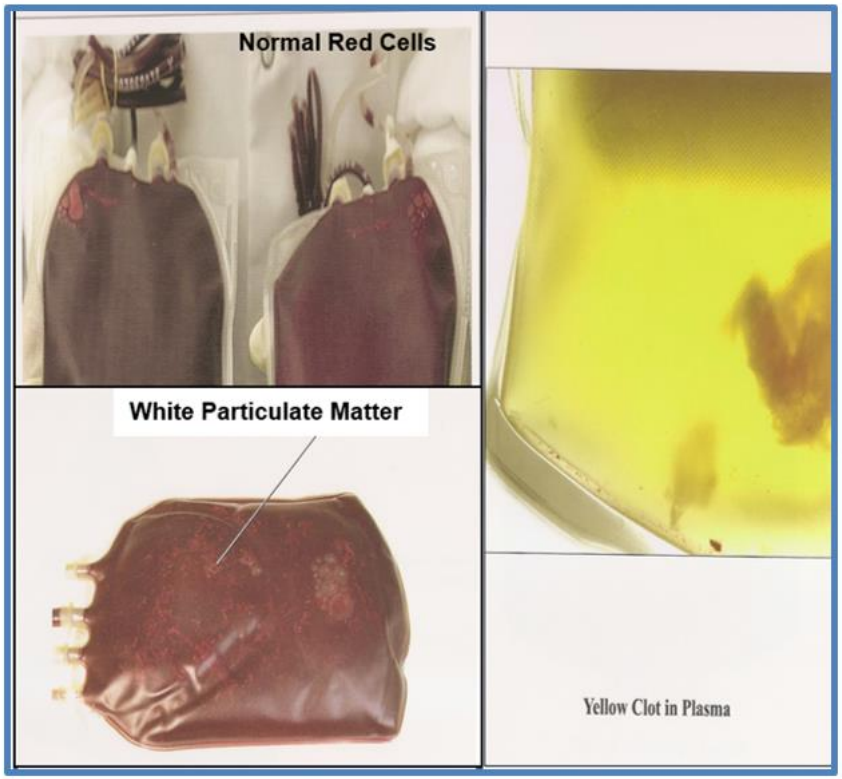
- **Prepregnancy counselling**
- **Prophylactic IVIG (1 g/kg) can be given on a weekly basis to the mother to reduce fetal thrombocytopenia and intracranial hemorrhage.**
- **After birth, high dose IVIG (eg, 400 mg / kg / day for 3 - 5 days) may increase the infant's platelet count within 24 - 48 hours.**
- **Platelet transfusion**
  - **ABO / Rh compatible , CMV reduced risk components**
  - **Compatible (antigen-negative) platelets**
  - **Minimize incompatible plasma (eg, volume reduction or washing)**
  - **If maternal platelets are used, wash and irradiate before transfusion in neonates**

Pediatric Transfusion A Physician's Handbook, 2nd (2006).

Pimpun Kitpoka,M.D.

I Administration of Blood Components

- Positive identification of the recipient and the designated blood unit to be transfused.
- Time limits for infusion. Components should be infused within 4 hours. The blood bank can divide components into aliquots as needed.



- Various blood elements, formed in the routine process of collection , manufacturing and storage, consisted of RBC , WBC , platelets, tissue plugs, fat or protein. Further classified into clots, fibrin strands , aggregates

- All blood components must be transfused through filters. Use a standard blood filter (150-280 micron).

Look It Up! (A Quick Reference in Transfusion Medicine) AABB Press Bethesda,Maryland 2006

Pimpun Kitpoka,M.D.

II Administration of Blood Components
Lipemic Plasma

Lipemic Plasma

Normal Plasma

- Excessive amount of fatty substances in blood
- Temporary and normal, following a high fat meal
- Chronic , associated with diseases
- Lipemia itself does not affect the safety of blood product

III Administration of Blood Components

- Use 0.9% Sodium Chloride for Injection, USP.
- DO NOT use 5% Dextrose solutions (may induce hemolysis).
- DO NOT use Lactated Ringer's
  (contains Ca^{++} which may induce clot formation in the blood bag and/or administration set).
- DO NOT add medication to blood or infusion set.
- Plasma (type compatible) or albumin (5%) are acceptable in special circumstances.

Look It Up! (A Quick Reference in Transfusion Medicine) AABB Press Bethesda,Maryland 2006

I Transfusion Support in Thalassemia

- **The availability of access to outpatient transfusion services on weekdays, weekends, and evenings is important for school-aged children and working adults.**
- **Serologic testing for hepatitis B and C and HIV should be performed as baseline measures.**
- **All patients who do not have serologic immunity to hepatitis B should start the vaccination program prior to transfusion and show evidence of immunity before the start of the transfusion.**
- **Transfusion reactions should be investigated and managed**

Standards for the clinical care of children and adults with Thalassemia in the UK (2016)
Standards of Care Guidelines for Thalassemia ; 2012: 1-5
Guidelines for the clinical care of patients with thalassemia in Canada, 2009.

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I Recommended Blood Product

- **Leucoreduced RBC (preferred pre-storage filtration) with a minimum haemoglobin content of 40 g**

- **Reduction to ≤1x 10^6 leucocytes per unit for eliminating adverse reactions attributed to contaminated WBC**
    - **FNHTR caused by HLA-antibodies in patients, cytokine reactions produced by donor leucocytes**
    - **HLA-alloimmunization**
    - **Transfusion-transmitted infections from cell-associated infectious agents such as cytomegalovirus**

- **When possible, large units less than 2 weeks of age are recommended.**

Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd edittion(2014)
Thalassemia International Federation

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II Recommended Blood Product

Blood Products for Special Patient Populations

- **Washed red cells** may be beneficial for patients who have repeated severe allergic transfusion reaction and IgA deficiency. Washing removes plasma proteins that target the antibodies in the recipient. Washed red cells that are not resuspended in storage solution must be transfused within 24 hours
- **Frozen red cells** are used to supply rare donor units for patients who have unusual red cell antibodies or who are missing common red cell antigens. 20% of the donor cells are lost in the washing after the freezing process.
- **Single donor red cells by apheresis** is prepared by collection of 2 units of red cells from the same donor for transfusion of one patient. The reduction of donor exposures decrease the risk of transmission of infections, alloimmunization and other transfusion-related complications.

Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd edittion(2014) Thalassemia International Federation

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Transfusion considerations
Blood selection and alloimmunization

- **The risk of alloimmunization is 1–16% per unit of blood.**
- **An alloantibody screen should be performed prior to each transfusion.**
- **Once alloimmunized, patients may be at risk for developing an autoantibody. Up to 10 percent of patients who have alloantibodies will develop an autoantibody. The presence of an autoantibody does not always result in decreased red cell survival.**
- **The patient's red cells should be phenotyped as fully as possible prior to transfusion. If the patients have already been transfused, antigen typing can be performed using molecular rather than serologic testing.**

Standards of Care Guidelines for Thalassemia ; 2012: 1-5

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Recommendations for Transfusion Therapy for Transfusion-dependent Thalassemia

	Thalassemia International Federation
Laboratory criteria initiating regular transfusion	Hb < 7 g/dL on 2 occasions, > 2 wk apart
Clinical criteria for initiating regular transfusion	facial changes; Poor growth ; fractures; clinically significant extramedullary hematopoiesis
Target **pretransfusion Hb** levels	Maintain between 9 and 10.5 g/dL; a higher target of 11-12 g/dL may be appropiate for patients with heart disease, clinically significant extramedullary hematopoiesis or other medical conditions , in adequate suppression of bone marrow activity

American Society of Hematology 2015. 454-461.

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Recommendations for Transfusion Therapy for Transfusion-dependent Thalassemia

	Thalassemia International Federation
Target postransfusion Hb levels	Should not exceed 14-15 g/dL
Frequency of transfusion	Every 2-5 wk
Product selection	Leukocytedepleted RBC with 40g Hb < 1 x 10^6 leukocyte per unit RBC matched for at least D,C,c,E,e and K Units stored in additive solution for < 2 wk Washed units for patients with repeated severe allergic transfusion reactions or IgA deficiency

American Society of Hematology 2015. 454-461.

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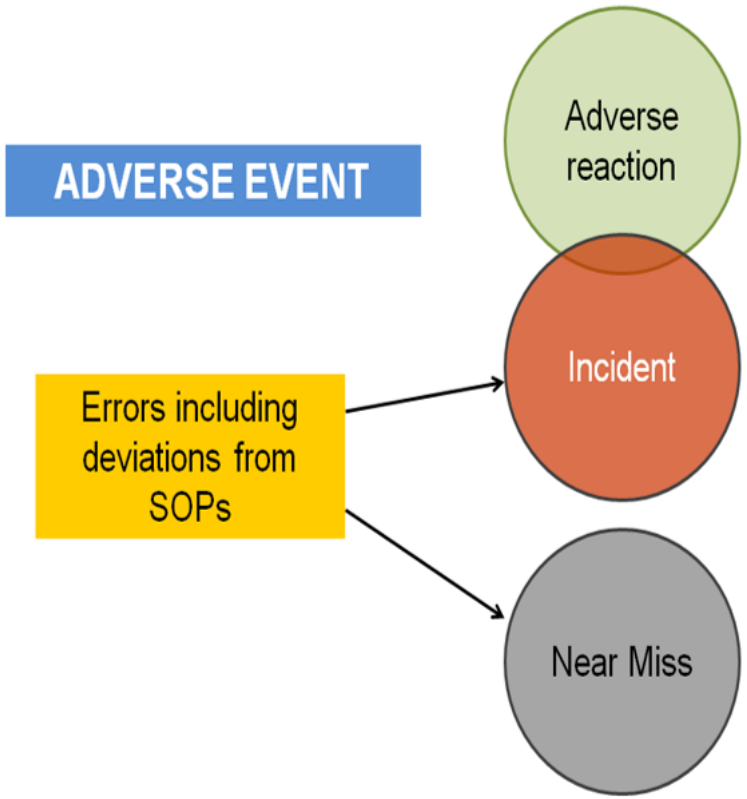
Transfusion Reactions



- **Transfusion Reaction :**
  Any unfavourable events which occur in patients during or following transfusion of blood product that can relate to that transfusion

- **Near miss : A near miss is an error or deviation from standard procedures or policies that is covered before the start of the transfusion and that could have led to a wrong transfusion**

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Acute Transfusion Reaction (ATR)

Reactions occurring at any time up to 24 hours following transfusion

- **Incorrect blood component being transfused (IBCT)**
- **Haemolytic transfusion reaction (HTR)**

- **Transfusion-related acute lung injury (TRALI)**
- **Transfusion-associated circulatory overload (TACO)**
- **Transfusion-associated dyspnea (TAD)**

- **Suspected bacterial contamination of the component (TTI)**

- **Febrile type reaction / febrile reactions associated with chills or involving a 2°C temp rise over baseline, or an absolute temp of 39°C**
- **Allergic type reaction**
- **Reactions with both febrile and allergic features**

Standards of Care Guidelines for Thalassemia ; 2012: 1-5

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Incorrect Blood Component Transfused-Specific Requirements Not Met (IBCT-SRNM)

- Transfusion of inappropriate specification blood or that did not meet the patient individual requirements
  - CMV - negative
  - Irradiated components
  - Antigen-negative red cells for patient with known antibodies
  - Failure to use blood warmer

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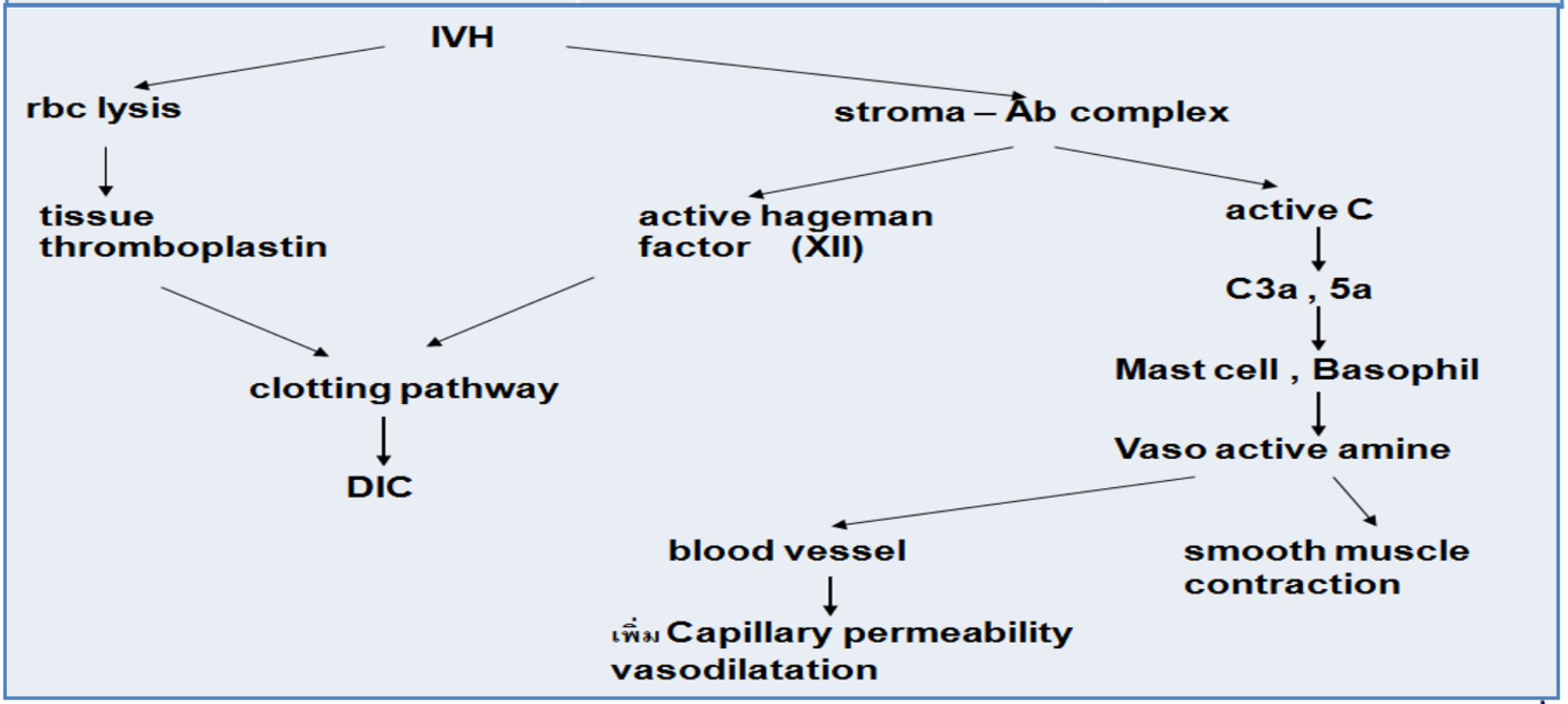
Immediate Immunologic Effects

