Therapeutic Apheresis and Specialized Procedures in Apheresis: an overview

THE CHILDREN’S HOSPITAL
F. BERNADETTE WEST MD
AUGUST 11, 2010
Objectives

- Background
- Definitions
- Instruments
- Indications and Guidelines
- Replacement fluids / Volumes
- Vascular Access
- Other Therapeutic Uses
History of Apheresis

- **1902**
  - France, removal of whole blood with return of red cells and removal of plasma
- **1914**
  - Russia, same
  - Johns Hopkins University: Roundtree and Turner used plasmapheresis in artificial kidney research
- **1960**
  - Solomon and Fahey: manual plasmapheresis in patient with hyperviscosity symptoms multiple myeloma
Semantics

- Apheresis
  - Greek word aphairesis meaning “to take out”

  *True removal only*

- Plasmapheresis, leukapheresis, plateletapheresis, etc.

  *vs. Replacement with another fluid*

- Plasma exchange, Red cell exchange

- Terms are often used interchangeably
## Types of Therapeutic Apheresis Procedures

<table>
<thead>
<tr>
<th>Procedure/term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis</td>
<td>A procedure in which blood of the patient or donor is passed through a medical device, which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.</td>
</tr>
<tr>
<td>Extracorporeal photopheresis (ECP)</td>
<td>A therapeutic procedure in which buffy coat, separated from patient’s blood, is treated extracorporeally with a photosensitive compound (e.g., porfimer) and exposed to ultraviolet A light and subsequently reinfused to the patient during the same procedure.</td>
</tr>
<tr>
<td>Erythrocytapheresis</td>
<td>A procedure in which blood of the patient or donor is passed through a medical device, which separates red blood cells from other components of blood, the red blood cells are removed and replaced with crystalloid or colloid solution, when necessary.</td>
</tr>
<tr>
<td>Filtration selective removal</td>
<td>A procedure which uses a filter to remove components from the blood based upon size. Depending upon the pore size of the filters used, different components can be removed. Filtration based instruments can be used to perform plasma exchange or LDL apheresis. They can also be used to perform donor plasmapheresis where plasma is collected for transfusion or further manufacture.</td>
</tr>
<tr>
<td>Immunoabsorption (IA)</td>
<td>A therapeutic procedure in which plasma of the patient, after separation from the blood, is passed through a medical device, which has a capacity to remove immunoglobulins by specifically binding them to the active component (e.g., Staphylococcal protein A) of the device.</td>
</tr>
<tr>
<td>LDL Apheresis</td>
<td>The selective removal of low density lipoproteins from the blood with the return of the remaining components. A variety of instruments are available which remove LDL cholesterol based upon charge (dextran sulfate and polyanion), size (double-membrane filtration), precipitation at low pH (HELP), or immunoadsorption with anti-Apo B-100 antibodies.</td>
</tr>
<tr>
<td>Leukocytapheresis (LCP)</td>
<td>A procedure in which blood of the patient or the donor is passed through a medical device, which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns remainder of the patient’s or the donor’s blood with or without addition of replacement fluid, such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in preparation of blood components.</td>
</tr>
<tr>
<td>Plasma exchange (TPE)</td>
<td>A therapeutic procedure in which blood of the patient is passed through a medical device, which separates 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/collod solution.</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>A procedure in which blood of the patient or the donor is passed through a medical device, which separates out plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of replacement solution.</td>
</tr>
<tr>
<td>Plateletapheresis</td>
<td>A procedure, in which blood of the donor is passed through a medical device, which separates out platelets, collects the platelets, and returns remainder of the donor’s blood. This procedure is used in preparation of blood components (e.g., apheresis platelets).</td>
</tr>
<tr>
<td>RBC exchange</td>
<td>A therapeutic procedure in which blood of the patient is passed through a medical device, which separates red blood cells from other components of blood, the red blood cells are removed and replaced with donor red blood cells alone and colloid solution.</td>
</tr>
<tr>
<td>Therapeutic apheresis (TA)</td>
<td>A therapeutic procedure in which a blood of the patient is passed through an extracorporeal medical device, which separates components of blood to treat a disease. This is a general term which includes all apheresis based procedures used therapeutically.</td>
</tr>
<tr>
<td>Thrombocytapheresis</td>
<td>A therapeutic procedure, in which blood of the patient is passed through a medical device, which separates out platelets, removes the platelets and returns remainder of the patient’s blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.</td>
</tr>
</tbody>
</table>
### Table 41-1. Apheresis Devices Used in the United States for Donor Collection and Patient Therapeutics

