

COVID-19 and neuromuscular disorders

Amanda C. Guidon, MD, and Anthony A. Amato, MD

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Correspondence

Dr. Guidon
aguidon@partners.org
or Dr. Amato
aamato@bwh.harvard.edu

Abstract

The coronavirus 2019 (COVID-19) pandemic has potential to disproportionately and severely affect patients with neuromuscular disorders. In a short period of time, it has already caused reorganization of neuromuscular clinical care delivery and education, which will likely have lasting effects on the field. This article reviews (1) potential neuromuscular complications of COVID-19, (2) assessment and mitigation of COVID-19-related risk for patients with pre-existing neuromuscular disease, (3) guidance for management of immunosuppressive and immunomodulatory therapies, (4) practical guidance regarding neuromuscular care delivery, telemedicine, and education, and (5) effect on neuromuscular research. We outline key unanswered clinical questions and highlight the need for team-based and interspecialty collaboration. Primary goals of clinical research during this time are to develop evidence-based best practices and to minimize morbidity and mortality related to COVID-19 for patients with neuromuscular disorders.

Introduction

Whereas several human coronaviruses, including hCoV-229E, OC43, NL63, and HKU1, are associated with mild respiratory symptoms, more severe coronavirus infections have appeared over the last 2 decades. These newer coronavirus infections can result in severe acute respiratory syndrome (SARS) and include Middle East respiratory syndrome (MERS) and most recently coronavirus disease 2019 (COVID-19). These severe coronavirus infections have been associated with headache, seizures, and stroke, but literature regarding neuromuscular complications is scant. It is possible that associated neuromuscular disorders (NMDs) have occurred previously but have been overshadowed by systemic manifestations.

During the current COVID-19 pandemic, we need to be vigilant for neuromuscular complications that may be directly or indirectly related to coronavirus infection (table 1). We should also plan to adjust our clinical practices to prevent the spread of COVID-19 and to care for patients with NMDs and the complications they experience during this time. Finally, since the effects of the pandemic are expected to persist for longer than several weeks, we will want to adapt neuromuscular educational training programs. This article reviews the current state of knowledge and practice in these 3 areas, provides guidance, and raises clinical questions for future investigation.

Assessment of overall risk from COVID-19 in patients with NMD

Our current discussions with patients center upon risk and risk mitigation. Risks will depend upon the specific NMD, other comorbidities, age, and what immunotherapies the patients may be receiving (table 2). We do not expect the majority of patients, even in the higher risk categories, to have severe complications of COVID-19. We also can reassure patients that NMDs that spare swallowing and breathing muscles and where treatment does not involve immunosuppression are

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From the Division of Neuromuscular Medicine, Department of Neurology, Massachusetts General Hospital (A.C.G.), and Division of Neuromuscular Medicine, Department of Neurology, Brigham and Women's Hospital (A.A.A.), Harvard Medical School, Boston, MA.

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Glossary

AANEM = American Academy of Neuromuscular and Electrodiagnostic Medicine; **ALS** = amyotrophic lateral sclerosis; **CK** = creatine kinase; **COVID-19** = coronavirus disease 2019; **FcRn** = neonatal Fc receptor; **FDA** = Food and Drug Administration; **GBS** = Guillain-Barré syndrome; **IST** = immunosuppressive therapy; **MERS** = Middle East respiratory syndrome; **MG** = myasthenia gravis; **NMD** = neuromuscular disorder; **SARS** = severe acute respiratory syndrome; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

not considered to be high risk in COVID-19. On the other hand, patients may be in an overall higher-risk category due to other demographic factors or health considerations. At this time, the primary advice for all patients and their caregivers is to reduce the risk of contracting the virus through social distancing, handwashing, and stricter isolation in patients who are most at risk. Internationally, neurologic (International MG/COVID Working Group), rheumatologic (COVID-19 Global Rheumatology Alliance), and gastroenterologic (Surveillance Epidemiology of Coronavirus [COVID-19] Under Research Exclusion [SECURE-IBD]) groups have begun to publish consensus guidance statements to address clinical care and risk mitigation during COVID-19 for specific patient populations, with plans for updates as outcomes data become available.

