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COVID-19 and neuromuscular disorders

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Abstract:

The coronavirus-19 (COVID-19) pandemic has potential to disproportionately and severely affect patients with neuromuscular (NM) disorders. In a short period of time, it has already caused reorganization of neuromuscular clinical care delivery and education, which will likely have lasting impact on the field. This paper reviews 1) potential NM complications of COVID-19, 2) assessment and mitigation of COVID-19-related risk for patients with pre-existing NM disease, 3) guidance for management of immunosuppressive and immunomodulatory therapies, 4) practical guidance regarding NM care delivery, telemedicine and education, and 5) impact on neuromuscular research. We outline key unanswered clinical questions and highlight the need for team-based and inter-specialty 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:

While several human coronaviruses, including hCoV-229E, OC43, NL63, and HKU1 are associated with mild respiratory symptoms, more severe coronavirus infections have appeared over the past two decades. These newer viruses can result in severe acute respiratory syndrome and include coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus, and most recently, "2019 novel coronavirus", or "2019-nCoV" which causes 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 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 neuromuscular patients 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 paper reviews the current state of knowledge and practice in these three areas, provides guidance and raises clinical questions for future investigation.

Assessment of Overall Risk from COVID-19 in Patients with Neuromuscular Disease

Our current discussions with patients center upon risk and risk mitigation. Risks will depend upon the specific NM disease, other co-morbidities, age, and importantly what immunotherapies they may be receiving (Table 2). It is important to emphasize that we do not expect the majority of patients, even in the higher risk categories, to suffer severe complications of COVID-19. We also can reassure patients that neuromuscular disorders which spare swallowing and breathing muscles and where treatment does not involve immunosuppression, are not considered to be

“high risk” during COVID-19. On the other hand, patients who are “low risk” because of their neuromuscular disorder 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 to reduce the risk of contracting the virus through social distancing, hand washing and through more strict isolation in patients who are most at risk. Internationally, neurologic (e.g. International MG/COVID-19 workgroup) and other specialty groups (COVID-19 Global Rheumatology Alliance) and gastroenterology (SECURE-IBD) 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 becomes available.

Risk of Infection Causing a New Neuromuscular Disorder

What comes to mind initially in most neurologists’ minds is Guillain-Barré syndrome (GBS) given known risks of GBS with viral infections (e.g., Influenza, H1N1, ZIKA, EBV, etc.). 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 one 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, etc.). In the literature, there is one report of a 3 year-old child with acute flaccid paralysis who was co-infected with 2 coronaviruses (HCoV 229E and OC43 co-infection).⁽⁴⁾ However, in our opinion, the diagnosis was questionable; the child had normal electromyogram and nerve conduction studies one and three weeks after onset, normal cerebral spinal fluid (CSF), and normal brain and spinal cord magnetic resonance imaging (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) Unfortunately, no additional work-up such as electromyography, 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 suggest that coronavirus infections may cause a viral myositis. Not surprisingly, very sick patients with coronavirus develop critical illness myopathy or polyneuropathy. (10-13) A risk factor for developing critical illness myopathy is use of non-depolarizing 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 one week in ill patients who are bedridden and therefore will be a consideration in COVID-19 patients.

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

There are no data regarding magnitude of risk of exacerbation due to COVID-19 or prior coronaviruses for rare neuromuscular disorders. Infection is a common trigger of exacerbation or disease progression in many neuromuscular disorders, both inherited and immune-mediated. For example, infection has been the leading cause of exacerbation of myasthenia gravis in 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, 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 of rhabdomyolysis with fever, infection or fasting (patients who are ill often lose their appetite and skip meals). Additionally, 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. Importantly, patients who develop COVID may not return to their prior baseline.

Risks of immunosuppressant and immunomodulating therapies in patients with autoimmune NMD

Patients with neuromuscular disorders who use immunosuppressive therapies (IST) are likely at increased risk of contracting COVID-19 or having a more severe course of the virus. This risk is variable however 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 immunosuppressive therapies.(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 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 which may be applicable in the future to immunocompromised neuromuscular patients at highest risk, namely, 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-CoV-2, especially in older patients or those with other

comorbidities.(17)

