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Objectivity, Practicality, and Significance of Practice Guidelines for the Practicing Neurologists: What We Learnt From Consensus Criteria in CIDP, Myasthenia Gravis and Inflammatory Myopathies

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Objectivity, practicality, and significance of practice guidelines for the practicing neurologists: What we learnt from consensus criteria in CIDP, Myasthenia Gravis and Inflammatory Myopathies

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***Abstract*:** The value of practice guidelines in the three most common autoimmune neuromuscular disorders, namely Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Myasthenia Gravis (MG) and Autoimmune Inflammatory Myopathies (AIM), has been extensively debated regarding their usefulness in clinical practice, objectivity and universal value considering that guidelines are also established regionally in certain countries. This commentary highlights common concerns on how guidelines are presently generated, pointing out: (a) non-sufficient diversity among Task-Force members to identify and address not only routine clinical and electrophysiology issues but also immunology, imaging, pathology, biomarkers, epidemiology or treatment economics; (b) Task-Force being often comprised by the same or seemingly like-minded members conveying the erroneous impression that experts with opposing views might have been excluded, even if this is clearly not the case; and (c) relying on web-based registries or retrospective data collections from heterogeneous sources. As a result, the existing practice guidelines in CIDP, MG and AIM remain an unfinished business but an excellent base for further enhancement. Guidelines can be extremely helpful not only for clinical trials but also in clinical practice if viewed as a living document with continuously updated versions by experts even with opposing views with precise information on diagnostics, pathomechanisms, therapeutic schemes, evolving biomarkers and economics of new therapies with validation of the post-guidelines criteria. Geographic diversity should be taken into consideration because the availability of biomarker testing, and therapies differ among countries. Patient preferences need to be also considered in therapeutic guidelines because newly marketed drugs offer more options steadily changing the therapeutic algorithms in autoimmune neuromuscular diseases generating also questions as to whether they also influence decisions on insurance coverage. Collectively, these startup considerations are aimed to make practice guidelines more objective, widely acceptable worldwide and more practical or easier to follow in clinical practice.

Keywords: CIDP, Myasthenia Gravis, Inflammatory Myopathies, practice guidelines, consensus criteria

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Introduction

Although practice guidelines are essential for the design of clinical trials, their use in clinical practice remains elusive. The commentary by Muley and Beydoun[1] on CIDP guidelines, as recently modified by the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS),[2] is the stimulus to critically address their significance for the practicing neurologists, along with their limitations or even inevitable bias. The issue is timely

because the newly proposed EAN/PNS guidelines,[2] despite the undisputed experience and expertise of the Task Force members, have been triggering criticisms by their equally expert colleagues generating confusion as to which voices should be heard and by whom not only for the design of future clinical trials but also for the everyday practice. Because not only in CIDP but also in two other autoimmune neuromuscular diseases, Myasthenia Gravis (MG) and Autoimmune Inflammatory Myopathies (AIM), several and often conflicting practice guidelines are frequently published, there is also concern on how best to reconcile opposing views to enhance a wider acceptance. Another issue is their universal applicability, especially when applied to specific biomarkers or immunotherapies, because their availability and cost are quite variable among countries. Accordingly, there is a need to discuss the usefulness, utility, and significance of the guidelines to practicing autoimmune neuromuscular specialists.

On this basis, this commentary addresses the methodology of consensus-oriented-decision-making process highlighting the potential impact a wider participation of experts might have in clinical practice with validated criteria and enhanced objectivity. Although it is focused more on CIDP, given the noise generated by the new EFNS/PNS criteria, it also comments on practice guidelines in MG and AIM, both diseases seen by autoimmune neuromuscular diseases experts because the same concerns are also applicable to these disorders where a much larger number of published guidelines convey even confusing messages. Importantly, it provides suggestions on how best to improve on the role of Task Force Committees in ensuring global endorsement taking into account the known variables in neuromuscular practice among practicing neurologists in several countries and continents. Finally, it addresses the need to clarify whether the guidelines are only limited to offering an educated opinion on practical guidance or they may also have a legally binding value influencing insurance decisions relevant to covering new expensive drugs, like those in MG.

