IVIG or Plasmapheresis for Neuromuscular Disease: Pros and Cons

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Texas Neurological Society
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Neuromuscular Diseases in which Immunosuppressive Therapy is Used

- Neuropathies
  - GBS
  - CIDP
  - Multifocal Motor Neuropathy
  - Multifocal Acquired Sensory and Motor (MADSAM) Neuropathy
  - Vasculitis
- Neuromuscular Junction
  - Myasthenia Gravis
  - Lambert-Eaton Syndrome
- Myopathy
  - Polymyositis/Dermatomyositis
  - Duchenne’s Muscular Dystrophy
Immunotherapeutic Options in Neuromuscular Disease

- Corticosteroids
- Azathioprine
- Cyclophosphamide
- Methotrexate
- Mycophenylate
- Cyclosporine
- IVIG
- Plasmapheresis
- Mycophenolate
- Rituximab
- Thymectomy
What is IVIG?

- Intravenous immunoglobulin – IVIG – is a polymeric, highly purified preparation of IgG that is derived from large pools of plasma donors.

- IVIG is used to treat an increasing number of immune mediated neurologic disorders that affect the peripheral nerve, neuromuscular junction, muscle, and CNS, because it has the potential to modulate numerous different effectors of autoimmune disease.
Screening of Plasma for IVIG Production

- Donors are screened
- Plasma is screened for units of HIV, HBV, HCV, and CJD
- Nucleic acid testing is performed on plasma pools for viral genomes
- No incidence of HIV, CJD or HBV
IVIG has multiple immunomodulatory mechanisms of action relevant to the development of different disorders:

- Inhibits complement activation and MAC formation (Dermatomyositis, MG, CIDP, GBS)
- Down-regulates antibody production (MG, LEMS, anti-MAG and anti-GM1 Ab syndromes)
- Neutralizes pathogenic cytokines (Dermatomyositis, GBS, CIDP, PM)
- Modulates macrophage-mediated phagocytosis through blockade of Fc receptors (Demyelinating dz, DM, PM)
- Modulates T-cell function and antigen recognition (GBS, CIDP, DM, PM)
Immunomodulatory Actions of IVIG in Autoimmune NM Diseases

Dalakas JAMA 2004;291:2367-2375
Neuromuscular Disorders Treated with IVIG

- Acute Inflammatory Demyelinating Polyneuropathies (GBS, Miller Fisher Syndrome)
- Multifocal Motor Neuropathy
- Multifocal Acquired Sensory and Motor Neuropathy
- Chronic Demyelinating Polyneuropathies
- Myasthenia Gravis
- Lambert-Eaton Syndrome
- Dermatomyositis
- Polymyositis
- Stiff-person Syndrome
IVIG Treatment in Neuromuscular Disease

Indications

- First Line Rx In:
  - GBS (off label)
  - MMN (FDA approved)
  - CIDP (FDA approved)

- Second Line Rx In:
  - CIDP (off label)
  - DM (off label)
  - MG (off label)
10 PLASMAPHERESIS

• Directly removes humoral factors such as autoantibodies, immune complexes, complement and other nonspecific inflammatory mediators.

• Remove 3-6 liters of plasma over several hours. Replace with albumin or purified protein fraction (PPF).

• Indications:
  - MG: crises; pre-thymectomy; severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs.
  - GBS/CIDP
  - LEMS
Plasmapheresis/Apheresis

- PE removes autoantibodies, immune complexes, complement & cytokines
- Boosts T-cell suppressor function
- Plasma exchange volume is 250 cc/kg
- Risks of central venous catheter placement
- Hypotension, cardiac arrhythmia, vasovagal
- Allergy to albumin
- Hypocalcemia, anemia, thrombocytopenia
- The first treatment shown to be effective in GBS based on randomized controlled trials within 2-4 weeks of onset

# Evidence-based guideline update:
## Plasmapheresis in neurologic disorders
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

### Table 1: Summary of evidence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Conclusion</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome</td>
<td>Established effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy, short-term treatment</td>
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<tr>
<td>Polyneuropathy with monoclonal gammopathies of undetermined significance</td>
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</tr>
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<td>Immunoglobulin A/Immunoglobulin G</td>
<td>Probably effective</td>
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</tr>
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<td>Immunoglobulin M</td>
<td>Probably ineffective</td>
<td>Class I</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative preparation</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Crisis</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Fulminant demyelinating CNS disease</td>
<td>Possibly effective</td>
<td>Class II</td>
</tr>
<tr>
<td>Chronic or secondary progressive multiple sclerosis</td>
<td>Established ineffective</td>
<td>Class I</td>
</tr>
<tr>
<td>Relapses in multiple sclerosis</td>
<td>Probably effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Sydenham chorea</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Acute obsessive-compulsive disorder and tics in PANDAS</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
</tbody>
</table>

