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Management of Pediatric Central Nervous System Demyelinating Disorders: Consensus of United States Neurologists

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Abstract

Demyelinating diseases are a group of autoimmune inflammatory disorders affecting the central nervous system in adults and children; however, the diagnosis, evaluation, and treatment of these disorders are primarily based on adult data. The purpose of this study was to assess the practice patterns of US physicians who specialize in treating acquired central nervous system demyelinating diseases in children and adolescents. The Delphi technique was used to identify areas of consensus in management and treatment. Forty-two experts in the field participated in the process. Intravenous methylprednisolone was the first-line treatment of choice for acute episodes of all forms of demyelinating disease; however, consensus was lacking regarding specific dose, treatment duration, and use of an oral taper. First-line disease-modifying therapies for pediatric multiple sclerosis were interferons and glatiramer acetate, chosen based on perceived efficacy and

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The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Ethical Approval
This study was not reviewed by an Institutional Review Board because no individual patient data were collected for this study.

Author Contributions
Conception and design: N.L.K., D.P.H.; construction of the questionnaires: A.T.W., M.P.G., M.R.R., N.L.K.; data collection: T.E.A.; data analysis and interpretation: A.T.W., M.P.G., M.R.R., T.E.A., D.P.H., N.L.K.; administrative support: T.E.A.; writing the manuscript: A.T.W., M.P.G., M.R.R., T.E.A., D.P.H., N.L.K.; revisions to the manuscript: A.T.W., M.P.G., M.R.R., D.P.H., N.L.K.

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tolerability, respectively. Areas lacking agreement among the expert panel and requiring further research are identified.

Keywords

multiple sclerosis; acute disseminated encephalomyelitis; optic neuritis

Clinical disorders characterized by episodes of central nervous system demyelination have been increasingly recognized in children.[1] Some children experience events such as acute disseminated encephalomyelitis, optic neuritis, or transverse myelitis as monophasic illnesses, whereas other children experience relapsing or recurrent disease.[2–5] Relapsing disease can occur in a focal area of the central nervous system, such as recurrent optic neuritis. In other children, generalized involvement recurs, including recurrent acute disseminated encephalomyelitis, multiphasic acute disseminated encephalomyelitis, neuromyelitis optica, or pediatric multiple sclerosis.[3] Pediatric multiple sclerosis and neuromyelitis optica have historically been diagnosed using adult criteria and treated using adult paradigms.[1,2,6] At the time of an initial central nervous system demyelinating event, the future course can be difficult to predict.[2–6] There are limited observations and no controlled scientific data regarding the diagnostic evaluation, treatment of acute episodes, or use of disease-modifying therapies in pediatric central nervous system demyelinating diseases.

Given the complexities of these diseases and limitations in the existing literature, there appear to be significant variations in practice across regions and disciplines with respect to acute and long-term treatment of children and adolescents with acquired central nervous system demyelinating disorders. To begin addressing this issue, the National Multiple Sclerosis Society established a Network of Pediatric Multiple Sclerosis Centers of Excellence and initiated an International Pediatric Multiple Sclerosis Study Group, which proposed working definitions for demyelinating diseases (acute disseminated encephalomyelitis, recurrent acute disseminated encephalomyelitis, multiphasic acute disseminated encephalomyelitis, neuromyelitis optica, clinically isolated syndrome, and pediatric multiple sclerosis) in children.[7] In addition, our international colleagues have suggested recommendations for the management of children with multiple sclerosis.[8] The purpose of this study was to use a systematic approach to obtain the expert opinion of neurologists in the United States regarding the diagnosis, evaluation, and treatment of children with acquired central nervous system demyelinating disorders.

Materials and Methods

The Delphi technique is an established consensus development method used in industry and medicine. It is a group process that builds consensus through anonymous written responses to a series of questionnaires presented and analyzed over the course of several months.[9] This technique has been used in 2 recent efforts to develop consensus on different pediatric illnesses.[10,11]

Expert Panel

Physicians associated with Pediatric Multiple Sclerosis Centers of Excellence were invited to participate. Additional neurologists with expertise in pediatric demyelinating disorders were identified through referrals to the Centers of Excellence, researchers in the field, personal contacts of the authors, and advertisements at national meetings.