<table>
<thead>
<tr>
<th>Manufacturer/Device</th>
<th>Type</th>
<th>Product/Procedure</th>
<th>Venous Access</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenwal CS 3000</td>
<td>C/CF</td>
<td>PLAP, HPC, TPE</td>
<td>1 or 2 arms</td>
<td>Donor or patient</td>
</tr>
<tr>
<td>Amicus</td>
<td>C/CF</td>
<td>PLAP, AFFP</td>
<td>1 or 2 arms</td>
<td>Donor</td>
</tr>
<tr>
<td>ALYX</td>
<td>C/CF</td>
<td>2RBC, RBCP</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>Autopheresis-C</td>
<td>SM/DF</td>
<td>AFFP, SP</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>Fresenius AS104</td>
<td>C/CF</td>
<td>PLAP, HPC, TPE</td>
<td>1 or 2 arms</td>
<td>Donor or patient</td>
</tr>
<tr>
<td>CaridianBCT Spectra</td>
<td>C/CF</td>
<td>PLAP, HPC, TPE</td>
<td>1 or 2 arms</td>
<td>Donor or patient</td>
</tr>
<tr>
<td>Trima/Trima Accel</td>
<td>C/CF</td>
<td>PLAP, AFFP, RBC, 2RBC</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>Optia</td>
<td>C/CF</td>
<td>TPE, HPC</td>
<td>1 or 2 arms</td>
<td>Patient</td>
</tr>
<tr>
<td>Haemonetics MC5+-(LV9000)</td>
<td>C/DF</td>
<td>PLAP, AFFP, TPE</td>
<td>1 or 2 arms</td>
<td>Donor or patient</td>
</tr>
<tr>
<td>MC5+-(LNR150)</td>
<td>C/DF</td>
<td>RBCP, 2RBC</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>Cymbal</td>
<td>C/DF</td>
<td>2RBC</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>PCS-2</td>
<td>C/DF</td>
<td>AFFP, SP</td>
<td>1 arm</td>
<td>Donor</td>
</tr>
<tr>
<td>Therakos UVAR-XTS</td>
<td>C/DF</td>
<td>PCWBC</td>
<td>1 arm</td>
<td>Patient</td>
</tr>
</tbody>
</table>

C = centrifugal; CF = continuous flow; DF = discontinuous flow; SM = spinning membrane; PLAP = platelet by apheresis; AFFP = apheresis fresh frozen plasma; RBC = red blood cell; 2RBC = 2-unit red blood cells; TPE = therapeutic plasma exchange; SP = source plasma; HPC = hematopoietic progenitor cells; PCWBC = photochemically modified white blood cells.
COBE Spectra (Caridian BCT (blood component technology))

1964: Gambro founded to develop and market an artificial kidney (inventor: Nils Alwall, of Lund, Sweden); Cobe (CO, USA) founded to develop/market dialysis systems.

1965: Cobe launches first product: plastic extracorporeal blood set for chronic hemodialysis treatments.

1967: Gambro begins production of the first commercial dialysis system.

1988: Cobe launches Spectra Apheresis system

1990: Gambro buys US-based rival Cobe

2008: Gambro BCT changes name to Caridian BCT (Caridian’s private ownership remains in Europe)

Spectra Optia (Caridian BCT)

Introduced in 2008

We currently use this instrument only for plasma exchange
Similarities?
Basic set-up—access and return lines

Anticoagulant
Blood

Optical Sensor In Instrument Senses Layer
Before Committing

- Discussion with and Formal consult from medical service desiring Apheresis services

- Clinical indication
  - Are you using evidence-based medicine? Why?
    - Reduces personal bias / anecdotal-based practice

- Endpoint
  - Biomarker?

- Stability of patient
  - Inpatient or outpatient?

- Replacement fluid and associated calculations
  - What is being removed?
  - How much?
  - How often?

