NEUROLOGICAL PRACTICE

# IGIV in Neurology – Evidence and Recommendations

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**ABSTRACT:** ***Objective:*** To summarize the evidence for neurologic uses of immunoglobulin, intravenous (IGIV) in light of present-day clinical usage. This summary guided the development of practice recommendations for the effective and efficient use of IGIV in Neurology. ***Methods:*** MEDLINE was searched to identify pertinent English-language review articles and original reports (n = 231) on the use of IGIV in neurology (excluding editorials, letters, and comments) published before March 1998. Evidence on alternative therapies was only included as compared to IGIV. The relevant original reports and review articles and older classic studies (n = 92) were synthesized into an information foundation. Extracted data included laboratory and clinical findings, objective measures, and clinical impressions. Clinical recommendations were based on evidence quality, graded by study design, clinical experiences of IGIV in Neurology Advisory Board members, and the conditions of IGIV use in therapy. ***Results and Conclusions:*** In neurology, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. As a result, it is fairly common for best-practice decisions to rest on weaker evidence. The usefulness of IGIV in neurology can be described by a "combined score" based on evidence quality and strength of impact. Combined scores ranged from A+ (strongly recommended) to C (recommended as a last resort). The following clinical recommendations are made: IGIV is: strongly recommended for the treatment of Guillain-Barré syndrome (A+); favorably recommended for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy, dermatomyositis, and multifocal motor neuropathy (A); recommended as a second resort for the treatment of multiple scerosis and myasthenia gravis (B); and recommended as a last resort for the treatment of polymyositis, inclusion-body myositis, intractable epilepsies, and stiff-man syndrome (C).

**RÉSUMÉ: IGIV en neurologie - observations et recommandations.** ***But:*** Nous faisons un sommaire des données en faveur de l'utilisation d'immunoglobuline intraveineuse (IGIV) en neurologie à la lumière de son utilisation actuelle en clinique. Ce sommaire a inspiré le développement de recommandations pour l'utilisation efficace de l'IGIV en neurologie. ***Méthodes:*** Nous avons procédé à une recherche dans MEDLINE pour identifier les articles de revue pertinents en langue anglaise et les présentations originales (n = 231) sur l'utilisation de l'IGIV en neurologie (à l'exclusion des éditoriaux, des lettres à l'éditeur et des commentaires) publiés avant mars 1998. Les données sur les traitements alternatifs ont été incluses seulement pour les comparer à l'IGIV. Les présentations originales pertinentes, les articles de revue et les études classiques plus anciennes (n = 92) ont été résumés en une fiche d'information. Les données ainsi extraites incluaient des observations cliniques et biochimiques, des mesures objectives et des impressions cliniques. Les recommandations cliniques étaient basées sur la qualité des observations, classées par plan d'étude, les expériences cliniques des membres du conseil aviseur sur l'IGIV en neurologie et les conditions d'utilisation de l'IGIV en clinique. ***Résultats et conclusions:*** En neurologie, plusieurs pathologies sont mal comprises et les mécanismes par lesquels certaines thérapies procurent un bénéfice le sont encore moins. Il est donc assez fréquent que la meilleure décision clinique repose sur des données faibles. L'utilité de l'IGIV en neurologie peut être présentée sous la forme d'une "cote combinée" basée sur la qualité des observations et la force de l'impact. Les cotes combinées variaient de A= (fortement recommandée) à C (recommandée en dernier recours). Nous faisons les recommandations suivantes: l'IVIG est recommandée dans le traitement de la polyradiculoneuropathie démyélinisante inflammatoire chronique, la dermatomyosite et la neuropathie motrice multifocale (A); recommandée en deuxième recours pour le traitement de la sclérose en plaques et la myasthénie grave (B); et recommandée en dernier recours pour le traitement de la polymyosite, la myosite à corps d'inclusion, les épilepsies résistantes au traitement et le syndrome de l'homme raide (C).

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The Advisory Board met in Toronto April 1 and 2, 1998, to discuss and clarify the state of IGIV use in Canadian Neurology practice. Practice conclusions were determined from discussions at the Advisory Board meeting.

Immunoglobulin (Ig) was fractionated out of whole blood more than 50 years ago. By 1979, an intravenous formulation of intact immunoglobulin (immunoglobulin, intravenous [IGIV]) was available. It was found that IGIV therapy was effective in

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the treatment of primary and various secondary immunodeficiency disorders, autoimmune diseases, and some infectious complications.[1] During the 1980s and '90s, new generations of IGIV were formulated. Today, IGIV is almost entirely composed of IgG, with trace amounts of IgA and IgM.[1,2]

IGIV comes in several forms. In general this guide does not distinguish between them, although manufacturing differences have been shown to exist. IGIV discussed in this article include: Sandoglobulin® (Sandoz, Minneapolis, MN); Intraglobulin® (Biotest, Frankfurt, Germany); Venoglobulin® I (Alpha Therapeutic, Los Angeles, CA, and Institut Merceux, France); Gamimune® N (Miles-Bayer, West Haven, CT); Gammagard® (Baxter, Glendale, CA); Gammar® IV (Centeon, Kankakee, IL); Iveegam Immuno® (Immuno Canada, Mississauga, ON); and Polygam® (Baxter, American Red Cross, Washington, DC).

It has been reported that IGIV is used in Canada for more than 90 indications,[3] although far fewer are labeled clinical indications. Several off-label usage recommendations have been published as a result of the overwhelming off-label use of IGIV. Generally, these have relied on the expertise of groups of specialists in tertiary care centers, and a mix of Level I, II and III evidence.

These recommendations have been especially exciting for the field of neurology. In many neurologic disorders, pathophysiology is poorly understood. As a result, it has been difficult to rationalize therapies from a pharmacobiologic basis. This article will clarify today's state of knowledge about the use of IGIV and directly compared alternatives, in treating neurologic disorders. Note, for legibility, some studies methods have been tabled in Addendum 1, as indicated.

## Evidence and Clinical Considerations Peripheral Nervous System Disorders

### Guillain-Barré Syndrome

#### *IGIV as Effective as PE*

The first randomized-controlled trial (RC-trial) of IGIV treatment in GBS appeared in 1992 (Addendum 1).[4] Improvement by one or more grades within four weeks on a seven-grade scale of motor function was the primary outcome of the trial.

Fifty-three percent of IGIV-users, and 34% of plasma exchange (PE)-treated patients showed functional improvement of one or more grades (19% difference, P = 0.024). The median time to improvement by one grade was 27 and 41 days for IGIV-users and PE-treated patients, respectively (P = 0.05). As well as the favorable secondary outcome results summarized in Table 1, IGIV-users had "significantly" fewer complications and less need for artificial ventilation than PE-treated patients.

It should be noted that these results reflected all patients from the trial's multinational centers. Differences were found between the PE arms of the studies at these centers, which suggested the IGIV:PE comparison was flawed.[5] On further analysis however, the authors concluded that IGIV was indeed at least as effective as the more complicated PE in treating GBS, and possibly superior.[6]

A later pilot study that compared IGIV and PE in the treatment of GBS patients corroborated these results.[7] Using a similar graded functionality scale, 69% of IGIV-users and 61% of PE-treated patients had improved by one disability grade at one month. Other standard outcome measures, including relapse rates, did not differ between the two groups.

#### *IGIV, PE and IVIG/PE Equivalence*

A 1997 randomized-controlled double-blind trial (RC-dB trial) again compared the relative efficacy of PE and IGIV, as well as a combined PE/IGIV therapy, for the treatment of GBS (Addendum 1).[8]

At four weeks, patients were assessed for changes on the seven-grade disability scale mentioned above. Whereas primary outcome improvements were significant (Table 1), differences between treatment groups' primary or secondary outcomes were not. Although not significant, it should be noted there were positive trends in some outcomes with the PE/IGIV combined treatment. It was concluded that PE and IGIV had equivalent efficacy in treating severe GBS within two weeks of neuropathic symptom onset, and that the studied PE/IGIV combination did not confer a significant advantage.

