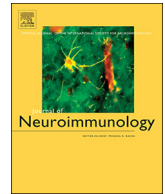




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## Neuromyelitis optica practice and prescribing changes in the setting of Covid19: A survey of neurologists

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### ABSTRACT

**Purpose:** This study reports and analyzes the findings from the responses of 192 neurologists in the United States and Canada to a new survey instrument distributed in April 2020 to assess NMO practice and prescribing changes during the Covid19 pandemic.

**Principal results:** 92% of responding neurologists considered their NMO patients to be at an elevated risk of acquiring Covid19. They also indicated sharp declines in visits, delays in treatment and related services, and several unmet needs deterring treatment.

**Major conclusions:** There is a need for evidence-based, comprehensive guidelines for treating NMO patients amid healthcare crises moving forward.

## 1. Introduction

Neuromyelitis optica (NMO) poses a unique set of health challenges that distinguish it from other similar disorders of the central nervous system. With an estimated 16,000–17,000 individuals living with NMO in the United States, (Flanagan et al., 2016) NMO affects a significantly smaller patient population than multiple sclerosis (MS), for which evolving treatment guidelines and approximately 20 Food and Drug Administration (FDA)-approved therapies exist. (Trebst et al., 2014) Issues of treatment accessibility and affordability already pose significant challenges to NMO patients, who predominantly come from ethnic minority groups commonly experiencing health disparities in North America. (Flanagan et al., 2016; Kessler et al., 2016) Even during non-crisis times when health systems function as usual, NMO requires individualized care due to the high rates of morbidity from NMO attacks and the need for a high degree of immunosuppression with few treatment options available. (Shahmohammadi et al., 2019; Papadopoulos et al., 2014; Collongues et al., 2019)

The Sars-CoV-2 (Covid19) pandemic, which first reached the United States in early January 2020, has the potential to disrupt the care of NMO patients to a great extent. As of late June 2020, there have been > 1.5 million reported cases of Covid19 and > 100,000 deaths. The disease has been reported in all 50 states, 29 of which have

reported more than 10,000 cases each. (Contentti and Correa, 2020) While some countries have provided limited guidance on Covid19-related precautions to be taken by NMO patients and their healthcare providers, a unified and thorough set of guidelines for NMO management across countries has yet to be established. (NHS, 2020; Tan et al., 2016) Analyzing and synthesizing the approach of neurologists who care for NMO patients amid these conditions could inform future actionable steps that neurologists could take to optimally manage NMO.

The objective of this study is to document the prescribing and treatment patterns of neurologists with expertise in NMO patient care during the Covid19 pandemic. The findings are reported from an online survey distributed in April 2020 to neurologists practicing across the United States and Canada.

## 2. Materials and methods

### 2.1. Human subjects protections

The Partners Healthcare Research Committee's Institutional Review Board reviewed and approved this study.

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## 2.2. Survey instrument

The authors created a new survey instrument to query the practices, decision-making, and perspectives of a group of neuroimmunology-focused neurologists who actively care for patients with NMO in the USA or Canada. The survey questions are based on controversies arising in the course of clinical practice, informal discussions by NMO providers, and NMO patients' queries to the authors. Survey responses included rating of statements for agreement, open-ended questions, multiple choice, and estimates of current practices in gradient forms.

## 2.3. Distribution

Inclusion criteria into the study were (1) actively practicing as a neurologist in the USA or Canada, (2) self-reported expertise in NMO, and (3) caring for a minimum of 2 NMO patients in the past 6 months. Neurologist participants were recruited through various means, including through multiple sclerosis clinic forums and the American Academy of Neurology's "synapse" communities. (Peto, 2020) Surveys were piloted first. The survey was distributed between April 14 and May 4, 2020.

## 2.4. Analysis

Results are depicted descriptively where appropriate (e.g. qualitative responses). Numerical responses are given as percentages by category or as averages with ranges. All analyses were performed using STATA (version 16.0, College Station, TX, USA).

