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# Apheresis:
## physiology & application

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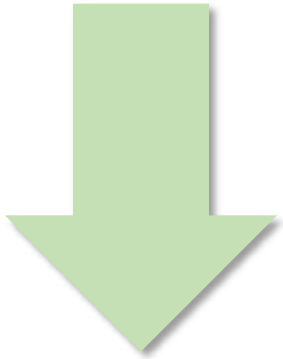
# APHERESIS PROCEDURES



- Worldwide implemented nowadays.
- Most of Asian Countries also involved.
- The usage of this procedure varies between countries.

# APHERESIS

- Derived from Greek word “Phaeresis” which means “taking away”
- Apheresis constitutes a number of procedures in which donor/patient blood is processed to remove or manipulate a specific portion of blood.
- The remaining blood is returned back to the donor/patient

# APHERESIS IS AIMED TO:

- Collect a therapeutic dose of a particular component e.g. Plateletpheresis
- Therapeutically reduce the circulating amount of a particularly harmful component e.g. TPE
- Collect a particular blood cell/ precursor from a patient for re-infusion e.g. PBSC Collections

# SPECTRUM OF APHERESIS

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## Therapeutic Apheresis

- TPE
- Leukocytapheresis
- Thrombocytapheresis
- Erythrocytapheresis
- RBC exchange
- LDL apheresis
- Adsorptive cytapheresis
- Lymphocytapheresis
- ECP
- Rheopheresis

