Advances with Therapeutic Apheresis

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Medical Director, Therapeutic Apheresis Program.
Associate Medical Director, Kidney/Pancreas Transplantation.
Apheresis modalities

Trends in utilization of apheresis modalities

UCSD Therapeutic Apheresis Program, San Diego, USA.
Statistical report, 2010

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Plasmapheresis applications

- **Autoantibody:** Anti-GBM GN (& Goodpasture’s), Myasthenia gravis (MG), ANCA-nephritis (& Wegener’s), Immune Thrombocytopenia (ITP), Thrombotic Thrombocytopenic Purpura (TTP), Antiphospholipid crisis, Guillain-Barré syndrome (GBS), Autoimmune Dilated Cardiomyopathy, Neuromyelitis Optica (NMO), Stiff Person syndrome, Pemphigus, etc.
- **Probable autoantibody:** Multiple sclerosis (also cell-mediated component), 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), etc.
- **Endogenous toxins:** Hypercholesterolemia, Liver failure, Systemic Inflammatory Response Syndrome (SIRS), etc.
- **Exogenous poisons:** *Amanita*, drugs, etc.
## Plasmapheresis for autoantibody disease

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>Autoantibody reacts with</th>
<th>External trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-GBM GN (&amp; Goodpasture’s)</td>
<td>Alpha-3 chain collagen IV</td>
<td>?</td>
</tr>
<tr>
<td>Myasthenia Gravis (1) classic</td>
<td>Acetylcholine receptor</td>
<td>?</td>
</tr>
<tr>
<td>(2) MuSK antibody subtype</td>
<td>Muscle-specific kinase</td>
<td>?</td>
</tr>
<tr>
<td>ANCA GN (&amp; Wegener’s, etc.)</td>
<td>MPO, PR3, etc. ?LAMP2*</td>
<td>*?bacterial fimbriae</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>GAD65 (glutamic decarb..)</td>
<td>?</td>
</tr>
<tr>
<td>Thrombotic Thrombocytopenic Purpura (TTP)</td>
<td>ADAMTS13 (von Willebrand factor protease)</td>
<td>?</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Neuronal gangliosides</td>
<td>Bacterial lipo-oligo-saccharides (LOS)</td>
</tr>
<tr>
<td>(1) Miller-Fisher variant</td>
<td>(1) GQ1b</td>
<td>- Campylobacter</td>
</tr>
<tr>
<td>(2) other variants</td>
<td>(2) GM1, GM1b, GD1a, GalNAcGD1a, GD1b, GD3, etc.</td>
<td>- other bacteria</td>
</tr>
<tr>
<td>Neuromyelitis Optica (NMO)</td>
<td>Aquaporin 4</td>
<td>?</td>
</tr>
<tr>
<td>Glomerular Disease</td>
<td>Auto-Ab (Autoantibody)</td>
<td>Use of TPE</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Anti-GBM nephritis</strong> (including Goodpasture’s)</td>
<td>Reacts with non-collagenous domain (NC1) of alpha-3 chain of type IV collagen of GBM</td>
<td><strong>TPE only if serum creatinine &lt;6 mg/dl,</strong> plus cyclophosphamide and steroids. If &gt;6, too late to salvage.</td>
</tr>
<tr>
<td><strong>Anti-Neutrophil Cytoplasmic Ab (ANCA) GN</strong> (Focal necrotizing GN, Wegener’s and polyangiitis) (“Pauci-immune GN”)</td>
<td>ANCA recognize soluble lysosomal enzymes (MPO, PR3, etc.). May also have lysosomal membrane protein-2 (LAMP2) Ab (?).</td>
<td><strong>TPE only if serum creatinine &gt;6 mg/dl.</strong> If creat &lt;6, usually enough to use corticosteroid plus cytotoxic drugs.</td>
</tr>
<tr>
<td><strong>Membranous GN</strong> (primary idiopathic)</td>
<td>70% of adult cases have Ab to Type-M Phospholipase A2 Receptor (PLA2R) on podocyte foot processes. (Beck, 2009)</td>
<td><strong>TPE not indicated.</strong> Slowly developing disease. Steroids and cytotoxics used in selected cases; many get no immunosuppression.</td>
</tr>
</tbody>
</table>
Plasmapheresis for cryoglobulinemic vasculitis