## 3. Results

There were 250 respondents to our survey (21.8% response rate), 192 of whom met our study inclusion criteria. Respondents had an average practice duration of 13 years. The most commonly represented states were New York, California, Massachusetts, and Florida. Respondents personally managed an average of 14 NMO patients in the prior 6 months. The majority of neurologists practiced in smaller urban areas (100,000 to 1 million residents) (44%) and large cities (> 1 million residents) (37%). The most common practice setting among these neurologists was academic hospitals (51%), followed by single specialty groups (21%), multi-specialty groups (17%), community hospitals (6%) and solo private practices (5%). Most respondents fell within the range of 35 to 55 years old (58%).

### 3.1. Testing and exposure to Covid19

Six percent of neurologists reported testing their patients for Covid19, and 11% indicated that their patients had been exposed to Covid19. Seven percent suspected that one or more of their patients had Covid19 but never received a confirmed diagnosis via testing. Twenty-six percent of neurologists indicated that their patients have experienced difficulty getting tested for Covid19.

### 3.2. Changes to prescribing

Neurologists' prescribing patterns are provided in Table 1. Neurologists estimated that on average, prior to Covid19, their NMO patients were most commonly taking rituximab (52%), mycophenolate mofetil (12%), azathioprine (11%) and eculizumab (11%) (Table 1). 13% of patients were taking two or more immunosuppressive therapies, and 2% were currently enrolled in a therapeutic clinical trial.

Twenty-seven percent of neurologists believed certain NMO treatments are safer than others during the pandemic, 13% did not think so and 60% were unsure (Fig. 1). Among neurologists who believed certain NMO treatments are safer during the pandemic, the treatments most commonly determined as safer were IVIg (51%) and tocilizumab

**Table 1**  
Neurologists' (n = 192) prescribing patterns pre- and during Covid19.

Treatment name	NMO patients receiving treatment pre-Covid19 (mean %)	Consider starting NMO patients on treatment in light of Covid19 (%)	Not consider prescribing treatment to new or switching patients in light of Covid19 (%)
Azathioprine	11	32	21
Eculizumab	11	41	22
Inebilizumab	N/A	15	15
IVIg (recurrent)	6	40	5
Methotrexate	2	15	18
Mycophenolate mofetil	12	36	20
PLEX (recurrent)	5	30	7
Rituximab	52	45	20
Satralizumab	N/A	18	13
Steroids	8	17	26
Tocilizumab	1	27	13
No Treatment	4	N/A	N/A
None of the above	3	16	49

N/A = Not Applicable

(36%) (Fig. 1). Roughly half of all neurologists were uncomfortable with prescribing tocilizumab (48%), though 19% of neurologists anticipated using tocilizumab more often for their NMO patients given its current investigation as a treatment for Covid19. More than half were uncomfortable with prescribing hydroxychloroquine to their NMO patients (55%).

Many neurologists indicated patients were delaying their scheduled MRIs of the brain or spinal cord (57%), two-thirds indicated patients were delaying clinical visits (67%) and roughly half indicated their patients were delaying laboratory testing (52%) due to fear of contracting Covid19.

### 3.3. Adjustments to treatment plans

Prior to the Covid19 pandemic, neurologists who saw NMO patients would see an average of 4 NMO patients in-person in a typical month. As a result of the Covid19 pandemic, neurologists saw an average of less than 1 NMO patient in-person in the previous month (approximately the month of April 2020). Neurologists most commonly responded that it is not reasonable to delay the next B-cell therapy dose for their NMO patients during the pandemic. However, 17% of neurologists had already deferred one or more doses of immunosuppressant treatment for their NMO patients, 16% changed the dosing interval of the treatment, and 15% switched health facility-based infusions to home-based infusions.

Ten percent of neurologists are aware of patients who have self-discontinued their NMO treatment altogether due to worry about contracting Covid19. Out of all of the NMO drugs, rituximab was most often changed: 74% of neurologists who deferred a dose of an immunosuppressant did so for rituximab, 90% of neurologists who changed the dosing interval of treatment did so for rituximab, and 68% of neurologists who changed to home infusions did so for rituximab (Table 2).

