Extracorporeal Blood Purification; From Apheresis to Hemodialysis
ASFA Annual Meeting
May 23, 2013 4:00- 4:30PM

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Disclosure

• No relevant financial relationships
• Non-relevant financial relationships
  – Advisory group  Octapharma, Alexion
• FDA: Non-FDA approved will be noted
• Therapeutic Apheresis Academy: Conference
  Unrestricted educational grants to institution
  – TerumoBCT, Therakos, Gambro
Outline: Therapeutic Apheresis vs Hemodialysis

- Definition: Extracorporeal Therapies
- Historical Perspectives. TAM vs Hemodialysis
- TAM is (neglected) part of clinical nephrology
- Existing Evidence Base: JCA Special Issue
- Challenges and Barriers to Expanding Knowledge in TAM
Case study:

- A 40 year old man is admitted with fever, mental status changes and bilateral pedal edema
- Clinical diagnosis of TTP is made
- He has concurrent Acute Kidney Injury
- Consultation for necessary therapy is called...the cause and effect are in the blood
- Treatment: What to do? Dialysis vs Apheresis
- One or the other, or both?
Bloodletting is the removal or large amounts of blood from a patient’s body.

The practice of bloodletting began in the ancient world.

Ancient Greeks, Aztecs, and Egyptians used bloodletting because they believed that many diseases were caused by having too much blood.
Extracorporeal Therapies: procedures .... include .. diversion of blood through an external artificial circuit for ... blood “purification,” gas exchange, or correction of metabolic abnormalities.

### Evolution of circulatory system

Not everyone has a 4-chambered heart


<table>
<thead>
<tr>
<th>Animal</th>
<th>Heart Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>2 chamber</td>
</tr>
<tr>
<td>Amphibian</td>
<td>3 chamber</td>
</tr>
<tr>
<td>Reptiles</td>
<td>3 chamber</td>
</tr>
<tr>
<td>Birds &amp; Mammals</td>
<td>4 chamber</td>
</tr>
</tbody>
</table>

![Diagram showing heart structures for different animal groups](image)
Extracorporeal Therapies

Lungs
PLASMA REMOVAL WITH RETURN OF CORPUSCLES
(PLASMAPHARESIS)

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

J Clin Apher. 2010 00;25(5):240-249.
Okafor C, Ward DM .... Balogun RA.
John Jacob Abel (1857–1938)
Father of (American) pharmacology and the
Inventor of the artificial kidney machine (vividiffusion)

ON THE REMOVAL OF DIFFUSIBLE SUBSTANCES FROM THE CIRCULATING BLOOD OF LIVING ANIMALS BY DIALYSIS

JOHN J. ABEL, LEONARD G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, December 18, 1913

J Pharmacol Exp Ther July 1914 5:611-623
Apheresis and Hemodialysis

- Purpose
- Size Matters (solute, drug, toxin etc)
- Volume of Distribution
- Vascular Access & Venous Blood
- Blood Flow
- Pumps!
- Anticoagulation
- Complications
Extracorporeal Therapies
<table>
<thead>
<tr>
<th><strong>Hemodialysis</strong></th>
<th><strong>Therapeutic Apheresis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Removal of waste from the body</strong> (usually endogenous)</td>
<td>• <strong>Removal of pathologic material from the body</strong></td>
</tr>
<tr>
<td>• <strong>Kidney is ideal model for hemodialysis</strong></td>
<td>• <strong>No single ideal model for Th Apheresis</strong></td>
</tr>
<tr>
<td>• <strong>Water retention / removal</strong></td>
<td>• <strong>No appreciable role in water retention/removal</strong></td>
</tr>
<tr>
<td>• <strong>Salt retention/removal</strong></td>
<td>• <strong>No appreciable role in salt retention/removal</strong></td>
</tr>
<tr>
<td>• <strong>Protein retention</strong></td>
<td>• <strong>Protein removal</strong></td>
</tr>
</tbody>
</table>
A tale of two circuits: HD vs mApheresis

http://www.labspaces.net/99292/Hello_wearable_kidney_goodbye_dialysis_machine

http://www.apheresis.com/img/substitution.gif
Blood from the patient is circulated through a synthetic extracorporeal membrane and returned to the patient. The opposite side of that membrane is washed with an electrolyte solution (dialysate) containing the normal constituents of plasma water.
Blood Purification Technology: Membrane Separation