Hep C virus CD81 tropism

- Hepatocytes
  - Hepatitis
- B-lymphocytes
  - Protects from apoptosis
    - MGUS
    - B-cell lymphoma
  - Induces autoimmune aspects of HCV disease
    - Other autoimmune
      - Sicca syndrome
      - Renal Tubular Acidosis
      - etc.
- Circulating immune complexes (mixed cryoglobulinemia)
  - Low complement (i C4, i C3)
  - Vasculitis
  - Glomerulonephritis (MPGN / Cryo GN)

Antigenemia (Hep C virus)

η Antiviral Ab (IgG)

Rheumatoid factor (IgM)
Plasmapheresis for cryoglobulinemic vasculitis

Reduce antigenemia
- Ribovirin
- Interferon

Reduce antibody response
- Corticosteroids
- Cyclophosphamide

Reduce antigenemia
- Ribovirin
- Interferon

Reduce antibody response
- Corticosteroids
- Cyclophosphamide

Reduce B-lymphocyte overactivity
- Rituximab (anti CD-20)
  (“off-label” indication)

Rituximab in 16 cases of cryoglobulinemic vasculitis:
- 10 complete remissions
- 5 partial remissions
- 1 no benefit
- no increase in virus count
- 2 relapsed in 1.5 years

Saadoun D, et al.
Plasmapheresis for cryoglobulinemic vasculitis

Recurrent cutaneous Hep C vasculitis in a leg previously devastated by occlusive vasculitis (status post below-knee amputation), despite antiviral, corticosteroid and rituximab therapy. Clearing of cutaneous vasculitis (disappearance of red patches) after 3 daily plasmapheresis procedures.
Treatment of antibody-mediated rejection

Anti-HLA-B12 level

Serum Creat mg/dl

Living donor kidney txp

Biopsy: Acute humoral rejection (C4d +++)

August 17th

August 24th

August 31st

September 7th

0.87

4.0

2.7

1.6

1.25

7.4

6.2

IVIG

Thymo

Plasmapheresis + IVIG x 5

Rituxan

UCSD patient
Plasmapheresis treatment choices

Centrifugal TPE
- Citrate (usually)
- Lower blood flow rate
- Peripheral veins or central line
- Process ~1.5x blood volume
- Plasma extraction ~80%

Membrane TPE
- Heparin (usually)
- Higher blood flow rate
- Central venous line
- Process ~3x blood volume
- Plasma extraction ~30%

Plasma replacement
- FFP for TTP
- 5% albumin (+ saline) for other indications

Plasma regeneration
- Adsorption column
- Cascade filtration
Plasma regeneration systems

- Whole plasma
- Purified plasma

blood return

from patient
Double-Filtration (Cascade) Plasmapheresis

#1: Plasma-filter
Pore size: ~0.3 µm
Cut-off: >1,000,000 Da

#2: Plasma-fractionator
Pore size: 0.01-0.03 µm
Cut-off: ~ 100,000 Da
(Albumin ~ 67,000 Da)
(IgG ~140,000 Da)
(IgM ~970,000 Da)
Immunoadsorption Plasmapheresis

Purified plasma

Whole plasma

Blood return

Waste

Perfusion column(s) containing immobilized antibody to human IgG.

- Binds IgG (all subclasses).
- Brands:
  - TheraSorb™ (Miltenyi Biotec)
  - others

Not FDA-approved
Antigen (Ag) columns for Immunoadsorption (IA)

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 IA

Purified plasma

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

Whole plasma

for Autoimmune-type Idiopathic Dilated Cardiomyopathy which is due to autoantibodies to
(1) Beta-1 adrenergic receptor
(2) now known to cross-react also with cardiac myosin.


But Ab’s against different epitopes may cause similar disease.

Not yet FDA-approved
Coupled Plasma Filtration Adsorption (CPFA)

Continuous Plasmaseparation with Adsorption Column

Continuous High-volume Hemo(dia)filtration

Bellomo R, Tetta C, Ronco C.
Coupled plasma filtration adsorption.
Plasmapheresis applications

- **Autoantibody**: Anti-GBM GN (& Goodpasture’s), Myasthenia gravis (MG), ANCA-nephritis (& Wegener’s), Immune Thrombocytopenia (ITP), Thrombotic Thrombocytopenic Purpura (TTP), Antiphospholipid crisis, Guillain-Barré syndrome (GBS), Autoimmune Dilated Cardiomyopathy, Neuromyelitis Optica (NMO), Stiff Person syndrome, Pemphigus, etc.

