Workshop B02

Tuesday February 14th, 4:00 p.m. - 5:30 p.m.

Plasma Exchange Therapy and Hybrid Techniques

David M. Ward, MD
Hiroyuki Hirasawa, MD
Plasma Exchange Therapy and Hybrid Techniques

(1) Introduction & Methods

David M. Ward, MD, FRCP.
Professor of Medicine, Division of Nephrology, UCSD.
Medical Director, Therapeutic Apheresis Program.
Associate Medical Director, Kidney/Pancreas Transplantation.
WARNING:
Many of the hybrid extracorporeal blood circuits shown in this talk, and some of the disease applications, are not FDA-approved.

DISCLOSURE:
The speaker has received support in the past from:
- CaridianBCT, Inc. (soon to be Terumo BCT)
- Therakos, Inc. (makers of photopheresis systems)
- others of no relevance to this presentation
Plasma Exchange Therapy and Hybrid Techniques
(1) Introduction & methods

OUTLINE

- Case reports.
- Fundamentals of plasmapheresis therapy (therapeutic plasma exchange = TPE)
- Secondary plasma-processing techniques.
- Hybrid systems (plasmapheresis plus dialysis, etc.)
Case reports

- All with end-stage liver disease.
- All received liver transplants that were ABO incompatible (“A” liver into “O” recipient.)
- All developed post-operative acute renal failure requiring continuous renal replacement therapy (CRRT).
- All required plasmapheresis (therapeutic plasma exchange = TPE) for removal of anti-A antibodies.
- All recovered renal function and survived with good function of the liver transplant.
Case reports

- All received citrate-anticoagulated Continuous Hemodiafiltration

Citrate-anticoagulated CRRT was first used in February 1989.

Since 1992 at UCSD, CRRT has been veno-venous (CVVHDF).

Also all received intermittent centrifugal plasmapheresis (TPE)

- Plasmapheresis goal: to keep anti-A antibody titer below 1:8

**Case reports**

**Plasmapheresis**

- From patient
- Citrate
- Transfuse with Group “O” red cells
- Blood return
- Ca++
- CENTRIFUGAL PLASMAPHERESIS
  - Remove Anti-A
  - FFP replacement Group “A” or “AB”

**Hemodialfiltration**

- Prefilter Dilution
- Hemofilter
- Ca++- free Dialysate
- Postfilter Replacement
- Ultra-filtrate + Effluent Dialysate
- CONTINUOUS HEMODIAFILTRATION

- Transfuse with Group “O” red cells
- Group “O” red cells
Plasma Exchange Therapy and Hybrid Techniques

(1) Introduction & methods

OUTLINE

- Case reports.
- Fundamentals of plasmapheresis therapy (therapeutic plasma exchange = TPE)
- Secondary plasma-processing techniques.
- Hybrid systems (plasmapheresis plus dialysis, etc.)
PLASMA REMOVAL WITH RETURN OF CORPUSCLES (PLASMAPHAERESIS)

FIRST PAPER

JOHN J. ABEL, L. G. ROWNTREE AND B. B. TURNER
From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, July 16, 1914

I. In connection with our experiments on vividiffusion with a view to the ultimate use of the method for the relief of toxae-mia the idea suggested itself to try the effects of the repeated removal of considerable quantities of blood, replacing the plasma by Locke’s solution and reinjecting this together with the sedi-mented corpuscles.

J. Pharmacol Exp Ther, 5:625, 1914
Removal of pathogenetic macromolecules from the bloodstream:

- Autoantibody
- Probable autoantibody
- Antigen-Antibody complexes (circulating immune complexes)
- Alloantibody
- Paraproteins (light chains, monoclonal cryoglobulins, etc.)
- Non-immunoglobulin proteins
- Endogenous toxins
- Exogenous poisons
Plasmapheresis applications

- **Autoantibody**: Thrombotic Thrombocytopenic Purpura (TTP), Myasthenia gravis (MG), Neuromyelitis Optica (NMO), Anti-GBM GN (& Goodpasture’s), ANCA-nephritis (& Wegener’s), Antiphospholipid crisis, Immune Thrombocytopenia (ITP), etc.