## Component Donation

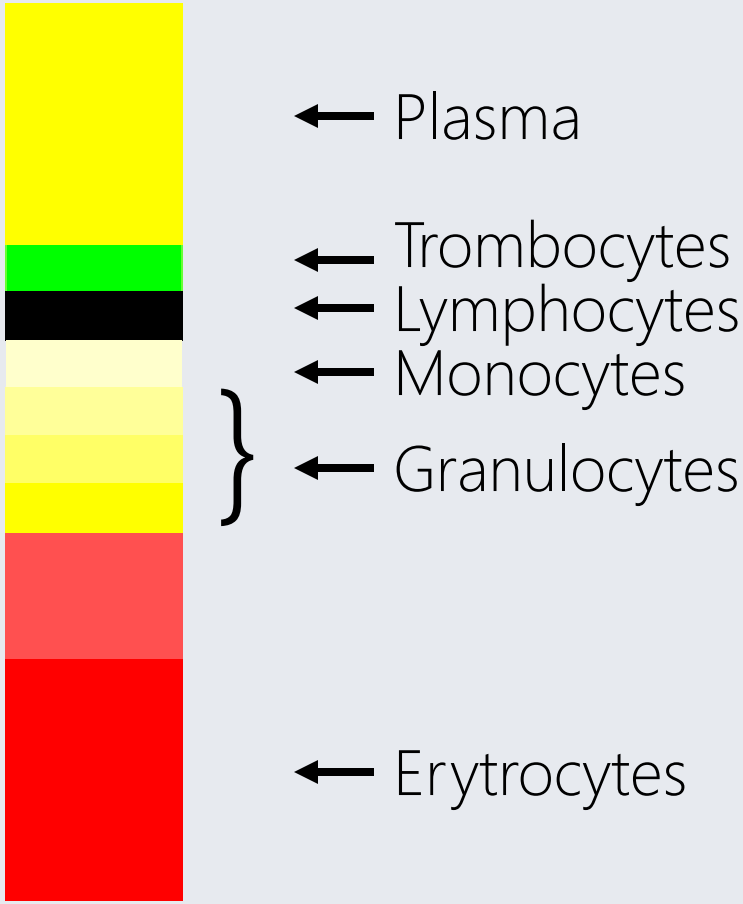
- Platelet
- Red cell
- Plasma

## Specific Procedure

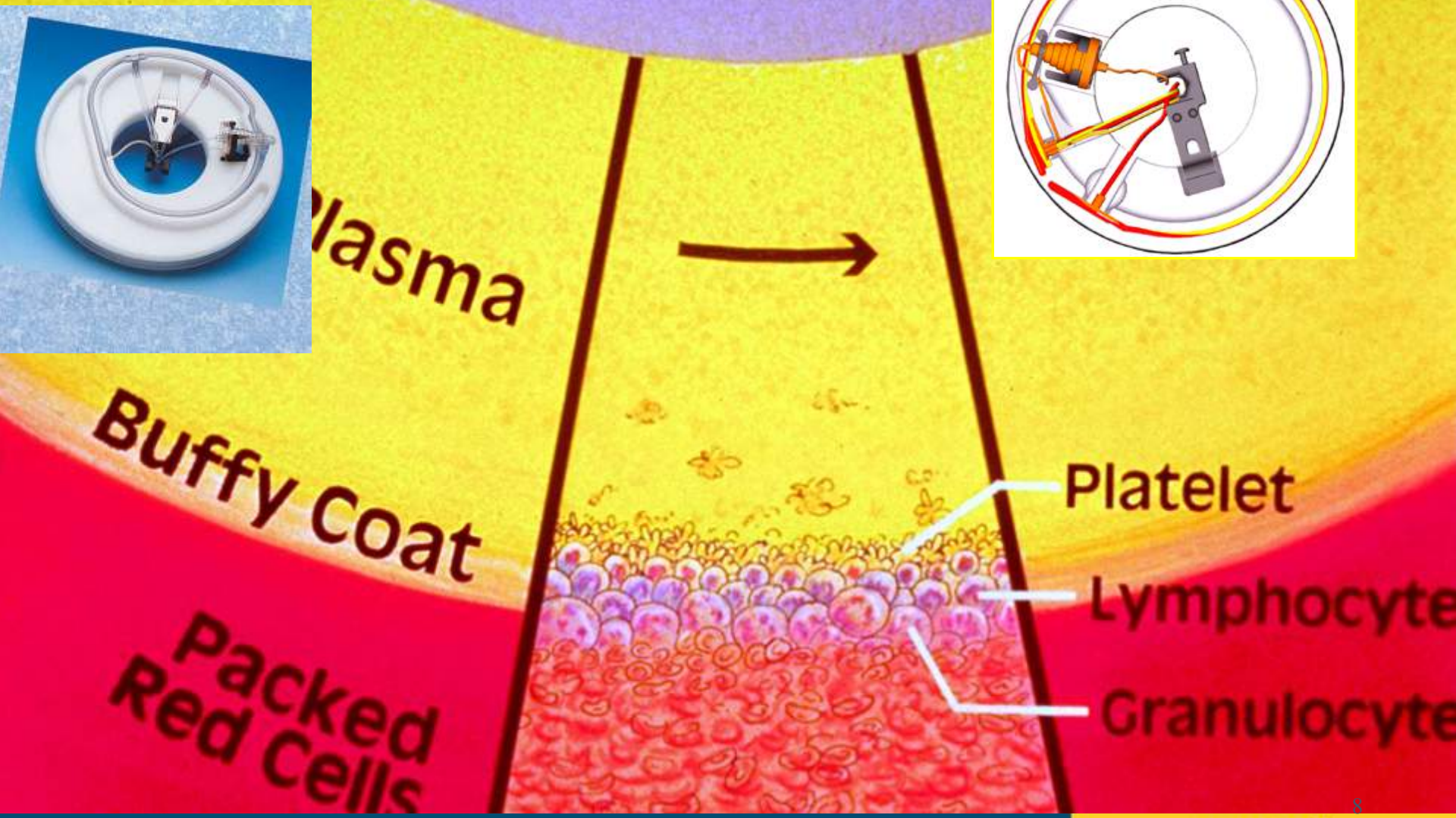
- PBSC Collection

# APHERESIS EQUIPMENT

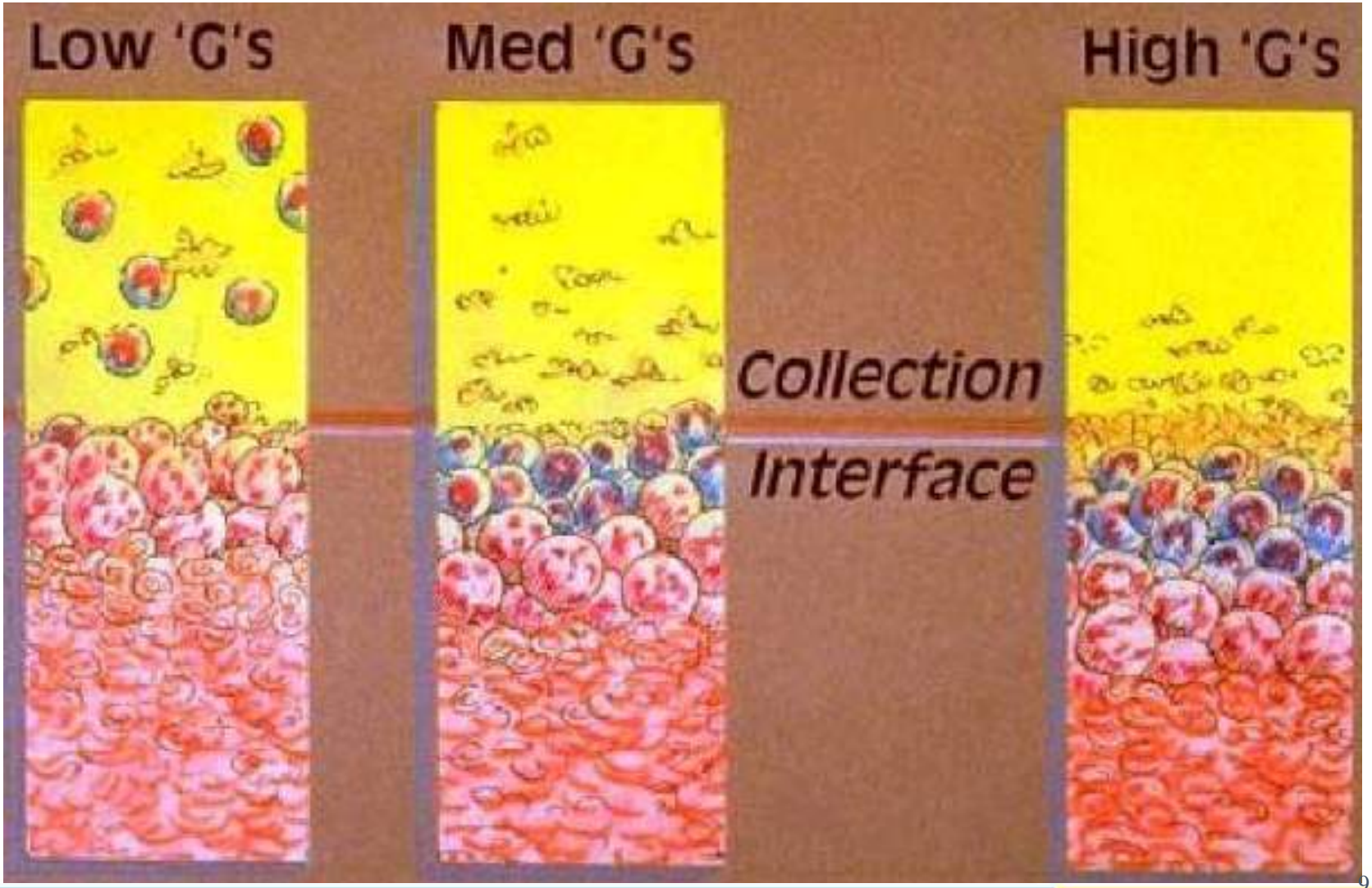
# SEPARATION IN THE SYSTEM

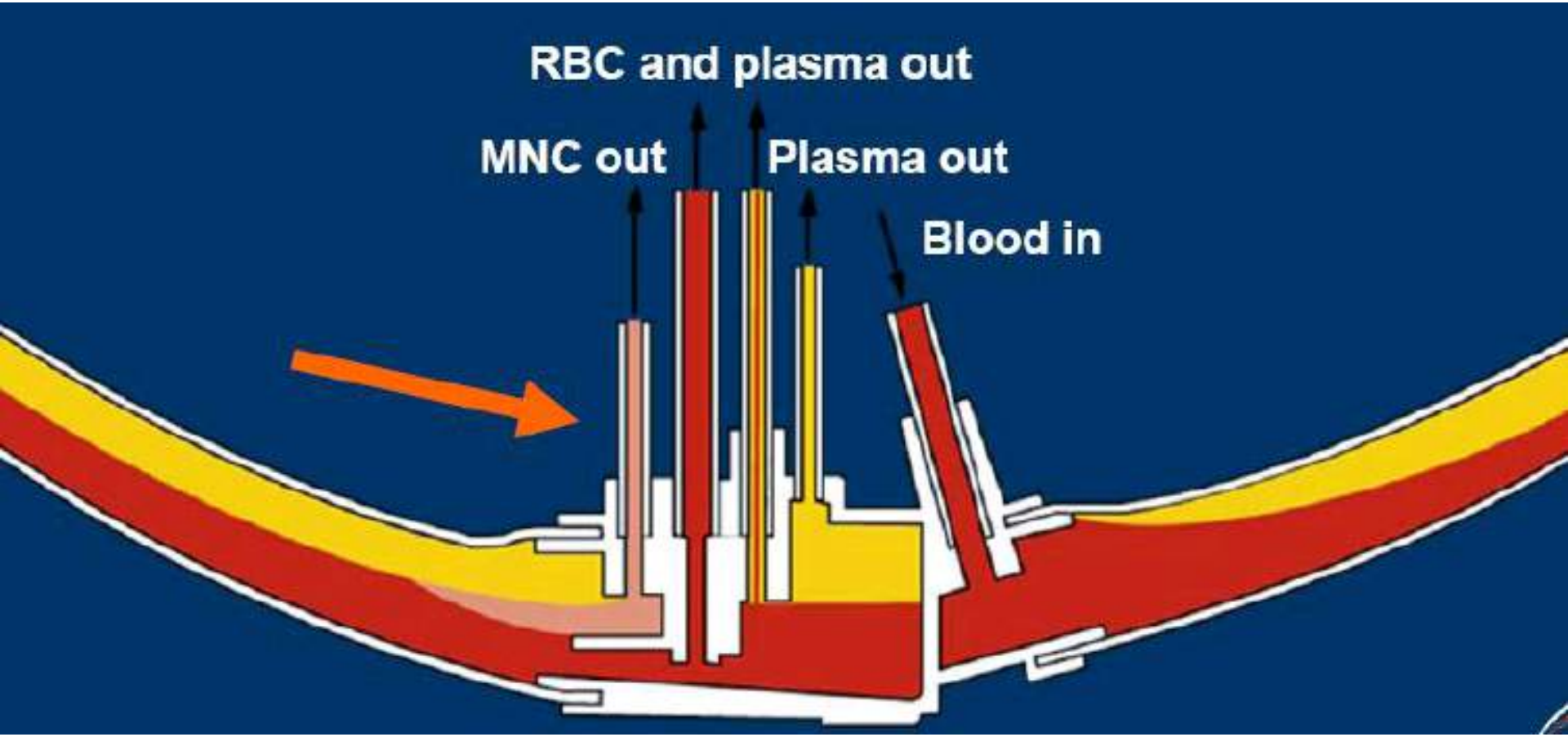


# CENTRIFUGE CHANNEL



# CENTRIFUGE CHANNEL AND 'RPM'




RBC and plasma out
MNC out
Plasma out
Blood in

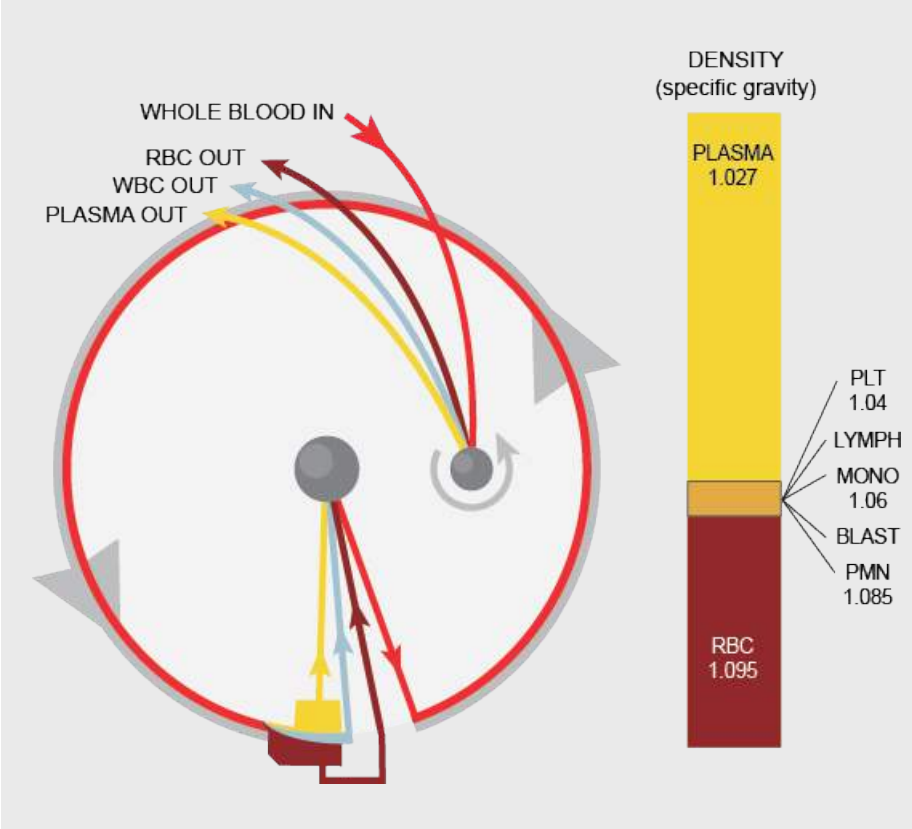
# METHODS OF APHERESIS

- Conventional/ manual
- Automatic/ Cell Separator Machines
  - Intermittent flow separation
  - Continuous flow separation

# PRINCIPLE OF PROCEDURES

- **Centrifugation**
