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Evidence-Based Practice Summary

Immunoglobulins for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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BACKGROUND AND RATIONALE

Chronic inflammatory demyelinating Polyradiculoneuropathy (CIDP) is an acquired peripheral neuropathy. It is the most common peripheral autoimmune demyelinating neuropathy with a prevalence of 1.2 to 7.7 per 100,000 worldwide, and with a slight male predominance. The disease involves progressive loss of immunologic tolerance to peripheral nerve components. The demyelination affects spinal roots, proximal nerve trunks and major plexi that lead to loss of strength and sensation. The most commonly used treatments for CIDP include; corticosteroids, intravenous or subcutaneous immunoglobulin (IVIg or SCIg) and plasma exchange (PE)[1].

Immunoglobulins rank among the top hospital drug expenses. In addition to the high drug costs, IVIg treatments require the use of hospital resources for recurrent infusions. Home infusion has been used since the 1990s, and for some populations, is now considered to be a safe alternative to hospital care [2]. Another alternative to IVIg treatment is SCIg which can be self-administered at home[3].

This evidence brief seeks to determine the benefits and harms of treatment for CIDP with immunoglobulins.

ASK THE QUESTION

In patients with chronic inflammatory demyelinating polyneuropathy (CIDP), does treatment with immunoglobulins (either intravenous or subcutaneous) improve clinical and patient important outcomes (e.g. muscle strength and quality of life)?

SEARCH FOR EVIDENCE

Databases included: Ovid MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials

Search strategy included: MeSH terms: Immunoglobulins, Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Filters/limits included: Articles published in English from the past 5 years

For full search strategy please see Appendix A.

CRITICALLY ANALYZE THE EVIDENCE

Summary of the Primary Literature:

The **2010 European Federation of Neurological Societies/Peripheral Nerve Society Guideline** on Management of chronic inflammatory demyelinating polyradiculoneuropathy recommends[4]:

1) IVIg (level A recommendation) or corticosteroids (level C recommendation) should be considered in sensory and motor CIDP in the presence of disabling symptoms. PE is similarly effective (level A recommendation) but may be less tolerated. The presence of relative contraindications to any of these treatments should influence the choice (Good Practice Points). The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).
2) In pure motor CIDP, IVIg should be considered as the initial treatment (Good Practice Point).
3) If the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose reduced to find the lowest effective maintenance dose (Good Practice Point).
4) If the response is inadequate or the maintenance doses of the initial treatment (IVIg, steroids, or PE)result in adverse effects, the other first-line treatment alternatives should be tried before considering combination treatments or adding an immuno-suppressant or immunomodulatory drug may be considered, but there is no sufficient evidence to recommend any particular drug (Good Practice Point).

See appendix C for the Trustworthy Guideline grading.

Eleven studies are included in the appraisal of the question regarding the treatment of CIDP with Immunoglobulins. The assessments are divided by: treatment type and comparator (either IVIG or SCIG compared to placebo or each other) and the outcomes of cost, efficacy, patient satisfaction, and adverse events. Overall there is *very low quality* evidence to support either home or hospital administration of IVIG for the treatment of CIDP[2, 5], *low quality* evidence to support both IVIG and SCIG for the treatment of CIDP compared to placebo[1,3,6,7], and *low quality evidence* to support that SCIG is as efficacious as IVIG for the treatment of CIDP [8-11].

Primary Literature:

Intervention: IVIG

Outcome: Cost

Studies Included: 1 economic evaluation and 1 non-randomized

The economic evaluation [5] consisted of a Markov model that aimed to conduct an economic evaluation (EE) of IVIG plus corticosteroids in steroid-resistant CIDP in Thailand. The model was constructed to estimate the lifetime costs and outcomes for IVIG plus corticosteroids in comparison with immunosuppressants plus corticosteroids in steroid-resistant CIDP patients from a societal perspective. Efficacy and utility data were obtained from clinical literature, meta-analyses,

medical record reviews, and patient interviews. Cost data were obtained from list prices, an electronic hospital database. In the base-case, the incremental costs and quality-adjusted life years (QALYs) of IVIG plus corticosteroids versus immunosuppressants plus corticosteroids were US$2112.02 and 1.263 QALYs, respectively, resulting in an incremental cost-effectiveness ratio (ICER) of US$1672.71 per QALY gained. Sensitivity analyses revealed that the utility value of disabled patients was the greatest influence on ICER. At a societal willingness-to-pay threshold in Thailand of US$4672 per QALY gained, IVIG plus corticosteroids had a 92.1 % probability of being cost effective.

The second study [2] was a prospective, dual-center, cost minimization analysis to evaluate IVIg administration (5% concentrated) at home versus in hospital with regard to costs, patients' autonomy, and patients' quality of life. The primary endpoint was the overall cost of treatment, and we adopted the perspective of the payer. Nine-month total costs per patient extrapolated to 1 year of treatment were 48,189 +/- 26,105 versus 91,798 +/- 51,125 in the home and hospital groups, respectively (P < .0001). The most frequently reported factors for choosing home treatment were the good tolerance and absence of side effects of IVIg administration, as well as a good understanding of the advantages and drawbacks of home treatment (75% of respondents).

Overall there is *very low quality evidence* to support either home or hospital administration of IVIG for the treatment of CIDP.

Intervention: IVIG vs. placebo

Outcome: Efficacy

Studies Included: 2 Systematic Reviews and 1 RCT

The first systematic review[1] aimed to prospectively review the literature to determine the effectiveness of therapies for chronic inflammatory demyelinating polyradiculoneuropathy. Their study in IVIG treatment included 3 RCTs with 163 total patients. Due to heterogeneity, they were unable to pool the results of the studies, opting for a narrative instead. The first included RCT found that at 4 months 77.8% (7/9) of participants who received IVIg first and 22.2% (2/9) who received the placebo responded well to the self-evaluation parameters (OR 12.25, 95% CI 1.33-113.06, P=0.03). Although the trial was small and not powered significantly, it did show IVIg was effective treating the symptoms of in CIDP. The second included study observed no significant difference between the treatment and placebo groups. The third RCT reported that 54% (32/ 59) treated with IVIg were clinical responders versus 20.7% (12/58) of subjects who received the placebo (OR 4.54, 95% CI 2.01-10.28, P<0.001).

