PART 2

SHOW ME THE EVIDENCE

Alane Ferguson
Apheresis: Clinical Indications

Clinical Vignettes:
• Hematology
• Cardiology/Vascular
• Neurology
• Solid Organ Transplantation
• Anatomy of an ASFA Fact Sheet
Hematology

- 40 yo M presenting to the Emergency Room: “I woke up and saw blood all over my pillow”
- Vital Signs Stable
- + Epistaxis
- Labs: CBC: Hb 9gm/dl. Platelets 5000/micL
- LDH 2000. Haptoglobin- Undetectable
- What should we do?
Hematology

• Diagnosis: Thrombotic Thrombocytopenic Purpura
• Deficiency of ADAMTS13 enzyme (cleaves multimeric vwf) typically due to an autoantibody
• Treatment:
  (a) Remove evil humor (autoantibody): TPE
  (b) Provide ADAMTS13 enzyme: TPE
  (c) Suppress autoantibody formation (eg. Steroids)
TTP

TPE:

- ASFA Category I
- Frequency typically once daily with or without a taper
- 1-1.5 PV per exchange
- Clinical and Laboratory monitoring (Platelets, Hb, LDH, haptoglobin, ADAMTS13 activity)
- Lifesaving and primary treatment in this disease
Hematology-II

- AA male brought to the ED with symptoms of slurred speech and hemiplegia
- Labs: Hb 8. Bilirubin elevated
- History of multiple admissions for pain crisis
- No family history of disease
- Hb electrophoresis: 97% HbS
- Is there a role for Apheresis?
Pathogenesis of Sickle cell Disease

- Single nucleotide substitution in the beta chain of hemoglobin results in an amino acid change
  - $\beta^6(\text{Glu}\rightarrow\text{Val}); \alpha_2\beta^S_2$
  - Changes the charge at a critical pocket
    - Glu (-ve); Val (neutral) $\rightarrow$ loss of negative charge
CLINICAL MANIFESTATIONS

- Painful crises - Bones, Viscera
- Acute chest syndrome
- CNS disease: Strokes, Chronic ischemic white matter disease
- Priapism
- Acute/chronic sequestration
- Aplastic crises
Treatment Options for SCD

• Current therapies:
  • Hydration
  • Antibiotics
  • Analgesics for pain crisis
  • Hydroxyurea (Increases HbF levels)
  • Allogeneic Stem Cell Transplantion (SCT) remains the only curative treatment
  • Red Cell Exchange
Erythrocytapheresis

• Highly effective in sickle cell disease the treatment of sickle cell disease

In the setting of Sickle Cell dx, used for:
• Prevention/recurrence of stroke (Cat I)
• Acute chest syndrome (Cat II)
• Multiorgan failure (Cat III)
• Priapism
Probability of Stroke Recurrence with Chronic Blood Transfusions

Cardiac/Vascular

- “Doc, I have high cholesterol and a family history of premature heart disease”
- 35 yo M with both parents deceased due to complications of CAD
- One angioplasty procedure performed previously
- Labs: Cholesterol 500. LDL 250
- On maximal doses of statins
Xanthomas on knees
Xanthoma on right elbow
Treatment Alternatives for Severe Hypercholesterolemia

- Plasma exchange
- LDL Apheresis

Rarely:
- Liver transplantation
Plasma Exchange

Removes LDL-C but:

- Non-specific and removes the beneficial parts of plasma
- HDL-C (good cholesterol)
- Clotting factors
LDL Apheresis

A form of apheresis that eliminates the low density lipoprotein cholesterol fraction from blood by one of two methods:

- Works by leading venous blood through a column which removes LDL cholesterol
- By precipitating LDL with heparin at low pH
How It Works

Blood Withdrawal

Blood Pump

Plasma Separator

Blood Return

Plasma Pump

Re-Primming Solution

Regeneration Solution

Regeneration Pump

LIPOSORBER® Column

Plasma Line

Waste Line
LDL-C Removed
“Saw tooth” Pattern of Lowering LDL-C with regular treatment

LDL-C

Diet Therapy

Diet & Drug Therapy

LIPOSORBER® Treatment

Pre

Time Average

Post

LIPOSORBER® SYSTEM
Neurology

- 35 yo F presenting with difficulty swallowing and ambulation, and with “droopy” eyelids
- Laboratory values: Within Normal Limits
- Tensilon test: Positive
- AChR antibody: Positive
- Diagnosis?
Myasthenia Gravis