- Vascular access

- Complications –consider throughout

- Consent
LETTER TO THE EDITOR

Acute Inflammatory Desequilibrating Polyneuropathy (Guillain-Barré Syndrome)

Incidence: 1.2 per 100,000/year

| Procedure | TEP | TEP
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Branches</td>
<td>95</td>
<td>105</td>
</tr>
<tr>
<td>Type of evidence</td>
<td>Type 1</td>
<td></td>
</tr>
</tbody>
</table>

Description of the disease
Acute inflammatory demyelinating polyneuropathy (AIDP) or the Guillain-Barré Syndrome is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically, the disease begins with symmetric muscle weakness and paresthesias that rapidly progress, which may occur swiftly over several weeks, may involve upper and lower extremities in an asymmetric manner, and may rapidly progress to bulbar paralysis. The pathophysiology of AIDP is thought to involve an immune-mediated mechanism, with the demyelinating process leading to clinical symptoms such as progressive weakness and paresthesias.

Current management/treatment
Early corticosteroid therapy is a mainstay of treatment in most patients, especially those in the United States, characterized by a dosing regimen of 1 g of methylprednisolone intravenously over several hours for 3 to 5 days followed by tapering over 1 to 2 weeks. Other therapeutic modalities include plasma exchange, intravenous immunoglobulin (IVIG), and intravenous immunoglobulin-IVIG. IVIG is recommended as the first-line therapy for patients with Guillain-Barré Syndrome and is associated with faster clinical improvement compared to controls. Plasma exchange is also effective and may be considered in patients with rapid progression or in those who do not respond adequately to IVIG.

Rational for therapeutic apheresis
The rationale for therapeutic apheresis lies in the removal of potentially toxic substances from the circulation. Apheresis is a procedure that involves the removal of plasma or blood components from the circulation, with the aim of either removing or reducing toxic substances. Apheresis is particularly useful in the treatment of Guillain-Barré Syndrome, where it may help to reduce the circulating inflammatory mediators and improve clinical outcomes.

Technical notes
The frequency of apheresis sessions varies widely and is often tailored to the individual patient's response. Typically, sessions are performed daily or every other day for a few weeks, followed by a tapering schedule. The duration of treatment can range from a few days to several weeks, depending on the patient's clinical response.

References

Fig. 2. Systematic approach to category assignment, grade recommendation and ASFA Fact Sheet generation and revisions used in the ASFA Special Issue 2010.

Journal of Clinical Apheresis DOI 10.1002/jca

use as a quick reference. The design of the fact sheet and explanation of information contained is included in Figure 1. The authors encourage the reader to use this figure as a guide to interpretation of all entries in the fact sheets as substantial condensing of available information was required to achieve this user friendly format. The references provided are not meant to be exhaustive but rather serve as a starting point in a search for more information.