The second systematic review[6] aimed to review the evidence concerning the efficacy and safety of IVIg in CIDP. This review included five trials with 253 participants and observed that a significantly higher proportion of participants improved after IVIg therapy as compared with placebo, with a pooled RR of 2.40 (95% CI 1.72 to 3.36).

The only RCT [7] included 20 participants with the goal of measuring changes in spatiotemporal gait parameters of patients with CIDP at baseline and following treatment with intravenous immunoglobulin (IVIG), using GAITRite a computerized walkway system with embedded sensors. The investigators observed that following treatment, the entire group showed statistically significant improvements in MRC sum score (P=0.03) and grip strength (P=0.03), but not disability score and improvement in most gait parameters, with the most statistically significant differences seen in velocity (P=0.0004), stance phase (P=0.0002), and swing phase (P=0.0002). Changes from baseline in step time and base (or step width) were not significant.

Overall there is *low quality evidence* to support IVIG for the treatment of CIDP compared to placebo.

Intervention: IVIG vs. placebo

Outcome: Adverse Events

Studies Included: 2 Systematic Reviews and 1 RCT

The first systematic review[1] aimed to prospectively review the literature to determine the effectiveness of therapies for chronic inflammatory demyelinating polyradiculoneuropathy. Their study in IVIG treatment included 3 RCTs with 163 total patients. None of the three included trials reported serious adverse events

The second systematic review[6] aimed to review the evidence concerning the efficacy and safety of IVIg in CIDP. This review included five trials with 253 participants and reported that mild and transient adverse events were found in 49% of participants treated with IVIg, while serious adverse events were found in 6%.

The only RCT [7] included 20 participants with the goal of measuring changes in spatiotemporal gait parameters of patients with CIDP at baseline and following treatment with intravenous immunoglobulin (IVIG), using GAITRite a computerized walkway system with embedded sensors. The investigators observed no adverse events.

Overall there is *low quality evidence* to support the finding that IVIG for the treatment of CIDP does not cause serious adverse events.

Intervention: IVIG vs. SCIG

Outcome: Efficacy

Studies Included: 2 Systematic Reviews, 1 RCT, and 1 observational study

The first systematic review [8] aimed to compare the efficacy and safety of SC-Ig versus IVig for treating patients with CIDP and multifocal motor neuropathy (MMN). This review included 4 trials with 50 CIDP patients. There were no significant differences in muscle strength outcomes in MMN and CIDP with SCIg (CIDP: Effect Size= 0.84, 95% CI = -0.01-1 .69). Additionally SCIg had a 28% reduction in relative risk (RR) of moderate and/or systemic adverse effects (95% CI = 0.11-0.76).

The second systematic review[9] aimed to review the review the efficacy of SCIg administration in terms of muscle strength maintenance and patient satisfaction comparing with IVIg in the treatment of auto-immune neuromuscular diseases. Analysis on ONLS scores found a significant improvement, or reduction in ONLS scores, in patients after switching to SCIg administration: difference in means (df) was 0.206, 95% CI [0.025–0.388], P=0.026. This difference was not significant in random effects model (P=0.570). The difference of MRCss was 0.949 (95% CI [0.612–1.287]) and 1.024 (95% CI [0.521–1.528]), in fixed and random effects model, respectively. Both differences were significant in favor of switching to SCIg treatment. Health-related quality of life was significantly improved after switching to SCIg, with a mean score difference of 1.602 (95% CI [0.711–2.494], P< 0.0001). A significant preference for SCIg administration was observed in data pooled from the 113 patients in 5 studies using the Life Quality Index (P<0.0001).

The RCT [10] included 20 participants with the goal investigating whether multiple subcutaneous infusions are as effective as conventional therapy with intravenous loading doses in treatment-naive patients with CIDP. The authors reported that overall combined isokinetic muscle strength increased by 7.4 +/- 14.5%

(P = 0.0003) during SCIG and by 6.9 +/- 16.8% (P = 0.002) during IVIG, the effect being similar (P = 0.80). Improvement of cIKS peaked 2 weeks after IVIG and 5 weeks after SCIG. Disability improved during SCIG treatment only (P=0.002). Muscle strength determined by manual muscle testing improved after 5 and 10 weeks during SCIG but only after 5 weeks during IVIG. The remaining parameters improved equally during both treatments.

The observational study [11] compared variation in isokinetic muscle strength and function in CIDP and multifocal motor neuropathy (MMN) patients during treatment with IVIg to the variation observed after changing treatment to SCig and included 23 patients. The coefficient of variance of cIKS during the IVIg and SCIg treatment periods was unchanged (mean +/- SD: 6.97 +/- 4.83% vs. 5.50 +/- 3.13%, P = 0.21). The variations in the 9-HPT and 40-MWT were significantly lower in the SCIg group (P =0.01 and P = 0.005, respectively).

Overall there is *low quality evidence* to support the finding that SCIg is as efficacious as IVIg for treating CIDP.

Intervention: IVIG vs. SCIG

Outcome: Adverse Events

Studies Included: 1 RCT, and 1 observational study

The RCT [10] included 20 participants with the goal investigating whether multiple subcutaneous infusions are as effective as conventional therapy with intravenous loading doses in treatment-naive patients with CIDP. The authors reported no events.