Type	Usual Etiology	Prevention
Acute intravascular hemolysis	Red cell incompatibility (mostly ABO)	Avoid clerical errors ; insure proper sample and recipient identification



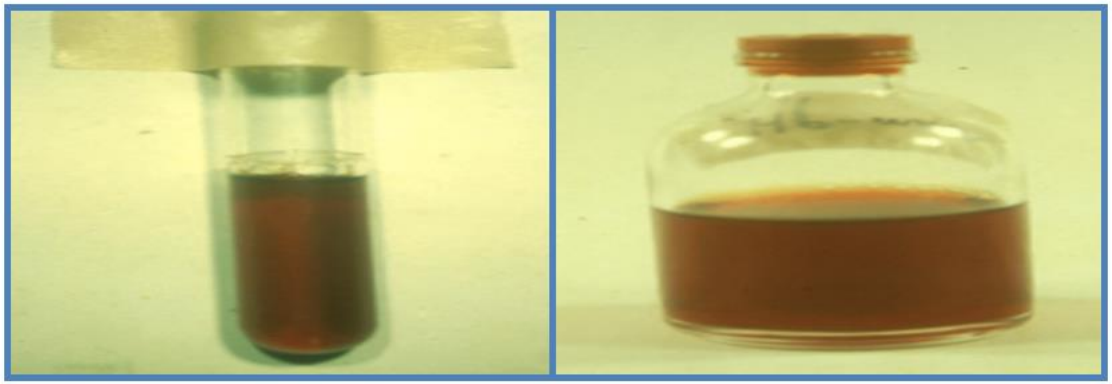
Immunologic Hemolytic Transfusion Reaction is Proven or Strongly Suspected When :

Acute HTRs are defined as fever and other symptoms/ signs of hemolysis within 24 hours of transfusion ; confirmed by one or more of the following :

- **A fall of Hb**
- **Rise in LDH**
- **Positive crossmatch**
- **Presence of free Hb in serum of posttransfusion specimens**
- **Disagreement of ABO typing on the patient's samples with a mixed-field pattern (2 cell population)**
- **Positive direct antiglobulin test (DAT) on posttransfusion sample**
- **Rising bilirubin level within 4-6 hours**

RBC Hemolysis

	Intravascular	Extravascular
• Complement activation	C5-C9 complex	C3b
• Destruction of incompatible RBC	within blood circulation	Ab-coated RBC with or without c') will be removed by RE cell in spleen
• Laboratory finding	Hemoglobinaemia Hemoglobinuria ↓ Haptoglobin ↑ Indirect bilirubin	↑ indirect bilirubin



Haemoglobinemia Haemoglobinuria

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Intravascular Hemolysis

- **Treatment**
  - **stop transfusion, keep vein open**
  - **supportive and specific Rx**
- **Management for further blood transfusion**
  - **RBC compatible with patient and donor PLASMA**
  - **Plasma compatible with patient and donor RBC**
- **Example patient gr. O received blood gr. A**
  - **RBC group O**
  - **Plasma group A, AB**

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Immediate Immunologic Effects

Type	Usual Etiology	Prevention
Febrile nonhemolytic reaction	Antibodies to donor's WBC Cytokines	Pretransfusion antipyretic; leukocyte reduced blood component
Allergic	Antibodies to plasma protein	Pretransfusion antihistamine : washed red cell component
Anaphylaxis	Antibodies to IgA	Plasma from IgA deficient donor : washed red cell component

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Transfusion Management of Patients with Circulating IgA Antibodies

- **RBC transfusions : Give RBCs from unselected donors after washing in 0.9% NaCl.**
- **Platelet transfusions : Give single-donor platelets collected from IgA-deficient (< 0.05 mg/dL) donors by plateletpheresis. Alternatively, give fresh platelets from unselected donors after washing in buffered saline / PAS**
- **Fresh frozen plasma and cryoprecipitate transfusions : Give components collected from IgA-deficient donors by plasmapheresis**

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Transfusion-Related Acute Lung Injury (TRALI)

Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within 6 hours of transfusion, not due to circulatory overload or other likely causes.

HLA antibodies in donor

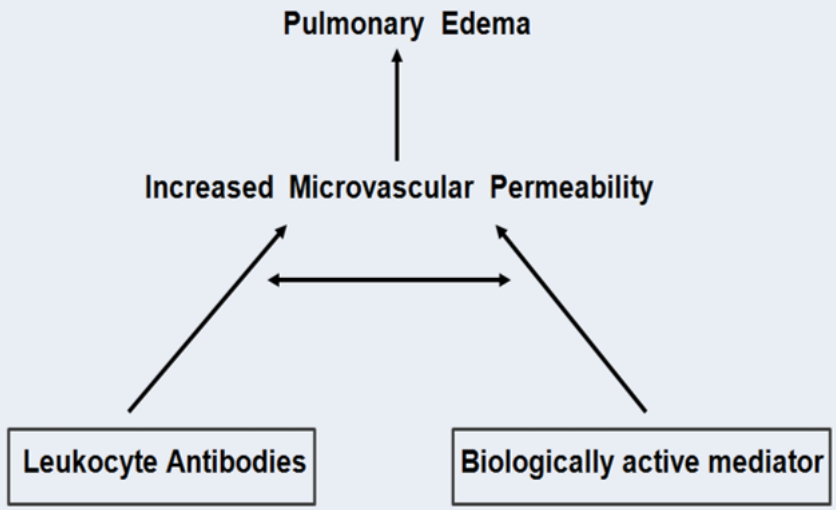
tissue Ag of recipient

Complement

Severe capillary damage

Leakage

Acute non cardiogenic pulmonary edema



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Transfusion-Associated Circulatory Overload (TACO)	Transfusion-Associated Dyspnea (TAD)
Cause of TACO characterised by any 4 of the following which occur within 6 hours of transfusion • Acute respiratory distress • Tachycardia • Increased blood pressure • Acute or worsening pulmonary edema • Evidence of positive fluid balance	TAD is characterised by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction. Respiratory distress in such cases should not be explained by the patient's underlying condition.

Transfusion-Transmitted Infections (TTI)

- **The recipient had evidence of infection post-transfusion, without evidence prior to transfusion, and an alternative source of infection.**

- **Plus**
  - **Either at least 1 component received by the infected recipient was donated by a donor with evidence of the same transmissible infection.**
  - **Or at least 1 component received by the infected recipient was shown contain the agent of infection.**

- **Cause currently include**
  - **Bacterial transmission from blood components.**
  - **Transmissions of viruses**
  - **Transmissions of other agents such as prions, protozoa and filaria.**

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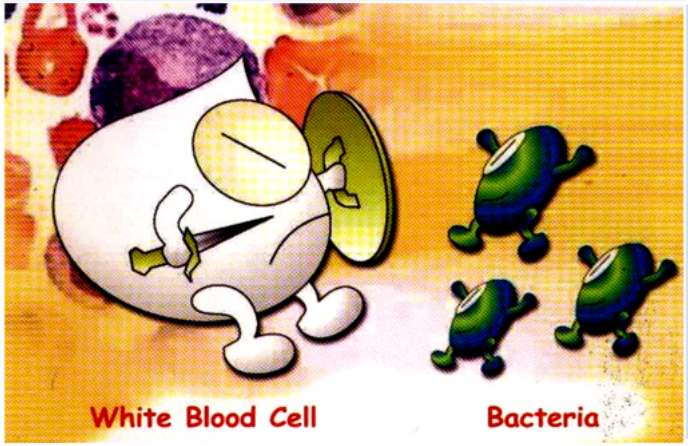
Immediate Nonimmunologic Effects

Type	Usual Etiology	Prevention
Bacterial sepsis	Contaminated blood component	Care in blood storage and collection



- 4 to 5% of transfusion hazards.
- 10 to 16% of transfusion reaction related death.
- Incidence 0.2 to 3.5 %
- More common in platelet than red cells.

Clinical Presentations of Transfusion Reactions Frequently Characterized by Fever

Signs/Symptoms	FNHTR	TRALI	Acute Hemolytic Reaction	Bacterial Contamination
Fever	+	++	++	++
Chills	++	++	++	++
Nausea/vomiting	+	-	++	+
Dypsnea	+	++	++	-
Cyanosis	-	++	-	-
Hypotension/shock	-	++	++	++
DIC	-	-	++	++
Hemoglobinuria	-	-	++	+
Renal failure	-	-	++	++
Back pain	-	-	++	-

From Transfusion Reaction AABB press, 2nd Edition, 2001

Septic Transfusion Reaction

- **Clinical Criteria within 4 hours of transfusion :**
  - **Fever > 39 °C or a change of > 2 °C.**
  - **or tachycardia > 120 bpm or a change of > 40 bpm,**
  - **or an change of > 30 mmHg in blood pressure**

- **Definite : Clinical criteria plus**

  Matching culture-positive residual component and recipient with the same bacteria as determined by antibiotic sensitivity

- **Probable : Clinical criteria plus**
  - **Culture-positive residual component,**
  - **or matching culture results in two different recipients of co-components**

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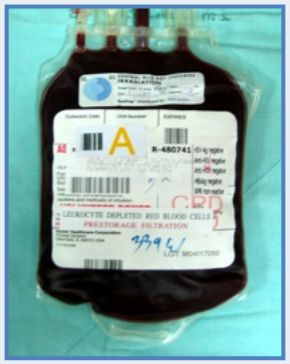
Delayed Immunologic Effects

Type	Usual Etiology	Prevention
Graft-vs-host disease 	Engraftment of transfused functional T lymphocytes	Irradiation of all cellular blood components containing lymphocytes

TA-GVHD is characterised by fever , rash , liver dysfunction, diarrhoea, pancytopenia and bone marrow hypoplasia occurring less than 30 days after transfusion. The condition is due to engraftment and clonal expansion of viable donor lymphocyte in a susceptible host.

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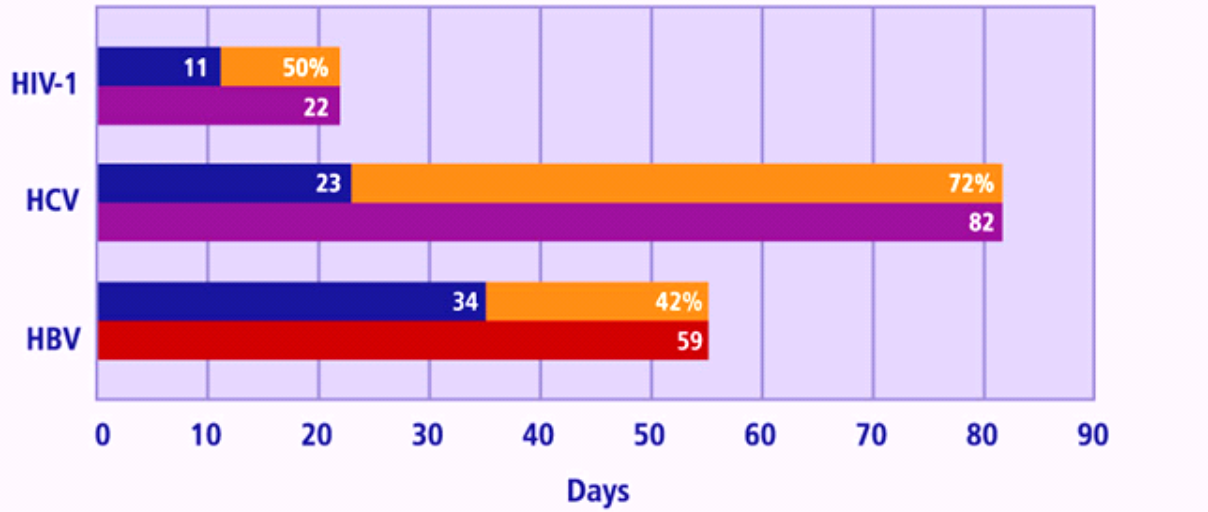
NAT Reduces Window of Detection

	Days of Infection to Procleix Detection	Days of Infection to Ab or Ag Detection	Reduction of Window by NAT
HIV-1	11	22	50%
HCV	23	82	72%
HBV	34	59	42%



1.J Linnen et al. Effect of Donor Mini-Pool Size on Closure of the Hepatitis B Virus (HBV) Donation Window: A Comparison of Triplex TMA to Surface Antigen Detection. Poster presentation. ISBT 2002 Vancouver, BC August 24-28, 2002
2. Package Insert for the Procleix HIV-1/HCV Assay, IN0076.I