1. **Membrane Dialysis** – passive diffusion through a semi-permeable membrane – 100 to 1,000,000 D

2. **Membrane Filtration** – applied pressure across a selective membrane. 3 types based on size range:
   a. **Macrofiltration** – 5 μm and up
      (Woven Mesh Screens)
   a. **Microfiltration** – 0.05 – 5 μm
      (Direct Flow and Tangential Flow)
   b. **Ultrafiltration** (Molecular filtration) – 5 kD to 0.05 μm
      (Tangential Flow only)
Blood Purification; Size Matters

Molecular Weight kDa

Immunoglobulin G
160kDa; 2 LC: 23-25 kDa each; 2 HC:~53 kDa each

<table>
<thead>
<tr>
<th>BUN</th>
<th>Cr</th>
<th>VitB12</th>
<th>B2-mic</th>
<th>K Lig C</th>
<th>L Lig C</th>
<th>Album</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>0.113</td>
<td>1.355</td>
<td>11.8</td>
<td>25</td>
<td>50</td>
<td>66</td>
<td>160</td>
</tr>
</tbody>
</table>

Small Molecules

Middle Molecules

Hemodialysis: Diffusion Clearance

Hemofiltration: Convective Clearance

Large Molecules

Therapeutic Plasma Exchange
Sieving curves for low-flux and high-flux dialysis membranes and human glomerular basement membrane.

Ledebo I, and Blankestijn P J NDT Plus 2010;3:8-16

© The Author 2009. Published by Oxford University Press [on behalf of ERA-EDTA].
Hemodialysis Membranes: Not one “size” fits all
Hollow Fiber Examples

Blood

Plasma

Cells
Asahi Hollow Fiber Plasma Separator

- cellulose di-acetate
- priming volume of 65ml
- 0.5m² surface area
- Max pore size is 0.2μm
- clearance of up to 3 million daltons
Hemodialysis

http://healthsciences.merlot.org/images/18loop.gif
Separation by Centrifugation

Whole Blood in

RBC out

WBC out

Plasma out

out
# Ultrafiltration

<table>
<thead>
<tr>
<th>Stirred Cell</th>
<th>Tangential flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous flow</td>
<td>Continuous flow</td>
</tr>
<tr>
<td>Discontinuous flow</td>
<td>Discontinuous flow</td>
</tr>
</tbody>
</table>

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## Normal Flow Filtration

- **Feed Flow**
- **Pressure**
- **Membrane**
- **Filtrate**

## Tangential Flow Filtration

- **Feed Flow**
- **Pressure**
- **Membrane**
- **Filtrate**
Apheresis Technology

- Separation of blood components
- Removal of the selected component
- Re-infusion of the remaining components
- It allows for processing large volumes of blood to collect or exchange different types of cells or blood components.
Blood stem cells (for BM transplant)

Less-Conventional Apheresis Modalities (require additional equipment)

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

Conventional Therapeutic Apheresis Modalities

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

Online WBC processing
- Photopheresis (= ECP)
- other

Beyond Dialysis: Current and Emerging Blood Purification Techniques

Bernd Stegmayr,* Wolfgang Ramlow,† and Rasheed A. Balogun‡

*Department of Public Health and Medicine, Umeå University and Division of Nephrology, Department of Internal Medicine, University Hospital, Umeå, Sweden, †Dialysis Center North, Rostock, Germany, and ‡Division of Nephrology, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia

ABSTRACT

Extracorporeal blood purification using various techniques and hardware is a major part of the modern day practice of clinical nephrology. Although the various modalities of hemodialysis and hemofiltration are the most commonly used extracorporeal therapies in clinical nephrology, blood purification using other techniques have become necessary to remove pathogenic, toxic, or waste substances not easily cleared by hemodialysis or hemofiltration due to factors such as molecular size, protein binding, and lipid solubility. The following review is an up to date summary of extracorporeal therapies, beyond hemodialysis and hemofiltration, in current clinical use as practiced by nephrologists and others in the United States and beyond. This comprises therapeutic apheresis (plasma exchange and cytapheresis), plasma adsorption, hemoperfusion, and the bio-artificial devices.

