Apheresis Medicine for Immunological Disorders; Successes and Failures
ASFA Annual Meeting
May 24, 2013 11:30-12:15 PM
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: Apheresis Medicine in Immunological Disorders

• Physiology of the immune system in health and in disease
• Mechanism of Autoimmune Disorders
• Etiological pathogenic material removed by Apheresis will be discussed
• Existing Clinical Trial Evidence Basis
• Challenges and Barriers
Immunological System

- **Leukocytes**
  - Phagocytes (phagocytosis): neutrophils, eosinophils, monocytes, macrophages, dendritic cells (skin)
  - Lymphocytes: Bs and Ts, natural killer cells
  - Mast cells

- **Lymphoid tissues**
  - primary lymphoid tissues (bone marrow and thymus)
  - secondary lymphoid tissues
Summary of the Primary Immune Response

[Diagram showing the primary immune response process, including innate and adaptive defenses, antigen presentation, activation of B and T cells, and the role of cytokines and antibodies.]
Immune System: Lymphocytes

- **B Lymphocytes:**
  - Immune competence occurs in bone marrow
  - Produce Antibodies
  - Conduct Humoral Immunity

- **T Lymphocytes:**
  - Immune competence occurs in thymus
  - Non antibody producing cells
  - Conduct Cellular Immunity

www.academic.brooklyn.cuny.edu/biology/bio4fv/page/aviruses/cellular-immune.html
Types of antibodies

- Antibody = immunoglobulin = Ig

- **IgG** → Most abundant. mostly in blood, lymph. able to cross the placenta

- **IgA** → Found in tears, milk, blood, lymph

- **IgM** → First antibody to be secreted. found in blood, lymph. unable to cross placenta

- **IgD** → Found in blood, lymph, on B cells

- **IgE** → Found on mast cells, basophils. involved in allergic reaction.
The immunological equilibrium: balancing lymphocyte activation and control

**Activation**

*Effector T cells*

Normal: reactions against pathogens
Pathologic: inflammatory disease, e.g. caused by reactions against self

**Tolerance**

*Regulatory T cells*

No response to self
Controlled response to pathogens
Immunological Disorders

- Hyper-sensitivity
- Autoimmune Disease
- Immuno-deficiency
Autoimmune Diseases

- Failure of autoantibodies and T cells to recognize own cells
- Autoantibodies and T cells launch attack against own cells
- Perhaps due to overactive or an overabundance of helper T lymphocytes
Two types of autoimmune disease

<table>
<thead>
<tr>
<th>organ-specific</th>
<th>non-organ-specific</th>
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<tbody>
<tr>
<td>brain</td>
<td>muscle</td>
</tr>
<tr>
<td>multiple sclerosis(?)</td>
<td>dermatomyositis</td>
</tr>
<tr>
<td>thyroid</td>
<td>kidney</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>SLE</td>
</tr>
<tr>
<td>primary myxoedema</td>
<td>skin</td>
</tr>
<tr>
<td>thyrotoxicosis</td>
<td>scleroderma</td>
</tr>
<tr>
<td>stomach</td>
<td>SLE</td>
</tr>
<tr>
<td>pernicious anaemia</td>
<td>joints</td>
</tr>
<tr>
<td>adrenal</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>Addison's disease</td>
<td></td>
</tr>
<tr>
<td>pancreas</td>
<td></td>
</tr>
<tr>
<td>insulin-dependent</td>
<td></td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td></td>
</tr>
</tbody>
</table>
The spectrum of autoimmune diseases

organ-specific

Hashimoto’s thyroiditis
primary myxoedema
thyrotoxicosis
pernicious anaemia
autoimmune atrophic gastritis
Addison’s disease
premature menopause (few cases)
insulin-dependent diabetes mellitus
stiff-man syndrome
Goodpasture’s syndrome
myasthenia gravis
male infertility (few cases)
pemphigus vulgaris
pemphigoid
sympathetic ophthalmia
phacogenic uveitis
multiple sclerosis (?)
autoimmune haemolytic anaemia
idiopathic thrombocytopenic purpura
idiopathic leucopenia
primary biliary cirrhosis
active chronic hepatitis (HBsAg negative)
cryptogenic cirrhosis (some cases)
ulcerative colitis
atherosclerosis (?)
Sjögren’s syndrome
rheumatoid arthritis
dermatomyositis
scleroderma
mixed connective tissue disease
anti-phospholipid syndrome
discoid lupus erythematosus
systemic lupus erythematosus (SLE)

non-organ-specific
Blood Purification; Size Matters

Molecular Weight kD
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>
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<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>
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</table>