Current risks of blood transfusion

Bacteria
Introduced during collection

Leukocytes
Advance immune responses
and transfusion reactions

TNV
'The Next Virus'

Known Pathogens
For which no assay is available

False Negatives
Limits of detection of current assays
(e.g., window period issues)

Photochemical Inactivation of Pathogens

Broad inactivation spectrum of known and emerging pathogens as well as leukocytes demonstrated in in vitro studies

Enveloped Viruses
- HIV-1/2
- HBV
- DHBV
- HCV
- BVDV
- HTLV- I/II
- CMV
- LCMV
- WNV
- SARS-CoV
- Vaccinia
- Chikungunya
- Dengue
- Influenza A virus

Non-Enveloped Viruses
- Bluetongue virus, type 11
- Feline calicivirus
- Parvovirus B19
- Human adenovirus 5

Gram-Negative Bacteria
- *Klebsiella pneumoniae*
- *Yersinia enterocolitica*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Salmonella choleraesuis*
- *Enterobacter cloacae*
- *Serratia marcescens*
- *Anaplasma phagocytophilum*
- *Orientia tsutsugamushi*

Gram-Positive Bacteria
- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Listeria monocytogenes*
- *Corynebacterium minutissimum*
- *Bacillus cereus (vegetative)*
- *Lactobacillus sp.*
- *Bifidobacterium adolescentis*
- *Propionibacterium acnes*
- *Clostridium perfringens*

Spirochetes
- *Treponema pallidum*
- *Borrelia burgdorferi*

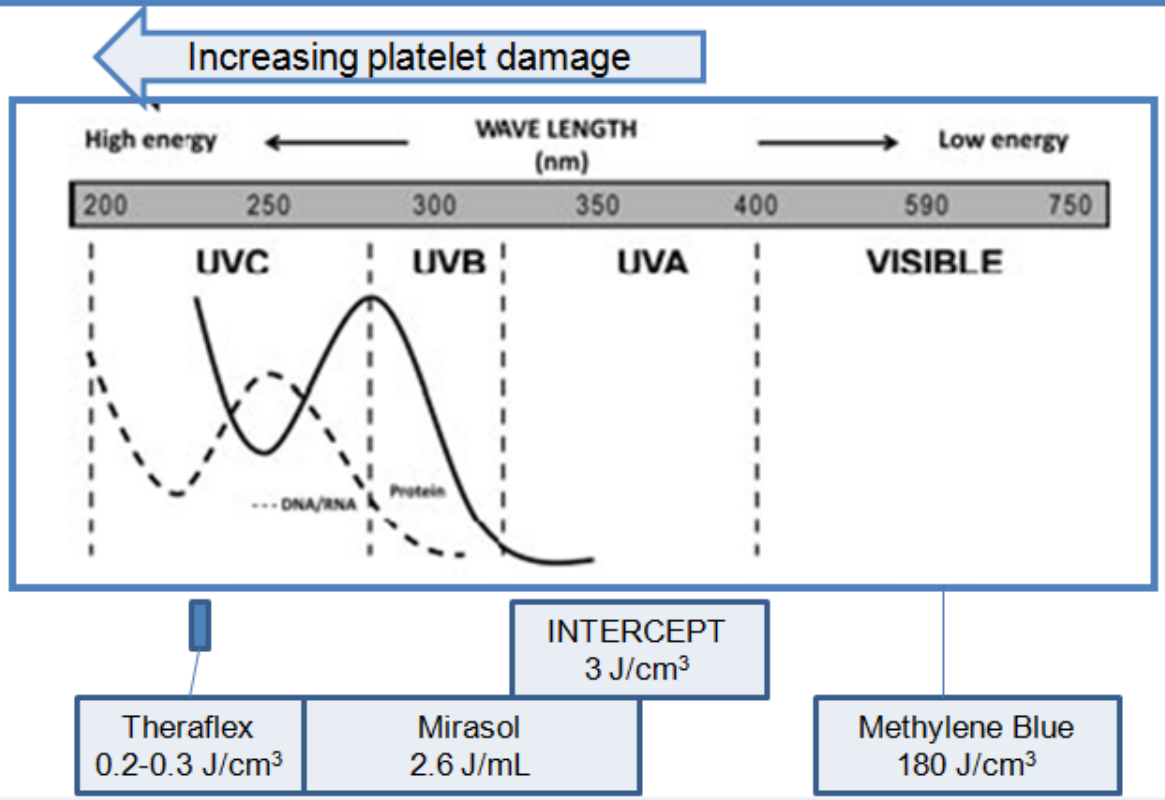
Parasites
- *Trypanosoma cruzi*
- *Plasmodium falciparum*
- *Leishmania sp.*
- *Babesia microti*

Leukocytes

Potential to replace gamma irradiation, bacterial detection and CMV testing

Pimpun Kitpoka,M.D.

Technologies for Platelet and Plasma Pathogen Inactivation
Comparison of Energy and Dose



- Due to the absorption spectrum of proteins and nucleic acids shown, UVC radiation is directly damaging to blood components at high doses.
- This impact is progressively less for UVB, UVA and visible light

C.V. ProwseSang .2013; 104.:183-199

Pimpun Kitpoka,M.D.

Plasma Pathogen Reduction Options

Process	Company	CE Marked	US (FDA)	Mechanism
Solvent detergent (Octaplas)	Octapharma (Switzerland)	Yes	No	Chemical ; pooled
Methylene blue + visible light (Theraflex)	Macopharma (France)	Yes	No	Photodynamic ; single donor
Amotosalen + UV (Intercept)	Cerus USA (CA , USA)	Yes	Yes	Photochemical ; Pooled
Riboflavin + UV (Mirasol)	Caridian (CO , USA)	Yes	No	Photochemical / photodynamic ; single donor

Transfusion Medicine Reviews, April , 2009; 23(2) : 124 - 133

Coagulation Factor Yields (%) for Various Plasma Pathogen Reduction Technologies

	Untreated	MB	SD	Amotosalen	Riboflavin
Fibrinogen	100	79	91	81	79
Factor V	100	90	65	96	79
Factor VIII	100	71	70	75	69
Factor XI	100	88	86	89	68
von Willebrand's factor multimers	100	100	50	100	70
ADAMTS 13	100	100	100	98	73
Protein S	100	100	57	95	98

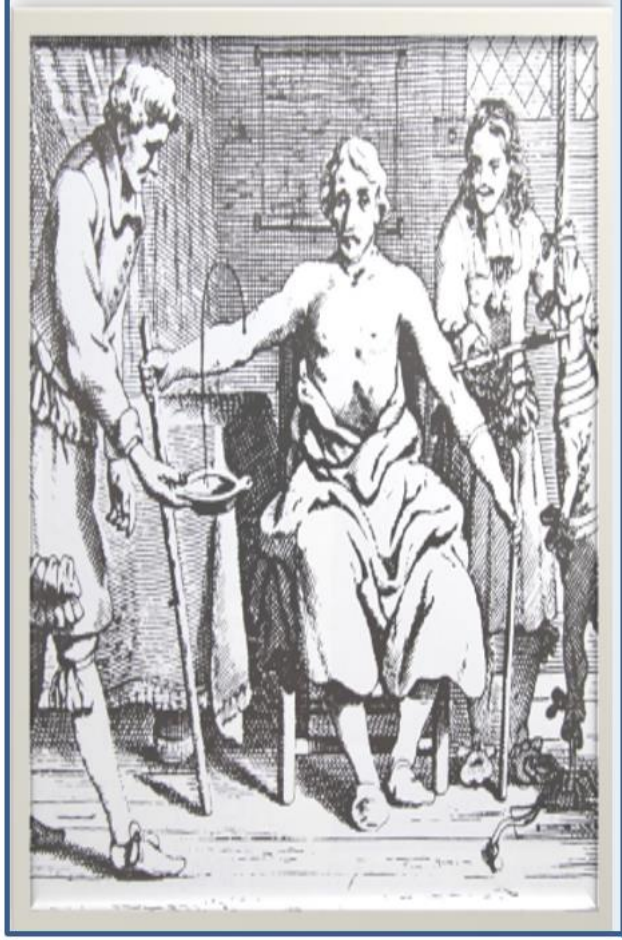
Christopher P. Propertiens of Pathogen-Inactivated Plasma Components. Transfusion Medicine Reviews, April, 2009;23(2):124 - 133

Technologies for Platelet Pathogen Inactivation

Product	Company	Compound / Technology	Trial / License Status
Plateles	Cerus	Amotosalen + UVA light[a] IINTERCEPT™ wavelength 320 - 420 nm	CE marked May 2002 (buffy coat εt apheresis to 7d storage) FDA Approval 2015
Platelets	TerumoBCT	Riboflavia εt UV light[c] *Mirasol*® wavelength 265 - 370 nm	CE marked Oct 2007 (buffy coat εt apheresis to 5d storage)
Platelets	Macopharma	UVC (254 nm) light *Teraflex*®	CE marked 2009 At phase II/III trial

C.V. Prowse. Component pathogen inactivation : a critical review. Vox Sanguinis (2013) 104, 183-199

Therapeutic Apheresis



- **Evolved since 1970**
- **The American Society for Apheresis (ASFA) Journal of Clinical Apheresis (JCA) Special Issue Writing Committee is charged with reviewing, updating and categorizing indications for the evidence-based use of therapeutic apheresis in human disease since 1985.**

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis:The Eighth Special Issue. J Clin Apher. 2019;34:171–354.

Pimpun Kitpoka,M.D.

Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary stand alone treatment or in conjunction with other treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a stand alone treatment or in conjunction with other treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis:The Eighth Special Issue. J Clin Apher. 2019;34:171–354.

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I Grading Recommendations, Strength and Quality of Evidence

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available

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II Grading Recommendations, Strength and Quality of Evidence

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

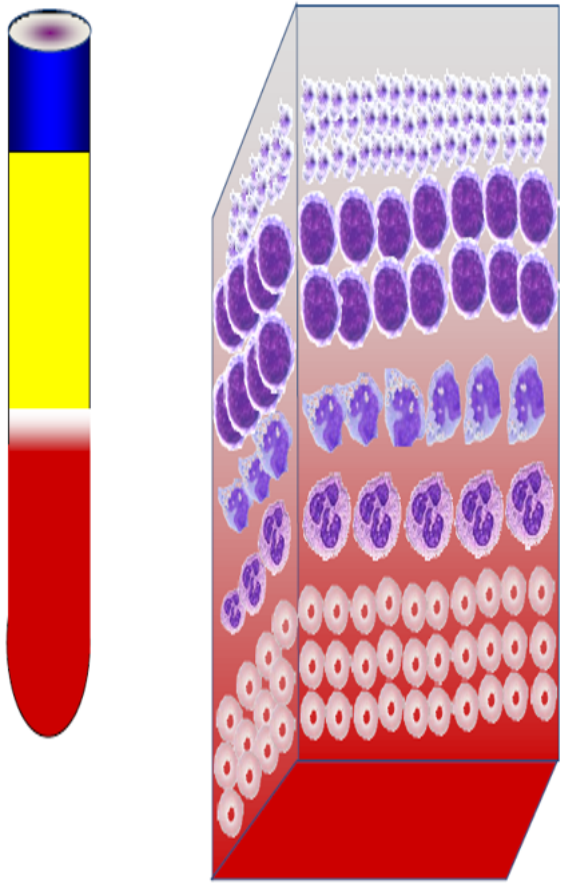
Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis:The Eighth Special Issue. J Clin Apher. 2019;34:171–354.

Principle of Blood Separation

Membrane Filtration	Centrifugation
Limited to plasma exchange	Multiple procedures Opportunity to provide both plasma and cellular therapies
Heparin	Citrate

Dobri Kiprov. Principles of Blood Separation and Apheresis Instrumentation

Separation of Blood Components within A Centrifugal Separation Chamber



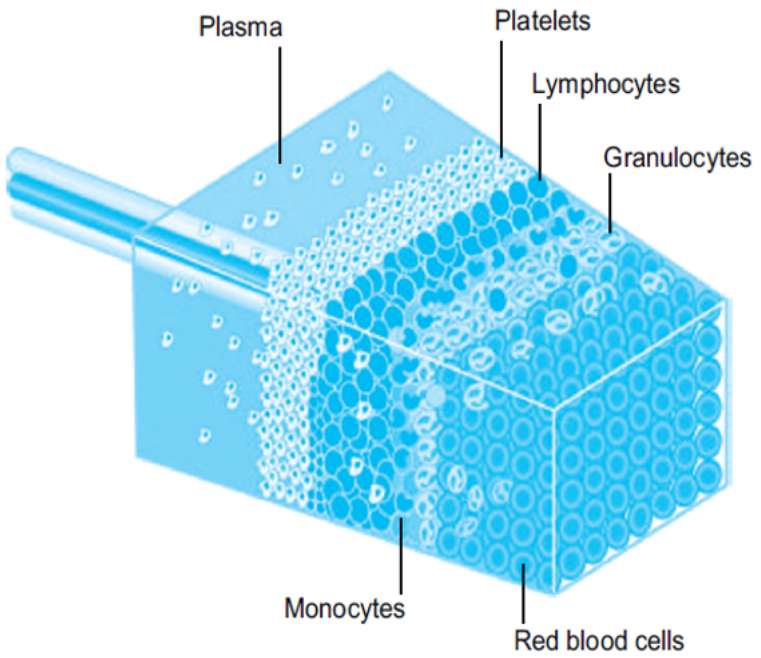
Platelets (1.040)

Lymphocytes (1.050-1.061)

Monocytes (1.065-1.069)

Granolocytes (1.087-1.092)