The observational study [11] compared variation in isokinetic muscle strength and function in CIDP and multifocal motor neuropathy (MMN) patients during treatment with IVIg to the variation observed after changing treatment to SCig and included 23 patients. One patient experienced a spontaneous and remitting severe hemolytic anemia following IVIG therapy with a decrease in hemoglobin of 42 g/L leading to hospitalization. Otherwise, side effects after IVIG were mild with two further cases of hemolytic anemia, two of fever/chill and nausea, two of a mild dermatological reaction and six of headache. During SCIG, three patients had local skin reactions at the infusion sites and two complained of nausea.

Overall there is very *low quality evidence* to support the finding that IVIg and SCIg for the treatment of CIDP does not cause serious adverse events.

Intervention: SCIG vs. Placebo

Outcome: Efficacy, Patient Satisfaction, and Adverse Events

Studies Included: 1 RCT

The RCT [3] included 172 participants with the goal of comparing two doses of SCIg IgPro20 with placebo for maintenance treatment of patients with CIDP. In the intention-to-treat set, 36 (63% [95% CI 50-74]) patients on placebo, 22 (39% [27-52]) on low-dose SCIg, and 19 (33% [22-46]) on high-dose SCIg had a relapse or were withdrawn from the study for other reasons (P=0.0007). Absolute risk reductions were 25% (95% CI 6-41) for low-dose versus placebo (P=0.007), 30% (12-46) for high-dose versus placebo (P=0.001), and 6% (-11 to 23) for high-dose versus low-dose (P=0.32).

Health-related quality-of-life measures generally showed better outcomes for both SCIg groups than for placebo. 135 (88%) patients reported that learning the technique of self-administration was easy (42 [93%] in the placebo group, 49 [91%] in the low-dose group, and 44 [80%] in the high-dose group). 61 (53%) of 115 patients who received SCIg preferred their current treatment (30 [53%] in the low-dose group and 31 [53%] in the high-dose group) versus 22 (39%) of 57 patients who received placebo, whereas 21 (18%) patients receiving SCIg (ten [18%] and 11 [19%]) and 14 (25%) patients receiving placebo preferred their previous IVIg treatment. Reasons for patients preferring weekly SCIg to monthly IVIg included a gain in independence and fewer side effects.

Causally related adverse events occurred in 47 (27%) patients (ten [18%] in the placebo group, 17 [30%] in the low-dose group, and 20 [34%] in the high-dose group). Six (3%) patients had 11 serious adverse events: one (2%) patient in the placebo group, three (5%) in the low-dose group, and two (3%) in the high-dose group; only one (an acute allergic skin reaction in the low-dose group) was assessed to be causally related.

Overall there is *low quality evidence* to support the finding that SCIg for the treatment of CIDP is efficacious, preferred by patients, and with low incidence of serious adverse events.

REFERENCES:

1. Bright, R.J., J. Wilkinson, and B.J. Coventry, *Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. [Review].* 2014. **1**: p. 26.
2. Le Masson, G., et al., *Home versus hospital immunoglobulin treatment for autoimmune neuropathies: A cost minimization analysis.* 2018. **1**(2): p. e00923.
3. van Schaik, I.N., et al., *Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial.* 2018. **1**(1): p. 35-46.
4. Joint Task Force of the, E. and P.N.S. the, *European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--First Revision. [48 refs].* 2010. **1**(1): p. 1-9.
5. Bamrungsawad, N., et al., *Economic Evaluation of Intravenous Immunoglobulin plus Corticosteroids for the Treatment of Steroid-Resistant Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Thailand.* 2016. **1**(7): p. 557-66.
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10. Markvardsen, L.H., et al., *Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study.* 2017. **1**(2): p. 412-418.
11. Christiansen, I., L.H. Markvardsen, and J. Jakobsen, *Comparisons in fluctuation of muscle strength and function in patients with immune-mediated neuropathy treated with intravenous versus subcutaneous immunoglobulin.* 2018. **1**(4): p. 610-614.

Appendix A. Search Strategy

Search Strategy:

1 exp Polyradiculoneuropathy, Chronic Inflammatory Demyelinating/ (1342)
2 exp immunoglobulins/ or immunoglobulin g/ (853757)
3 exp Immunoglobulins, Intravenous/ (12441)
4 1 and 3 (350)
5 (((chronic* adj3 inflammat* adj3 (demyelin* or de-myelin*) adj3 (polyneuropath* or polyradiculoneuropath*)) or cidp) adj10 ((antibod* or immunoglobulin*) adj5 (intraven* or iv))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (235)
6 4 or 5 (447)
7 limit 6 to english language (394)
8 limit 7 to (meta analysis or "systematic review") (10)
9 limit 7 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) (30)
10 limit 7 to (comparative study or evaluation studies or practice guideline or validation studies) (28)
11 9 or 10 (51)
12 exp "Outcome and Process Assessment (Health Care)"/ (1024556)
13 7 and 12 (126)
14 exp Epidemiologic Studies/ (2299936)
15 7 and 14 (92)
16 11 not 8 (50)
17 13 not (11 or 8) (102)
18 15 not (13 or 11 or 8) (33)
19 7 not (15 or 13 or 11 or 8) (199)

Appendix B. Evidence Evaluation and GRADE criteria for rating a body of evidence on an intervention

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
Modality: Intravenous Immunoglobulin (IVIG)
Outcome: Cost

