Literature Review: The Year in Apheresis

Selected Publications

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Disclosure of Conflicts of Interest

“Literature Review: The Year in Apheresis”

Jan Hofmann, MD has reported the following financial relationships with commercial interests related to the content of this educational activity:

Consulting Fees: Fresenius Medical Care
Yearly Apheresis Literature Review

2013:
• HCV-associated Cryoglobulinemia
• Catastrophic Antiphospholipid Antibody Syndrome
• Antibody-mediated Cardiac Transplant Rejection
• NMDA-receptor Encephalitis

2014:
• Hypertriglyceridemic Pancreatitis
• Refractory/accelerated Hyperthyroidism
• Hyperviscosity Syndromes

2015:
• Sepsis and Multiorgan Failure (use of adjunctive TPE)
• Hereditary Hemochromatosis (use of Therapeutic Erythrocytapheresis)
• Ebola Virus Disease and Apheresis (Lectin-Affinity Plasmapheresis)

Yearly Apheresis Literature Review

2016:
• Antibody Mediated Rejection in Lung Transplantation
• Diffuse Alveolar Hemorrhage (use of adjunctive TPE)

2017:
• Acute Hepatic Failure (use of high-volume TPE txs)
• Idiopathic Dilated Cardiomyopathy (use of TPE and IA txs)

2018:
• ABOi Liver Transplantation (use of TPE in desensitization and AMR)
• Sudden Sensorineural Hearing Loss (use of LDL apheresis and Rheopheresis).
Apheresis Literature Review
2019 - Outline

• Highlights of the last 12-24 months in Therapeutic Apheresis:
  - a systematic way to read the literature (a brief review)

• Pediatric Autoimmune Neuropsychiatric Disorders Associated with
  Streptococcal Infections (PANDAS) (use of antibiotics, TPE, and
  immunosuppressive therapy).

• Bilateral Diffuse Uveal Melanocytic Proliferation (BDUMP) (use of
  TPE and immunosuppressive therapy).

• ANCA-Associated Vasculitis (preliminary data from the PEXIVAS trial)

• Update: changes/trends in apheresis opportunities:
  • Evolving Sub-specialities (Immu-no-oncology; Neuro-inflammation; Transplant
    immunology; Cardio-oncology).
  • Emerging Diseases (Nephrogenic Systemic Fibrosis; NMDA-R encephalitis
    (autoimmune encephalitides), etc).
  • New Diagnostics (NextGen aHUS genetic panels; new assays for HIT, etc)
  • New Medications (New monoclonal ab treatments for acq.TTP; refractory MG)

Apheresis Literature Review
Critical Reading of the Medical Literature

• Article title (subject matter; review vs. original study; type of study design)
• Source (journal, authors, institution)
• Type of study design:
  • Randomized controlled trial (RCT)
  • Cohort (observation) study; case-control study
  • Case series
  • Case report (expert opinion)
• Grading study design:
  • RCT (size/similarity of each study group; blinding; effect size; power; etc)
  • Cohort study (prospective or retrospective; size of cohort group; etc)
  • Case series (size of study group; etc)
  • Case report (often reported because case is novel, unusual)
**Definition of Quality of Evidence from the Literature**  
(ASFA 2016 Category Indications)

<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 trial 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>

**Recommendation Grades for Therapeutic Apheresis**  
(to enhance clinical value of ASFA 2016 Categories)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
<th>Method / Quality</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade IA:</td>
<td>Strong recommendation; high quality evidence (HQE).</td>
<td>RCTs w/o limitations</td>
<td>Strong recommend.</td>
</tr>
<tr>
<td>Grade IB:</td>
<td>Strong recommendation; moderate quality evidence (MQE).</td>
<td>RCTs w/limitations</td>
<td>Strong recommend.</td>
</tr>
<tr>
<td>Grade IC:</td>
<td>Strong recommendation; low quality evidence (LQE).</td>
<td>Observational studies or case series.</td>
<td>Strong recommend.</td>
</tr>
<tr>
<td>Grade 2A:</td>
<td>Weak recommendation; HQE</td>
<td>RCTs w/o limitations</td>
<td>Weak recommend.</td>
</tr>
<tr>
<td>Grade 2B:</td>
<td>Weak recommendation; MQE</td>
<td>RCTs w/limitations</td>
<td>Weak recommend.</td>
</tr>
<tr>
<td>Grade 2C:</td>
<td>Weak recommendation; LQE (or very LQE)</td>
<td>Observational studies or case series.</td>
<td>Very weak recommend.</td>
</tr>
</tbody>
</table>
Indications for Therapeutic Apheresis

**ASFA 2016 Categories**

- **Category I:** Disorders for which apheresis is accepted as a first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment (*TPE in GBS; TPE in myasthenia gravis*).
- **Category II:** Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment (*TPE in relapsing, remitting MS*).
- **Category III:** Optimum role of apheresis therapy is not established. Decision making should be individualized (*TPE or ECP in nephrogenic systemic fibrosis*).
- **Category 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 (*TPE in SLE nephritis; TPE in gemcitabine-associated TMA*).

### ASFA TA Treatment Guidelines

(ASFA 2016 Categories)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Category</th>
<th>Rec. Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANDAS; Sydenham’s Chorea:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PANDAS (TPE)</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>• Sydenham’s Chorea (TPE)</td>
<td>III</td>
<td>2B</td>
</tr>
<tr>
<td>Bilateral Diffuse Uveal Melanocytic Proliferation</td>
<td>III</td>
<td>? 2C</td>
</tr>
<tr>
<td>Autoimmune Retinopathy</td>
<td>III</td>
<td>? 2C</td>
</tr>
</tbody>
</table>

| ANCA-Associated RPGN:                        |          |            |
| • Dialysis dependence (TPE)                 | I        | 1A         |
| • DAH (TPE)                                 | I        | 1C         |
| • Dialysis independence (TPE)               | III      | 2C         |

Burchi E, Pallanti S. Prim Care Companion CNS Disord 2018; 20: pii: 17r02232 (systematic review of efficacy of antibiotics in PANDAS, PANS, or new-onset pediatric OCD).

Barzman DH et al. Case Rep Care Companion CNS Disord 2018; 20: pii: 17r02232 (systematic review of efficacy of antibiotics in PANDAS, PANS, or new-onset pediatric OCD).

Nave AH et al. BMC Neurol 2018; 18: 60 (PANDAS pt w/dramatic response to TPE)


Orefici G et al. In Streptococcus Pyogenes (Ferretti JJ eds) 2016 (basic biology of PANDAS)


• Epidemiology/description of disease:
  - Incidence: PANDAS: unknown; Sydenham’s Chorea (SC): 10-50% of ARF pts
  - PANDAS (first described in 50 children in 19981): 1) presence of OCD and/or tic disorder; 2) prepubertal onset; 3) abrupt onset or exacerbation of sxs with episodic (relapsing-remitting) course; 4) temporal assoc. of sxs with GABHS infx, 5) association with neurological abnormalities, including choreiform movements.
  - Clinical manifestations of PANDAS: 1) acute, abrupt onset; 2) co-morbid neurological sxs: mood liability, ADHD, separation anxiety, enuresis, tactile/sensory defensiveness, and catatonia; 3) severe sxs often last several weeks to months (or longer), then gradually subside; 4) peak age of onset: 6-7 years; 5) male:female = 3:1.

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections)

- **SC** (neuropsychiatric manifestation of Acute Rheumatic Fever (ARF)): 1) clinical sx's: emotional lability, hypotonia, chorea; 2) self-limiting, resolves in 6-18 months; 3) 30-40% recur rate; 4) peak age of onset: 8-9 years; 5) female:male = 2:1.

- **Laboratory Tests** (for both dxs): 1) evidence of GABHS infx (+throat cx +/- antistreptolysin O (ASO) ab titer) supports diagnosis; 2) ↑ levels of anti-neuronal and/or anti-basal ganglia abs; 3) brain MRI: striatal enlargement in basal ganglia.