In terms of managing immunosuppressant therapies, 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 immunosuppressive therapy or be treated with a different, less immunosuppressive option. This involves a discussion of potential risks and benefits related to COVID and underlying neuromuscular disease when adjusting doses or stopping immunosuppressant or immunomodulatory therapies. Examples of risk include age, co-morbid 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 (either 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 completely reduce 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 immunosuppressive therapy 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

pre-emptive 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 neuromuscular patients based on drug regimen is outlined (Table 4). For all patients, steps towards efficient prescribing to promote social distancing by minimizing trips to pharmacies is appropriate. This may include refilling prescriptions for 90 day supplies 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 NM Disorders

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 pre-clinical development. Two which are currently in phase I clinical trials are RNA and non-replicating vector vaccines.(21) To our knowledge, there are no live virus vaccines under consideration. This is important for immunosuppressed patients as live vaccines are avoided. Whether immunosuppressive and/or immunomodulatory therapy will make the COVID-19 vaccines less effective is highly relevant for patients with NM disorders and will need future study. Recommendations for timing of vaccine administration with relation to dosing schedule of immunosuppressive or immunomodulatory therapies, including IVIG, TPE, FcRn antagonists and B cell depleting therapies, will be needed to maximize protective benefits. Additionally, challenges of adequate vaccine supply during a pandemic and fair allocation based on risk are being addressed.(21) We anticipate that data provided by disease-specific neuromuscular groups during this time on risk for and outcomes of COVID in these groups will greatly inform risk stratifications

in the future. Pragmatically, we will also need to consider how NM patients 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 neuromuscular patients closely for the possibility of more 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 however are sometimes used in sepsis. A discussion of the potential pros and cons of additional corticosteroids is discussed.(23) Neuromuscular patients already on corticosteroids may require stress doses. Typically, other immunosuppression is held or continued based on the patient's clinical status from COVID and the severity of their underlying neuromuscular disorder. 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 trials for treatment of COVID-19 including lopinavir/ritonavir (LPV/RTV), used for HIV infection, and remdesivir (RDV), 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 LPV/RTV 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 LPR/RTV 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 pre-existing polyneuropathy with LPV/RTV is likely to be low. However, a toxic myopathy with rhabdomyolysis has been reported in several cases of LPR/RTV 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 effective in reducing 2019-nCoV infection in vitro (33) and clinical trials of these agents are underway. Of note, no definite neuromuscular disorders 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 unfortunately, without proven benefit, as prophylaxis. Both drugs are associated with potential NM 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 amplitudes with slightly slow conduction velocities. Needle electromyography 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 improvement in MERS-CoV RNA clearance in a study of patients with Middle East respiratory syndrome.(46) Importantly, macrolides also may cause worsening of myasthenia gravis.(15)

Risk of Incident NMD with COVID-19 vaccine

Another potential risk of vaccines is Guillain-Barré syndrome (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 (48,49) but not all (50) and regardless, the risks 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 epidemiological 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 non-urgent 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 impact have been generated. The American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM) published guidance regarding clinical visits, electrodiagnostic testing (EDX) 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 versus those that can be delayed without impact on patient care or outcomes and “carefully consider when to cancel non-urgent 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 (PPE).” 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, muscle and nerve biopsies may be postponed unless of urgent need and would change management (e.g., new ALS, myasthenia, immune-mediated neuropathy or myopathy). Relevant patient-related and disease-specific outcomes, and systems-based measurements of care metrics should be evaluated to assess impact of these modifications.

Access to ancillary services and evaluation has been impacted 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 do remote video swallow assessment prior to COVID 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 therapist and occupational therapists have mainly been communicating with patients by phone and patient portal sessions, often sending

photos and videos of exercises or equipment. Most outpatient and home therapists are seeing only essential post-operative patients in our region. The American Physical Therapy Association (APTA) and state-based PT organizations are organizing regarding telemedicine. Some of our local occupational therapist 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. Reference related to virtual ancillary services are referenced.(58,59) We have compiled a list of common resources for patients who have general inquiries about COVID-19 (Table 5). Directing them to websites and other resources which are regularly updated is paramount, so that they have up to date information when they choose to access the information. Disease specific links for 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. Additionally, high flow non-invasive ventilation aerosolizes infectious particles to the local environment and requires appropriate measures to prevent spread.