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☐ Medium ☒ Low	☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Bamrungsawad, N., et al. Year Published: 2016 Location: Thailand Journal: *Clinical Drug Investigation*	This study aimed to conduct an economic evaluation (EE) of IVIG plus corticosteroids in steroid-resistant CIDP in Thailand.	**Size:** N/A **Inclusion Criteria:** Patients with steroid resistant CIDP.	**Type:** Modeling Study **Intervention:** A Markov model was constructed to estimate the lifetime costs and outcomes for IVIG plus corticosteroids in comparison with immunosuppressants plus corticosteroids in steroid-resistant CIDP patients from a societal perspective. Efficacy and utility data were obtained from clinical literature, meta-analyses, medical record reviews, and patient interviews. Cost data were	**Results:** In the base-case, the incremental costs and quality-adjusted life years (QALYs) of IVIG plus corticosteroids versus immunosuppressants plus corticosteroids were US$2112.02 and 1.263 QALYs, respectively, resulting in an incremental cost-effectiveness ratio (ICER) of US$1672.71 per QALY gained. Sensitivity analyses revealed that the utility value of disabled patients was the greatest influence on ICER. At a societal willingness-to-pay threshold in Thailand of	**Study Limitations:** ☒ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

			obtained from list prices, an electronic hospital database, published source, and patient interviews. All costs [in 2015 US dollars (US$)] and outcomes were discounted at 3 % annually.	US$4672 per QALY gained, IVIG plus corticosteroids had a 92.1 % probability of being cost effective.	
Author: Le Masson, G., et al. Year Published: 2018 Location: France Journal: *Brain and Behavior*	To estimate and compare the costs of home-based vs. hospital-based recurrent infusions of IVIG	**Size:** 24 **Inclusion Criteria:** Patients treated for autoimmune neuropathy with IVIG in a hospital outpatient setting. **Exclusion Criteria:** Had combined neuropathy and monoclonal anti myelin-associated glycoprotein.	**Type:** Before and After Study **Intervention:** A French prospective, dual-center, cost minimization analysis was carried out to evaluate IVIg administration (5% concentrated) at home versus in hospital with regard to costs, patients' autonomy, and patients' quality of life. The primary endpoint was the overall cost of treatment, and we adopted the perspective of the payer (French Social Health Insurance).	**Results:** Nine-month total costs per patient extrapolated to 1 year of treatment were 48,189 +/- 26,105 versus 91,798 +/- 51,125 in the home and hospital groups, respectively (P < .0001). The most frequently reported factors for choosing home treatment were the good tolerance and absence of side effects of IVIg administration, as well as a good understanding of the advantages and drawbacks of home treatment (75% of respondents).	**Study Limitations:** ☒ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

References:
Le Masson, G., et al. (2018). "Home versus hospital immunoglobulin treatment for autoimmune neuropathies: A cost minimization analysis." Brain and Behavior 8(2): e00923.
Bamrungsawad, N., et al. (2016). "Economic Evaluation of Intravenous Immunoglobulin plus Corticosteroids for the Treatment of Steroid-Resistant Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Thailand." Clinical Drug Investigation 36(7): 557-566.

BODY OF EVIDENCE APPRAISAL TABLE FOR: Population: Patients with CIDP Modality: IVIG vs. placebo Outcome: Efficacy		
Quality (certainty) of evidence for: (outcome) ☐ High ☐ Moderate ☒ Low ☐ Very Low		
Risk of Bias across studies: ☐ High ☒ Medium ☐ Low	**Lower Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*)	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)*

		☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Bright, R. J., et al. Year Published: 2014 Location: Australia Journal: *BMC Neurology*	The aim of this study was to prospectively review the literature to determine the effectiveness of therapies for chronic inflammatory demyelinating polyradiculoneuropathy.	**Size:** 3 trials, 163 participants **Inclusion Criteria:** RCTs published from January 1990 to December 2012 were searched for studies to treat adults with chronic inflammatory demyelinating polyradiculoneuropathy.	**Type:** Systematic Review **Intervention:** Outcomes of interest included: MRC score, nerve conduction and self-evaluation parameters.	**Results:** RCT 1: At four months 77.8% (7/9) of participants who received IVIg first and 22.2% (2/ 9) who received the placebo responded well to the self-evaluation parameters (OR 12.25, 95% CI I.33-II3.06, P = 0.03). No serious treatment related effects were noted in this study. Although the trial was small and not powered significantly, it did show IVIg was effective treating the symptoms of in CIDP. RCT2: 4/15 (26.7%) and 3/13 (23.6%) subjects who received IVIg and placebo respectively improved by one point on the Rankin scale (OR 1.21, 95% CI 0.21-6.80). No significant difference was observed between the treatment and placebo groups. RCT3: 54% (32/ 59) treated with IVIg were clinical responders versus 20.7% (12/58) of subjects who received the placebo (OR 4.54, 95% CI 2.01-10.28, P<0.001).	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

Author: Eftimov, F., et al. Year Published: 2013 Location: Journal: *Cochrane Database of Systematic Reviews*	To review systematically the evidence from randomised controlled trials (RCTs) concerning the efficacy and safety of IVIg in CIDP.	**Size:** 5 trials, 235 participants **Inclusion Criteria:** RCTs or quasi-RCTs examining the effects of IVIg treatment in participants with CIDP. **Exclusion Criteria:** Participants were excluded if they had mutilation of hands or feet, retinitis pigmentosa, ichthyosis, drug or toxic exposure known to cause a peripheral neuropathy, a family history of demyelinating polyneuropathy, clinical suspicion of a vasculitic disorder, sensory level at examination, or unequivocal sphincter disturbances.	**Type:** SR **Intervention:** Primary outcome measure as the proportion of participants with a significant improvement in disability within six weeks after the onset of treatment as determined and defined by the original authors.	**Results:** A significantly higher proportion of participants improved after IVIg therapy as compared with placebo, with a pooled RR of 2.40 (95% CI 1.72 to 3.36). The NNTB was 3.03 (95% CI 2.33 to 4.55)	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Vo, M. L., et al. Year Published: 2017 Location: USA Journal: *Muscle & Nerve*	To measure changes in spatiotemporal gait parameters of patients with CIDP at baseline and following treatment with intravenous immunoglobulin (IVIG), using GAITRite a computerized walkway system with embedded sensors.	**Size:** 20 **Inclusion Criteria**: Patients diagnosed with probable or definite CIDP over a 2-year period, were included in the study. They underwent a complete neurological and physical examination and 3-limb electro diagnostic study before enrollment **Exclusion Criteria**: Patients were excluded if they had other causes for neuropathy or if they had co-morbid conditions including lumbosacral radiculopathy, orthopedic disease, or extrapyramidal movement disorders. All were able to ambulate at least 30 feet	**Type:** RCT **Intervention**: All 20 patients were treated with MG with a 2 g/ kg loading dose followed by 1 g/ kg every 3 weeks. Neurological assessments at baseline and following treatment with IVIC consisted of MRC sum score, INCAT disability score ,2 dominant-hand grip strength, and gait assessment using the GAITRite Walkway System.	**Results:** No adverse events were reported. INCAT Disability Score, MRC Sum Score, and Grip Strength: Following treatment, the entire group showed statistically significant improvements in MRC sum score (P=0.03) and grip strength(P=0.03), but not disability score. Change in Gait Parameters: Following treatment with IVIG, the entire group showed improvement in most gait parameters, with the most statistically significant differences seen in velocity (P=0.0004), stance phase (P=0.0002), and swing phase (P=0.0002). Changes from	**Study Limitations:** ☐ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		without use of assistive devices		baseline in step time and base (or step width) were not significant. In the overall group, change in velocity correlated inversely with change in INCAT score (r = -0.52; P= 0.02). There was no statistically significant correlation between mean change in gait parameters and MRC sum score or grip strength.	