- **Current management/treatment** (of PANDAS):
  - **Initial Tx:** 1) cognitive behavioral therapy and/or anti-obsessional medication; 2) prompt antibiotic tx in pts with tonsillo-pharyngitis and +GABHS throat culture.
  
  - In RCT of 23 pts, Snider et al\(^1\) showed that PCN & azithromycin prophylaxis effective in decreasing strep infxs and sx exacerbation in pts with PANDAS. Tonsillectomy may be effective prophylactic tx option (if indicated)\(^2\).
  
  - In severe cases (PANDAS or SC): 1) IVIG (1 gm/kg/day x 2 days) or 2) TPE found to be effective in decreasing symptom severity or shortening the course\(^3-6\).


Rationale for TPE:

- **Theory:** possible role of anti-neuronal abs in pathogenesis of PANDAS & SC

- In RCT of 29 pts w/PANDAS (comparing IVIG vs TPE tx) (Perlmutter et al\(^6\)): mean improvement (45% w/IVIG) vs (58% w/TPE) in OCD sx's over 1 year (including anxiety, tic sx's, & overall functioning).

- In retrospective case series (Latimer et al\(^4\)): 78% reduction in symptom severity was seen during follow-up (6 months to 5.4 years) in 35 pts with severe PANDAS (tx'd with 3 TPE txs (1.5 PVs) over 3-6 days).

- In retrospective obs. study (Calaprice et al\(^7\)): of 698 pts with self-reported PANS or PANDAS, 15/25 pts treated with TPE tx showed response (6/15 showed durable response).

- In RCT of 18 pts with SC (Garvey et al\(^1\)): mean chorea severity scores decreased by 72% (w/IVIG), 50% (w/TPE), and 29% (w/corticosteroids) (p<0.05)

- Typical TPE course: 3-6 TPE txs (over 1-2 wks); 5% albumin (1-1.5 PV)

Treatment of PANDAS and PANS: a systematic review

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2 University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
3 Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

Table 1
Diagnostic criteria for PANDAS, PANS and CANE.

<table>
<thead>
<tr>
<th>PANDAS (Swedo et al., 1998)</th>
<th>PANS (Swedo et al., 2013)</th>
<th>CANE (Sigrán et al., 2012)</th>
<th>PITTAD (Olson et al., 1995)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OOP and/or tic syndrome (1044.1)</td>
<td>Acute inflammatory or ischemic stroke or transient ischemic attack (433.21)</td>
<td>Acute inflammatory or ischemic stroke or transient ischemic attack (433.21)</td>
<td>Acute inflammatory or ischemic stroke or transient ischemic attack (433.21)</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>Neurological symptoms</td>
<td>Neurological symptoms</td>
<td>Neurological symptoms</td>
</tr>
<tr>
<td>Abnormal dystonia or apraxia</td>
<td>Abnormal dystonia or apraxia</td>
<td>Abnormal dystonia or apraxia</td>
<td>Abnormal dystonia or apraxia</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>Abnormal gait</td>
<td>Abnormal gait</td>
<td>Abnormal gait</td>
</tr>
<tr>
<td>Abnormal movements</td>
<td>Abnormal movements</td>
<td>Abnormal movements</td>
<td>Abnormal movements</td>
</tr>
</tbody>
</table>

PANDAS: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.
PANS: Pediatric acute-onset neuropsychiatric syndrome.
CANE: Childhood acute neuropsychiatric syndrome.
PITTAD: Pediatric infection-triggered autoimmune neuropsychiatric disorders.

Fig. 1. Flowchart of literature search and inclusion of articles. The Boxset follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Total 12 studies (4 RCTs, 5 large observational studies, total of 1,227 pts)

65 case reports

Reported on:

- Study design & study population
- Intervention (antibiotics, TPE, IVIG, CBT, corticosteroids, NSAIDS, etc.)
- Outcome measures (neuropsychiatric symptom severity scales used)
- Results (subject vs controls): with 1-month, 6-week, & 1-year follow-up
- Analysis of risk of bias (selection, performance, detection, reporting bias, etc)
- Support for judgement (no study reported blinding of any treatment)

Conclusion: no definitive evidence to recommend antibiotics, immunomodulation, CBT, or SSRIs, yet in many cases, authors noted significant improvement after tx with antibiotics, TPE, and IVIG, and decrease in flare duration with corticosteroids or NSAIDS.

Excellent review of basic biology of PANS & PANDAS:

- PANDAS (subtype of PANS)
- Not all PANS cases have underlying strep infxs
- β-lactam antibiotics can be successful (proposed to be neuroprotective)
- Higher antistreptococcal antibody (ab) titers correlate with higher OCD severity
- Anti-neuronal antibodies react with brain antigens (ags), including dopamine receptors, lysoganglioside, and tubulin, and may activate CaM KII in human neuronal cells (Kirvan et al, 2003).
- Evidence strongly suggests human brain autoabs induced by *streptococcus pyogenes* infxs effectively target dopamine receptors (Cox et al, 2013).
- Animal models immunized with *S. pyogenes* ag develop obsessive behaviors & movement disorders, along with abs that react with dopamine receptors and signal CaM KII (Brimberg et al, 2012; Lotan et al, 2014).

CaM KII = calcium calmodulin-dependent protein kinase II
Potential pathogenic mechanism of anti-neuronal signaling in PANDAS:

- anti-neuronal ab (IgG) binds to receptor → triggers signaling cascade of CaMKII, tyrosine kinase, & dopamine release → leading to excess dopamine → manifestations of chorea.

CaMKII = calcium calmodulin-dependent protein kinase II

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Prospective cohort study:

- 311 study pts (4-27 yrs; 66% male) with knowledge of GABHS infx.
- 16 healthy control pts (5-14 yrs; 81% male)
- Anti-neuronal IgG ab titers of lysoganglioside, tubulin, and dopamine receptors (D1R, D2R), and ab-mediated signaling of CaM KII activity obtained.

Results:

- 71% (222/311) pts had GABHS infx (assoc. with tics and/or OCD status) (p=0.0087).
- Sera from pts with tics and/or OCD (n=261): had higher serum IgG abs to D1R (p<0.0001) and lysoganglioside (p=0.0001), and higher CaM KII activity (p<0.0001) than healthy controls.

CaM KII = calcium calmodulin-dependent protein kinase II

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**Antineuronal Antibodies in a Heterogeneous Group of Youth and Young Adults with Tics and Obsessive-Compulsive Disorder**


- Study suggests significant correlation of streptococcal-associated tics and/or OCD behavior with elevated anti-D1R and anti-lysoganglioside anti-neuronal abs concomitant with higher activation of CaM KII in human neuronal cells.

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**Bilateral Diffuse Uveal Melanocytic Proliferation (BDUMP) Autoimmune Retinopathy (AIR)**


Alasii T et al. Retin Cases Brief Rep 2017; 11: 71-74 (case w/metastatic ovarian CA, tx w/TPE)


Comlekoglu DU et al. Curr Opin Ophthalmol 2013; 24: 598-605 (excellent review of AIR)

Miles S et al 2012; Retina: 32; 1959-66 (demonstrated factor found in IgG fraction of serum of pts with BDUMP causes proliferation of cultured melanocytes; defined sCMEP factor).