- **Small Molecules**
- **Middle Molecules**
- **Large Molecules**

Hemodialysis: Diffusion Clearance

Hemofiltration: Convective Clearance

Therapeutic Plasma Exchange
## Treatment diagnosis (%)


<table>
<thead>
<tr>
<th>Disease</th>
<th>Asia</th>
<th>Europe</th>
<th>USA</th>
<th>S.Am</th>
<th>Total</th>
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<td>Immunology</td>
<td>19</td>
<td>15</td>
<td>4</td>
<td>0</td>
<td>15</td>
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<td>21</td>
<td>7</td>
<td>6</td>
<td>13</td>
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<tr>
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<td>5</td>
<td>17</td>
<td>4</td>
<td>17</td>
<td>8</td>
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<tr>
<td>GI</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Neoplasm</td>
<td>4</td>
<td>3</td>
<td>24</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>GU</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hematology</td>
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<td>5</td>
<td>10</td>
<td>17</td>
<td>5</td>
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## Top 6 treatment diagnosis

No of patients


<table>
<thead>
<tr>
<th></th>
<th>Asia</th>
<th>Europe</th>
<th>USA</th>
<th>SAm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MG</td>
<td>H-chol</td>
<td>Neoplasm</td>
<td>S/S</td>
<td>MG</td>
</tr>
<tr>
<td>2</td>
<td>Liver</td>
<td>MG</td>
<td>MS</td>
<td>GBS</td>
<td>GBS</td>
</tr>
<tr>
<td>3</td>
<td>RA</td>
<td>Sclero</td>
<td>MG</td>
<td>Platelet↓</td>
<td>H-chol</td>
</tr>
<tr>
<td>4</td>
<td>SLE</td>
<td>GBS</td>
<td>GBS</td>
<td>MG</td>
<td>Liver</td>
</tr>
<tr>
<td>5</td>
<td>L-GN</td>
<td>Circulat.</td>
<td>Breast Ca</td>
<td>TTP</td>
<td>RA</td>
</tr>
<tr>
<td>6</td>
<td>GBS</td>
<td>GN</td>
<td>S/S</td>
<td>ITP</td>
<td>ScleroD</td>
</tr>
</tbody>
</table>
Successes
Rapidly Progressive Glomerulonephritis

- Anti-GBM
- Immune-Complex
- Pauci-Immune

  - Post-Strep
  - S.B.E.
  - Lupus

  - IgA
  - Cryoglobulines
  - Membrano-Proliferative

  - Wegener's
  - PAN
  - Idiopathic
Anti-GBM Antibody and Goodpasture’s Syndrome

- Pathogenic antibody capable of causing alveolar hemorrhage and rapidly progressive glomerulonephritis
- Only one randomized, controlled trial: *Johnson et al. Medicine 64:219, 1985*
- Plasmapheresis results in rapid lowering of anti-GBM antibody, lower post RX creatinine and reduced incidence of ESRD
GOODPASTURE’S SYNDROME

Recovery from Goodpasture's Syndrome after Immunosuppressive Treatment and Plasmapheresis
C. M. LOCKWOOD, J. M. BOULTON-JONES, R. M. LOWENTHAL, I. J. SIMPSON,
D. K. PETERS, C. B. WILSON
British Medical Journal, 1975, 2, 252-254
Treatment of Goodpasture's disease by plasma exchange and immunosuppression

C. P. SWAINSON, J. S. ROBSON, S. J. URBANIAK, A. J. KELLER & A. B. KAY MedicalRenal Unit and Edinburgh and South-East Scotland Regional Blood Transfusion Service, Royal Infirmary, Edinburgh