### 3.4. Assessing risks and dangers

Ninety-two percent of neurologists considered their NMO patients to be at an elevated risk of Covid19 compared to the general population, with 62% considering the risk to be moderate to significantly increased due to their having NMO. Seventy-five percent of neurologists responded that their patients believe that Covid19 poses a level 5 or above (major) danger to their health (1 being no danger, 7 being major danger).

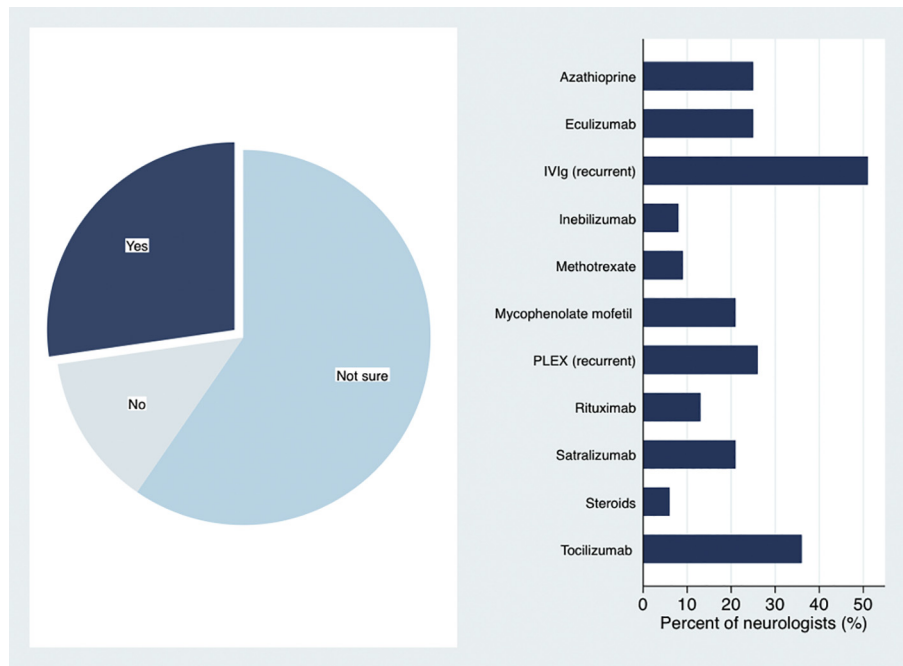


Fig. 1. Pie chart and bar graph of neurologists' (n = 192) response to: "Do you believe that certain NMO treatments are safer during the pandemic? If yes, which ones?"

3.5. Qualitative data

Open response questions were asked to qualitatively assess other aspects of providing care to NMO patients during the pandemic. For patients older than 60 years old, respondents recommended increased precautions, including that NMO patients stay at home, adhere to stricter self-isolation and social distancing practices, and conduct visits remotely through telemedicine. Neurologists responded that they would like to see the following changes to NMO patient care: increased access to home infusions, updated guidelines on how to best treat NMO patients during the crisis, and prioritization of these patients for social services. Neurologists also indicated several unmet needs for their NMO

patients, including improved testing for Covid19, more information on the risks of NMO treatment in this context, and increased telemedicine access. A list of selected open responses from neurologists that elaborates on these unmet needs is provided in Table 3.

4. Discussion

Neurologists across the United States and Canada believe that Covid19 poses a higher-than-baseline risk of disease among their NMO patients, in part due to the immunosuppressive nature of most NMO treatments currently available and necessarily in use. (Peto, 2020) Although evidence has not been found to indicate that Covid19 directly

Table 2  
NMO treatment decisions as a result of Covid19 (n = 192).