Abbreviation: PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.
Acute Inflammatory Demyelinating Polyneuropathies

(Guillain–Barre Syndrome)
GBS

Plasmapheresis
North American Study
(Neurology 1985; 35:1096)

- 245 pts/21 centers
- Randomized/Not Blinded
- Time to Walk Unaided
  - Pheresis pts dec. time by: 32 days (all)
    - 72 days (respirator)
- Average Time on Vent. Dec. by 12 Days
Appropriate Number of Plasma Exchanges in GBS

French Coop Group  
Ann Neurol 1997; 41:298

- Each Exchange 1.5 Plasma Volume
- Mild GBS (#91):
  - 2 exchanges better than none
  - 4 exchanges no better than 2
- Moderate GBS (#304):
  - 4 exchanges better than 2
- Severe GBS (#161):
  - 6 exchanges no better than 4
- Rec:
  - Mild GBS – 2 exchanges
  - Mod/Sev GBS – 4 exchanges
### Dutch IVIG vs. Plasmapheresis Studies Compared to the North American Plasmapheresis Study

<table>
<thead>
<tr>
<th></th>
<th>Dutch</th>
<th>Dutch</th>
<th>North American</th>
<th>North American</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IVIG</td>
<td>PE</td>
<td>PE</td>
<td>Control</td>
</tr>
<tr>
<td>Total patients</td>
<td>74</td>
<td>73</td>
<td>108</td>
<td>120</td>
</tr>
<tr>
<td>Improved 1 grade (4 wk)</td>
<td>53%</td>
<td>34%</td>
<td>59%</td>
<td>39%</td>
</tr>
<tr>
<td>Median days to 1 grade</td>
<td>27</td>
<td>41</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days grade 2</td>
<td>55</td>
<td>69</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td># multiple complications</td>
<td>5</td>
<td>6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ventilator by week 2</td>
<td>27%</td>
<td>42%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

### PE, IVIG, and PE + IVIG for GBS

<table>
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<tr>
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<th>PE (N=121)</th>
<th>IVIG (N=130)</th>
<th>PE + IVIG (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in disability</td>
<td>.9</td>
<td>.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Number of patients ventilated</td>
<td>28</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Days to stopping ventilation</td>
<td>29</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Days to unaided walking</td>
<td>49</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Days to hospital discharge</td>
<td>63</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Days to returning to work</td>
<td>290</td>
<td>371</td>
<td>281</td>
</tr>
<tr>
<td>Unable to walk after 48 days</td>
<td>19</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Deaths</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

Practice Parameters: Immunotherapy for GBS
(Quality Standards Subcommittee AAN)

- Treatment with plasma exchange (PE) or IVIG hastens recovery from GBS
- IVIG is recommended for non-ambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms
- PE and IVIG are treatment options for children with severe GBS
- Corticosteroids are not recommended for the management of GBS

PE & IVIG in GBS
AAN Practice Parameters 2003

- **PLEX**
  - First effective therapy
  - Nonambulant patients within 4 wks of onset  (Level A)
  - Ambulant patients within 2 wks of onset  (Level B)
- **IVIG:**
  - Nonambulant patients within 2 weeks  (level A)
  - Nonambulant patients within 4 weeks of onset (Level B)
- **PLEX & IVIG:** treatment options for children with severe GBS
- **Corticosteroids NOT recommended** in GBS  (level A)

*Hughes RA et al. Neurology. 2003;61:736-74*
Immunotherapy for GBS: A Systematic Review

- 4 PE trials (585):
  - cases improved by 0.89 more grades at 4 weeks as compared to placebo
- 4 IVIG trials (536):
  - cases improvement similar to PE at 4 weeks
- 1 PE followed by IVIG (148): no additional benefit
- 6 corticosteroids trials (587): Less/no improvement compared to no treatment

Hughes RA et al. Brain. 2007;130:2245-2257
GBS in Adults: Conclusions
AAN Therapeutics & Tech Subcommittee. Neurology. 78;1009; 2012.

• Based on 2 Class I studies, IVIG is as efficacious as plasmapheresis for treating GBS in adults. Because plasmapheresis is established as effective GBS treatment, we conclude that IVIG also has established effectiveness.