Risk of infection causing a new NMD

There is a known risk of Guillain-Barré syndrome (GBS) attributable to viral infections (e.g., influenza, H1N1, Zika, Epstein-Barr virus). The rationale is that molecular mimicry exists between specific viral proteins and proteins on peripheral nerves (e.g., gangliosides) leading to an innocent bystander attack against the myelin or axon of peripheral nerves. There is 1 reported case of GBS in association with COVID-19; however, direct causality is uncertain.¹ GBS has been reported rarely with other coronavirus infections.^{2,3}

There is no current evidence of direct viral invasion with inflammation and degeneration of motor neurons and peripheral nerves as seen in some viral infections (e.g., poliovirus, enterovirus D68, West Nile, herpes zoster, cytomegalovirus). In the literature, there is 1 report of a 3-year-old child with acute flaccid paralysis who was coinfecting with 2 coronaviruses (HCoV 229E and OC43).⁴ However, the diagnosis was questionable; the child had normal EMG and nerve conduction studies 1 and 3 weeks after onset, normal CSF, and normal brain and spinal cord MRI. Nevertheless, it is possible that the virus may be neurotropic and directly infect and damage motor neurons and peripheral nerves.

Coronavirus infections may be associated with myopathies. In recently published studies of COVID-19 in China, myalgia or fatigue affected 44%–70% of hospitalized patients and increased creatine kinase (CK) was present in up to 33% of admitted patients.^{5,6} No additional workup such as EMG, muscle imaging, or histopathology was reported. Likewise, as many as a third of patients infected with other coronavirus infections manifested with myalgias and elevated CKs^{7,8} and

rhabdomyolysis.^{9,10} This suggests that coronavirus infections may cause a viral myositis. Very sick patients with coronavirus develop critical illness myopathy or polyneuropathy.^{10–13} A risk factor for developing critical illness myopathy is use of nondepolarizing neuromuscular blocking agents. Nevertheless, this has not been reported in patients with other coronavirus receiving short courses of these medications.¹⁴ Weakness related to type 2 muscle fiber atrophy from disuse typically presents after 1 week in ill patients who are bedridden and therefore will be a consideration in patients with COVID-19.

Risk of COVID-19 infection exacerbating known or unmasking previously unrecognized NMDs

There are no data regarding magnitude of risk of exacerbation due to COVID-19 or prior coronaviruses for rare NMDs. Infection is a common trigger of exacerbation or disease progression in many NMDs, both inherited and immune-mediated. For example, infection has been the leading cause of exacerbation of myasthenia gravis (MG) in a retrospective study.¹⁵ As such, we expect that we will observe both increased rates of disease worsening and an increased incidence of new presentations during the COVID-19 pandemic.

Considerations for exacerbation in acquired and inherited disorders are primarily related to degree of baseline cardiac and respiratory dysfunction, bulbar weakness, underlying pathophysiology of disease, and related comorbid conditions. An updated review of consideration by disease has been compiled.¹⁶ Patients with motor neuron disease (e.g., amyotrophic lateral sclerosis [ALS], spinal muscular atrophy) and hereditary neuropathies with ventilatory muscle involvement may be particularly susceptible to infection. Those with metabolic myopathies (e.g., lipid storage diseases and mitochondrial disorders) are at increased risk of rhabdomyolysis with fever, infection, or fasting (attributable to loss of appetite). In addition, patients with various muscular dystrophies, including myotonic dystrophy, and metabolic diseases (e.g., Pompe disease) who have ventilatory muscle weakness or cardiomyopathy are likely at increased risk for severe COVID-19. Patients who develop COVID-19 may not return to their prior baseline.

Table 1 Potential neuromuscular complications of coronavirus 2019 (COVID-19)

1. Risk of infection causing a new NMD
a. Guillain-Barré syndrome
b. Myositis
c. Critical illness myopathy or polyneuropathy
2. Risk of infection exacerbating known or unmasking previously unrecognized NMD
a. Autoimmune disorders such as CIDP, MADSAM, MMN, MG, LEMS, myositis
b. Degenerative disorders such as ALS, SMA, hereditary neuropathies, muscular dystrophies, congenital myopathies, mitochondrial myopathies, metabolic myopathies, and others
3. Risks of immunosuppressant/immunomodulating therapies in patients with autoimmune NMD
a. Increased risk of COVID-19 infection and more severe disease
b. Increased risks and severity of other infections in patients with COVID-19 in the setting of NMD treated with certain immunotherapies
c. Immunotherapies might make vaccines less effective
4. Risks of treatments for COVID-19
a. Hydroxychloroquine and chloroquine can cause a toxic neuropathy and myopathy
b. Antiviral treatments: lopinavir/ritonavir, remdesivir, others
5. Risks of vaccinations
a. Possible inflammatory neuropathy (e.g., Guillain-Barré syndrome, plexitis, mononeuritis)

Abbreviations: ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyneuropathy; LEMS = Lambert-Eaton myasthenic syndrome; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; MG = myasthenia gravis; MMN = multifocal motor neuropathy; NMD = neuromuscular disorder; SMA = spinal muscular atrophy.