Concerns with the practice guidelines in CIDP

At the 2022 PNS meeting, one of the speakers, a member in the recent CIDP guidelines group,[2] asked the audience before starting his talk on how many people are following CIDP guidelines in their clinical practice. Only very few raised their hands! Being at the podium as one of the other speakers, I recognized that those few, who enthusiastically stood up, were also members of the Task Force. The speaker, being surprised because so very few among the hundreds in the audience follow practice guidelines, started his talk by defending their importance. The message is that practicing neurologists, especially those with expertise in peripheral neuropathies, do not seem to have the need to look at the committee's notes to confirm if a patient fulfills the diagnostic criteria of CIDP nor do they seek justification to initiate a specific therapy. The same applies to neurologists diagnosing and treating patients with MG and AIM; it is almost sure that similar reactions would have also occurred in their respective meetings, collectively questioning whether the recommendations by the Task Force are even counterproductive, possibly because they give the impression of challenging the clinicians' expertise in their evidence-based practice.

There is no doubt that guidelines in all autoimmune neuromuscular diseases are not only essential but should be a living document as biotechnology, immunobiology and immunotherapies are constantly evolving, steadily changing not only the diagnostics and disease biomarkers but also treatment algorithms in view of the many ongoing trials and promising therapeutics. It has also become obvious that an informed participation with experts from many parts of the world and from many different subdisciplines will not only enhance the accuracy and practicality of the guidelines but would also ensure a better communication among practicing and academic neurologists worldwide.

Critical observations and consequences of the current guidelines

The CIDP Task Force did a great procedural job following the Population/Intervention/Comparison/Outcome (PICO) questions and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) summaries, including the Evidence-to Decision frameworks. The governing body however in charge of directing everything remained the *Task Force*. When viewed objectively based on publicly expressed comments, and clearly without being judgmental considering that these are highly respected and

esteemed colleagues or personal friends, one can point out that: (a) the present Task Force was very similar to the one that directed the criteria 10 years ago,[3] including same collaborators who subsequently supported the validity of the guidelines in several review papers by their co-authors (numerous collaborative-citations counted); (b) at least six members were from the same institutions while some others were co-authors in review papers, subconsciously projecting the erroneous impression that no other experts have performed fundamentally scholarly or pioneering work in the field; and (c) there was a rather narrow diversity in sub-specialty expertise among the Task Force members. CIDP, being an immune demyelinating neuropathy, requires a highly heterogeneous group of experts not only with general interest and knowledge in CIDP by clinicians running 'CIDP clinics', but with much broader strengths including: neuroimmunologists to assess the value and the changing scenery of new antibodies and objectively determine the rationale and response to various immunotherapeutic approaches based on disease immunobiology; experts electrophysiologists to judge new and old electrophysiologic methodology and criteria; nerve morphologists to evaluate any progress on histology, imaging or immunopathology that could serve as possible biomarkers; neuroepidemiologists to provide advice on practical issues on frequency in CIDP in various age groups, association with diabetes and other comorbidities or gender predominance; geographic diversity of neurologists with expertise in neuroeconomics and diagnostic or neurotherapeutic variables in different countries; and biostatisticians to advise on the power of sample sizes and how best to evaluate patients' preference when it comes to clinical trials. Importantly, the weight and validity of data screened by the Task Force were mostly based on various institutional web-based registries on retrospective data collections or multicenter registry databases with heterogeneous definitions and assessments of response to various therapies.