With very few exceptions the World Wide Web resources that were utilized by the committee members were excluded from the reference section and are available on the ASFA website (www.apheresis.org). This decision was made to minimize the risk of sending a reader to resources, which may not be available any longer, while at the same time allowing the subcommittee to periodically review the content of the websites.
<table>
<thead>
<tr>
<th>Disease name*</th>
<th>Special condition</th>
<th>TA modality</th>
<th>Category</th>
<th>Recommendation grade</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO incompatible hematopoietic stem cell transplantation</td>
<td>HPC, Marrow</td>
<td>TPE</td>
<td>II</td>
<td>1B</td>
<td>95</td>
</tr>
<tr>
<td>ABO incompatible solid organ transplantation</td>
<td>Kidney</td>
<td>TPE</td>
<td>II</td>
<td>1B</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Heart (&lt;40 months of age)</td>
<td>TPE</td>
<td>II</td>
<td>1C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver perioperative</td>
<td>TPE</td>
<td>III</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy (Guillain-Barré Syndrome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age related macular degeneration</td>
<td>Dry AMD</td>
<td>TPE</td>
<td>IV</td>
<td>2C</td>
<td>NA</td>
</tr>
<tr>
<td>Amyloidosis, systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANCA- associated rapidly progressive glomerulonephritis (Wegener's Granulomatosis)</td>
<td>Dialysis dependence</td>
<td>TPE</td>
<td>I</td>
<td>1A</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>TPE</td>
<td>I</td>
<td>1C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysis independence</td>
<td>TPE</td>
<td>III</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture's syndrome)</td>
<td>Dialysis dependence</td>
<td>TPE</td>
<td>I</td>
<td>1A</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>TPE</td>
<td>I</td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysis dependent and no DAH</td>
<td>TPE</td>
<td>IV</td>
<td>1A</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia; pure red cell aplasia</td>
<td>Aplastic anemia</td>
<td>TPE</td>
<td>III</td>
<td>2C</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Pure red cell aplasia</td>
<td>TPE</td>
<td>II</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia; warm autoimmune hemolytic anemia; cold agglutinin disease</td>
<td>Warm autoimmune hemolytic anemia</td>
<td>TPE</td>
<td>III</td>
<td>2C</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>Cold agglutinin disease</td>
<td>TPE</td>
<td>II</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Severe</td>
<td>RBC exchange</td>
<td></td>
<td>1B</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>High-risk population</td>
<td>RBC exchange</td>
<td></td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Barn burn resuscitation</td>
<td></td>
<td>TPE</td>
<td>IV</td>
<td>2B</td>
<td>106</td>
</tr>
<tr>
<td>Cardiac allograft rejection</td>
<td>Preperfusion</td>
<td>ECP</td>
<td></td>
<td>1A</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>Treatment of rejection</td>
<td>ECP</td>
<td></td>
<td>1B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment of antibody mediated rejection</td>
<td>TPE</td>
<td></td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome</td>
<td></td>
<td>TPE</td>
<td>II</td>
<td>2C</td>
<td>108</td>
</tr>
<tr>
<td>Chronic focal encephalitis (Rasmussen’s Encephalitis)</td>
<td></td>
<td>TPE</td>
<td>II</td>
<td>2C</td>
<td>109</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td></td>
<td>TPE</td>
<td>I</td>
<td>1B</td>
<td>110</td>
</tr>
<tr>
<td>Congenital factor inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Severe symptomatic</td>
<td>TPE</td>
<td>I</td>
<td>1B</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>Secondary to Hepatitis C virus</td>
<td>TPE</td>
<td>I</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma; mycosis fungoides Sézary syndrome</td>
<td>Erythrodermic</td>
<td>ECP</td>
<td>I</td>
<td>1B</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>Non-erythrodermic</td>
<td>ECP</td>
<td>III</td>
<td>2C</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis or polymyositis</td>
<td></td>
<td>TPE</td>
<td>IV</td>
<td>1B</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Leukocytapheresis</td>
<td></td>
<td>IV</td>
<td>1B</td>
<td>NA</td>
</tr>
</tbody>
</table>
Clinical Indication
ASFA, American Society for Apheresis

84 Szczepiorkowski et al.

| TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories |
|---|---|
| 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. [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. [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. [Example: plasma exchange for active rheumatoid arthritis]. |

*The description of the ASFA categories have been amended and simplified in comparison to the Third and Fourth Edition of the Special Issue [1,16]. Category P, which was introduced in the Fourth Edition, has been eliminated.*

| TABLE II. Level of Evidence Used in the ASFA Special Issue 2010 |
|---|---|
| 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 |

*Adopted from the criteria used by the University HealthCare Consortium [6].
### TABLE III. Grading Recommendations Adopted from Guyatt et al. [13]

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Grade 1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>Grade 2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients' or societal values</td>
</tr>
<tr>
<td>Grade 2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on circumstances or patients' or societal values</td>
</tr>
<tr>
<td>Grade 2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

