Management challenges for chronic dysimmune neuropathies during the COVID-19 pandemic

Yusuf A. Rajabally MD, FRCP1,2 | H. Stephan Goedee MD, PhD3 | Shahram Attarian MD, PhD4,5 | Hans-Peter Hartung MD, PhD, FRCP6

1Inflammatory Neuropathy Clinic, University Hospitals Birmingham, Birmingham, United Kingdom
2Aston Medical School, Aston University, Birmingham, United Kingdom
3Brain Center Rudolf Magnus, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Heidelbergaan 100, 3584 CX, Utrecht, The Netherlands
4Reference Centre for Neuromuscular Diseases and ALS, Centre Hospitalier Universitaire La Timone, 264 rue Saint-Pierre, 13385, Marseille, France
5Aix-Marseille University, Inserm, GMGF, Marseille, France
6Department of Neurology, Medical Faculty and Center of Neurology and Neuropsychiatry, LVR Klinikum, Heinrich-Heine University, Düsseldorf, Germany

Abstract
Since March 2020, the COVID-19 pandemic has led to the need to re-think the delivery of services to patients with chronic dysimmune neuropathies. Telephone/video consultations have become widespread but have compounded concerns about objective evaluation. Therapeutic decisions need, more than ever before, to be considered in the best interests of both patients, and society, while not denying function-preserving/restoring treatment. Immunoglobulin therapy and plasma exchange, for those treated outside of the home, expose patients to the hazards of hospital or outpatient infusion centers. Steroid therapy initiation and continuation pose increased infectious risk. Immunosuppressant therapy similarly becomes highly problematic, with the risks of treatment continuation enhanced by uncertainties regarding duration of the pandemic. The required processes necessitate considerable time and effort especially as resources and staff are re-deployed to face the pandemic, but are essential for protecting this group of patients and as an integral part of wider public health actions.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, COVID-19, dysimmune, multifocal motor neuropathy, pandemic, paraproteinemic neuropathy

1 | INTRODUCTION
Medical practice has significantly changed since March 2020 as a result of the COVID-19 pandemic, and neurology is no exception.1 Neurologists looking after subjects with chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), or paraproteinemic neuropathies, are compelled to react rapidly to offer optimal, safe care. This differs from best practice
only a month ago. Social distancing suggests that decisions can no longer be based solely on the affected individual, but also on the need to protect that individual’s immediate family and society at large.

Opinions and recommendations on the diagnosis, monitoring, and treatment of chronic dysimmune neuropathies during the current pandemic are here offered. These are summarized in Tables 1 and 2. Current international measures to curb the progression of the pandemic will have to be maintained for an indeterminate period of time, albeit in different forms. Many uncertainties will remain, although several changes in our practice, aimed at offering optimal care to our patients as neurologists while adhering to our public health responsibilities as physicians, have become essential and urgent. We discuss these crucial changes in practice and their implementation in routine clinical care.

### 2 | Diagnostic Considerations

Prompt identification of a treatable disorder such as CIDP is highly desirable. Delays in treatment initiation may result in worse prognosis due to axonal loss. CIDP, however, may present with widely varying disability and modes of progression. Whereas decision-making may be easier in patients with severe impairment, often of rapid onset, many patients present with slow progressive, moderate deficits. Difficulties with tasks involving hand and arm function that nevertheless remain partially preserved, or with lower limb function not impacting independent mobility, require particular attention and caution. In such patients, the urgency of diagnosis should be balanced against the risks of hospital/medical facility attendance for clinical evaluation and diagnostic tests. These tests themselves, usually considered helpful, now...
require consideration of their benefit-to-risk ratio. The American Association of Neuromuscular & Electrodiagnostic Medicine recently published helpful guidance for managing electrodiagnostic testing requests during COVID-19, emphasizing the importance of clinical urgency.\(^4\) In this regard, as was previously proposed, clinically typical forms of CIDP, may, in these times of COVID-19, require therapeutic decisions without electrophysiologic confirmation.\(^5\) Suspected atypical forms of CIDP with rapid progression appear the main ones to consider for urgent electrodiagnosis, particularly, when multifocal as in Lewis-Sumner syndrome (to differentiate from axonal mononeuropathy multiplex of possible vasculitic origin), when pure motor (to differentiate from motor neuron disease, and thereby justify high-dose immunoglobulin treatment), or when pure sensory and associated with profound ataxia (to differentiate from sensory ganglionopathies of possible paraneoplastic etiology).