Pediatric Multiple Sclerosis Delphi Process

Qualitative information was gleaned from responses to open-ended questions in an initial questionnaire sent to each physician via e-mail. A Delphi Advisory Committee, consisting of 4 neurologists (1 adult multiple sclerosis and 3 pediatric multiple sclerosis specialists), reviewed the responses and developed further questions that were distributed to the expert panel in subsequent questionnaires using a computerized response program. Forced choice and ranking methods were attempted but not always followed in the latter questionnaires. Although full participation was encouraged, not all respondents replied to each questionnaire nor were all questions within the questionnaire addressed by each respondent. Three questionnaires were administered over a 5-month period from January 2008 to May 2008. The iterative nature of the process served to clarify practice recommendations. To protect anonymity, identifying information of panel members was removed by one of the authors (T.E.A.) prior to forwarding responses to the advisory committee for the first questionnaire. Identifying information was not available through the computerized response system. No honorarium was provided to study participants.

Descriptive statistics were applied to determine the agreement among respondents. Results are reported using the actual number and proportion of respondents for each question. Operationally, *consensus* was defined greater than 75% accord, *majority* as 50% to 75% accord, and *lack of agreement* as less than 50% accord. Regarding the use of secondary therapies in children with multiple sclerosis and neuromyelitis optica, respondents were asked to rank their choices from 1 (most preferred) to 9 (least preferred). The responses were reverse-scored and tallied using a point system.

Results

Expert Panel

Sixty-seven neurologists from across the United States, identified as having particular interest and expertise in diagnosis and treatment of pediatric multiple sclerosis and other acquired central nervous system demyelinating disorders in children, were invited to participate. Forty-two of 67 individuals (63%) accepted the initial invitation to participate. Members of the expert panel are listed in the appendix.

Response Rates and Demographics

Among the 42 physicians who agreed to participate, the response rate for the questionnaires was 88%, 83%, and 90% for questionnaires 1, 2, and 3, respectively. Further demographic breakdown of the expert panel is listed in Table 1. For each individual question, the response rate was greater than 90% except where noted in the following.

International Pediatric Multiple Sclerosis Study Group Definitions of Demyelinating Diseases in Children

The majority of the panel (54%) supported the current working definitions established by the International Pediatric Multiple Sclerosis Study Group, whereas 35% generally agreed with the definitions but suggested modifications. Three respondents disagreed (8%) with the definitions, and there was 1 unclear response (3%). Among the respondents who suggested modifications or disagreed with the definitions, 62% questioned the definition or requirement of encephalopathy in patients with acute disseminated encephalomyelitis. The majority of respondents (54%) in questionnaire 3 stated that a prior episode of acute disseminated encephalomyelitis should be considered as a “first event” in meeting criteria for the diagnosis of multiple sclerosis.

The panel reached a consensus regarding age at presentation: 83% believed that the age of the patient influenced the diagnostic criteria they used. This sentiment was expressed by both adult neurologists (72%) and child neurologists (91%). Specific comments addressed the difficulty of determining encephalopathy in the very youngest children and the differences in the appearance of magnetic resonance imaging changes in these patients.

Initial Diagnostic Evaluation for Patients Presenting With Central Nervous System Demyelinating Diseases

When evaluating patients with a suspected central nervous system demyelinating disorder, the panel reached a consensus regarding specific tests to be performed as part of the initial evaluation: magnetic resonance imaging of the brain, complete blood count, erythrocyte sedimentation rate, and basic metabolic panel (Table 2). A majority of the panel ordered a spine magnetic resonance imaging, antinuclear antibody, angiotensin-converting enzyme, C-reactive protein, thyroid-stimulating hormone, B_{12} level, and folate (Table 2). Additional tests were recommended by a consensus or majority depending on the specified clinical phenotypes (Table 2). For example, consensus was reached regarding ordering cerebrospinal fluid oligoclonal bands, immunoglobulin index, and immunoglobulin synthesis rate for patients presenting with a polyregional syndrome that includes encephalopathy or myelitis; however, cerebrospinal fluid tests were not ordered as frequently for patients presenting with isolated optic neuritis. In contrast to other cerebral spinal fluid tests, there was a lack of consensus regarding the utility of myelin basic protein: 50% or fewer of respondents reported that they always ordered this regardless of the clinical presentation (Table 2).

The age of the patient influenced the minimum diagnostic evaluation recommended by 77% of the respondents. These physicians agreed that other disorders (metabolic and genetic) should be considered more strongly in younger patients, although a clear age cutoff or specific modification did not emerge.