Risks of immunosuppressant and immunomodulating therapies in patients with autoimmune NMDs

Patients with NMDs who use immunosuppressive therapies (ISTs) are likely at increased risk of contracting COVID-19 or having a more severe course of the virus. This risk is variable even among patients on ISTs and with the same disease (table 3). Published experience from Wuhan, China, to date has not examined neuromuscular comorbidities or patients on ISTs.^{5,6} In looking to similar immunocompromised populations where there has been work published, recent data suggest a trend toward increased incidence rate of COVID-19 and increased rate of severe disease in patients with cancer and cancer survivors in China.¹⁷ As a result, the authors made recommendations for this population that may be applicable to immunocompromised patients with NMD at highest risk: (1) intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer in endemic areas, (2) stronger personal protection provisions for patients with cancer or cancer survivors, and (3) consideration of more intensive surveillance or treatment when patients with cancer are infected with SARS coronavirus 2 (SARS-CoV-2), especially in older patients or those with other comorbidities.¹⁷

In terms of managing ISTs, consensus statements are emerging to guide patients and clinicians until we have data published on outcomes.¹⁸ Most outpatients without infection should continue to take their medications, with instructions to call their neurologist and temporarily hold the medication if they develop symptoms of infection. In some cases, after discussion of risk and benefit between the patient and provider, some patients may be able to continue ISTs or be treated with a different, less immunosuppressive option. This involves a discussion of potential risks and benefits related to COVID-19 and underlying

neuromuscular disease when adjusting doses or stopping immunosuppressant or immunomodulatory therapies. Examples of risk include age, comorbid medical problems, geographic location, household or occupational risk factors, and underlying neuromuscular disease severity. Avoiding abrupt cessation of a medication that may precipitate a flare of the underlying condition, which could in turn necessitate higher doses of prednisone, IST, or hospital admission, is the goal. Holding or suspending prednisone is not recommended.

Some therapies are not expected to increase the risk of COVID-19 or severe disease, including immunoglobulin therapy (intravenous or subcutaneous), complement inhibitor therapy (e.g., eculizumab), therapeutic plasma exchange, or neonatal Fc receptor (FcRn) antagonists (various forms are now being assessed in clinical research trials). Reliance on infusion centers may increase the overall risks for patients, so switching to home visits with or without visiting nurses for these therapies (visiting nurses are not necessary after training for subcutaneous infusions) may mitigate but not eliminate the risks. Therefore, requirement for IV administration needs to be taken into risk/benefit discussions. Importantly, guidance statements are changing and risks and benefits of IST may change over time. Check-ins from high-risk patients with changes in circumstances are appropriate. At this time, for most patients, we are working primarily on education regarding risk reduction. Infrequently, we make preemptive COVID-19–related medication adjustments in dosing or drug. In the future, vaccination or knowledge that a patient has developed immunity to COVID-19 could be incorporated into risk stratification and treatment decisions regarding further IST.¹⁹

Additional specific guidance for patients with NMDs based on drug regimen is outlined in table 4. For all patients, steps towards efficient prescribing to promote social distancing by

Table 2 Coronavirus 2019 (COVID-19) risk by neuromuscular disease

Disorder	Level of risk for COVID-19 or having severe COVID-19 disease course	Comments
Motor neuron disease	Moderate/high	Higher risk related to more advanced disease, use of ventilator or noninvasive ventilation, dysphagia, comorbid diseases
Neuropathies		
Inherited	All levels	Low with uncomplicated neuropathy High with autonomic involvement or cardiac involvement (e.g., amyloidosis), scoliosis with respiratory involvement
Immune-mediated	All levels	Related to degree of immunosuppressive therapy and respiratory/bulbar weakness
Idiopathic, nutritional, toxic	Low	No appreciable increased risks
NMJ		
LEMS	All levels	Consider underlying malignancy/chemotherapy
gMG	All levels	Risk related to bulbar and respiratory weakness, immunosuppressive therapy
CMS	All levels	Adult-onset, stable for >10 years without bulbar or respiratory weakness likely low risk Actual or possible (based on mutation) bulbar or respiratory muscle weakness higher risk
Muscle		
Inherited	All levels	Risk related to bulbar and respiratory weakness Related disease-specific comorbidities (i.e., diabetes, cardiac disease) influences risk
Inflammatory/immune-mediated	All levels	IST determines risk

Abbreviations: CMS = congenital myasthenic syndromes; gMG = generalized myasthenia gravis; IST = immunosuppressive therapy; LEMS = Lambert-Eaton myasthenic syndrome; NMJ = *neuromuscular junction*.

minimizing trips to pharmacies is appropriate. This may include refilling prescriptions for 90 days and encouraging delivery through mail order pharmacies. Weighing benefits of transitioning from infusion centers to home infusions will depend on patients' overall COVID-19 risk, transportation needs, geography/local resources, and insurance coverage. The relative risk of COVID-19 at hospital-based centers compared to home infusion is unknown.

