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Updated consensus statement: Intravenous immunoglobulin in the treatment of neuromuscular disorders report of the AANEM ad hoc committee

Jinny Tavee MD[1] | Thomas H. Brannagan III MD[2] | Michael W. Lenihan MD[3] | Sri Muppidi MD[4] | Liz Kellermeyer BA, MLS[5] | Peter D Donofrio MD[6] | AANEM

[1]National Jewish Health, Division of Neurology, Denver, Colorado, USA

[2]Vagelos College of Physicians and Surgeons, Neurological Institute, Columbia University, New York, New York, USA

[3]Adirondack Neurology Associates, PC, Glens Falls, New York, USA

[4]Stanford Neuroscience Health Center, Palo Alto, California, USA

[5]National Jewish Health, Denver, Colorado, USA

[6]Neurology Clinic, Vanderbilt University, Nashville, Tennessee, USA

Correspondence
AANEM, Policy Department, 2621 Superior Dr. NW, Rochester, MN 55901, USA.
Email: policy@aanem.org

Jinny Tavee, National Jewish Health, Division of Neurology, Denver, Colorado 80209, USA.
Email: taveej@njhealth.org

Abstract

Intravenous immune globulin (IVIG) is an immune-modulating biologic therapy that is increasingly being used in neuromuscular disorders despite the paucity of high-quality evidence for various specific diseases. To address this, the AANEM created the 2009 consensus statement to provide guidance on the use of IVIG in neuromuscular disorders. Since then, there have been several randomized controlled trials for IVIG, a new FDA-approved indication for dermatomyositis and a revised classification system for myositis, prompting the AANEM to convene an ad hoc panel to update the existing guidelines.New recommendations based on an updated systemic review of the literature were categorized as Class I-IV. Based on Class I evidence, IVIG is recommended in the treatment of chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome (GBS) in adults, multifocal motor neuropathy, dermatomyositis, stiff-person syndrome and myasthenia gravis exacerbations but not stable disease. Based on Class II evidence, IVIG is also recommended for Lambert-Eaton myasthenic syndrome and pediatric GBS. In contrast, based on Class I evidence, IVIG is not recommended for inclusion body myositis, post-polio syndrome, IgM paraproteinemic neuropathy and small fiber neuropathy that is idiopathic or associated with tri-sulfated heparin disaccharide or fibroblast growth factor receptor-3 autoantibodies. Although only Class IV evidence exists for IVIG use in necrotizing autoimmune myopathy, it should be considered for anti-hydroxy-3-methyl-glutaryl-coenzyme A reductase myositis given the risk of long-term disability. Insufficient evidence exists for the use of IVIG in Miller-Fisher syndrome, IgG and IgA paraproteinemic neuropathy, autonomic neuropathy, chronic autoimmune neuropathy, polymyositis, idiopathic brachial plexopathy and diabetic lumbosacral radiculoplexopathy.

KEYWORDS
gammaglobulin, IVIG, myasthenia gravis, myositis, neuropathy

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1 | INTRODUCTION

Intravenous immune globulin (IVIG) is a biologic therapy that improves disability and quality of life in patients with a variety of immune-mediated neurologic disorders. Produced from pooled human plasma from thousands of donors through a cold ethanol fractionation process, commercial IVIG consists of over 95% immunoglobulin (Ig) G with small amounts of IgA and trace IgM.[1] Proposed mechanisms of action include complement inhibition, antibody binding and neutralization, downregulation of proinflammatory cytokines and chemokines, inhibition of differentiated dendritic cells, and saturation of neonatal Fc receptors leading to lysosomal degradation of pathogenic antibodies.[1–3]

With respect to neuromuscular disorders, IVIG is United States Food and Drug Administration (FDA)-approved for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and dermatomyositis. While controlled studies also support its use in off-label conditions such as Guillain-Barré syndrome (GBS) and stiff-person syndrome,[4] IVIG is increasingly being used to treat other neurologic disorders in the absence of high-quality evidence or a clear underlying immune-mediated pathophysiology.[1,5,6] Given the limited supply of IVIG, this has contributed to worldwide shortages, rationing, and increased healthcare costs.[5]

In 2009, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) created a consensus statement based on the existing evidence to provide guidance on the use of IVIG in neuromuscular disorders.[7] There have since been several new randomized controlled trials (RCTs) for IVIG and a new FDA-approved indication. In addition, the field of neuromuscular disease has evolved to include a revised classification system for inflammatory myositis and advances in the understanding of small fiber neuropathy (SFN) and autonomic disease. In conjunction with the widespread use of IVIG, these factors all support the need for an updated systematic review of the literature. The aim of this updated consensus statement is to provide evidence-based guidelines for the use of IVIG that will inform the care of patients with neuromuscular disease.

2 | METHODS

In 2020, the AANEM convened a panel to update the 2009 consensus statement on the use of IVIG in the treatment of neuromuscular disorders. A systematic review of the literature was performed by a medical librarian (L.K.) using Ovid MEDLINE, Ovid Embase, and Ovid Cochrane Central Register of Controlled Trials databases from January 1, 2008 (end date of literature search from previous review) through July 19, 2021, with update in November 2022. Search terms for each database included intravenous immunoglobulin combined with the following neuromuscular disorders: CIDP, GBS, myasthenia gravis (MG), MMN, dermatomyositis, inclusion body myositis (IBM), polymyositis, idiopathic brachial plexopathy, diabetic radiculoplexoneuropathy, stiff-person syndrome (SPS), paraproteinemic neuropathy, chronic autoimmune neuropathy, Lambert-Eaton myasthenic syndrome (LEMS), and Miller-Fisher syndrome (MFS). Autonomic neuropathy, SFN, necrotizing autoimmune myositis, and post-polio syndrome (PPS), which were not part of the 2009 guidelines, were included in this updated review using a search from January 1990 through July 19, 2021, and an update in November 2022. See Appendix A for full search strategies.

Selected articles were limited to RCTs involving IVIG for neuromuscular disorders. Published systematic literature reviews were also included to help ensure that all clinical trials were captured. Cohort studies, case reports, and case series were excluded. Filters were used to limit results to human studies and English language. Following the search, all identified studies were uploaded and duplications were removed using EndNote20. Rayyan systematic review tool was used for screening and full text review. For the 2023 consensus statement recommendations, we included only Class I and II studies.[8]

3 | RESULTS

The initial literature search yielded 5980 unique results after duplicates were removed. Six citations were added via hand-searching, for a total of 5986 results. Of those results, 240 potentially relevant publications were included in the first screening. The retrieved abstracts were independently screened by two reviewers (J.T. and P.D.) and 160 were selected for full text examination, of which 14 met the inclusion criteria. The selected full text articles were circulated to members of the panel for review and comments. A targeted update in November 2022 using the same databases identified an additional 1303 potentially relevant results, 5 of which met the inclusion criteria for a total of 19 publications. All clinical studies from the 2009 consensus statement were reviewed and reclassified by at least two panelists. Those reclassified as Class I and II were included. The conclusions from the literature review formed the basis of the updated recommendations, which were revised and recirculated until consensus was reached by all members of the panel. The results are summarized in Table 1.