- **Probable autoantibody**: Multiple sclerosis (MS), Guillain-Barré (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), etc.

- **Antigen-Antibody complexes**: Hepatitis C vasculitis, S.L.E., etc.

- **Alloantibody**: Transplant sensitization, Transplant rejection (humoral), Transfusion reactions, etc.

- **Paraproteins**: Waldenstrom’s, Hyperviscosity, Light-chain neuropathy, Light-chain glomerulopathy, Myeloma cast nephropathy, etc.

- **Non-Ig proteins**: Focal Segmental Glomerulosclerosis (FSGS).

- **Endogenous toxins**: Hypercholesterolemia, Liver failure, Systemic Inflammatory Response Syndrome (SIRS), etc.

- **Exogenous poisons**: *Amanita*, drugs, etc.
Indications for therapeutic apheresis

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. Shaz10*

1 Transfusion Medicine Service, Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire
2 Division of Transfusion Medicine, Mayo Clinic, Rochester, Minnesota
3 Transfusion Service, Department of Pathology, Duke University, Durham, North Carolina
4 Apheresis Service, Division of Hematology, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania
5 The Department of Medicine, Division of Hematology, University of Washington, Seattle, Washington
6 Division of Laboratory Medicine, Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama
7 Transfusion Medicine and Coagulation Laboratory, University of Texas, Southwestern Medical Center, Dallas, Texas
8 Transfusion Medicine and Cellular Therapy Section, Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York
9 Division of Transfusion Medicine, Department of Pathology, University of Massachusetts Medical School, Worcester, Massachusetts
10 Center for Transfusion and Cellular Therapies, Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia

The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (fourth edition), the subcommittee has incorporated systematic review and evidence-based approach in the grading and categorization of indications. This Fifth ASFA Special Issue has further improved the process of using evidence-based medicine in the recommendations by refining the category definitions and by adding a grade of recommendation based on widely accepted GRADE system. The concept of a fact sheet was introduced in the Fourth edition and is only slightly modified in this current edition. The fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis. The article consists of 59 fact sheets devoted to each disease entity currently categorized by the ASFA as category I through III. Category IV indications are also listed. J. Clin. Apheresis 25:83-177, 2010. © 2010 American Society for Apheresis

Key words: apheresis; plasma exchange; immunoabsorption; leukocytapheresis; photopheresis; categories; indications; evidence based
Indications for therapeutic apheresis

This “ASFA Special Issue” was published every 7 years (1986, 1993, 2000, 2007), now every 3 years (2010).

- The new 2010 version incorporates
  - a structured review of all published literature
  - evidence-based ratings (using criteria of the University HealthCare Consortium)
  - assignment to categories I, II, III, IV
  - fact sheets that present comprehensive condensed information in a standardized format on >100 indications.

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice

Also see


3. Conventional Apheresis Therapies: a Review
Example: **ANCA-associated RPGN** (Wegener’s Granulomatosis)

### ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (WEGENER’S GRANULOMATOSIS)

| Incidence (0.55 per 100,000/year) | Procedure | Recommendation | Category | Type of evidence **

<table>
<thead>
<tr>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>320</td>
<td>120</td>
<td>22</td>
<td>NA</td>
<td>Type 1</td>
</tr>
</tbody>
</table>

**Note:** RCT = Randomized Controlled Trial; CT = Case Report; CS = Case Series; CR = Case Report; Type of evidence: Type 1 = Evidence from randomized controlled trials, Type 2 = Evidence from non-randomized controlled trials, Type 3 = Evidence from observational studies, Type 4 = Expert opinion or clinical experience.

### Description of the disease

ANCA-associated rapidly progressive glomerulonephritis (RPGN) is a disease characterized by the development of glomerulonephritis due to the presence of ANCA-associated immune complexes that target different parts of the glomerulus. These complexes activate the complement system and lead to inflammation and damage of the glomerulus.