Several recent case-reports of severely compromised GBS patients have corroborated the conclusion that IGIV is an effective treatment, and have suggested that IGIV is an excellent first-line therapy for acutely ill patients.[9,10] It should also be noted however, that at least one recent non-human GBS model has not shown a positive benefit from IGIV, although results remain ambiguous.[11]

#### *Pediatric GBS*

In general, it is accepted that morbidity and mortality outcomes are better in children than in adults, possibly because of a higher tolerance for more intense IGIV dosing. Three open trials have demonstrated that IGIV has an especially rapid impact in

**Table 1:** Significant Improvements.

| 1992 RC-trial with Open Treatment[4] | 1997 RC-dB Trial[8] |
|---|---|
| **Primary Outcome Criteria:** | **Primary Outcome Criteria:** |
| 19% more IGIV-users achieved ≥ 1 grade improvement, compared to PE-treated patients (P = 0.024) | mean improvement on 7-graded scale... |
| | IGIV-users (n = 130): 0.8 grades (SD 1.3) |
| | PE-treated patients (n = 121): 0.9 grades (SD 1.3) |
| **Secondary Outcome Criteria:** | |
| time until one grade improvement: favoring IGIV – p = 0.05 | PE/IGIV-users (n = 128): 1.1 grades (1.4 SD) |
| time until independent locomotion: favoring IGIV – p = 0.07 | |
| need for assisted ventilation in the second week: favoring IGIV – p ≤ 0.05 | **Secondary Outcome Criteria:** |
| complication rate: favoring IGIV – p ≤ 0.01 | none |



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**Table 2:** Greater Dosages over Shorter Periods Support Faster Recovery in Pediatric GBS.

| | IGIV-users | | Non-users |
|---|---|---|---|
| | **Canadian Patients** | **Turkish Patients** | **Turkish Patients** |
| Mean No. Days to Improve by 1 Grade (Range) | 17.4 (5–51) | 20.8 (3–60) | 62.4 (9–270) |
| Change in Disability Grade at 4 Weeks | not recorded | 1 grade | 0.35 grades |

**Table 3:** Five Factors Promoting the Impact of IGIV in CIDP.

1- disease duration ≤ 1 year
2- progression of weakness until treatment
3- symmetry in arm and leg weakness
4- arm areflexia
5- decreased motor nerve conduction velocity of the median nerve

Note: highest chance of improvement after IGIV – those with active CIDP and weakness in arms and legs.

treating pediatric GBS. In dosages of 0.4 g/kg/day for five days,[12] 1 g/kg/day for two days,[13] or 2g/kg in a single dose,[14] children appeared to recover more quickly than adults.

In one of these open trials, the mean time required to improve by one or more grades on the motor-function scale (above) was 3.5 days after treatment and the mean period to regain ambulation, 11.2 days (Addendum 1).[14] During the follow-up period (mean 14.5 months), one patient relapsed at five months, whereas the others demonstrated full mobilization throughout. No IGIV-related side-effects were reported. The authors concluded that the early use of a single IGIV dose may prevent further progression of GBS, thereby shortening its clinical course.

A faster rate of recovery with greater dosages for shorter periods was confirmed in a retrospective study of pediatric GBS patients treated in Turkey and Canada (Addendum 1).[15] IGIV-users showed a significantly faster recovery by functional disability grades than non-users, and the greater/shorter regimen correlated with faster recovery times (Table 2). It should be noted that although the authors cautioned readers that site-specific biases may have influenced the Canadian:Turkish comparative results, they concluded that the study did demonstrate a difference in recovery time due to dosage size per period.

Using the strongest evidence above, the "usefulness" of IGIV in GBS was rated at an A+, based on an A+[7],[11] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

## Chronic Inflammatory Demyelinating Polyradiculoneuropathy

The first clinical case-reports showing the potential of IGIV in treating chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) emerged in the early 1980s. Most of the IGIV literature in this area relates to idiopathic CIDP, as opposed to polyneuropathy associated with a paraprotein (monoclonal Ig). Whereas it may be that the same regimen would be effective for idiopathic CIDP and paraprotein-associated polyneuropathy, this has not been supported by the results of available studies.

### *Idiopathic CIDP*

Two retrospective studies suggested that IGIV improved clinical outcomes.[16] The first found that 62% of CIDP patients improved after IGIV administration – the need for intermittent IGIV infusions to maintain clinical improvement in about one-third of these patients suggested IGIV was responsible for the improvement. The second showed the chance of improvement after IGIV treatment was over 90% if five factors were present (Table 3).

*IGIV better than placebo.* In an early RC-dB trial, CIDP patients who were positively maintained on IGIV were crossed-over to non-treatment – all patients deteriorated.[17] All patients were then randomized to IGIV (0.4 g/kg/day) or placebo (albumin) for five consecutive days – IGIV-users responded within one week, while placebo-users did not ever. As well, IGIV appeared to leave a residual positive impact; after the trial, all patients were returned to non-treatment – IGIV-users had a mean 6.4 weeks prior to deterioration whereas placebo-users had 1.3.

However, a subsequent RC-dB trial in untreated CIDP patients did not corroborate these findings of significant difference between IGIV and placebo groups.[18] Indeed, in this trial, three placebo-users who showed slow and progressive deterioration before the trial had a dramatic clinical improvement (four of the IGIV-users did as well) – the degree of improvement in both groups was equivalent. Further analysis suggested that IGIV's shortcomings in this trial reflected a skewed sample – it is possible that only a specific subgroup of CIDP patients respond to IGIV treatment.

*Objective demonstration that IGIV helps in CIDP.* One six-week RC crossover trial comparing PE with IGIV found that IGIV was comparable to PE in significantly improving endpoints compared to baseline (neurologic disability score [NDS], summed compound muscle action potentials [CMAP], muscle weakness of the NDS – $P \leq 0.001$–$0.006$), (Addendum 1).[19]

More recently, chronic-progressive or -relapsing CIDP patients were treated in an RC-dB crossover trial (Addendum 1).[20] Significant differences that favored IGIV were seen in all neurologic function assessments completed in two separate analyses (Table 4). After randomized treatment, placebo patients were crossed-over to IGIV. Nineteen (63%) patients improved in their NDS, clinical grade, and grip strength ($P \leq 0.002$). There were no significant differences between chronic-progressive and -relapsing patients. Eight of the nine chronic-progressive IGIV responders gradually improved to normal function, and were stabilized with a single five-day course of IGIV, and in five of these eight, small doses of immunosuppressive drugs.

Among the 10 chronic-relapsing IGIV responders, improvements lasted a median six weeks, and were reproducible with open label treatments; a single IGIV dose (≤ 1 g/kg) prior to expected relapses stabilized these patients. A positive response to IGIV was most likely in patients with acute relapse, or with evident CIDP for one year or less.

Table 5 summarizes the results of the discussed RC-dB studies.[17,18,20] Several recent case-reports, and long-term case

Table 4: 1996 RC-dB CIDP trial – Five Neurologic Function Assessments and Summary Comparison.

| | Improvements (mean + SD) | Re-analysis: Improvements (mean + SD) |
|---|---|---|
| neurologic disability score (NDS) | 24.4 + 5.4 grades ($P \leq 0.002$) | 35.6 + 25 grades ($P \leq 0.0001$) |
| clinical grade (CG) | 1 + 0.3 grades ($P \leq 0.001$) | 1.3 + 1.9 grades ($P \leq 0.002$) |
| grip strength (GS) | 6.3 + 1.7 kg ($P \leq 0.005$) | 9.8 + 7.7 kg ($P \leq 0.001$) |
| electrophysiological studies (at 4 weeks) | Statistically significant | NA |
| summed motor conduction velocities (MCV) | (sigma MCV; $P \leq -0.0001$) | NA |
| summed compound muscle action potentials | (sigma proximal CMAP, $P \leq 0.03$) | |
| (CMAP) evoked with proximal stimulation | of median, ulnar, peroneal and tibial nerves. | NA |

Scores unchanged or worse with placebo in both analyses, compared to IGIV.

Table 5: RC-dB trials with CIDP Patients Treated with IGIV.

| | | % Improved |
|---|---|---|
| 1990 – crossover[17] | IGIV* (n = 15) | 100 |
| | -vs.- | significant- |
| | placebo (n = 13) | 0 |
| 1993 – no crossover[18] | IGIV* (n = 7) | 27 |
| | -vs.- | -not significant- |
| | placebo (n = 7) | 23 |
| 1996 – crossover[20] | IGIV* (n = 30) | 63 |
| | -vs.- | -significant- |
| | placebo (n = 30) | 17 |

*0.4 g/kg/day for 5 consecutive days

follow-ups in adults and children have corroborated IGIV's beneficial impact in CIDP,[21-23] and have suggested that focal upper limb demyelinating neuropathy – a probable CIDP variant – may be particularly responsive to IGIV.[24]

*Long-term Maintenance with IGIV.* Over long periods of time, pediatric CIDP patients often have a more rapidly fluctuating illness course than adults, and children show a relapsing course significantly more frequently.[22] However, children's recovery from relapse is often complete, more-so than adults'. One review found that courses of IGIV were generally effective in treating relapses over the long-term.[22]

A retrospective study of CIDP patients compared IGIV (n = 22) and PE (n = 33) as long-term therapy.[25] Approximately 64% of the IGIV, and 70% of the PE treated patients responded well. Of the IGIV-responders, most required only one course of treatment, while seven received repeated courses for 6–51 months. Importantly, long-term treatment with PE showed transient complications (hypotension [n = 3], poor venous access [n = 3], hematoma [n = 1], bleeding diathesis [n = 1], hypocalcemia [n = 1], and septicemia [n = 1]), whereas no "significant" complications were observed in long-term IGIV-users. This study suggested that whereas PE and IGIV were effective long-term treatments for CIDP, PE had more side-effects.

A recent open trial of IGIV in 18 patients with CIDP or multifocal motor neuropathy (MMN) showed a benefit from IGIV even after a long disease duration (≤ 19.5 years).[26] Sixteen patients responded very well to treatment of at least six months. Six of these were able to stop treatment, and remain in remission for up to 63 months, while the remaining 10 patients continued to receive IGIV in different dosages. The authors concluded that IGIV was effective and safe as a long-term maintenance therapy for CIDP and MMN.