4 | GUILLAIN BARRÉ SYNDROME

4.1 | Adult GBS

Four Class I studies[9–12] evaluating the use of IVIG in GBS in adults were identified including one new Class I study since the 2009 guideline was published.[7] There are no studies comparing IVIG to placebo since plasmapheresis was established as an effective treatment for GBS.[13]

4.1.1 | IVIG versus Plasma Exchange

In a Class I study, 150 patients with GBS were randomized within 14 days of onset to receive either 0.4 gm/kg/day IVIG for 5 days or five plasma exchanges (PLEX).[9] At 4 weeks, 34% of patients receiving

TABLE 1 Class of evidence supporting use of IVIG in the treatment of specific neuromuscular disorders[8]

Neuromuscular disorder	Class of evidence
Gullain-Barre syndrome in adults[9,10]	I
Gullain-Barre syndrome in children[19]	II
Miller-Fisher syndrome[28]	IV
Chronic inflammatory demyelinating polyneuropathy[29–32,35]	I
Multifocal motor neuropathy[42–44,46]	I
Paraproteinemic neuropathy (PPN)[48,49]	I–no long-term benefit for IgM PPN IV–insufficient evidence for IgA and IgG PPN
Chronic autoimmune large fiber neuropathy	IV
Small fiber neuropathy (SFN)[70,71]	I–not effective in idiopathic SFN I–not effective in SFN associated with TSHDS/FGFR3* autoantibodies IV–insufficient evidence for other SFN
Myasthenia gravis (acute exacerbation only)[76]	I
Lambert-Eaton myasthenic syndrome[83]	II
Dermatomyositis[84,86]	I
Inclusion body myositis[87–89]	I–not effective
Necrotizing autoimmune myopathy[94]	IV–insufficient evidence but consider for anti-HMGCR** myositis
Polymyositis	IV
Post-polio syndrome[96–99]	I–not effective
Dysautonomia	IV
Diabetic lumbosacral radiculoplexopathy	IV
Idiopathic brachial plexopathy (neuralgic amyotrophy)	IV
Stiff person syndrome[4]	I

*anti-HMGCR3 = anti-hydroxy-3-methyl-glutaryl-coenzyme A reductase.
**TSHDS/FGFR3 = tri-sulfated heparin disaccharide (TSHDS) or fibroblast growth factor receptor-3 (FGFR3).

PLEX met the primary endpoint of ≥1-grade on a seven-point functional motor scale compared to 53% in the IVIG group ($p = .024$). Median time to improvement with PLEX was 41 days compared to 27 days in patients receiving IVIG ($p = .05$), with those in the latter group experiencing fewer complications and less need for mechanical ventilation.

In a Class I RCT, 379 patients with severe GBS (defined as requiring an aid to walk or worse) received one of three treatments: (1) 0.4 gm/kg/day IVIG for 5 days; (2) five PLEX of 250 mL/kg total; or (3) five PLEX of 50 mL/kg immediately followed by IVIG 0.4 gm/kg/day for 5 days.[10] The primary outcome measure was improvement at 4 weeks on a seven-point disability grade scale ranging from 0 (healthy) to 6 (death). At 4 weeks, no difference was seen between the two groups of PLEX alone and IVIG alone with mean improvement changes of 0.9 ± 1.3 in the PLEX group; 0.8 ± 1.3 in the IVIG group (95% confidence interval [CI]: −0.22 to 0.42). In addition, no difference was seen between the combined (PLEX and IVIG) and individual treatment group.

Three additional Class III studies comparing IVIG to PLEX also showed no difference in outcomes between the two interventions.[14–16] A Cochrane analysis from 2014 concluded that IVIG was equivalent to PLEX in expediting recovery.[17]

4.1.2 | Optimal dose regimen of IVIG

In a Class I RCT, 39 patients received 400 mg/kg/day for either 3 days or 6 days.[11] The primary outcome measure was time needed to regain the ability to walk 5 meters with assistance. Overall, there was no significant difference between the two groups with a recovery time of 84 days (23–121) for the 6 day group versus 131 days (54–332) for the 3 day group; $p = .08$. However, a significantly faster recovery time of 86 days (13–151) was seen for ventilated patients in the 6 day group versus 152 days (54–332) in the 3 day group; $p = .04$.

4.1.3 | Second dose of IVIG

In a Class I RCT, 93 patients aged ≥12 y with GBS and poor prognosis (defined as score of ≥6 on the modified Erasmus GBS Outcome Score [mEGOS]) received either a second IVIG dose of 2 gm/kg over 5 days or placebo.[12] The mEGOS is graded on a 0 (best prognosis) to 12 (worst prognosis) scale and is based on Medical Research Council (MRC) sumscore, preceding diarrhea and age. At 4 weeks, there was no difference in the primary outcome of GBS disability score between those who received a second IVIG dose and placebo. Adjusted common odds ratio for improvement on the GBS disability score was 1.4 (95% CI: 0.6–3.3; $p = .45$). There was also no difference in disability at weeks 8, 12, and 26 or difference in duration of hospital or intensive care unit stay and artificial ventilation. Serious adverse events, including pulmonary embolus (PE), were more common in those receiving a second dose (35%) compared to placebo (16%).

CONCLUSION (Adult GBS): There is Class I evidence that IVIG and PLEX are equally effective in treating GBS with no additional benefit from combined treatment.[9,10] There is also Class I evidence that a second dose of IVIG confers no clinically meaningful benefit in patients with GBS and a poor prognosis.[12]

4.2 | Pediatric GBS

There are three Class II studies evaluating the use of IVIG in children with GBS, with one new Class II study since the last review.[18,19]

4.2.1 | IVIG versus no treatment

In a Class II randomized unblinded study from the prior review, the use of 2 gm/kg IVIG over 2 days was compared to no treatment in 21 children with mild GBS (defined as able to walk ≥5 meters unassisted).[19] At the end of the study, there was no difference between the IVIG and untreated groups in the primary outcome of maximal degree of disability, although signs of improvement were seen earlier in the IVIG group at a median of 4.5 days (95% CI: 2–14 days) compared to 30 days (95% CI: 6–83 days) in the untreated group ($p = .001$). Additional studies with Class III and IV evidence also demonstrated improved recovery times in children treated with IVIG compared to those receiving supportive care.[20–22] A Cochrane analysis from 2014 acknowledged the limited quality of evidence for the use of IVIG in children with GBS, but concluded that IVIG was beneficial in this population based on the consistent results favoring IVIG found in these studies.[17]

4.2.2 | Optimal dosing of IVIG

In another Class II randomized unblinded study presented in the same article by Korinthenberg et al., 2 gm/kg IVIG over 2 days was compared to 2 gm/kg over 5 days in 51 children with severe GBS (defined as unable to walk 5 meters unassisted).[19] There was no significant difference in recovery time to walk unassisted between the two dose regimens, although secondary transient worsening was seen more frequently in those receiving 2 gm/kg over 2 days.

4.2.3 | IVIG versus PLEX

In a more recent Class II study, IVIG was compared to PLEX in children with rapidly progressive GBS requiring mechanical ventilation.[18] In this randomized unblinded trial, 41 children with severe GBS who required mechanical ventilation within 14 days of disease onset received either 2 gm/kg IVIG over 5 days or one PLEX daily for 5 days. At the end of the study, children who received PLEX had a slight but significant reduction in the primary outcome of mechanical ventilation duration of 11.0 ± 1.5 days compared to 13 ± 2.1 days in the IVIG group ($p = .037$). However, there was no difference in the secondary outcomes of intensive care unit (ICU) stay or ability to ambulate 10 m unassisted.

CONCLUSION (Pediatric GBS): There is Class II evidence that IVIG is beneficial in treating GBS in children.[19] However, there is additional Class II evidence suggesting that PLEX may be slightly more effective in treating children with rapidly progressive GBS requiring MV.[18]

5 | MILLER-FISHER SYNDROME

No RCTs were identified evaluating the use of IVIG in MFS. Although uncontrolled case series and reports[23–27] showed benefit with IVIG, the largest series[25] of MFS patients found that most patients experienced a complete recovery even in the absence of immune-modulating treatment. In a retrospective review of 92 patients, there was no significant difference in clinical outcomes at 1 year in those receiving IVIG ($n = 28$), PLEX ($n = 23$), or supportive treatment ($n = 41$) although median recovery time for ophthalmoplegia ($p = .04$) and ataxia ($p = .027$) were slightly faster with IVIG.[25] A Cochrane analysis from 2007 found no studies to base a conclusion on the treatment of MFS.[28] However, in cases complicated by severe ataxia or marked bulbar palsy, or those considered to be GBS overlap syndrome with respiratory or limb involvement, IVIG, or PLEX may be considered based on evidence from GBS studies.

CONCLUSION: There is insufficient evidence to recommend IVIG for treating MFS, although it may be considered in patients with severe ataxia, bulbar palsy, or GBS overlap syndrome with respiratory or limb involvement.[28]

6 | CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Ten Class I studies[29–38] and 2 Class II studies[39,40] evaluating the use of IVIG in CIDP were identified, including 6 new Class I studies since the 2009 guideline[7] was published.