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Bright, R. J., et al. (2014). "Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review." BMC Neurology 14: 26.
Vo, M. L., et al. (2017). "Changes in spatiotemporal gait parameters following intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy." Muscle & Nerve 56(4): 732-736.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: IVIG vs. placebo
Outcome: Adverse Events

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**

Author: Bright, R. J., et al. Year Published: 2014 Location: Australia Journal: *BMC Neurology*	The aim of this study was to prospectively review the literature to determine the effectiveness of therapies for chronic inflammatory demyelinating polyradiculoneuropathy.	**Size:** 3 trials, 163 participants **Inclusion Criteria:** RCTs published from January 1990 to December 2012 were searched for studies to treat adults with chronic inflammatory demyelinating polyradiculoneuropathy.	**Type:** Systematic Review **Intervention:** Outcomes of interest included: MRC score, nerve conduction and self-evaluation parameters.	**Results:** RCT 1: No serious treatment related effects. RCT2: The study did not mention adverse treatment related events. RCT3: No serious adverse events reported.	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Eftimov, F., et al. Year Published: 2013 Location: Journal: *Cochrane Database of Systematic Reviews*	To review systematically the evidence from randomised controlled trials (RCTs) concerning the efficacy and safety of IVIg in CIDP.	**Size:** 5 trials, 235 participants **Inclusion Criteria:** RCTs or quasi-RCTs examining the effects of IVIg treatment in participants with CIDP. **Exclusion Criteria**: Participants were excluded if they had mutilation of hands or feet, retinitis pigmentosa, ichthyosis, drug or toxic exposure known to cause a peripheral neuropathy, a family history of demyelinating polyneuropathy, clinical suspicion of a vasculitic disorder, sensory level at examination, or unequivocal sphincter disturbances.	**Type:** SR **Intervention:** Primary outcome measure as the proportion of participants with a significant improvement in disability within six weeks after the onset of treatment as determined and defined by the original authors.	**Results:** Mild and transient adverse events were found in 49% of participants treated with IVIg, while serious adverse events were found in 6%.	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Vo, M. L., et al. Year Published: 2017 Location: USA Journal: *Muscle & Nerve*	To measure changes in spatiotemporal gait parameters of patients with CIDP at baseline and following treatment with intravenous immunoglobulin (IVIG), using GAITRite a computerized walkway system with embedded sensors.	**Size:** 20 **Inclusion Criteria:** Patients diagnosed with probable or definite CIDP over a 2-year period, were included in the study. They underwent a complete neurological and physical examination and 3-limb electro diagnostic study before enrollment.	**Type:** RCT **Intervention:** All 20 patients were treated with MG with a 2 g/ kg loading dose followed by 1 g/ kg every 3 weeks. Neurological assessments at baseline and following treatment with IVIC consisted of MRC sum score, INCAT disability score ,2	**Results:** No adverse events were reported.	**Study Limitations:** ☐ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		Exclusion Criteria: Patients were excluded if they had other causes for neuropathy or if they had co-morbid conditions including lumbosacral radiculopathy, orthopedic disease, or extrapyramidal movement disorders. All were able to ambulate at least 30 feet without use of assistive devices.	dominant-hand grip strength, and gait assessment using the GAITRite Walkway System.		

References:
Eftimov, F., et al. (2013). "Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy." Cochrane Database of Systematic Reviews(12): CD001797.
Bright, R. J., et al. (2014). "Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review." BMC Neurology 14: 26.
Vo, M. L., et al. (2017). "Changes in spatiotemporal gait parameters following intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy." Muscle & Nerve 56(4): 732-736.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: IVIG vs. SCIG
Outcome: Efficacy

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☒ High ☐ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**

