AMERICAN ACADEMY OF NEUROLOGY

Special Article

CME

Practice parameter: Immunotherapy for Guillain–Barré syndrome

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Abstract—*Objective:* To provide an evidence-based statement to guide physicians in the management of Guillain–Barré syndrome (GBS). *Methods:* Literature search and derivation of evidence-based statements concerning the use of immunotherapy were performed. *Results:* Treatment with plasma exchange (PE) or IV immunoglobulin (IVIg) hastens recovery from GBS. Combining the two treatments is not beneficial. Steroid treatment given alone is not beneficial. Recommendations: 1) PE is recommended for nonambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms. PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms; 2) IVIg is recommended for nonambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms. The effects of PE and IVIg are equivalent; 3) Corticosteroids are not recommended for the management of GBS; 4) Sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg is not recommended for patients with GBS; and 5) PE and IVIg are treatment options for children with severe GBS.

NEUROLOGY 2003;61:736–740

Guillain–Barré syndrome (GBS) affects between 1 and 4 per 100,000 of the population annually throughout the world,[1] causing respiratory failure requiring ventilation in approximately 25%, death in 4 to 15%,[2-6] persistent disability in approximately 20%,[7] and persistent fatigue in 67%.[8] The costs in the United States have been estimated as $110,000 for direct health care and $360,000 in lost productivity per patient.[9] This practice parameter classifies the relevant evidence on immunotherapy to provide evidence-based recommendations for the management of GBS.[10]

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the September 23 issue to find the title link for this article.

Evidence review. A search of MEDLINE from 1966 and of the Cochrane library was performed in March 2002. "Polyradiculoneuritis" was limited by "human" and cross-referenced with "therapy." The search results were reviewed for each question by at least two members of the practice parameter group and supplemented from the reference lists in the articles retrieved and the personal reference lists of the members of the practice parameter group. Those titles representing relevant randomized controlled trials (RCTs) are included in the tables on the *Neurology* Web site for this article (www.neurology.org). Recommendations were graded according to the levels established by the AAN Quality Standards Subcommittee at the inception of this project (table).

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Dr. R. Hughes has received honoraria for speaking at meetings from Bayer, LFB, Novartis, and Octapharma, which manufacture brands of IVIg, and his department has received a research grant from Novartis. Dr. D. Cornblath has received honoraria for speaking and consulting on use of IVIg from Novartis, Octapharma, and Bayer and received a research grant from Novartis. Dr. A. Hahn has received honoraria for participating in conferences and expert panels on research and use of IVIg sponsored by Novartis and Bayer Corporation. Drs. R. Barohn, J. Meythaler, J. Sladky, J. Stevens and E. Wijdicks and Mrs. E. Benson have nothing to disclose.

Received December 12, 2002. Accepted in final form July 16, 2003.

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Table *Definitions for the classification of evidence as recommended by the AAN Quality Standards Subcommittee*

Class of evidence for therapy	Recommendations
Class I. High quality randomized controlled trials (RCTs)	A = established as effective, ineffective or harmful, or as useful/predictive or not useful/predictive
Class II. Prospective matched group cohort studies or RCTs lacking adequate randomization concealment or blinding or potentially liable to attrition or outcome ascertainment bias	B = probably effective, ineffective or harmful, or as useful/predictive or not useful/predictive
Class III. Other studies such as natural history studies	C = possibly effective, ineffective or harmful, or as useful/predictive or not useful/predictive
Class IV. Uncontrolled studies, case series, or expert opinion.	U = data inadequate or conflicting. Treatment, test, or predictor unproven.

Analysis of the evidence. *Does initial immunotherapy hasten recovery?* All studies used similar diagnostic criteria.[11,12] In most, the primary outcome measure used a disability scale (0 = normal, 1 = symptoms but able to run, 2 = unable to run, 3 = unable to walk unaided, 4 = bed-bound, 5 = needing ventilation, 6 = dead).[13] Most studies included patients with severe disease (at least grade 3 on that scale).

Plasma exchange. A Cochrane systematic review obtained data from six class II trials comparing plasma exchange (PE) alone with supportive care.[14] The PE regimens involved exchanging approximately one plasma volume, 50 mL/kg, on five separate occasions over 1 to 2 weeks, except in one trial that used two plasma volume exchanges on alternate days for four total exchanges.[15,16] One trial involving 29 participants showed a trend toward more improvement in disability after 4 weeks with PE.[17] The other five trials showed significantly more improvement in disability grade or more patients improved in disability grade after 4 weeks.[15,16,18-21] In a meta-analysis of all six studies, the proportion of patients on the ventilator 4 weeks after randomization was reduced to 48 of 321 in the PE group compared with 106 of 325 in the control group (relative risk [RR], 0.56; 95% CI, 0.41 to 0.76; $p = 0.0003$).[14] In a meta-analysis of four studies for which the outcome was available, 135 of 199 PE and 112 of 205 control patients had recovered full muscle strength after 1 year (RR, 1.24 in favor of PE; 95% CI, 1.07 to 1.45; $p = 0.005$).[14-16,20,21] One class II trial demonstrated a convincing beneficial effect of PE in more mildly affected ambulant patients.[21] In the meta-analysis, the RR of serious adverse events was similar in the PE and control groups.[14-16,19,21]