COVID-19 vaccine efficacy and access in NMDs

Robust COVID-19 vaccine development programs with multiple candidates have launched.^{19–21} Typically a years-long process, the timeline has been accelerated. Multiple types of vaccine candidates are in preclinical development. Two that are currently in phase I clinical trials are RNA and nonreplicating vector vaccines.²¹ To our knowledge, there are no live virus vaccines under consideration. This is important for immunosuppressed patients as live vaccines must be avoided. Whether immunosuppressive or immunomodulatory therapy will make the COVID-19 vaccines less effective is highly relevant for patients with NMDs and

will need study. Recommendations for timing of vaccine administration with relation to dosing schedule of immunosuppressive or immunomodulatory therapies, including IV immunoglobulin, therapeutic plasma exchange, FcRn antagonists, and B-cell-depleting therapies, will be needed to maximize protective benefits. In addition, challenges of adequate vaccine supply during a pandemic and fair allocation based on risk are being addressed.^{21,22} We anticipate that data provided by disease-specific neuromuscular groups during this time on risk for and outcomes of COVID-19 in these groups will greatly inform risk stratifications in the future. Pragmatically, we will also need to consider how patients with NMD receiving telemedicine or who are self-isolating will receive vaccination, when available.

Management of patients with NMD who develop COVID-19

At this time, there are no neuromuscular-specific recommendations for patients who contract COVID-19 and additional outcome data are needed. Monitoring moderate to high risk patients with NMDs closely for the possibility of more

Table 3 Factors increasing risk of contracting coronavirus 2019 (COVID-19) or having more severe disease

Underlying immunotherapy
Immunosuppression with multiple agents
Additional factors
High doses of immunosuppressive therapy or cell/antibody-depleting therapies
Multiple immunosuppressive therapies, concurrently or sequentially
Highly active immune-mediated neuromuscular disease
Swallowing or respiratory muscle weakness
Other medical comorbidities
Pulmonary disease
Pulmonary hypertension
Renal impairments
Neutropenia or lymphopenia
Liver disease
Diabetes mellitus
Ischemic heart disease
Older age
Pregnancy (possible)

rapid decline in respiratory function or for worsening of their underlying neuromuscular disease is recommended. Telehealth applications could be considered in the future for this remote monitoring. Corticosteroids are not routinely given for treatment of COVID-19 but are sometimes used in sepsis. A discussion of the potential pros and cons of additional corticosteroids is available.²³ Patients with NMD already on corticosteroids may require stress doses. Typically, other immunosuppression is held or continued based on the patient's clinical status from COVID-19 and the severity of their underlying NMD. Discussion with the patient's primary neurologist and inpatient consult team if unavailable is recommended.

Risks of treatments for COVID-19

Several antiviral drugs are in clinical trial for treatment of COVID-19, including lopinavir/ritonavir, used for HIV infection, and remdesivir, which inhibits viral RNA polymerases and appears to show potent activity in vitro against members of the filoviruses (e.g., Ebola virus) and coronaviruses (e.g., SARS-CoV, MERS-CoV).²⁴ A recently published trial from China found no efficacy of lopinavir/ritonavir in COVID-19,²⁵ but other trials are ongoing and in preparation. With this in mind, certain protease inhibitors may increase the risk of peripheral neuropathy in patients with HIV,²⁶ but other studies have found lopinavir/ritonavir does not increase the risk and may actually reduce the risk of distal sensory polyneuropathy in HIV-infected individuals.^{27,28} Given the duration of treatment in patients with COVID-19 infection, we would suspect the likelihood of

inducing or worsening a preexisting polyneuropathy with lopinavir/ritonavir is likely to be low. However, a toxic myopathy with rhabdomyolysis has been reported in several cases of lopinavir/ritonavir treatment in combination with a statin.^{29–32} This is particularly important given early use of empiric high-dose statins for COVID-19 and the independent association of statins with rhabdomyolysis.⁴³ A small study suggested that remdesivir and chloroquine may be effective in reducing 2019-nCoV infection in vitro³³ and clinical trials of these agents are underway. Of note, no definite NMDs were associated with remdesivir in a trial for Ebola, though pain in the arms and legs was noted as a common complaint in healthy controls.³⁴