6.1 | IVIG versus Placebo

As noted in the previous guideline,[7] four Class I RCT compared 2 gm/kg of IVIG to placebo in patients with CIDP using disability as the primary endpoint at various time points.[29–32] At the end of the studies, more patients improved with IVIG than placebo. The largest of the trials, the IVIG (10% caprylate-chromatography purified) for the treatment of CIDP (ICE) study, resulted in FDA-approval of IVIG for CIDP.[30] In the study, 117 patients were randomized to receive either 2 gm/kg of IVIG followed by maintenance dosing of 1 gm/kg every 3 weeks for 24 weeks versus placebo. The primary endpoint was the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. At the end of the 24 weeks, the proportion of responders was significantly greater in the IVIG group (54%) compared to the placebo group (21%) with maximum benefit seen at 6 weeks in 60% of responders ($p = .0002$). In the extension phase, IVIG responders were re-randomized to IVIG or placebo for an additional 24 weeks. At the end of the study, 87% in the IVIG group remained relapse-free compared to 58% in the placebo group ($p = .001$).

6.2 | IVIG versus PLEX

In a Class II crossover study[39] that was described in the previous guideline,[7] 20 patients with CIDP were randomized to receive either PLEX for 6 weeks followed by a washout period and then IVIG for 6 weeks or the reverse. Several endpoints were used but no significant difference was seen in disability scores.

6.3 | IVIG versus Corticosteroids

In a Class II double-blinded crossover study, 32 patients were randomized to either IVIG 2 gm/kg given over 1 to 2 days or a 6 weeks taper of prednisolone followed by the other treatment.[40] Although both groups improved in the primary outcome measure of disability scores at 2 weeks following treatment, there was no significant difference between the two groups. The study was not designed or powered to detect equivalence. In addition, eight patients were withdrawn from the study.

In a Class I RCT, the efficacy and tolerability of IVIG was compared to IV corticosteroids.[33] A total of 45 patients with CIDP received monthly doses of either IVIG 2 gm/kg over 4 days or methylprednisolone (MP) 2 gm per day for 4 days for 6 mo. The primary endpoint was the difference in number of patients discontinuing therapy in each group due to adverse effects, reduced tolerability or efficacy defined as absence of improvement after 2 mo of treatment or worsening after 15 days. At 6 mo, 52% patients receiving IV MP discontinued treatment compared to 13% receiving IVIG. Of the 11 patients who discontinued MP, 8 were due to progressive worsening or failure to improve, 1 was due to gastritis, and 2 for unknown reasons. Of note, however, 8 of 21 (38%) patients in the IVIG arm worsened in the 6 mo after therapy discontinuation requiring additional therapy whereas none of the 10 patients in the MP arm worsened.

A Cochrane review from 2017 concluded that IVIG was superior to placebo in reducing disability in CIDP.[41] However, IVIG appeared to be equivalent to PLEX, and there was little to no difference in short-term improvement between IVIG and IV MP as well as IVIG and oral prednisolone.

6.4 | Maintenance

In a Class I randomized crossover study involving 22 patients with CIDP that were IVIG-dependent at baseline, the efficacy of more frequent lower dosing IVIG was compared to conventional high-dose, low-frequency treatment.[34] During the double-blind phases, patients in the intervention arm were given half of their usual dose at twice the frequency while those in the control arm received their usual dose and intermittent placebo infusions. At the end of the study, there was no difference between the two groups in the primary endpoint of handgrip strength. In addition, more frequent lower dosing did not result in higher IgG trough levels or reduced adverse effects.

In the Progress in CIDP (ProCID) study, a Class I RCT, the efficacy of IVIG as maintenance treatment at three different doses was evaluated in 142 patients with active CIDP.[35] Patients were randomized to receive seven maintenance doses of 0.5, 1.0, or 2.0 gm/kg of IVIG every 3 weeks after an induction dose of 2 gm/kg of IVIG. The primary endpoint was the proportion of patients in the 1.0 gm/kg group with ≥1 point improvement in the adjusted INCAT score at 6 weeks compared to baseline and maintained at week 24 (with threshold of lower CI limit of 42%). At the end of the study, the primary endpoint was met with response rates of 65%, 80%, and 92% for the 0.5 gm/kg (22/34 patients; 95% CI: 48–79%), 1.0 gm/kg (55/69 patients; 95% CI: 69–88%), and 2.0 gm/kg (33/36 patients; 95% CI: 78–97%) groups, respectively. Although a dose-dependent response was suggested, the only between-group difference was seen between the 0.5 and 2.0 gm/kg groups. The incidence of adverse effects was similar among all groups although a dose effect was seen on incidence of headache, which was highest at 24% in the 2 gm/kg group.

To assess ongoing need for IVIG, a Class I RCT evaluated whether IVIG withdrawal was non-inferior to IVIG continuation in 60 patients with stable CIDP.[36] Patients in the withdrawal arm received 75%, 50%, and then 25% of their baseline pre-study IVIG dose followed by 100% placebo (normal saline) at their previous dose intervals, while controls received their usual dose and frequency.[36] The primary endpoint was the mean change in disability scores at 24 weeks or earlier in the case of a relapse. The results of the study were inconclusive as the difference between the two groups was −0.47 (95% CI: −1.24 to 0.31), with the lower bound of the CI crossing the non-inferiority margin of −0.65. Thus, non-inferiority of IVIG withdrawal could not be demonstrated. However, 41% remained stable in the IVIG withdrawal group at 24 weeks compared to 58% in the IVIG continuation group (95% CI: −39 to 8).

6.5 | Brands

In a Class I parallel RCT, 27 patients with active but stable CIDP on maintenance IVIG therapy were randomized to receive four infusions of either 10% liquid IVIG (Kiovig) or freeze dried 5% IVIG (Gammagard S/D) at their usual dose and frequency.[37] At the end of the study, no difference was seen in the primary outcome of efficacy as measured by disability scores or safety.

6.6 | Demyelinating Polyneuropathy and Diabetes

As diabetes is often an exclusion criterion for CIDP trials, one Class I RCT evaluated IVIG compared to placebo in 25 patients with diabetes mellitus and demyelinating polyneuropathy in a double-blinded crossover study. The definition of demyelination in this study was conduction velocity <90% of the lower limit of normal, distal latency >110% upper limit of normal (ULN), or minimal F-wave latency >110% ULN, which is less severe slowing than required for the diagnosis of CIDP. Patients were randomized to receive either IVIG 2 gm/kg over 2 days with 3 monthly maintenance doses of 1 gm/kg or placebo followed by a 3 mo washout period and then the other treatment.[38] At the end of the study, no difference was seen in the primary outcome of disability reduction between the two phases with mean change in disability score of −0.2 points for the IVIG phase versus 0 points in the placebo phase ($p = .23$). There was also no change in secondary endpoints.

CONCLUSION: Based on Class I studies, IVIG is effective in treating CIDP and results in reduced disability up to 24 and

possibly 48 weeks compared to placebo.[29–32] The efficacy of short-term IVIG use is also equivalent to PLEX (Class II)[39] and oral (Class II)[40] as well as IV corticosteroids (Class I)[33] although IVIG is better tolerated than IV MP. With respect to long-term therapy, there is Class I evidence that a maintenance dose of 1 gm/kg every 3 weeks is effective in reducing disability although no difference was seen with more frequent lower dosing compared to more conventional high-dose, low-frequency treatments.[34,35] Finally, based on one Class I study, IVIG is not effective in the setting of diabetes and polyneuropathy with mild slowing.[38]

7 | MULTIFOCAL MOTOR NEUROPATHY

Four Class I[42–45] and one Class II studies[46] evaluating the use of IVIG in MMN with conduction block were identified including two new Class I studies since the 2009 guideline.[7]

In a Class II crossover study, five treatment-naïve patients received either 2 gm/kg of IVIG over 5 days or placebo followed by the other treatment.[46] Improved muscle strength was seen in all patients after IVIG treatment that was significant at 28 days compared to placebo but not 56 days although it was still increased over baseline. In a Class I crossover study, 16 treatment-naïve patients received 0.4 gm/kg/day IVIG for 5 days or placebo.[42] At 28 days, a 6.7 ± 3.3 point improvement on the Neurologic Disability Score was seen in the IVIG group compared to a 2.1 ± 3.0 point worsening in the placebo group. In a Class I crossover study involving 10 treatment-naïve patients and 9 who had previously received IVIG, subjects were given 2.5 gm/kg IVIG over 5 days monthly for 3 mo or placebo after cross-over.[43] At 4 mo, improvement was seen in the primary endpoint of muscle strength in 12 of 18 patients, 4 of which were treatment naïve.