	17	16	15	4	3	2
	Deferred one or more doses of DMT	Changed the dosing interval of the treatment	Changed to home infusions	Switched their DMTs	Changed their dose of DMT	Discontinued their current medications
Rituximab	74	90	68	33	50	25
Eculizumab	23	7	21	17	17	50
Azathioprine	19	7	N/A	33	33	0
Mycophenolate mofetil	13	10	N/A	17	33	50
PLEX	10	7	11	17	17	0
Methotrexate	3	10	N/A	17	33	25
Steroids	3	14	N/A	33	33	75
IVig	0	3	39	0	0	0
Tocilizumab	N/A	3	N/A	N/A	17	25
Inebilizumab	N/A	N/A	N/A	N/A	17	N/A
Satralizumab	N/A	N/A	N/A	N/A	17	N/A

Percent of neurologists who indicated treatment decision impacted particular therapy (%)

**Table 3**  
 Select verbatim text from neurologists' open responses to: "What do you think the unmet needs are for your NMO patients in the setting of COVID-19?"

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Uncertain guidance for continuation or discontinuation of treatment. We know nothing.
Healthcare access remotely, financial assistance, mobility
Support for delivering groceries and medicine, financial support for getting medicines if they have lost jobs/insurance
Testing for symptomatic/asymptomatic
Treatment of COVID
Knowing what factors prevent or predict severity of COVID
Concern if they lose their insurance, will they have access to therapies
Greater risk assessment by thought leaders
Knowledge of what to do if they contract COVID-19
None of these patients have access to telemedicine and I think it's the biggest need given
Like them to stay home and not come to the office
Drugs which are less immunosuppressive
Guidance on delaying immunosuppressive therapy
We do not have any information about NMO and the COVID-19 pandemic as well as medications to treat NMO during the pandemic
Increased awareness of high risks of contracting infection in setting of immunosuppression
Data for how patients with NMO on certain treatments do when they've caught coronavirus
We need better treatments that are more effective and safer
The unmet need is not really any different than before COVID
Psychological support
Availability of newer disease modifying therapies in Canada
Knowledge of the actual risk of COVID-19 in the setting of NMO and disability level and also of the specific immunosuppressant
Several of our patients have resigned or taken leave of absence from work due to lack of accommodation for social distancing at their workplace
Lack of home infusion options

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affects the disease course in NMO or that NMO treatment causes increased susceptibility to Covid19 infection, this perceived high risk for NMO patients during the pandemic largely stems from the impact of immunosuppression on the overall risk of infection and the need for safety monitoring for the available therapies. (Brownlee et al., 2020) Though some neurologists have been able to test their patients for Covid19, many more have had difficulty gaining access to the appropriate tests, a situation which has posed a significant challenge for healthcare providers worldwide. (Wingerchuk et al., 2015) This lack of clarity on Covid19 risk, leading to delays in both NMO treatment and supportive services, may increase a patient's risk for an NMO attack. A national French study (Louapre et al., 2020) did not observe a difference by DMT type on the risk of acquiring Covid19 in MS. Instead of the DMT used by a patient, the risk factors of older age, advanced disability, and higher body mass index were each noted. However, the disease pathophysiology and DMT options differ between MS and NMO to question whether these findings can be directly applied to the NMO patient experience in this case.

The Covid19 pandemic has altered the decisions that neurologists are making to treat people living with NMO. As described in the open responses, the lack of adequate home infusion services and inability to connect with NMO patients via telemedicine in many cases have posed large barriers to care. The number of in-person visits has declined significantly alongside experts' perceptions of the changing risk-benefit balance of various medications. In particular, rituximab, which was the most commonly prescribed medication before Covid19, is not considered one of the safer medications to prescribe among the providers who consider certain medications safer than others in the era of Covid19. Rituximab treatment decisions—dosage deferrals, dosage intervals, home infusions—have also been subject to the most change among the menu of NMO treatments available to neurologists.

#### 4.1. Roadblocks to providing care

The study also indicates that challenging decisions will need to be

made by neurologists when attempting to improve treatments amid the pandemic. For example, while nearly half of all respondents indicated discomfort with using tocilizumab in light of Covid19, approximately 1/5 of respondents anticipated that they are considering increasing the usage of this medication given its potential as a Covid19 treatment. Such discrepancies among neurologists indicate a need for a streamlined and comprehensive protocol for the treatment of NMO amid the pandemic and related precautions to be taken by health care providers and patients alike. Furthermore, neurologists have indicated a dearth in knowledge on the impact of adjustments to medications on NMO patient safety and risk of Covid19 infection, demonstrating a need for further research on differing dosing schedules across the few available treatments.