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Immune injury in autoimmunity & transplant rejection

**ANTIBODY-MEDIATED**

Therapeutic Approach

Reduce antibodies.

Rx

Immunosuppressive drugs

Therapeutic plasmapheresis = Therapeutic Plasma Exchange = TPE

**CELL-MEDIATED**

Rx

Immunosuppressive drugs

Suppress Cytotoxic T-cells. Modulate toward tolerance.

Therapeutic photopheresis = Extracorporeal Photopheresis = ECP

Rx

Immunosuppressive drugs
Photopheresis machine (Therakos ® UVAR XTS)

Automated collection of WBC’s, with return of RBC’s and plasma to patient.

Single-needle access

Centrifuge: 3 to 6 cycles of collection per procedure

WBC product is treated with UV light and psoralan

8 methoxy psoralan (“8-MOP”) is added to WBC product

Photoactivation: WBC’s exposed to UV-A (352 nm), typically 25-35 mins

Treated WBC product is reinfused to patient

Treatment Frequency
2 on successive days:
• repeat q. 2 wks
• or repeat q. 1 - 4 wks

Mode of action
• 8-MOP, activated by UV-A, causes cross-linking of DNA in WBCs.
• Apoptotic T-cells return to patient and modify immune response.
Apoptotic Cells Inhibit Proinflammatory Cytokine Production by APCs (Antigen Presenting Cells)


(Graphic figures courtesy of the authors)
Generation of Regulatory T-Cells \textit{in-vivo}

Intravenous infusion of syngeneic apoptotic cells by photopheresis induces antigen specific regulatory T cells.
\textit{J Immunol} 174: 5968-76, 2005 (Graphics courtesy of the authors)
Mechanism of action of Photopheresis (ECP)

Key points:

• Apoptosis of mononuclear WBC’s (mainly T-cells)
• Phagocytosis of apoptotic cells by APCs (antigen presenting cells)
• Inhibition of pro-inflammatory cytokines (TNF, etc.)
• Generation of anti-inflammatory cytokines (IL-10, etc.)
• Generation of antigen-specific T-reg (regulatory T-cells)
Possible mechanism of ECP (Photopheresis)

Foreign antigens are ingested by APCs (Antigen-Presenting Cell) (Macrophages, etc.)

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Foreign antigens are ingested by APCs (Antigen-Presenting Cells). This activates the APCs to stimulate effector T-cells (via pro-inflammatory cytokines), leading to an active immune response.
Possible mechanism of ECP (Photopheresis)

Foreign antigens are ingested by APCs (Antigen-Presenting Cells) (Macrophages, etc.). This activates the APCs to stimulate effector T-cells (via pro-inflammatory cytokines) which cause APCs to favor regulatory T-cells (via anti-inflammatory cytokines) Apoptotic T-cells are ingested by APCs deliver inhibitory signals to APCs which cause APCs to favor regulatory T-cells (via anti-inflammatory cytokines) Apoptotic cells express specific membrane proteins, which are recognized by receptors on the APCs (“Apoptotic Cell-Associated Membrane Protein Receptors”) Several of these receptors on APCs, e.g. TAM, have specific inhibitory signalling capacity, which cause APCs to favor regulatory T-cells Apoptotic T-cells are made apoptotic by ECP, then returned to patient “Tolerance” (clonal specific)

Active Immune Response

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Possible mechanism of ECP

Foreign antigens are ingested by APCs.
This activates the APCs to stimulate effector T-cells (via pro-inflammatory cytokines).

Active Immune Response

APC (Antigen-Presenting Cell) (Macrophages, etc.)