Rapid Integration of Telemedicine

Before COVID-19, the roll-out of telehealth in neurology and particularly in neuromuscular medicine had been slow.(60) Now, within a two week time period, many institutions in the USA have transitioned heavily to telemedicine due to relaxation of prior regulatory limitations and necessity.(61) Contributing factors to slow adaptation before COVID-19 were reliance on a nuanced strength, sensation and reflex exam in neuromuscular encounters. ALS clinics have been early adapters prior to COVID-19.(62) Neuromuscular clinics and information about incorporation of trainees are under-represented 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 current 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, 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 which 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⁾ Additionally, best practices for performance of and billing for virtual disease specific neuromuscular exams and scales as well as incorporation of trainees into outpatient telemedicine settings is needed. To date, the visits which 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 Impact 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 impact 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 differed 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 even 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 which have positively impacted training.

COVID-19 Impact on Neuromuscular Research

Impact of COVID-19 is of course not limited to neuromuscular research but will impact all medical specialties and neurology subspecialties. We will focus on impact in clinical research, but certainly basic science and translation research will be affected. For example, basic/translational researchers, 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 have 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. FDA guidance suggests limiting on-site study visits to only those with conditions in which available treatment options are limited available 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 and may be deployed from research duties to help manage patients in the hospital. Likewise, research phlebotomists, pharmacists and other research staff to areas of the hospital where they may be more needed. Study coordinators may not be considered “essential employees.” Back-ups 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 convert as many study visits as possible to virtual/phone visits, arrange for study labs to be done locally close to where a participant lives and results sent back to the research site. We will need regulators (e.g., FDA, EU) to understand that these labs 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., like creatine kinase levels in myositis trials). We may need to add blinded coordinators to be assigned to handle mail and faxes for these participants from their local labs to be placed in research binders. We also need to address how to hand missing data, particularly those involving primary outcome measures. Importantly, we have to arrange for study drugs to 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 still require submissions to IRBs 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.

We suspect 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.

Conclusions

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 neuromuscular patients for potential NM complications of COVID-19, and work towards mitigation of COVID-19-related risk for patients with pre-existing NM disease. Collaborative efforts among institutions will be able to generate the data needed to inform management for rare neuromuscular disorders with COVID-19 and maintain clinical trials and research, despite current challenges.

Appendix 1. Authors

Name	Location	Contribution
Amanda C. Guidon, MD	Division of Neuromuscular Medicine, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA	Major role in departmental actions contributing to content in paper, drafted and revised the manuscript for intellectual content
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TABLE 1. POTENTIAL NEUROMUSCULAR COMPLICATIONS OF COVID-19	
1.	Risk of infection causing a new NMD <ol style="list-style-type: none"> a. Guillain-Barré Syndrome (GBS) b. Myositis c. Critical illness myopathy and/or polyneuropathy
2.	Risk of infection exacerbating known or unmasking previously unrecognized NMD <ol style="list-style-type: none"> 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 <ol style="list-style-type: none"> a. Increased risk of COVID-19 infection and more severe disease b. Increased risks and severity of other infections in patients with COVID-19 infection in patients with NMD patients treated with certain immunotherapies c. Immunotherapies might make vaccines less effective
4.	Risks of Treatments for COVID-19 <ol style="list-style-type: none"> a. Hydroxychloroquine and chloroquine can cause a toxic neuropathy and myopathy b. Antiviral treatments: lopinavir/ritonavir (LPV/RTV), remdesivir (RDV), others
5.	Risks of Vaccinations <ol style="list-style-type: none"> a. Possible inflammatory neuropathy (e.g., GBS, plexitis, mononeuritis)

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

TABLE 2. COVID-19 RISK BASED BY NEUROMUSCULAR DISEASE

Disorder	Level of Risk for COVID or having severe COVID disease course (L=Low, M=Moderate, H=High)	Comments
Motor Neuron Disease	<ul style="list-style-type: none"> M/H 	<ul style="list-style-type: none"> Higher risk related to: more advance disease, use of ventilator or non-invasive ventilation, dysphagia, comorbid diseases
Neuropathies		
<ul style="list-style-type: none"> Inherited 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> Low with uncomplicated neuropathy High with autonomic involvement or cardiac involvement (e.g. amyloidosis), scoliosis with respiratory involvement
<ul style="list-style-type: none"> Immune-Mediated 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> Related to degree of immunosuppressive therapy and respiratory/bulbar weakness
<ul style="list-style-type: none"> Idiopathic, Nutritional, Toxic 	<ul style="list-style-type: none"> L 	<ul style="list-style-type: none"> No appreciable increased risks
NMJ		
<ul style="list-style-type: none"> LEMS 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> Consider underlying malignancy/chemotherapy
<ul style="list-style-type: none"> gMG 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> Risk related to bulbar and respiratory weakness, immunosuppressive therapy
<ul style="list-style-type: none"> CMS 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> 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		
<ul style="list-style-type: none"> Inherited 	<ul style="list-style-type: none"> All levels 	<ul style="list-style-type: none"> Risk related to bulbar and respiratory