Chloroquine and hydroxychloroquine have also been mentioned as possible treatment for COVID-19. They are being used in patients with infection and without proven benefit as prophylaxis. Both drugs are associated with potential neuromuscular side effects.^{35,36} In vitro studies have demonstrated that chloroquine blocked COVID-19 infection, as mentioned above.³⁶ A short report of 100 patients in China noted that chloroquine seemed to be beneficial, but without supportive data.³⁷

Rarely, patients taking chloroquine or hydroxychloroquine develop slowly progressive, painless, proximal weakness and atrophy in the legs more than the arms.^{38–43} In addition, length-dependent sensory loss and reduced muscle stretch reflexes, particularly at the ankle, may be related to a concomitant neuropathy. Cardiac muscle can also be affected, leading to a cardiomyopathy. Serum CK levels are usually slightly elevated. Motor and sensory nerve conductions may show reduced

Table 4 Patients with neuromuscular disease without coronavirus 2019 (COVID-19): treatment-specific guidance

Treatment type/medication class	Examples	Disorders included	Guidance
Symptomatic and other therapies	Riluzole, botulinum toxins, antiepileptics, benzodiazepines, pyridostigmine, diaminopyridine, SSRIs, SNRIs, oral albuterol, mexiletine	ALS ALS-related sialorrhea Neuropathic pain Muscle cramps MG/LEMS CMS Myotonic disorders	No specific dose change Consider risk/benefit of routine monitoring laboratory studies Postpone nonurgent botulinum toxin injections Rx of controlled substances now typically approved via virtual care with standard safeguards
Nonimmunomodulatory infusion and intrathecal therapies, gene therapies	Edaravone, nusinersen/zolgensma, patisiran/inotersen, lumizyme/myozyme	ALS SMA Hereditary aTTR amyloidosis Pompe	Consider home infusions Consider risk of exposures with infusions vs risk of treatment interruption
Immunomodulatory therapies	IVIg SCIg Plasma exchange FcRn antagonists	GBS CIDP/MADSAM MMN MG LEMS Myositis	Consider home infusions Consider reducing frequency in stable patients Likely do not increase risk of virus
Complement inhibitors	Eculizumab, clinical trials (zilucoplan, ravulizumab)	MG Immune-mediated necrotizing myopathy	Consider home infusions May encounter logistical challenges for meningococcal immunizations: limited availability of walk-in facilities, etc. Likely does not increase COVID-19 risk
Corticosteroids	Prednisone, methylprednisolone, deflazacort	CIDP/MADSAM MG LEMS Myositis DMD	Consider lowest possible effective dose that will prevent disease flare Continue steroids unchanged in DMD Consider stress dose as usual for illness Avoid abrupt cessation for patients on chronic steroids
Immunosuppressive therapies	Azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine	CIDP/MADSAM MG LEMS Myositis	Consider risk/benefit of routine monitoring laboratories, consider spacing Continuation of therapy typically recommended, consider dose reduction if otherwise medically indicated Consider delaying initiation in stable patient with mild disease until height of pandemic has passed
Immunosuppressive/cell depleting therapies	Rituximab, ocrelizumab, cyclophosphamide, clinical trial drugs	CIDP/MADSAM MMN MG LEMS Myositis	Consider postponing infusions, spacing dosing interval, or switching to a different therapy Avoid new starts unless no other good alternative
Ancillary services/evaluations	Physical therapy, occupational therapy, speech therapy, clinical swallow evaluation, DME	All	Indication is primarily urgent appointments when ADL are limited and safety a concern Consider telemedicine possibilities

Abbreviations: ADL = activities of daily living; ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyneuropathy; CMS = congenital myasthenic syndromes; DMD = Duchenne muscular dystrophy; DME = durable medical equipment; FcRn = neonatal Fc receptor; GBS = Guillain-Barré syndrome; IVIg = IV immunoglobulin; LEMS = Lambert-Eaton myasthenic syndrome; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; MG = myasthenia gravis; MMN = multifocal motor neuropathy; SCIg = subcutaneous immunoglobulin; SMA = spinal muscular atrophy; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

amplitudes with slightly slow conduction velocities. Needle EMG can demonstrate positive sharp waves, fibrillation potentials, and myotonic discharges, particularly in proximal muscles. Autophagic vacuoles are often evident in skeletal and cardiac muscle fibers on biopsy. Usually, but not invariably, this toxic neuromyopathy does not develop unless patients are on high dosages for a year or more. Given that patients would receive a much shorter course of chloroquine and hydroxychloroquine, this toxic neuromyopathy

is unlikely to occur. Chloroquine and hydroxychloroquine have also been associated with new-onset or worsening MG and are typically used with caution in this patient group.^{44,45}