• Patient develops autoantibodies to the ACh receptor in the motor neuron junction
• Results in weakness
• Thymomas often associated with MG
• Can progress to respiratory distress that can become life threatening
• ASFA Category I – (1) Moderate-Severe MG (2) Prethymectomy
Solid Organ Transplantation

- 42 yo male presenting with hemodynamic instability
- H/O Cardiac transplantation. High PRA. Recurrent rejection episodes
- Cardiac Biopsy: Evidence of Acute Cellular Rejection
- Treatment with immunosuppressives and steroid boluses ineffective
- Can apheresis be useful?
ECP steps

1) Blood is drawn into instrument
2) Whole blood centrifuged; RBCs and plasma returned to the patient
3) WBCs collected and treated with 8-MOP
4) WBCs photoactivated with UVA light
5) Treated WBCs returned to patient

UVADEX®
ECP: What’s in the bag?

- Plasma
- Buffy Coat
- RBCs
- Lymphocytes
- Platelets
- Granulocytes
- Macrophage
- Antigen Presenting Cells
- T cell
- B cell
- NK cell
- Dendritic cell
Photoactivation

• After buffy coat is collected, 8-MOP directly injected into the bag.

• Cells exposed to 1-2 J/cm² of UVA light

• Photoactivation time depends on:
  – Treatment volume
  – Hematocrit of the buffy coat
  – Intensity of the light bulb
Mechanism of Action

DNA

Cytoplasm

Nucleus

8 MOP

Modified from Gasparro FP.
Photoactivation of 8-MOP

1. Cell membrane damage
2. Irreversible binding to DNA

Adapted from Gasparro FP.
ECP in Cardiac Transplantation

- Successful use of ECP in human cardiac transplant recipients was first published in 1992
- A multicenter, international, randomized, double-blind study on ECP use in rejection prophylaxis was published in 1999
Cardiac Rejection: Prophylaxis

- 60 consecutive eligible recipients of primary cardiac transplants
- 2 Arms: Standard vs ECP
- Photopheresis group received a total of 24 ECP treatments (over 6 mo)

Barr et al, NEJM, 1999
Cardiac Rejection: Prophylaxis

After 6 mo:

• Mean episodes of acute rejection per patient was higher in standard-therapy arm
• More patients in the ECP arm had one rejection episode or none, and
• Fewer patients in the ECP arm had two or more rejection episodes

Barr et al, NEJM, 1999
ECP in Cardiac Rejection

• Several reports show beneficial effects of ECP in the management of cardiac rejection (biopsy proven)

• All studies are retrospective

• Used to treat refractory rejection (typically cellular)
ECP Decreases Risk of Rejection With Hemodynamic Compromise

Kirklin J et al. J Heart Lung Transplant 2006;25:283
ECP-Treated Cells Transferred to Another Mouse Confer Increased Cardiac Transplant Survival

![Graph showing survival rates with ECP and control groups. The graph indicates a statistically significant difference between the two groups with p=0.005.](image)

George J. J Heart Lung Transplant 2008;27:616
ECP Induces Tolerogenic Dendritic Cells In Vitro and Regulatory T Cells In Vivo

Cardiac Transplantation & ECP: ASFA Recommendations

- Category I: Cardiac Rejection Prophylaxis
- Category II: Treatment of Cardiac Rejection (Cellular Rejection)
Transplantation: Renal

• “I need a kidney”
• 55 M Hypertensive male with ESRD
• Blood group O. Wife is Blood group A and wants to donate her kidney
• Can apheresis enable this transplant?
Plasmapheresis
Transplantation Waitlist

• Demand (~100,000) exceeds supply (~15,000) for solid organs

• April 2009 (US Renal Tx waitlist):
  • Total ~84,000
  • O 44,385
  • A 23,779
  • B 13,672
  • AB 2,363
Why do we need ABOi renal Tx?