*RCF: randomized controlled trial.*
Description of the disease

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) or the Guillain-Barré Syndrome is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically, the disease begins with symmetrical muscle weakness and paresthesia that spread proximally. Progression, which can occur briskly over several weeks, may involve respiratory and oropharyngeal muscles in more severe cases. Thus, mechanical ventilation is required for approximately 25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur, however up to 75% of patients develop long-term neurologic deficits. Mortality is estimated at 5%. The Miller-Fisher variant is characterized by ophthalmoplegia, ataxia, and areflexia. AIDP is distinguished from Chronic Inflammatory Demyelinating Polyradiculoneuropathy which is a chronic disorder (see separate fact sheet). An autoimmune pathogenesis is strongly suggested due to the presence of antibodies to the myelin sheath constituents in the majority of patients as well as in animal models of the disease. Observations of preceding infections illness, such as Campylobacter infection, suggest cross-reactive antibodies may be a component in disease pathogenesis.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients with AIDP. Severely affected patients may require intensive care, mechanical ventilation, and assistance through the paraplegia and necessary rehabilitations over several months to a year or more. Corticosteroids have not been shown helpful when used alone. TPE was the first therapeutic modality to impact the disease favorably and several major randomized controlled clinical trials have confirmed its efficacy. An international randomized trial compared TPE, IVIG, and TPE followed by IVIG in 303 adult patients with severe AIDP and found all three modalities to be equivalent. There were no differences in the three treatment groups in mean disability improvement at 4 weeks or the time to be able to walk without assistance (TPE group 69 days, IVIG group 51 days and TPE/IVIG group 40 days). Other therapeutic modalities studied include immunoadsorption apheresis, C5F, filomena, and double filtration plasmapheresis. Since IVIG is readily available, it is frequently used as initial therapy; the typical dose is 0.45 g/kg for 5 consecutive days.

Rationale for therapeutic apheresis

The favored etiology of AIDP is autoimmune antibody-mediated damage to the peripheral nerve myelin. The results of several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. For example in the Cooperative Study, median time to wean from mechanical ventilation was 18 days versus 31 days for TPE compared to control, respectively. In the North American Trial the median time to walk without assistance was 53 days versus 85 days. Of note, the Cochrane Neuromuscular Disease Group review of TPE in AIDP found that TPE is most effective when initiated within 7 days of disease onset.

Technical notes

The typical TPE strategy is to exchange 200-250 mL of plasma per kg body weight over 10-14 days. This will generally require 5-6 TPE procedures with 5% albumin replacement. Fresh frozen plasma is not routinely used for replacement. Since autonomic dysfuction may be present, affected patients may be more susceptible to volume shifts, blood pressure and heart rate changes during extracorporeal treatment. Relapses may occur in approximately 10% of patients 2-5 weeks following either treatment with TPE or IVIG. When relapses occur, additional therapy, usually TPE, can be helpful. In AIDP patients with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG.

Volume treated: 1 to 1.5 TPV
Replacement fluid: albumin
Frequency: every other day

Duration and discontinuation/number of procedures

Five to six TPE over 10-14 days are recommended, see technical notes above for details.

References [43,48-67]

*As of December 31, 2009 using PubMed and the MeSH search terms acute inflammatory demyelinating poly radiculoneuropathy or Guillain Barré and plasmapheresis, plasma exchange, or apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Stability of Patient

- Always consider the patient’s safety first
- Inpatient
  - Most TPEs
  - All leukoreduction
  - Other...
- Outpatient
  - Red cell exchange
  - Some TPE
  - Some Photopheresis
  - Stem cell collections
Replacement Fluids

- **5% human serum albumin (natural colloid)**
  - Alone or followed by 0.9% normal saline (crystalloid)
  - Pasteurized, very low risk of infectious diseases (?)Prion?)
  - $$$
  - Risk of reaction low

- **Fresh frozen plasma (natural colloid)**
  - Usual risks of blood transfusion
  - Use only when needed to replace plasma factors due to nature of disease process (TTP, coagulopathy)

- **Hydroxyethyl starch (artificial colloid)**
  - Not commonly used, can cause hypotensive reaction, inexpensive

- **SD plasma (solvent-detergent)**
  - Not available in USA

- **Packed red cells—red cell exchange**
  - Usual risks of blood transfusion
Total blood volume estimates
- Pay attention to body habitus
- Apheresis instrument will also calculate total plasma volume (and more) based on height, weight, sex and hematocrit entered

<table>
<thead>
<tr>
<th>Gender</th>
<th>Body mass/build</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Thin</td>
</tr>
<tr>
<td>Man</td>
<td>60</td>
</tr>
<tr>
<td>Woman</td>
<td>55</td>
</tr>
<tr>
<td>&lt; 3mos</td>
<td>80-100 mL/kg</td>
</tr>
<tr>
<td>&gt;3mos – 12?</td>
<td>65-75 mL/kg</td>
</tr>
</tbody>
</table>

Values are mL/kg
mL of whole blood per kg of body weight

Estimating blood volume; modified rule of 5’s; adapted from Table 41-9 Rossi text; additional information from Pediatric Transfusion Medicine Text
Volumes