Brathwaite T et al. Ophthalmologica 2012; 228: 131-42 (excellent review of AIR)


**BDUMP (Bilateral Diffuse Uveal Melanocytic Proliferation)**

**Epidemiology/description of disease:**
- **Incidence:** BDUMP: unknown; first described in 1966 (Machemer R)
- **BDUMP:**
- associated with visceral carcinomas (female gynecologic tract, lung, and pancreas most prevalent).
- presents with progressive loss of vision characterized by 5 cardinal ophthalmologic signs (incl. diffuse thickening of uveal tract w/focal tumors, exudative retinal detachment, and rapid cataract formation).
- without tx, pts develop near total blindness (or succumb to malignancy)
- pathology: hyperplastic proliferation of spindled melanocytes (benign paraneoplastic phenomena, usually not malignant uveal tract melanomas).
- many pts: also develop these lesions in skin, mucous membranes → suggest presence of systemic growth factor or immunoglobulin (produced in response to the tumor) inducing hyperplasia of melanocytes → such growth factor could be removed by TPE tx.
- presence of melanocyte-specific growth factor in IgG enriched serum from pts → “cultured melanocyte elongation & proliferation (CMEP) factor”


**Autoimmune Retinopathy (CAR; MAR; npAIR)**

- **Epidemiology/description of disease:**
  - **Incidence:** AIR: unknown
  - **Autoimmune Retinopathy:**
  - 3 syndromes: cancer-assoc retinopathy (CAR), melanoma-assoc retinopathy (MAR), and nonparaneoplastic autoimmune retinopathy (npAIR).
  - caused (in theory) by production of autoabs directed toward retinal ags that elicit apoptosis within cellular constituents of the retina → visual dysfunction.
  - **CAR:** presents bilaterally, involves dysfunction of both rods and cones (confirmed by abnormal electoretinography, ERG). Visual sx often present prior to diagnosis of malignancy. Disease is progressive and without tx, pts develop total blindness.
  - most common assoc cancer: small cell cancer of lung → breast & gynecological cancers.
  - most common autoabs are directed against retina-associated ags including recoverin, alpha-enolase, transducin, and carbonic anhydrase II.
  - **Treatment:** high dose oral CS, azathioprine, cyclosporine; IVIG & TPE tx (although no established treatment protocol exists for CAR).

Excellent review: evaluating the role of apheresis in the treatment of ophthalmologic diseases of the eye, such as: age-related macular degeneration, BDUMP, autoimmune (CAR, MAR) retinopathy, atopic keratoconjunctivitis, and endocrine ophthalmopathy.

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**BDUMP tx with TPE:**
- 7-12 txs/course; QOD (MWF) txs; 5% albumin (1 PV); visual acuity often improves/ stabilizes after 1 course; disease eventually progresses after TPE treatment is halted.

**CAR tx with TPE:**
- 3 txs/course (multiple course txs have been used); QOD txs; 5% albumin (or not specified) (1 PV); TPE tx reinitiated upon disease progression; TPE tx often combined with corticosteroid tx and chemotherapy.

**Endocrine Ophthalmopathy tx with TPE:**
- 6-10 txs/course; TPE (or filtration plasmapheresis); 2.4 L (~1 PV); 5% albumin (or albumin with FFP); 2-3X/week; tx continues for set amount of procedures; TPE tx in conjunction with standard immunosuppressive medications.
2 cases of BDUMP:

- 2 female pts (71 y.o.) w/advanced gynecologic tract carcinoma treated with TPE (7 txs over 16 days, 1 PV) → with stabilization of vision loss (9-13 mos. post-TPE tx, both pts reported no worsening of vision).
- 72 y.o. male pt w/advanced bronchogenic carcinoma treated with TPE (3 weekly txs) → improvement of visual acuity, resolution of serous retinal detachment → cont. weekly maintenance TPE tx → visual acuity stable after 7 mos.

In this study (Miles et al), cultured melanocytes were incubated with plasma from:

- 1) pts w/confirmed BDUMP
- 2) pts with cancer w/o evidence of paraneoplastic syndrome
- 3) pts with cancer and neurologic (non-BDUMP) paraneoplastic disease

Evaluation of cultured melanocytes (after incubation) showed increased cell numbers and disordered growth of melanocytes only in cultures incubated with plasma removed from BDUMP pts during TPE (p<0.001).

These results confirm presence of melanocytic-specific growth factor subsequently found in the IgG enriched fraction of serum from BDUMP pts → coined “cultured melanocytic elongation and proliferation (CMEP) factor”.

A factor found in the IgG fraction of serum of patients with paraneoplastic bilateral diffuse uveal melanocytic proliferation causes proliferation of cultured human melanocytes.

Fig. 1. Normal human melanocytes (HN-90) grown in the presence of various patient serum samples. Melanocytic proliferation after 7 days (A) and 6 days (B) of treatment with various patient serum samples. Cells treated with M16U and M16K (K ethanol) demonstrated statistically significant increase in proliferation compared with both untreated cells and cells treated with serum representing other oncogenic disease states (P < 0.001). Graph is representative of two biological samples each conducted in triplicate.

Numerous retinal antigens associated with autoimmune retinopathies.

Table 1. Retinal antigens commonly associated with autoimmune retinopathies.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>autoantigen Identified</th>
<th>autoantigen Identified</th>
<th>autoantigen Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>Retina-specific antigen</td>
<td>Retina-specific antigen</td>
<td>Retina-specific antigen</td>
</tr>
<tr>
<td>Macula</td>
<td>Macula-specific antigen</td>
<td>Macula-specific antigen</td>
<td>Macula-specific antigen</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Optic nerve-specific antigen</td>
<td>Optic nerve-specific antigen</td>
<td>Optic nerve-specific antigen</td>
</tr>
</tbody>
</table>

Numerous retinal antigens associated with autoimmune retinopathies.

ANCA-Associated Vasculitis


**Treatment Allocation Protocol (PEXIVAS):**
(2-by-2 factorial, RCT):
- standard tx with cyclophosphamide or rituximab
- randomized to TPE or no TPE
- randomized to standard or reduced-dose glucocorticoids

**Table 1 Glucocorticoid dosing in the standard and reduced-dose groups of PEXIVAS**

<table>
<thead>
<tr>
<th>Week</th>
<th>Standard Dosing</th>
<th>Reduced-Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mg/kg</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>50 mg/kg</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>50 mg/kg</td>
<td>40 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>30 mg/kg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>5</td>
<td>25 mg/kg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>6</td>
<td>20 mg/kg</td>
<td>10 mg/kg</td>
</tr>
</tbody>
</table>

**ABSTRACT NUMBER: 2786**

**The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis**

- **PEXIVAS**: 2-by-2, factorial, RCT: to evaluate TPE and 2 different regimens of oral glucocorticoids in pts with new or relapsing severe ANCA-assoc. vasculitis (including DAH and/or GN (GFR<50 ml/min).
- Pts randomized to TPE (7 ttxs ?QOD) or no TPE
- Pts then randomized to standard or reduced-dose (<60% standard regime by 6 months) oral glucocorticoids (GC)
- All pts received either cyclophosphamide or rituximab
- Pts followed up to 7 years: primary composite outcome: death from any cause or ESRD.
The Effects of Plasma Exchange and Reduced-Dose Glucocorticoids during Remission-Induction for Treatment of Severe ANCA-Associated Vasculitis

Michael Varen1, Peter A. Marcks1 and David Jayne3, Rheumatology, McMaster University, Hamilton, ON, Canada; 2Division of Rheumatology, Division of Rheumatology, University of Pennsylvania, Philadephia, PA, Department of Medicine, University of Cambridge, Cambridge, United Kingdom

Results:
- 704 participants (from 98 sites in 15 countries): 397 (56%) men; 289 (41%) PR3-ANCA; 209 (59%) MPO-ANCA; 691 (98%) w/renal involvement; 191 (27%) w/DAH; 595 (85%) received cyclophosphamide; 109 (15%) received rituximab.
- 1º outcome occurred: 28% (TPE group) vs 31% (no TPE group) (p=0.27)
- 1º outcome occurred: 28% (reduced GC group) vs 26% (standard GC group) (absolute risk difference 2.3%; 90% CI (-3.4% to 8.0%).
- Serious infxs (first year): occurred less often in reduced GC group vs standard GC group (incident rate ratio 0.70 (95% CI 0.52 to 0.94; p=0.02).

Conclusions:
- TPE does not reduce the risk of ESRD or death in pts with ANCA-assoc vasculitis.
- Compared to standard dose, reduced GC did not increase risk of ESRD or death, and resulted in fewer serious infections.