• Based on one adequately powered Class I study, the combination of plasmapheresis and IVIG is probably not better than either treatment alone.
# PE and IVIG for GBS

<table>
<thead>
<tr>
<th></th>
<th>Plasma Exchange</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
<td>200-259 ml/kg plasma x 4 sessions over 7-14 days</td>
<td>0.4 g/Kg IV x 5 days</td>
</tr>
<tr>
<td><strong>Rationale</strong></td>
<td>Removal of autoantibodies and other humoral factors</td>
<td>Reduces inflammatory cytokine production and inhibits C’</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Limited availability; requires an experienced team</td>
<td>Allergy, headache, transient LFT, meningitis</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Coagulopathy, thrombocytopenia, hemodynamic instability, poor venous access</td>
<td>Prior allergy, antibodies to IgA, poor renal function</td>
</tr>
</tbody>
</table>

van der Meche et al. *Current Treatment Options in Neurology*. 2000;2:507-516
GBS
Treatment Caveats

• After PE or IVIG, Be Patient, Don’t Expect Dramatic Results

• No Reason to Use Both PLEX and IVIG

• No Reason to Use Steroids
CIDP: Clinical Features

- Symmetric proximal and distal weakness
- Generalized areflexia
- Progressive or relapsing course over 8 weeks
- CSF protein typically > 60 mg/dl
- 15% have a monoclonal (IgM or IgG)
- Electrodiagnostic Criteria:
  - NCV <75% LLN in 2 or more nerves
  - DL > 130% ULN in 2 or more nerves
  - Unequivocal TD or CB in 1 or more nerves
  - F wave latency > 130% ULN in 1 or more nerves
CIDP: Plasmapheresis

- Each PLEX reduces IgG by 45%; 3-5 PLEX removes 90%
- 2 RCTs demonstrated transient NDS & NCS improvement:
  - Sham-controlled, 33% response at 3 weeks
  - Cross-over with 5-week washout, 80% response at 4 weeks
- Efficacy equivalent to that of IVIG
- Risks of central venous catheter placement
- Hypotension, cardiac arrhythmia, vasovagal
- Allergy to albumin
- Hypocalcemia, anemia, thrombocytopenia
- Citrate toxicity (use heparin)

Hahn AF et al Brain 1986:1055-6
## Randomized Controlled Trials of IGIV in CIDP Before 2008

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Therapy</th>
<th>No. of Pts</th>
<th>Design/Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Doorn et al⁴</td>
<td>1990</td>
<td>IGIV</td>
<td>7</td>
<td>Double-blind, placebo-controlled, crossover; single-dose comparison</td>
<td>Improvement in all patients</td>
</tr>
<tr>
<td>Vermeulen et al²</td>
<td>1993</td>
<td>IGIV</td>
<td>28</td>
<td>Double-blind, placebo-controlled, parallel-group comparison of 5 consecutive daily doses</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Hahn et al³</td>
<td>1996</td>
<td>IGIV</td>
<td>30</td>
<td>Double-blind, placebo-controlled, crossover; 4 weeks</td>
<td>Improvement in 63% of patients</td>
</tr>
<tr>
<td>Thompson et al⁴</td>
<td>1996</td>
<td>IGIV</td>
<td>7</td>
<td>Double-blind, placebo-controlled, crossover; 24 weeks (stopped early)</td>
<td>Improvement in 3 of 7 patients</td>
</tr>
<tr>
<td>Mendell et al⁵</td>
<td>2001</td>
<td>IGIV</td>
<td>53</td>
<td>Double-blind, placebo-controlled; 6 weeks</td>
<td>Improvement in 75% of patients</td>
</tr>
<tr>
<td>Hughes et al⁶</td>
<td>2001</td>
<td>IGIV vs prednisolone</td>
<td>32</td>
<td>Double-blind, placebo-controlled, crossover; 6 weeks</td>
<td>Improvement but no significant difference between groups</td>
</tr>
<tr>
<td>Dyck et al⁷</td>
<td>1994</td>
<td>IGIV vs plasma exchange</td>
<td>15</td>
<td>Randomized, observer-blinded, crossover; 6 weeks</td>
<td>Improvement but no significant difference between groups</td>
</tr>
</tbody>
</table>

Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar SJ Merkies, Pieter A van Doorn, on behalf of the ICE Study Group
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Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

Methods 117 patients with CIDP who met specific neurophysiological inflammatory neuropathy cause and treatment (INCAT) criteria participated in a randomised, double-blind, placebo-controlled, response-conditional crossover trial. IGIV-C (Gamunex) or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period, and patients who did not show an improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. The primary outcome was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through to week 24. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00220740.

