Distal symmetric polyneuropathy: A definition for clinical research

Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation

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Abstract—The objective of this report was to develop a case definition of distal symmetric polyneuropathy to standardize and facilitate clinical research and epidemiologic studies. A formalized consensus process was employed to reach agreement after a systematic review and classification of evidence from the literature. The literature indicates that symptoms alone have relatively poor diagnostic accuracy in predicting the presence of polyneuropathy; signs are better predictors of polyneuropathy than symptoms; and single abnormalities on examination are less sensitive than multiple abnormalities in predicting the presence of polyneuropathy. The combination of neuropathic symptoms, signs, and electrodiagnostic findings provides the most accurate diagnosis of distal symmetric polyneuropathy. A set of case definitions was rank ordered by likelihood of disease. The highest likelihood of polyneuropathy (useful for clinical trials) occurs with a combination of multiple symptoms, multiple signs, and abnormal electrodiagnostic studies. A modest likelihood of polyneuropathy (useful for field or epidemiologic studies) occurs with a combination of multiple symptoms and multiple signs when the results of electrodiagnostic studies are not available. A lower likelihood of polyneuropathy occurs when electrodiagnostic studies and signs are discordant. For research purposes, the best approach to defining distal symmetric polyneuropathy is a set of case definitions rank ordered by estimated likelihood of disease. The inclusion of this formalized case definition in clinical and epidemiologic research studies will ensure greater consistency of case selection.

Mission statement. The American Academy of Neurology (AAN) in conjunction with the American Association of Electrodiagnostic Medicine (AAEM) and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) determined that there was a need for a formal case definition of polyneuropathy. Because of inconsistency in the literature, no consistent case definition exists. The use of a formal case definition across future research studies would ensure greater consistency of patient selection. This review describes the development of such a case definition for distal symmetric polyneuropathy.

Justification. Polyneuropathy is a common neurologic disorder of diverse etiologies. Although experienced clinicians can usually diagnose polyneuropathy in patients presenting with the characteristic history and classic neurologic examination findings, the exact criteria for the diagnosis are not formalized. In particular, accurate criteria for the diagnosis of distal symmetric polyneuropathy are debated.

The principal purpose of this project was to develop a definition of distal symmetric polyneuropathy with a reasonably high sensitivity and specificity that would serve as a basis for future research studies. Clinicians...
may find the criteria useful for routine clinical diagnosis. To achieve greater focus, other neuropathy phenotypes including polyradiculopathy, mononeuropathy multiplex, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and related conditions were excluded from the final case definition. Although small-fiber polyneuropathy is an important subset of distal symmetric polyneuropathy, the evidence-based medical literature is insufficient to provide an adequate case definition for isolated or pure small-fiber polyneuropathy at this time.

The case definition of distal symmetric polyneuropathy described herein is based upon a systematic analysis of peer-reviewed literature supplemented by consensus from an expert panel.

**Process.** Formation of expert panel. The Polyneuropathy Task Force included 14 physicians with representatives from AAN, AAEM, and AAPM&R. All of the task force members had extensive experience and expertise in the area of polyneuropathy. Additionally, three physicians with expertise in evidence-based methodology and practice parameter development participated in the project.

Finding the best evidence. The literature search included OVID MEDLINE (1970 to April 2004), OVID Excerpta Medica (EMBASE; 1980 to April 2004), and OVID Current Contents (2000 to April 2004). The search included articles on humans only and in all languages. The search terms selected were polynuropathy, distal symmetric polyneuropathy, distal axonopathy, fiber length dependent polyneuropathy, and distal axonal loss polyneuropathy. The search terms mononeuropathy, mononeuropathy multiplex, radiculopathy, polyradiculopathy,plexopathy, multifocal motor neuropathy, acute inflammatory demyelinating polyneuropathy, Guillain–Barré syndrome, and chronic inflammatory demyelinating polyneuropathy were included only when they appeared in studies whose primary focus was distal symmetric polyneuropathy.

Panel experts were asked to identify additional articles missed by the initial search strategy. Furthermore, the bibliographies of the selected articles were reviewed for potentially relevant articles. Three committee members reviewed the titles and abstracts of citations identified from this original search for those that were potentially relevant to defining distal symmetric polyneuropathy. Articles deemed potentially relevant by any panel member were also obtained.