• Longer average wait for blood group O and B individuals
  – B 5.8 yrs
  – O 5.2 yrs
  – A 3.4 yrs
  – AB 2.4 yrs

• In the US, the probability that a pair of individuals will be ABO incompatible is 36%
ABO Incompatible Renal Transplants

Plasma Exchange Protocols

• Goal is to reduce preformed anti-donor antibodies to prevent hyperacute rejection at the time of transplant

• Goal is to maintain low antibody titers immediately post-transplant to allow for graft accommodation
TABLE 1. Guidelines for the number of TPE/CMVlg treatments based on initial antibody titer

<table>
<thead>
<tr>
<th>ABO antibody titer*</th>
<th>Number of treatments</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before transplant</td>
<td>After transplant</td>
</tr>
<tr>
<td>&lt;16</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>32</td>
<td>3</td>
<td>3</td>
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<tr>
<td>64</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>128</td>
<td>5-6</td>
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<td>256</td>
<td>7-8</td>
<td>4</td>
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<tr>
<td>512</td>
<td>9-10</td>
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<tr>
<td>1024</td>
<td>10-12</td>
<td>4</td>
</tr>
<tr>
<td>&gt;1024</td>
<td>&gt;15</td>
<td>5</td>
</tr>
</tbody>
</table>

* Antibody titer at the AHG phase.
Plasmapheresis Protocols

- Pre-transplant:
  - Number:
    - Determined by ABO titer: in most published series with a target of < 8 or < 16 at time of transplant
  - Frequency:
    - Johns Hopkins protocol – Every other day
    - Mayo protocol - Daily
Pre-Transplant Plasmapheresis

Padmanabhan et al. Transplantation 2009
ABOI titers - Response to PEX

Padmanabhan et al. Transplantation 2009
Post-Transplant Plasmapheresis

Padmanabhan et al. Transplantation 2009
- Diseases listed in alphabetical order
- Single Page
- Consistent layout/information for each disease
- Goal is to be practical
## Thrombotic Thrombocytopenic Purpura

**Incidence:** 0.37 per 100,000/year in the US

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>Grade 1A</td>
<td>I</td>
</tr>
</tbody>
</table>

### Description of the Disease

Thrombotic Thrombocytopenic Purpura (TTP) is a systemic thrombotic illness affecting mostly small vessels. When initially described, TTP was defined by a panel of clinical findings: thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fragmented red cells on blood smear and elevated lactate dehydrogenase, mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Treatment should not be initiated until other causes of systemic thrombotic microangiopathy (TMA) such as disseminated intravascular coagulopathy or severe malignant hypertension, hemolytic uremic syndrome (HUS) and post-streptococcal TMA are ruled out. Recently, TTP has been shown to be associated with a severe (<1%) deficiency of plasma ADAMTS13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) enzyme activity, which is responsible for maintaining normal distribution of a vWF multimers by clearing ultralarge multimers released from the endothelium. The severe deficiency of ADAMTS13 is documented in 100% of patients with idiopathic TTP in 10 of 12 studies and in 78% to 83% of patients in the remaining studies. An autoantibody is identified in the majority of the patients with idiopathic acquired TTP. In a recent study, IgG was found to be most common anti-ADAMTS13 antibody and was suggested to be related to recurrence of the disease. Congenital TTP is associated with autosomal mutations resulting in severely deficient ADAMTS13 function. Severely deficient ADAMTS13 deficiency appears to be an important pathogenic factor of TTP. However, as is noted above, some patients with idiopathic TTP have no detectable ADAMTS13 function. The role of laboratory assays that measure plasma activity and anti-plasmin activity antibody level in medical decision-making in TTP is still evolving. At this time, TTP remains a clinical diagnosis. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presenting TTP. Work to distinguish TTP from HUS (characterized by TMA, thrombocytopenia, and renal failure) is currently underway. Better understanding of which individuals suffer from HUS or TTP may result in improved treatment by identification of patients who would benefit from emergent plasma exchange. Congenital TTP is a rare disease, and the median age at diagnosis is 18 months.