- TBV = wt in kg \times \text{value}
  - 50\text{kg} \times 70\text{mL/kg} = 3500\text{mL}

- Plasma volume = TBV \times (1-hct)
  - PV = 3500 \times (1-0.40)
  - PV = 2100 \text{mL}

(Hct = \frac{\text{RBC}}{\text{whole blood}} \times 100)
### Plasma Volumes Exchanged

**Table 41-8 from Rossi text**

<table>
<thead>
<tr>
<th>Plasma volume removed</th>
<th>Fraction removed</th>
<th>Fraction remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>1</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>1.5</td>
<td>78%</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>2.5</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>3</td>
<td>94%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Assumptions**
- No change in TBV
- No movement of substance from extra- to intravascular space
- Mixing of plasma/replacement fluid instantaneous

---

**Figure 15-2.** Theoretical depletion of soluble substances from the plasma by plasma exchange according to the one-compartment model. A fixed proportion of the remaining intravascular mass of the soluble substance is removed with each increment of plasma volume removed. (Adapted with permission from Chopek and McCullough.24)
Removal of Plasma Constituents

Laboratory value changes: small prolongation in PT/INR and PTT, might still lie in reference range
Fibrinogen, being very intravascular may be very low!

Also removes medications
- If possible, hold medications until after TPE

| Table 15-2. Alteration in Blood Constituents by a 1-Plasma Volume Exchange* |
|-----------------------------|-----------------------------|
| **Constituent**             | **Percent decrease from baseline** | **Percent recovery 48 hours after plasma exchange** |
| Clotting factors            | 25 - 50                      | 80 - 100                               |
| Fibrinogen                  | 63                           | 65                                    |
| Immunoglobulins             | 63                           | ~45                                   |
| Paraproteins                | 30 - 60                      | Variable                              |
| Liver enzymes               | 55 - 60                      | 100                                   |
| Bilirubin                   | 45                           | 100                                   |
| C3                          | 63                           | 60 - 100                              |
| Platelets                   | 25 - 30                      | 75 - 100                              |

*Replacement fluid consisting of 4-5% albumin in 0.9% sodium chloride.
Exchange Efficiency

- Removal rate of pathogenic substance
  - Volume of plasma exchange (next slide)
    - TPE best limited to 1 – 1.5 X plasma volume
  - Less efficient as exchange proceeds
    - Increasing proportion of volume removed is the replacement volume
  - Distribution in body
    - Different strategies for pathologic IgG vs IgM

---

Table 15-1. Metabolic Characteristics of Some Plasma Proteins*

<table>
<thead>
<tr>
<th>Protein</th>
<th>mg/mL</th>
<th>M' (kDa)</th>
<th>Percentage Intravascular</th>
<th>FCR† (%)</th>
<th>Change in FCR with concentration</th>
<th>TER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>12.1</td>
<td>150</td>
<td>45</td>
<td>6.7</td>
<td>↓</td>
<td>3</td>
</tr>
<tr>
<td>IgA</td>
<td>2.6</td>
<td>(160),</td>
<td>42</td>
<td>25</td>
<td>constant</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>0.9</td>
<td>950</td>
<td>76</td>
<td>18</td>
<td>constant</td>
<td>1-2</td>
</tr>
<tr>
<td>IgD</td>
<td>0.02</td>
<td>175</td>
<td>75</td>
<td>37</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>IgE</td>
<td>0.0001</td>
<td>190</td>
<td>41</td>
<td>94</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>42±3.5</td>
<td>66</td>
<td>40</td>
<td>10</td>
<td>↓</td>
<td>5-6</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2-4</td>
<td>340</td>
<td>80</td>
<td>25</td>
<td>constant</td>
<td>2-3</td>
</tr>
<tr>
<td>C3</td>
<td>1.5</td>
<td>240</td>
<td>53</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1-macro-globulin</td>
<td>2.6</td>
<td>820</td>
<td>100</td>
<td>8.2</td>
<td>constant</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted with permission from Chopek and McCullough.†
†Concentration in normal serum or plasma.
‡Fractional catabolic rate (FCR): As percent of intravascular mass per day.
§Transcapillary escape rate (TER): Total transfer of protein from intravascular to extravascular compartment as percentage of intravascular mass per hour.
Apheresis Kinetics

- IgM is about 90% intravascular
- IgG is about 50/50
- Reduction of IgG levels by TPE does not produce a meaningful rebound in IgG synthesis (mouse model)
- How does this work?