RBC



Blood component are separated based on their density. The densest elements (RBC) are farthest from the axis of rotation and the least dense (plasma) is closest

P. Huy P. et al. Overview of Therapeutic Apheresis. Transfusion Medicine and Hemostasis. .2013; 467-480
Dobri Kiprov. Principles of Blood Separation and Apheresis Instrumentation

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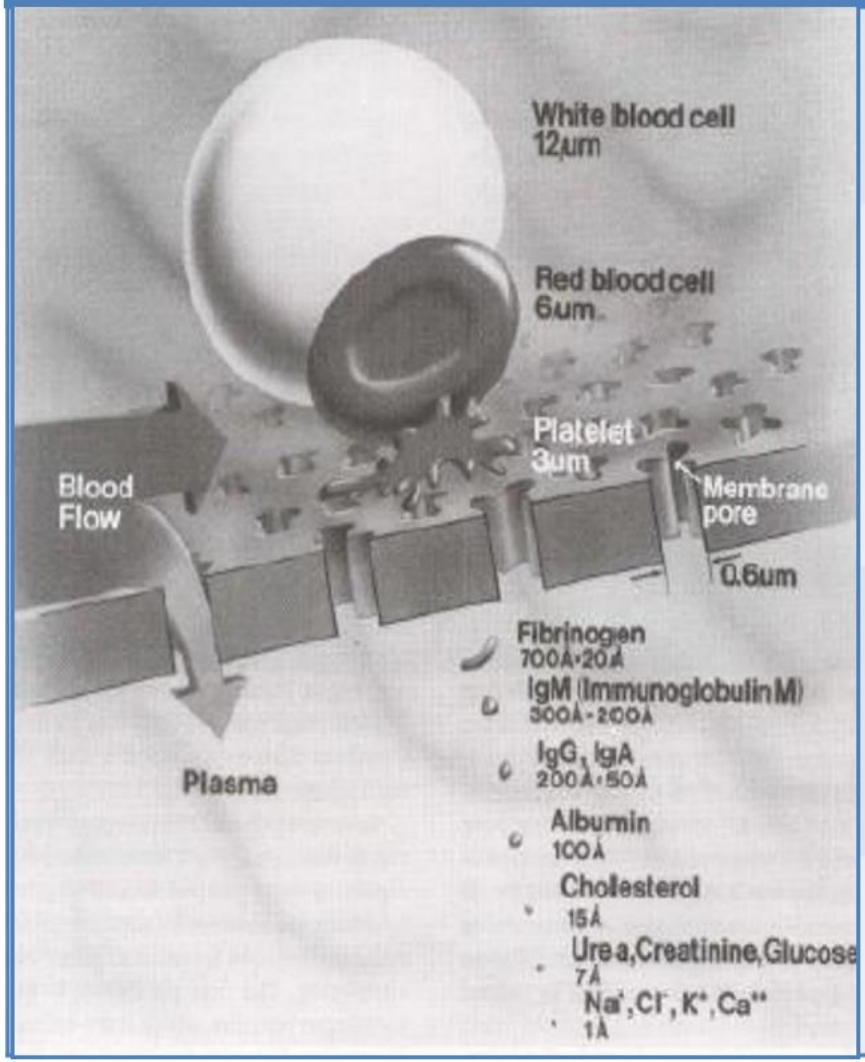
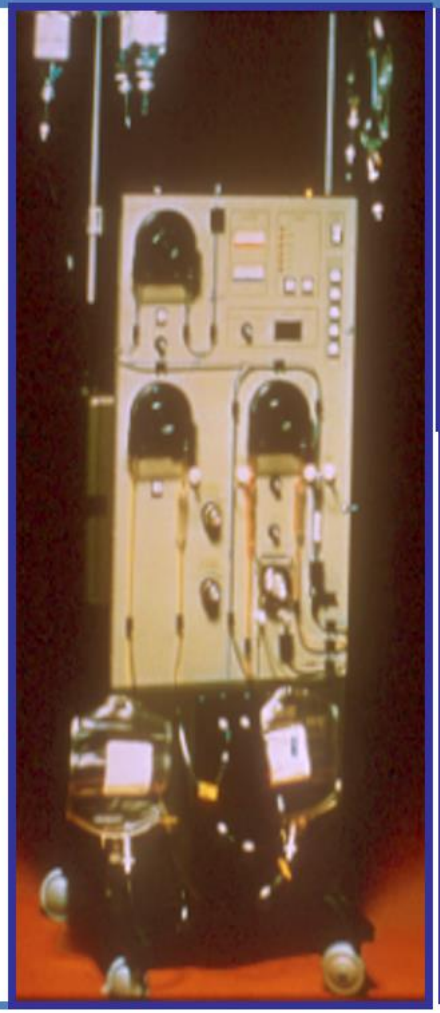
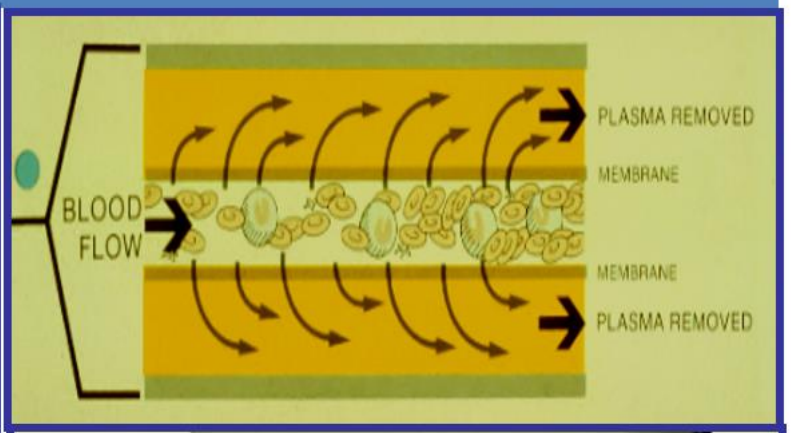
Membrane Plasma Separation

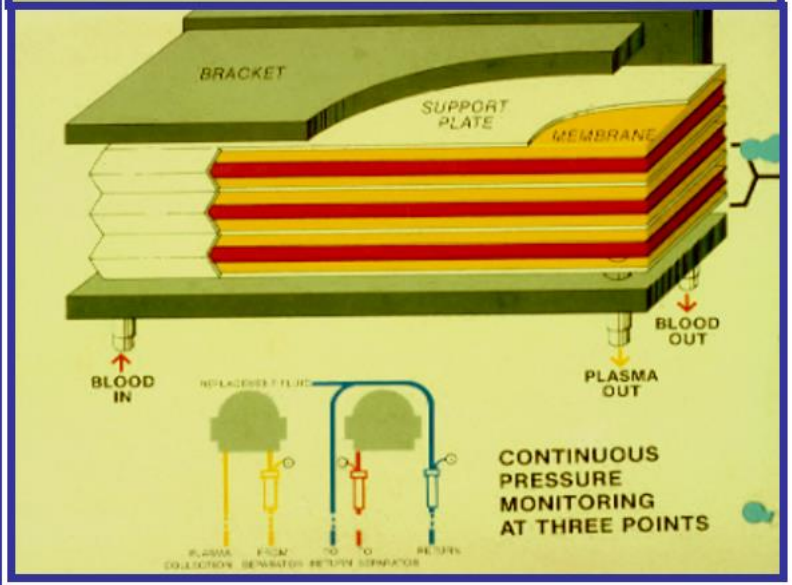


- Comparative sizes of blood components
- Blood is pumped through a membrane with pores allowing plasma to pass through whilst retaining blood cells.
- Available as a hollow fiber membrane. Older devices used parallel-plate membranes.
- Pore diameter for plasma separation : 0.2 -0.6µm