### Current Management/Treatment

TPE has decreased the overall mortality of idiopathic TTP from uniformly fatal to <1%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma exchange may be given until TPE can be initiated. Both fresh frozen plasma (FFP) and plasma cryoprecipitate reduced (PCR) have been used as replacement for TPE, with similar results in patient outcome. Countermeasures are used as an adjunct at 1 mg/kg/day. However, no definitive trials to prove their efficacy have been performed. Recombinant ADAMTS13 is now often used to treat refractory or relapsing TTP. Since TTP is usually treated with TPE, two-hour in-hospital in addition to TPE has been practiced. Otherwise, plasma exchange may be very low, with patients with TTP having thrombotic rather than hemorrhagic tendency. Bleeding, if present, is typically noted on skin and mucous membranes. Risk factors should not be treated unless clinically indicated. Because of frequent relapse, TTP can be characterized by a decrease in ADAMTS13 activity without an inhibitor, simple infusions of plasma (10 to 15 mL/kg) or cryoprecipitate (which contains ADAMTS13) or plasma derived von Willebrand factor concentrate (used to treat von Willebrand disease) have been used.

### Radiology for TPE

TPE with plasma replacement has significantly improved patients' clinical outcomes. No other intervention has had as significant an impact on the treatment of TTP. One hypothesis is that TPE removes an antithrombin-like activity from plasma, which is responsible for the clinical outcome. Clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels and other.

### Technical Notes

- **Volume treated:** 1 to 1.5 TPF
- **Replacement fluid:** plasma, cryoprecipitate removed
- **Duration and discontinuation:** TPE is generally performed daily until the platelet count is above 150 x 10^9/L, and LDH is near normal for 2 to 3 consecutive days. LDH is removed from the TPE. Therefore, may not reflect response to TPE. The role of the remaining TPE, or longer duration, has not been studied prospectively. Persistence of antibodies to albumin on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

### References [768-791]

*As of November 8, 2000 using PubMed and the Medline search terms thrombotic thrombocytopenic purpura, plasma exchange, plasmapheresis and minimal reports published in the English language. References of the identified articles were searched for additional cases and trials.*
Anatomy of a Worksheet-I

- Incidence
- Procedure
- Recommendation
- Category
- Number of patients
- Type of study
- Type of Evidence
# ASFA Categories

## TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>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].</td>
</tr>
<tr>
<td>II</td>
<td>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]</td>
</tr>
<tr>
<td>III</td>
<td>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].</td>
</tr>
<tr>
<td>IV</td>
<td>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].</td>
</tr>
</tbody>
</table>

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*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.*
# Level of Evidence

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

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*Adopted from the criteria used by the University HealthCare Consortium [6].*
# Grading Recommendations

<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>

RCT: randomized controlled trial.
**Description of the Disease**

Thrombotic Thrombocytopenic Purpura (TTP) is a systemic thrombotic disease affecting mainly small vessels. When initially described, TTP was defined by a panel of clinical findings: thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fragmented red cells on blood smear and elevated lactate dehydrogenase, mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Treatment should not be initiated until other causes of systemic thrombotic microangiopathy (TMA) such as disseminated intravascular coagulopathy are excluded. Renal failure and fever are absence of severe microangiopathic hemolytic anemia. A trial of plasma exchange may be of benefit in those patients who do not respond to treatment. However, these findings can be misleading in some patients with idiopathic TTP, as up to 80% of patients with idiopathic TTP have no detectable TMA at presentation. The role of laboratory tests in monitoring plasma protein and anti-TNF activity is currently under investigation. Better understanding of the pathophysiology of TTP and TMA may lead to improved therapeutic strategies.

**Current management/treatment**

TPE has been shown to improve patient outcomes, with a reduction in mortality rate and improvement in renal function. One study found that TPE reduced the risk of death or renal failure. TPE is usually performed daily, and the duration of therapy is determined by the clinical response. The presence of platelet microaggregates, which are commonly seen in patients with TTP, is a marker of disease activity. The procedure is performed in an intensive care setting, and patients are monitored closely for signs of worsening renal function and fluid overload.

**Technical notes**

Dosing of RBCs: when needed, may be given on a daily basis during TPE. Clinical response with correction of mental status usually occurs within 24 hours of initiation of TPE. The median number of TPE procedures is established hemoglobin recovery is 7 to 10 days. The patient's platelet response is variable and patients with severe TTP may require several courses of TPE. The role of TPE in the treatment of TTP is controversial, and it has been associated with a higher incidence of adverse events than standard therapy.
Anatomy of a Worksheet-II

- Description of Disease
- Current Management & Treatment
- Rationale for Therapeutic Apheresis
- Technical Notes
- Duration/Discontinuation and Number of Procedures
- References