In the largest Class I cross-over study, the efficacy of maintenance IVIG therapy was evaluated in 44 patients with MMN on IVIG.[44] Patients were given either IVIG at the pre-treatment dose followed by placebo for 12 weeks or the reverse. Significant improvement was seen in the co-primary endpoint of grip strength (3.75%) in the IVIG treatment group compared to a decline (−31.4%) in the placebo group ($p = .005$). For the other co-primary endpoint, 35.7% of patients had worsening disability scores during treatment with placebo compared to 11.9% with IVIG ($p = .021$). Finally, 69% of patients required premature switch-back from placebo to open label IVIG versus only one subject from blinded IVIG to open label treatment. Although rates of adverse effects were similar in the IVIG and placebo groups, one patient developed a PE while receiving IVIG.

In a Class I cross-over non-inferiority RCT comparing two IVIG brands, 22 patients on maintenance IVIG were randomized to receive either 10% IgYmune or Kiovig for 21 to 25 weeks followed by the other treatment.[45] At the end of the study, IgYmune was found to be non-inferior to Kiovig in the primary endpoint of muscle strength. There was also no significant difference in the number of adverse effects.

A Cochrane review in 2022 concluded that IVIG may improve muscle strength and disability in patients with MMN compared with placebo.[47] Conversely, IVIG withdrawal may lead to deterioration in muscle strength and disability in this population.

CONCLUSION: Based on Class I evidence, IVIG is effective in treating MMN,[42–44,46] while withdrawal of maintenance therapy may result in clinical worsening.[44]

8 | PARAPROTEINEMIC NEUROPATHY

One Class I[48] and one Class II[49] studies were identified evaluating the use of IVIG in patients with IgM paraproteinemic neuropathy with no new studies since the last review. In a Class I double-blind crossover study, 22 patients with IgM-associated neuropathy were randomized to 2 gm/kg IVIG or placebo followed by the other treatment.[48] There was no difference between the two groups in the primary outcome of INCAT disability score at 2 weeks, although there was improvement at 4 weeks (secondary outcome) in the IVIG group ($p = .0001$). Of the 22 patients, 11 had anti-myelin associated glycoprotein (anti-MAG) antibodies, but no data were available for this subgroup. In a Class II placebo-controlled crossover study, 11 patients with IgM-associated neuropathy were randomized to 2 gm/kg IVIG or placebo monthly for 3 mo followed by the other treatment.[49] No significant difference was seen in the endpoints except for improved strength in 2 of 11 patients and sensory changes in one patient. A Cochrane analysis from 2016 concluded that there was low quality evidence for short-term improvement of IVIG in IgM neuropathy that may not be clinically significant.[50] Similarly, EFNS guidelines do not recommend the routine use of IVIG in IgM-associated neuropathy unless there is rapid worsening or significant disability.[51]

There are no double-blind, placebo-controlled studies evaluating the use of IVIG in treating IgG and IgA-associated neuropathy, although the results of two Class IV studies suggest a beneficial response with IVIG in IgG neuropathy.[52,53]

CONCLUSION: Based on Class I and Class II studies, there are no long-term benefits of IVIG in the treatment of IgM-associated neuropathy.[48,49] There is also insufficient evidence to support IVIG in treating IgG or IgA-associated neuropathy.

9 | CHRONIC AUTOIMMUNE LARGE FIBER NEUROPATHY

No double-blind, placebo-controlled studies were identified evaluating the use of IVIG in treating chronic autoimmune large fiber polyneuropathy. However, a number of case series and anecdotal reports have shown benefit in patients with polyneuropathy associated with Sjögren syndrome,[54–56] systemic lupus erythematosus,[57,58] sarcoidosis,[59] systemic sclerosis,[60] inflammatory bowel disease,[61] and CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, monoclonal protein, agglutination, and disialosyl antibodies)[62,63] with mixed results in paraneoplastic neuropathy.[64,65] There is also evidence suggesting that

IVIG may be detrimental in patients with cryoglobulinemic neuropathy due to immune complex precipitation, organ failure, and other complications.[66–69]

CONCLUSION: There is insufficient evidence to recommend IVIG for treating chronic autoimmune neuropathy. However, IVIG is not recommended in the setting of cryoglobulinemic neuropathy given the severe adverse effects.

10 | SMALL FIBER NEUROPATHY

Two Class I studies evaluated the use of IVIG in SFN.[70,71] In a Class I RCT, 60 patients with idiopathic SFN received either 2 gm/kg IVIG over 2 days followed by three additional infusions of 1 gm/kg at 3 weeks intervals or placebo.[70] At 12 weeks, there was no difference between the two groups in the proportion of patients who achieved the primary endpoint of ≥1-point change in the Pain Intensity Numerical Rating Scale (PI-NRS) score at 12 weeks (40% in the IVIG group compared to 30% receiving placebo; $p = .588$). There was also no significant difference between IVIG and placebo for most of the secondary endpoints, which included proportion of patients with ≥2-point improvement in PI-NRS, autonomic symptoms, pain relief, and overall disability. However, patients in the IVIG group did experience a statistically significant improvement in the health change portion of the SF-36 compared to placebo. Of note, 100% of patients receiving IVIG experienced headache compared to 57% receiving placebo. Similarly, nausea, vomiting, and rash were seen more commonly in the IVIG group compared to placebo.

In the second Class I RCT, 20 patients with a length-dependent SFN associated with trisulfated heparin disaccharide (TS-HDS) or fibroblast growth factor receptor-3 (FGFR-3) autoantibodies were randomized in a double-blind pilot study to receive either 2 gm/kg IVIG over 2 days followed by seven additional infusions of 1 gm/kg at 3 weeks intervals for 21 weeks or placebo.[71] The primary endpoint was change in intraepidermal nerve fiber density at 24 weeks compared to baseline with a clinically relevant change defined as >2 fibers/mm increase. At the end of the study, there was no significant difference between the IVIG group (0.6 ± 0.6 fibers/mm) and placebo (0.5 ± 0.8 fibers/mm; $p = .55$), with no patients achieving a clinically relevant change except for one in the placebo group.

A number of retrospective case series evaluating the use of IVIG in immune-mediated small fiber neuropathy due to Sjögren's,[55,72] sarcoidosis,[73] celiac disease,[74] and conditions associated with autoimmune markers[75] reported beneficial effects on pain.

CONCLUSION: Based on two Class I studies, IVIG is not effective for treating SFN that is idiopathic or associated with TS-HDS or FGFR-3 autoantibodies. There is also insufficient evidence to support IVIG for treating SFN due to other autoimmune conditions.

11 | MYASTHENIA GRAVIS

Three Class I[76–78] and one Class II studies[79] evaluating the use of IVIG in MG were identified including one new Class I and one new Class II studies. In a Class I RCT comparing IVIG to placebo in patients with MG, 51 patients with MG and worsening weakness were randomized to either IVIG 2 gm/kg divided over 2 days or placebo.[76] At 14 days, patients who received IVIG had a small but significant improvement in the primary outcome of change in Quantitative Myasthenia Gravis (QMG) score (−2.54) compared to placebo (−0.89; $p = .047$), which persisted at 28 days. In a subgroup analysis, the benefit was significant in patients with moderate to severe disease, but no effect was seen in those with mild disease.