Apheresis Literature Review
Update: changes & trends in Apheresis Opportunities

- Evolving & Developing Fields:
  - Immuno-oncology (“Immune surveillance” protocols: WBC cell therapies (CAR-T cell, etc); checkpoint inhibition, etc).
  - Neuro-inflammation
  - Transplant immunology (“Immune tolerance” protocols; persistent mixed chimerism).
  - Cardio-oncology

- Emerging Diseases:
  - NMDA-R encephalitis (autoimmune encephalitidies) – first cases ~2007
  - Nephrogenic Systemic Fibrosis – first cases ~2000
  - Thrombotic Microangiopathy (refining of acq. TTP, HUS, aHUS, & other TMAs)

- New Diagnostics:
  - rTAT aHUS (NextGen) genetic panels; new assays for HIT; other

- New Medications:
  - New monoclonal abs: acq. TTP (caplacizumab); refractory MG (eculizumab)
  - Other new medications for acq. TTP (bortezomib, rADAMTS13, etc)
Heparin-Induced Thrombocytopenia
(Recent improvement in lab assays/testing for HIT)


Summary

• The use of adjunctive plasma exchange (along with antibiotic therapy and other immunosuppressive agents) in the treatment of PANDAS appears to have a role, but data is still evolving.

• The role of plasma exchange in the treatment of autoimmune retinopathies, especially bilateral diffuse uveal melanocytic proliferation (B-DUMP), has potential, but has not yet been clarified, and the standard of care probably varies significantly as a result of our lack of knowledge.

• The preliminary results of the PEXIVAS trial in ANCA-associated vasculitis may change the current standard of care with respect to the use of TPE therapy, but peer-reviewed publication is still pending.

• And finally, evolving new fields of medicine, new diagnostics, new medications (to better treat current diseases), and emerging diseases offer significant challenges and opportunities in apheresis medicine.
Thank you for your attention

CPMC: New Van Ness Campus, San Francisco
Plasma exchange in thrombotic microangiopathies (TMA) other than thrombotic thrombocytopenic purpura (TTP)

Jeffrey L. Winters, MD

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Disclosures

• Financial
  • None

• Off-label drug use
  • None
Learning Objectives

• List the characteristics of thrombotic microangiopathies (TMAs) and those disorders considered to be TMAs.
• Describe the pathophysiology of common TMAs.
• Describe the role of therapeutic plasma exchange (TPE) in the treatment of these TMAs.

Thrombotic Microangiopathies

• Diverse group of disorders
• Characterized by microvascular thrombosis
• May be acquired or inherited
• Historically defined as:
  • Thrombotic thrombocytopenic purpura
  • Idiopathic
  • Secondary
  • Hemolytic uremic syndrome
    • Typical or diarrhea associated
    • Atypical

Table 1. Laboratory and clinical features of TMA

<table>
<thead>
<tr>
<th>Laboratory features</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microangiopathic hemolytic anemia</td>
<td>Evidence of end-organ damage/sclerosis</td>
</tr>
<tr>
<td>Anemia</td>
<td>Elevated lactate dehydrogenase levels</td>
</tr>
<tr>
<td>Fragmented red blood cells (schistocytes)</td>
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<tr>
<td>Decreased haptoglobin</td>
<td>Brain, neurologic dysfunction</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Kidneys, elevated creatinine/renal failure</td>
</tr>
<tr>
<td>Evidence of end-organ damage/sclerosis</td>
<td>Fever</td>
</tr>
</tbody>
</table>
Thrombotic Thrombocytopenic Purpura and Therapeutic Plasma Exchange (TPE)

• Characterized by TMA findings

• Results from an inherited or acquired deficiency in ADAMTS13
  • Inherited mutations in ADAMTS13
  • Development of inhibitory autoantibodies directed toward ADAMTS13

• Universally fatal until application of exchange transfusions and plasma infusion

Randomized controlled trial of TPE vs plasma infusion by Rock et al – 1991

• Superior survival with TPE

• TPE subsequently applied to all TMA’s

Table 2. Characteristics of TPE Procedures in TMA

| Frequency: Daily |
| Duration: Until resolution of neurologic symptoms, lactate dehydrogenase levels approaching normal, and platelet count ≥ 150,000/µL for 2 consecutive days. This may be followed by discontinuing therapy or weaning. See Discussion. |
| Volume exchanged: 1 to 1.5 plasma volumes. See Discussion. |
| Replacement fluid: Plasmas (e.g., fresh frozen plasma, thawed plasma, frozen plasma 24 hours) with the potential exception of TMA-S pneumoniae associated, in which albumin is recommended by some authors. See Discussion. |


Therapeutic Plasma Exchange

- Mechanisms of action of TPE
  - Removal of pathologic substance
  - Replacement of missing substance
  - Sensitization of antibody producing cells
  - Improvement in macrophage/monocyte function
  - Removal of cytokines and adhesion molecules
  - Alterations in immune system function


American Society for Apheresis Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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</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.</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.</td>
</tr>
<tr>
<td>III</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</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.</td>
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</table>

**TMA – Shiga toxin mediated**

- 0.5 to 2/100,000
- Predominantly seen in children <5 y.o.
- Presents with bloody diarrhea, abdominal pain, and fever
- TMA with renal failure within 2 to 10 days after symptom onset
  - 1/3 require dialysis
  - 1/3 ESRD, HTN, or neurologic symptoms
  - Death - 1 to 5%

**TMA – Shiga toxin mediated**

- Direct endothelial injury by Shiga toxin
  - Prothrombotic effects
  - Release of ultra-large von Willebrand multimers
- Most common causative organisms
  - United States - *Escherichia coli* O157:H7
  - Developing countries – *Shigella dysenteriae* type I
TMA – Shiga toxin mediated

- Direct cytotoxic effect of toxin on endothelium
  - Removal of toxin?
  - Removal of ultra-large vWF?
  - Removal of cytokines?
- Retrospective case-control study of 2011 European outbreak reported no benefit for steroids, TPE, and eculizumab.*
- ASFA Category IV indication for TPE in the absence of severe neurologic symptoms.
- ASFA Category III indication for TPE in the presence of severe neurologic symptoms.


TMA – Complement Mediated

- 3.3/100,000 ≥18 y.o.
- 7/100,000 <18 y.o.
- May present as:
  - Catastrophic TMA with renal injury
  - Chronic progressive renal disease with crises: AKI, stroke, retinal vein thrombosis, liver and pancreas injury, peripheral thrombosis, pulmonary hemorrhage, bloody diarrhea
- 73% develop ESRD within 5 years with up to 100% recurrence in transplanted kidneys
TMA – Complement Mediated

- Dysregulation of complement system due to:
  - Mutations resulting in loss of function of regulatory proteins – Factor H, MCP, Factor I – 60%
  - Mutations resulting in gain in function of Factor B and C3
  - Development of autoantibodies to Factor H – 6 to 10%
- Result is complement mediated endothelial damage
- Testing
  - Screening with CH50 and AH50 – low AH50
  - Molecular testing for mutations - >400 mutations identified

TMA – Complement Mediated

- TPE results in:
  - Removal of aberrant complement regulatory proteins or abnormally activated complement factors
  - Removal of autoantibodies to Factor H
  - Replacement of complement regulatory proteins and factors.
- Response varies depending upon mutation
  - 55-80% - Factor H and C3 mutations or Factor H autoantibodies
  - 25% - Factor I mutations
  - Does not correct underlying defect in MCP mutations but 90% resolve without TPE
- Discontinue TPE if patient is refractory or dependent and treat with eculizumab
- ASFA Category III indication for TPE for complement regulatory protein or factor mutations
- ASFA Category I indication for TPE for Factor H auto-antibodies

TMA – Hematopoietic Stem Cell Transplantation Associated

• Unclear incidence due to lack of uniform diagnostic criteria
  • 12.7% of adult allogeneic HSCT
  • 39% of pediatric allogeneic HSCT
• TMA symptoms within 6 months of HSCT
  • Hypertension and proteinuria may proceed thrombocytopenia and MAHA
• 75% mortality within 3 months of diagnosis

TMA – Hematopoietic Stem Cell Transplantation Associated

• Pathophysiology – endothelial damage due to infection, chemotherapy, radiation therapy, and GVHD
• Study of 6 affected pediatric patients identified high prevalence of Factor H mutations (83%) versus general population or donors (33%)

TMA – Hematopoietic Stem Cell Transplantation Associated

• Reported TPE response rates vary:
  • 1991 to 2003 – 0 to 80%
  • 2003 to 2011 – 27 to 80%

• 2005 Blood and Marrow Transplant Clinical Trials Network Toxicity Committee consensus statement recommended TPE not be considered standard of care

• ASFA Category III indication for TPE based upon identification of Factor H mutations in some patients.