Therapeutic Apheresis Modalities

**Plasmapheresis**
- **Superflux Hemofiltration**
  - Albumin as substitute
- **Single filtration/Centrifugation**
  - Plasma removal
  - Albumin as substitute
  - Plasma as substitute
  - Combinations
- **Cascade filtration**
  - (Albumin as substitute)
- **Filtration + Adsorption**
  - (Albumin as substitute)
  - Precipitation i.e., heparin
  - Combinations
- **Biological devices**
  - (Albumin as substitute)

**Hemoperfusion**
- **Adsorption principles**
  - Hydrostatic
  - Ionic
  - Antibody mediated
  - Combinations/other
- **Leukapheresis principles**
  - Filtration, selectively
  - Fcy-receptor adhesion
  - other

**Cytapheresis**
- **Cell removal/replacement**
  - Erythrocytes (sickle cells etc)
  - Platelets (thrombocytosis)
  - Leukocytes (leukemia, ECP)
- **Leukocyte collection**
  - Stem cells
  - ex-vivo immune modulation

Apheresis: Methods

Manual
• 2-bag tech + blood bank centrifuge

• Immunomodulation/Adsorption columns-eg Prosorba-Protein A

Cell Separators (Auto)
• Centrifugation
  – Continuous
  – intermittent

• Membrane Filtration
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.

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

Membrane Plasmapheresis
Vascular access options for therapeutic apheresis (TA): Catheters and arteriovenous fistulas/grafts

- The literature on access in TA is sparse
- All data on access management comes from the hemodialysis (HD) literature

### Comparison of chronic TA to intermittent outpatient HD

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of tx</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Heparin</td>
<td>Heparin or Citrate</td>
</tr>
<tr>
<td>Blood flow rate (ml/min)</td>
<td>&gt;300</td>
<td>50-100</td>
</tr>
<tr>
<td>Use of peripheral veins</td>
<td>Never</td>
<td>Short-term use</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>3-4 hours</td>
<td>Often &lt;3 hrs</td>
</tr>
<tr>
<td>Frequency of treatment</td>
<td>Thrice weekly</td>
<td>Weekly to every 3 months</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>62</td>
<td>49</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Coordinator of Care</td>
<td>Nephrologists/dialysis nurses</td>
<td>Hematologists, oncologists, blood bank specialists, nephrologists</td>
</tr>
</tbody>
</table>

© Michele Mokrzycki, MD

Okafor C, Kalantarinia K. Sem Dial 2012
Non-Tunneled vs. Tunneled Catheters (TC):
Consider TC if anticipate > 2 weeks treatment duration
<table>
<thead>
<tr>
<th></th>
<th>Europe</th>
<th>Australia</th>
<th>Asia</th>
<th>North America</th>
<th>Central/ South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Vein</td>
<td>77%</td>
<td>60%</td>
<td>15%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Central Vein</td>
<td>16%</td>
<td>37%</td>
<td>84%</td>
<td>91%</td>
<td>98%</td>
</tr>
<tr>
<td>AVF/AVG</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
<td>---</td>
</tr>
</tbody>
</table>

Malchesky et al. Ther Apher Dial 14(1), 2010
Differences in vascular access type can not be explained by the TPE treatment number, nor by the procedure type.

<table>
<thead>
<tr>
<th>TPE #</th>
<th>Europe</th>
<th>Australia</th>
<th>Asia</th>
<th>North America</th>
<th>Central/South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>58%</td>
<td>41%</td>
<td>81%</td>
<td>45%</td>
<td>100%</td>
</tr>
<tr>
<td>6-10</td>
<td>22%</td>
<td>18%</td>
<td>15%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>20%</td>
<td>41%</td>
<td>4%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPE</td>
<td>72%</td>
<td>60%</td>
<td>46%</td>
<td>38%</td>
<td>19%</td>
</tr>
<tr>
<td>PT</td>
<td>11%</td>
<td>---</td>
<td>13%</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>SCI</td>
<td>8%</td>
<td>8%</td>
<td>30%</td>
<td>62%</td>
<td>81%</td>
</tr>
</tbody>
</table>

TPE: plasma exchange, PT: plasma treatment, SCI: Stem cell infusion