**ANCA-AV**: ANCA is an acronym for antineutrophil cytoplasmic antibodies, a type of antibody that is present in patients with ANCA-associated vasculitis. ANCA is divided into two categories based on the target antigens: c-ANCA (anti-proteinase 3) and p-ANCA (anti-myeloperoxidase).

### Current management/treatment

The standard treatment approach for ANCA-associated RPGN includes therapeutic intervention with glucocorticoids, immunosuppressive agents, and plasma exchange. The treatment is guided by the severity of the disease and the patient’s response to initial therapy. In cases of severe renal involvement, plasma exchange is often used to remove circulating immune complexes and antigen.

### Technical notes

- **Volume treated:** 1 to 1.5 L
- **Replacement fluid:** albumin plasma solution
- **Frequency:** daily or every other day

### Duration and discontinuation number of procedures

Consider daily procedures in leukopenic patients until stable hemoglobin and platelet count are achieved. Consider reducing the frequency of plasma exchange in patients with stable renal function.

### References

[93-117]

<ref>ASFA guidelines</ref>

*As of December 31, 2014, using PubMed and Medline search terms ANCA or anti-neutrophil cytoplasmic antibody and plasma exchange or plasma exchange for articles published in the English language. References of the included articles were searched for additional titles and trials.*
PLASMA REMOVAL WITH RETURN OF CORPUSCLES (PLASMA PHAERESIS)

FIRST PAPER

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Apheresis methods

- Manual Plasmapheresis
  - still used in pediatrics
  - or when urgent and no machine is available

- Centrifugal Plasmapheresis and Cytapheresis

- Membrane Plasmapheresis
Separation by membrane filtration

Hollow-fiber plasma-filter
Pore size: ~0.3 microns
Cut-off: ~1000 kDa

Membrane specifications are those of Asahi products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8, 101 - Japan)
Separation by centrifugation
Separation by centrifugation

Whole Blood in
RBC out
WBC out
Plasma out
Separation by centrifugation

**Specific Gravity**

- **Plasma**: 1.027
- **Platelets (Plt's)**: 1.04
- **Lymphocytes**: (Lymph’s)
- **Monocytes (Mono’s)**: 1.06
- **Blasts**: (Blasts)
- **Polymorphonuclear Neutrophils (PMN’s)**: 1.085
- **Red Blood Cells (RBC’s)**: 1.095

---

Whole Blood in

RBC out

WBC out

Plasma out
To get pure cell product:
(1) interface position
(2) accurate RPM’s (G’s)
(3) flow rate (dwell time)

High G-force (= high RPM’s) to create a platelet-poor plasma

Low G-force to keep WBC’s out of packed RBC’s

**Plasmapheresis (TPE)**
(plasma removal or exchange)

**Thrombocytapheresis**
(platelet removal)

**Leukocytapheresis = Leukapheresis**
(WBC removal)

**Erythrocytapheresis**
(red cell exchange)

**Specific Gravity**

- Plasma 1.027
- Platelets 1.04
- Lymph 1.06
- Mono’s 1.04
- Blasts
- PMN’s 1.085
- RBC’s 1.095

Separation by centrifugation
Separation by centrifugation

Apheresis (blood component removal or exchange)

Cytapheresis (blood cell removal or exchange)

Plasmapheresis (TPE) (plasma removal or exchange)

Thrombocytapheresis (platelet removal)

Leukocytapheresis = Leukapheresis (WBC removal)

Erythrocytapheresis (red cell exchange)

Specific Gravity

Plasma 1.027

RBC’s 1.095

PMN’s 1.085

Blasts

Mono’s 1.06

Lymph’s

Plt’s 1.04
**Conventional Therapeutic Apheresis Modalities**

**Plasmapheresis**
- = plasma removal or exchange
- (requires centrifugal machine or plasmafiltration system)

- Replace with FFP (for TTP)
- Replace with albumin (for all other uses)

**Cytapheresis**
- = cell removal or exchange
- (requires centrifugal machine)

- Erythrocyt-apheresis = red cell exchange (sickle cell, etc.)
- Thrombocyt-apheresis = platelet reduction (thrombocytosis)
- Leukapheresis = white cell apheresis
  - WBC reduction (leukemia)
  - Blood stem cells (for BM transplant)