Treatment of Acute Attacks of Central Nervous System Demyelination

The questionnaires addressed practice patterns regarding the treatment of acute attacks of central nervous system demyelination. A consensus (86%) agreed that acute attacks of central nervous system demyelination do not always require treatment. Among respondents who indicated that they decide whether to treat acute attacks of central nervous system

demyelination on a case-by-case basis, clinical features of the attack were the most important determinants of this decision, with severity of the attack being the most significant (Table 3). The timing of the attack relative to the time of medical evaluation was also a factor. Most respondents considered treating, but did not always treat, attacks with isolated sensory symptoms. Findings on magnetic resonance imaging influenced the decision. The specific magnetic resonance imaging features that were considered in the decision of whether to treat an acute attack include gadolinium enhancement, the presence/absence of T2 lesions at the central nervous system site where the symptoms/signs localize, T2 lesion number, and T2 lesion volume (Table 3).

Intravenous methylprednisolone was the first-line treatment of choice for optic neuritis, acute disseminated encephalomyelitis, transverse myelitis, acute attacks of established multiple sclerosis, and acute attacks of established neuromyelitis optica (Table 4). Of those respondents who specified a dose for methylprednisolone, weight-based calculation was recommended by the majority of the panel; however, there was no agreement on the actual dose (in mg/kg) for these disorders. Of the respondents who did not use weight-based dosing, nearly all indicated a dose of 1 g/d.

As for the duration of the initial intravenous steroid treatment, 3 to 5 days of therapy was recommended. Oral steroid tapers were always used by 50% of the panel for all relapses of neuromyelitis optica. Oral steroid tapers were considered, but not automatically used, by a majority of the panel following optic neuritis (62%), transverse myelitis (58%), acute disseminated encephalomyelitis (56%), and relapses of multiple sclerosis (50%).

The questionnaire also addressed the issue of first-line treatment failure for acute attacks of central nervous system demyelination. The clinical features were considered most important by more than 90% of the panel in determining whether a first-line treatment failed for an acute attack of central nervous system demyelination. A majority of the panel (56%) used their global impression of the patient in determining treatment failure, although specific clinical parameters were not identified. The recommended time interval between completion of acute treatment and declaration of treatment failure was not uniform. The wide range of time frames mentioned by the respondents (from 1 day to several months) precluded quantification. Although additional intravenous corticosteroids, intravenous immunoglobulin, and plasmapheresis were commonly mentioned as second-line treatments, there was lack of agreement on which of these was the optimal choice. The wide range of approaches could not be quantified, because many respondents listed several treatment options at once without ranking them.

First-Line Disease-Modifying Therapy

The panel supported the use of disease-modifying therapies in patients with the clinical diagnosis of multiple sclerosis or in clinically isolated syndromes if the magnetic resonance imaging at presentation was considered “active or high risk” (59%). Active or high-risk magnetic resonance imaging was defined as at least 1 new gadolinium-enhancing lesion of the brain or spinal cord by 66% and 84% of respondents, respectively. As a group, interferons were used as the first-line disease-modifying therapy by the majority (63%) of the panel, whereas glatiramer acetate was the first choice for 37% of the respondents.

Respondents most often cited efficacy and tolerability as the reasons for choosing interferons and glatiramer acetate, respectively, as the first-line agent. Twenty-two percent of the respondents would not consider using disease-modifying therapy in children younger than 5 years. Forty-four percent of the expert panel stated that they would never consider using a disease-modifying therapy to treat recurrent or multiphasic acute disseminated encephalomyelitis, whereas 24%would consider this after a first relapse and another 26% would consider starting disease-modifying therapy after the second relapse.

Monitoring Patients

The monitoring of children and adolescents was similar for the diagnoses of multiple sclerosis, clinically isolated syndrome, and neuromyelitis optica. During the first year after the diagnosis, physical examinations were recommended by the majority of respondents every 3 months during periods of clinical stability in patients with neuromyelitis optica, clinically isolated syndromes, and acute disseminated encephalomyelitis, whereas 49% of respondents would follow patients with multiple sclerosis as regularly during periods of stability. There was a lack of agreement regarding the frequency of magnetic resonance imaging scans, and these questions were not answered by up to 19% of respondents.

Neutralizing antibodies were checked by the panel only for clinical reasons by 74% and at scheduled intervals by 15% and were never checked by 11%.