Author: Christiansen, I., et al. Year Published: 2018 Location: Denmark Journal: *Muscle & Nerve*	To compare variation in isokinetic muscle strength and function in CIDP and multifocal motor neuropathy (MMN) patients during treatment with IVIg to the variation observed after changing treatment to SCig.	**Size:** 23 patients **Inclusion Criteria:** All subjects had demonstrated a sustained response to IVIg treatment with end-of-dose phenomena resulting from prolongation of their treatment-free interval. SCig was not initiated unless muscle strength and motor performance 2 weeks after IVIg administration were as good as or better than those before IVig treatment. **Exclusion Criteria:** Patients treated with other immune-modulating therapies, malignancies, or other severe medical diseases	**Type:** a prospective, open-label study **Intervention:** The IVIg treatment intervals were standardized to either 3 or 6 weeks with an unchanged weekly dose of IVIg. SCIg and IVIg treatments were given at a dose of 1:1. The first SCig injection was administered at the hospital under the surveillance of a study nurse. Subsequently, injections were administered at home. Injections were given 2 or 3 times weekly at a maximal volume of 20 ml at each injection site, with the total volume of immunoglobulin ranging from 76 to 303 ml weekly and the infusion time lasting from 0.5 to 2.0 hours each time. The primary endpoint was variation in isokinetic muscle strength (cIKS). Secondary endpoints were variations in Medical Research Council (MRC) score, grip strength (GS), 9-hole-peg test (9-HPT), and 40-meter-walk test (40-MWT).	**Results:** The coefficient of variance of cIKS during the IVIg and SCIg treatment periods was unchanged (mean +/- SD: 6.97 +/- 4.83% vs. 5.50 +/- 3.13%, P = 0.21). The variations in the 9-HPT and 40-MWT were significantly lower in the SCIg group (P =0.01 and P = 0.005, respectively).	**Study Limitations:** ☒ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Markvardsen, L. H., et al. Year Published: 2017 Location: Denmark Journal: *European Journal of Neurology*	To investigate whether multiple subcutaneous infusions are as effective as conventional therapy with intravenous loading doses in treatment-naive patients with CIDP.	**Size:** 20 **Inclusion Criteria:** Patients with CIDP naïve to immune modulatory therapy. **Exclusion Criteria:** <18 or >80 years of age, patients treated with other immune-modulating therapies,	**Type:** RCT **Intervention:** Patients fulfilling the clinical and electrophysiological criteria for CIDP were included and treated with either SCIG (0.4 g/kg/week) for 5 weeks or intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for 5 days. After 10 weeks, patients	**Results:** Overall, cIKS increased by 7.4 +/- 14.5% (P = 0.0003) during SCIG and by 6.9 +/- 16.8% (P = 0.002) during IVIG, the effect being similar (P = 0.80). Improvement of cIKS peaked 2 weeks after IVIG and 5 weeks after SCIG.	**Study Limitations:** ☐ None ***RCTs*** ☒ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT

		malignancies, or other severe medical diseases.	were switched to the opposite treatment arm and followed for a further 10 weeks. All participants were evaluated at weeks 0, 2, 5 and 10 during both therapies. Primary outcome was combined isokinetic muscle strength (cIKS). Secondary outcomes were disability, clinical evaluation of muscle strength and the performance of various function tests.	Disability improved during SCIG treatment only (P=0.002). Muscle strength determined by manual muscle testing improved after 5 and 10 weeks during SCIG but only after 5 weeks during IVIG. The remaining parameters improved equally during both treatments.	☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline
Author: Racosta, J. M., et al. Year Published: 2017 Location: Europe Journal: *Muscle & Nerve*	To compare the efficacy and safety of SC-Ig versus IVig for treating patients with CIDP and multifocal motor neuropathy (MMN).	**Size:** 4 studies (50 patients) **Inclusion Criteria:** (1) Patients with CIDP and/ or MMN diagnosed (2) outcomes compared by the end of a treatment period with IVIg or SC-Ig, (3) a clear report of results of muscle strength assessment using the Medical Research Council sum score (MRC-SS);and (4) written in English, Spanish, or French. **Exclusion Criteria:** Studies that reported duplicated cohort.	**Type:** Systematic Review **Intervention:** Outcomes compared by the end of a treatment period with IVIG or SCIg, and by the end of a treatment period with the alternative administration route. The primary endpoint used for the meta-analysis was the change in strength in patients switched from IVIg to SC-Ig. The secondary endpoint used for the metaanalysis was the risk of drug-related systemic and/ or moderate adverse effects (e.g., fever, headache, nausea). The severity of the adverse effects (mild, moderate, or severe) was deemed according to the intensity, duration, and type of reaction.	**Results:** There were no significant differences in muscle strength outcomes in MMN and CIDP with Scig (CIDP: Effect Size= 0.84, 95% CI = -0.01-1 .69). Additionally SC-Ig had a 28% reduction in relative risk (RR) of moderate and/or systemic adverse effects (95% CI = 0.11-0.76).	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Sala, T. P., et al. Year Published: 2018 Location: France Journal: *Autoimmunity Reviews*	To review the efficacy of SCIg administration in terms of muscle strength maintenance and patient satisfaction comparing with IVIg in the treatment of auto-immune neuromuscular diseases.	**Size:** 11 studies (210 patients) **Inclusion Criteria:** (1) Adults with treated with immunoglobulins for chronic immune-mediated neuromuscular disorders (2) Remission from symptoms	**Type:** Systematic Review **Intervention:** Study populations were restricted to patients suffering from an auto-immune neuromuscular disease and that had been exposed to	**Results:** Analysis on ONLS scores found a significant improvement, or reduction in ONLS scores, in patients after switching to SCIg administration: difference in means (df) was 0.206, 95% CI	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised

		using usual scores and patient preferences. **Exclusion Criteria:** Studies that reported duplicated cohort.	treatment with SCIg, for which efficacy and health-related quality of life comparisons with IVIg treatments were retained for data extraction.	[0.025–0.388], p=0.026. This difference was not significant in random effects model (p=0.570). The high I2 value (89.25%) shows that most of the variability across studies is due to heterogeneity rather than chance. MRCss: The difference of means was 0.949 (95% CI [0.612–1.287]) and 1.024 (95% CI [0.521–1.528]), in fixed and random effects model, respectively. Both differences were significant in favor of switching to SCIg treatment. Health-related quality of life was significantly improved after switching to SCIg, with a mean score difference of 1.602 (95% CI [0.711–2.494], P< 0.0001) in fixed model. No significant differences were observed for PCS and MCS scores available in 3 studies. A significant preference for SCIg administration was observed in data pooled from the 113 patients in 5 studies using the Life Quality Index (LQI) [42]. Mean difference indicated a highly significant preference for SCIg treatment in fixed (df=17.80, 95% CI [16.152–19.420], p < 0.0001).	☐ Inappropriate pooled analysis

References:
Christiansen, I., et al. (2018). "Comparisons in fluctuation of muscle strength and function in patients with immune-mediated neuropathy treated with intravenous versus subcutaneous immunoglobulin." Muscle & Nerve 57(4): 610-614.
Markvardsen, L. H., et al. (2016). "Improvement of hemoglobin levels after a switch from intravenous to subcutaneous administration of immunoglobulin in chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy." Transfusion 56(10): 2443-2448.
Racosta, J. M., et al. (2017). "Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis." Muscle & Nerve 55(6): 802-809.