The rate of misdiagnosis of CIDP may be high,\(^6\) potentially posing a public health hazard. Several mimics need to be recognized, given the important management implications. Establishing a correct alternative diagnosis of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes) syndrome or of FAP (familial amyloid polyneuropathy, or hereditary transthyretin amyloidosis [hTTR] amyloidosis) is urgent in view of the prognosis without adequate treatment. In contrast, urgent investigations are less critical for suspected diagnoses such as a neuropathy associated with IgG/A monoclonal gammopathy of undetermined significance (MGUS), or with kappa light chains or IgM MGUS with anti-myelin associated glycoprotein (anti-MAG) activity, because management is unlikely to be altered by prompt exact syndromic diagnosis. Consequently, it would appear appropriate to evaluate with urgency only those with rapidly progressive disease, causing loss of independent ambulation or of upper limb function, those with severe atypical neuropathic pain, or those with dysautonomia.

Patients with MMN are most commonly middle-aged males who present with progressive, predominantly upper limb deficits.\(^7\) These may cause varying degrees of functional impairment, and disability levels may be relatively mild.\(^8\) This should be considered when prioritizing patients for clinical assessment and electrodiagnostic testing. The most commonly considered differential diagnosis of MMN, motor neuron disease, may be associated with early bulbar or respiratory involvement, resulting in enhanced morbidity and mortality from COVID-19 infection. It is important to urgently evaluate only those patients with acutely presenting/deteriorating, life-threatening, or function-threatening symptoms without an established diagnosis, so as to identify those with severe MMN or other treatable causes (eg, myasthenia gravis), rather than bringing in all such patients systematically.

There will be occasional patients for whom hospital inpatient admission, or urgent out-patient evaluation, may be the most appropriate course. Such patients should be queried about respiratory symptoms in themselves or others in their household before attendance, and should take their temperature on the day before attending. Adequate protective masks are appropriate for the patient and the accompanying caregiver, with when possible, private rooms. Systematic testing for COVID-19 infection still clearly poses challenges in many countries for asymptomatic patients, but is highly advisable, if possible. Protective measures for the involved healthcare professionals depend on previsit risk evaluation, ranging from use of gloves and general hygiene to full personal protective equipment (PPE). In view of known asymptomatic carrier status, and of potential extreme COVID-19 disease severity including in subjects without risk factors, the case for generalization of PPE use may become more compelling.

The greater risk of transmission of COVID-19 within hospital environments, despite descriptions of frequencies exceeding 40% in early reports,\(^9\) remains uncertain. More studies of this important question are currently underway in the Netherlands and elsewhere, and the findings will inform future best practice.

3 | EVALUATION OF CLINICAL STATUS, DISEASE PROGRESSION, AND TREATMENT RESPONSE

The telephone and video consultations necessitated by social distancing and the lack of PPE, are in many ways adequate for the assessments required. Muscle strength is often evaluated through more objective and reproducible grip strength measurements, which have been found to correlate well with general disability.\(^10\) Other outcome measures have been proposed, mainly for CIDP, but also more recently for MMN. The Inflammatory Neuropathy Cause and Treatment (INCAT) scale,\(^11\) and its derivative the Overall Neuropathy Limitation Scale (ONLS)\(^12\) are easy and rapid to administer.\(^13\) Rasch-built scales, including the inflammatory Rasch-built Overall Disability Scale (I-RODS)\(^14\) and its equivalent for MMN, the MMN-RODS,\(^15\) have been proposed, and are now frequently used.\(^13\) INCAT, ONLS, I-RODS, and MMN-RODS scales have routinely been used through paper or web-based questionnaires to be completed by patients themselves. Additional questions to evaluate proximal upper limb strength, proprioceptive function and balance, fatigue levels, and stamina are also useful and may be assessed without in-person contact.