In a Class I study that focused on the optimal IVIG dose for MG exacerbation, 173 patients were randomized to receive either 2 gm/kg IVIG over 2 days or 1 gm/kg on day 1 and then placebo on day 2.[77] The primary endpoint was improvement in the myasthenic muscular score at 2 weeks. Mean improvement at 2 weeks was 19.33 points (95% CI 15.82 to 22.85) in the group receiving 2 gm/kg of IVIG compared to 15.49 points (95% CI 12.09 to 18.09) in the group receiving 1 gm/kg. The difference was not statistically significant. Adverse effects were also similar in the two groups except for headache, which was seen in 22.7% of patients in the 2 gm/kg group compared to 13.1% in the 1 gm/kg group.

In a Class I study comparing IVIG to PLEX (1.0 plasma volume), 84 patients with moderate to severe MG (QMG score >10.5) and worsening weakness were randomized to receive either 2 gm/kg of IVIG over 2 days or one PLEX with 5% albumin every other day for 5 days.[78] There was no difference between the two groups in the primary outcome of change in QMG score at 14 days (−3.2 ± 4.1 in the IVIG group vs. 4.7 ± 4.9 in the PLEX group ($p = .13$)). Similarly, 51% of the patients in the IVIG group were responders (defined as a reduction of at least 3.5 units on the QMG) compared to 57% in the PLEX group ($p = .5$). In addition, both groups had a persistent reduction in QMG score at 28 days. Of note, 20% (10 in the IVIG group and 8 in the PLEX group) required additional treatment, which included changes in oral immunosuppressive medications and additional PLEX or IVIG.

In a recent Class II study that evaluated the efficacy of IVIG in reducing the dose of corticosteroids in corticosteroid-dependent MG patients compared to placebo, 60 patients were randomized to receive either 2 gm/kg of IVIG followed by 12 maintenance doses of 1 gm/kg every 3 weeks or placebo.[79] The primary endpoint was the percentage of patients achieving a 50% reduction in corticosteroid dose at week 39. No significant difference was seen between the two groups with 60% of patients in the IVIG group reaching a 50% reduction compared to 63% in the placebo group. Only 38 patients (63%) completed the study.

Two additional Class III studies evaluated the use of IVIG in chronic, stable MG.[80,81] One study compared IVIG to placebo but was underpowered,[80] while the other compared IVIG to PLEX but participants were unblinded and treatment allocation was skewed.[81] No significant difference was seen between the two groups in either study. A 2012 Cochrane analysis concluded that IVIG was beneficial in the treatment of MG exacerbation with comparable efficacy to PLEX, but there was insufficient evidence of efficacy in stable MG.[82]

CONCLUSION: There is Class I evidence that IVIG is effective in treating MG exacerbation especially in those with moderate to severe

disease. While the optimal dose of IVIG in treating acute MG exacerbation has not yet been established, no statistically significant difference was seen in efficacy with treatment using 1 versus 2 gm/kg of IVIG. Similarly, there is no difference in efficacy between IVIG and PLEX in treating clinically worsening MG.

In contrast, there is Class II evidence that IVIG does not help with tapering of corticosteroid doses in corticosteroid-dependent MG patients. There is also insufficient evidence to recommend IVIG in treating chronic, stable MG.

12 | LAMBERT-EATON MYASTHENIC SYNDROME

There is only one Class II study[83] evaluating the use of IVIG in LEMS with no new studies since the last guideline.[7] In a randomized controlled double-blinded crossover trial, nine patients with LEMS were given either IVIG 2 gm/kg over 2 days or placebo followed by the other treatment after an 8-weeks washout period.[83] The outcome measures were limb, respiratory, and bulbar muscle strength and serum calcium channel antibody titers at 2-weeks intervals over a period of 8 weeks. At the end of the study, those in the IVIG group had a significant increase in muscle strength that peaked at 2–4 weeks and a reduction in calcium channel antibody titers with nadir at 2 weeks.

CONCLUSION: There is modest evidence based on one Class II study that IVIG may be helpful in improving strength and reducing calcium channel antibody levels in patients with LEMS.

13 | DERMATOMYOSITIS

Two Class I[84,85] and one Class II[86] studies were identified that evaluated IVIG compared to placebo in patients with dermatomyositis including two new Class I studies. In a Class II randomized controlled crossover study, 15 patients with treatment-resistant dermatomyositis were given either IVIG 2 gm/kg over 2 days per month for 3 mo or placebo.[86] Although there was no specified primary endpoint, various outcome measures included muscle strength, Neuromuscular Symptom Score (NSS), change in rash and muscle biopsy findings. At 3 mo, a significant improvement in muscle strength ($p < .018$) and NSS ($p < .035$) was seen in the IVIG group with no change for placebo. Improvement of rash and muscle biopsy findings was also reported. In the crossover phase, four of seven patients initially given placebo improved, while four of eight patients in the IVIG group had no change or worsening when switched to placebo. In contrast, a small Class I crossover study involving 10 patients with corticosteroid-resistant dermatomyositis showed no difference in the primary endpoint of muscle strength in those receiving placebo and 2 gm/kg IVIG. This may have been due to the unequal improvements in the run-in period, which were increased in the placebo group.[85]

In the recently published Class I Progress in Dermatomyositis (ProDERM) study, 95 patients with active dermatomyositis were randomized to either 2 gm/kg IVIG every 4 weeks or placebo for 16 weeks.[84] The primary endpoint of the double-blind study was proportion of responders, defined as improvement of ≥20 points on the Total Improvement Score (TIS) at 16 weeks and no clinical worsening. In the second part of the study, patients in the placebo group and those with no clinical worsening in the IVIG were entered into the 24-weeks open-label extension period where all participants received 2 gm/kg every 4 weeks. At 16 weeks, the proportion of responders was 79% (37/47) in the IVIG group compared to 44% (21/48) in the placebo group ($p = .0008$). No patients worsened in the IVIG group compared to three receiving placebo. Also, mean TIS was significantly higher in the IVIG group at 48.4 ± 24.4 points compared to 21.6 ± 20.2 in the placebo group. After completion of the open-label extension period, patients who previously received placebo had a similar response rate of 70%. The study findings resulted in FDA approval of IVIG for use in dermatomyositis in 2021. Adverse events were seen in 58% of patients receiving IVIG (including 6 thrombotic events) compared to 23% receiving placebo.

CONCLUSION: There is Class I and II evidence that IVIG is beneficial in treating muscle weakness in dermatomyositis.

14 | INCLUSION BODY MYOSITIS

Two Class I[87,88] and one Class II[89] studies were identified that evaluated IVIG compared to placebo in patients with IBM with no new studies since the last guideline. In a Class I crossover study, 19 patients were randomized to either a monthly dose of 2 gm/kg IVIG for 3 mo or placebo followed by the other treatment.[87] While there was some evidence of improvement with respect to swallowing and leg strength as well as a trend toward improved muscle strength during IVIG treatment and worsening during the placebo phase, there was no significant difference in the primary outcome of overall muscle strength between the two groups at the end of the study ($p < .1$), which may have been due to the small sample size.

In a Class I study that evaluated whether or not the addition of steroids would have a synergistic effect with IVIG, 36 patients were randomized to receive 2 gm/kg/month IVIG combined with high dose prednisone (60 mg every other day) for 3 mo or prednisone alone.[88] All patients initially received 60 mg prednisone daily for 4 weeks followed by a taper down to 60 mg every other day for the 3 mo IVIG/placebo treatment period. At 4 mo, no significant change in the primary outcome of muscle strength was seen between the two groups.

In a Class II crossover study, 22 patients were randomized to receive monthly IVIG 2 gm/kg or placebo for 6 mo followed by the other treatment.[89] Outcome measures included muscle strength and NSS, but no specific primary endpoint was identified. At the end of 1 y, no change was seen in muscle strength or NSS compared to baseline although there was a significant but transient improvement in NSS during the IVIG treatment phase.

CONCLUSION: Based on Class I and II studies, IVIG is not recommended for treating IBM. There is also no evidence to recommend combination therapy with IVIG and corticosteroids.