*J Clin Apheresis 2002;17:207-211*
FcRn controls the catabolism of IgG in the adult body, allowing IgG to be recycled to the cell surface and back into the bloodstream. This recycling and regulation of catabolism gives IgG a much longer half-life than other antibodies (Janeway et al., 2001).

- Transcytosis by FcRn occurs in multiple places in humans: carrying IgG into the fetal bloodstream, in the adult liver, and from blood to milk in the lactating mammary glands.

- IVIG (Intravenous Immune Globulin) is a useful drug
  - Exogenous immune globulin competes with endogenous IgG for the FcRn receptors and therefore promotes accelerated catabolism of endogenous IgG.

---

Figure 1: transport of IgG across the placenta in humans. Courtesy University of Glasgow, Division of Immunology, Infection, and Inflammation.
Vascular Access

- **Consider the duration of treatment**
  - Red cell exchange? Emergent?
  - A week long stem cell collection?
  - Inpatient plasma exchange series for MG?
  - What does the pt already have?

- **Peripheral venous access**
  - Antecubital fossae (16-18g needle)
  - PICC lines (peripherally inserted central catheter)
Vascular access

- **Central venous access**—double lumen, hemodialysis-type or apheresis-type
  - Internal jugular, subclavian, femoral
  - Broviac / Hickman type
  - Infection risk greater than with peripheral. Pneumothorax/hemothorax, carotid puncture, chylothorax

- **Indwelling ports**
  - Red cell exchange.
“no-neck” patients
PICCs are quick!
Conscious sedation for small children, local anesthetic for teens
SVC or cavoatrial junction
Cook® TurboFlo allows fast flow rates similar to CVCs
Vascular Access

- Instructions must be very clear on who is managing the catheter / line
  - What was used to flush and what was used to ‘lock’ the lines—must label lines, give report to primary RN, etc.
  - Must a waste amount be drawn from lines before obtaining labs?
  - Watch for complications (chest pain, arrhythmia, infection etc)
  - Discharge instructions if patient is an outpatient
Complications

- Thrombocytopenia with plasma exchange
- Bleeding
- Thrombosis
- Arrhythmia
- Volume overload
- Citrate reactions
  - Tetany, spasms, tingling, intra-procedural worsening of sx of MG, etc
- Alterations of pharmacodynamics
- Hypocalcemia, hypomagnesemia
- Circulatory effects
  - ACE inhibitors
- Infections (line related or product related)
- Allergic reactions to albumin or other product
- Any reaction usually associated with blood product transfusion (allergic, febrile non hemolytic, hemolytic, TACO, TRALI, death)
- Fatality from plasma exchange: 3/10,000 procedures (Huestis et.al)
Consent may be given by any person 18 years of age or older who is legally capable of comprehending information, deliberating the risks and benefits and understanding the full force and effect of his or her acts.

- Adult
- Incapacitated adult → spouse or legally appointed representative (LAR)
- Mentally Disabled persons of any age (parent / guardian / LAR)
- Minor (parent or guardian consent); minor can provide assent
- Emancipated minor—probably wise to have proof

Make sure you are consenting the right person!
- Use a translator or translation service if needed
- Obtain consent proximal in time to the treatment (and prospectively)
Consent and Disclosure of Risks

- **Disclosure**
  - Overview of procedure
  - Benefit
  - Alternatives (always includes NOT performing the procedure)
  - Risks include:
    - Blood usage
    - Anticoagulant
    - Lines
    - Replacement fluid
    - Infection
    - Air embolus
    - Death
Extracorporeal Photopheresis (ECP)

- **THERAKOS™ UVAR™ XTS™ Photopheresis System (2nd Generation)** or **THERAKOS™ CELLEX™ Photopheresis (3rd Generation instrument)**
  - Withdraw a volume of whole blood
  - Centrifuge
  - RBC and plasma are immediately returned to the patient.
  - WBC are treated with methoxsalen, which is photoactivated after exposure to UVA light.
  - Treated white blood cells are then reinfused into the patient. Clinical studies suggest that the treated white blood cells, when reinfused into the body, may bring the immune system into balance by controlling the activity of overactive immune cells.