Findings During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (treatment difference 33.5%, 95% CI 15.4–51.7; p=0.0002). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10.9 kPa, 4.6–17.2; p=0.0008) and the non-dominant hand (8.6 kPa, 2.6–14.6; p=0.005). Results were similar during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo (p=0.011). The incidence of serious adverse events per infusion was 0.8% (9/1096) with IGIV-C versus 1.9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypotension.

Interpretation This study, the largest reported trial of any CIDP treatment, shows the short-term and long-term efficacy and safety of IGIV-C and supports use of IGIV-C as a therapy for CIDP.
Inflammatory Neuropathy Care and Treatment Score (INCAT)

**INCAT – Upper Extremity**
- **Arm Disability Score**
  - **0** No upper limb problems
  - **1** Minor symptoms in one or both arms, but not affecting any of the functions (zips and buttons, washing or brushing).
  - **2** Disability in one or both arms affecting any of the above mentioned functions.
  - **3** Disability in one or both arms preventing one or two of the above mentioned functions.
  - **4** Disability in both arms preventing three or all functions.
  - **5** Inability to use either arm for any purposeful movement.

**INCAT – Lower Extremity**
- **0** Walking not affected
- **1** Walking affected but walks independently outdoors
- **2** Usually uses unilateral support to walk outdoors (stick, single crutch, one arm)
- **3** Usually uses bilateral support to walk outdoors (stick, crutches, frame, two arms)
- **4** Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps
- **5** Restricted to wheelchair, unable to stand and walk a few steps with help

INCAT Disability scores and total below:
- **Upper Extremity Disability Score =**
- **Lower Extremity Disability Score =**
- **Overall Extremity Disability Score =** (Sum of Upper and Lower Disability Scores)

**Responder** = change (decrease) or ≥ 1 point
**Relapse** = increase in score
GAMUNEX-C Significantly Improved CIDP in 24 weeks (Disability Scores, INCAT)

\[ P = 0.006 \]

- **Gamunex-C**
  - Percentage of Responders: 47.5%
  - Number of Participants: n=59

- **Placebo**
  - Percentage of Responders: 22.4%
  - Number of Participants: n=58
CIDP Rx Recommendations

• 1st Line:
  • IVIG 2 gm/kg, then 0.4 to 1 gm/kg/q 3-4 weeks
  • Pred 100 mg/d x 2 wks, then 100 mg qod

• 2nd Line (Relapse or Non-Responder):
  • IVIG or Pred if not 1st line
  • PE 5-10x over 1-6 wks
  • AZA 2-3 mg/kg/d

• 3rd Line:
  • Mycophenylate 2-3 gm/d
  • Cyclosporine 3-6 mg/kg/d
  • Cyclophosphamide 1.5-2 mg/kg/d
  • Methotrexate 20 mg/week
Multifocal Motor Neuropathy

- Clinical:
  - Adults, Male > female, initially in nerve distribution
  - Slowly progressive distal weakness of hands > feet
  - No sensory symps/signs & No UMN signs

- Lab:
  - Serum-elevated GM-1 AB in 50-80%
  - EDX-CB or other demyel features
  - CSF – usually normal
  - Sensory nerve Bx – normal or minimally abnl

- Treatment options limited:
  - No response to pred; +/- pheresis
  - IVIG is Rx of choice based on RCT phase III
  - Cyclophosphamide is 2nd line of Rx
  - ? Rituximab monoclonal Ab to CD20 cells
<table>
<thead>
<tr>
<th>Study</th>
<th>Dosing</th>
<th>Duration</th>
<th>Patients</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azulay, et al, 1994</td>
<td>0.4 gm/kg/5 days</td>
<td>56 days</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>Van den Berg, et al, 1995</td>
<td>0.4 gm/kg/5 days</td>
<td>14 days</td>
<td>16</td>
<td>83%</td>
</tr>
<tr>
<td>Federico, et al, 2000</td>
<td>0.4 gm/kg/5 days</td>
<td>28 days</td>
<td>16</td>
<td>67%</td>
</tr>
<tr>
<td>Léger, et al, 2001</td>
<td>0.5 gm/kg/5 days/3 months</td>
<td>120 days</td>
<td>18</td>
<td>78%</td>
</tr>
</tbody>
</table>
10% IVIG in treated MMN