**Less-Conventional Apheresis Modalities**
- (require additional equipment)

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Blood stem cells (for BM transplant)

Less-Conventional Apheresis Modalities (require additional equipment)

Conventional Therapeutic Apheresis Modalities

Plasmapheresis
- plasma removal or exchange (requires centrifugal machine or plasmafiltration system)
  - Replace with FFP (for TTP)
  - Replace with albumin (for all other uses)

Cytapheresis
- cell removal or exchange (requires centrifugal machine)
  - Erythrocyt-apheresis
    - red cell exchange (sickle cell, etc.)
  - Thrombocyt-apheresis
    - platelet reduction (thrombocytosis)
  - Leukapheresis
    - white cell apheresis
    - WBC reduction (leukemia)
    - Blood stem cells (for BM transplant)

Online plasma purification
- Immuno-adsorption
- Filtration selective removal
- LDL apheresis

Online WBC processing
- Photopheresis (= ECP)
- other

WBC’s (for ex-vivo immune modulation)

Blood stem cells (for ex-vivo genetic modification)

Plasmapheresis types

By intensity / frequency

- **Intermittent plasmapheresis**
  - meaning as used in “intermittent” hemodialysis
  - 2 to 4 hour procedure, daily or a few times per week

- **Continuous plasmapheresis**
  - meaning “continuous” as used in “CRRT”
  - ~ 24 hour per day treatment, usually in Critical Care Unit

By machine type

- **Continuous-flow centrifuges**
  - do not confuse with “continuous” as used above
  - Caridian, Fresenius, etc.

- **Discontinuous-flow centrifuges**
  - Latham-bowl types, e.g. Haemonetics

- **Membrane plasma filters**
  - Asahi Plasmaflo, etc.
Intermittent plasmapheresis depends on disease characteristics.

Example:
“Rx daily x3, then q.o.d. x3, then reassess”

Prescribed volume of each plasma exchange procedure depends on patient’s size (plasma volume).

Example:
“Volume to remove: 3.6 liters”

Number and frequency of procedures depends on disease characteristics.
Volume exchanged depends on the patient’s size:

Adult blood volume (BV) ~ 70ml/Kg.
Plasma vol (PV) = BV x (1 - Hct/100)

Example: 70 Kg woman:
BV = 70ml/Kg x 70Kg = 4.9 liter
Hematocrit = 39%
PV = 4.9 liter x (61%) = 3 liter

1.0 PV exchange = 3 liters
1.5 PV exchange = 4.5 liters

Choose 3.6 liter TPE
x = 3.6 / 3.0 = 1.2
y = e^{-x} = e^{-1.2} = 0.30
Therefore removes 70%

A 1.0-vol exchange removes 63%.
A 1.5-vol exchange removes 78%.
Plasmapheresis procedures

- IgM is large (~970,000 Daltons)
- 90% of IgM stays intravascular

Removal of IgM

(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)
Plasmapheresis procedures

Monoclonal IgM (mg/dl)

- IgM is large (~970,000 Daltons)
- 90% of IgM stays intravascular

IgM Autoantibody titer

- Only 25%-30% is intravascular

Removal of IgM
(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)

Removal of IgG
(Ward DM, Updates to Harrison’s Principle’s of Internal Medicine, Volume V, 1984)

Most antibody mediated diseases:

- IgG is smaller (~146,000 Daltons)
- Only 25%-30% is intravascular
Extracellular fluid = 35 - 40% of TBW, say 37.5% = 15 liters

Total body water (TBW) = 50% - 60% of weight, say 57% = 40 liters

Intracellular fluid = 60 - 65% of TBW, say 62.5% = 25 liters

Interstitial fluid (third space) = 25 - 30% of TBW, say 30% = 12 liters

Plasma ~8% = 3 liters

Extracellular fluid = 35 - 40% of TBW, say 37.5% = 15 liters

Standard 70 Kg Adult

dmward@ucsd.edu
Number of plasmaphereses needed

Removing IgM from plasma

\[ y = e^{-x} \]