- Separation based on specific gravity
- **Continuous flow**

**SEPARATION BY CENTRIFUGATION**



# Separation based on specific weight / size

| | Spec Weight (g/mL) | Size (µm |
|---|---|---|
| • Plasma | 1.026 | |
| • Platelets | 1.040 | 1-4 |
| • Lymphocytes | 1.050-1.061 | 6-10 |
| • Monocytes | 1.077 | 10-30 |
| • Granulocytes | 1.080 -1.088 | 10-15 |
| • Erytrocytes | 1.093-1.100 | 6-8 |

# DONOR APHERESIS

# DONOR APHERESIS

- Plasmapheresis
- Cytaferese
  - Trombocytapheresis
  - Lymphocytapheresis
  - Stemcelapheresis
  - Monocytapheresis → **Cell therapy**
  - Granulocytapheresis
  - Erytrocytapheresis
- Multicomponent apheresis

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# PLATELET PHERESIS

- Plateletpheresis : collection of platelets from a donor with return of donor RBCs

- Plateletpheresis is the most common application of apheresis

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# 2 TYPES OF PLATELET COMPONENTS :

- random donor platelets or whole blood derived platelets (RDP)
- single donor platelets or apheresis platelets (SDP)

# PLATELETPHERESIS (SDP)

- 2 to 5 x 10e11 platelet yield
- 30% drop in donor platelet count replaced in 48 hours
- Low white cell contamination
- Minimal donor red cell loss
- Fewer donor reactions than whole blood donations.