(Received 24 January 1978)

SUMMARY

Three cases of Goodpasture's disease are described who were treated with intensive plasma exchange and immunosuppression. There was no improvement in renal function and the patients required chronic haemodialysis, but renal function did recover with treatment for recurrence of disease in a transplanted kidney. Anti-GBM antibody levels were not controlled and substantial reductions in fibrinogen and complement were only achieved with daily treatment. A controlled trial of this regime is urgently required.
## RCT in Goodpasture’s Syndrome
(only 1 of 2146 pubs)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Diagnosis</th>
<th>N</th>
<th>Outcome</th>
<th>Signif</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Johnson etal</td>
<td>2/3 anti GBM ab -linear IF -anti GBM eluted</td>
<td>17</td>
<td>Pulmonary hemorrhage No dialysis Serum creatinine</td>
<td>ND ND SD*</td>
</tr>
</tbody>
</table>

*Significant creatinine change correlates with morphology not treatment (failure of randomization due to low power)*
• **Design**: Retrospective review of 71 patients treated for confirmed anti-GBM antibody disease over 25 years.

• **Results**: Patients who presented with a creatinine concentration less than 500 mmol/L (5.7 mg/dL) \( (n = 19) \) had 100% patient survival and 95% renal survival at 1 year and 84% patient survival and 74% renal survival at last follow-up. In patients who presented with a creatinine concentration of 500 mmol/L or more \( (>5.7 \text{ mg/dL}) \ (n = 13) \) but did not require immediate dialysis, patient and renal survival were 83% and 82% at 1 year and 62% and 69% at last follow-up.
Results

• In patients who presented with dialysis-dependent renal failure (n = 39), patient and renal survival were 65% and 8% at 1 year and 36% and 5% at last follow-up.
• All patients who required immediate dialysis and had 100%
• crescents on renal biopsy remained dialysis dependent.

Conclusions: PLEX and urgent immunosuppression recommended
Rapidly Progressive Glomerulonephritis

- Anti-GBM
- Immune-Complex
  - Post-Strep
  - S.B.E.
  - Lupus
  - IgA
  - Cryoglobulines
  - Membrano-Proliferative
- Pauci-Immune
  - Wegener's
  - PAN
  - Idiopathic

RPGN
Rapidly Progressive Glomerulonephritis

- Anti-GBM
  - Post-Strep
  - S.B.E.
  - Lupus
- Immune-Complex
  - IgA
  - Cryoglobulines
  - Membrano-Proliferative
- Pauci-Immune
  - Wegener's
  - PAN
  - Idiopathic
# Plasmapheresis in Neurology

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definition</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>Established</td>
<td>I</td>
</tr>
<tr>
<td>CIDP</td>
<td>Established</td>
<td>I</td>
</tr>
<tr>
<td>MS - acute; refractory to steroid</td>
<td>Established</td>
<td>I</td>
</tr>
<tr>
<td>MGUS - IgG/A</td>
<td>Established</td>
<td>I</td>
</tr>
<tr>
<td>MG – preop &amp; crisis</td>
<td>Established</td>
<td>III</td>
</tr>
<tr>
<td>MGUS - IgM</td>
<td>Investigational</td>
<td>I</td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>Possibly useful</td>
<td>II/III</td>
</tr>
</tbody>
</table>

*Investigational*: Refsum disease, acquired neuromyotonia, Stiff-man syndrome, Cryoglobulinemic neuropathy, CNS lupus, ADEM
Plasma Exchange - MG

• Dose: 5 exchanges over 9 to 10 days

• Indications:
  – Acutely ill MG patient
  – Pre-thymectomy (respiratory/bulbar involvement)

• Advantages
  – Very short onset of action (3 to 10 days)
  – Probably more effective in crisis than IVIG

• Disadvantages
  – Requires specialized equipment & personnel
  – Complications more frequent in elderly
  – High cost with short-term effects (weeks)
Clinical response