Using the strongest evidence above, the "usefulness" of IGIV in CIDP was rated at an A, based on an A+[20,21,23] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

### Paraprotein-associated Polyneuropathy

Polyneuropathy associated with IgM paraprotein targeted at myelin associated glycoprotein (IgM anti-MAG) is etiologically distinct from idiopathic CIDP. An open trial examined the relative efficacy of IGIV and recombinant interferon-alpha with the IgM anti-MAG CIDP variant (Addendum 1).[27] Ten percent of IGIV-users and 80% of IFN-alpha-users showed an NDS improvement greater than 20% at six months ($P = 0.005$). This response difference was reflected in IGIV-users' lower mean NDS – it decreased by 8%, whereas it improved by 31% in the IFN-alpha-users for at least 12 months. It should be noted that IFN-alpha-users' improvement was primarily sensory ($P = 0.02$) – the NDS motor component was unchanged ($P = 0.39$). The authors concluded that IGIV was not effective in these patients, whereas IFN-alpha was.

In contrast, IGIV showed a greater impact in 67 CIDP patients with monoclonal gammopathy of uncertain significance (CIDP-MGUS).[28] EMG-assessed conduction block was present in about three-quarters of patients, but only about one-third had a pure demyelinating neuropathy. Sixty-six percent of the patients responded to either IGIV, PE or steroids – Rankin scores (i.e., functional improvement) were greatest with PE. CIDP-MGUS patients showed characteristic symptomatology compared to idiopathic CIDP patients, but responded to PE, IGIV and steroids equivalently.

These two studies suggest that whereas IGIV may not be effective in polyneuropathy associated with IgM anti-MAG paraprotein, it probably is in polyneuropathy associated with IgG, IgA, and IgM non anti-MAG paraproteins.

### Multifocal Motor Neuropathy

Early case-reports suggested that patients with MMN improve after cyclophosphamide (CTx) therapy, but not after prednisone or PE.[29] Because of the involvement of autoimmune factors in MMN, IGIV was a natural choice for further exploration.

An early RC-dB crossover trial in MMN patients showed that IGIV had a significant beneficial effect in patients who demonstrated complete conduction block, especially in muscle strength



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(Addendum 1).[30] The benefits of IGIV have been corroborated by more recent studies – a recent review summarized the comparative benefits of IGIV against steroids, immunosuppressors and PE.[31] It concluded there were strong indications of IGIV's short term efficacy in MMN, especially as early treatment, although strict proof was not yet available. Similar conclusions have been reported in two other extensive reviews.[32,33]

### *A Short-term Benefit from IGIV*

One recent open trial looking at the impact of IGIV treatment for long-term MMN showed clinical improvements in 67% of patients (mean isometric strength increase 54.5%) – high titers of IgM anti-GM1 antibodies were predictive of a positive response to IGIV (Addendum 1).[34] Unfortunately, the impact of IGIV did not last.

### *Maintenance of Short-term Benefit from IGIV*

A second open trial with seven MMN patients more precisely explored the durability of IGIV's impact. It found that treatment with IGIV 0.4 g/kg/day for five consecutive days improved muscle strength until a maximum of 12 weeks.[35]

Thereafter, patients required an IGIV maintenance regimen for 2 - 4 years to remain stable (one dose of 0.4 g/kg/week). The regimen eventually failed in three patients, as measured by muscle strength deterioration in four of the 28 muscle groups that had initially shown an improvement, and in two groups with normal strength at the start of IGIV treatment. Electrophysiological studies of those patients revealed an alleviation of initial conduction blocks paralleled the advent of new blocks and ongoing axonal degeneration.

### *IGIV/CTx Combination*

An open trial explored the long term effect of an IGIV/oral-CTx combination in MMN patients (Addendum 1).[36] The purpose of the trial was to determine whether oral-CTx use would allow the suspension of IGIV after a fixed treatment period. All patients improved significantly with the combination treatment in terms of the primary outcome variables (median Rankin [P = 0.0335] and mean MRC-scale [P = 0.0561]). Improvement correlated with a reduction in the number of nerves with partial motor conduction block (P = 0.0197), and antiglycolipid antibody titers, in all but one patient.

It was found that IGIV courses were indispensable to maintain improvement, although the interval between courses could be progressively prolonged after 3 - 7 months of oral CTx. Eventually, in three patients, IGIV and CTx were both stopped for up to two years before relapse.

The finding that CTx led to hemorrhagic cystitis in two patients and persistent amenorrhea in one patient, whereas IGIV showed no side-effects, suggests that the risk/benefit balance of IGIV must include a good understanding of IGIV's benign nature. Indeed, the authors concluded that, whereas oral CTx may help to induce a sustained remission, its side-effects suggest it should be reserved for MMN patients who are unreasonably dependent on frequent IGIV courses to remain in remission.

Using the strongest evidence above, the "usefulness" of IGIV in MMN was rated at an A, based on an A+[33] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

## Neuromuscular Junction Disorders

### Myasthenia Gravis

IGIV has a long history as a treatment for MG – small weekly IM injections were used beneficially through the 1970s. Three reviews of 13 1980s trials provide data on a total of 132 patients, most of whom had acute MG and a previous thymectomy.[37-39] Patients received IGIV manufactured by several companies, as 0.4 g/kg/day for five days (n = 110), 0.6 - 0.9 g/kg/day for five days (n = 16), and 10 g/day for five days (n = 6).

In most trials, IGIV was administered as a 3 - 6% solution in normal saline. Anticholinesterases, corticosteroids or azathioprine were almost always being taken prior to, and during IGIV administration. Acute exacerbation or respiratory failure were coincident with about half of patients' IGIV use. Overall, 74% of patients improved with IGIV. Improvement was noted in 50 - 100% of each trial's sample, except for in one trial's six patients, who received IGIV 10 g/day for five days, with no improvement.[40]

It should be noted that the conclusion that IGIV was responsible for the results above is confounded by: 1) spontaneous improvement after the first 1 - 3 years in the majority of patients;[41] and 2) improvement accelerations due to other common interventions, such as corticosteroids, cytotoxic immunosuppressant drugs and thymectomy.

### *Benefit from IGIV/Steroid Combination*

In a more complex open trial, muscle strength and vital capacity improvements were seen after 22 of 31 IGIV courses in 11 patients (79%) (Addendum 1).[38] Co-administration with a corticosteroid was twice as likely as IGIV alone to cause improvement, and caused a longer beneficial impact (64 vs. 34 days).

### *Benefit from IGIV Alone*

A 1998 open trial showed that 56% of IGIV courses benefited patients (Addendum 1).[42] In benefiting patients, improvement was demonstrated after a median of three days (range 1 - 12) – the peak benefit occurred after seven days (range 4 - 30).

Patients with a Grade-III University of Virginia's Modification of Osserman's (UVMO) classification did not benefit from IGIV, whereas Grade-V patients improved in five of the seven courses. Acutely-relapsing and subacutely-deteriorating or chronic-static patients responded equally to IGIV (50% vs. 60%). The authors concluded that high-dose IGIV can be an effective therapy in deteriorating generalized-MG patients, with an improvement within a few days of IGIV treatment that peaks by week-2 of therapy.

### *IGIV vs. PE*

Several reviews and controlled trials (C-trails) have shown that IGIV and PE both benefit MG patients.[32,43,44] A recent RC-trial compared the efficacy and tolerance of IGIV to PE in MG exacerbations, using two IGIV dosages (Addendum 1).[45] Myasthenic muscular score (MSS) variations were similar across the PE and IGIV groups (median 18 vs. 15.5, p = 0.65). Eight PE patients reported side-effects, whereas only one IGIV patient did (p = 0.01). Interestingly, the efficacy of the five-day IGIV course was slightly less than the three-day – the authors were unable to analyze this difference significantly with such a small sample size.

**Table 6:** RC-trial of IGIV in Dermatomyositis – Primary Outcomes.

| | Strong improvement? | | |
|---|---|---|---|
| | **IGIV (n = 8)** | **Placebo (n = 7)** | **Placebo, after crossed from IGIV (n = 8)** |
| Muscle strength test | yes (n = 8) | no | no |
| Neuromuscular symptom score | yes (n = 8) | no | no |
| Changes in skin rash | yes (n = 8) | no | no |
| Histologic changes in muscle biopsies | yes (n = 8) | no | no |

### *PE Followed by IGIV*

The similar efficacy of IGIV and PE has led some researchers to study sequenced use of these therapies. In one C-trial, significant improvement in UVMO classification, clinical involvement and functional activity grades was shown (Addendum 1).[44]

Improvements began 1 - 6 days following IGIV administration, lasting through the 16-week follow-up period. The authors concluded that the PE/IGIV sequenced combination in exacerbated MG may be synergistic, with each therapy affecting a different immune mechanism.

### *Pediatric MG*

A few studies have shown that the impact of IGIV in adult patients can be extrapolated to neonates and children.[46,47] However, these data are far from complete, and confirmation of IGIV's use in pediatric MG awaits RC-trials.