Sala, T. P., et al. (2018). "Efficacy and patient satisfaction in the use of subcutaneous immunoglobulin immunotherapy for the treatment of auto-immune neuromuscular diseases." Autoimmunity Reviews 17(9): 873-881.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: IVIG vs. SCIG
Outcome: Adverse Events

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☒ High ☐ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Christiansen, I., et al. Year Published: 2018 Location: Denmark Journal: *Muscle & Nerve*	To compare variation in isokinetic muscle strength and function in CIDP and multifocal motor neuropathy (MMN) patients during treatment with IVIg to the variation observed after changing treatment to SCig.	**Size:** 23 patients **Inclusion Criteria:** All subjects had demonstrated a sustained response to IVIg treatment with end-of-dose phenomena resulting from prolongation of their treatment-free interval. SCig was not initiated unless muscle strength and motor performance 2 weeks after IVIg administration were as good as or better than those before IVig treatment.	**Type:** A prospective, open-label study. **Intervention:** The IVIg treatment intervals were standardized to either 3 or 6 weeks with an unchanged weekly dose of IVIg. SCIg and IVIg treatments were given at a dose of 1:1. The first SCig injection was administered at the hospital under the surveillance of a study nurse. Subsequently, injections were administered at home. Injections were given 2 or 3	**Results:** No adverse effects reported.	**Study Limitations:** ☒ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		Exclusion Criteria: Patients treated with other immune-modulating therapies, malignancies, or other severe medical diseases.	times weekly at a maximal volume of 20 ml at each injection site, with the total volume of immunoglobulin ranging from 76 to 303 ml weekly and the infusion time lasting from 0.5 to 2.0 hours each time. The primary endpoint was variation in isokinetic muscle strength (cIKS). Secondary endpoints were variations in Medical Research Council (MRC) score, grip strength (GS), 9-hole-peg test (9-HPT), and 40-meter-walk test (40-MWT).		
Author: Markvardsen, L. H., et al. Year Published: 2017 Location: Denmark Journal: *European Journal of Neurology*	To investigate whether multiple subcutaneous infusions are as effective as conventional therapy with intravenous loading doses in treatment-naive patients with CIDP.	**Size:** 20 **Inclusion Criteria:** Patients with CIDP naïve to immune modulatory therapy. **Exclusion Criteria**: <18 or >80 years of age, patients treated with other immune-modulating therapies, malignancies, or other severe medical diseases.	**Type:** RCT **Intervention:** Patients fulfilling the clinical and electrophysiological criteria for CIDP were included and treated with either SCIG (0.4 g/kg/week) for 5 weeks or intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for 5 days. After 10 weeks, patients were switched to the opposite treatment arm and followed for a further 10 weeks. All participants were evaluated at weeks 0, 2, 5 and 10 during both therapies. Primary outcome was combined isokinetic muscle strength (cIKS). Secondary outcomes were disability, clinical evaluation of muscle strength and the performance of various function tests.	**Results:** One patient experienced a spontaneous and remitting severe hemolytic anemia following IVIG therapy with a decrease in hemoglobin of 42 g/L leading to hospitalization. Otherwise, side effects after IVIG were mild with two further cases of hemolytic anemia, two of fever/chill and nausea, two of a mild dermatological reaction and six of headache. During SCIG, three patients had local skin reactions at the infusion sites and two complained of nausea.	**Study Limitations:** ☐ None ***RCTs*** ☒ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:
Christiansen, I., et al. (2018). "Comparisons in fluctuation of muscle strength and function in patients with immune-mediated neuropathy treated with intravenous versus subcutaneous immunoglobulin." Muscle & Nerve 57(4): 610-614.

Markvardsen, L. H., et al. (2016). "Improvement of hemoglobin levels after a switch from intravenous to subcutaneous administration of immunoglobulin in chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy." Transfusion 56(10): 2443-2448.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: SCIG vs. Placebo
Outcome: Efficacy

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☐ Medium ☒ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) N/A ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	Aim of Study	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Author: van Schaik, I. N., et al. Year Published: 2018 Location: International Journal: *Lancet Neurology*	To compare two doses of SCIg IgPro20 with placebo for maintenance treatment of patients with CIDP.	**Size:** 172 patients: 57 (33%) to the placebo group, 57 (33%) to the low-dose group, and 58 (34%) to the high-dose group. **Inclusion Criteria:** At least 18 years of age and had been diagnosed with definite or probable CIDP and if they received their last IVIg treatment at least within 8 weeks before enrollment.	**Type:** RCT **Intervention:** Patients were randomly allocated to 0.2 g/kg or 0.4 g/kg of a 20% SCIg solution weekly versus placebo (2% human albumin solution) for maintenance treatment for 24 weeks. The primary outcome was the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment. Patients, caregivers, and study personnel, including	**Results:** In the intention-to-treat set, 36 (63% [95% CI 50-74]) patients on placebo, 22 (39% [27-52]) on low-dose SCIg, and 19 (33% [22-46]) on high-dose SCIg had a relapse or were withdrawn from the study for other reasons (P=0.0007). Absolute risk reductions were 25% (95% CI 6-41) for low-dose versus placebo (P=0.007), 30% (12-46) for high-dose versus placebo (P=0.001), and 6% (-	**Study Limitations:** ☒ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

		Exclusion Criteria: Any polyneuropathy of other causes; any other disease that could cause neurological symptoms and signs or could interfere with treatment or outcome assessments; severe known allergic or other severe reactions to blood products; HIV or hepatitis B or C; abnormal laboratory variables; pregnancy or being a nursing mother.	those assessing outcomes, were masked to treatment assignment. Analyses were done in the intention-to-treat and per-protocol sets.	11 to 23) for high-dose versus low-dose (P=0.32).	