Azithromycin, a macrolide antibiotic, is also being used with chloroquine or hydroxychloroquine for COVID-19. Macrolide therapy, however, the most common being azithromycin, was not associated with reduced 90-day mortality or

Table 5 Educational resources for patients

1. Centers for Disease Control and Prevention (cdc.gov/coronavirus/2019-nCoV/index.html)
2. General resources compiled by the Muscular Dystrophy Association (mda.org/covid19)
3. Guidance for the management of myasthenia gravis and Lambert-Eaton myasthenic syndrome during COVID-19 by the International MG/COVID Working Group and a Webinar on myasthenia gravis and COVID by MGNET available on YouTube (myasthenia.org)
4. Recommendations for amyotrophic lateral sclerosis and specifically helpful suggestions for managing interactions with home health aides during COVID-19 (als.ca/wp-content/uploads/2020/03/COVID-19-ALS-Clinician-Guidance-Document-2020-03-17-FINAL-EN.pdf)

improvement in MERS-CoV RNA clearance in a study of patients with MERS.⁴⁶ Importantly, macrolides also may cause worsening of MG.¹⁵

Risk of incident NMD with COVID-19 vaccine

Another potential risk of vaccines is GBS and other acute inflammatory neuropathies (e.g., plexitis). This association is strongest for swine flu. A slight increased risk of GBS has been found in some studies of seasonal flu (influenza) vaccination^{47–49} but not all⁵⁰ and regardless, the risk of influenza in most individuals outweighs the rare risk, if any, of GBS. Likewise, a small risk of GBS was reported in some^{51–55} but not all series^{56,57} following H1N1 vaccination. These inflammatory neuropathies are thought to arise due to molecular mimicry as discussed previously between proteins on the virus and those on peripheral nerves. Certainly, this will be important to measure in future epidemiologic studies. There is no indication that a history of GBS or other immune-mediated neuromuscular disease would preclude vaccination against COVID-19 at this time.

Changes in neuromuscular systems of care

The COVID-19 pandemic has forced a rapid and unprecedented reorganization of clinical care delivery worldwide. In the United States, we are in the early stages of these modifications. Approach has been tailored by geographic location, local COVID-19 prevalence, patient population, and practice or institutional structures. Currently, the volume of elective or nonurgent outpatient care has been significantly reduced. The goal is to limit exposure to patients, communities, and medical staff. No data regarding the scope of this effect have been generated. The American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM) published guidance regarding clinical visits, electrodiagnostic testing, and telemedicine during COVID-19.⁵⁷ Currently, the AANEM encourages physicians to “discuss issues related to patient care with their hospitals and provide their recommendations regarding which patients need to be seen vs those that can be delayed without impact on patient care or outcomes” and “carefully consider when to cancel nonurgent procedures or prioritize their more urgent patients in order to reduce

potential exposure and to ensure judicious use of potentially limited supplies of personal protective equipment.” Like many other institutions, we have adapted a triage system to allocate scheduled outpatients to in-person encounters, telemedicine encounters, or to delay the visit or procedure if medically appropriate. Most outpatient electrodiagnostic studies and muscle and nerve biopsies may be postponed unless in case of urgent need and the results would change management (e.g., new ALS, MG, immune-mediated neuropathy or myopathy). Relevant patient-related and disease-specific outcomes and systems-based measurements of care metrics should be evaluated to assess the effect of these modifications.

Access to ancillary services and evaluation has been affected by COVID-19. Outpatient pulmonary function tests may not be performed due to increased risks. On a local level, our speech therapy department had become credentialed to perform remote video swallow assessment prior to COVID-19 and therefore is able to continue this program. Fluoroscopic swallowing studies are currently performed only for patients whose dysphagia is unmanaged and may result in an unplanned hospitalization. Overall, however, dysphagia is being evaluated and treated as much as possible with video sessions. Outpatient physical therapists and occupational therapists have mainly been communicating with patients by phone and patient portal sessions, often sending photographs and videos of exercises or equipment. Most outpatient and home therapists are seeing only essential postoperative patients in our region. The American Physical Therapy Association and state-based physical therapy organizations are organizing regarding telemedicine. Some of our local occupational therapists can provide virtual visits for follow-up for established patients. Medical equipment (e.g., wheelchairs, Hoyer lifts) deliveries and custom bracing have been significantly delayed in some regions. Virtual ancillary services have been discussed in previous publications.^{58,59}