TMA – Drug Associated

• 78 medications have been associated with TMA
  • 22 definitive evidence
  • 9 responsible for 76% of reports

• Variable time between exposure and onset of TMA
  • Ticlopidine - less than 2 weeks
  • Mitomycin C - up to 4 months

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pathophysiology</th>
<th>Reported responses to TPE</th>
<th>ASFA category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>ADAMTS13 antibodies</td>
<td>87%</td>
<td>I</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Endothelial damage</td>
<td>50%</td>
<td>II</td>
</tr>
<tr>
<td>Calcium channel inhibitors</td>
<td>Endothelial damage</td>
<td>NA</td>
<td>II</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Endothelial damage</td>
<td>18%</td>
<td>N</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>Endothelial damage</td>
<td>90%</td>
<td>NC</td>
</tr>
<tr>
<td>Quinine</td>
<td>Drug-dependent antibodies</td>
<td>NA</td>
<td>N</td>
</tr>
<tr>
<td>VEGF inhibitors</td>
<td>Renal podocyte injury</td>
<td>NA</td>
<td>NC</td>
</tr>
</tbody>
</table>

N: not available; VEGF: vascular endothelial growth factor. Other abbreviations are explained in Table 3.

TMA – Drug Associated

- Variable pathophysiology
  - ADAMTS13 autoantibodies
  - Drug dependent antibodies
  - Direct endothelial injury

- Response to TPE variable, possibly dependent on mechanism of TMA
  - Ticlopidine – ADAMTS13 autoantibody – 87% survival with TPE
  - Clopidogrel – direct endothelial injury – 50% survival with TPE

TMA – Malignancy Associated

- Possibly related to therapy or malignancy itself
- Criteria for diagnosis
  - Cancer diagnosis
  - DAT negative MAHA
  - Thrombocytopenia
  - Decreased haptoglobin
  - Indirect hyperbilirubinemia

- Other findings according to Elliott et al:
  - elevated D-dimers
  - ADAMTS13 activity >10%
  - median creatinine 1.2 mg/dL
  - bone pain
  - respiratory symptoms
  - Anorexia
  - weight loss

TMA – Malignancy Associated

- Most commonly associated malignancies:
  - Stomach
  - Breast
  - Pancreas
  - Prostate
  - Lung
- Pathophysiology – unclear but mutations in Factor H have been reported.
- Role and efficacy of TPE is uncertain
  - May delay treatment of underlying malignancy
- ASFA has not categorized the role of TPE

TMA – *S. pneumoniae* Associated

- Children < 2 y.o. with *S. pneumoniae* pneumonia or meningitis.
  - 0.4 to 0.6% of invasive infections
- Pathophysiology – direct endothelial injury, RBC lysis, and thrombocytopenia through complement activation
  - *S. pneumoniae* produced neuraminidase cleaves sialic acid exposing the Thomsen-Friedenreich antigen
  - Naturally occurring anti-TF fixes complement resulting in injury to endothelium and lysis of RBC
  - Sialic acid removal also disrupts Factor-H binding sites leading to complement dysregulation
**TMA – S pneumoniae Associated**

- Rationale for the use of TPE is removal of neuraminidase and anti-TF.
  - Usual therapy is supportive care
- Suggested that albumin or “low titer anti-TF” plasma used as replacement
  - Series have not reported worsening with exposure to plasma or unwashed red blood cells
  - Crookston et al found red cell removal in the absence of anti-TF
- ASFA Category III indication for TPE


**TMA – Coagulation Mediated**

- Due to mutations in diacylglycerol kinase-ε (DGKE), plasminogen, or thrombomodulin (THBD).
- Presents in the first year of life
- Treated with plasma infusion
- Case series of 6 patients found no benefit of TPE compared to plasma infusion.
- ASFA Category III indication for TPE
HELLP Syndrome

- Obstetrical syndrome characterized by:
  - Hemolysis
  - Elevated Liver enzymes
  - Low Platelets
- Occurs after 20 weeks gestation with associated hypertension
- May also present with:
  - Proteinuria
  - Abdominal pain
  - Headache
  - Visual changes
- Complicated by hepatic rupture, DIC, and multiorgan failure

HELLP Syndrome

- Pathophysiology – Uncertain but evidence suggests mutations in complement regulatory proteins
- Treatment – immediate delivery with possible delays for 24 to 48 hours to allow steroid administration
- TPE is used if there is no improvement within 72 hours of delivery
- TPE is NOT used antepartum
  - Delay in delivery associated with maternal and fetal mortality
- ASFA Category III indication for TPE postpartum
- ASFA Category IV indication for TPE antepartum


Conclusions

• Application of TPE based upon its efficacy in TTP
• No randomized controlled trials and only small case series or case reports for the use of TPE in these disorders
• Variable pathophysiology for the disorders, some of which should NOT be amenable to TPE (direct endothelial injury)
• Evidence of mutations complement component or complement regulatory protein mutations in a subset of patients:
  • TMA – complement associated
  • TMA – hematopoietic stem cell transplant associated
  • TMA – malignancy associated
  • TMA – S pneumoniae associated
  • HELLP syndrome

Questions?
Plasma Exchange 2019: Neurologic Disease Indications

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Disclosure

Relevant Financial Relationships
None

Off Label Usage
None
Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

- **Incidence**
  - 1-2/100,000

- **Demographics**
  - Male predominance
  - Increasing incidence with age (1/100,000 <30 versus 4/100,000 >75)

- **Signs and Symptoms**
  - Symmetrical muscle weakness and paresthesia that spread proximally
  - Progresses over 12 hours to 28 days
  - May involve respiratory and oropharyngeal muscles
    - 10 to 23% require ventilator assistance
  - Autonomic dysfunction may be present

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

- **Associations**
  - 75% give history of infectious illness in the weeks prior to onset
  - Influenza vaccine

- **Pathophysiology**
  - Demyelination of peripheral neurons due to autoantibodies toward GM1, GD1a, GT1a, and GQ1b
  - Evidence of axonal damage in some patients involving motor and sensory neurons (AMSAN) or only motor neurons (AMAN)
Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

- Treatment
  - Spontaneous recovery
    - 66-75% residual deficits
  - Supportive care
  - IVIG
  - Plasma exchange

- Response to plasma exchange
  - Cochrane database found 6 eligible trials enrolling 649 patients
    - Shorter time to recovery of walking, smaller percentage requiring artificial ventilation, shorter duration of ventilation, better muscle strength at 1 year, fewer severe deficits at 1 year
    - “First and only treatment proven superior to supportive care”
  - Second Cochrane database study found equivalence between TPE and IVIG though IVIG course more likely to be completed
  - Economic analysis found the costs of IVIG therapy to be twice that of TPE
Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

- Response to plasma exchange
  - Axonal involvement has been reported to be more responsive to TPE than IVIG
  - Retrospective studies suggest that TPE in the setting of failure to respond to IVIG has limited benefit

- Course of TPE therapy
  - 1 to 1.5 plasma volume exchanges with albumin as replacement
  - Mild AIDP – 2 TPE
  - Moderate to severe AIDP – 4 TPE
  - Best benefit of TPE if started within 7 days of symptom onset

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

- AIDP
  - ASFA Category - I
  - ASFA Recommendation Grade – 1A

- AIDP after failure of IVIG
  - ASFA Category - III
  - ASFA Recommendation Grade – 2C

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<th>RCT</th>
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<tbody>
<tr>
<td>AIDP</td>
<td>19(1770)</td>
<td>0</td>
<td>9(369)</td>
<td>NA</td>
</tr>
<tr>
<td>After IVIG</td>
<td>0</td>
<td>0</td>
<td>1(46)</td>
<td>NA</td>
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</table>

- AAN – Established effective, Class I
Chronic Inflammatory Demyelinating Polyneuropathy