Synchronous videoconferencing permits evaluation of the patient’s ability to raise the arms above the head or place them on the posterior neck, stand from a chair, walk a short distance, or perform a finger-to-nose test with and without visual control. Asking specific questions about activities of daily living, such as the ability to shower and dress, walk indoors and climb stairs, prepare food and cook, walk outdoors, garden, or exercise, are important in the remote verbal evaluation. It may be consequently argued that most of the vital information necessary for treatment decisions can and should, be obtained virtually.\(^16\) Although criticism can be made about the disability outcome measures and methods for remote score ascertainment, important limitations equally hinder examination-based assessments particularly given the low reliability of Medical Research Council (MRC) sum scores\(^17\) as well as the potential variability of grip strength measurements.\(^18\)
4 | THERAPEUTIC CONSIDERATIONS

The COVID-19 pandemic has resulted in several new issues directly impacting the treatment of dysimmune neuropathies. These relate not only to the patients themselves, including their age, medical history, personal and familial circumstances, but also to the disease subtype, the resulting severity of disability, and the treatments.

CIDP is known to affect more commonly elderly subjects, particularly males.19 This group is at higher risk of severe COVID-19 infection and fatal outcome.20 These patients in addition, frequently have co-morbidities, including diabetes, hypertension, and cardiovascular disease, all also risk factors for COVID-19 infection severity.21 Many such individuals live with a partner of similar age, and with similar co-morbidities. Exposing such individuals to clinical environments for treatment requires careful consideration of each individual case. Use of outpatient infusion treatment centers, although not without risks, would appear clearly safer than hospital, particularly inpatient, administration. Adequate precautions, in compliance with social distancing recommendations and use of PPE, remain essential in any the provision of care.

Home IVIg therapy is well-established in some countries but difficult to access in others. Even when involving a single or limited number of nurses/caregivers, adequate precautions appear mandatory particularly with patients at high-risk, as evidenced by a study from the Netherlands, which showed a 4.1% COVID-19 infection rate among healthcare workers with only mild respiratory complaints and without epidemiological link to the infection.22 Although remaining a very good alternative in the current situation, switching to home therapy is unfortunately an unrealistic challenge for many, in view of enhanced staff shortages. Home therapy, when available, is frequently unsuitable for treatment initiation in view of the possibility of adverse reactions and absence of immediate medical access. In new patients, the decision should be purely clinically based and in those without immediate and serious threat to function, consideration may need to be given to delaying treatment.

Subcutaneous immunoglobulin (SCIg) therapy has recently been demonstrated to be as effective as the intravenous form (IVlg) for CIDP.23 This represents the preferred and recommended option for those on established long-term treatment during the current pandemic. However, switching from IVlg to SCIg may also in practice prove complex, as we have found out recently in Europe, mainly for reasons of product availability as well as reduced specialist staff availability for patient training, caused by re-deployment toward COVID-19-related activity.

IVlg over-treatment of CIDP is a well-known and discussed issue,24 which in this unprecedented situation, becomes a critical topic. Continuing IVlg requirements require urgent re-evaluation for all patients, particularly those with clinical stability over at least 6 mo, without residual end-of-dose effect or ongoing improvement. Previously performed, slow dose reductions in cases of suspected remission now instead justify interruption of treatment altogether, with regular virtual monitoring, as well as education of patients and caregivers to contact their healthcare provider immediately for any deterioration in their clinical status.

In addition to real treatment needs, precise treatment effects and potential consequences of withdrawal need to be carefully re-interpreted. The very rare patients with respiratory muscle compromise should be given priority consideration for urgent home IVlg or SCIg therapy. In contrast, therapy considered effective by patient and physician may be unjustified in view of the new risk to benefit ratio. In numerous subjects, improvement levels corresponding to 1 point on the INCAT or ONLS scale, or of 4 points or less on the I-RODS, have justified ongoing treatment. It may now be more appropriate to consider larger levels of improvement necessary to justify continuation. As concrete examples, mild difficulties with dexterity and slight gait abnormalities (suggesting for each, a 1-point drop on INCAT and ONLS scales), without other disability, should now lead to re-consideration of the need for ongoing therapy. Consequently, lengthier, more thorough evaluation and discussion, both effectively possible remotely, are now needed.