- Blinded cross-over design with stabilization phase before & after blinded phases over 15 months
- 40 subjects: 5 phases / subject, each phase for 3 months
- Primary endpoint measures:
  - Grip strength* (DynEX)
  - Upper arm section of Guy’s Neurological Disability Scale
- Secondary endpoint measures:
  - % of subjects with ≥ 30% grip strength decline*
  - # & % of subjects with decline in less affected hand
  - # of subjects with accelerated switch
  - Patient disability assessment
  - Overall Disability Sum Score
  - Timed Peg Board Test
  - Patient VAS assessment

*In the more affected hand
Forty-four enrolled cases, 17 sites & 41 completed the study

Accelerated switch to open-label IVIG if grip strength decreased ≥ 50% in the more affected hand or intolerable functional deterioration was objectified

Substantially greater decline from baseline (34%) in the mean grip strength in the more affected hand following placebo administration, as compared to IGIV (p=0.005)

A greater proportion of subjects had a ≥ 30% decline in grip strength of the more affected hand (43% vs. 5%; p<0.001), as well as the less affected hand (31% vs. 0%; p<0.001), PBO vs. IVIG

69% of PBO required accelerated switch compared to only 1 (2.4%) on blinded IVIG

IVIG was demonstrated to be safe, well-tolerated and an effective treatment for MMN in this phase III study

FDA-approval and labeling indication
Myasthenia Gravis
Plasmapheresis vs. IVIG for MG

Gajdos et al, Ann Neurol 1997

- 87 pts with MG exacerbation
- Randomized: 3 PLEX vs. 3 or 5 IVIG 0.4 gm/kg
- Endpoint – Myasthenic muscular score day 15
- Results – Equal improvements with both Rx:
  - PLEX + 18 pts
  - IVIG + 15.5 points
  - \( p = 0.65 \)
- Fewer side effects with IVIG (1) vs. PLEX (8)
IV Immunoglobulin in Patients with Myasthenia Gravis
Zinman, Eduardo, Bril Neurology 2007; 68:837-881

- 51 pts IVIG vs. placebo
- QMG: Sig diff at day 14 (p=0.047)
- Persisted at day 28
- Change in
  - IVIG: -2.54
  - PLAC: -0.89
- Post intervention status at day 14
  - IVIG imp 25%
  - Plac imp 6%
- RNS/SFEMG-no sig diff
- Meriggioli editorial:
  - Getting enough “bang for the buck”
Evidence-based guideline update: Plasmapheresis in neurologic disorders
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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<td>Preoperative preparation</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Crisis</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Fulminant demyelinating CNS disease</td>
<td>Possibly effective</td>
<td>Class II</td>
</tr>
<tr>
<td>Chronic or secondary progressive multiple sclerosis</td>
<td>Established ineffective</td>
<td>Class I</td>
</tr>
<tr>
<td>Relapses in multiple sclerosis</td>
<td>Probably effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Sydenham chorea</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Acute obsessive-compulsive disorder and tics in PANDAS</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
</tbody>
</table>

Abbreviation: PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

Phereses for MG: Recommendations Level U (Unknown)
Comparison of IVIG & Plex in MG
Barth, et al Neurology 2011;76

- 84 pts to IVIG PE 1g/kg/d x 2 days
  - Or PE x 5
- QMG > 10.5 and “worsening”

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean ± SD change in QMGS for disease severity from baseline to days 14, 21, and 28a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVlg (n = 41)</td>
</tr>
<tr>
<td>Baseline QMGS</td>
<td>14.2 ± 4</td>
</tr>
<tr>
<td>Δ QMGS</td>
<td></td>
</tr>
<tr>
<td>Day 0-14a</td>
<td>2.2 ± 4.1</td>
</tr>
<tr>
<td>Day 0-21</td>
<td>2.3 ± 3.6</td>
</tr>
<tr>
<td>Day 0-28</td>
<td>2.6 ± 4.0</td>
</tr>
</tbody>
</table>

Abbreviations: IVlg = IV immunoglobulin; PLEX = plasma exchange; QMGS = Quantitative Myasthenia Gravis Score for disease severity.

a This table demonstrates that the changes of QMGS for disease severity did not differ between the 2 treatment groups for the 28-day study duration.

b p Values are for QMGS differences from baseline with IVlg compared to PLEX.

c Primary efficacy parameter.

Improved: 69% IVIG and 65% PE
Conclusion: IVIG & PE both effective Rx
IVIG for MG: Summation

• IVIG appears to have a role in treatment of MG, when patients are not responding to corticosteroids and other immunosuppressive drugs.