Membrane Plasma Separation

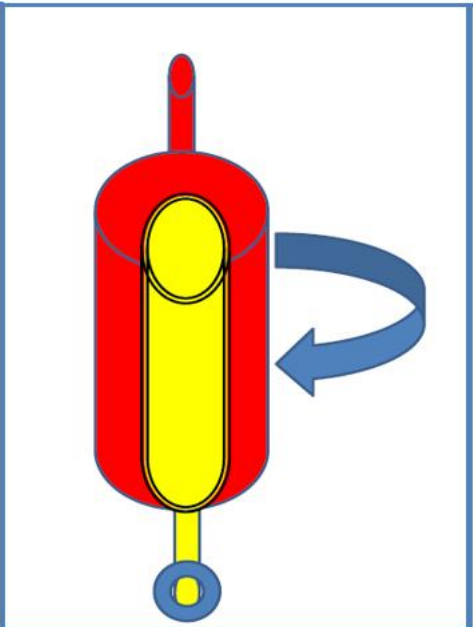


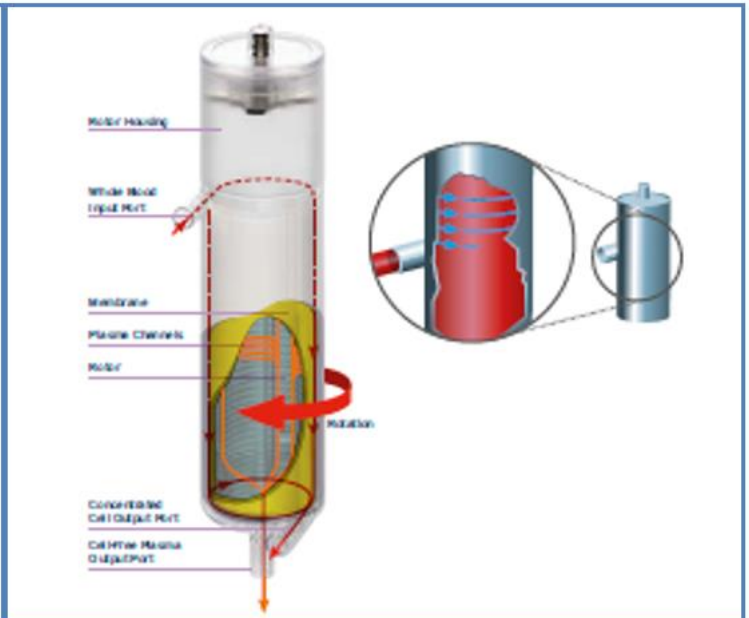


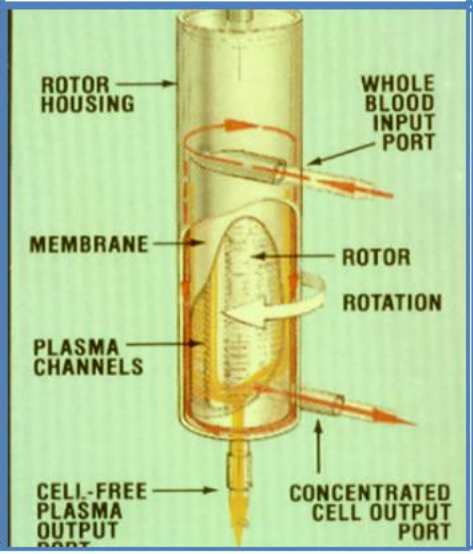


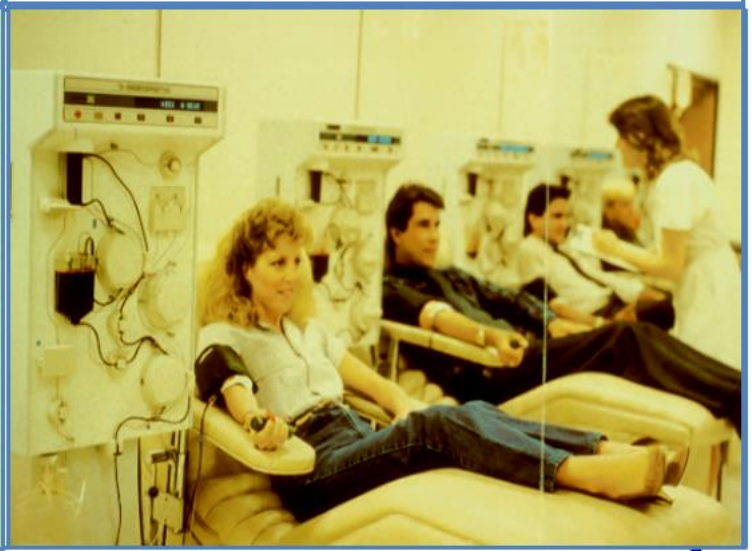
COBE Centry TPE

Hollow fiber membrane/ Automated plasma collection





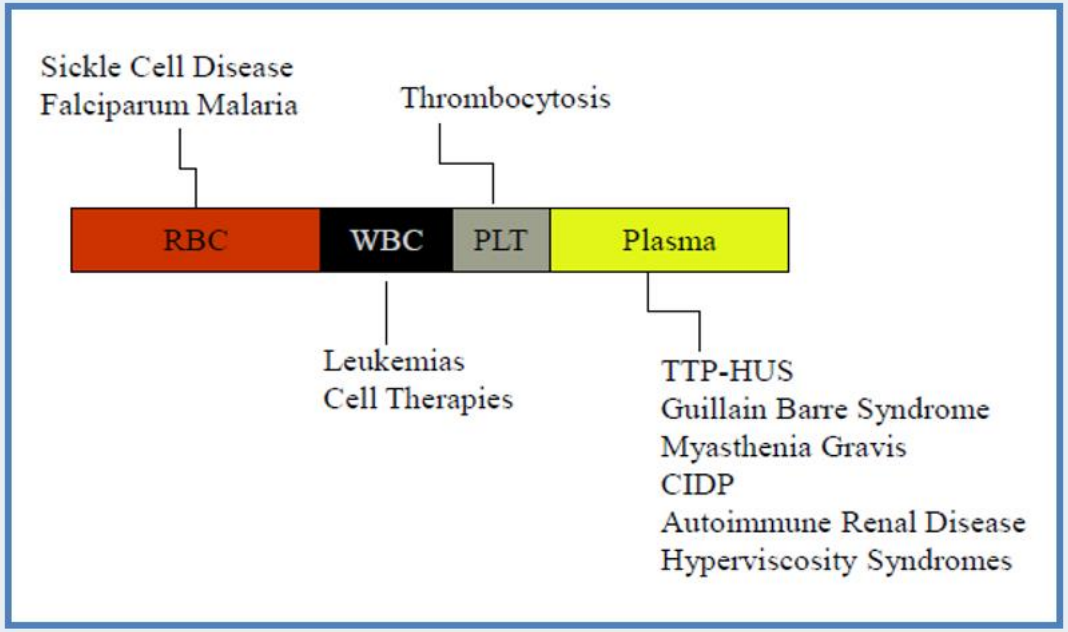


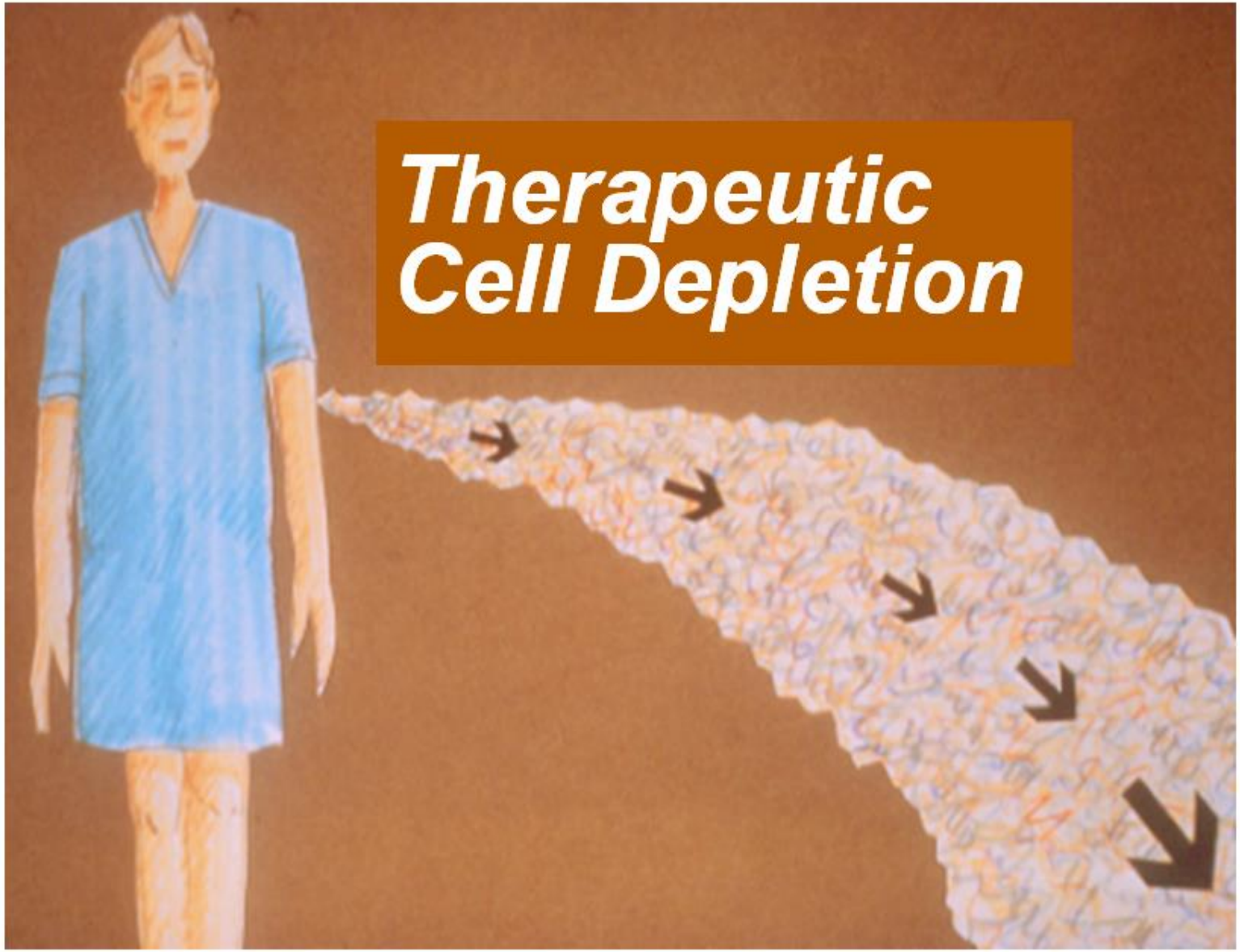


Dobri Kiprov. Principles of Blood Separation and Apheresis Instrumentation

Therapeutic Apheresis

- **Cell Depletion**
- **Plasma Exchange**





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I Therapeutic Apheresis Modality Definitions

Procedure/ Term	Definition
Leukocytapheresis	A procedure in which blood of the patient is passed through a medical device which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns the remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.
Thrombocytapheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out platelets, removes the platelets and returns the remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

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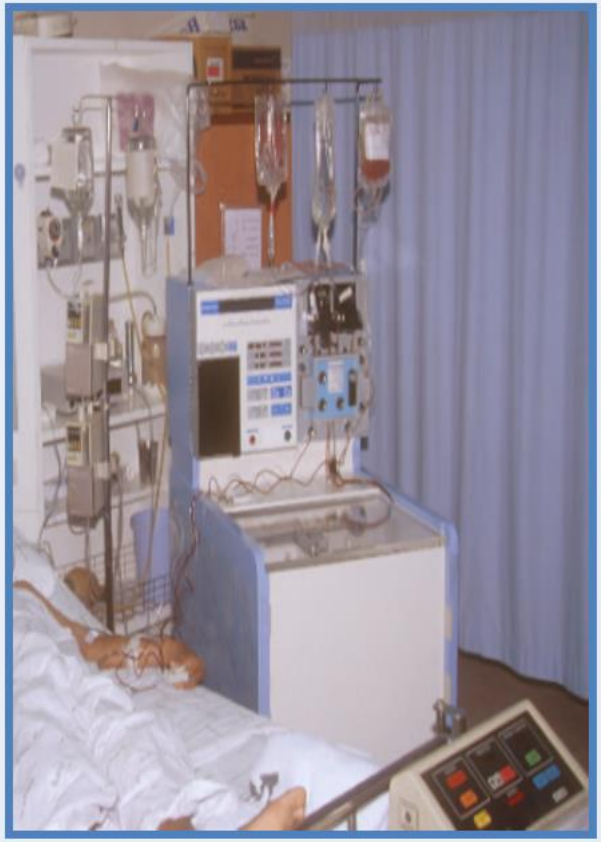
ASFA Indication Categories for Therapeutic Cytapheresis

Disease	Procedure	Category
Thrombocytosis	Thrombocytapheresis	II
Hyperleukocytosis		
Leukostasis	Leukocytapheresis	I
Prophylaxis	Leukocytapheresis	III

ECP : Extracorporal Photopheresis

Therapeutic Apheresis: A Physician's handbook . 2nd Edition.2008

Therapeutic Cell Depletion



- **Hyperleukocytosis WBC count**

  ≥ 100,000 / uL
- **The optimal time is before chemotherapy that induced leukemic cell lysis**
- **Reduce the risk of**
  - **Leukemic – thrombo aggregate in vascular system, most common CNS, lung**
  - **Tumor lysis syndrome**

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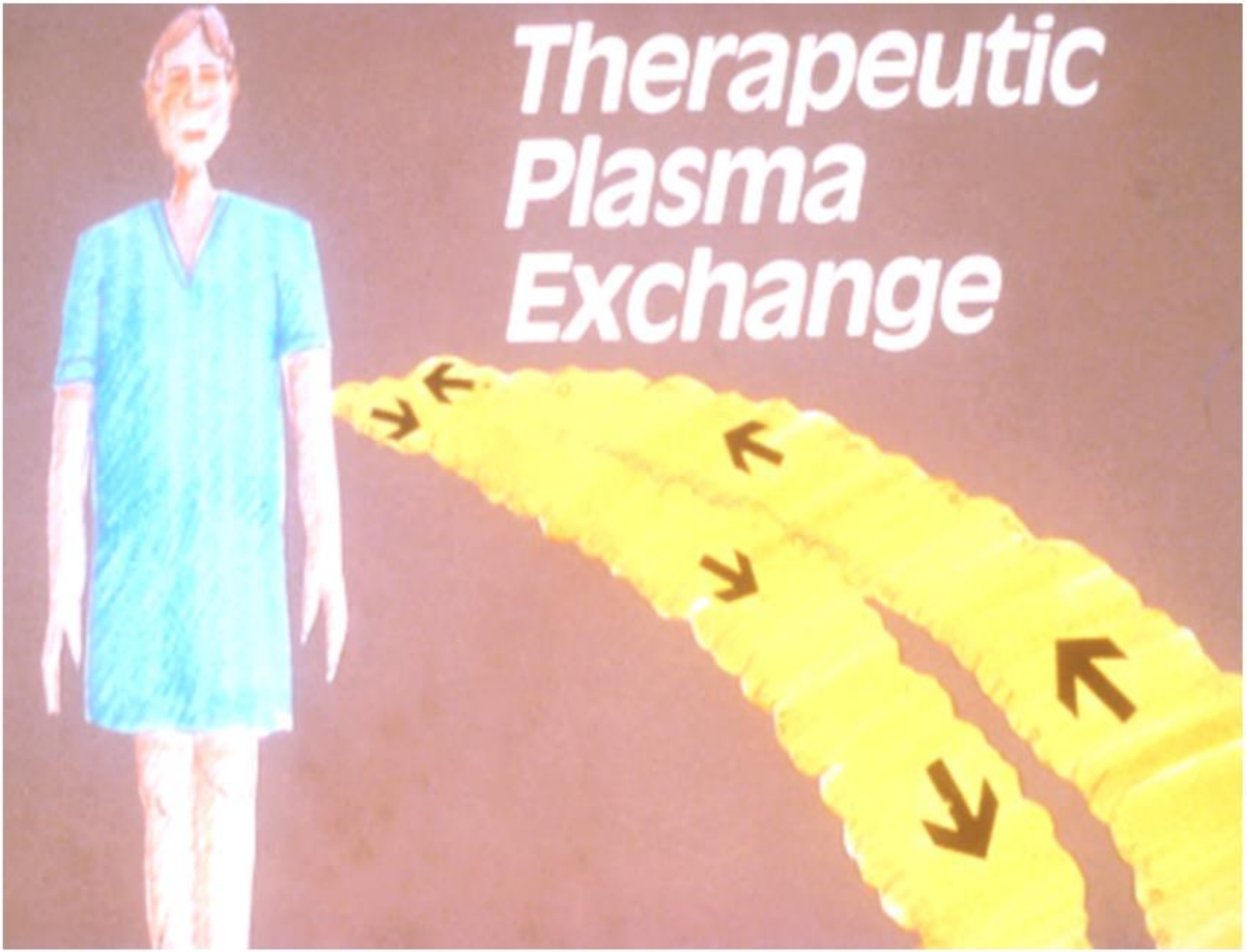

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Plasmapheresis in Clinical Practice

- **Standard therapeutic plasma exchange**
  - **Centrifugation**
  - **Membrane**
- **Selective removal plasma exchange**
  - **Double filtration**
  - **Immunoadsorption**
- **Extracorporeal Photopheresis**

II Therapeutic Apheresis Modality Definitions

Procedure/ Term	Definition
Therapeutic plasma exchange (TPE)	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.
Double filtration plasmapheresis (DFPP)	A filter based therapeutic procedure that removes pathogenic substances from separated plasma based on their size, which is mainly determined by molecular weight and three- dimensional configuration (e.g., autoantibodies, immune complexes, lipoproteins, etc.), by using plasma filters with different pore sizes.
Immunoadsorption (IA)	A therapeutic procedure in which plasma of the patient, after membrane based or centrifugal separation from the blood, is passed through a medical device (adsorber column) which has a capacity to remove immunoglobulins by binding them to select ligands on the backing matrix surface (membranes or beads) of the adsorber column.