We have compiled a list of common resources for patients who have general inquiries about COVID-19 (table 5). Directing patients to websites and other resources that are updated regularly is paramount, so that they have up-to-date information when they choose to access the information. Disease-specific links relating to ALS, MG, and recommendations for patients who require home health aides are included. Family and caregivers should be aware of their own ability to spread COVID-19. In addition, high-flow noninvasive ventilation

Table 6 Telemedicine: Proposed utility/appropriateness by neuromuscular outpatient visit type during coronavirus 2019 (COVID-19)

High utility/ appropriateness	Moderate utility/appropriateness	Low utility/appropriateness
NMD follow-up PN follow-up: stable or management of neuropathic pain MG follow-up: stable Myositis follow-up: stable Inherited neuropathy or myopathy follow-up: stable	New or unstable NMD New or unstable PN New MG: well-established diagnosis or unstable new/follow-up All patients with worsening symptoms to triage need and timeframe for further or more urgent care	All patients with discrepancy between reported symptoms and abnormal examination findings All disorders: second opinions for patients where nuances of physical examination will highly influence medical decision-making and diagnostic evaluation Primary management of unstable patients

Abbreviations: MG = myasthenia gravis; NMD = neuromuscular disorder; PN = peripheral neuropathy.

aerosolizes infectious particles to the local environment and requires appropriate measures to prevent spread.

Rapid integration of telemedicine

Before COVID-19, the rollout of telehealth in neurology and particularly in neuromuscular medicine had been slow.⁶⁰ Now, within a 2-week time period, many institutions in the United States have transitioned heavily to telemedicine due to necessity and relaxation of prior regulatory limitations.⁶¹ Contributing factors to slow adaptation before COVID-19 were reliance on a nuanced strength, sensation, and reflex examination in neuromuscular encounters. ALS clinics were early adapters prior to COVID-19.⁶² Neuromuscular clinics and information about incorporation of trainees are underrepresented in the limited data about outpatient telemedicine in neurology.^{63,64} Resources and telemedicine references have been created by numerous professional societies including the American Academy of Neurology and the American Association for Neuromuscular and Electrodiagnostic Medicine.

With necessity to switch to telemedicine for most outpatient encounters, neurologists are quickly discovering the strengths and limitations of telemedicine, and new tools and skills required. It is important to keep in mind that these strengths and limitations are not likely fully reflective of care in absence of the pandemic.⁶⁵ For example, coordinating local laboratory or imaging evaluation and pulmonary function testing, which is typically straightforward, is now layered with additional challenge and discussion of potential added COVID-19 exposure. We have transformed most attending only and resident/fellows clinics into telemedicine clinics to continue to provide both patient care and clinical training. Limitations in the physical examination preclude billing based on current complexity requirements in most circumstances. Currently, for virtual/phone visits that replace outpatient visits, billing is based primarily on the attending's synchronous video face-to-face time or time-based synchronous phone interaction time with the patient. This billing structure has been reviewed in detail elsewhere and will likely need modification if ongoing incorporation of residents and fellows in outpatient neuromuscular telemedicine will continue.⁶⁶ In addition, best practices for performance of and billing

for virtual disease-specific neuromuscular examinations and scales as well as incorporation of trainees into outpatient telemedicine settings is needed. To date, the visits that we perceive have the highest and lowest benefit for telemedicine during the COVID-19 pandemic are outlined in table 6. Further studies on outcomes and resource utilization as well as patient and provider satisfaction with virtual visits will further inform what portions of this emergency telemedicine will endure beyond COVID.

COVID-19's effect on neuromuscular training

In addition to professional and personal challenges for trainees and teaching faculty and clinical reassignments, the COVID-19 pandemic has posed limitations on formal neuromuscular training in residencies and fellowships. We see the immediate effect for this year's cohort, but anticipate that next year will also be affected, either by ongoing reallocated clinical volume or the need to catch up on deferred routine outpatient care. To adapt to these changes in real time and plan for the months ahead, we have added new or modified fellowship activities, and involved fellows in creating and testing these new structures (table 7). We have found that new communication platforms (e.g., Microsoft Teams or other) have been essential for ongoing formal and informal communications and to facilitate synchronous supervision of fellows remotely in clinic. Readers of *Neurology*[®] will have developed additional novel educational strategies. We anticipate that there will be future collaboration around these innovations to build and, after COVID-19, continuing those that have positively affected training.