- **Inflammatory/Immune Mediated**

- All levels

- weakness
 - Related disease specific co-morbidities (ie diabetes, cardiac disease) influences risk
 - IST determines risk
-

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TABLE 3. FACTORS INCREASING RISKS OF CONTRACTING 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 HTN**
 - **Renal impairments**
 - **Neutropenia or lymphopenia**
 - **Liver disease**
 - **Diabetes Mellitus**
 - **Ischemic heart disease**
 - **Older age**
 - **Pregnancy (possible)**

			consider dose reduction if otherwise medically indicated <ul style="list-style-type: none"> • Consider delaying initiation in stable patient with mild disease until height of pandemic has passed
Immunosuppressive/Cell Depleting Therapies	mab, Ocrelizumab, Cyclophosphamide, clinical trial drugs	MADSAM is	<ul style="list-style-type: none"> • Consider postponing infusions, spacing dosing interval or switching to a different therapy • Avoid new starts unless no other good alternative
Ancillary Services/Evaluations	al therapy, occupational therapy, speech therapy, clinical swallow evaluation, DME		<ul style="list-style-type: none"> • Indication is primarily urgent appointments when ADLS are limited and safety a concern • Consider telemedicine possibilities

Abbreviations: GBS, Guillain-Barre syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MMN, multifocal motor neuropathy; MG, myasthenia gravis; LEMS, Lambert-Eaton myasthenic syndrome; ALS, amyotrophic lateral sclerosis; SMA, spinal muscular atrophy; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin

Table 5. RESOURCES FOR PATIENTS

- Centers for Disease Control and Prevention (CDC) <https://www.cdc.gov/coronavirus/2019-nCoV/index.html>
- The MDA has compiled general resources (<https://www.mda.org/covid19>)
- MFGA (MG/Covid International Workgroup) – myasthenia.org. Guidance for the management of Myasthenia Gravis (MG) and Lambert-Eaton Myasthenic Syndrome (LEMS) during the COVID19 by the International MG/COVID Working Group and a Webinar on MG and COVID by MGNET which is available on Youtube.
- Recommendations for ALS and specifically helpful suggestions for managing interactions with home health aides during COVID-19. (<https://www.als.ca/wp-content/uploads/2020/03/COVID-19-ALS-Clinician-Guidance-Document-2020-03-17-FINAL-EN.pdf>).

Table 6. Telemedicine:

Proposed Utility/Appropriateness by Neuromuscular Outpatient Visit Type during COVID-19

<i>High Utility/Appropriateness</i>	<i>Moderate Utility/Appropriateness</i>	<i>Low Utility/Appropriateness</i>
<ul style="list-style-type: none">• MND f/u• PN f/u – stable or management of neuropathic pain• MG f/u – stable• Myositis f/u - stable• Inherited neuropathy or myopathy f/u - stable	<ul style="list-style-type: none">• MND new or MND unstable• PN new or unstable• MG new – well-established diagnosis or unstable new/f/u• All patients with worsening symptoms – to triage need and timeframe for further or more urgent care	<ul style="list-style-type: none">• All patients with discrepancy between reported symptoms and abnormal exam findings• All disorders - Second opinions for patients where nuances of physical exam will highly influence medical decision making and diagnostic evaluation• Primary management of unstable patients

Table 7
Early Impact of COVID-19 on Neuromuscular Training Activities

<i>Increased</i>	<i>Decreased</i>	<i>Skill Development</i>
<ul style="list-style-type: none"> • Virtual education (Lecture series, waveform conference, pathology conference, grand rounds) • EDX, NM medicine, Muscle and nerve histopathology self-study • NM U/S self-study • Communication with patients by phone and patient portal 	<ul style="list-style-type: none"> • Bedside teaching • In-person and Multidisciplinary Clinics • EDX Study Volume– inpatient and outpatient • Biopsy performance • NM U/S performance • Time spent on clinical notes • Work exclusively within the NM division • Work in established systems of care 	<ul style="list-style-type: none"> • 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 those immediately relevant to COVID-19 • Training in formal and informal “remote working” skills – individual and team-based

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