- Incidence
  - 1-2/100,000

- Demographics
  - Male predominance

- Signs and Symptoms
  - Symmetrical proximal and distal muscle weakness with or without numbness that progresses and relapses over two or more months
  - Pain in 42% of patients
  - NCV demonstrates slow conduction, conduction block, and prolonged latencies in more than 1 nerve
  - CSF demonstrates protein >55 mg/dL with cell count <10/µL

Chronic Inflammatory Demyelinating Polyneuropathy

- Associations
  - Hepatitis, inflammatory bowel disease, Hodgkin disease, connective tissue diseases, HIV, diabetes mellitus

- Pathophysiology
  - Inflammatory demyelination of peripheral nerves with secondary axonal degeneration
  - Both humoral and cell-mediated immune responses have been documented
  - Antibodies to myelin components GM1, P0, and MAG have been identified in some patients
Chronic Inflammatory Demyelinating Polyneuropathy

• Treatment
  • Primary – corticosteroids, plasma exchange, IVIG
  • Secondary – rituximab, cyclosporine, interferon, azathioprine, and cyclophosphamide

• Response to plasma exchange
  • Dyck – 29 patients randomized to shame versus TPE twice weekly for three weeks. Significantly better NCV testing and clinical improvement.
  • Hahn – 18 patients randomized to shame versus 10 TPE over 5 weeks followed by washout period and opposite therapy. 80% with substantial improvement. 66% relapsed within 1 to 2 weeks but responded to additional TPE.
  • Dyck – 20 patients randomized to IVIG versus TPE. Both with significant improvement but no difference between the two.

Chronic Inflammatory Demyelinating Polyneuropathy

• Course of TPE therapy
  • 1 to 1.5 plasma volume exchanges with albumin as replacement
  • 3 TPE per week for 2 weeks followed by 2 per week for 4 weeks.
  • Relapse occurs within 2 weeks of cessation but responds to additional TPE.
  • With relapse, maintenance therapy necessary with frequency adjusted to control symptoms.
Chronic Inflammatory Demyelinating Polyneuropathy

- ASFA Category - I
- ASFA Recommendation Grade – 1B

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<tr>
<td>3(67)</td>
<td>0</td>
<td>32(1021)</td>
<td>31(32)</td>
</tr>
</tbody>
</table>

- AAN – Established effective, Class I

Myasthenia Gravis

- Incidence
  - 1/100,000

- Demographics
  - Most prevalent in 20 to 40 year-old women

- Signs and Symptoms
  - Weakness and fatigability with repetitive physical activity that improves with rest
  - Ptosis, diplopia, facial weakness, bulbar weakness, and limb weakness
  - Bulbar weakness associated with dysphagia, aspiration, and respiratory failure
Myasthenia Gravis

• Associations
  • Thymic pathology in 75%
    • 85% thymic hyperplasia
    • 15% tumor, predominantly thymoma

• Pathophysiology
  • Autoantibodies directed against acetylcholine receptors (AChR) or muscle-specific receptor tyrosine kinase (MuSK) on the postsynaptic motor end plate results in decreased number of AChR and decreased action potentials on stimulation
  • 80 to 90% of patients have IgG1 or IgG3 antibodies to AChR
  • 40 to 70% of “seronegative” cases have IgG4 antibodies to MuSK
    • MuSK recruits AChR binding proteins leading to AChR clustering and neuromuscular junction formation

Myasthenia Gravis

• Treatment
  • Cholinesterase inhibitors – pyridostigmine and neostigmine
  • Thymectomy
  • Immunosuppressants – corticosteroids, azathioprine, cyclosporine, tacrolimus
  • IVIG
  • Plasma exchange

• Response to plasma exchange
  • 3 randomized controlled trials comparing TPE to IVIG have found equivalency
  • One comparison study of IVIG and TPE found IVIG to be more cost effective with a shorter length of hospital stay but patients in the study treated with TPE more likely to be on ventilator and have respiratory failure
  • Trials of routine TPE prior to thymectomy versus supportive care have shown equivalency
Myasthenia Gravis

• Course of TPE therapy
  • 1 to 1.5 plasma volume exchanges with albumin as replacement
  • 5 to 6 TPE daily or every-other-day
  • Mild exacerbations in stable patients can be treated with 2 to 3 TPE
  • Maintenance TPE at weekly intervals followed by weaning may be performed

Myasthenia Gravis

• MG moderate to severe
  • ASFA Category - I
  • ASFA Recommendation Grade – 1B

• MG pre-thymectomy
  • ASFA Category - I
  • ASFA Recommendation Grade – 1C

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<th>RCT</th>
<th>CT</th>
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<tbody>
<tr>
<td>Moderate - severe</td>
<td>8(279)</td>
<td>8(2837)</td>
<td>30(556)</td>
<td>NA</td>
</tr>
<tr>
<td>Pre-thymectomy</td>
<td>0</td>
<td>5(342)</td>
<td>2(51)</td>
<td>NA</td>
</tr>
</tbody>
</table>

• AAN
  • Crisis – Insufficient evidence, Class III
  • Preoperative preparation – Insufficient evidence, Class III
Multiple Sclerosis

• Incidence
  • 5-30/100,000

• Demographics
  • Female predominance
  • Most common in Caucasians of Northern European ancestry
  • More common in temperate climates
  • Genetic predisposition

• Signs and Symptoms
  • Variety of neurologic symptoms resulting from multifocal demyelination of the central nervous system
  • Include fatigue, visual problems, bladder/bowel dysfunction, sensory changes, emotional changes, weakness, balance difficulty, cognitive changes, etc.

Multiple Sclerosis

• Disease course
  • 80 to 85% relapsing and remitting
    • Acute focal or multifocal inflammatory demyelination
    • Development of symptoms over days to weeks
    • Symptoms plateau in 1 to 2 weeks
    • Gradual recovery within 3 months
      • May take up to 6 to 12 months
  • 15 to 20% primary progressive
    • Chronic demyelination, axonal loss, and gliosis
    • Progression of disability from onset with no or only minor remissions or plateaus
Multiple Sclerosis

• **Pathophysiology**
  - T-cells and B-cells penetrate blood-brain barrier with injury to myelin and axons
  - Both cell mediated immunity and humoral immunity involved

• **Treatment**
  - Methylprednisolone for acute exacerbations
  - Disease modifying agents for chronic therapy – IFN-β1a, IFN-β1b, glatiramer, mitoxantone, natalizumab, azathioprine, fingolimod, dalfampridine, rituximab
  - Response to plasma exchange
    - Acute CNS demyelination unresponsive to steroids – Blinded trials have demonstrated moderate to marked improvement in 42% of patients. Case series have reported improvement in 37 to 100% of treated patients
    - Primary progressive MS – Meta-analysis of 6 prospective trials found decreased odds of worsening at 12 and 24 months and increased odds of improvement at 6 and 12 months
Multiple Sclerosis

• Course of TPE therapy
  • Acute CNS demyelination unresponsive to steroids
    • 1 to 1.5 plasma volume exchanges with albumin as replacement
    • 5 to 7 TPE over 14 days
  • Primary progressive MS
    • 1 to 1.5 plasma volume exchanges with albumin as replacement
    • Weekly long-term therapy with tapering as tolerated

Multiple Sclerosis

• Acute CNS demyelination unresponsive to steroids
  • ASFA Category – II
  • ASFA Recommendation Grade – 1B

• Primary progressive
  • ASFA Category – III
  • ASFA Recommendation Grade – 2B

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<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
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</thead>
<tbody>
<tr>
<td>Acute CNS demyelination</td>
<td>3(306)</td>
<td>1(41)</td>
<td>10(169)</td>
<td>NA</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>7(285)</td>
<td>0</td>
<td>10(165)</td>
<td>NA</td>
</tr>
</tbody>
</table>

• AAN
  • Relapses in MS – Probably effective, Class I
  • Primary progressive MS – Established ineffective, Class I
Neuromyelitis Optica (NMO)

- **Incidence**
  - Unknown

- **Demographics**
  - Female predominance (66% overall, 80% in relapsing form)
  - More common in non-Caucasians than MS (e.g. 1% of Caucasians versus 30% of Japanese and 48% of East Asians)
  - Older age of onset than MS

- **Signs and Symptoms**
  - Inflammatory demyelination within the spinal cord and optic nerve with blindness, paraparesis, bilateral sensory loss, sphincter dysfunction, radicular pain and spasms
  - Brainstem and hypothalamic involvement in 15% with vertigo, nausea and vomiting, facial weakness trigeminal neuralgia, diplopia, intractable hiccups, respiratory failure, and endocrine dysfunction.