• AAN Tech and Therapeutics: 1 Class I study showed IVIG probably effective in treatment MG (Neurology 2012)

• Evidence insufficient to compare IVIG and plasmapheresis in MG

• Role in crises still unclear
PLASMAPHERESIS

• Directly removes humoral factors such as autoantibodies, immune complexes, complement and other nonspecific inflammatory mediators.

• Remove 3-6 liters of plasma over several hours. Replace with albumin or purified protein fraction (PPF).

• Indications for MG:
  • Crises
  • pre-thymectomy
  • severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs
  • chronic treatment monthly
Indications for Plasmapheresis in MG

- Crisis
- Pre-surgery
- Worsening while adjusting meds
- Chronic Rx
## Myasthenia Gravis

### My Rx Recommendations - prior to 2007

- **1st Line:** Tensilon  
  Mestinon  
  Prednisone  
  Thymectomy
- **2nd Line:** Azathioprine  
  Mycophenolate Mofetil  
  Cyclosporine
- **3rd Line:** IVIg  
  Plasmapheresis

### My Rx Recommendations – 2014

- **1st Line:** Enlon  
  Pyridostigmine  
  Prednisone  
  Thymectomy
- **2nd Line:** Azathioprine  
  Cyclosporine  
  IVIg
- **3rd Line:** Mycophenolate Mofetil  
  Plasmapheresis
- **4th Line:** Methotrexate  
  Rituximab
- **5th Line:** Cyclophosphamide  
  Tacrolimus
Additional Disorders Benefiting From IVIG

- Lambert-Eaton Syndrome

- Dermatomyositis

- Polymyositis

- Stiff-Person Syndrome
## Class of Evidence Supporting Use of IVIG

<table>
<thead>
<tr>
<th>Neuromuscular Disorder</th>
<th>Class of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS in Adults</td>
<td>I</td>
</tr>
<tr>
<td>GBS in Children</td>
<td>II</td>
</tr>
<tr>
<td>CIDP</td>
<td>I</td>
</tr>
<tr>
<td>Multifocal Motor Neuropathy</td>
<td>I</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>I</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>I</td>
</tr>
<tr>
<td>Stiff Person Syndrome</td>
<td>I</td>
</tr>
</tbody>
</table>

*Neurology 2012;78:1009*
### Class of Evidence Supporting Use of IVIG

<table>
<thead>
<tr>
<th>Neuromuscular Disorder</th>
<th>Class of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher Syndrome</td>
<td>IV</td>
</tr>
<tr>
<td>Neuropathies Associated with Monoclonal Proteins</td>
<td>IV</td>
</tr>
<tr>
<td>Neuropathies Associated with Cryoglobulinemia</td>
<td>IV</td>
</tr>
<tr>
<td>Idiopathic Neuropathies</td>
<td>IV</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>IV</td>
</tr>
<tr>
<td>Inclusion Body Myositis</td>
<td>None</td>
</tr>
<tr>
<td>Idiopathic Brachial Plexopathy</td>
<td>IV</td>
</tr>
<tr>
<td>Diabetic Lumbosacral Radiculoplexopathy</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Neurology 2012;78:1009*
IVIG RX in Neuromuscular Disease

Dosing

• Induction Dose: 2 gm/kg
  • Either: 0.4 gm/kg x 5 days
    or 0.6-0.7 gm/kg x 3 days

• Maintenance Dose (For Chronic Diseases)
  • 0.4 to 1.0 gm/kg every 3-4 weeks
  • But may need infusion q 2 weeks or only q 8 weeks
IVIG Rx in Chronic Neuromuscular Diseases

- For chronic disease usually determine effectiveness in 2-3 months
- Usually Rx lasts at least 6-12 months
- Reassess for continued use every 6 months
- Eventually either in time between infusions (6-8-12 wks) then discontinue or decrease number of grams per infusion
Contraindications for IVIG

- Known allergy to blood products, especially anaphylactic reaction after exposure to human immunoglobulin
- IgA Deficiency
- Severe renal dysfunction
- Severe congestive heart failure
Patients receiving IVIG should be closely monitored during the first 5 minutes of administration, and also every time the infusion rate is increased.

Transfusion reactions generally occur 30 to 60 minutes after administration is initiated, and each time the infusion rate is increased.

The patient’s vital signs and symptoms of adverse effects should be continually monitored throughout the administration of IVIG.
Adverse Effects

• The majority of adverse effects from IVIG are infusion rate-related and usually mitigated by reducing the infusion rate or by interruption of the infusion until symptoms subside.