In one class II study comparing PE with supportive therapy in Scandinavia,[18] the cost of PE was more than offset by the savings in health care costs as a result of shorter hospital stay. Similar conclusions have been reached in the United Kingdom.[22] For patients with moderately severe GBS, Raphael et al.[23] have calculated that four PEs are more cost effective than two.

PE has been compared with CSF filtration in one class II trial involving 37 participants.[24,25] There was no difference in outcomes between the groups; however, the numbers were too small to demonstrate equivalence convincingly, and the procedure risks intrathecal infection.

Conclusion. PE hastens recovery in nonambulant patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms (class II evidence). PE also hastens recovery in ambulant patients who are examined within 2 weeks, but the evidence is limited to one trial (class II evidence). Treatment with CSF filtration has not been adequately tested (limited class II evidence).

Recommendation. PE is recommended for nonambulant patients within 4 weeks of onset (level A, class II evidence) and for ambulant patients within 2 weeks of onset (level B, limited class II evidence). The effects of PE and IV immunoglobulin (IVIg) are equivalent (see below). There is insufficient evidence to recommend the use of CSF filtration (level U, limited class II evidence).

Immunoabsorption. Immunoabsorption is an alternative technique to PE that removes immunoglobulins and has the advantage of not requiring the use of a human blood product as a replacement fluid. In a prospective trial with a block sequential design, there were no differences in outcome between 11 patients treated with PE and 13 treated with immunoabsorption.[26]

Conclusion. There is only limited class IV evidence from one small nonrandomized unblinded study.

Recommendation. The evidence is insufficient to recommend the use of immunoabsorption (level U recommendation, class IV evidence).

IV immunoglobulin. A Cochrane systematic review found no trials comparing IVIg with placebo.[27] In one class III trial[28] comparing IVIg with supportive treatment, seven of nine children who received IVIg recovered completely by 4 weeks compared with two of nine untreated children.

Three trials compared IVIg with PE. The mean improvement in disability grade 4 weeks after randomization was available for three trials.[7,29,30] In a meta-analysis the weighted mean difference was 0.11 more improvement in 204 patients treated with

IVIg than in 194 patients treated with PE, a nonsignificant difference (95% CI, −0.14 to 0.37). There was a nonsignificant trend toward faster recovery of unaided walking in favor of IVIg in both these trials. In the third trial, these outcome measures were not available, but related measures (proportion of patients improving one grade after 4 weeks and time to recover the ability to do manual work) showed a trend in favor of IVIg compared with PE.[30] There were no significant differences in the meta-analysis of time until discontinuation of mechanical ventilation and the proportions of patients dead or disabled after 1 year between the IVIg- and PE-treated groups. In each trial, there were more adverse events in the PE group than in the IVIg group, but because of different definitions of adverse events, meta-analysis could not be performed. In the Dutch trial, pneumonia, atelectasis, thrombosis, and hemodynamic difficulties occurred more often with PE than IVIg. Sixteen of 73 patients (22%) had multiple complications with PE compared with 5 of 74 (7%) with IVIg.[29] In the largest trial, adverse events occurred in 8 of 121 patients (7%) in the PE group (hypotension, septicemia, pneumonia, malaise, abnormal clotting, and hypocalcemia) and in 6 of 130 (5%) patients in the IVIg group (vomiting, meningism, renal failure, myocardial infarction, and infusion site erythema).[7] In the two largest trials, treatment was much less likely to be discontinued in the IVIg group than in the PE-treated patients (RR, 0.11; 95% CI, 0.04 to 0.32).[7,29]

Conclusion. IVIg has not been adequately compared with placebo (limited class II evidence). Such comparison is not now needed because, when started within 2 weeks of the onset, IVIg has equivalent efficacy to PE in hastening recovery for patients with GBS who require aid to walk (class I evidence). Multiple complications were significantly less frequent with IVIg than with PE (class I evidence). There is no evidence concerning the relative efficacy of PE and IVIg in patients with axonal forms of GBS.

Recommendation. IVIg is recommended for patients with GBS who require aid to walk within 2 (level A recommendation) or 4 weeks from the onset of neuropathic symptoms (level B recommendation derived from class II evidence concerning PE started within the first 4 weeks and class I evidence concerning the comparisons between PE and IVIg started within the first 2 weeks). The effects of IVIg and PE are equivalent.