References:

van Schaik, I. N., et al. (2018). "Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Neurology 17(1): 35-46.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: SCIG vs. Placebo
Outcome: Satisfaction

Quality (certainty) of evidence for: (outcome)					
☐ High ☐ Moderate ☒ Low ☐ Very Low					
Risk of Bias across studies: ☐ High ☐ Medium ☒ Low		**Lower Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) N/A ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: van Schaik, I. N., et al.	To compare two doses of SCIg IgPro20 with placebo for	**Size:** 172 patients: 57 (33%) to the placebo group, 57 (33%) to	**Type:** RCT	**Results:**	**Study Limitations:** ☒ None

Year Published: 2018 Location: International Journal: *Lancet Neurology*	maintenance treatment of patients with CIDP.	the low-dose group, and 58 (34%) to the high-dose group. **Inclusion Criteria:** At least 18 years of age and had been diagnosed with definite or probable CIDP and if they received their last IVIg treatment at least within 8 weeks before enrollment. **Exclusion Criteria:** Any polyneuropathy of other causes; any other disease that could cause neurological symptoms and signs or could interfere with treatment or outcome assessments; severe known allergic or other severe reactions to blood products; HIV or hepatitis B or C; abnormal laboratory variables; pregnancy or being a nursing mother.	**Intervention:** Patients were randomly allocated to 0.2 g/kg or 0.4 g/kg of a 20% SCIg solution weekly versus placebo (2% human albumin solution) for maintenance treatment for 24 weeks. The primary outcome was the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment. Patients, caregivers, and study personnel, including those assessing outcomes, were masked to treatment assignment. Analyses were done in the intention-to-treat and per-protocol sets.	Health-related quality-of-life measures generally showed better outcomes for both SCIg groups than for placebo. 135 (88%) patients reported that learning the technique of self-administration was easy (42 [93%] in the placebo group, 49 [91%] in the low-dose group, and 44 [80%] in the high-dose group). 61 (53%) of 115 patients who received SCIg preferred their current treatment (30 [53%] in the low-dose group and 31 [53%] in the high-dose group) versus 22 (39%) of 57 patients who received placebo, whereas 21 (18%) patients receiving SCIg (ten [18%] and 11 [19%]) and 14 (25%) patients receiving placebo preferred their previous IVIg treatment. Reasons for patients preferring weekly SCIg to monthly IVIg included a gain in independence and fewer side-effects.	***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

van Schaik, I. N., et al. (2018). "Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Neurology 17(1): 35-46.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Patients with CIDP
Modality: SCIG vs. Placebo
Outcome: Adverse Events

Quality (certainty) of evidence for: (outcome) ☐ High ☐ Moderate ☒ Low ☐ Very Low					
Risk of Bias across studies: ☐ High ☐ Medium ☒ Low		**Lower Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) N/A ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: van Schaik, I. N., et al. Year Published: 2018 Location: International Journal: *Lancet Neurology*	To compare two doses of SCIg IgPro20 with placebo for maintenance treatment of patients with CIDP.	**Size:** 172 patients: 57 (33%) to the placebo group, 57 (33%) to the low-dose group, and 58 (34%) to the high-dose group. **Inclusion Criteria:** At least 18 years of age and had been diagnosed with definite or probable CIDP and if they received their last IVIg treatment at least within 8 weeks before enrollment. **Exclusion Criteria:** Any polyneuropathy of other causes; any other disease that could cause neurological symptoms and signs or could interfere with treatment or outcome assessments; severe known allergic or other severe reactions to blood products; HIV or hepatitis B or C; abnormal laboratory variables; pregnancy or being a	**Type:** RCT **Intervention:** Patients were randomly allocated to 0.2 g/kg or 0.4 g/kg of a 20% SCIg solution weekly versus placebo (2% human albumin solution) for maintenance treatment for 24 weeks. The primary outcome was the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment. Patients, caregivers, and study personnel, including those assessing outcomes, were masked to treatment assignment. Analyses were done in the intention-to-treat and per-protocol sets.	**Results:** Causally related adverse events occurred in 47 (27%) patients (ten [18%] in the placebo group, 17 [30%] in the low-dose group, and 20 [34%] in the high-dose group). Six (3%) patients had 11 serious adverse events: one (2%) patient in the placebo group, three (5%) in the low-dose group, and two (3%) in the high-dose group; only one (an acute allergic skin reaction in the low-dose group) was assessed to be causally related.	**Study Limitations:** ☒ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

		nursing mother.			

References:

van Schaik, I. N., et al. (2018). "Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet Neurology 17(1): 35-46.

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level:

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level:

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix C. Trustworthy Guideline rating scale

Guideline Issuer	2010 European Federation of Neurological Societies/Peripheral Nerve Society
1. Transparency	A
2. Conflict of interest	A
3. Development group	A
4. Systematic Review	A
5. Supporting evidence	A
6. Recommendations	A
7. External Review	A
8. Currency and updates	B

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported.

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases .
Define the scope of the review (including key questions and the applicable population).
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated.

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded.
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met.

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like "should" or "should not" for strong recommendations, and passive language like "consider" for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.