The need for treatment for a newly identified patient with chronic dysimmune neuropathy also concurrently infected by COVID-19 will likely be a rare occurrence, and treatment delay is probably appropriate in acute stages. In cases where COVID-19 infection is suspected in a patient with CIDP on maintenance treatment, immunoglobulin continuation, while possibly still justified for neurological function, poses other questions. First, delaying treatment until well after the COVID-19 symptoms have settled appears fair and in line with normal practice, for example, fever or flu-like symptoms present before administration are contra-indications to proceed. However, the adequate interval is uncertain. Second, if treatment is performed in hospital in mild or subclinical presentations, COVID-19 infections may go unnoticed, exposing other patients and caregivers to potential risk of infection. Finally, coagulation disorders have been noted in early reports in patients with severe COVID-19 infection with a negative impact on outcome, mostly due to disseminated intravascular coagulation (DIC) that appears to occur as a response to the infection, with reported potential benefits of anticoagulation.25 However, as tentative as it may seem, the question whether immunoglobulin exposure and co-infection with COVID-19 could further alter thrombotic risk remains to be answered. On balance, treatment interruption and proactive anticoagulation may be best in these subjects until full recovery.

The issue of corticosteroid therapy is more straightforward for those who have been receiving pulse therapy, as opposed to those on daily regimens. Pulse therapy may be planned, initially for 6 mo, without oral taper, using 2 g of IV methylprednisolone26 or 160 mg of oral dexamethasone,27 every 4 weeks. With pulse administration, interrupting further courses is the logical precaution, while giving early thought to eventual alternatives. Of note, high cumulative corticosteroid administration has been found to substantially increase risk of infection in other populations28 and shielding, through distancing and home confinement, may be appropriate for previously treated patients, irrespective of age and co-morbidities.
In case of severely disabling CIDP refractory to IVlg and plasma exchange, resorting to pulse corticosteroid therapy may be the only option. In such exceptional cases, oral, home administration, with adequate social distancing and close remote monitoring, requires cautious consideration. With daily oral regimens, given the increased risks particularly with higher dosages, the decision will depend on the disease severity and the actual risks of major functional decline with withdrawal. The decision not to alter the treatment cannot be based solely on consideration of the immediate infectious risk but should also consider the possible prolongation of the pandemic, making social distancing unsustainable as means of protection in the medium and longer term.

Patients in whom high-dose corticosteroids are maintained should be considered at increased risk, resulting in additional necessary precautions. The dose of steroids that should be considered as high remains unclear. A recent large study of patients with polymyalgia rheumatica or giant cell arteritis showed an excess infectious risk even at daily doses of <5 mg daily of prednisolone, casting doubt on the safety derived from dose reductions.

Plasma exchanges are infrequently used long-term in CIDP. They usually provide short-term effects requiring repeated treatments, and so pose the problem of hospital attendance. Similar to IVlg, careful reassessment of treatment needs is essential in this subset of patients, bearing in mind that most of them have failed other first-line treatments and, therefore, are at high risk of neurologic deterioration on withdrawal. Plasma exchange, importantly, now requires earlier consideration, ahead of corticosteroids when available and in appropriate cases. However, this too may be hindered by availability during the pandemic.

The use of immunosuppressant therapy is, outside the pandemic context, controversial due to lack of evidence in CIDP. This now of particular relevance. In practice, for severe refractory cases, further treatments with high-dose and high-frequency IVlg, or continuing regular repeated plasma exchange treatments, are justified in place of early consideration of for example, cyclophosphamide, rituximab, or mycophenolate. For those already on long-term immunosuppression, however, particularly in the absence of definite evidence of efficacy, awareness and great caution are now imperative, as continuing such therapies may be highly inappropriate, again considering that social distancing and home confinement do not offer long-term solutions for these individuals in view of the uncertainty regarding the pandemic duration.

Also of concern, the infection risk with immunosuppressants probably lasts for several months after interruption (although there are only few studies of single agents used for sufficiently long to confirm this). Despite little available data comparing corticosteroids vs other immunosuppressants for infection risk, the benefit of the former is generally well-accepted for CIDP, thereby offering potential justification, as opposed to the latter. Use of long-term methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil exposures, often of unproven benefit as usually used in conjunction with continuing first-line agents, now, therefore, carry unacceptable risks. Although it has been suggested that the infectious risk may be highest with cyclophosphamide, it may also be that previous use of three or more immunosuppressants carries an even greater risk. This is a situation not infrequently encountered in subjects with CIDP.