15 | NECROTIZING AUTOIMMUNE MYOPATHY

No controlled studies were identified evaluating the use of IVIG in treating necrotizing autoimmune myopathy (NAM). A recently described type of idiopathic inflammatory myopathy, NAM is characterized by myofiber necrosis and is often associated with myositis-specific autoantibodies to signal recognition particle (SRP) and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), the latter of which usually occurs in the setting of statin use.[90] Current evidence for using IVIG in NAM remains empirical based on expert opinion, case series and one prospective pilot study that included six patients with NAM.[90–94] Favorable treatment responses with respect to improved muscle strength and reduced creatinine kinase levels have been reported in statin-induced myositis. Despite the lack of controlled clinical trials, IVIG has been recommended as second line therapy for anti-HMGCR myopathy in the 2016 European Neuromuscular Centre consensus guidelines due to the aggressive nature of the disease.[94]

CONCLUSION: There is insufficient evidence to recommend IVIG for treating NAM. However, based on the aggressive nature of the disease, international consensus guidelines recommend IVIG as a second line agent for anti-HMGCR myopathy to avoid long-term disability.

16 | POLYMYOSITIS

Although polymyositis (PM) is still a part of the 2017 EULAR/ACR classification of idiopathic inflammatory myopathies, it is now thought to be rare. Using newer criteria based on clinical presentation, histopathology and the presence of autoantibodies, many cases originally diagnosed as PM are now being reclassified as NAM (see above), anti-synthetase syndrome or overlap myositis.[95] There are currently no RCT evaluating the use of IVIG in PM (or any of the other inflammatory myopathies outside of DM and IBM) according to the evolving diagnostic criteria. It is also unknown if PM will be retained as a subtype in future classification systems.

17 | POST-POLIO SYNDROME

Three Class I studies were identified that evaluated IVIG compared to placebo in patients with PPS.[96–98] In a RCT that included 20 patients randomized to either 2 gm/kg of IVIG or placebo, significant improvement was seen in the primary endpoint of pain at 3 mo that was not sustained at 6 mo.[96] No improvement of the other primary endpoints of muscle strength and fatigue was seen at either timepoint.

In a Class I RCT, 142 patients with PPS were randomized to either 90 gm IVIG over 3 days that was repeated in 3 mo or placebo.[97] While there was an improvement of 8.6% ($p = .029$) in the primary endpoint of muscle strength after two doses of IVIG, this did not meet their pre-defined clinically meaningful target of 15%. Similarly, no improvement over placebo was seen in the co-primary endpoint of QOL or secondary endpoints, which included pain and fatigue. Multiple adverse effects were reported in the IVIG group with 59% classified as "nervous system disorder" (most commonly headache) compared to 19% in the placebo group.

In the most recent Class I RCT, 51 patients were randomized to a single dose of IVIG 2 gm/kg or placebo.[98] The primary outcome measure was QOL as measured by the physical role domain (PCS) of the SF-36 at 2 and 4 mo. While the SF-36 PCS significantly improved at 2 mo in the intervention group, this was not sustained at 4 mo and there was no difference in the total SF-36 score at either time point. The results of a Cochrane analysis from 2015, which included the above three articles, found that IVIG has no beneficial effect on activity limitation, fatigue, and pain, and had inconsistent effects on muscle strength.[99]

CONCLUSION: Based on Class I studies, IVIG is not recommended for treating symptoms of PPS.

18 | DYSAUTONOMIA

No controlled studies were identified evaluating the use of IVIG in peripheral dysautonomia, which includes autonomic ganglionopathy, autonomic neuropathy and postural orthostatic tachycardia syndrome (POTS). Results in Class IV studies have demonstrated mixed results for IVIG treatment of autoimmune autonomic ganglionopathy (AAG) and autonomic neuropathy with some benefit reported in the setting of systemic disorders (e.g., Sjögren, sarcoidosis), paraneoplastic disease and auto-antibodies (e.g., ganglionic receptor and voltage-gated potassium receptor antibodies).[73,100–103] However, patients with AAG in the absence of any associated systemic disorder or auto-antibodies often showed no improvement with IVIG either alone or in combination with other immunosuppressive therapies.[104,105]

In contrast, results from retrospective series assessing IVIG treatment for POTS, defined as tachycardia of ≥30 beats per minute within 10 min of standing, are more favorable with reports of improved dysautonomia symptoms and functional scores.[106–108] However, adverse effects were more common in this population prompting changes from conventional doses of 2 gm/kg IVIG over 2 to 5 days to regimens of smaller once weekly doses for several weeks. The iSTAND trial is an ongoing prospective double-blind crossover study that will evaluate the effects of IVIG versus albumin.

CONCLUSION: There is insufficient evidence to recommend IVIG in the treatment of dysautonomia.

19 | DIABETIC LUMBOSACRAL RADICULOPLEXOPATHY

No controlled studies were identified evaluating the use of IVIG in diabetic lumbosacral radiculoplexopathy (DLRP). In addition to various anecdotal reports, three retrospective and one prospective case series involving a total of 19 patients with DLRP reported improvement of

weakness and/or pain with IVIG monotherapy.[109–112] However, a case series of two patients with DLRP reported no improvement with IVIG and continued progression of symptoms following treatment.[113] A Cochrane review in 2017 found no randomized studies involving IVIG and concluded that there was no evidence to support immunotherapy for DLRP.[114]

CONCLUSION: There is insufficient evidence to recommend IVIG in the treatment of DLRP.

20 | IDIOPATHIC BRACHIAL PLEXOPATHY (NEURALGIC AMYOTROPHY)

No controlled studies were identified evaluating the use of IVIG in idiopathic brachial plexopathy (neuralgic amyotrophy). A limited number of Class IV studies showed improved motor recovery with IVIG alone or in combination with corticosteroids.[115–119]

CONCLUSION: There is insufficient evidence to recommend IVIG for idiopathic brachial plexopathy.

21 | STIFF-PERSON SYNDROME

There is one Class I study evaluating the use of IVIG in SPS with no new studies since the last guideline.[4] In a double-blinded crossover study, 16 patients were randomized to either IVIG 2 gm/kg over 2 days or placebo for 3 mo followed by the alternative treatment.[4] At the end of the study, those receiving IVIG had improvement in the primary endpoints of reduced stiffness ($p = .01$) and sensitivity to spasms ($p = .03$) compared to placebo. In addition, 11 of 16 patients had improved gait and activities of daily living. Benefits of IVIG in SPS were also noted in Class IV studies. A recent retrospective study evaluated the long-term effectiveness of maintenance IVIG in 36 patients with SPS over a 40 mo period.[120] Twenty-four of 36 (67%) patients had a beneficial response characterized by improved balance, gait, and stiffness.

CONCLUSION: Based on one Class I study, IVIG is effective in treating SPS.

22 | ADVERSE EFFECTS

While IVIG has a relatively favorable safety profile, multiple side effects have been reported that vary in incidence and severity depending on factors such as the brand (e.g., preparations containing higher rates of IgA and anti-Rh blood group D antigen may increase the risk of adverse events), rate of infusion, dose, and history of adverse effects with previous infusions.[121,122] More recent studies suggest that patients with certain disorders such as SFN and POTS may be more prone to adverse effects (notably headache) and may require adjusted dosing regimens.[70,75,106] Side effects of IVIG are usually minor and include headache, fatigue, dizziness, nausea, vomiting, myalgias, arthralgias, flushing, rash, fevers, chills, and other flu-like symptoms.[123,124]

Less commonly seen are major complications. Thrombotic events have a reported incidence of 1 to 13% (for both neurologic and non-neurologic indications) and include deep venous thrombosis, PE, myocardial infarction, stroke, and cerebral venous sinus thrombosis.[12,124–127] However, studies focused on neurologic populations have reported lower incidences especially with respect to myocardial infarction and ischemic stroke compared to venous thromboses.[128–130] In a retrospective study involving 62 patients who received a total of 616 IVIG infusions for inflammatory neuropathy, a thrombotic event was seen in 7 patients, 5 of which occurred within 14 days of infusion although overall incidence was 1% per infusion.[129] Prior thromboses, coronary disease, immobility, and doses of ≥35 gm per day were found to be risk factors. The primary mechanism of IVIG-related thrombotic events is thought to be an acute increase in plasma viscosity with one study demonstrating an 11% increase within the first 25 h among 15 patients receiving 2 gm/kg.[131] Additional mechanisms may include platelet activation, trigger of coagulation cascade due to presence of activated factor XI and release of vasoactive peptides.[123]