Combination treatments. One class I trial showed that PE followed by IVIg showed no significant benefit compared with PE alone in any measured outcome.[7] After 4 weeks, there was 0.20 of a grade more improvement in the 128 patients who received both treatments than in the 121 patients who received PE alone, but this small difference favoring combined treatment was not significant (95% CI, −0.54 to 0.14). The median (interquartile range) time to recover unaided walking was 40 days (range, 19 to 137 days) in the 128 patients who received both treatments and 49 days (range, 19 to 148 days) in the 121 patients who received PE alone. This difference between the treatments was also not significant. There were more complications of treatment in the combined treatment group than in either of the single treatment groups. In the same trial, there were also no significant differences in any outcome between patients treated with PE followed by IVIg and those treated with IVIg alone.[7]

A class III study comparing immunoabsorption with tryptophan polyvinyl exchange alone and immunoabsorption followed by IVIg in 34 participants showed no significant difference between these regimens after 1 and 12 months.[26]

Conclusion. Sequential treatment with PE followed by IVIg does not have a superior effect to either treatment given alone (class I evidence). Sequential treatment with immunoabsorption followed by IVIg has not been adequately tested (limited class IV evidence).

Recommendation. Sequential treatment with PE followed by IVIg (level A recommendation, class I evidence) or immunoabsorption followed by IVIg (level U recommendation, class IV evidence) is not recommended.

Steroids. A Cochrane systematic review sought all trials of any form of corticosteroid or adrenocorticotrophic hormone (ACTH) treatment for patients with GBS.[31] Six randomized trials were identified including 195 corticosteroid-treated patients and 187 control subjects (class I evidence).[13,32-36] The corticosteroid regimens included IM ACTH, 100 units daily for 10 days;[32] IV methylprednisolone, 500 mg daily for 5 days;[35] oral prednisolone, starting daily dose 40 mg[36] or 60 mg;[13,34] or prednisone, 100 mg.[33] The primary outcome measure in the systematic review was the improvement in disability grade[13] 4 weeks after randomization. There was no difference in this outcome between the steroid patients and the no steroid/placebo patients; the weighted mean difference of the three trials was only −0.06 (95% CI, −0.32 to 0.19) grade in favor of the control group. There was also no significant difference between the groups for secondary outcome measures of recovery, time to recovery of unaided walking, time to discontinue ventilation in the subgroup who needed ventilation, mortality, and combined mortality and disability after 1 year.[31] Complications were similar in the corticosteroid and placebo groups, except for hypertension, for which the RR was less (0.2; 95% CI, 0.04 to 0.66) in the corticosteroid group (2/124, 1.2%) than in the control group (12/118, 10.2%).[31]

A comparison of a series of corticosteroid-treated patients with historical control subjects suggested a beneficial effect from corticosteroids when given in combination with IVIg.[37] The effect of IV methylprednisolone combined with IVIg for managing GBS has been tested in a seventh randomized trial involv-

ing 233 patients, but the results have not yet been published and were not available for review.

Conclusion. The combined evidence from all trials shows no benefit from corticosteroids (class I evidence). The results of a trial of the combination of IV methylprednisolone and IVIg are awaited.

Recommendation. Corticosteroids are not recommended for the treatment of patients with GBS (level A, class I evidence).

Are there special issues for the treatment of children with GBS? The clinical features of GBS in children are similar to those in adults except that severe sequelae are less common and axonal forms of the disease are more frequent in some populations.[38] In younger children, in particular, pain is frequently the only symptom they are able to articulate, and evidence of subtle weakness and loss of reflexes may be overlooked.[39,40] There is a lack of adequate randomized controlled treatment trials in children to define the role of either PE[41-44] or IVIg.[45,46,28]

Conclusion. There are no adequate randomized controlled trials of treatment in children.

Recommendation. PE and IVIg are treatment options for children with severe GBS (level B recommendation derived from class II evidence in adults).

Future research. More research is needed to evaluate immunotherapy for patients with GBS, particularly the use of combination treatments and further treatment after the initial course, especially for those patients who do not respond. There is a need to identify patients who are at greater risk of an adverse outcome and to discover whether subgroups, including children, and people with axonal forms of GBS and Fisher's syndrome have differential responses to treatment. Research should also investigate the best methods of supportive care for monitoring autonomic and pulmonary function, weaning from ventilation, treating pain, managing fatigue, and rehabilitation.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Acknowledgment

The GBS Practice Parameter Group thank Drs. D. Annane, S. Chevret, F.G.A. van der Meché, P.A. van Doorn, J.C. Raphael, and A.V. Swan, the authors of the Cochrane systematic reviews on which this practice parameter is in part based, Dr. Allan Ropper, and the Guillain–Barré Syndrome Foundation International for assistance.

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Neurology 2003;61;736-740
DOI 10.1212/WNL.61.6.736