• Premedication with acetaminophen (1000mg) and/or diphenhydramine (50mg) may be useful for mitigating infusion-related adverse effects.

• Rarely use methylprednisolone 100mg pre infusion.
IVIG: Toxicity

- Headaches infusion related (20-30%)
- Chills/fever
- Diaphoresis/flushing
- Hypotension
- Tachycardia/shortness of breath
- Nausea/vomiting
- Backaches/myalgias
- Flushing
**IVIG: Toxicity**

- Anaphylaxis - rare; most cases reported in setting of IgA deficiency
- Hepatitis
- Neurotropenia
- Hives
- Red, macular palm/sole/trunk with desquamation of skin on palms/soles
- Renal insufficiency
- Thrombosis: PE/CVA – Very Rare!
IVIG-induced Rash
IVIG Cost

- Wholesale Price:
  - 40-100 per gram
- Cost to Consumer May 2x
- Ex: $100/gm
  - Induction 70 kg at 2 gm/kg
    - 140 gm = $14,000
  - Maintenance at 0.4 gm/kg
    - 28 gm = $2,800/mo
PLASMAPHERESIS Rx

LIMITATIONS

- Trained technician
- Equipment
- IV Access - Often Requires Large Double-Lumen Catheter
- Complications: Pneumothorax, Hypotension, Sepsis, Pulmonary Embolism
- Expensive
- Benefit Lasts Several Weeks
Chronic Outpatient Plasma Exchange
Ahmed, Dimachkie, Barohn et al 2009

- 12 patients (10 MG, 1 LEMS, 1 CIDP)
- 13 double-lumen tunneled internal jugular catheters
- Mean retention time: 2 months
- Complications: infection (38%) and clotting (31%)

- 9 AV fistulas placed
- Average time to mature: 6-8 weeks
- Mean retention time: 6 months (still working in 6 patients)
- Complications: thrombosis 3 (33%), 1 while taking ASA
- Adverse effects during outpatient PLEX (n=91)
  - Transient dizziness (6%) with resumption of PLEX after fluid bolos in most
  - Nausea (1%)
## Plasma Exchange vs. IVIG: Pros & Cons

<table>
<thead>
<tr>
<th>Pro-PLEX:</th>
<th>Pro-IVIG:</th>
</tr>
</thead>
<tbody>
<tr>
<td>It makes sense</td>
<td>Easy to give</td>
</tr>
<tr>
<td>It works</td>
<td>Faster to give full course</td>
</tr>
<tr>
<td>Longer track record</td>
<td>No sophisticated equipment needed</td>
</tr>
<tr>
<td>? Works faster</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Con-PLEX:</th>
<th>Con-IVIG:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central line</td>
<td>Makes less sense</td>
</tr>
<tr>
<td>Morbidity</td>
<td>Not as long a track record</td>
</tr>
<tr>
<td>Need sophisticated equipment and PLEX team</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Expense</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Expense</td>
</tr>
<tr>
<td></td>
<td>Availability</td>
</tr>
<tr>
<td></td>
<td>? Works slower</td>
</tr>
<tr>
<td></td>
<td>May not work</td>
</tr>
<tr>
<td></td>
<td>If fails – PLEX out!</td>
</tr>
</tbody>
</table>
## PE vs. IVIG

<table>
<thead>
<tr>
<th>Pro-PE</th>
<th>Con-PE</th>
<th>Pro-IVIG</th>
<th>Con-IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>It works</td>
<td>Morbidity</td>
<td>Easy to give</td>
<td>Not as long as track record</td>
</tr>
<tr>
<td>Longer track record</td>
<td>Need sophisticated equipment and PE team</td>
<td>Faster to give full course</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Expense</td>
<td></td>
<td>Expense</td>
</tr>
<tr>
<td></td>
<td>?Rebound</td>
<td>Less side effects</td>
<td>?Rebound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Product shortage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insurance issues</td>
</tr>
</tbody>
</table>
What Is Subcutaneous Ig (SCIg)?