More than 70%of respondents said they do not routinely order neuropsychological testing in patients with clinically isolated syndromes, acute disseminated encephalomyelitis, or neuromyelitis optica. Routine neuropsychological evaluations for children with multiple sclerosis were recommended by approximately 46% of the panel. Among the physicians who do order these tests routinely for acute disseminated encephalomyelitis, clinically isolated syndromes, multiple sclerosis, and neuromyelitis optica, more than 89%do not perform the testing during an acute clinical episode. More than 64% of respondents wait 3 months after an attack before performing neuropsychological testing. Steroid use further influenced the decision about the timing of neuropsychological testing, with most respondents recommending an interval of 1 to 3 months after steroid completion.

Failure of Disease-Modifying Therapies/Second-Line Therapies

Treatment failure with disease-modifying therapy was variably defined. The global clinical impression of the patient was most influential in determining treatment failure (55%). Deterioration in the Extended Disability Status Scale was recommended as an objective measure of treatment failure by some respondents. However, others commented that the Extended Disability Status Scale is not convenient or practical as a measure of disability in clinical practice. The appearance of new T2 lesions and that of gadolinium enhancement on magnetic resonance imaging were equally weighted as important determinants of treatment failure (25%).

Despite variability in the definition of treatment failure, 94% of respondents would stop or change the disease-modifying therapy if the relapse rate increased or the patient experienced side effects interfering with daily activities. A majority of respondents (82%) would stop or change the disease-modifying therapy if the patient experienced progression of disability,

and 58%would stop or change therapy if a magnetic resonance imaging scan revealed more than 1 new enhancing lesion. Some respondents provided alternatives to changing the disease-modifying therapy such as adding scheduled corticosteroids, checking neutralizing antibodies, or obtaining a second opinion to confirm the diagnosis. Other agents were suggested if the patient experienced multiple clinical relapses, an increase in the magnetic resonance imaging lesion burden, progression of disease, lack of clinical recovery, or relapses on corticosteroids.

Recommended second-line therapies varied depending on the clinical syndrome. In children with multiple sclerosis, scheduled corticosteroids, intravenous immunoglobulin, and plasma exchange were the most common second-line therapies, followed by natalizumab (Table 5). There was a dichotomy in the use of natalizumab as a second-line therapy: 50% selected the medication as their first, second, third, or fourth choice, whereas 27% ranked it as their eighth or ninth (last) choice and another 23% did not rank it at all. For patients with neuromyelitis optica, the most frequently recommended therapies were rituximab, intravenous immunoglobulin, and plasma exchange, in that order. This question was skipped by 19% of respondents.

Discussion

Through the Delphi method and a series of questionnaires, this study assessed the practice patterns of US neurologists in evaluating, diagnosing, and treating central nervous system demyelinating disorders in children. A few areas of consensus were identified, primarily relating to treatment of acute episodes of central nervous system demyelination in children and adolescents. There was widespread consensus that intravenous methylprednisolone is the treatment of choice for acute attacks of central nervous system demyelination. However, greater variability existed with respect to dosage and duration, with a majority of respondents recommending 20 to 30 mg/kg/d for 3 to 5 days. Respondents did not believe that all acute attacks of central nervous system demyelination required treatment, with the clinical features of the attack (particularly the severity) being the most important determinant of the decision to treat.

A majority of respondents (54%) agreed with the current definitions of acquired central nervous system demyelinating diseases in children as set forth by the International Pediatric Multiple Sclerosis Study Group. These criteria were proposed as working definitions that need validation with prospective trials. They were created to establish uniform language with the understanding that exceptions would occur. Further research may help to clarify the presence or absence of encephalopathy and the extent of the mental status changes required to fulfill these criteria.

A majority (54%) of the panel believed that in the setting of a second episode of acquired central nervous system demyelinating disease, a previous episode of acute disseminated encephalomyelitis should be considered as the first event toward a diagnosis of multiple sclerosis. Nearly 20% of the expert panel identified the requirement of encephalopathy for a diagnosis of acute disseminated encephalomyelitis as problematic because milder degrees of

encephalopathy can be difficult to differentiate from appropriate age-related mood changes in children who are unwell.