Using the strongest evidence above, the "usefulness" of IGIV in MG was rated at a B, based on an A[49] and C[46] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

### *Stiff-person Syndrome*

Two open trials of IGIV use in stiff-person syndrome showed six of six patients improved, although improvement parameters were loosely defined.[48,49] Other anecdotal reports and case-reports have reported similar findings.[50]

Using the strongest evidence above, the "usefulness" of IGIV in stiff-person syndrome was rated at a C, based on a C[52,53] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

## Idiopathic Inflammatory Myopathies

Inclusion-body myositis (IBM), dermatomyositis (DMS), and polymyositis (PM) are distinct idiopathic inflammatory myopathies regarded as autoimmune diseases.[51] High-dose steroid therapy is very effective for many patients with DMS and PM, but is encumbered by several difficult management issues:[52] 1) disease relapse is common as steroid therapy is discontinued; 2) side-effects, such as steroid myopathy, diabetes, avascular necrosis, cataracts, or hypertension are common; and 3) some patients are wholly or partially unresponsive clinically.

Small open trials and case-reports have shown that immunosuppressant medications and treatments can be useful adjunctives in PM and DMS (e.g., azathioprine, methotrexate, cyclosporine, and PE).[53-57] These therapies' significant side-effects contrast IGIV's benign nature,[52] a strong alternative as a result of the variety of immune mechanisms involved in DMS and PM pathogenesis.

The first reported successful use of IGIV in treating myositis patients was with a PM patient who was resistant to steroid therapy.[58] Later, 20 adult patients with refractory DMS or PM, the majority of which had failed adjunctive immunosuppressant treatment, were treated with IGIV.[59] Seventy-five percent of patients improved significantly.

Another small open trial (n = 11) showed that monthly IGIV dosages alone, for a mean of four months, beneficially influenced serum creatine phosphokinase (CPK) levels in 73% of patients, but only had a clinical impact in 27% of patients.[60]

### *IBM*

IBM is distinguished from other idiopathic inflammatory myopathies by histopathologic abnormalities,[61] although histopathologic exceptions have been reported.[62] The molecular basis for the disease remains unknown.[63]

IBM presents as sporadic-IBM or hereditary-IBM. Sporadic-IBM is the most common progressive muscle disease of older persons. Unfortunately, IBM is generally unresponsive to treatment.

### *DMS*

A number of small open trials of IGIV in DMS and PM have shown promising results.[64] Indeed, a recent dermatological review listed high-dose IGIV as an acceptable treatment for DMS, along with the autoimmune bullous disorders (epidermolysis bullosa acquisita, pemphigoid, and pemphigus).[52]

One RC-trial of IGIV in treating 15 patients who had treatment-resistant DMS provides the strongest evidence for the use of IGIV in this variant of idiopathic inflammatory myopathy.[65] Primary outcomes are listed in Table 6. As well, decreases in IGIV-users' serum CPK, improvement in skin rash, and eradication of membrane attack complex in biopsies suggested that IGIV interfered with the pathogenic process of the disease.

*Juvenile DMS.* Juvenile DMS patients failing to improve with high-dose steroids and adjunctive immunosuppressants have also been successfully treated with IGIV. In one open trial, DMS-specific rashes and muscle strength showed dramatic improvement within 2 - 4 months of IGIV treatment.[66] Importantly in these patients, it was then possible to diminish, or discontinue corticosteroid doses. Other open trials (n = 7,[67] n = 9[68]) have shown similar results, albeit with variations in IGIV regimen.

A more recent open trial (n = 7) of juvenile-DMS patients looked at the impact of monthly IGIV treatments in conjunction with other ongoing therapies.[69] The reasons for adding IGIV included: disease exacerbation, continued need for high-dose steroid for maintenance, other drug cytotoxicity, or concern over other therapies' ability to quickly induce remission in patients with severe symptoms.

Only one patient failed to benefit from IGIV. Three showed quick clinical responses, from day-2-3 of treatment – two improved slowly, and could thereafter be maintained on a greatly reduced steroid dose – one responded favorably to the first



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**Table 7:** RC-dB trial of IGIV in Polymyositis (in IBM Patients).

| | **IGIV**<br>**n = 9**<br>**mean age 61.2 yrs**<br>**mean disease duration 5.6 years** | **Placebo**<br>**n = 10**<br>**mean age 66.1 yrs**<br>**mean disease duration 7.4 years** |
|---|---|---|
| expanded MRC-scale | +4.2 (-16 to +39.8), (not sig) | +2.7 (-10 to +8), ($p \leq 0.1$) |
| Maximum Voluntary Isometric Contraction (MVIC) | | |
| -in lower limbs | sig improvement relative to placebo in 39% | N/A |
| -in other limbs | sig decrease in 28% | N/A |
| Quantitative swallowing studies | sig improvement relative to placebo | N/A |

three courses only. Unfortunately, four of the patients who benefited from IGIV showed an aggravation of symptoms some time after discontinuing IGIV.

The authors concluded that IGIV is valuable as a quick, potent adjuvant, especially to reduce juvenile-DMS patients' exposure to other immunosuppressive therapies for various reasons. However, they added that their results suggested the durability of IGIV's effect is doubtful.

### *PM in IBM Patients*

The impact of IGIV in PM is less clear than in DMS. In an RC-dB crossover trial of IGIV in 19 IBM patients, patients received monthly IGIV infusions of 2 g/kg or placebo for three months, with subsequent crossover.[70] Primary outcomes and results are listed in Table 7.

Modest gains in the IGIV group compared to placebo were evident, but the clinical importance of these gains was unclear. However, for six patients (28%), IGIV had a definite beneficial impact on functionality, greater than 10 MRC-scale points.

Using the strongest evidence above, the "usefulness" of IGIV in DMS was rated at an A, based on an A[69] evidence quality and its impact. The "usefulness" of IGIV in PM and IBM was rated in the same manner at a C, based on an A+[74] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

## Central Nervous System Disorders

### Demyelination Syndromes: Multiple Sclerosis

Open trials in the 1980s showed that IGIV reduced acute multiple sclerosis (MS) exacerbations and arrested disease progression,[71,72] whereas IM-IgG[73] had similar but less consistent results. Other trials in MS have shown that IGIV treatment may be followed by recovery of visual function in patients with chronic optic neuritis who failed to respond to steroids,[74] or by improvement in isometric muscle testing,[75] although general clinical opinion is that fixed deficits reflecting neuronal degeneration cannot be reversed.

More recently, the results of a C-trial suggested that IGIV suppressed the ongoing pathologic process in MS (Addendum 1).[76] Relapsing-remitting MS patients' mean annual exacerbation rate (AER) was almost one-quarter the initial AER after one year of therapy, while remaining unchanged in the controls. This rate continued to decrease during the second and third years of the trial, and the difference between IGIV-treated and control patients remained significant (Table 8). Among the IGIV-users at three years, duration of IGIV treatment correlated with neurologic ability and lower AER. As well, most IGIV-users experienced mild to moderate, whereas controls experienced moderate to severe acute exacerbations.[77]

Among IGIV-users, mean Kurtzke Expanded Disability Status Scale (EDSS) scores decreased after one year of IGIV treatment, while scores increased in controls – mean changes in EDSS scores at one, two and three years were significant (Table 9).

### *Objective Demonstration of Benefit from IGIV*

In the more recent AIMS RC-dB trial (Addendum 1),[78,79] IGIV-using relapsing-remitting MS patients' exacerbation rate was about halved (Table 8).[79] The EDSS score decreased in the IGIV-treated patients and increased in the placebo group (Table 9).[78] The decrease in IGIV-users' EDSS score relative to placebo-users was significant, but modest. It was concluded that the early improvement in IGIV-users' EDSS scores suggested the activation of repair mechanisms (e.g., remyelination), whereas fewer exacerbations throughout the trial probably resulted from immunoregulatory effects.

Another 1997 RC-dB trial with relapsing-remitting or -progressive MS in 25 patients corroborated these results, although significance was not achieved. The authors concluded that IGIV treatment may help to prevent exacerbations in patients with relapsing MS.[80]

### *Further Confirmation of Benefit from IGIV*

A 1998 RC-dB trial in 40 patients whose MS status was confirmed with magnetic resonance imaging (MRI) also corroborated earlier results (Addendum 1).[86] IGIV-treated patients showed a decreased AER, reflecting a 38.6% reduction in relapse rate (Table 8).

The median post-treatment time for IGIV-users until first exacerbation was 233 days, vs. 82 days for placebo-users ($p = 0.003$). Six IGIV-users had no exacerbations throughout the two-year follow-up, while all placebo-users had exacerbations. IGIV-users' EDSS scores were significantly less than placebo-users' (Table 9), although changes in total lesion scores evaluated by brain MRI did not show a significant difference between groups.