One TPE

2 hours

0 1 2 3 4

Liters exchanged

Removing IgG from extracellular fluid

\[ y = e^{-x} \]

7 TPE procedures

11 days

0 3 6 9 12 15 18 21

Liters exchanged

Intracellular
25 liters

Interstitial
12 liters

Plasma
3 liters

Intracellular
25 liters

Extracellular
15 liters

Plasma

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Plasma Liters cleared

Hemodialysis (HD)
Total body water
40 liters

Removing urea from total body water

One HD (3+ hrs)

Kt/V = 1.2
URR 70%

Urea moves quickly from ECF to blood
Plasma

Plasmapheresis (TPE)

Extracellular fluid
15 liters

No Ig in intracellular fluid
IgM minimal in ECF
IgG moves slowly from ECF

Protein reduced 70%
Plasma volumes exchanged = 1.2

y = e^{-x}
x = 3L

IgM minimal rebound
IgG rebound from ECF

One TPE (<2 hrs)

Plasmapheresis (TPE)

Kinetics of intermittent clearance procedures

Removing protein from plasma

y = e^{-x}
x = 40L

Plasma 3 liters

Total body water
40 liters

y = e^{-x}
x = 3L

One HD (3+ hrs)

IgG synthesis

Urea moves quickly from ICF to ECF

Urea moves quickly from ECF to blood

y = e^{-x}
x = 40L

Kt/V = 1.2
URR 70%

IgG moves slowly from ECF

IgM minimal in ECF

Plasma volumes exchanged = 1.2

Protein reduced 70%
# Intermittent plasmapheresis - choices

<table>
<thead>
<tr>
<th>Machine type</th>
<th>Centrifugal plasmapheresis</th>
<th>Membrane plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma removal</td>
<td>~ 30 ml/min</td>
<td>~ 30 ml/min</td>
</tr>
<tr>
<td>Blood flow rate</td>
<td>~ 70 ml/min</td>
<td>~ 140 ml/min</td>
</tr>
<tr>
<td>Plasma extraction ratio</td>
<td>80 - 85%</td>
<td>30 - 35%</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Bilateral arm vein needles or Central venous catheter</td>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Citrate (or heparin)</td>
<td>Heparin (or citrate)</td>
</tr>
<tr>
<td>Replacement</td>
<td>5% albumin or FFP</td>
<td>5% albumin or FFP</td>
</tr>
<tr>
<td>Calcium</td>
<td>I.V. calcium (for citrate)</td>
<td>None (for heparin)</td>
</tr>
</tbody>
</table>
### Anticoagulation

#### Citrate:
1. Familiar in blood-banking.
2. Short-acting: prescribe ratio to blood flow
3. No systemic anticoagulant effect; risk of “citrate toxicity”
4. Suitable for low-flow circuits

#### Heparin:
1. Familiar in dialysis.
2. Long-acting: prescribe units / Kg body wt / hour
3. Excess causes systemic bleeding; no other toxicity.
4. Suitable for high-flow circuits
# Anti-coagulation comparisons: citrate load

<table>
<thead>
<tr>
<th>Method</th>
<th>Citrate for a/c (mmol)</th>
<th>Citrate if FFP replacement* (+ extra = total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrifugal TPE using citrate</td>
<td>14 /hr</td>
<td>+ 50 = 64/hr</td>
</tr>
<tr>
<td>Membrane TPE using citrate</td>
<td>*28-56 /hr</td>
<td>+ 50 = 80+/hr</td>
</tr>
<tr>
<td>Membrane TPE using heparin</td>
<td>0</td>
<td>+ 50 = 50/hr</td>
</tr>
<tr>
<td>Continuous hemodiafiltration</td>
<td>20 /hr</td>
<td></td>
</tr>
<tr>
<td>(UCSD citrate-anticoagulated CRRT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFP (1 unit = ~250 ml) *</td>
<td>~ 7 /unit</td>
<td>FFP at 30ml/min = 1800 ml/hr = 7+ units/hr</td>
</tr>
<tr>
<td>Packed RBC’s (1 unit = ~300 ml)</td>
<td>2-3 /unit</td>
<td>⇒ citrate at ~50 mmol/hr</td>
</tr>
</tbody>
</table>