In addition to these concerns regarding the working definitions of demyelinating diseases in children, a number of other important issues emerged from this process lacking consensus and, therefore, are identified as areas that will also benefit from future research. Despite agreement that the diagnosis of multiple sclerosis in younger patients is challenging, no specific recommendations were made or consensus reached regarding changes to diagnostic criteria for acquired central nervous system demyelinating disorders based on the age of the patient. Additional questions clarifying the challenges of diagnosing younger patients, such as differences in clinical presentation or magnetic resonance imaging findings, were not pursued in subsequent questionnaires. Other important issues, such as the use of oral steroid taper after initial intravenous steroid treatment of acute demyelinating episodes, need to be studied.

The definition of and approach to treatment failure in acute attacks of central nervous system demyelination require further study. Although intravenous immunoglobulin[12] and plasma exchange[13] have both been reported to be effective in steroid-refractory cases of central nervous system demyelination, there is lack of agreement on the preferred second-line therapy of acute episodes.

The use of disease-modifying therapy is off-label in children and adolescents with multiple sclerosis because they have not been included as subjects in the pivotal treatment trials of multiple sclerosis therapies. Small case series of children and adolescents treated with disease-modifying therapy for multiple sclerosis have been reported in the literature, documenting a rate of safety and tolerability similar to adults.[14] Nevertheless, our data suggest that some physicians are reluctant to use these drugs in young children (<5 years of age); therefore, this needs to be studied. Choice of initial disease-modifying therapy, definition of disease-modifying therapy treatment failure, choice of second-line disease-modifying therapy, and the role of chemotherapeutic agents and monoclonal antibodies all remain to be studied in children. Further research is also necessary to determine the optimum use of disease-modifying therapy in children and adolescents with clinically isolated syndromes and to determine appropriate treatment for recurrent disorders that do not meet criteria for pediatric multiple sclerosis or neuromyelitis optica (eg, recurrent or multiphasic acute disseminated encephalomyelitis, recurrent optic neuritis, recurrent transverse myelitis). Use of immunosuppressive preventive therapies in neuromyelitis optica has not been studied in children.

A strength of the Delphi technique is that it begins with open-ended questions inviting identified experts to share their experience and opinions. Anonymity was an advantage of this study, and the respondents were able to share their concerns and opinions without academic pressure from peers. However, because the iterative questionnaires were created using existing software (to maximize efficiency and minimize cost), some participants retrospectively reported lack of clarity regarding requested responses for some questions. The variation in numbers of individuals responding to each question is another weakness of this effort. Agreement among respondents was calculated using the number of experts who

responded to that particular question as the denominator rather than using the percentage of the number of questionnaires administered. Therefore, a smaller number of responses may have been returned for more challenging questions, and the data may be skewed to reflect the opinions of selected experts. However, there were only a few questions for which more than 10% did not respond. Panel members were self-selected and varied in experience.

The practice patterns of US physicians were assessed to determine areas of consensus and those lacking agreement in the diagnosis, evaluation, and treatment of acquired central nervous system demyelinating disorders in children. This project was intended to gather information on the current practice of adult and pediatric neurologists who treat children with demyelinating disease to identify topics requiring further research. The definitions of demyelinating diseases in children require validation in a multicenter cohort, especially regarding the presence of encephalopathy and the relationship between acute disseminated encephalomyelitis and pediatric multiple sclerosis. The utility of diagnostic tests, such as magnetic resonance imaging scans, lumbar punctures, and blood tests, can be evaluated through analytic studies, and randomized clinical trials are needed to investigate acute and disease-modifying therapies for pediatric demyelinating diseases. The US network of Pediatric Multiple Sclerosis Centers is planning to expand its reach by involving other sites across the country interested in collaborative investigations of children with demyelinating disorders. A data coordination center will be used to enhance this collaboration and the collection of prospective data. This expert panel has highlighted the areas of consensus and controversy to guide future studies.

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Appendix

Expert Consensus Panel Membership

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Table 1

Practice Demographics of the Expert Panel

Feature	No. of Physicians	Percentage of Total Respondents
Adult neurologist	13	37
Child neurologist	22	63
Academic appointment	31	87
Teaching appointment	9	26
Private practice	4	11
<5 years post residency	8	23
5–9 years post residency	3	9
>9 years post residency	34	69
No. of children seen with all central nervous system demyelinating disorders over the past 5 years		
1–5	0	0
6–10	3	9
11–20	5	14
21–50	14	40
>50	13	37

Table 2

Initial Diagnostic Evaluation of All Children With a Suspected Central Nervous System Demyelinating Disorder