Personalized medicine is no doubt being practiced for NMO patients in the setting of Covid19, but evidence to guide these practices remains limited. For instance, several immunosuppressive medications that are inexpensive – and therefore accessible – are not studied through randomized controlled trials (RCTs) for NMO, although both clinical acumen and non-RCT designs strongly support these medications' efficacy. The dosing of these medications is therefore non-standard at baseline and may vary based on patient age, disease severity, laboratory values, tolerability, patient or provider preference, perceived short and long-term risks of a variety of outcomes, and cost. Although infections have always been an important consideration in the choice and dosing of NMO therapies, including CNS and non-CNS infections, it is difficult to assess the risk Covid19 poses to immunosuppressed patients when making prescribing decisions given the unprecedented nature of this public health crisis.

There are some prescribing considerations that neurologists should make when treating NMO patients during the pandemic in light of the evolving clinical knowledge. Currently, MOG-IgG-associated NMO lacks any formally approved therapies. The most appropriate way to treat MOG-IgG-associated disease is still debated. Many MOG-IgG positive patients experience fewer and less disabling attacks. They are also overall younger and can have a monophasic disease course. (Jarius et al., 2018) The use of chronic steroids in MOG-IgG seropositive patients may increase the risk of Covid19 while use of IVIg may not; potentially these two standard treatments for MOG-IgG disease (Chen et al., 2020) may even mitigate a person's risk of severe Covid19 manifestations if exposed to Sars-CoV-2.

The current literature has also indicated that, while aquaporin-4-IgG serotype positive and negative NMO are oftentimes treated the same way, they may respond differently to immunosuppressive treatment. (Cree et al., 2019; Yamamura et al., 2019) Lastly, the possibility of a vaccination against Sars-CoV2 is a significant consideration that neurologists may have to incorporate into their future prescribing patterns. Though the specific interactions between a potential vaccine and immunosuppressive therapies require further study, neurologists treating NMO patients must prepare to weigh the consequences of vaccination on their treatment plans, including spacing doses to vaccinate, timing of vaccination, and multiple vaccination rounds. The efficacy of a future vaccine among immunosuppressed patients with NMO is in question.

#### 4.2. Strengths and limitations

There are several notable strengths to this study. We include close to 200 responses from neurologists who care for NMO patients, widely distributed geographically across the United States and Canada and from different practice settings. This allows a comprehensive view into clinical practices taking place on the continent. The survey also asks a broad range of questions that both qualitatively and quantitatively assess overall treatment plans, specific prescribing adjustments, and the level of concern documented by neurologists around the health of their NMO patients. Along with the novelty of the survey instrument and absence of such data on NMO treatment amid the pandemic, this study



can inform future courses of action. Neurologists' perceptions on therapies anticipated to become available in the future is also provided, beyond the FDA-approved and "off-label" therapies that are in widespread use.

There are also some limitations inherent in this study's design. Most notably, all the data collected during the study comes from the perspective of the neurologist, and so the perceived risks and dangers to NMO patients are filtered through that lens. This also means that this study does not document the exact facts on the ground, but rather assumes the accuracy and reliability of the neurologists' responses. Furthermore, this study captures responses regarding NMO treatment at one moment in time and does not track how such responses changed over the passage of time. The study also did not disaggregate NMO patients based on socio-economic status or ethnicity. Given the higher incidence of NMO among non-Caucasian populations, this level of detail could have informed the trajectory of NMO's health inequities, particularly in the USA where access to expert care remains variable. We also did not disaggregate scenarios based on aquaporin-4 antibody positivity status, since in our experience the therapeutic approach infrequently differs in seropositive and seronegative patients. Disease activity status, patient location referent to the health center, and patient social distancing are all relevant to medical decision-making but were not probed as specific scenarios. Most importantly, our study is not population-based, although we believe we have a fairly accurate representation of NMO-subspecialized neurologists, across most locations where they practice.