- **Diagnostic Criteria**
  - Optic neuritis
  - Transverse myelitis
  - Two of the following:
    - Brain MRI normal or non-specific white matter lesions
    - Spinal cord MRI with lesion extending 3 or more contiguous vertebral segments
    - NMO-IgG seropositive
  - NMO-IgG has sensitivity of 91% and specificity of 100%

Neuromyelitis Optica (NMO)

• Associations
  • Autoimmune diseases: SLE, Sjögren’s, myasthenia gravis, polyarteritis nodosa, pernicious anemia, ulcerative colitis, ITP
  • Recent infection: URI, mumps, EBV, varicella-zoster, Mycobacterium tuberculosis, Treponema pallidum

• Pathophysiology
  • Development of an autoantibody to aquaporin-4 (NMO-IgG) with disruption of blood brain barrier allowing entry into CNS
  • Direct complement mediated lysis of astrocytes or immune complex formation leads to inflammatory demyelination

Neuromyelitis Optica (NMO)

• Disease course
  • Monophasic – 32%
    • Vision loss – 20% by 5 years
    • Monoparesis or paraparesis – 30% by 5 years
  • Relapsing – 68%
    • Paraplegia, quadriplegia, or vision loss – 50% by 5 years
    • Death due to respiratory failure – 32% by 5 years
Neuromyelitis Optica (NMO)

- Treatment
  - Methylprednisolone
  - Prevent relapse: oral steroids, azathioprine, mycophenolate mofetil, mitoxantrone, rituximab, IVIG
  - Biologic response modifiers used in MS are not effective

- Response to plasma exchange
  - Acute
    - Controlled trial showed better visual acuity in 16 patients treated with TPE and steroids compared to 19 treated with steroids
    - Case reports and case series report 30 patients with improvement compared to 12 without

Neuromyelitis Optica (NMO)

- Response to plasma exchange
  - Maintenance
    - Miyamoto and Kusunoki – 4 patients with relapsing course
      - 2/4 responded to azathioprine or cyclophosphamide with decreased relapses
      - 2/2 responded to TPE with decreased relapses
    - Khatri et al – 7 patients
      - 7/7 responded to TPE with decreased relapses
      - 5 patients had TPE interrupted due to insurance issues – all experienced worsening of symptoms
      - 3/5 improved with resumption of TPE
      - 2/5 died of disease following discontinuation

Neuromyelitis Optica (NMO)

- Course of TPE therapy
  - Acute
    - 1 to 1.5 plasma volume exchanges with albumin as replacement
    - 5 to 7 TPE daily or over 14 days
  - Maintenance
    - 1 to 1.5 plasma volume exchanges with albumin as replacement
    - 3 per week for 3 weeks then 2 per week for 2 weeks then weekly for 3 to 5 weeks with additional procedures titrated to control relapses.

Neuromyelitis Optica (NMO)

- Acute NMO
  - ASFA Category – II
  - ASFA Recommendation Grade – 1B
- Maintenance therapy
  - ASFA Category – III
  - ASFA Recommendation Grade – 2C

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<tbody>
<tr>
<td>Acute NMO</td>
<td>0</td>
<td>2(59)</td>
<td>12(104)</td>
<td>31(41)</td>
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- AAN
  - Fulminant CNS demyelination – Possibly effective, Class II
Acute Disseminated Encephalomyelitis (ADEM)

- **Incidence**
  - Children: 0.5 to 0.9/100,000
  - Adults: unknown but less common

- **Demographics**
  - Equivalent sex distribution
  - Age range in adults of 30 to 50

- **Signs and Symptoms**
  - Monophasic inflammatory demyelination
  - Acute onset with maximum neurologic deficit within hours to days
  - Duration of 2 to 4 weeks
  - Focal neurologic signs and encephalopathy depending upon degree of demyelination
  - MRI – disseminated demyelination of white matter with spinal cord involvement in 50 to 68% and peripheral nerve involvement in 25 to 44% of adults.
  - Oligoclonal bands in the CSF in only 10% of patients

- **Associations**
  - Occurs 2 to 30 days following upper respiratory or gastrointestinal illness or immunization
    - Infectious associations: measles, mumps, influenza, EBV, rubella, varicella-zoster, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*
    - Immunizations: rabies, influenza, measles, mumps, rubella, vaccinia, diphtheria/pertussis/tetanus, Japanese B encephalitis, accidental injection of swine vaccine

- **Pathophysiology**
  - Molecular mimicry leading to T cell activation and generation of anti-myelin antibodies
  - Infection of CNS with disruption of blood brain barrier and release of myelin leading to an inflammatory immune response
Acute Disseminated Encephalomyelitis (ADEM)

• Treatment
  - Corticosteroids – first line therapy
    - Up to 30% of patients will fail to respond
  - IVIG
  - Plasma exchange

• Response to plasma exchange
  - Responses reported when used as stand-alone, first-line therapy and following failure to respond to corticosteroids
  - Total of 52 patients reported in the literature with:
    - 41 responding to TPE
    - 11 demonstrating no response
  - Retrospective case series: 4/10 and 7/13 with response
  - Reported time to response ranges from improvement immediately after TPE to weeks after completion of course

• Outcomes
  - 5% mortality rate
  - 50 to 75% complete recovery rate
  - Up to 28% relapse rate

Acute Disseminated Encephalomyelitis (ADEM)

• ASFA Category - II
• ASFA Recommendation Grade – 2C

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• References
Anti-NMDA receptor Encephalitis

• Incidence
  • 4% of patients with encephalitis
  • Second most common autoimmune encephalitis after ADEM

• Demographics
  • 80% are female
  • Age range of 22 months to 45 years

• Signs and Symptoms
  • Prodrome – headache, fever, nausea, vomiting diarrhea, URI symptoms up to two weeks prior to onset of symptoms in 70%
  • Early – anxiety, insomnia, fear, grandiose delusions, hypersexuality, violent behavior, paranoia, social withdrawal, stereotypical behaviors, short-term memory loss, echolalia, mutism, seizure.
  • Late – agitation altering with catatonia
    • Abnormal movements – oro-lingual-facial dyskinesia, choreoathetosis, opisthotonic posture, dystonia, rigidity.
    • Autonomic instability - hyperthermia, tachycardia, hypersalivation, hypotension, urinary incontinence, hypoventilation requiring ventilator support.

• Associations
  • 65% of patients have or develop mature teratomas of the ovary, mediastinum, or testis.
  • Tumors usually seen in those over 18 years of age
  • 25/25 teratomas in one study expressed NMDA receptors

• Pathophysiology

Anti-NMDA receptor Encephalitis

**Treatment**
- Tumor resection
- Corticosteroids
- IVIG
- Plasma exchange
- Rituximab
- Cyclophosphamide

**Response to plasma exchange**
- Response in 6/8 case reports
- Response in 10/10 patients in case series
- Shorter time between admission and TPE in those with significant improvement (11 days) compared to limited improvement (21 days).