### *Magnetic Resonance Imaging – Impact of IGIV in MS*

In general, it is accepted that the beneficial effect of drugs reducing the frequency of MS relapses and neurologic disability can be confirmed by MRI findings.[82] In some studies, MRI scores from IGIV or placebo groups have suggested that IGIV treatment arrested disease progression,[83] although contradictory results have also been found.[84]

**Table 8:** Multiple Sclerosis Trials – Exacerbation Rates.

| | 1994 C-trial[77] – Change in Mean Annual Exacerbation Rate<br><br>IGIV vs. Placebo | 1997 RC-dB trial[79] – Percentage of Patients at Two Years Who Showed Significantly... | 1998 RC-dB trial[81] – Change in Mean Annual Exacerbation Rate<br><br>IGIV vs. Placebo |
|---|---|---|---|
| year 1 | -2.7 vs. 0.0, P ≤ 0.001 | | -1.1 vs. 0.25 |
| year 2 | -2.9 vs. -0.6, P = 0.005 | ...Less Exacerbations — IGIV 31% placebo 14%<br>...More Exacerbations— IGIV 16% placebo 23% | -1.43 vs. -0.15<br><br>p = 0.0006 overall |
| year 3 | -3.2 vs. -2.0, P ≤ 0.001 | | |

A 1998 RC-dB crossover trial assessed whether IGIV decreased disease activity, as MRIs suggested, in relapsing MS (Addendum 1).[85] Patients showed fewer enhancing lesions per MRI with IGIV (median 0.4, range 0 - 9.3) than with placebo (median 1.3, 0.2 - 25.7, p = 0.03). Fifteen IGIV-period patients and seven placebo-period patients were exacerbation free (p = 0.02), although the difference between the number of exacerbations in the IGIV and placebo periods was not significant (Table 10). Indeed, the difference between the two periods did not reach significance in any of the remaining secondary measures.

Using the strongest evidence above, the "usefulness" of IGIV in MS was rated at a B, based on an A+[83,85,86] evidence quality and its impact (see the Usefulness of IGIV to Treat Neurologic Disorders section).

### Adult and Pediatric Intractable Epilepsies

A 1994 review of 24 open trials involving a total of 368 patients with intractable epilepsy receiving IGIV (age ≤ 1 - 35 years, mean 7.3 years), found that the mean clinical seizure reduction and the mean EEG improvement due to IGIV was 52% and 45%, respectively.[86] IGIV dosages varied between 0.3 and 6.8 g/kg during a period of 0.15 - 12 months. Complete seizure remission was reported in 23% of patients. Whereas the lack of C-trials (or better) surveyed in this review means that reported results are not conclusive, they strongly suggest that IGIV may be effective in some patients.

An open trial in West or Lennox-Gastaut syndrome patients demonstrated the effectiveness of a biphasic IGIV regimen (Addendum 1).[87] The patient group experienced a 70% reduction in clinical seizures, coincident with a 40% reduction in spike-wave discharges on EEG. All 15 patients showed acceleration of EEG background activity and improved psychomotor development. The authors concluded IGIV should be considered when other treatments have failed.

A C-dB trial in refractory epileptic patients showed a positive trend in favor of IGIV – decreasing the daily seizure frequency at six months by at least 50%, albeit this was not significant (P = 0.095) (Addendum 1).[88] As well, no relationship was seen between dose and efficacy (P = 0.31).

Inconclusive results were also reported in an open trial in 19 Rasmussen's syndrome patients treated with IGIV, and in an uncontrolled manner, steroids.[89]

A recent case-report illustrated the dramatic impact of IGIV in an eight-year-old Landau-Kleffner syndrome (LKS) patient refractory to known therapies.[90] LKS is a pediatric condition, characterized by acquired aphasia associated with epileptiform discharges in the form of ESES (electrographic status epilepticus during sleep). After two of three initial treatment courses,

**Table 9:** Multiple Sclerosis Trials – Mean Change in EDSS Score (IGIV vs. Placebo).

| | 1994 C trial[77] | 1997 RC-dB trial[79] | 1998 RC-dB trial[81] |
|---|---|---|---|
| year 1 | -0.3+0.58 vs. 0.2+1, P = 0.182 | | |
| year 2 | | -0.23+0.2 vs. 0.12+25, p = 0.008 | -0.3 vs 0.15, p = 0.001 |
| year 3 | 0.35+0.58 vs. 1.7+0.98, p = 0.001 | | |

**Table 10:** Clinical and MRI-outcomes – RC-dB Crossover Trial End-points.

| | End-points | Results That Reached Significance |
|---|---|---|
| Primary | median number of gadolinium-enhancing lesions on monthly serial MRI | IGIV period better than placebo (IGIV 0.4 : placebo 1.3, p = 0.03) |
| Secondary | number of patients with exacerbations | IGIV period better than placebo (IGIV 3/18 : placebo 11/18, p = 0.02) |
| | frequency of exacerbations | nil |
| | clinical neurologic ratings | nil |
| | total MS lesion load on T2-weighted MRI | nil |
| | multimodal evoked potentials | nil |



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clinical and electrographic improvement lasted a few months. After the third, remission was continuous past 16 months.

Another case-report of a pediatric LKS patient demonstrated that IGIV had a very dramatic effect in the third of three relapses.[91] The first two relapses were reversed with steroid therapy, with an effect comparable to IGIVs in the third relapse.

Using the strongest evidence above, the "usefulness" of IGIV in Cryptogenic West and Lennox-Gastaut syndrome was rated at a C, based on a C[92] evidence quality and its impact. In the same manner, the "usefulness" of IGIV in Landau-Kleffner syndrome (E[95,96] evidence quality), refractory epilepsies (B[95,96] evidence quality), and Rasmussen's syndrome (C[94] evidence quality) were rated at a C (see the Usefulness of IGIV to Treat Neurologic Disorders section).

## Clinical Recommendations

The evidence from RC-dB trials is the strongest level of clinical evidence available. In well-understood disorders, where a strongly supported therapy is available, evidence of benefit from RC-dB trials is required to switch to a new alternative.

In neurology, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. As a result, it is fairly common for best-practice decisions to rest on somewhat-less-than RC-dB trial evidence. This article used a grading of evidence quality, loosely based on U.S. Preventive Services Task Force guidelines, to clarify clinical recommendations (Table 11).

**Table 11:** Evidence Grades.

| | |
|---|---|
| A+ | RC-dB Trials |
| A | RC-trials |
| B | C-trials |
| C | Open Trials |
| D | Retrospective Audits |
| E | Case-reports, Expert Opinion |

## The Usefulness of IGIV to treat Neurologic Disorders

In the author's opinion, best-practice use of IGIV in neurology is two-phased: "initial" and "later."

### Recommendations for the Initial Phase

In an initial therapy phase, best-practice begins with treatment based on comparing alternative therapies – first, in terms of the quality of substantiating evidence; and second, when the evidence quality is of equal weight, in terms of demonstrated treatment impact.

Grading the evidence for IGIV in an indication, and rating the shown impact of IGIV treatment allows us to rank IGIV's "usefulness" in neurology for the purpose of comparison. The "usefulness" of IGIV in neurology can be described by a "combined score" based on evidence quality and strength of impact. Combined scores range from A+ (strongly recommended) to C (recommended as a last resort). Table 12 lists the better evidence for each indication discussed in this article, and the combined scores resulting from this evidence. This ranking compares favorably with another recent set of Canadian recommendations,[92] and two reviews.[32,51] The reviews listed GBS, CIDP, and MMN as acceptable bff-label indications, with dispute around IGIV use in DMS.

### Recommendations for the Later Phase

In a later therapy phase, best-practice is based on comparing alternative therapies as above (quality of evidence and demonstrated treatment impact), and in terms of the individual patient's previous response to each possible therapy.

## Conclusion

In neurology today, many disorders are poorly understood, and the mechanisms behind beneficial regimens even less so. IGIV has been conclusively shown in some indications to be an effective therapy. In other indications, study results have only hinted at potential benefits, because of lack of study rigor or possible confounding influences.

In one set of Canadian recommendations,[92] six non-label neurologic disorders were recommended for current IGIV use, and a further nine recommended for investigation. Several reviews have listed Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN) as acceptable off-label indications,

**Table 12:** Evidence and "Combined Scores".

| Quality of Evidence of Benefit + | Shown Outcomes of Significance in... = | Combined Score |
|---|---|---|
| A+[4,8] | GBS | A+ |
| A+[17,18,20] | CIDP | A |
| A[65] | DMS | |
| A+[30] | MMN | |
| A[45], C[42] | MG | B |
| A+[78,80,81] | MS | |
| A+[70] | PM and IBM | C |
| C[87] | Cryptogenic West and Lennox-Gastaut syndrome | |
| E[90,91] | Landau-Kleffner syndrome | |
| B[88] | Refractory epilepsies | |
| C[89] | Rasmussen's syndrome | |
| C[48,49] | Stiff-person syndrome | |



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with dispute around IGIV use in dermatomyositis (DMS).[32,51] These same reviews suggested that randomized-controlled trials (RC-trial) will substantiate today's suspicions of IGIV's beneficial effect in DMS and polymyositis (PM), myasthenia gravis (MG), and inflammatory neuropathies.

The evidence discussed in this article suggests that IGIV is: strongly recommended for the treatment of GBS; favorably recommended for the treatment of CIDP, DMS, and MMN; recommended as a second resort for the treatment of MS and MG; and recommended as a last resort for the treatment of PM, IBM, intractable epilepsies, and stiff-person syndrome.