Since 1975 when CIDP appeared on the map, more than 15 sets of diagnostic criteria have been proposed, most by the same core of experts or their mentors and trainees, as witnessed within the present Task Force. Over the years and in many countries, criteria have been heavily tailored toward electrophysiology and clinical patterns while data on histology, immunopathology, immunobiology and immunotherapeutics were on a second or third tier. The consequences of all the above are reflected in the critical comments, correspondence, and commentaries about the new but also the old guidelines highlighting also concerns or the need for different criteria in certain countries. Among the many published critiques, in addition to the commentary by Muley and Beydoun,[1] that cast a cloud on the practical value of the practice guidelines, include the following few, specifically selected only to highlight concerns in different countries:

(1) Italian clinicians (that also included members of the Task Force), found among 330 of their own CIDP patients, that the new EAN/PNS diagnostic criteria had reduced sensitivity and specificity compared to the 2010 EFNS/PNS criteria.[4]
(2) In a German study, 10.3% among 182 CIDP patients did not fulfill the new EAN/PNS criteria because of inadequate electrodiagnostic data, even though their patients had signs of demyelination and responded to therapy; they suggested the need to also include ultrasound as a complementary diagnostic tool.[5]
(3) Among Dutch neurologists (that also included members of the Task Force) there was considerable variation in the diagnosis of CIDP with 77% not adhering to the EFNS/PNS criteria while only 50% followed treatment guidelines, suggesting the use of nerve imaging.[6]
(4) A Japanese study raised concerns about the EAN/PNS criteria advising the use of peripheral nerve imaging with ultrasound and/or MRI to increase specificity.[7]
(5) French experts[8] when comparing the implementation of the EFNS/PNS treatment guidelines among 182 studied patients, provided their own recommendations and suggested the need for more long-term treatment with IVIg for further improvement.

Concerns with the practice guidelines in MG and AIM

Similar, if not identical, issues are encountered in MG and AIM. There are more than 20 major, but not consistent with each other, practice guidelines in MG. We have commented several years ago[9] that convening an experienced panel to provide consensus guidance on how best to treat MG[10] is

extremely helpful, but the effort poses difficulties if you predominantly include the views of like-minded experts while choosing the right methodology remains challenging.[9] It was pointed out that several of the non-evidence-based consensus opinions are not necessarily shared by other experts and some opinions need highlighting, while some old or untested views merit revisiting.[9]

Today, consensus on MG treatment is very timely but also a complex task that should be viewed as work in progress considering the diversity of opinions in reference to the newly available and steadily expanding list of therapeutics. Having now four approved but expensive biologics (eculizumab, efgatrigimod, ravulizumab and rozanolizumab) along with the extensive use of rituximab and IVIg[11] and the newly promising controlled trials especially with zilucoplan,[12] new treatment guidelines should be in the offing and rapidly expanding, especially as we are also witnessing that thymectomies are steadily declining. These drugs however pose several complexities in the MG practice algorithm because their cost and availability are diverse among different countries. Here, patient preference should also play a fundamental role because of the availability of short-acting or long-acting intravenously given agents but also self-administered subcutaneous drugs.[12] There are at least 20 major practice guidelines published in MG based on PubMed and we expect more to come as several international surveys point to global disparities regarding the best treatment options to follow.

In Autoimmune AIM the issue is even more chaotic. The previous criteria based on histopathology and immunopathology established by scholars in the field[13,14] are now obsolete being side-lined by the availability of autoantibodies even if almost all are non-pathogenic and several non-specific.[15] Practice guidelines mostly from EULAR/ACR and other related organizations remain abundant, counting at least 15 the last few years in PubMed, especially as the field is now moving from neuromuscular neurologists with expertise and emphasis on histology, immunopathology and detailed neuromuscular examinations, to several like-minded groups of rheumatologists, internists or rheumatoneurolgists, all collectively agreeing to put more weight on the Creatine Kinase (CK) level and autoantibodies rather than muscle histopathology and neuromuscular examinations. This is clearly exemplified by the recent negative trial in necrotizing autoimmune myositis with zilucoplan[16] where not only the scientific basis was unjustified because complement is integrally connected to muscle fiber necrosis being unrelated to these antibodies,[15] but the primary efficacy endpoint was based on changes in the CK level,[16] a marker that has been considered obsolete in disease monitoring several decades ago.[14] Guidelines in AIM are too many to list or comment on, other than stressing that they are all heterogeneous. The different views among neurologists and rheumatologists, expressed in a sarcastic title several years ago by Christopher-Stine[17] that 'Neurologists are from Mars; Rheumatologists are from Venus', are now growing more. The opinions of rheumatologists along with some rheumatoneurolgists are now becoming more dominant, placing priority on the antibodies and muscle imaging rather than the clinical neuromuscular profile with patterns of muscle involvement and immunopathological diagnostic criteria. Clinical practice guidance for juvenile dermatomyositis remains also abundant but very confusing among different pediatric rheumatology experts and the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. A large group concluded that practice guidelines in AIM are heterogeneous with only half of the 14 listed being evidence-based, highlighting the lack of large multidisciplinary working groups, patients' preferences, and the necessity to improve on diagnosis, management, and other co-morbidities, concluding that crucial unmet needs should be identified by patients and clinicians.[18]