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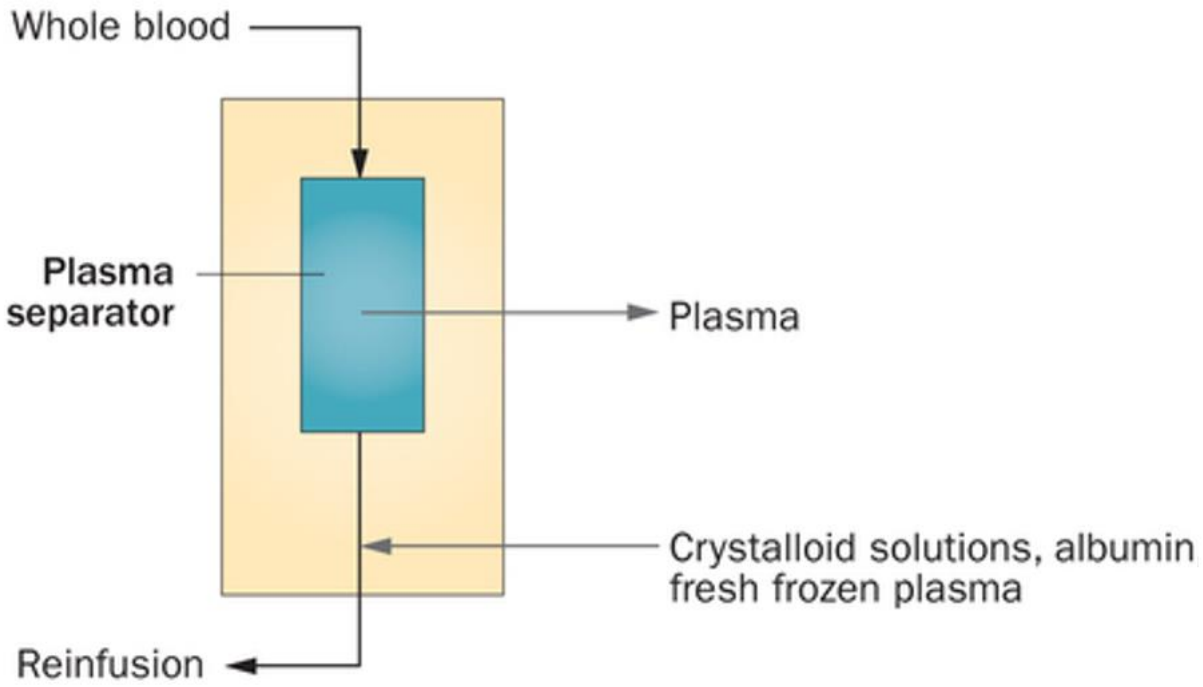
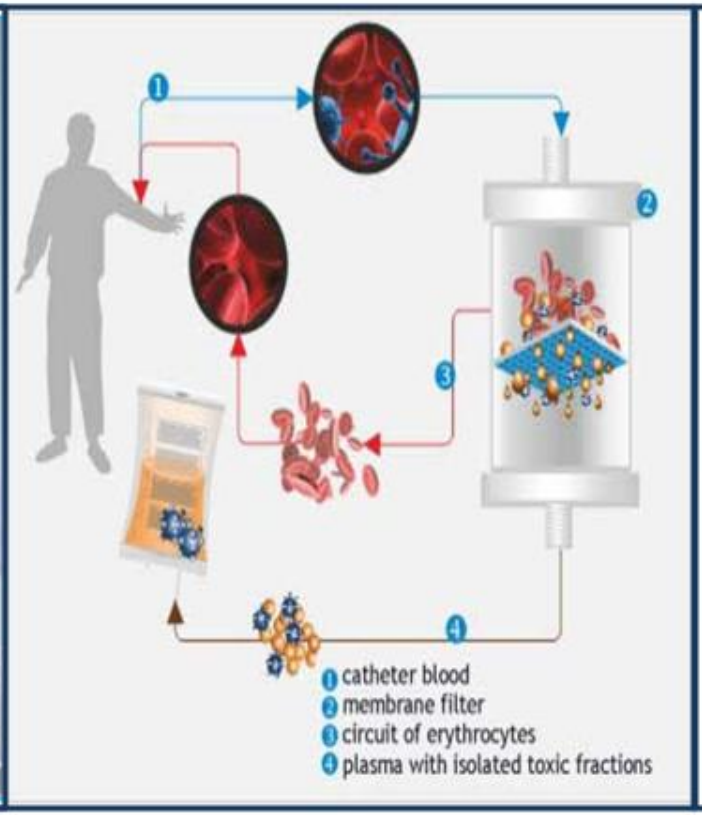
Standard Plasmapheresis Techniques

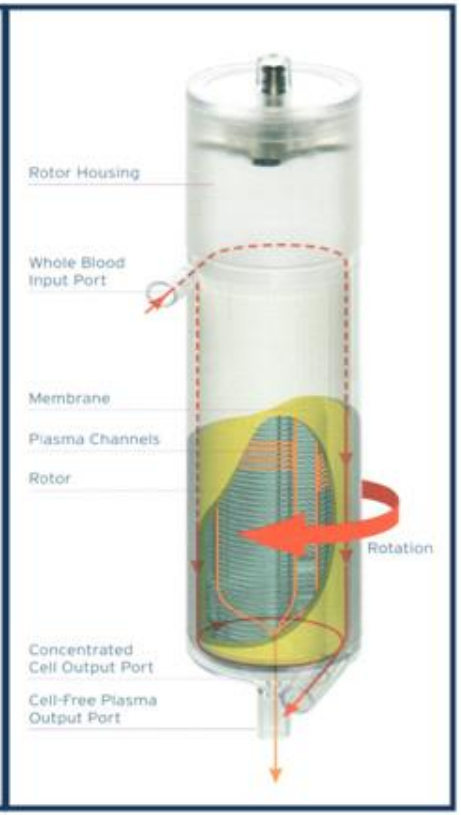


Plasmapheresis involves removal of patient plasma using centrifugation or a plasma separator. The discarded plasma is replaced with crystalloid solutions , albumin and / or fresh frozen plasma

Bohmig, G.A. *et al*. Strategies to overcome the ABO barrier in kidney transplantation. Nature Reviewa Nephrology. Advance online publication 1 Sep 2015

Membrane Plasmapheresis





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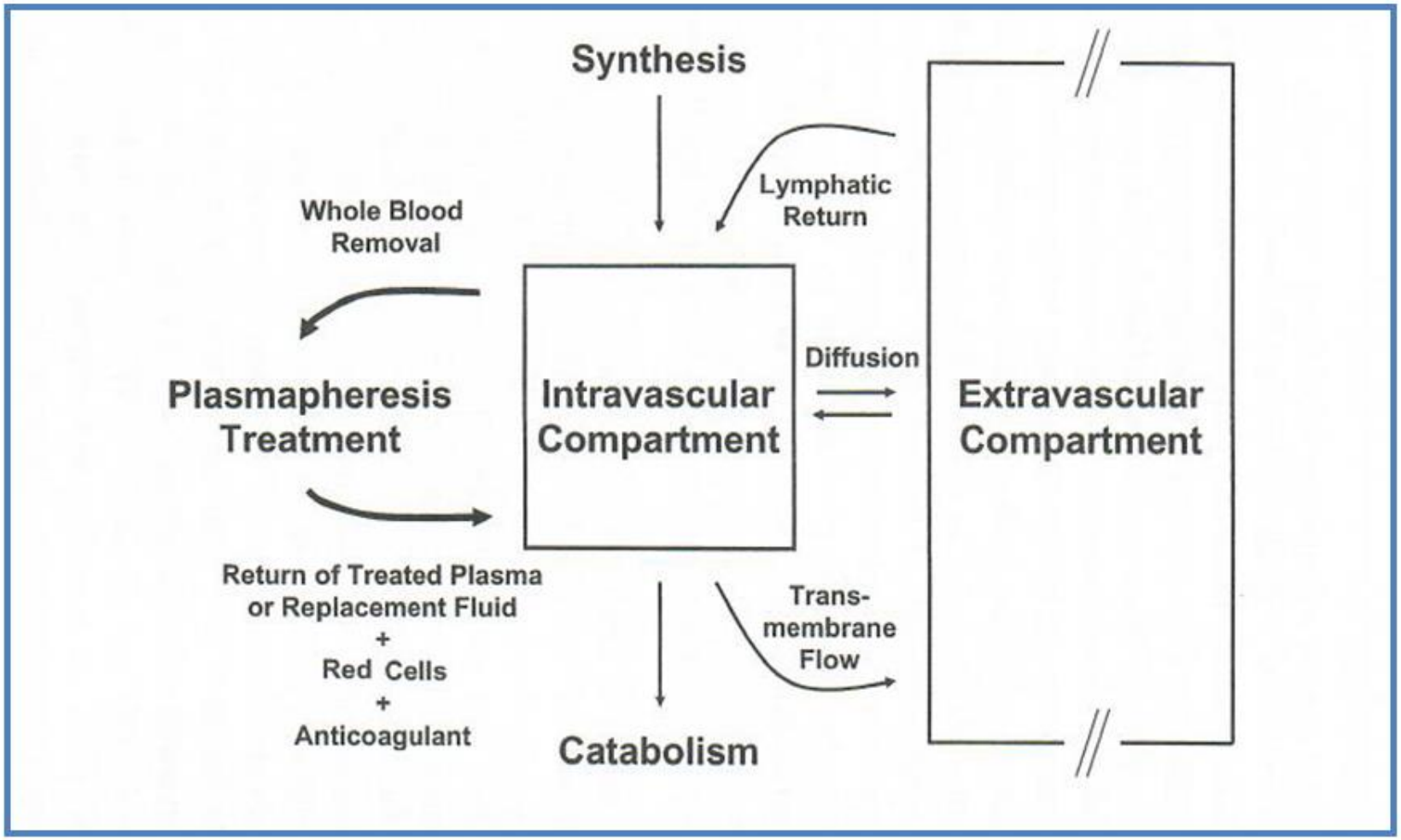
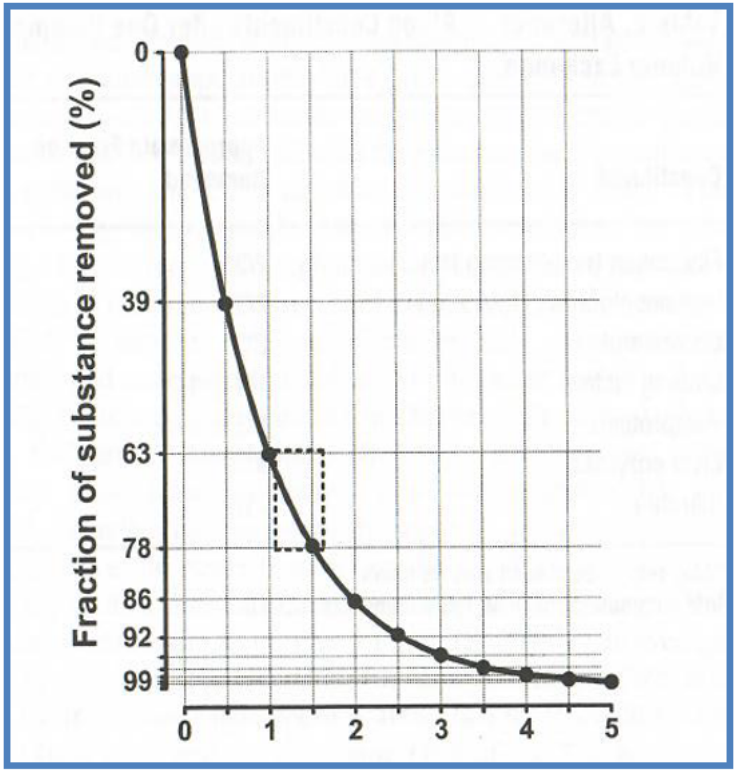
Compartment Model of Substances Removed by TPE



Therapeutic Apheresis: A Physician's handbook . 3rd Edition.2011

Efficiency of TPE



Plasma Volumes Exchanged	Fraction Remaining	% Removed
1.0	0.37	63
1.5	0.22	78
2.0	0.14	86
2.5	0.08	92
3.0	0.05	95

Therapeutic Apheresis: A Physician's handbook . 3rd Edition.2011

Alteration in Blood Constituents after 1 PV Exchanged

Constituent	Approximate Fraction Removed
Fibrinogen	2/3*
Immunoglobulins (IgM>IgG)	2/3*
Cholesterol	2/3*
Clotting factors	1/4 to 1/2
Liver enzymes	> 1/2
Bilirubin	~ 1/2

* May remain decrease after 48 hours.

Therapeutic Apheresis: A Physician's handbook . 3rd Edition.2011

Comparison of Replacement Fluids

Replacement Solution	Advantages	Disadvantages
Crystalloids	Low cost Nonallergenic No viral risk	Two-to threefold more volume required Hypo-oncotic Lacking coagulation factors and immunoglobulins
Albumin	Iso-oncotic Low risk of reactions	Higher cost Lacking coagulation factors and immunoglobulins
Plasma	Iso-oncotic Normal levels of coagulation factors, immunoglobulins, and other plasma proteins	Viral transmission risk Increased citrate load ABO compatibility required Higher risk of allergic reactions
Cryoprecipitrate -reduced plasma	Iso-oncotic Reduced high-molecular-weight von Willebrand factor and fibrinogen Normal levels of most other plasma proteins	Same as plasma

A. Chester et al. Therapeutic Apheresis. AABB Technical Manual. .19th edition.2017

Reported Frequency of Adverse Reactions to Apheresis

Reaction	Frequency (%)
Paresthesia	1.30
Hypotension	0.91
Urticaria	0.63
Nausea	0.39
Shivering	0.29
Flushing	0.16
Dyspnea	0.15
Vertigo	0.17
Arrhythmia	0.11
Abdominal pain	0.12
Anaphylaxis	0.02
Total	4.25

A. Chester et al. Therapeutic Apheresis. AABB Technical Manual. .19th edition.2017

Pediatric Apheresis

- Saline prime for adults and older children
- Red cell prime
  - Children < 20 Kgm
  - Extracorporeal blood volume > 10% of the child total blood volume
  - Intraprocedure HCT < 20%
- Patient-compatible, leucocyte-reduced RBC