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## References

1. Pirofsky B, Kinzey DM. Intravenous immune globulins: a review of their uses in selected immunodeficiency and autoimmune disease. Drugs 1992; 43: 6-14.
2. Infectious Diseases and Immunization Committee, Ottawa, Ontario, Canada. Intravenous immune globulin use in children. Can Med Assoc J 1992; 146: 121-124.
3. Rivet C. Canadian Blood Agency/Agence Canadienne du sang: Utilization management of albumin and intravenous immune globulin. Canadian Apheresis Group Bulletin 1995: 7-8.
4. van der Meché FG, Schmitz PI, for the Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326: 1123-1129.
5. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992; 326: 1130-1136.
6. van der Meché FG. The Guillain-Barré syndrome. *In*: McLeod JG, ed. Inflammatory Neuropathies. BailliPre's Clin Neurol 1994; 3: 73-94.
7. Bril V, Ilse WK, Pearce R, et al. Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barré syndrome. Neurology 1996; 46: 100-103.
8. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome Lancet 1997; 349(9047): 225-230.
9. Corbanese U, Martinuzzi A, Possamai C, et al. Guillain-Barré syndrome with associated thrombocytopenia: prompt response to combined corticosteroid and immunoglobulin treatment. Neuromuscul Disord 1998; 8: 50-52.
10. Imai N, Miyata K, Terayama Y, Ishihara N. [A case of Guillain-Barré syndrome treated with plasma exchange and intravenous high-dose immune globulin]. Rinsho Shinkeigaku 1997; 37: 520-522.
11. Enders U, Toyka KV, Hartung HP, Gold R. Failure of intravenous immunoglobulin (IVIg) therapy in experimental autoimmune neuritis (EAN) of the Lewis rat. J Neuroimmunol 1997; 76: 112-116.
12. Reisin RC, Pociecha J, Rodriguez E, et al. Severe Guillain-Barré syndrome in childhood treated with human immune globulin. Pediatr Neurol 1996 May; 14: 308-312.
13. Shahar E, Shorer Z, Roifman CM, et al. Immune globulins are effective in severe pediatric Guillain-Barré syndrome. Pediatr Neurol 1997; 16: 32-36.
14. Zafeiriou DI, Kontopoulos EE, Katzos GS, Gombakis NP, Kanakoudi FG. Single dose immunoglobulin therapy for childhood Guillain-Barré syndrome. Brain Dev 1997; 19: 323-325.
15. Kanra G, Ozon A, Vajsar J, et al. Intravenous immunoglobulin treatment in children with Guillain-Barré syndrome. Eur J Pediatr 1997; 1: 7-12.
16. van Doorn PA, Vermeulen M, Brand A, Mulder PG, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy. Clinical and laboratory characteristics associated with improvement. Arch Neurol 1991; 48: 217-220.
17. van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind placebo controlled cross-over study. Neurology 1990; 40: 209-212.
18. Vermeulen M, van Doorn PA, Brand A, et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 1993; 56: 36-39.
19. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 1994; 36: 838-845.
20. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controled, cross-over study. Brain 1996; 119(Pt 4): 1067-1077.
21. van Dijk GW, Notermans NC, Franssen H, Oey PL, Wokke JH. Response to intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy with only sensory symptoms. J Neurol 1996; 243: 318-322.
22. Simmons Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: II. Long-term follow-up, with comparison to adults. Muscle Nerve 1997; 20: 1569-1575.
23. Simmons Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: I. Presentation, electrodiagnostic studies, and initial clinical course, with comparison to adults. Muscle Nerve 1997; 20: 1008-1015.
24. Thomas PK, Claus D, Jaspert A, et al. Focal upper limb demyelinating neuropathy. Brain 1996; 119 ( Pt 3): 765-774.
25. Choudhary PP, Hughes RA. Long-term treatment of chronic inflammatory demyelinating polyradiculoneuropathy with plasma exchange or intravenous immunoglobulin. QJM 1995; 88: 493-502.
26. Grehl H, Jaspert A, Claus D, Neundorfer B. Immunglobulintherapie chronisch-entzundlicher Neuropathien [Immunoglobulin therapy of chronic inflammatory neuropathies]. Nervenarzt 1996; 67: 1003-1010.
27. Mariette X, Chastang C, Clavelou P, et al., for The IgM-associated Polyneuropathy Study Group. A randomized clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. J Neurol Neurosurg Psychiatry 1997; 63: 28-34.
28. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997; 48: 321-328.
29. Chaudhry V, Corse AM, Cornblath DR, et al. Multifocal motor neuropathy: response to human immune globulin [see comments]. Ann Neurol 1993; 33: 237-242.
30. Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1antibodies: a double-blind, placebo-controlled study. Neurology 1994; 44(3 Pt 1): 429-432.
31. Comi G, Nemni R, Amadio S, Galardi G, Leocani L. Intravenous immunoglobulin treatment in multifocal motor neuropathy and other chronic immune-mediated neuropathies. Mult Scler 1997; 3: 93-97.
32. Stangel M, Hartung HP, Marx P, Gold R. Intravenous immunoglobulin treatment of neurological autoimmune diseases. J Neurol Sci 1998; 153: 203-214.
33. Dalakas MC. Intravenous immune globulin therapy for neurologic diseases. Ann Intern Med 1997; 126: 721-730.
34. Azulay JP, Rihet P, Pouget J, et al. Long term follow up of multifocal motor neuropathy with conduction block under treatment. J Neurol Neurosurg Psychiatry 1997; 62: 391-394.

35. van den Berg LH, Franssen H, Wokke JH. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. Brain 1998; 121( Pt 3): 421-428.
36. Meucci N, Cappellari A, Barbieri S, Scarlato G, Nobile-Orazio E. Long term effect of intravenous immunoglobulins and oral cyclophosphamide in multifocal motor neuropathy. J Neurol Neurosurg Psychiatry 1997; 63: 765-769.
37. Ferrero B, Durelli L, Cavallo R, et al. The mechanism of action of high-dose immunoglobulin G. Ann NY Acad Sci 1993; 681: 563-566.
38. Arsura EL. Experience with intravenous immunoglobulin in myasthenia gravis. Clin Immunol Immunopathol 1989; 53: S170-S179.
39. Edan G, Landgraf F. Experience with intravenous immunoglobulin in myasthenia gravis: a review. J Neurol Neurosurg Psychiatry 1994; 57: 55-56.
40. Uchiyama M, Yukinovu I, Takaya N, et al. High-dose gammaglobulin therapy of generalized myasthenia gravis. Ann NY Acad Sci 1987; 505: 868-871.
41. Grob D, Arsura EL, Brunner NG, Namba T. The course of myasthenia gravis and therapies affecting outcome. Arm NY Acad Sci 1987; 505: 472-499.
42. Jongen JL, van Doorn PA, van der Meché FG. High-dose intravenous immunoglobulin therapy for myasthenia gravis. J Neurol 1998; 245: 26-31.
43. van der Meché FG, van Doorn PA. The current place of high-dose immunoglobulins in the treatment of neuromuscular disorders. Muscle Nerve 1997; 20: 136-147.
44. Tatay J, Diez-Tejedor E, Frank A, et al. [Association of plasmapheresis and high doses of intravenous immunoglobulins in the treatment of myasthenia gravis]. Rev Neurol 1997; 25: 1402-1406.
45. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C, for the Myasthenia Gravis Clinical Study Group. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Ann Neurol 1997; 41: 789-796.
46. Bassan H, Muhlbaur B, Tomer A, Spirer Z. High-dose intravenous immunoglobulin in transient neonatal myasthenia gravis. Pediatr Neurol 1998; 18: 181-183.
47. Herrmann DN, Carney PR, Wald JJ. Juvenile myasthenia gravis: treatment with immune globulin and thymectomy. Pediatr Neurol 1998; 18: 63-66.
48. Amato AA, Cornman EW, Kissel JT. Treatment of stiff-person syndrome with intravenous immunoglobulin. Neurology 1994; 44: 1652-1654.
49. Karlson EW, Sudarsky L, Ruderman E, et al. Treatment of stiff-person syndrome with intravenous immune globulin. Arthritis Rheum 1994; 37: 915-918.
50. Barker RA, Marsden CD. Successful treatment of stiff-person syndrome with intravenous immunoglobulin. J Neurol Neurosurg Psychiatry 1997; 62(letter): 426-427.
51. Lepidi H, Frances V, Figarella-Branger D, et al. Local expression of cytokines in neuropathology. Appl Neurobiol 1998; 24: 73-79.
52. Jolles S, Hughes J, Whittaker S. Dermatological uses of high-dose intravenous immunoglobulin. Arch Dermatol 1998; 134: 80-86.
53. Heckmatt J, Saunders C, Peters AM, et al. Cyclosporin in juvenile dermatomyositis. Lancet 1989; 1(8646): 1063-1066.
54. Lueck CJ, Trend P, Swash M. Cyclosporin in the management of polymyositis and dermatomyositis. J Neurol 1991; 54: 1007-1008.
55. Miller LC, Sisson BA, Tucker LB, DeNardo BA, Schaller JG. Methotrexate treatment of recalcitrant childhood dermatomyositis. Arthritis Rheum 1992; 35: 1143-1149.
56. Miller FW, Leitman SF, Cronin ME, et al. Controlled trial of plasma exchange and leukpaheresis in polymyositis and dermatomyositis. N Engl J Med 1992; 326: 1380-1384.
57. Olson NY, Lindsley CB. Adjunctive use of hydroxychloroquine in childhood dermatomyositis. J Rheumatol 1989; 16: 1545-1547.
58. Roifman CM, Schaffer FM, Wachsmuth SE, Murphy G, Gelfand EW. Reversal of chronic polymyositis following intravenous immune serum globulin therapy. JAMA 1987; 258: 513-515.
59. Cherin P, Herson S, Wechsler B, et al. Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. Am J Med 1991; 91: 162-168.
60. Cherin P, Piette JC, Wechsler B, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. J Rheum 1994; 21: 1092-1097.
61. Barohn RJ. The therapeutic dilemma of inclusion body myositis. Neurology 1997; 48: 567-568.
62. van der Meulen MF, Hoogendijk JE, Jansen GH, Veldman H, Wokke JH. Absence of characteristic features in two patients with inclusion body myositis. J Neurol Neurosurg Psychiatry 1998; 64(3): 396-398.
63. Horvath R, Fu K, Johns T, et al. Characterization of the mitochondrial DNA abnormalities in the skeletal muscle of patients with inclusion body myositis. J Neuropathol Exp Neurol 1998; 57(5): 396-403.
64. Sussman GL, Pruzanski W. The role of intravenous infusions of gamma globulin in the therapy of polymyositis and dermatomyositis. J Rheum 1994; 21: 990-992.
65. Dalakas MC, Illia I, Dambrosia J, et al. A controlled trial of high dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993; 329: 1993-2000.
66. Lang BA, Laxer RM, Murphy G, Silverman ED, Roifman CM. Treatment of dermatomyositis with intravenous gammaglobulin. Am J Med 1991; 91: 169-172.
67. Collet E, Dalac S, Maerens B, et al. Juvenile dermatomyositis: treatment with intravenous gammaglobulin. Br J Dermatol 1994; 130: 231-234.
68. Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis-four year review of nine cases. Arch Dis Child 1995; 72: 25-28.
69. Tsai MJ, Lai CC, Lin SC, et al. Intravenous immunoglobulin therapy in juvenile dermatomyositis. Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih 1997; 38: 111-115.
70. Dalakas MC, Sonies B, Dambrosia J, et al. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology 1997; 48: 712-716.
71. Rotherfelder U, Neu I, Pelka R. Therapy for multiple sclerosis with immunoglobulin G. Munch Med Wochenschr 1982; 124: 74-78.
72. Soukop W, Tschabitscher H. Gamma globulin therapy in multiple sclerosis. Theoretical considerations and initial clinical experience with 7S immunoglobulins in MS therapy. Wien Med Wochenschr 1986; 136: 477-480.
73. Schuller E, Govaerts A. First results of immunotherapy with immunoglobulin G in multiple sclerosis patients. Eur Neurol 1983; 22: 205-212.
74. van Engelen BG, Hommes OR, Pinckers A, et al. Improved vision after intravenous immunoglobulin in stable demyelinating optic neuritis. Arm Neurol 1992; 32: 834-835.
75. Noseworthy JH, Rodriguez M, An KN, et al. IVIG treatment in multiple sclerosis: pilot study results and design of placebo-controlled, double-blind clinical trial. Arm Neurol 1994; A(abstr): 325(P266).
76. Achiron A, Pras E, Gilad R, et al. Open controlled therapeutic trial of high-dose intravenous immunoglobulins in relapsing-remitting multiple sclerosis. Arch Neurol 1992; 49: 1233-1236.
77. Achiron A, Gilad R, Margalit R, et al. Intravenous gammaglobulin treatment in multiple sclerosis and experimental autoimmune diseases: delineation of usage and mode of action. J Neurol Neurosurg Psychiatry 1994; 57(Suppl.): 57-61.
78. Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B, for the Austrian Immunoglobulin in Multiple Sclerosis Study Group. Randomized placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Lancet 1997; 349(9052): 589-593.
79. Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B. Treatment effects of monthly intravenous immunoglobulin on patients with relapsing-remitting multiple sclerosis: further analyses of the Austrian Immunoglobulin in MS study. Mult Scler 1997; 3: 137-141.
80. Sorensen PS, Wanscher B, Schreiber K, et al. A double-blind, cross-over trial of intravenous immunoglobulin G in multiple sclerosis: preliminary results. Mult Scler 1997; 3: 145-148.
81. Achiron A, Gabbay U, Gilad R, et al. Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. Neurology 1998; 50: 398-402.