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**Outcomes**
- 4% mortality rate
  - Sepsis, cardiac arrest, respiratory arrest, status epilepticus
- Tumor present
  - 80% with substantial improvement after tumor removal and first-line immunotherapy
- No tumor present
  - 48% with substantial improvement with first-line immunotherapy
  - 65% with substantial improvement with second-line therapy
- Overall response similar
  - Tumor – 84% substantial improvement
  - No tumor – 71% substantial improvement
- 20 to 25% relapse rate
Anti-NMDA receptor Encephalitis

• ASFA Category – I
• ASFA Recommendation Grade – 1C

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• References

References


CASES FOR THE EXPERTS

SATURDAY, MARCH 9TH, 2019

- Cases presented anonymously by attendees in advance by email
- Cases were selected based on potential for thoughtful discussion and to complement program agenda this year
- Will take questions from audience at end of each case discussion
- If time allows at the end of the session, attendees may also come to the microphone with other specific case questions for the experts focused on apheresis-related issues.
EXPERT PANEL

- Jill Adamski, MD, PhD
- Rasheed A. Balogun, MBBS
- Nadine Benador, MD
- Patricia Kopko, MD
- Isagani Marquez, RN, MSN, QIA
- David M. Ward, MD, FRCP, HP(ASCP)
- Jeffrey Winters, MD

CASES: GVHD AND TIMING OF ECP

- Case 1: 28 year old male with mucocutaneous GVHD. ECP was initiated for severe oral GVHD preventing proper nutrition and mild cutaneous GVHD on arms & abdomen
- Weekly ECP for 12 weeks, oral lesions completely resolved. Patient eating normally, cutaneous lesions stable, steroid taper in progress
- Attempts to lengthen ECP interval to 2 weeks result in recurrence of oral lesions
- Should patient remain on weekly ECP or should steroids be re-initiated so taper can occur?
- ASFA guidelines offer recommendations for treatment schedules, do most programs adhere to these guidelines or are treatment schedules individualized based on patient response?
CASES: GVHD AND TIMING OF ECP

• Case 2: 23 year old female received an allogeneic stem cell transplant for CML. She developed GVHD of lungs and will be listed for lung transplant. Lung transplant team is requesting weekly ECP until patient is transplanted.
  • Is this a standard therapy in the pre-transplant setting for BOS? How are other programs managing this patient population?
  • Should we initiate ECP following transplant to prevent recurrent BOS? [patient currently has very mild mucocutaneous GVHD]

CASE: ECP INTERVAL/DURATION LUNG TRANSPLANT REJECTION

• 62 year old female received lung transplant 15 years ago. She developed BOS ~5 years ago and has been treated/stabilized with ECP during this time. Patient was on 4 week intervals for ~2 years then pulmonologist recommended taper to 8 weeks for ~1 year then 12 weeks intervals.
  • Patient switched to new pulmonologist who is requesting decreasing interval back to 4 weeks indefinitely. PFT have been stable since starting ECP.
  • Is it ever appropriate to stop ECP in the setting of BOS if patient appears stable?
  • What is the longest acceptable interval between ECP in order to achieve continued benefit?
OTHER MISCELLANEOUS ECP QUESTIONS FOR PANEL

• Is it safe for patients to receive vaccinations while undergoing ECP therapy? Should there be consideration for timing of vaccinations and ECP procedure schedule?
• If a patient is sick with an unrelated illness (e.g. pneumonia, staph skin infection) should ECP be held until patient has recovered?
• Who should lead the tapering of ECP – the referring physician or the apheresis physician?

CASE: DELAYED RBC ENGRAFTMENT IN PATIENT WHO RECEIVED ABO INCOMPATIBLE ALLOGENEIC TRANSPLANT

• 58 year old male with history of AML underwent allogenic stem cell transplant
• Patient blood group “O positive”, only 1 MUD identified and the donor is “A positive”
• Patient anti-A titer at the time of transplant 1:8,192 and the stem cell product underwent RBC reduction prior to infusion
• 5.6x10⁶ CD34 cells/kg infused
• 6 months later patient remains transfusion dependent although WBC and platelet counts are normal (WBC 4.2, platelet 209k)
• Bone marrow biopsy shows trilineage hematopoiesis
CASE: DELAYED RBC ENGRAFTMENT IN PATIENT WHO RECEIVED ABO INCOMPATIBLE ALLOGENEIC TRANSPLANT

- Patient transfused with group O, no evidence of group A in current blood bank samples (no microscopic agglutination)
- Anti-A titer is 1:512
- Should TPE be considered? Is there a goal anti-A titer that should be targeted?
- Knowing that the anti-A titer was so high at the time of transplant should TPE have been initiated early in engraftment?
- Would you consider TPE during the peri-transplant period for patients with high titers who are receiving an ABO incompatible transplant to prevent delayed engraftment?

CASE: TMA DUE TO CARFILZOMIB

- 53yo woman with HTN, DM2 and IgG kappa multiple myeloma diagnosed in 2016 who is s/p multiple chemo regimens followed by allogeneic stem cell transplant (from her sister, May 2018) who subsequently had refractory, relapsing disease and was started on daratumomab/carfilzomib, venetoclax, and dexamethasone on 1/14/19. On 1/17/19 she was found obtunded in bed, and brought to hospital with admission VS: 101.3F, HR 165, and BP 128/88. RR 48 and requiring 2L NC with subsequent increase in O2 requirements and eventual intubation, started on broad spectrum Abx, Cr 2.37 from 0.75 on 1/14/19 and oliguric despite Lasix. LDH >2500 from 288, Hgb 8.3 to 6.8 in 7h (from 9.3), +schistocytes on smear, and platelet count from 129K on 1/14/19 to 29K to 8K within 7 hours of admission.
- Fever, AMS, renal failure, microangiopathic hemolytic anemia and thrombocytopenia
- Leading differential diagnosis: TTP vs drug induced TMA (carfilzomib)
- ADAMTS13 requested, TPE initiated
CASE: TMA DUE TO CARFILZOMIB

- She had daily TPE with full plasma replacement for 5 days, she also required dialysis for AKI
- Platelet count 8 → 7 → 11 → 9 → 11 → 20 (also receiving platelet transfusions)
- LDH >2500 → 1442 → 2168 → 1957 → 1135 (with full plasma exchange)
- After TPE on the 5th day the ADAMTS13 activity level returned at 37%
- Review of carfilzomib induced TMA literature did not appear supportive of use of TPE, one case report of using eculizumab
- TPE was stopped, however platelets continued to fall and after a 5 day break in TPE, heme/onc asked us to resume TPE again – another 4 sessions done without improvement in platelets, respiratory status worsened, so further TPE held. Heme/onc agreed to eculizumab, gave one dose, then held off on further doses. Patient if off dialysis now with a creatinine of 2.3, LDH 284 and platelet count of 40-60k.
CASE: TMA DUE TO CARFILZOMIB

- Would you have resumed the second course of TPE?
- Would you have recommended eculizumab?
- Experience with other drug-induced TMAs that are less well described in the literature?

CASE: PATIENT WITH AHUS UNDERGOING KIDNEY TRANSPLANT

- 26 year old female with “history” of Wegner’s granulomatosis underwent a living donor kidney transplant. Within 48 hours kidney no longer producing urine. Biopsy shows TMA. Plasma exchange initiated immediately. Testing for aHUS is positive for homozygous mutations in CFH (no anti-CFH detected) and eculizumab is initiated ~1 week after transplant. Despite these efforts allograft is lost.
- 2 years later patient is being relisted for transplant and TPE has been requested pre/post transplant.
- In the absence of anti-CFH is TPE appropriate?
- Do you think the potential risks (bleeding due to anticoagulation, exposure to plasma due to recent surgery) and increased cost of multi-dosing eculizumab following each TPE are balanced by potential benefit?
CASE: RESISTANT PRIMARY FSGS IN A YOUNG ADULT

- 28yo woman with biopsy proven FSGS diagnosed in 2015, creatinine remains ~0.8, partial response to steroids, then tried: CSA → MMF → ACTHAR → rituximab plus steroids. Was started on LDL Apheresis 10/2018. Albumin was 1.5 prior to starting LDL-A, and peaked at 3.1 on 1/7/19 after 17 treatments.
CASE: RESISTANT PRIMARY FSGS IN A YOUNG ADULT

- What would you do next?
- Increase immunosuppression: go back up on steroids even though patient reluctant? Add an additional immunosuppression such as CNI or other to the combo of steroids and LDL-A?
- Switch to TPE?

GENERAL QUESTIONS FOR THE EXPERTS
THANK YOU!

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Have a challenging case for next year?

Submit it now!
a6sanchez@ucsd.edu