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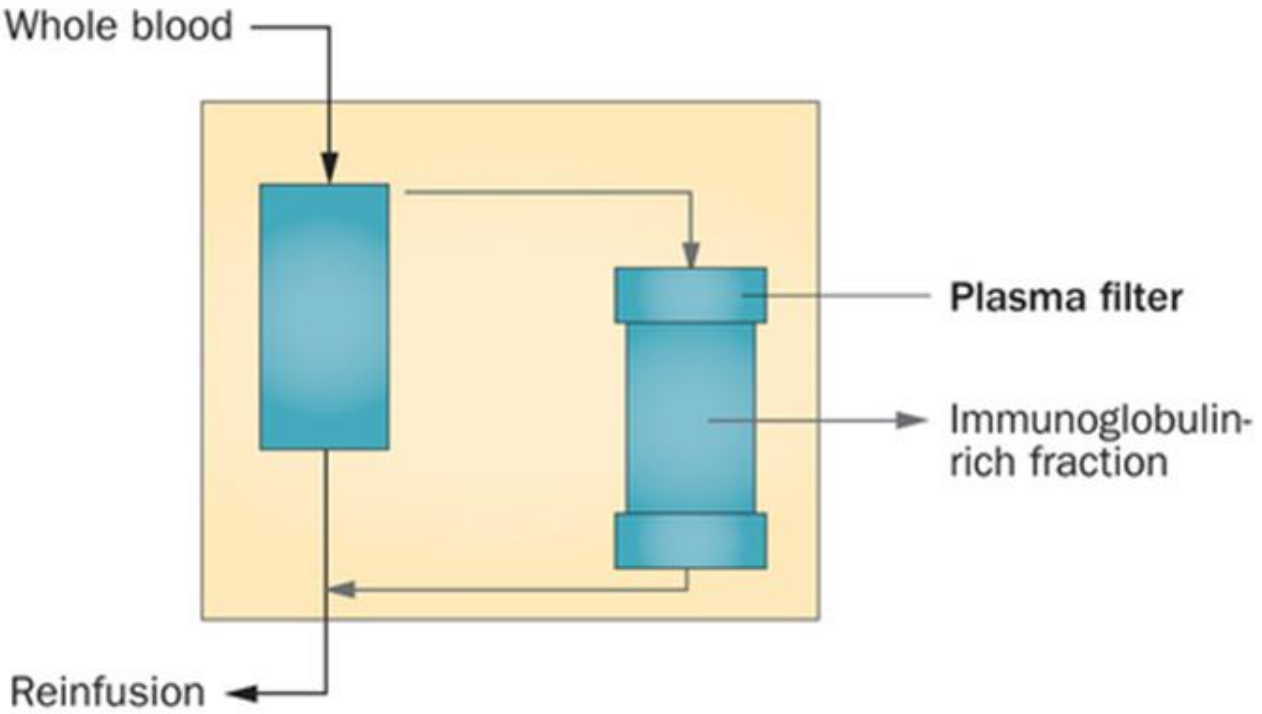
Double Filtration Plasmapheresis



Double filtration plasmapheresis includes a first filter that separates plasma from wholeblood and a second filter that removes an immunoglobulin-rich plasma fraction. The remaining plasma components are reinfused .

Bohmig, G.A. *et al*. Strategies to overcome the ABO barrier in kidney transplantation. Nature Reviewa Nephrology. Advance online publication 1 Sep 2015

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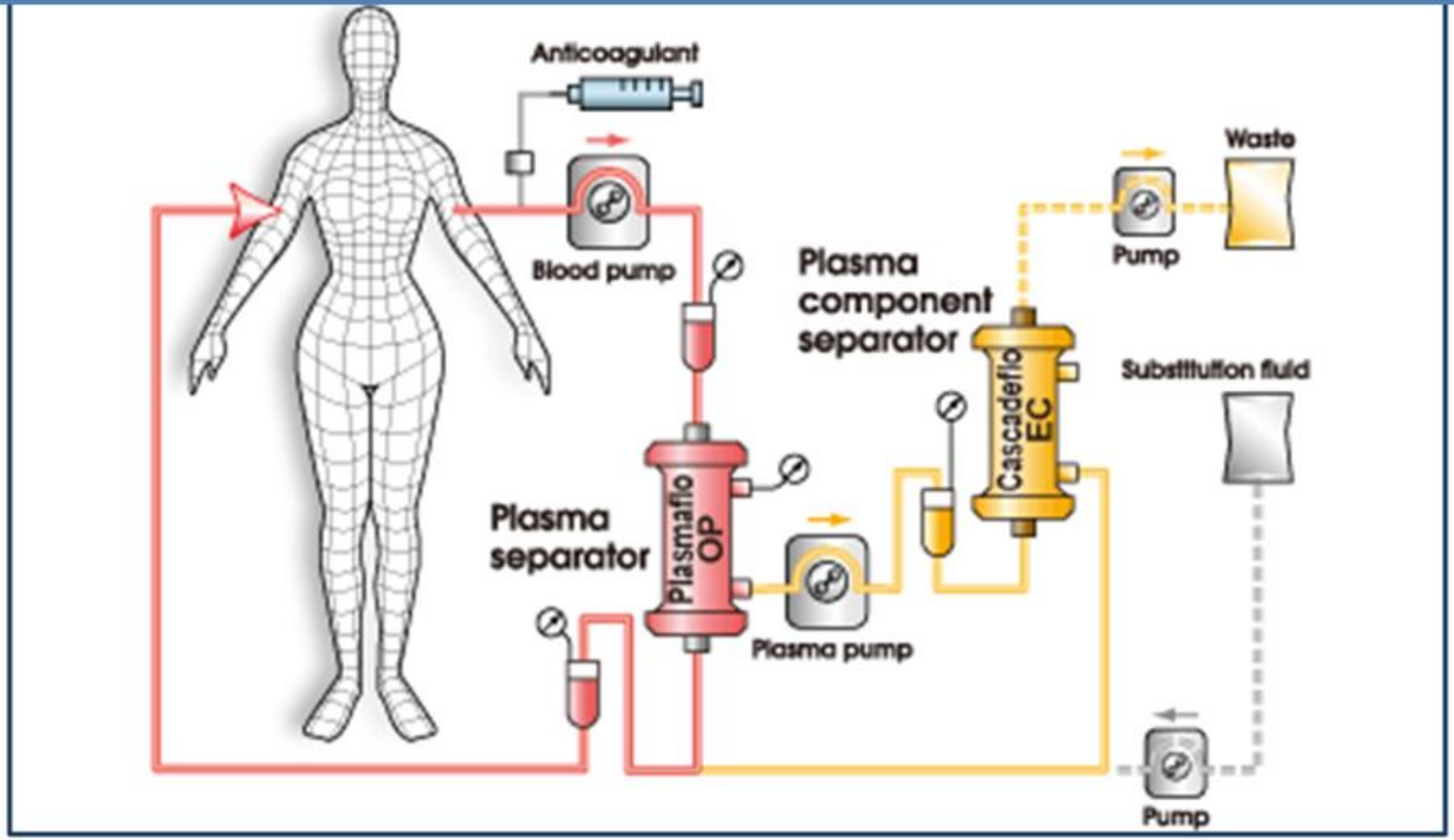
Double Filtration Plasmapheresis (DFPP) Treatment Diagram



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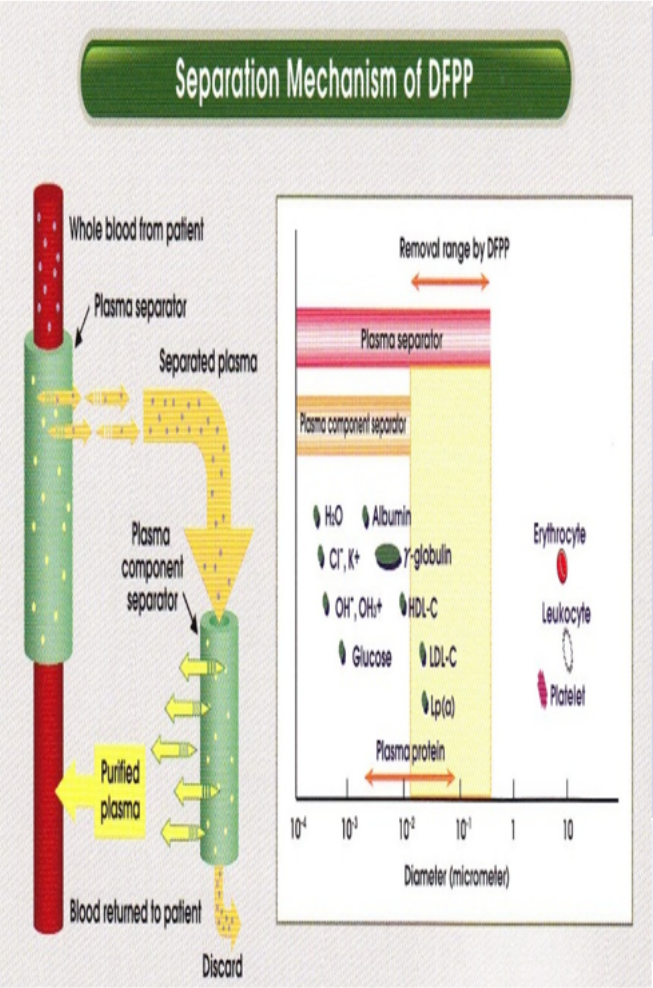
Double Filtration Plasmapheresis



- **Membrane differential filtration apheresis/selective removal of plasma components on the basis of molecular size**
- **Anticoagulation can be either heparin or citrate**
- **Whole blood is separated into cellular and plasma component. The plasma is then filtered through a second filter, with a smaller pore size that allows the passage of albumin and smaller molecules but retains larger molecules such as immunoglobulins, lipoproteins, immune complexes and fibrinogen.**
- **Require a minimal amount of replacement fluid**

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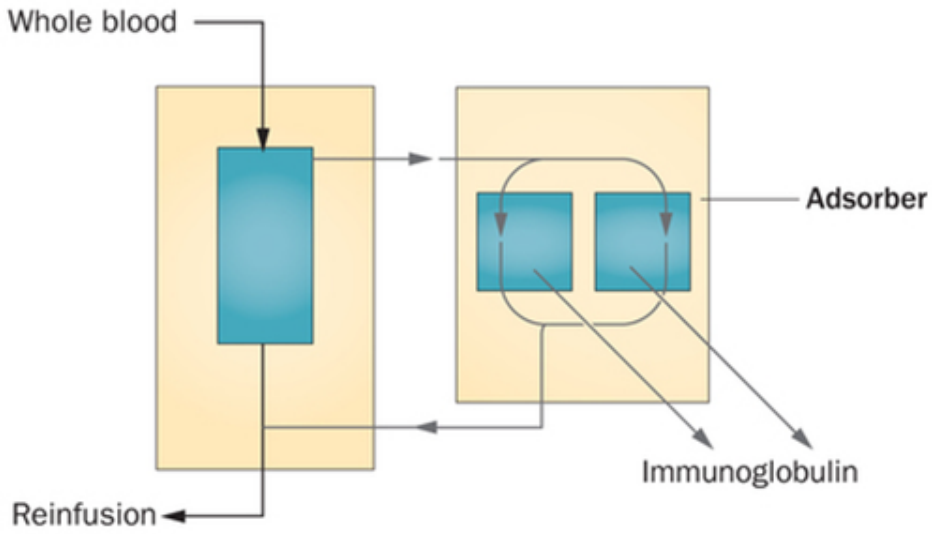
Selective Immunoadsorption



During semiselective immunoadsorption, separated plasma is pumped alternatively through a regenerative twin-column system that selectively removes immunoglobulin by immunoadsorption, for example using staphylococcal protein A or sheep anti-immunoglobulin.

Bohmig, G.A. *et al*. Strategies to overcome the ABO barrier in kidney transplantation. Nature Reviewa Nephrology. Advance online publication 1 Sep 2015

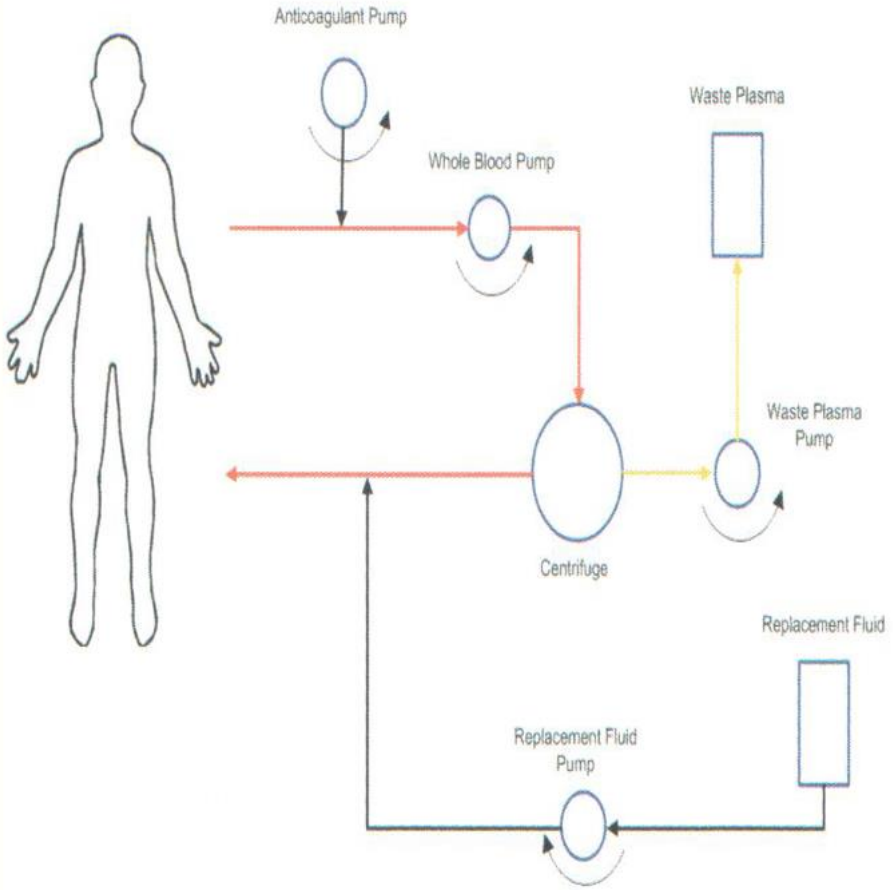
I Immunoadsorption systems

- The capacity to remove immunoglobulins by binding them to select ligands on the backing matrix surface (membranes or beads) of the adsorber column.
- A major advantage of IA compared to TPE is that no substitution of human plasma products which have risks of transmission of infectious agents, or compromise of the coagulation system.
- Most IA columns are broadband immunoglobulin adsorbers using different ligands (e.g., staphylococcal or recombinant protein A, sheep polyclonal anti-human antibodies
- Specific antibody columns exist for ABO-blood group antigens (carbohydrate ligands).
- The use of IA systems in routine care is not universal due to the economic resources of health care systems.