82. Paty DW, Li DKB, for the UBC MS/MRI Study Group and IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 662-667.
83. Achiron A, Barak Y, Goren M, et al. Intravenous immunoglobulin in multiple sclerosis: clinical and neuroradiologic results and implications for possible mechanisms of action. Clin Exp Immunol 1996; 104(Suppl.-1): 67-70.
84. Francis GS, Freedman MS, Antel JP. Failure of intravenous immunoglobulin to arrest progression of multiple sclerosis: a clinical and MRI based study. Mult Scler 1997; 3: 370-376.
85. Sorensen PS, Wanscher B, Jensen CV, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. Neurology 1998; 50(5): 12731281.
86. van Engelen BG, Renier WO, Weemaes CM, Gabreels FJ, Meinardi H. Immunoglobulin treatment in epilepsy, a review of the literature. Epilepsy Res 1994; 19: 181-190.
87. van Engelen BG, Renier WO, Weemaes CM, et al. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome: an add-on study. Eur J Pediatr 1994; 153: 762-769.
88. van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. Int J Clin Lab Res 1994; 24: 162-166.
89. Hart YM, Cortez M, Andermann F, et al. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients [see comments]. Neurology 1994; 44: 1030-1036.
90. Fayad MN, Choueiri R, Mikati M. Landau-Kleffner syndrome: consistent response to repeated intravenous gamma-globulin doses: a case report. Epilepsia 1997; 38: 489-494.
91. Lagae LG, Silberstein J, Gillis PL, Casaer PJ. Successful use of intravenous immunoglobulins in Landau-Kleffner syndrome. Pediatr Neurol 1998; 18: 165-168.
92. Roifman C (chair), Balter M, Blanchette V, et al., for The Consensus Working Group. Present and future uses of IVIG. McLean Hunter Healthcare (newsletter) 1997.

**ADDENDUM 1: SELECTED STUDIES' METHODS**

| | |
|---|---|
| Reference: | GBS[4] |
| Design: | RC-trial - (IGIV openly compared to PE, follow-up blinded) |
| Patients: | n = 147 - GBS diagnosis for less than two weeks (dependent ambulation). |
| Outcomes: | 7-grade scale - 0 = healthy, 1 = minor symptoms and fully capable of manual work, 2 = able to walk at least 10 m without assistance, 3 = able to walk at least 10 m with a walker or support, 4 = bedridden or chairbound, 5 = requiring assisted ventilation for at least part of the day, 6 = dead. |
| Therapies: | $ IGIV treatment (n = 74); 0.4 g/kg/day for 5 consecutive days begun on the day of randomization.<br>$ Five PE treatments within 7B14 days (n = 73); 200B250 ml/kg/treatment median delay of one day to begin therapy. |
| Reference: | GBS[8] |
| Design: | RC-dB Trial. |
| Patients: | n = 379 - GBS diagnosis for less than two weeks (dependent ambulation). |
| Outcomes: | As above. |
| Therapies: | $ IGIV (0.4 g/kg/day for 5 days).<br>$ PE (5-50 ml/kg exchanges over 8B13 days).<br>$ PE regimen followed by the IGIV regimen. |
| Reference: | GBS[14] |
| Design: | Open Trial. |
| Patients: | n = 9 - Pediatric GBS diagnosis (2.5B13.5 years old). |
| Outcomes: | Improvement by one or more grades on the scale above - (mean follow-up period, 14.5 months). |
| Therapies: | IGIV single dose, 2g/kg. |
| Reference: | GBS[15] |
| Design: | Retrospective Study. |
| Patients: | n = 75 - Pediatric GBS diagnosis (Turkish n = 51, Canadian n = 24). |
| Outcomes: | Rate of recovery by functional disability grades - (influence of age or initial disability grade on treatment impact was weak [r = 0.53, p ≤ 0.50]). |
| Therapies: | IGIV (2g/kg)...<br>$ Canadian patients received the greater/shorter dosage regimen (1 g/kg/day for 2 days).<br>$ Turkish patients (0.4 g/kg/day for 5 days n = 23).<br>$ Turkish patients (n = 28) other supportive therapy only. |
| Reference: | CIDP[19] |
| Design: | RC Crossover Trial. |
| Patients: | n = 20 (13 completed the study) - CIDP diagnosis. |
| Outcomes: | NDS, CMAP, muscle weakness of the NDS. |
| Therapies: | $ Two PE sessions through three weeks, followed by one session through three following weeks.<br>$ Weekly doses of IGIV 0.4 g/kg in week-1B3, followed by 0.2 g/kg in week-4B6. |
| Reference: | CIDP[20] |
| Design: | RC-dB Crossover Trial. |
| Patients: | n = 30 (25 completed the study) - Chronic-progressive (n = 16) or Chronic -relapsing (n = 14) diagnosis. |
| Outcomes: | NDS, Clinical grade, grip strength, electrophysiologic studies, motor nerve conduction velocities (MCV), CMAP. |
| Therapies: | $ IGIV 0.4 g/kg/day IGIV for five consecutive days.<br>$ Placebo of the same regimen.<br>$ After randomized treatment, placebo patients were crossed-over to IGIV. |
| Reference: | CIDP[27] |
| Design: | Open Trial. |
| Patients: | n = 20 - IgM anti-MAG CIDP variant diagnosis. |
| Therapies: | $ IGIV 2g/kg loading and then 1 g/kg every three weeks.<br>$ IFN-alpha 3 MU/m$^2$ subcutaneously three times weekly. |
| Reference: | MMN[30] |
| Design: | RC-dB Crossover Trial. |
| Patients: | n = 12 - MMN diagnosis. |
| Outcomes: | Muscle strength, Norris scale for disability, MCV, immunologic markers. |
| Therapies: | $ IGIV 0.4 g/kg/day for five consecutive days.<br>$ Placebo of the same regimen. |
| Reference: | MMN[34] |
| Design: | Open Trial. |
| Patients: | n = 18 - Median of 5.8 years had elapsed between onset of symptoms and IGIV treatment. |
| Outcomes: | Isometric strength. |
| Therapies: | IGIV 0.4 g/day for 3B5 days (4 initially treated with prednisone 1 mg/kg/day without significant improvement). |
| Reference: | MMN[36] |
| Design: | Open Trial. |
| Patients: | n = 6 - Known IGIV responders who had been followed for a mean of 47 months with MMN treatment. |
| Outcomes: | Rankin disability, Medical Research Council strength rating scale (MRC-scale) measures on the 20 most affected muscles. |
| Therapies: | Oral CTX 1B3 mg/kg/day, and IGIV 0.4 g/kg/day for two days at clinical exacerbations. |