# PHERESIS PLATELETS

**Storage:** at 20°C to 24°C under constant agitation. Maximum storage time = 5 days

**Therapeutic dose:** between 2.0 – 5.0 x $10^{11}$
Platelets = 4-8 whole blood collections.

# Pheresis Donation Vs Whole Blood Donation

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## Pheresis Donation

- Blood Cell Separator
- Ave 1.5 to 2 hours
- No shows, rejections, deferrals very costly
- Hospital/blood center
- By appointment
- Lab & medical access

## Whole Blood Donation

- *No specialized equipment*
- *10 mins*
- *More uniform work flow*
- *Mobile collection*
- *Walk-ins*
- *Autonomous operation*

# Risks Of Platelet Transfusion

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## Contamination of Platelets

The risk of platelet sepsis is greater with a transfusion of pooled platelet concentrates from multiple donors than from a single donor.

# Risks Of Platelet Transfusion

- Platelet transfusion can transmit viral or bacterial disease.
- Contaminating red cells in the product may transmit malaria.
- Graft-versus-host disease (preventable by irradiation)
- Cytomegalovirus (preventable by serological screening)
- Alloimmunization caused by contaminating white cells.

# Risks Of Platelet Transfusion

- Leukocyte removed could possibly prevent all these problems, but this is not established.
- Febrile reactions are common and are reduced but not totally eliminated by Leukocyte removal
- Platelet themselves may cause fever.

# Advantages of Single Donor Platelets Over Pooled Platelet Concentrate Transfusions

- One donor exposure only
- For special feature collections (HLA-matched, CMV-negative)
- Lower reaction rate
- Lower risk of alloimmunization and transmission of viruses
- Increased donor productivity

# Advantages of Single Donor Platelets Over Pooled Platelet Concentrate Transfusions

- One Pretransfusion Test
- Lower Cost than Manual Collection
- Prompt Transfusion Possible
- Less Unit Handling
- Compliance with Quality System Standards

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# THERAPEUTIC APHERESIS

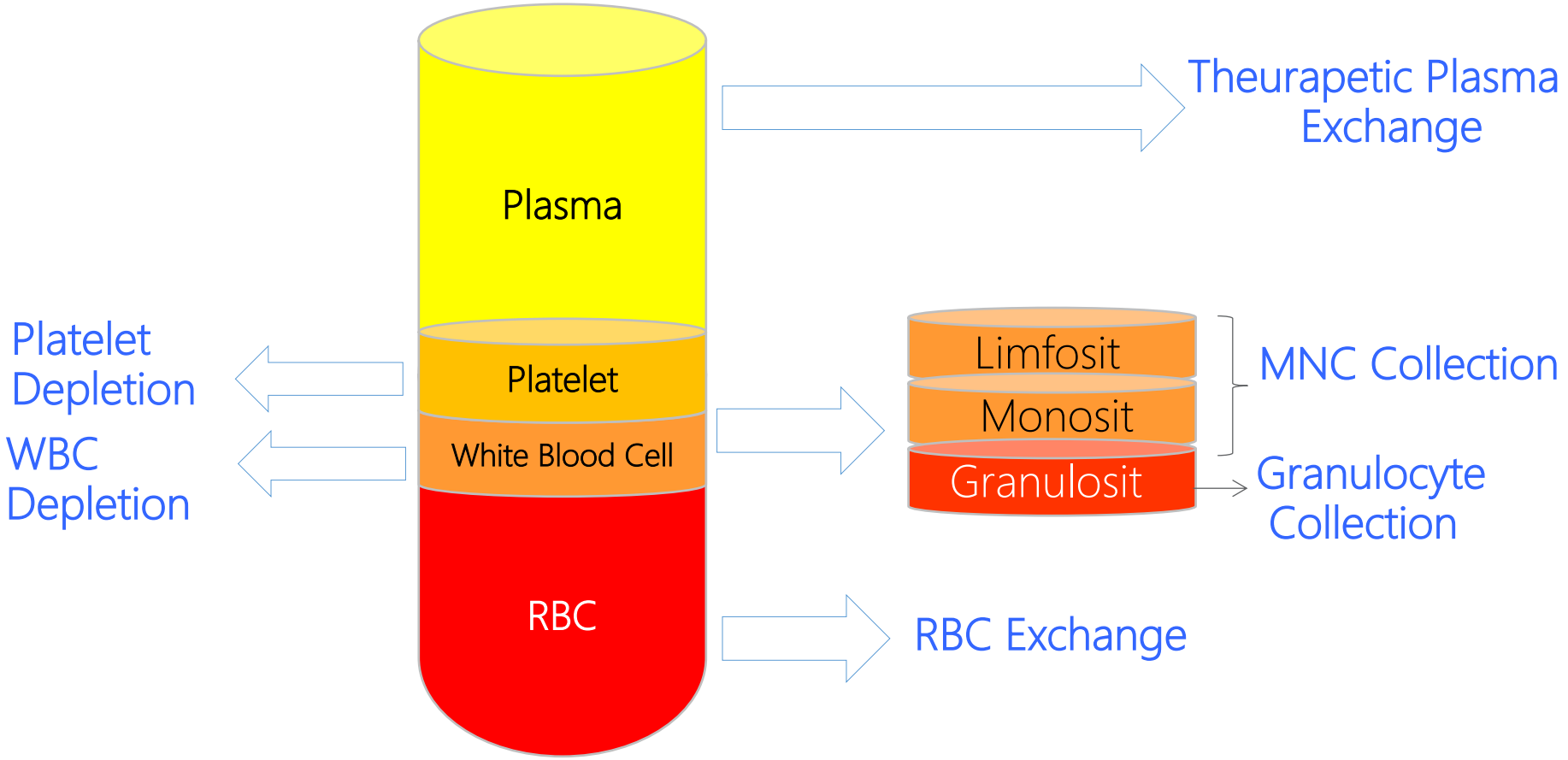
# Patient Apheresis (reduction of cells)