Apopotic T-cells are ingested by APCs.
Apopotic T-cells deliver inhibitory signals to APCs
... which cause APCs to favor regulatory T-cells (via anti-inflammatory cytokines)

“Tolerance” (clonal specific)

Donor APC

Active clones of CTLs (Cytotoxic T-lymphocytes)

Apoptotic cells express specific membrane proteins, which are recognized by receptors on the APCs ("Apoptotic Cell-Associated Membrane Protein Receptors")

Several of these receptors on APCs, e.g. TAM, have specific inhibitory signalling capacity,

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Photopheresis (ECP)

Clinical applications:

- Heart transplantation
- Lung transplantation
- Liver transplantation
- Kidney transplantation
- Graft versus host disease (after BMT allotransplantation)
- Cutaneous T-cell lymphoma (incl. Sezary syndrome)
- Crohn’s disease
- Other diseases
Photopheresis (ECP)

Heart transplant rejection
Univ. of Southern California

60 cardiac transplant recipients

- Standard therapy, 6 mos
  - n = 27
  - Acute rejection episodes
    - Zero or 1 rejection
      - 14 of 27
    - 2 or 3 rejections
      - 13 of 27

- + ECP: 2 days q 2 wks x 6 mos
  - n = 33
  - Acute rejection episodes
    - Zero or 1 rejection
      - 27 of 33
    - 2 or 3 rejections
      - 6 of 33

Barr M, Meiser BM, Eisen HJ, et al.
Photopheresis (ECP)

Heart transplant rejection
Univ. of Alabama

Standard photopheresis (ECP) treatment:
2 ECP’s q. 1wk x 4
2 ECP’s q. 2wk x 2
2 ECP’s q. 4wk x 4
total 20 treatments (10 pairs) in 26 weeks

Results (retrospective):
343 heart transplants (excluding lymphoid irradiation cases)
36 had ECP (added to conventional therapy).
• ECP reduced the incidence of rejection
• ECP reduced the incidence of death from rejection.

Kirklin JK, Brown RN, Huang ST, et al.,
Rejection with hemodynamic compromise:
objective evidence for efficacy of photopheresis.
Photopheresis (ECP)

Lung transplant rejection

Washington University, St. Louis, Missouri

Conclusion:
ECP is associated with a reduction in the rate of decline in lung function associated with progressive BOS (Bronchiolitis Obliterans Syndrome)

NOTE: The FEV1 improved in 15 patients (25%) after the initiation of ECP, with a mean increase of 20.1 ml/month.

The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation.
J Heart Lung Transplantation 29:424, 2010
### Liver transplant rejection/ Hepatitis C

University of Pisa, Italy

<table>
<thead>
<tr>
<th>Group</th>
<th>Pts n =</th>
<th>Median donor age (range)</th>
<th>Immunosuppression</th>
<th>For Acute Rejection (biopsy)</th>
<th>Mortality at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (1996 - 2000)</td>
<td>133</td>
<td>54</td>
<td>none</td>
<td>Steroid boluses</td>
<td>28.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pred + CSA + azathioprine</td>
<td>OKT-3</td>
<td></td>
</tr>
<tr>
<td>Group 2 (2001 - 2003)</td>
<td>91</td>
<td>60</td>
<td>Anti-CD25</td>
<td>Increase or switch calcineurin inhibitor (CNI)</td>
<td>22.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pred + CSA</td>
<td>Steroid boluses ECP</td>
<td></td>
</tr>
<tr>
<td>Group 3 (2004 - Jun 2006)</td>
<td>78</td>
<td>66</td>
<td>Anti-CD25</td>
<td>Increase or switch CNI Re-Txp</td>
<td>10.2% (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSA + ECP + antivirals*</td>
<td>Steroid boluses Re-Txp</td>
<td></td>
</tr>
</tbody>
</table>

*Of 36 pts who completed the interferon/ribavirin protocol, 39% (14) had sustained viral clearance

Photopheresis (ECP)

Kidney transplant rejection
Royal Prince Alfred Hospital, Sydney, Australia

UNCONTROLLED COHORT OBSERVATION:
• 10 renal transplants with problematic rejection
• Photopheresis + methylprednisolone + antilymphocyte therapy.
• Rejection resolved in all 10 patients (median follow-up 66.7 months).
• 6 have stable graft function (median creat 2.17 mg/dl) (at median follow-up 71.0 months). One patient death from sepsis, 2 from malignancy with functioning grafts, one graft lost to disease recurrence.

CONCLUSIONS:
• Photopheresis may have a role as adjuvant or salvage antirejection therapy.
• Randomized controlled clinical trials needed.