Renal failure, hypotension, aseptic meningitis, elevated transaminases, transient hematologic abnormalities (e.g., hemolytic anemia, neutropenia), and posterior reversible encephalopathy syndrome (reported in patients receiving IVIG for MFS) are other major side effects that have been reported with IVIG.[123,124,132–134]

23 | SUMMARY RECOMMENDATIONS

1. Based on Class I evidence, IVIG is recommended in the treatment of CIDP, GBS (adults), MMN, dermatomyositis, MG exacerbations (but not chronic stable disease) and SPS.
2. Based on Class II evidence, IVIG is recommended in the treatment of LEMS and pediatric cases of GBS.
3. Conversely, based on Class I evidence, IVIG is not recommended for the treatment of IBM, PPS (no long-term benefit), IgM paraproteinemic neuropathy (no long-term benefit), or SFN that is idiopathic or associated with TS-HDS or FGFR-3 autoantibodies.
4. Although the use of IVIG in the treatment of necrotizing autoimmune myopathy is based on Class IV evidence only, it is recommended that IVIG strongly be considered for anti-HMGCR myositis given the risk of long-term disability.

Currently, there is insufficient evidence for the use of IVIG in MFS, IgG, and IgA paraproteinemic neuropathy, autonomic neuropathy, chronic autoimmune neuropathy, polymyositis, idiopathic brachial plexopathy, and diabetic lumbosacral radiculoplexopathy.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Liz Kellermeyer https://orcid.org/0000-0001-6115-4343

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APPENDIX A: Full search strategy

Ovid MEDLINE

1	exp Autoimmune diseases of the nervous system/or exp Autonomic Nervous System Diseases/or exp Neuromuscular Diseases/
2	(radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$ or myopath$).mp.
3	1 or 2
4	(guillain barre or acute polyradiculoneuritis or acute polyneuritis or (inflammatory adj5 (neuropath$3 or polyneuropath$3))).mp.
5	(Fisher$ Syndrome$ or (Miller adj2 Fisher)).mp.
6	((chronic adj3 inflammatory adj3 demyelinating adj3 polyradiculoneuropathy) or (chronic adj3 inflammatory adj3 demyelinating adj3 polyneuropathy) or cidp).mp.
7	((polyneuritis or polyradiculoneuritis or polyradiculoneuropath$3 or polyneuropath$3 or inflammatory demyelinat$) and chronic disease$).mp.
8	(Myasthenia Gravis or musk mg).mp.
9	(Polymyosit$ or dermatomyosit$ or dermatopolymyosit$ or (myosit$ adj multiple)).mp.
10	(((small fiber or small fiber) adj2 neuropath$) or (Dysautonomia$ or ans diseas$ or ((parasympathetic or sympathetic) adj nervous system disease$) or (autonomic adj3 (disease$ or dysfunction$ or nervous or disorder$)))).mp.
11	((hyperekplexia$ adj (familial or hereditary)) or (moersch woltmann or startle syndrome$) or (stiff adj (person or man or trunk)) or (stiffman adj syndrome$)).mp.
12	(postpolio$ or post polio$).mp.
13	Postural Orthostatic Tachycardia Syndrome/ or ((Postural adj2 Tachycardia Syndrome$) or (POTS and tachycardia) or postural orthostatic tachycardia).mp.
14	Diabetic Neuropathies/ or (diabet$ adj3 (neuropath$ or amyotroph$ or polyradiculopath$ or myelopath$ or mononeur$ or neuralgia$ or polyneuropath$)).mp. or paralytic neuropath$.mp.
15	exp Lumbosacral Plexus/ or (lumb$ plexus or sacral plexus or lumb$ plexopath$).mp.
16	14 and 15
17	(Bruns Garland or Diabet$ lumb$ radiculoplex$ or DLRPN or diabet$ mononeurit$ multiplex$ or diabet$ lumbo$ plexopath$).mp.
18	16 or 17
19	Inclusion body myo$.mp.
20	((brachial adj2 (neuropath$ or plexitis or neuritis or plexopath$)) or (shoulder adj2 (neuritis or amyotroph$ or neuropath$)) or (amyotroph$ adj2 (neuralgi$ or neuritis)) or (parsonage turner or scapulohumeral paralys$ or brachial predilection) or (plexus adj2 (neuropath$ or neuritis or radiculoneuritis)) or (winged scapula or idiopathic polyneuritis)).mp.
21	(((muscular or muscle$) adj (diseas$ or disorder$)) or myosit$).mp.
22	Monoclonal Gammopathies, Benign/ or exp Paraproteinemias/ or exp immunoglobulin a/ or exp immunoglobulin g/ or exp immunoglobulin m/ or Myelin Associated Glycoprotein/ or "Monoclonal Gammopathy of Undetermined Significance"/
23	(MGUS or IgA or IgG or Immunoglobulin G or Immunoglobulin A or paraprotein$ or monoclonal gammopath$ or monoclonal protein$ or MAG or (myelin and glycoprotein$)).mp.
24	exp autoimmune diseases/ or exp "autoimmune diseases of the nervous system"/ or (autoimmun$ or immune mediated).mp.
25	cryoglobul$.mp.
26	or/22–25
27	exp Peripheral Nervous System Diseases/ or (neuropath$ or nervous system disease$ or polyradiculoneuropath$ or myopath$).mp.
28	(radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$ or myopath$ or nervous system disease$).mp.
29	27 or 28
30	26 and 29
31	exp Immunoglobulins, Intravenous/
32	(intravenous immu$ or intra venous immu$ or IV immunoglobulin$ or IVIG or IGIV or intravenous IG).tw.
33	(intraglob$ or intravenous antibod$ or IV antibod$).tw.
34	or/31–33
35	exp gamma globulins/ or exp immunoglobulins/
36	(gammaglobulin$ or gamma globulin$).tw.
37	immunoglobulin$.tw.

(Continues)

38	((immune$ or immuno$) adj5 (globulin$ or serum$)).tw.
39	or/35–38
40	exp injections intravenous/ or exp infusions intravenous/ or (intravenous or intra-venous or infusion$).tw.
41	39 and 40
42	34 or 41 [IVIG]
43	or/3–13,18-21,30
44	42 and 43
45	limit 44 to humans
46	limit 44 to animals
47	44 not 45 not 46
48	45 or 47
49	limit 48 to english
50	limit 48 to abstracts
51	49 or 50
52	limit 51 to yr = "2008-Current"

Ovid EBM Reviews-Cochrane Central Register of Controlled Trials.