- Cytaferese
  - Trombocytes
  - Lymphoblasts
  - Myeloblasts
  - Erytrocytes

# Patient Apheresis (exchange)

- Plasma exchange
- RBC exchange

# Function of Therapy



# 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 combination of crystalloid/colloid solution.

Schwartz et al. Journal of Clinical Apheresis 2013

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# Therapeutic Plasma Exchange (TPE)

- The most common use of TPE is for the treatment of autoimmune or immune mediated diseases or disorders
- TPE removes:
  - Monoclonal antibodies
  - Paraproteins
  - Autoimmune antibodies
  - Antigen-antibody complexes

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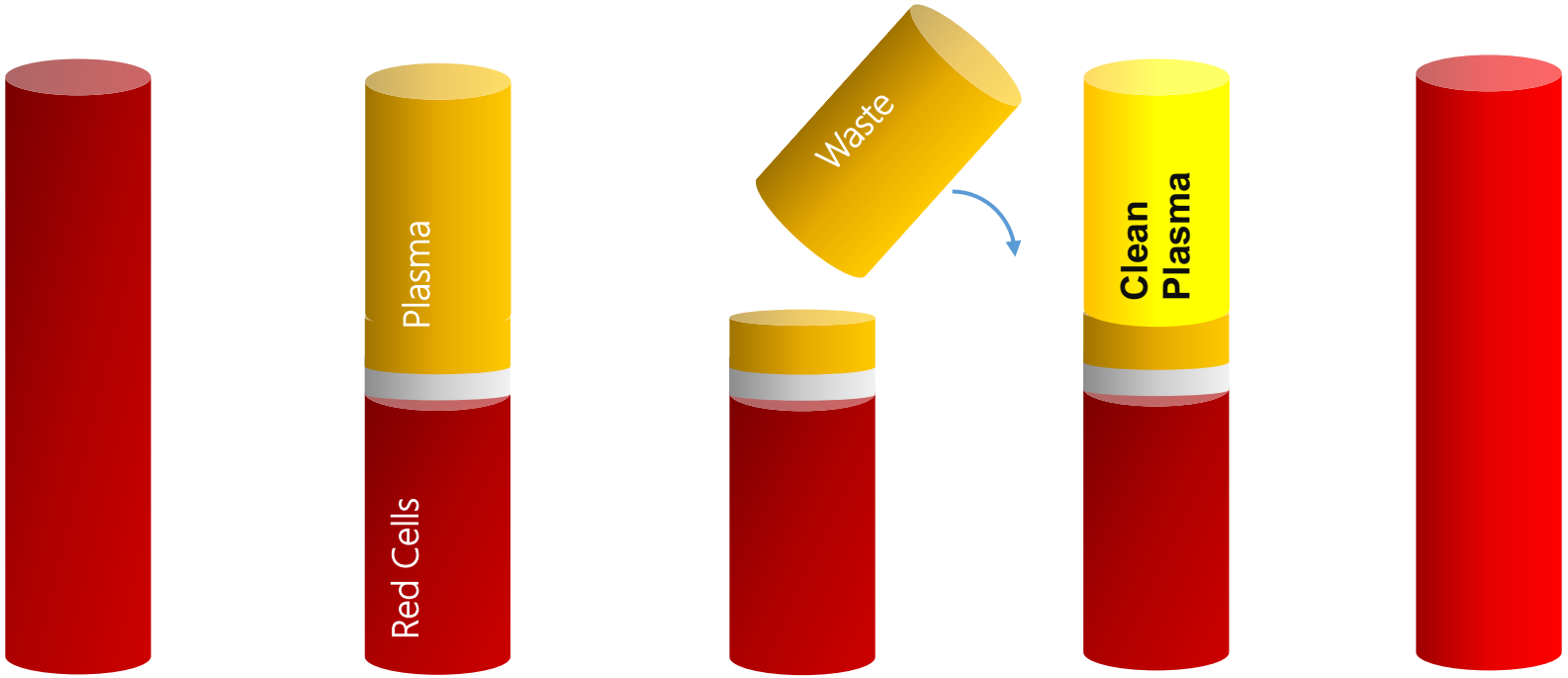
# Therapeutic Plasma Exchange (TPE)