Photopheresis therapy for problematic renal allograft rejection.
J Clin Apheresis 24:161-9, 2009
# Photopheresis (ECP)

## Graft Versus Host Disease (GVHD)

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Skin involvement</th>
<th>Liver involvement</th>
<th>Gut involvement</th>
<th>Overall survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sniecinski et al, 1995</td>
<td>11</td>
<td>50%</td>
<td>9%</td>
<td>60%</td>
<td>64%</td>
</tr>
<tr>
<td>Greinix et al, 1998</td>
<td>6</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Miller et al, 1998</td>
<td>4</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>Smith et al, 1998</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Greinix et al, 2000</td>
<td>21</td>
<td>81%</td>
<td>67%</td>
<td>0%</td>
<td>57%</td>
</tr>
<tr>
<td>Salvanesci et al, 2001</td>
<td>9</td>
<td>89%</td>
<td>20%</td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td>Padua (Dall'Amico and Messina, 2002)</td>
<td>14</td>
<td>79%</td>
<td>57%</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>Messina et al, 2003</td>
<td>33</td>
<td>82%</td>
<td>60%</td>
<td>75%</td>
<td>69% (Responders) 12% (nonresponders)</td>
</tr>
<tr>
<td>Greinix et al, 2006, and personal communication</td>
<td>59</td>
<td>93%</td>
<td>65%</td>
<td>74%</td>
<td>59% (Responders) 11% (nonresponders)</td>
</tr>
</tbody>
</table>

Knobler R, Barr ML, Couriel D, et al.
Review: Extracorporeal photopheresis: Past, present, and future
## Photopheresis (ECP)

### Cutaneous T-cell Lymphoma (CTCL)

<table>
<thead>
<tr>
<th>Stage</th>
<th>First line</th>
<th>Second line</th>
<th>Experimental</th>
<th>Not Suitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>topical or none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>topical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>topical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>XRT, TSEB, chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| III   | PUVA, interferon, **ECP** | | | ............
| IVA   | XRT, TSEB, chemo | | | |
| IVB   | XRT, chemo | | | |

**Photopheresis (ECP)**

**Crohn's disease**

Univ. of Miami, Florida

28 patients with Crohn’s disease (refractory to I.S. and anti-TNF) (baseline mean CDAI score 314)

Uncontrolled cohort study

- 14 patients (50%) responded by week 12 (13 of them within 6 wks).
- 7 patients (25%) attained remission by week 12.
- 3 of 5 patients with open fistulae at baseline had fistula closure.
- 9 of the 12 patients (75%) who entered the extension study maintained their response at week 24.

**CONCLUSIONS:** ECP was well tolerated and induced clinical response (50%) and remission (25%) in patients. Most patients were able to maintain a response with continued treatments

Abreu MT, von Tirpitz C, Hardi R, et al
Extracorporeal photopheresis for the treatment of refractory Crohn's disease: results of an open-label pilot study.

*Inflamm Bowel Dis. 15:829-36, 2009.*
Photopheresis = ECP

Practice guidelines:

- CTCL (Cutaneous T-cell Lymphoma)# x
  - Erythrodermic
  - Non-erythrodermic
- GVHD (Graft-versus-host disease)x
  - Skin (chronic)
  - Skin (acute)
  - Non-skin (acute and chronic)
- Heart transplant
  - Rejection x
  - Prophylaxis
- Lung transplant rejection
- Liver transplant rejection
- Kidney transplant rejection
- Crohn’s Disease
- others

**ASFA (2010)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>ECP (I)</th>
<th>ECP (II)</th>
<th>ECP (III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCL Erythrodermic</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>CTCL Non-erythrodermic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVHD Skin (chronic)</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>GVHD Skin (acute)</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>GVHD Non-skin (acute and chronic)</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Heart transplant Rejection</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Heart transplant Prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung transplant rejection</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Liver transplant rejection</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Kidney transplant rejection</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>others</td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
</tbody>
</table>

# = FDA approved
* = Medicare reimbursable
Recent reviews:

**Szczepiorkowski ZM, et al.,**
Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis.  
*J Clin Apheresis, 25:83-177, 2010*
Therapeutic Apheresis

Recent reviews:


Thank you for your attention.