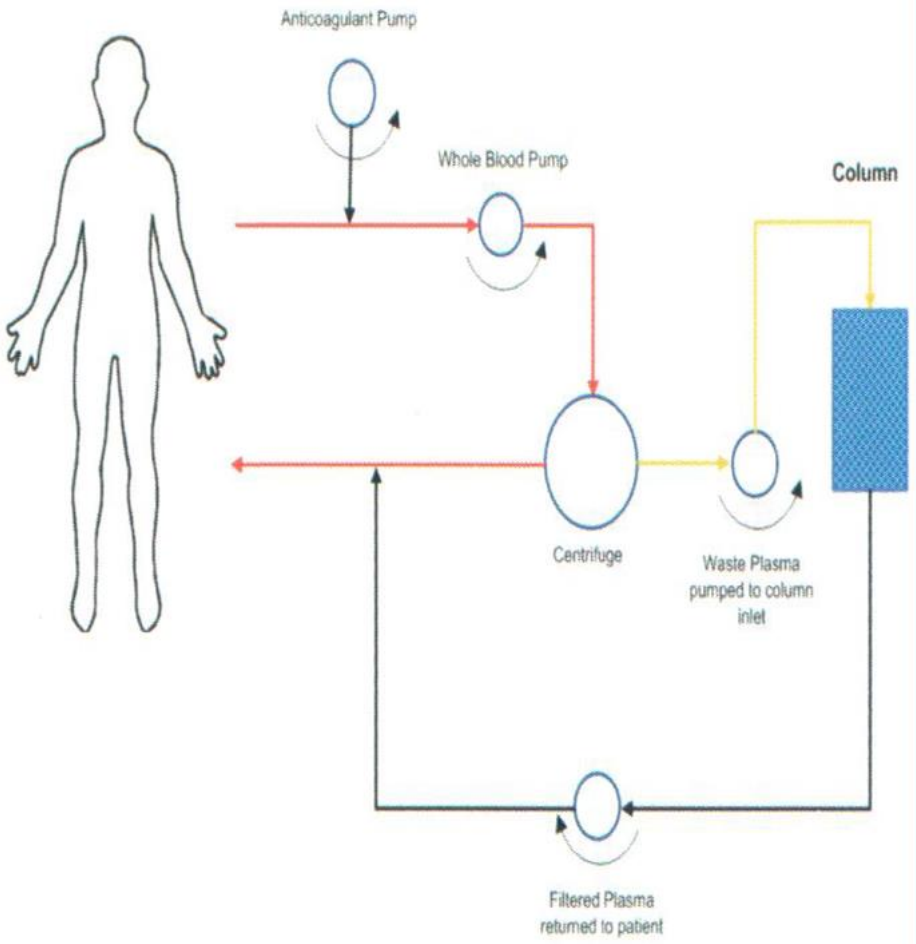
II Immunoadsorption systems

- **IA adsorbers are subdivided into non-regenerative and regenerative columns.**
- **Non-regenerative columns are single use adsorbers limited to the treatment of approximately 1 patient's plasma volume and have their main indication in acute situations of autoantibody-mediated diseases.**
- **Regenerative adsorber systems consist of column pairs, which are sequentially regenerated during a treatment session, and may be reusable. They can treat up to 3 patient's plasma volumes in a single session. These systems are favorable if antibodies must be reduced to low threshold titers, such as that required for the conditioning of kidney transplant recipients with ABO-incompatibility or HLA-sensitization.**

Process Flow for a Standard TPE Procedure



Process Flow for a Selective Removal Column Procedure



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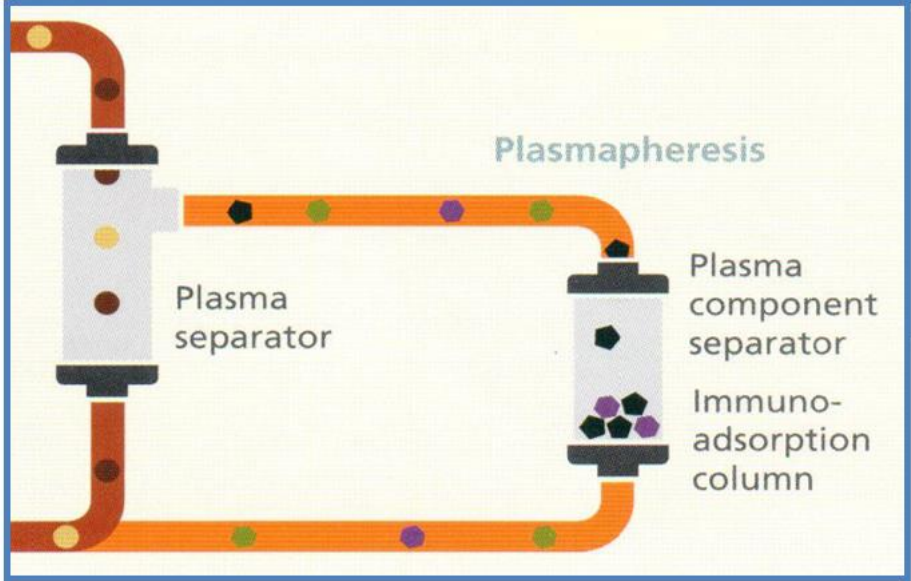
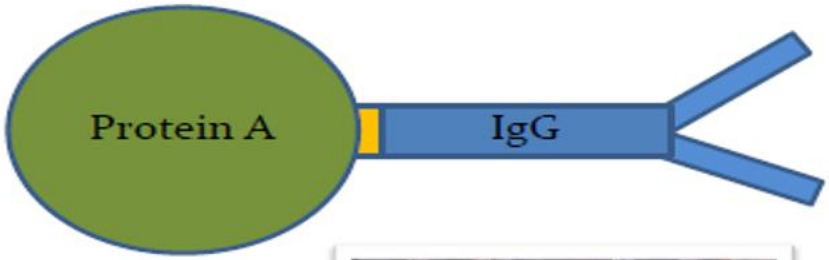
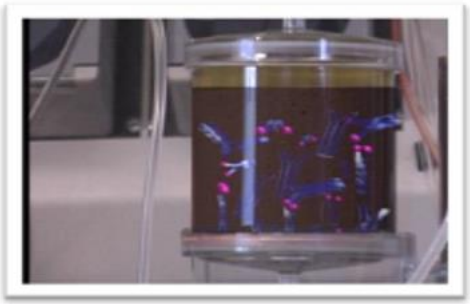
Staphylococcal Protein A Immunoadsorption Columns

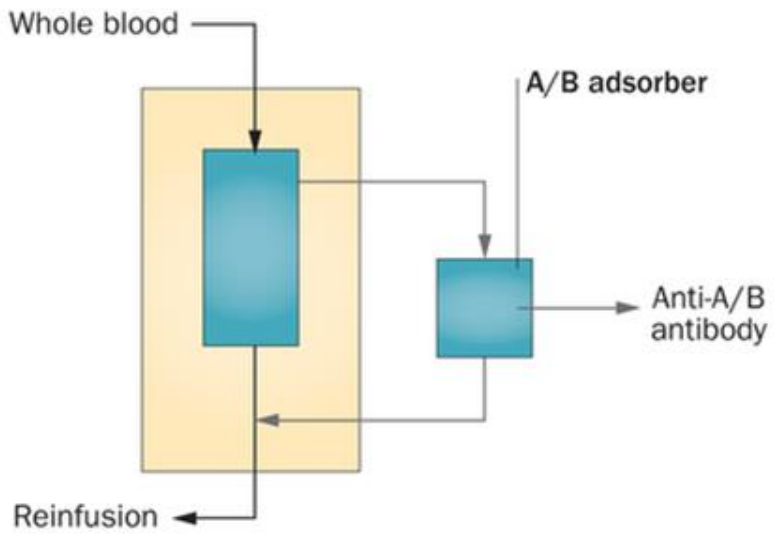






- A bacterial cell wall component that can bind to Fc portion of IgG, strongly to IgG1, IgG2 and IgG4, but variable to IgG3, IgM and IgA
- Selective removal columns to treat disease resulting from the presence of pathologic antibodies
- The plasma is separated from the cellular elements by a centrifugal or membrane plasma separator, then perfused through protien A column, recombined with the cellular elements, and returned to the patients

Apheresis Techniques for Anti-A/B Antibody Removal
Selective Immunoadsorption



ABO-specific immunoadsorption uses an antigen-specific adsorber consisting of blood group A or B antigens immobilized on a sepharose matrix.

Bohmig, G.A. *et al.* Strategies to overcome the ABO barrier in kidney transplantation. Nature Reviewa Nephrology. Advance online publication 1 Sep 2015

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ABO Antigen-Specific Immunoadsorption

- Sepharose columns that bind the terminal trisaccharides, which are responsible for the A and B antigens
- Glycorex Transplantation AB, Lund, Sweden. The columns contain either A or B antigen
- The plasma is separated, then perfused through the column to remove the desired antibodies and returned to the patient
- The columns have been used to avoid endothelial damage and vascular thrombosis (hyper acute rejection) seen in ABO incompatible transplants
- It have been used to treat humoral rejection after transplantation from ABO antibodies

I Category and Grade Recommendations for Therapeutic Apheresis

Disease	TA Modality	Indication	Category	Grade
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	TPE	Primary Treatment	I	1A
	IA	Primary Treatment	I	1B
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	TPE/ IA		I	1B
Myasthenia gravis	TPE/ IA	Acute, short-term treatment	I	IB
	TPE/ IA	Long-term treatment	II	2B
Neuromyelitis optica spectrum disorders (NMOSD)	TPE	Acute attrack/relapse	II	1B
	IA	Acute attrack/relapse	II	1C

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II Category and Grade Recommendations for Therapeutic Apheresis

Disease	TA Modality	Indication	Category	Grade
Catastrophic antiphospholipid syndrome (CAPS)	TPE		I	2C
Hyperviscosity in hypergammaglobulinemia	TPE TPE	Symtompmatic Prophylaxis for rituximab	I I	1B 1C
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)	TPE		I	1A

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III Category and Grade Recommendations for Therapeutic Apheresis

Disease	TA Modality	Indication	Category	Grade
Transplantation, hematopoietic stem cell, ABO incompatible (ABOi)	TPE	Major ABOi HPC	II	1B
Transplantation, liver	TPE	Desensitization, ABOi living donor	I	1C
Transplantation, renal, ABO compatible	TPE/ IA	Antibody mediated Rejection	I	1B
	TPE/ IA	Desensitization, living donor	I	1B
Transplantation, renal, ABO incompatible	TPE/ IA	Desensitization, living donor	I	1B
	TPE/ IA	Antibody mediated Rejection	II	1B

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis:The Eighth Special Issue. J Clin Apher. 2019;34:171–354.

I Techniques for Antibody Removal / Plasmapheresis

Method	Technical Remarks	Advantages	Disadvantages	Antibody Removal
Standard plasmapheresis	Plasma separation and subsequent removal Replacement by albumin or FFP	Standard technique which is available everywhere Highly efficient for all antibodies	Removes useful antibodies (infection risk) Disturbs coagulation (risk of perioperative bleeding)	All antibody isotypes
Double filtration plasmapheresis	First step : plasma separation Second step : plasma filtration → semi-selective immunoglobulin removal Replacement by albumin or FFP	Higher selectivity for immunoglobulins than standard plasmapheresis Highly efficient	Removes useful antibodies (infection risk) Disturbs coagulation (but less than standard plasmapheresis)	All antibody isotypes

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II Techniques for Antibody Removal / Plasmapheresis

Method	Product	Technical Remarks	Advantages	Disadvantages	Antibody Removal
Antigen-unspecific adsorption	Protein A-coated columns (Immunosorba)	First step : plasma separation Second step: immunoadsorption over protein A-coated columns	Efficient immunoglo bulin removal (mainly igG)	IVIG replacement probably required Not ideal for ABO-incompatiblility (IgM)	Mainly IgG
	Anti-immunoglo bulin-coated columns (Therasorb)	First step : plasma separation Second step : immunoadsorption over sheep anti-human immunoglobulin-coated columns	Efficient immunoglobulin removal (all immunoglobulin isotypes including IgM)	IVIG replacement probably required	Most antibody isotypes
Antigen-specific adsorption	Glycosorb columns (Glycorex)	First step : plasma separation Second step : immunoadsorption over blood group antigen-coated columns	Selective (antigen-specific) antibody removal No depletion of total immunoglobulin No replacement required	High cost without column reuse	Only anti-A or B antibodies

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I Conclusion
Choices of Safer Blood Products and Treatment

- Leukoreduction
- Additive solutions to extend storage for RBC and platelet
- Use of male donor plasma for preventing TRALI
- Multicomponent hemapheresis
- Autologous blood
- Pathogen inactivated plasma and platelets
- Therapeutic apheresis

Pimpun Kitpoka,M.D.

II Conclusion
Choices of Test

- **ABO identical / compatible blood**
- **Surgical blood orders**
- **Emergency request**
- **Massive blood transfusion protocol**

THANK YOU FOR YOUR ATTENTION