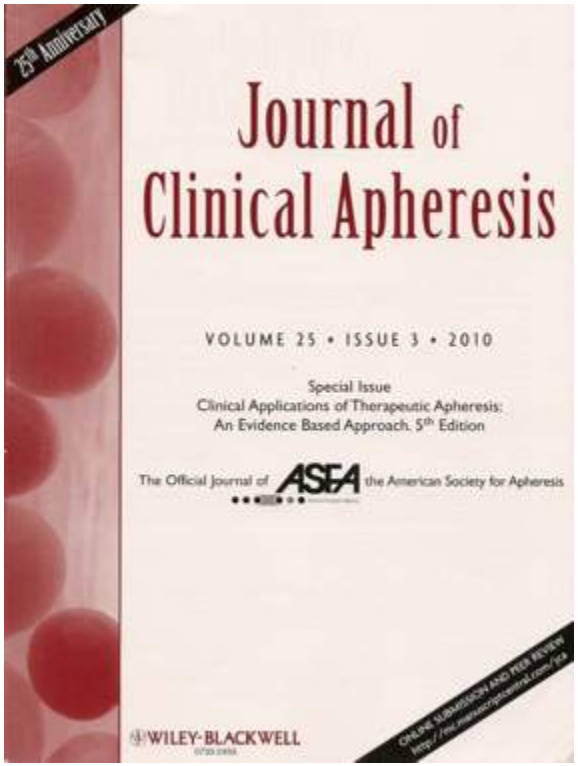


# Abnormal Substances Removed From the Circulation by TPE

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

# Procedural Elements & Practical Considerations

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



# VENOUS ACCESS

- Require large bore venous catheters to sustain the flow rates required (50-100 ml/min)
- Type of catheters: 17 gauge
- Location:

  Peripheral: antecubital fossa

  central: femoral/subclavian/jugular

  Arteriovenous shunt/fistula
- Number of lines: continuous flow devices : separate lines

# REPLACEMENT FLUID

- Must be FDA approved to use with blood products [get mixed with RBC before the return phase]
- Replacement solutions:

  Crystalloids–normal saline 0.9%

  Colloids–5% albumin; plasma
- Function of the replacement fluid is to

  maintain intravascular volume (primary)

  restoration of important plasma proteins

  maintenance of colloid osmotic pressure

  maintenance of electrolyte balance

# REPLACEMENT FLUID

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

# Comparison of Replacement Fluids

| Replacement fluid | Advantage | disadvantage |
|---|---|---|
| Crystalloid | Low cost<br>Hypoallergenic<br>No infectious risk | Hypo-oncotic<br>No coagulation factors<br>No immunoglobulins<br>2-3 volumes required |
| Albumin | Iso-oncotic<br>No infectious risk | Higher cost<br>No coagulation factors<br>No immunoglobulins |
| Plasma | Immunoglobulins<br>Coagulation factors<br>Iso-oncotic | Infectious risk<br>Citrate<br>Allergic reactions<br>ABO compatibility |

# Replacement Fluid and Balance

3 choices of fluid balance (FB):

100% FB –isovolemic –volume replaced=volume removed

<100% FB –hypovolemic (“dry”) -volume replaced < volume removed

>100% FB –hypervolemic (“wet”) -volume replaced > volume removed

# Normal/abnormal Constituents Removed TPE

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

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

# Volume of Patient Plasma Exchanged (PEX)

Little advantage beyond 1.0-1.5 volumes

- 1 pv = 63%↓
- 2 pv = 86%↓
- 3 pv = 95%↓

Removal of IgG and IgM by plasma exchange:

| **Measure** | IgG | IgM |
|---|---|---|
| **Intravascular amount** | 45% | 76 % |
| **"total body" removal** | | |
| • 1.0 PEX vol. | 28% | 48% |
| • 1.5 PEX vol. | 35% | 59% |
| • 2.0 PEX vol. | 39% | 65% |

# ANTICOAGULATION

**Anticoagulation citrate Dextrose (ACD):**

- Found in human cells, plant cells, and citrus fruits
- Chelates positively charged calcium ions (ionized calcium) and blocks calcium-dependent clotting factor reactions
- Works extracorporeally
- Metabolized in the liver almost immediately upon return
- Side effects: hypocalcemia.
- ↑ small pts, large vol. of citrated blood, liver dysfunction
- **Heparin:**
- Prevents conversion of fibrinogen to fibrin and prothrombin to thrombin
- Systemic anticoagulation
- Metabolized slowly 1-2 hours
- Individual sensitivity and elimination rates