*cont.*

**ADDENDUM 1: (CONTINUED)**

| | |
|---|---|
| Reference: | MG[38] |
| Design: | Open Trial. |
| Patients: | n = 14 - MG diagnosis. |
| Outcomes: | Muscle strength, vital capacity. |
| Therapies: | $ IGIV 0.4 g/kg daily for five consecutive days.<br>$ IGIV as above with corticosteroid. |
| Reference: | MG[42] |
| Design: | Open Trial. |
| Patients: | n = 14 (11 compeleted the study) - Generalized-MG diagnosis. |
| Outcomes: | A minimum one-grade improvement in The University of Virginia's Modification of Osserman's (UVMO) classification. |
| Therapies: | 7 courses of IGIV 0.4 g/kg/day for five consecutive days (that included at least one acute exacerbation. |
| Reference: | MG[45] |
| Design: | RC-trial. |
| Patients: | n = 87 - MG diagnosis. |
| Outcomes: | Myasthenic muscular score (MSS), on day of randomization and day-15. |
| Therapies: | $ Three PE courses (n = 41).<br>$ IGIV 0.4 g/kg/day for three days (n = 23).<br>$ IGIV 0.4 g/kg/day for five days (n = 23). |
| Reference: | MG[44] |
| Design: | C-trial. |
| Patients: | n = 10 - MG diagnosis with: UVMO classification II-B (n = 7), UVMO classification II-A (n = 1), UVMO classification III (n = 2). |
| Outcomes: | UVMO classification, clinical involvement grade, functional activity grade. |
| Therapies: | PE followed by IGIV 0.4 g/kg/day for five days. |
| Reference: | MS[76] |
| Design: | C-trial. |
| Patients: | n = 20 - Relapsing-remitting MS diagnosis. |
| Outcomes: | Mean annual exacerbation rate (AER), neurologic ability, Mean Kurtzke Expanded Disability Status Scale (EDSS) scores. |
| Therapies: | IGIV (0.4 g/kg/day) for five consecutive days - Matched patient group received no treatment. |
| Reference: | MS[78,79] |
| Design: | RC-dB Trial. |
| Patients: | n = 148 - Relapsing-remitting MS diagnosis - Patients were 15B65 years old and had 1 to 6 EDSS scores. |
| Outcomes: | AER, EDSS. |
| Therapies: | $ IGIV 0.15B0.2 g/kg once per month, for two years (n = 75).<br>$ Placebo in the same regimen. (n = 73). |
| Reference: | MS[81] |
| Design: | RC-dB Trial. |
| Patients: | n = 40 - Relapsing-remitting MS diagnosis confirmed by magnetic resonance imaging (MRI) - 19B60 years old. |
| Outcomes: | AER, EDSS, Total lesion scores evaluated by brain MRI. |
| Therapies: | $ Loading dose of IGIV (0.4 g/kg/day for 5 consecutive days), followed by single booster doses (0.4 g/kg once every 2 months) for two years.<br>$ Placebo in the same regimen. |
| Reference: | MS[85] |
| Design: | RC-dB Crossover Trial. |
| Patients: | n = 26 (18 completed the study). |
| Outcomes: | Gadolinium enhancing lesions per MRI, exacerbation rate, neurologic rating, MS lesion load on T2-weighted MRI, multimodal evoked potentials. |
| Therapies: | $ IGIV 1 g/kg/day for two consecutive days, monthly, during two 6-month treatment periods.<br>$ Placebo in the same regimen. |
| Reference: | Epilepsies[87] |
| Design: | Open. |
| Patients: | n = 15 - West (n = 3) or Lennox-Gastaut (n = 12) syndrome diagnosis. |
| Outcomes: | Clinical seizures, spike-wave discharges on EEG. |
| Therapies: | IGIV 0.4 g/kg/day for five days, and then bi-monthly for three months. |
| Reference: | Epilepsies[88] |
| Design: | C-dB trial. |
| Patients: | n = 61 (46 with partial epilepsy) - Patients were refractory. |
| Outcomes: | Daily seizure frequency over 6-months. |
| Therapies: | 7 infusions (4 in week-1, 1 in week-2, -3 and -6), of IGIV 0.1, 0.25 or 0.4 mg/kg per infusion respectively. |



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NEUROLOGICAL PRACTICE

# Minimal Standards for Digital/Quantitative Electroencephalography in Canada

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Digital electroencephalography (EEG) is rapidly replacing paper-based, analog EEG for a number of reasons, e.g., improved convenience, reduced cost (of paper and paper storage or microfilming records) and enhanced flexibility of recording and display. With increasingly widespread use of digital EEG technology from multiple manufacturers, there is a need for minimal standards for such equipment in patient care settings. This document represents a set of minimal standards for such technology and its utilization, as approved by the EEG Section of the Canadian Society of Clinical Neurophysiologists at its annual general meeting in June of 1998. The document meets Canadian standards and those recently developed by the International Federation of Clinical Neurophysiologists.[1-3] This document addresses some specific concerns relevant to digital technology. The aspects of patient documentation, length and principles of recording and charting are the same as those of previous Canadian documents and are not repeated in this paper.[1,3]

Optical disk or compact disk read-only-memory (CD-ROM) technology is an acceptable medium for storing digital EEG recordings. It is the user's responsibility to be aware of possible deteriorating legibility or impending technical obsolescence and make suitable arrangements for copying the information onto an updated storage medium or paper to meet storage requirements. Manufacturers should provide for a mechanism, e.g., the conversion of format, that allows electroencephalographers working with different equipment to interpret EEGs for clinical purposes.

To ensure the adequacy of waveform recording, a minimum sampling rate of 200 samples per second for each channel is used, but higher rates are recommended. The sampling rate should be even multiples of 50 or 64 Hz. When sampling at 200 Hz, an anti-aliasing filter of 70 Hz should be used, with a roll-off of at least 12dB/octave. Higher sampling rates require a proportionately higher anti-aliasing filter setting. A low frequency filter of 0.16 Hz should be available; as should a 60 Hz notch filter, for use when required. Digitization at voltage level of 12 bits or greater with the ability to resolve voltage to 0.5μV is recommended. Common mode rejection is 110 dB or greater at each amplifier input. Interchannel cross-talk must be less than 1%, i.e., 40db down or less.

The available technology is capable of displaying the recording on a video screen as well as on paper. With horizontal scaling, one second of time occupies 25-35 mm and contains at least 120 data points/channel; scaling at 0.5, 2 and 4 times should be feasible. On the vertical display, a minimum spacing of 10 mm between channels for a display of 16 or 18 channels is recommended. Adequate screen resolution is at least 4 pixel resolution per vertical millimetre. It is recommended that the screen have at least 1024 x 768 pixels, preferably 1280 x 1024 pixels. Playback systems should show the montage, filter and sensitivity settings, vertical voltage scale and horizontal time marking scale, technologist comments, event markers (e.g., for hyperventilation) and page number or time. The playback unit should also allow for montage selection changes and post-hoc alterations in sensitivity and filter settings.

Topographic mapping, frequency or power spectral analyses and other quantitative assessments of digital EEG data are not considered an alternative to traditional (standard) EEG display in either digital or analog systems. Interpretation of the quantitative EEG should involve analysis of the simultaneous standard EEG. When used in isolation, a quantitative EEG can yield misleading information.

*Developed for the Annual General Meeting of the Canadian Society of Clinical Neurophysiologists held in Montreal in June of 1998.*

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## References

1. Canadian Association of Electroneurophysiology Technologists. Minimal Technical Standards, EEG/EMG. 1991-93.
2. Nuwer MR, Comi G, Emerson R, et al. IFCN standards for the clinical recording of digital EEG. Electroencephalogr Clin Neurophysiol 1998; 106: 259-261.
3. Young GB. Minimal standards for electroencephalographic laboratories. Can Med Assoc J 1991; 144: 865-867.