COVID-19's effect on neuromuscular research

The effect of COVID-19 is of course not limited to neuromuscular research but will affect all medical specialties and neurology subspecialties. We will focus on the effect in clinical research, but certainly basic science and translation research will be affected. For example, basic/translational researchers,

Table 7 Early effect of coronavirus 2019 (COVID-19) on neuromuscular training activities

Increased	Decreased	Skill development
Virtual education (lecture series, waveform conference, pathology conference, grand rounds) Electrodiagnostic testing, neuromuscular medicine, muscle and nerve histopathology self-study Neuromuscular ultrasound self-study Communication with patients by phone and patient portal	Bedside teaching In-person and multidisciplinary clinics Electrodiagnostic testing study volume, inpatient and outpatient Biopsy performance Neuromuscular ultrasound performance Time spent on clinical notes Work exclusively within the neuromuscular division Work in established systems of care	Telemedicine Increased participation in hospital organization as a whole Developing new systems of care as a team, quality improvement processes New opportunities for formal teaching of medical students and residents Increased academic work, particularly that immediately relevant to COVID-19 Training in formal and informal remote working skills, individual and team-based

including graduate students and laboratory technicians, may not be considered essential employees and will need to work from home. Experimental studies on animals are being disrupted. From our perspective of clinical researchers, there are many challenges and we have selected some practical issues to highlight.

1. There are challenges to new study start-up and close out of recently completed trials. Site initiation visits and routine monitoring by the sponsor of studies is being prohibited in many academic hospitals. Those recently completed studies may not be able to analyze data until the monitor verifies source documents and what has been entered into study databases. These difficulties may be mitigated by allowing virtual study visits and monitoring.
2. Food and Drug Administration (FDA) guidance suggests limiting on-site study visits to only those with conditions in which available treatment options are limited and in which the research drug has potential for benefit. The clinical researcher weighs risks and benefits with each individual participant in each clinical trial.
3. Research sites need to have the appropriate staffing to maintain a clinical trial. Physician and nurse investigators may be deployed from research duties to help manage patients in the hospital. Likewise, research phlebotomists, pharmacists, and other research staff may be shifted to areas of the hospital where they may be more needed. Study coordinators may not be considered essential employees. Backups are needed for research personnel in case they get pulled away from research duties or become ill themselves.
4. It may be impossible for study participants to return to the site for their research appointments because their own illness puts them at increased risk in addition to what was mentioned above. We need to convert as many study visits as possible to virtual/phone visits, arrange for study laboratories to be done locally close to where a participant lives, and results to be sent back to the research site. We will need regulators (e.g., FDA, European Union) to understand that these laboratory studies that were supposed to be sent and analyzed by a previously approved central laboratory are going to be done locally in many cases. Research needs to figure out how to analyze the results coming from many laboratories.

Furthermore, we need to figure out how to handle laboratory results in which the investigator was to be blinded (e.g., such as CK levels in myositis trials). We may need to add blinded coordinators assigned to handle mail and faxes for these participants from their local laboratories to be placed in research binders. We also need to address how to handle missing data, particularly those involving primary outcome measures. Importantly, we have to arrange for study drugs to be shipped to participants and perform necessary oversight to ensure participants are taking the study drug (e.g., collecting and counting pills/syringes).

5. There is more administrative work for investigators and coordinators. The above changes to an approved protocol are considered protocol deviations (albeit minor given the situation), but require submissions to institutional review boards as well as approval of new amendments and informed consent forms.
6. Enrollment for clinical research is going to be slower and studies take longer to complete than anticipated. This is challenging to handle on a fixed budget on a grant.

Readers will think of more obstacles to research and how we might mitigate these and others. We will all need to learn from each other during these trying times.

Discussion

Data from the current COVID-19 pandemic regarding specific risks and outcomes for patients with neuromuscular disease are unknown. We will need new clinical structures including robust telemedicine platforms and procedures to care for our patients and to continue to educate trainees during this time. Expedited publication of updated evidence-based guidance will be informative. In the meantime, we can be vigilant in assessing patients with neuromuscular disease for potential neuromuscular complications of COVID-19 and work towards mitigation of COVID-19-related risk for patients with preexisting neuromuscular disease. Collaborative efforts among institutions will help generate the data needed to inform management of rare NMDs in the setting of COVID-19 and maintain clinical trials and research despite current challenges.

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Appendix Authors

Name	Location	Contribution
Amanda C. Guidon, MD	Division of Neuromuscular Medicine, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston	Major role in departmental actions contributing to content, drafted and revised the manuscript for intellectual content
Anthony A. Amato, MD	Division of Neuromuscular Medicine, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Major role in departmental actions contributing to content, drafted and revised the manuscript for intellectual content

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Amanda C. Guidon and Anthony A. Amato

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