<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>16%</td>
</tr>
<tr>
<td>Fair</td>
<td>62%</td>
</tr>
<tr>
<td>Good</td>
<td>22%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:2</td>
<td>2:12</td>
<td>5:3</td>
</tr>
<tr>
<td>1:5</td>
<td>3:8</td>
<td>6:2</td>
</tr>
<tr>
<td>4:8</td>
<td>:&gt;5</td>
<td></td>
</tr>
</tbody>
</table>
Favorable prognostic parameters


- High MG score
- Pathology of non-thymoma type
- Young age at onset
- Daily apheresis
- High removal rate for IgG
### Plasma exchange in GBS

**GBS Study Group, Neurology 1985,35,1094-104**

245 patients; 40-50 cc/kg for 3-5 PE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PE</th>
<th>No Tx</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve &gt; 1 grade at 4 wks</td>
<td>59%</td>
<td>39% *</td>
<td></td>
</tr>
<tr>
<td>Mean grade change at 4 wks</td>
<td>1.1 G</td>
<td>0.4 G</td>
<td>**</td>
</tr>
<tr>
<td>Median time to improve 1 G</td>
<td>19 D</td>
<td>40 D**</td>
<td></td>
</tr>
<tr>
<td>Median time to walk unaided</td>
<td>53 D</td>
<td>85 D**</td>
<td></td>
</tr>
<tr>
<td>Median time on ventilator</td>
<td>24 D</td>
<td>48 D*</td>
<td></td>
</tr>
<tr>
<td>Failed to improve 1 G at 6M</td>
<td>3%</td>
<td>13% *</td>
<td></td>
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</tbody>
</table>

Plasmapheresis appears to be of benefit in patients with GBS of recent onset (within 7 days).
Change of MRC-sum score during DF Plasmapheresis in GBS

*Chen et al, J Clin Apheresis 1999;14:126-9.*
# Plasmapheresis in GBS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>No</th>
<th>G at entry</th>
<th>Time to Tx</th>
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<tbody>
<tr>
<td>Osterman</td>
<td>84</td>
<td>Sweden</td>
<td>18</td>
<td>4.6</td>
<td>6.9</td>
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<tr>
<td>GBS study</td>
<td>85</td>
<td>USA</td>
<td>122</td>
<td>4.3</td>
<td>11.1</td>
</tr>
<tr>
<td>French</td>
<td>87</td>
<td>France</td>
<td>109</td>
<td>ND</td>
<td>6.3</td>
</tr>
<tr>
<td>Van der Meche</td>
<td>92</td>
<td>Neth</td>
<td>73</td>
<td>3.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Bril</td>
<td>96</td>
<td>Canada</td>
<td>24</td>
<td>4.1</td>
<td>4.7</td>
</tr>
<tr>
<td>PES/GBS</td>
<td>97</td>
<td>UK</td>
<td>121</td>
<td>3.9</td>
<td>6.9</td>
</tr>
<tr>
<td>SKH</td>
<td>98</td>
<td>Taiwan</td>
<td>16</td>
<td>3.6</td>
<td>8.1</td>
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</table>
# Plasmapheresis in GBS

<table>
<thead>
<tr>
<th>Author</th>
<th>↑1G at W4(%)</th>
<th>↑G at W4</th>
<th>Time to G2</th>
<th>Fail to G2 at M6</th>
<th>OFF respirator</th>
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<td>—</td>
<td>2.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>1.1</td>
<td>53</td>
<td>21</td>
<td>9</td>
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<tr>
<td>French</td>
<td>—</td>
<td>—</td>
<td>70</td>
<td>18</td>
<td>—</td>
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<tr>
<td>Van der Meche</td>
<td>34</td>
<td>0.4</td>
<td>69</td>
<td>—</td>
<td>22.6</td>
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<tr>
<td>Bril</td>
<td>61</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>PES/GBS</td>
<td>—</td>
<td>1.1</td>
<td>40</td>
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<td>—</td>
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<tr>
<td>SKH</td>
<td>81</td>
<td>1.5</td>
<td>19</td>
<td>13</td>
<td>11.2</td>
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Systemic Lupus Erythematosus

Thank You

• Questions?