* Ilamathi E et al. (Semin Dial 6:268, 1993) describe successful Asahi membrane plasmapheresis with 8.4% citrate @ 22 ml/hr for Q_B 50 ml/min
Extrapolated to Q_B 120 - 140 as above, citrate to patient = 14 - 18 mmol/hr
Figure 2. Comparison of characteristics of centrifugal and membrane plasmapheresis, with choices of plasma replacement or plasma regeneration.
OUTLINE

- Case reports.

- Fundamentals of plasmapheresis therapy (therapeutic plasma exchange = TPE)

- Secondary plasma-processing techniques.

- Hybrid systems (plasmapheresis plus dialysis, etc.)
Plasma regeneration (on-line purification)

**Centrifugal TPE**
- Blood return
- Whole plasma
- Centrifugal apheresis machine
- From patient

**Membrane TPE**
- Blood return
- Whole plasma
- Plasma separator (hollow fiber membrane with large pore size)
- From patient

Purified plasma
Plasma regeneration (on-line purification)

- cascade plasmafiltration
- adsorption columns containing
  - Staphylococcal Protein A
  - immobilized antibodies (Ab)
  - adsorption resins
  - immobilized antigen (Ag)
  - covalently-bound peptide ligands
Cascade Plasmafiltration (Double-Filtration)

#1: Plasma-filter
Pore size: large
Cut-off: >1000 kD

#2: Plasma-fractionator
Pore size: medium
Cut-off: ~ 100 kD
   (Albumin ~ 67 kD)
   (IgG    ~ 140 kD)
   (IgM    ~ 970 kD)

Additional colloid (optional)
Protein-A Immunoadsorption (PA-IA)

- Staph Protein A has high avidity for Fc portion of IgG (IgG\textsubscript{1}, IgG\textsubscript{2}, IgG\textsubscript{4})
- Removal of antibody or antigen-antibody complexes

Staphylococcal Protein A immuno-adsorption column (Prosurba\textregistered) (Immunosorba\textregistered)

- ITP: FDA-approved.
- RA: Double-blind sham-controlled trial positive (Felson, 1999).
- Refractory TTP (Mitomycin): anecdotal successes.

- But columns no longer available.
- Also controversy: super-antigen (pharmacological) mechanism?
Antibody Immunoadsorption with Anti-IgG

- Removes IgG (all subclasses)
- Used in Europe and Japan for:
  - autoimmune diseases
  - transplant alloimmunization
- Brands:
  - TheraSorb™ (Miltenyi Biotec)
  - others

Perfusion columns containing immobilized polyclonal antibody to human IgG.

blood return

from patient

Purified plasma

Whole plasma

Rinse

Waste

dmward@ucsd.edu
Dextran adsorption (Kaneka Liposorber®)

- Removes LDL, Lp(a), and VLDL.
- Minimal effect on HDL or albumin.
- Effective LDL apheresis

Whole plasma

Purified plasma

5% Saline

0.9% Saline

Perfusion columns containing Dextran sulfate

Waste

from patient

blood return

dmward@ucsd.edu

Kaneka ® system is FDA-approved
Braun “HELP”® System
(Heparin-induced Extracorporeal Lipoprotein Precipitation)

Acidity (pH 5.12) plus heparin causes precipitation of lipoprotein complexes.

Bicarbonate dialysis and ultrafiltration to correct pH and volume.

Precipitate filter captures lipoprotein complexes.