	No. of Physicians Who Always Order This Test/Total No. of Respondents (%)		
Test/Procedure	**Polyregional Demyelination With Encephalopathy**	**Myelitis**	**Optic Neuritis**
Brain magnetic resonance imaging	34/35 (97)	33/35 (94)	35/35 (100)
Complete blood count	33/34 (97)	30/34 (88)	30/34 (88)
Cerebrospinal fluid routine studies	34/35 (97)	34/35 (97)	24/35 (69)
Cerebrospinal fluid oligoclonal bands	33/35 (94)	33/35 (94)	24/35 (69)
Cerebrospinal fluid immunoglobulin G index	32/34 (94)	33/35 (94)	23/35 (66)
Basic metabolic panel	32/34 (92)	29/35 (83)	27/34 (79)
Erythrocyte sedimentation rate	30/34 (88)	26/34 (77)	27/33 (82)
Cerebrospinal fluid immunoglobulin G synthesis rate	29/35 (83)	28/35 (80)	20/34 (59)
Liver function tests	28/34 (82)	27/34 (79)	23/34 (68)
Antinuclear antibody	26/35 (74)	26/35 (74)	26/35 (74)
Angiotensin-converting enzyme	23/34 (68)	22/34 (65)	23/34 (68)
Urinalysis	22/34 (65)	22/34 (65)	<50%
C-reactive protein	21/33 (64)	24/34 (71)	22/34 (65)
Spine magnetic resonance imaging	20/35 (57)	34/35 (97)	19/35 (54)
Epstein-Barr virus titers	19/34 (56)	18/34 (53)	<50%
Thyroid-stimulating hormone	19/35 (54)	18/34 (53)	19/33 (58)
Serum B_{12} level	19/35 (54)	25/35 (71)	20/35 (57)
Serum Folate level	18/34 (53)	22/34 (65)	18/34 (53)
Cerebrospinal fluid myelin basic protein	16/33 (49)	17/34 (50)	12/33 (36)
Ophthalmology exam	16/34 (47)	13/34 (38)	29/34 (85)
Neuromyelitis optica immunoglobulin G antibody	3/35 (17)	19/35 (54)	13/35 (37)

Table 3

Deciding Whether to Treat an Acute Attack of Demyelination

Response	No. Agreed/No. Responding	Percentage
Acute attacks of central nervous system demyelination do not always need to be treated	32/37	86
Clinical features of the attack are the most important determinants of this decision	32/32	100
Severity of the attack	31/32	97
Timing of the attack relative to the time of medical evaluation	16/32	50
Attacks with isolated sensory symptoms can be treated on a case-by-case basis	21/36	58
Findings on magnetic resonance imaging also influence the decision	30/36	84
Gadolinium enhancement	29/30	97
Presence/absence of T2 lesions at the central nervous system site where the symptoms/signs localize	28/30	93
T2 lesion number	22/30	73
T2 lesion volume	21/30	70

Table 4

Choice of Agent, Dosing, and Duration for Acute Attacks of Central Nervous System Demyelination

	Acute Disseminated Encephalomyelitis		Optic Neuritis		Transverse Myelitis		Multiple Sclerosis		Neuromyelitis Optica	
	No. Agreed/No. Responding	%	No. Agreed/No. Responding	%	No. Agreed/No. Responding	%	No. Agreed/No. Responding	%	No. Agreed/No. Responding	%
First-line treatment: intravenous methylprednisolone	30/32	94	32/32	100	30/32	94	31/32	97	32/32	100
Dosing: weight-based	22/28	75	20/33	61	22/29	76	20/27	74	19/26	73
Duration: 3–5 days	27/31	87	32/33	97	28/31	90	24/25	96	24/26	92

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Table 5

Recommended Second-Line Preventive Therapies

Multiple Sclerosis	Score[a]	Neuromyelitis Optica	Score[a]
Scheduled corticosteroids	203	Rituximab	180
Pulse intravenous immunoglobulin	189	Pulse intravenous immunoglobulin	163
Plasma exchange	125	Plasma exchange	160
Natalizumab	124	Scheduled corticosteroids	154
Cyclophosphamide	119	Azathioprine	147
Azathioprine	112	Mycophenolate	106
Mycophenolate	109	Cyclophosphamide	99
Rituximab	107	Mitoxantrone	64
Mitoxantrone	82	Natalizumab	36

[a]Respondents were asked to rank order their treatment preference given failure of first-preventive therapy. Scores consisted of the sum of all responses, with higher points given for preferred treatments.