How best to make the practice guidelines uniformly accepted by both clinicians and clinical trialists

Because practice guidelines are essential for both, clinical practice and research, the committee members (or Task Force) should ensure member objectivity and practicality of the final opinion with universal value if the criteria are to be globally followed. Most importantly, the guidelines should be effectively communicated in a way that expert practitioners should feel like their voice has been heard. How best should the guidelines be technically obtained and constructed is not a simple process and clearly beyond the scope of this commentary. The main suggestions here are aimed for the future Task Force and Committee Members based on the critical comments already

published in reference to CIDP, MG and AIM and the observations discussed above clearly aimed not to highlight negativity but only to serve as an impetus to stimulate the interest to improve a complicated process. The following considerations may be helpful as startup principles:

(1) **Need to define the experts.** Expert should be a person who has performed scholarly but original work in the disease either in treatment, diagnosis or clinical assessments based on original peer-reviewed papers in high-impact journals.
(2) **Selection of the Chair.** The Chair should be a highly recognized and respected expert based on accomplishments and objectivity. Because it takes a lot of voluntary work and commitment, the chair should only serve one period, not repeatedly as is the current pattern; this may be the impetus to attract the very busy experts enhancing the overall quality of the Task-Force.
(3) **Independence of opinion among experts to prevent same-minded participants.** Experts should not be from the same institution and mentors/mentees should not participate. The chair should be sensitive to invite people with different areas of expertise within the disease to cover all needed disciplines mentioned earlier, not simply because they run a CIDP, a myositis or a MG clinic.
(4) **Geography should be proportionately represented among experts.** The chair should select experts from many countries active in the diagnosis and treatment of CIDP, MG or AIM. This international committee should take into account how the disease is diagnosed or treated in major geographic regions based on test availability, licensed drugs and cost, highlighting the best options, if certain agents or tests are not easily available.
(5) **Patient preference.** This should be considered in therapy guidelines especially with the new drugs but also in diagnostic guidelines when choosing invasive or expensive diagnostic tools, like spinal taps, special antibodies, MRI imaging or histology of nerve and muscle.
(6) **Periodic validation of the criteria in key patient cohorts around the world.** The value of the consensus guidelines in clinical practice can be only verified if the criteria are independently validated in follow-up prospective assessments.
(7) **What if no consensus.** This important information should be analyzed and extensively discussed highlighting the specific uncertainties or country diversities dictating the need for validation.
(8) **Duration of the Guidelines.** It should be stated that the proposed guidelines are a living document and will be reviewed yearly taking into account invited comments and validated data.
(9) **Acknowledging objectivity.** For universal adoption of the practice guidelines without skepticisms, it is critical to clarify and state that opposing views on certain areas have been seriously discussed and considered.
(10) **Clarity of the purpose.** The document needs to assure all clinicians that the goal of the Task Force's guidelines is only to offer practice guidance and does not have any legally binding value nor any power in dictating or influencing insurance coverage of certain drugs needed during the disease course. They should also stress that the guidelines are not dictating criteria for patient selection in FDA-approved or industry-sponsored clinical trials but may only serve as advising tools in their process of selecting and approving the most suitable criteria for patient enrollment.

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