# Patient History and Medications

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

# Frequency and Number of Procedures

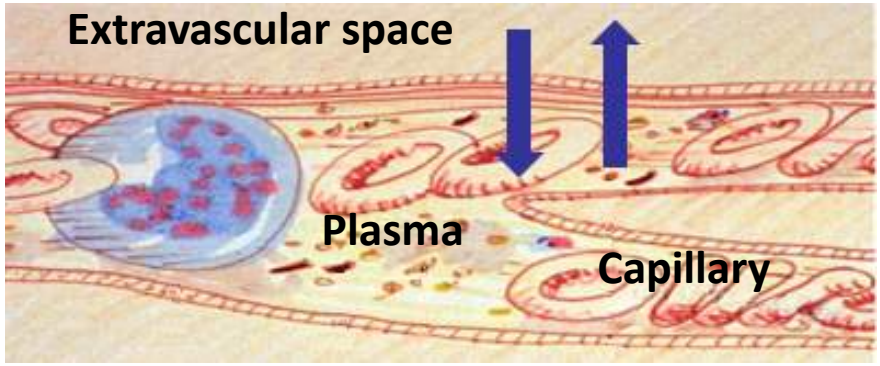
- Depends on: Disease being treated, Patient signs and symptoms, Lab values

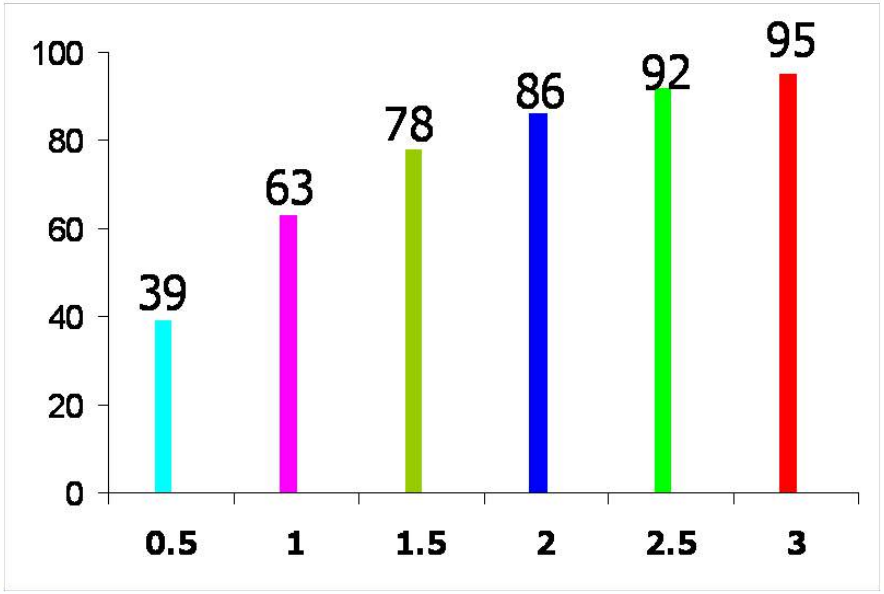
| Substance | Volume Treated (ml/kg) | Treatment Interval (hours) | Number of Treatment |
|---|---|---|---|
| Autoantibodies | 40-60 | 24-48 | 4-6 |
| Immune complexes | 40-60 | 24-48 | Treat to response |
| Paraproteins | 40-60 | 24 | Treat to response |
| Cryproteins | 40-60 | 24-48 | Treat to response |
| Toxins | 40-60 | 24-71 | Treat to response |
| TTP/HUS | 40 | 24 | To remission |

# TPE – Success Factors and Frequency

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

# TPE – Success Factors and Frequency




- The success of a TPE procedure is dependent on the:
  - Distribution of disease mediator
  - Volume of plasma removed

# Complications

- Hypotension
- Vasovagal syncope
- Hypocalcaemia
- Allergic reaction
- Other side effects

  Vascular access: hematoma, phlebitis, infection

  Air embolism

  Loss of blood components: → bleeding

  Thrombocytopenia (30% decrease)

  Hypofibrinogenemia (50% decrease)

# Indications for TA

Journal of Clinical Apheresis 25:83–177 (2010)

## Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

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**TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories[a]**

| Category | Description |
|---|---|
| I | Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.<br>[Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition]. |
| II | Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.<br>[Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease] |
| III | Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure]. |
| 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.<br>[Example: plasma exchange for active rheumatoid arthritis]. |

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**TABLE II. Level of Evidence Used in the ASFA Special Issue 2010[a]**

| Evidence level | Evidence quality |
|---|---|
| Type I | Obtained from at least one properly designed randomized controlled trial |
| Type II-1 | Obtained from a well-designed controlled trials without randomization |
| Type II-2 | Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group |
| Type II-3 | Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence |
| Type III | Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees |

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**TABLE III. Grading Recommendations Adopted from Guyatt et al. [13]**

| 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 |
| 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 |

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# TERIMA KASIH

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# PLATELET PHERESIS