Whole plasma

Purified plasma

Acid buffer/heparin

Heparin adsorber

Ultrafilter

 LDL-Apheresis
Braun HELP® system is FDA-approved

blood return

from patient

dmward@ucsd.edu
Perfusion columns containing immobilized antigen can extract specific autoantibodies for anti-GBM nephritis


for SLE


Clinically unsuccessful due to Ag leaching
Covalently-bound peptide ligands for Immunoadsorption (IA)

Peptide ligands covalently linked to sepharose mimic the epitope and specifically immuno-adsorb pathogenic autoantibodies.

effective in

**Autoimmune type Idiopathic Dilated Cardiomyopathy**

which is due to autoantibodies with

(1) agonist-like effect on the Beta-1 adrenergic receptor

(2) now known to cross-react with and damage cardiac myosin.

But Ab’s against different epitopes may cause similar disease

Covalently-bound ligands for Immunoadsorption (IA)

Column containing synthetic terminal trisaccharide A or B blood group antigen linked to a Sepharose matrix.

Glycosorb ABO column (Glycorex Transplantation AB),

Current use of on-line plasma purification

- **Cascade filtration**
  - Removes only molecules >100 kDa
  - Suitable for all immunoglobulins, but not for smaller molecules

- **Immunoadsorption columns (anti-IgG)**
  - Suitable for IgG antibody-mediated, but not IgA or IgM antibody

- Neither is suitable for:
  - Metabolic diseases (Refsum’s disease, etc.)
  - Poisonings
  - Light chain neuropathy (kappa 22.5 kDa; lambda dimers 45 kDa)
  - Myeloma kidney (free light chains, kappa or lambda)
  - FSGS (focal segmental glomerulosclerosis, type recurring post-transplantation):
    - classic glomerular permeability factors (< 50 kDa)
    - suPAR (22 - 45 kDa)
  - etc.
OUTLINE

- Case reports.
- Fundamentals of plasmapheresis therapy (therapeutic plasma exchange = TPE)
- Secondary plasma-processing techniques.
- Hybrid systems (plasmapheresis plus dialysis, etc.)
Coupled Plasmafiltration Adsorption (CPFA)

= Continuous Plasmaseparation with Adsorption Column + Continuous High-volume Hemo(dia)filtration

Plasmapheresis in septic shock

106 patients with severe sepsis or septic shock randomly assigned to centrifugal plasmapheresis or not in addition to standard sepsis treatment.

<table>
<thead>
<tr>
<th></th>
<th>Plasmapheresis (n =54)</th>
<th>Control group (n =52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APACHE III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>56.4 18.8</td>
<td>53.5 15.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Day 2</td>
<td>44.5 18.5*</td>
<td>49.0 19.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Difference days 1-2</td>
<td>11.5 15.6</td>
<td>4.5 15.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

| **28-DAY MORTALITY** |                       |                       |     |
| Total study population | 18 (33.3%)         | 28 (53.8%)            | 0.05|
| Abdominal group       | 11/33 (33.3%)       | 11/16 (68.5%)         | 0.03|
| Other groups          | 7/21 (33.3%)        | 17/36 (47.2%)         | 0.4 |

*Statistically significant

Membrane plasmapheresis:

**Anticoagulation**

1. for Intermittent

   - **Heparin**
     - 3 - 4 hr bleeding risk

   - **Citrate**
     - citrate toxicity risk

2. for Continuous

   - **Heparin**
     - 24 hr bleeding risk

   - **Citrate**
     - citrate accumulation
     - or reduce blood flow
     - or use less citrate (e.g. 20 mmol/hr)
Continuous Plasmapheresis + CRRT
IN SERIES: Membrane Plasmafilter before CVVHDF

Blood pump
(Blood pump)

Anti-coagulant
(heparin or citrate)

from patient

Replacement: Albumin/FFP

Effluent Plasma

MEMBRANE PLASMA-PHERESIS

Effluent + Ultrafiltrate

Dialysate

CONTINUOUS HEMODIAFILTRATION

Ultra-filtrate + Effluent Dialysate

Postfilter Replacement

Prefilter Dilution

Hemofilter

Dilution

Blood return

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Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running.