- **UVADEX® (methoxsalen) Sterile Solution**
  - contraindicated in patients with reactions to psoralen compounds, specific history of a light sensitive disease, or aphakia (no lens in eye).
- Not for use in pregnant women or those planning to become pregnant.

- **THERAKOS™ Photopheresis is not appropriate** for patients who cannot tolerate extracorporeal volume loss or shifts
Photopheresis: “restoration of immune balance”

- Less than 10% of total body Lymphocytes are processed during a treatment

- Methoxalen enters all WBC types
- UV activation → Methoxalen forms SS or DS DNA cross-links with pyrimidine residues → induces apoptosis
- Methoxsalen treated cells are returned to the body where they go to lymphoid organs and the liver and are recognized by antigen-presenting-cells from the ligands expressed as they undergo apoptosis

- These APCs engulf them and are in turn altered to become more immune-tolerant: decreased production of pro-inflammatory cytokines, increased production of anti-inflammatory cytokines (TGF-beta IL-10) and decreased ability to stimulate T cells.

- 1988 FDA approved UVAR system for treatment of cutaneous T-cell lymphoma

Now...
Heart & lung transplant rejection
Scleroderma
Graft versus host disease after bone marrow transplantation
Pemphigus
Nephrogenic systemic fibrosis
Cytoreduction--WBC

- Leukoreduction usually indicated in setting of acute leukemia with counts greater than 100,000 and evidence of cerebral/pulmonary dysfunction
- Requires chemotherapy to immediately follow or rebound will be impressive
- Caveat: RBC transfusions
- Prevention “tumor lysis syndrome” unproven
Cytoreduction--Platelets

- Usually indicated in patients with platelet counts greater than 1,000,000 and evidence of thrombosis or bleeding
- Not indicated in asymptomatic patients except for a severely thrombocytopenic pregnant woman felt to be at high risk for placental infarction/fetal death
Staphylococcal Protein A Immunoadsorption

- **Immunomodulating procedure**
  - Staph protein A column used with available separators
  - Plasma separated from whole blood
  - Plasma treated in column of silica beads coated with protein A
  - Plasma and remaining blood elements returned to patient
Staphylococcal Protein A Immunoadsorption

- 1987 FDA approved Prosorba immunosorbent column for treatment of ITP refractory to other therapy
- 1999 FDA approved Staph protein A immunoadsorption for Rheumatoid arthritis refractory to disease-modifying anti-rheumatic drugs
  - to remove IgG and circulating immune complexes (CIC)
  - therapy for adults with treatment-resistant immune thrombocytopenic purpura (ITP).
Staphylococcal Protein A Immunoadsorption

- **Mechanism of action**
  - Protein A has high affinity for IgG and circulating immune complexes (IgG/self antigens and IgG/IgM)
  - Circulating immune complexes may be immunosuppressive
  - Removal of Ig & immune complexes may activate immune system against “anti-self” clones
LDL Apheresis

- Familial hypercholesterolemia
- “Liposorber” FDA approved for therapy of LDL hypercholesterolemia
  - Patient must not have responded adequately to 6 months of drug and diet
  - LDL cholesterol $> 200$ mg/dL
  - LDL cholesterol $> 300$ mg/dL with documented coronary artery disease
LDL Apheresis

- Selective removal of LDL, lipoprotein A and VLDL fractions from plasma
  - Plasma separated from whole blood by membrane filtration
  - Plasma flows over dextran sulfate-cellulose beads
  - LDL-depleted plasma recombined with RBCS and returned to patient
  - 4.5 liters of plasma treated weekly or biweekly
  - *Lifetime apheresis commitment*
First do no harm
Follow evidence-based practices
References and Sources

- [kdf.org.sg/images/vas_03.jpg](http://www.kdf.org.sg/images/vas_03.jpg)
- [cdn.24.com/files/Cms/General/d/276/cdfc9fc5254b4c3ebdf8679ad2b3419f.jpg](http://cdn.24.com/files/Cms/General/d/276/cdfc9fc5254b4c3ebdf8679ad2b3419f.jpg)
- [www.bio.davidson.edu/Courses/Immunology/Students/Spring2003/Leese/transpic.gif](http://www.bio.davidson.edu/Courses/Immunology/Students/Spring2003/Leese/transpic.gif)