#### 4.3. Conclusions

Evidence relating to NMO treatments in times of Covid19 could not only better equip neurologists for the necessary preparations for caring for their patients, but would also serve to greatly reduce the high levels of worry and distress perceived to be occurring among their patients. The findings of this study indicate that neurologists are taking different—and sometimes diverging—stances on caring for their NMO patients. This emphasizes the complexity of the task at hand for this patient group with both a high risk of disability and a possibly increased risk of Covid19 from immunosuppression. Moving forward, clear guidelines to assist neurologists in caring for people living with NMO could be developed, the content of which this study could help to inform.

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#### Declaration of Competing Interest

None declared.

#### References

- Brownlee, W., Bourdette, D., Broadley, S., Killestein, J., Ciccarelli, O., 2020. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology*. 94 (22).
- Chen, John J., Flanagan, Eoin P., Bhatti, M. Tariq, et al., 2020. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. *Neurology*. <https://doi.org/10.1212/WNL.0000000000009758>.
- Collongues, N., Ayme-Dietrich, E., Monassier, L., de Seze, J., 2019. Pharmacotherapy for neuromyelitis optica spectrum disorders: current management and future options. *Drugs*. 79 (2), 125–142.
- Contentti, E.C., Correa, J., 2020. Immunosuppression during the COVID-19 pandemic in Neuromyelitis Optica Spectrum disorders patients: a new challenge. *Mult Scler Relat Disord*. 41, 102097.
- Cree, B.A., Bennett, J.L., Kim, H.J., Weinshenker, B.G., et al., 2019. Inebilizumab for the treatment of Neuromyelitis Optica Spectrum disorder (N-Momentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 394 (10206), 1352–1363.
- Flanagan, E.P., Cabre, P., Weinshenker, B.G., Sauver, J.S., et al., 2016. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann. Neurol*. 79 (5), 775–783.
- Jarius, S., Paul, F., Aktas, O., Asgari, N., 2018. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. *J. Neuroinflammation* 15 (1), 134.
- Kessler, R.A., Mealy, M.A., Levy, M., 2016. Treatment of neuromyelitis optica spectrum disorder: acute, preventive, and symptomatic. *Curr. Treat. Options Neurol*. 18 (1), 2.
- Louapre, C., Collongues, N., Stankoff, B., et al., 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. *JAMA Neurol.*, e202581. <https://jamanetwork.com/journals/jamaneurology/fullarticle/2767776>.
- NHS, 2020. Covid 19—Latest Guidance for Patients. <https://www.nationalmssociety.org/What-is-MS/>.
- Papadopoulos, M.C., Bennett, J.L., Verkman, A.S., 2014. *Nat. Rev. Neurol*. 10 (9), 493–506.
- Peto, J., 2020. Covid-19 mass testing facilities could end the epidemic rapidly. *BMJ*. 368, m1163.
- Shahmohammadi, S., Doosti, R., Shahmohammadi, A., et al., 2019. Autoimmune diseases associated with Neuromyelitis Optica Spectrum disorders: a literature review. *Mult Scler Relat Disord*. 27, 350–363.
- Tan, C.T., Mao, Z., Qiu, W., Hu, X., Wingerchuk, D.M., Weinshenker, B.G., 2016. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 86 (5), 491–492.
- Trebst, C., Jarius, S., Berthele, A., et al., 2014. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica study group (NEMOS). *J. Neurol*. 261 (1), 1–16.
- Wingerchuk, D.M., Banwell, B., Bennett, J.L., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 85 (2), 177–189.
- Yamamura, T., Kleiter, I., Fujihara, K., Palace, J., et al., 2019. Trial of Satralizumab in neuromyelitis optica spectrum disorder. *N. Engl. J. Med*. 381 (22), 2114–2124.