1	exp Autoimmune diseases of the nervous system/ or exp Autonomic Nervous System Diseases/ or exp Neuromuscular Diseases/
2	(radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$ or myopath$).mp.
3	1 or 2
4	(guillain barre or acute polyradiculoneuritis or acute polyneuritis or (inflammatory adj5 (neuropath$3 or polyneuropath$3))).mp.
5	(Fisher$ Syndrome$ or (Miller adj2 Fisher)).mp.
6	((chronic adj3 inflammatory adj3 demyelinating adj3 polyradiculoneuropathy) or (chronic adj3 inflammatory adj3 demyelinating adj3 polyneuropathy) or cidp).mp.
7	((polyneuritis or polyradiculoneuritis or polyradiculoneuropath$3 or polyneuropath$3 or inflammatory demyelinat$) and chronic disease$).mp.
8	(Myasthenia Gravis or musk mg).mp.
9	(Polymyosit$ or dermatomyosit$ or dermatopolymyosit$ or (myosit$ adj multiple)).mp.
10	(((small fiber or small fiber) adj2 neuropath$) or (Dysautonomia$ or ans diseas$ or ((parasympathetic or sympathetic) adj nervous system disease$) or (autonomic adj3 (disease$ or dysfunction$ or nervous or disorder$)))).mp.
11	((hyperekplexia$ adj (familial or hereditary)) or (moersch woltmann or startle syndrome$) or (stiff adj (person or man or trunk)) or (stiffman adj syndrome$)).mp.
12	(postpolio$ or post polio$).mp.
13	Postural Orthostatic Tachycardia Syndrome/ or ((Postural adj2 Tachycardia Syndrome$) or (POTS and tachycardia) or postural orthostatic tachycardia).mp.
14	Diabetic Neuropathies/ or (diabet$ adj3 (neuropath$ or amyotroph$ or polyradiculopath$ or myelopath$ or mononeur$ or neuralgia$ or polyneuropath$)).mp. or paralytic neuropath$.mp.
15	exp Lumbosacral Plexus/ or (lumb$ plexus or sacral plexus or lumb$ plexopath$).mp.
16	14 and 15
17	(Bruns Garland or Diabet$ lumb$ radiculoplex$ or DLRPN or diabet$ mononeurit$ multiplex$ or diabet$ lumbo$ plexopath$).mp.
18	16 or 17
19	Inclusion body myo$.mp.
20	((brachial adj2 (neuropath$ or plexitis or neuritis or plexopath$)) or (shoulder adj2 (neuritis or amyotroph$ or neuropath$)) or (amyotroph$ adj2 (neuralgi$ or neuritis)) or (parsonage turner or scapulohumeral paralys$ or brachial predilection) or (plexus adj2 (neuropath$ or neuritis or radiculoneuritis)) or (winged scapula or idiopathic polyneuritis)).mp.
21	(((muscular or muscle$) adj (diseas$ or disorder$)) or myosit$).mp.
22	Monoclonal Gammopathies, Benign/ or exp Paraproteinemias/ or exp immunoglobulin a/ or exp immunoglobulin g/ or exp immunoglobulin m/ or Myelin Associated Glycoprotein/ or "Monoclonal Gammopathy of Undetermined Significance"/

23	(MGUS or IgA or IgG or Immunoglobulin G or Immunoglobulin A or paraprotein$ or monoclonal gammopath$ or monoclonal protein$ or MAG or (myelin and glycoprotein$)).mp.
24	exp autoimmune diseases/ or exp "autoimmune diseases of the nervous system"/ or (autoimmun$ or immune mediated).mp.
25	cryoglobul$.mp.
26	or/22–25
27	exp Peripheral Nervous System Diseases/ or (neuropath$ or nervous system disease$ or polyradiculoneuropath$ or myopath$).mp.
28	(radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$ or myopath$ or nervous system disease$).mp.
29	27 or 28
30	26 and 29
31	exp Immunoglobulins, Intravenous/
32	(intravenous immu$ or intra venous immu$ or IV immunoglobulin$ or IVIG or IGIV or intravenous IG).tw.
33	(intraglob$ or intravenous antibod$ or IV antibod$).tw.
34	or/31–33
35	exp gamma globulins/ or exp immunoglobulins/
36	(gammaglobulin$ or gamma globulin$).tw.
37	immunoglobulin$.tw.
38	((immune$ or immuno$) adj5 (globulin$ or serum$)).tw.
39	or/35–38
40	exp injections intravenous/ or exp infusions intravenous/ or (intravenous or intra-venous or infusion$).tw.
41	39 and 40
42	34 or 41 [IVIG]
43	or/3–13,18-21,30
44	42 and 43
45	limit 44 to abstracts
46	limit 44 to english language
47	45 or 46
48	limit 47 to yr = "2008-Current"

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1	"neurologic disease"/exp OR "myositis"/exp OR "stiff man syndrome"/exp OR "autonomic dysfunction"/exp
2	"peripheral neuropathy"/exp AND ("m protein"/exp OR "cryoglobulinemia"/exp)
3	1 OR 2
4	radiculoneuropath*:ti OR polyradiculoneuropath*:ti OR polyneuropath*:ti OR neuropath*:ti OR myopath*:ti
5	"guillain barre":ti OR "acute polyradiculoneuritis":ti OR "acute polyneuritis":ti OR ((inflammatory NEAR/5 (neuropath* OR polyneuropath*)):ti)
6	"fisher* syndrome*":ti OR ((miller NEAR/2 fisher):ti)
7	((chronic NEAR/3 inflammatory NEAR/3 demyelinat* NEAR/3 polyradiculoneuropathy):ti) OR ((chronic NEAR/3 inflammatory NEAR/3 demyelinating NEAR/3 polyneuropathy):ti) OR cidp:ti
8	(polyneuritis:ti OR polyradiculoneuritis:ti OR polyradiculoneuropath*:ti OR polyneuropath*:ti OR "inflammatory demyelinating":ti) AND "chronic disease?":ti
9	"myasthenia gravis":ti OR "musk mg":ti
10	polymyosit*:ti OR dermatomyosit*:ti OR dermatopolymyosit*:ti OR ((myosit* NEXT/1 multiple):ti)
11	(((("small fiber" OR "small fiber") NEAR/2 neuropath*):ti) OR dysautonomia*:ti OR "ans diseas*":ti OR (((parasympathetic OR sympathetic) NEXT/1 "nervous system disease*"):ti) OR ((autonomic NEAR/3 (disease* OR dysfunction* OR nervous OR disorder*)):ti)
12	((hyperekplexia* NEXT/1 (familial OR hereditary)):ti) OR "moersch woltmann":ti OR "startle syndrome*":ti OR ((stiff NEXT/1 (person OR man OR trunk)):ti) OR ((stiffman NEXT/1 syndrome*):ti)
13	postpolio*:ti OR "post polio*":ti

(Continues)

14	"postural orthostatic tachycardia syndrome"/de OR (postural NEAR/2 "tachycardia syndrome?") OR (pots AND tachycardia) OR "postural orthostatic tachycardia"
15	"bruns garland":ti OR "diabet* lumb* radiculoplex*":ti OR dlrpn:ti OR "diabet* mononeurit* multiplex*":ti OR "diabet* lumbo* plexopath*":ti
16	"inclusion body myo*":ti
17	((brachial NEAR/2 (neuropath* OR plexitis OR neuritis OR plexopath*)):ti) OR ((shoulder NEAR/2 (neuritis OR amyotroph* OR neuropath*)):ti) OR ((amyotroph* NEAR/2 (neuralgi* OR neuritis)):ti) OR "parsonage turner":ti OR "scapulohumeral paralys*":ti OR "brachial predilection":ti OR ((plexus NEAR/2 (neuropath* OR neuritis OR radiculoneuritis)):ti) OR "winged scapula":ti OR "idiopathic polyneuritis":ti
18	(((muscular OR muscle*) NEXT/1 (diseas* OR disorder*)):ti) OR myosit*:ti
19	radiculoneuropath*:ti OR polyradiculoneuropath*:ti OR polyneuropath*:ti OR neuropath*:ti OR myopath*:ti OR "nervous system disease*":ti
20	mgus:ti OR iga:ti OR igg:ti OR "immunoglobulin g":ti OR "immunoglobulin a":ti OR paraprotein*:ti OR "monoclonal gammopath*":ti OR "monoclonal protein*":ti OR mag:ti OR (myelin:ti AND glycoprotein*:ti) OR cryoglobul*:ti
21	19 AND 20
22	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 21
23	3 OR 22
24	"immunoglobulin"/exp/mj/dd_iv
25	"intravenous immu*":ti OR "intra venous immu*":ti OR "iv immunoglobulin*":ti OR ivig:ti OR igiv:ti OR "intravenous ig":ti OR intraglob*:ti OR "intravenous antibod*":ti OR "iv antibod*":ti
26	24 OR 25
27	23 AND 26
28	23 AND 26 AND [abstracts]/lim
29	23 AND 26 AND [english]/lim
30	28 OR 29
31	(28 OR 29) AND [humans]/lim
32	(28 OR 29) AND [animals]/lim
33	30 NOT 31 NOT 32
34	31 OR 33
35	(31 OR 33) AND [2008–2022]/py
36	(31 OR 33) AND [2008–2022]/py AND [conference abstract]/lim
37	35 NOT 36