- Infusion of IgG into subcutaneous tissue, usually using an infusion pump or syringe driver
- Weekly dose usually ≈ ¼ monthly IVIG dose
- Typically self-administered at home
- Flexible schedule and regimens available
- Patient can be ambulatory during administration
- Once pt is trained and demonstrates competence, routine nursing intervention not necessary
Conversion from IVIG to SCIG

- Rec is 1: 1.5
- 1gm/kg dose of 80gm/4weeks = 120gm
- Weekly give aprox 30 gm or 15 gm per infusion twice a week
- 20% solution =75ml
- Use 2 pumps each w/ 2 ports
- 18-20cc per port
- Can infuse aprox 20 cc/hr/per port
### SCIG in CIDP: Published/Presented Reports

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type, duration</th>
<th>Study pop.</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koller, 2006</td>
<td>Case report</td>
<td>Previous IVIG, methylprednisolone, mycophenolate mofetil</td>
<td>1</td>
<td>Improved INCAT disability and MRC sum score with no relapses; SCIG well tolerated</td>
</tr>
<tr>
<td>Lee, 2008</td>
<td>Case report</td>
<td>IVIG responders</td>
<td>2</td>
<td>Pts remained clinically stable; SCIG well tolerated</td>
</tr>
<tr>
<td>Magy, 2009 (PNS)</td>
<td>Prospective, open label, 36 wks</td>
<td>IVIG responders</td>
<td>16</td>
<td>2 pts relapsed, 1 pt had slight sensory deterioration, 13 pts remained stable</td>
</tr>
<tr>
<td>Cocito, 2011</td>
<td>Prospective, 6 mo</td>
<td>IVIG responders, clinically stable</td>
<td>5</td>
<td>Pts remained clinically stable; SCIG well tolerated</td>
</tr>
<tr>
<td>Jakobsen, 2012 (AAN)</td>
<td>Prospective, placebo-controlled, 12 wks</td>
<td>IVIG responders, switched to SCIG or placebo</td>
<td>30</td>
<td>Muscle strength, disability, walking distance improved with SCIG vs placebo; local side effects only</td>
</tr>
<tr>
<td>Bayas, 2012</td>
<td>Case report</td>
<td>Lewis-Sumner syndrome, IVIG responders</td>
<td>2</td>
<td>Pts remained clinically stable with dosing adjustments; SCIG well tolerated</td>
</tr>
</tbody>
</table>

SCIG in CIDP

- Vivaglobin® 160 mg/ml & portable programmable pump
- Gradual build-up
- Case 1: IVIG dependent 0.4 gm/kg/month (60 gm)
- Weekly SCIG dose 16 g in 100 ml infused over 10 hours divided into 5 equal doses of 3.2 g over 3 days
- Case 2 responded to IVIG induction 40 g x 5 d
- Weekly SCIG dose 6.4 g in 40 ml divided into 2 equal doses of 3.2 g in 1 day

Lee et al MN 2008 Mar;37(3):406-9
Case Report #1

- 45 y/o WM presents with progressive R>L distal arm weakness over the past 2 years
- No associated neck pain or sensory changes.
- Normal laboratory workup including CSF analysis and MRI of cervical spine.
- NCS show normal SNAPs. Right median and ulnar CMAPs show prolonged distal latencies with proximal conduction block.
Case Report #1

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?
Case Report #2

- 25 y/o WF with a history of generalized antibody-positive MG presents with worsening dysphagia, proximal weakness, diplopia, and ptosis
- Medications include Mestinon 60mg TID and Cellcept 1 g BID
- Pregnancy test is positive
Case Report #2

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?
Case Report #3

- 25 y/o homosexual male presents with a 3 month history of progressive, symmetric, proximal and distal weakness with diffuse areflexia
- CSF shows a protein of 150 mg/dL and 60 WBC
- CMAPs show prolonged distal latencies with slowed CVs and conduction block
- SNAPs show prolonged peak latencies with decreased amplitudes
Case Report #3

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?
Case History

History

- 18 Male
- 3d PTA: N/V, Achy
- 1d PTA: Paresthesias
  
  Leg > Arm Weakness
- In ER: Dysphagia / Dyarthria
  
  Inc. Weakness
Case Study

Exam
- Ptosis OS / EOM Full / Pupils NL
- Nasal Speech / Could Not Swallow
- Facial Diplegia
- Neck Flex Grade 2 / Neck Ext 3
- UE 4 / LE Prox 4+, Distal 5
- DTR – Absent
- Dec Touch / Pin UE/LE
Case Study

Lab

- CSF:
  - Prot 28 mg/dl
    2 Weeks Later: 203 mg/dl

- NCS: F Waves Unobtainable
  Minimal LE CV Slowing
Case Study

Course
- PE 200 ml/kg Begun Hosp Day 1
- Subclav IV – Pneumothorax / Chest Tube
- On Vent Hosp Day 4
- Extubated Hosp Day 9
- Discharged Hosp Day 20
- At 2 Week F/U: No Bulbar Symps

Minimal Face / Arm Weakness