The discovery of new antinodal and paranodal antibodies in a small proportion of patients with CIDP, most often refractory to IVlg, poses a rarely encountered, but genuine clinical problem. Some such patients may respond to corticosteroid therapy and others only to rituximab. With regards to rituximab, for which the efficacy has also been described in CIDP without paranodal antibodies, and while randomized controlled trial evidence is awaited, the risk of infection may be heightened with cumulative dose (4% with every 100 mg) and reduced with time from administration (9% per year). Those already treated with rituximab, therefore, should be considered to be at high-risk. Clinical severity should be the sole driver of therapeutic decisions after greater persistence than previously with first-line agents, such as immunoglobulins (to which some patients with antiparanodal antibodies may also respond), plasma exchange, and, when essential, corticosteroids, and with clear information of risks being provided to patients and families.

In patients with MMN, the situation may appear straightforward, with a single evidence-based treatment available. Early switch from IVlg to SClg, with careful remote monitoring due to possible subsequent suboptimal results and increased dose requirements, should be considered in all when feasible. In established patients in need of regular IVlg, clinical re-evaluation is imperative. In many, although it is generally considered advisable to maintain immunoglobulins in view of the high likelihood of deterioration off-treatment, remission rates may be as high as 20% and the functional benefit of remaining on treatment may not override the risk of continuing hospital or infusion center attendance. Detailed assessment and communication are necessary on a case-by-case basis.

There is no current evidence for routine use of any treatment in anti-MAG neuropathy. However, in selected patients with severe and rapidly progressive disease, rituximab may be of benefit and is used by many. Again, precisely defining severity and speed of decline becomes essential through detailed remote consultation, with only severe disability justifying treatment consideration. In the setting of the pandemic, it may in such patients, be advisable to attempt IVlg in the first instance, which could produce short-term benefit, before considering rituximab. “CIDP-like” phenotypes have rarely been described in patients with anti-MAG antibodies. For such patients, first-line CIDP treatment (principally IVlg and plasma exchange), rather than rituximab, may be justified. In the wider setting of paraproteinemic neuropathy, greater collaborative neuro-hematologic interaction has become essential in current times, with careful multidisciplinary decisions.

Treatment recommendations are summarized in Tables 1 and 2.

5 CONCLUSIONS

Many weeks of profound uncertainty are ahead of us. Lockdown measures are hoped to effectively reduce COVID-19 transmission rates,
but what the future holds for the management of patients with chronic dysimmune neuropathies is unknown. Issues with reliability, availability, and generalization of testing persist worldwide and will necessarily impact on future practice. In the case of patients at high risk of severe infection and death from COVID-19, but who will remain seronegative, the question of when the re-implementation of routine face-to-face consultations, usual hospital or infusion center treatment and use of immune suppressive therapies, particularly corticosteroids, will become safe again, is, disturbingly, unanswered. Immunomodulatory and particularly immunosuppressive therapies may compromise the immune system’s ability to effectively fight off infection with COVID-19, and this concern will persist for an indeterminate time and impact upon patient management.

In practice, a focus on the severity of the clinical picture and especially of disability, acuteness of the presentation, and likelihood of treatment efficacy, are all essential in making diagnostic decisions. Therapy needs to be focused first and foremost on not exposing the patient, family, and society to harm. This involves choosing the least dangerous option when essential, not hesitating to alter previously established protocols if needed, and using new methods and locations for drug administration, all of which are aimed at ensuring that treatment requirements and expected benefits are justified in view of the known risks. The pandemic alters the order of preference of first-line treatments for CIDP, putting plasma exchange when available in second place, ahead of corticosteroids, now displaced to third, with immunoglobulins as first choice.

Remote assessments of these patients may be a part of clinical care for the foreseeable future, and prioritizing clinical judgement over use of test results for patients affected by chronic dysimmune neuropathy has never been more important.

6 | ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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