Can use two citrate pumps:
1. CRRT pump
2. Apheresis machine pump (which stops if apheresis blood-pump stops)

Intermittent Plasmapheresis + citrate CRRT IN PARALLEL: Centrifugal Plasmaseparator and CVVHDF

Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

Centrifugal Plasmapheresis:
- Citrate
- Can use two citrate pumps: (1) CRRT pump (2) Apheresis machine pump (which stops if apheresis blood-pump stops)
- Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose
- Blood return
- Replacement: Albumin/FFP

Continuous Hemodiafiltration:
- Prefilter Dilution
- Hemofilter
- Ultra-filtrate + Effluent Dialysate
- Prefilter Replacement
- Ca++- free Dialysate

Dilution
-Ca++

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**Intermittent Plasmapheresis + citrate CRRT**

**IN PARALLEL:** Centrifugal Plasmapheresis and CVVHDF

Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

**Q_B 200 ml/min**

**Q_B 100 ml/min**

**Alternative:**
**IN SERIES** instead of **IN PARALLEL**
**Continuous Plasmapheresis + citrate CRRT**

**IN SERIES:** Centrifugal Plasmaseparator and CVVHDF

**Q_B 100 ml/min**

---

**CENTRIFUGAL PLASMAPHERESIS**

- Effluent Plasma
- Replacement: Albumin/FFP

**CONTINUOUS HEMODIAFILTRATION**

- Prefilter Dilution
- Hemofilter
- Ca++- free Dialysate
- Postfilter Replacement
- Ultra-filtrate + Effluent Dialysate

blood return
Roller pump must stop when apheresis blood-pump stops, until bypass line is opened.

Use the apheresis machine’s citrate pump (Switch to CRRT citrate pump when apheresis is stopped and bypass line is in use)
Continuous Plasmapheresis + CRRT

IN SERIES: Membrane Plasmafilter before CVVHDF

- Blood return from patient
- Anti-coagulant
- Blood pump (roller pump)

Replacement: Albumin/FFP

Effluent Plasma

MEMBRANE PLASMA-PHERESIS

Standard heparin protocol or UCSD citrate-CRRT

Prefilter Dilution

Hemofilter

Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

CONTINUOUS HEMODIAFILTRATION
Continuous Plasmapheresis + CRRT IN SERIES: Membrane Plasmafilter before CVVHDF

- **Replacement:** Albumin/FFP
- **Effluent Plasma**
- **Ultrafiltrate + Effluent Dialysate**
- **Standard heparin protocol or UCSD citrate-CRRT**

**Blood pump (roller pump)**
- **Anticoagulant**
- **Blood return from patient**

**Membrane Plasmafilter**
- **Prefilter Dilution**
- **Dialysate**
- **Postfilter Replacement**
- **Ultrafiltrate + Effluent Dialysate**

**Continuous Hemodiafiltration**
Continuous Plasmapheresis + CRRT
IN SERIES: Membrane Plasmafilter before CVVHDF

Blood pump (roller pump)

Anti-coagulant

Blood return

Replacement: Albumin/FFP

Standard heparin protocol or UCSD citrate-CRRT

Membrane Plasmafilter before CVVHDF
Continuous Plasmapheresis + CRRT
IN SERIES: Membrane Plasmafilter before CVVHDF

- Prefilter
- Dilution
- Ultrafiltrate + Effluent
- Dialysate
- Dialysate
- Replacement: Albumin/FFP
- Hemofilter
- Postfilter
- Replacement

One alternative: Plasma regeneration instead of Plasma replacement

- Anti-coagulant
- Blood pump (roller pump)
- Blood return

Standard heparin protocol or UCSD citrate-CRRT

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Double Filtration Plasmapheresis + CRRT

CASCADE PLASMAFILTRATION

- Blood pump (roller pump)
- Anti-coagulant
- Whole plasma
- Additional colloid (optional): Alb, FFP
- Effluent
- Globulin fraction
- Albumin fraction

CRRT

- Prefilter dilution
- Hemofilter
- Dialysate
- Postfilter replacement
- Effluent dialysate + ultra-filtrate

Blood return from patient
SUMMARY

- Case reports.

- Fundamentals of plasmapheresis therapy (therapeutic plasma exchange = TPE)

- Secondary plasma-processing techniques.

- Hybrid systems (plasmapheresis plus dialysis, etc.)