Potentially relevant articles were subsequently reviewed in their entirety by three reviewers and were included in the initial analysis if they met the following criteria: 1) the study included patients with and without distal symmetric polyneuropathy. In order to assess the likelihood of spectrum bias, the characteristics of the comparison group without distal symmetric polyneuropathy were noted. Those studies in which the control group included subjects with neuropathic features that may mimic or overlap with distal symmetric polyneuropathy were rated as more relevant; (2) the patients had a potential diagnostic predictor (i.e., symptom, sign, or test result) measured; (3) the patients were determined to have a distal symmetric polyneuropathy by an explicitly defined independent reference standard (an acceptable standard was not prespecified by panel members); and (4) the presentation of the data in the article allowed calculation of sensitivities and specificities.

From each article the following methodologic characteristics were abstracted (see Appendix 1 for Glossary of Terms): the study design (case-control, cross-sectional, cohort survey), the number of patients, the target disorder including the spectrum of severity of the target disorder, the diagnostic predictor(s), the reference standard employed, whether the reference standard was measured without knowledge of the result of the diagnostic predictor, the proportion of patients with the target disorder who were positive for the diagnostic predictor (sensitivity), and the proportion of patients without the target disorder who were negative for the diagnostic predictor (specificity).

Each reviewer graded the risk of bias in each article by using the diagnostic test classification-of-evidence scheme in Appendix 2. In this scheme, articles attaining a grade of class IV are judged to have the highest risk of bias, and articles attaining class I are judged to have the lowest risk of bias. Only studies attaining a grade of class I, II, or III were further considered in the analysis. In the grading of studies, electrodiagnostic studies were considered an objective outcome. Disagreements among the reviewers regarding an article’s grade were resolved through discussion.

Consensus process. A formal consensus process (nominal group process)1,2 was used to develop the case definition. Since there is no single gold standard that defines distal symmetric polyneuropathy, the case definition must account for different levels of certainty for the presence or absence of the disorder. In line with this goal, participants were given several guidelines for developing a case definition. The case definition should 1) be restricted to distal symmetric polyneuropathy; 2) serve as a definition for the identification of cases in research studies; 3) acknowledge varying levels of diagnostic certainty by including a set of case definitions rank ordered by estimated ordinal likelihood of disease; 4) be simple, practical, and widely applicable by practicing clinicians; and 5) be based as much as possible on current best evidence.

Through several face-to-face meetings, electronic mail, and telephone conferences, committee members reviewed the results of the literature review and proposed case definitions of varying ordinal likelihood of distal symmetric polyneuropathy. Points of agreement and disagreement were identified, discussed, and resolved. The elements of the proposed case definitions were repeatedly tested against the conclusions from the literature review. What evolved
from this process was an ordered set of case definitions ranked by likelihood of disease. The essence of the case definition is contained in tables 1 and 2.

The Quality Standards Subcommittee of the AAN, the Practice Issues Review Panel of the AAEM, and the Practice Guidelines Committee of the AAPM&R (Appendices 4 through 6) reviewed and approved a draft of this article with the proposed case definition. The draft was next sent to members of the AAN, AAEM, and AAPM&R for further review and then to Neurology for peer review. Boards of the AAN, AAEM, and AAPM&R reviewed and approved the final version of the article. At each step of the review process, external reviewers' suggestions were explicit.

<table>
<thead>
<tr>
<th>Neurpathic symptoms</th>
<th>Decreased or absent ankle reflexes*</th>
<th>Decreased distal sensation</th>
<th>Distal muscle weakness or atrophy</th>
<th>NCSs†</th>
<th>Ordinal likelihood</th>
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Neuropathic symptoms: numbness, altered sensation, or pain in the feet. For clinical research studies enrollment should be limited to cases above the bold horizontal line (i.e., ++++).

* Ankle reflexes may be decreased in normal individuals older than 65 to 70 years.
† Abnormal NCSs is defined in the body of the article.
‡ This phenotype is common in "small-fiber" sensory polyneuropathy. Determination of intraepithelial nerve fiber density in skin biopsy may be useful to confirm the diagnosis (see text).
§ This phenotype in the presence of normal NCSs is not a distal symmetric polyneuropathy. This situation is given a negative (−) ordinal likelihood since the condition cannot be classified as a distal symmetric polyneuropathy. It is included here to emphasize the importance of including NCSs as part of the case definition for clinical research studies.

NCSs = nerve conduction studies.

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Neuropathic symptoms: numbness, altered sensation, or pain in the feet. For field epidemiology studies enrollment should be limited to cases above the bold horizontal line (i.e., ++).

* Ankle reflexes may be decreased in normal individuals older than 65 to 70 years.
† NCSs are not included as part of the case definitions for epidemiology studies: ND = not done.
‡ This phenotype is common in "small fiber" sensory polyneuropathy. Determination of intraepithelial nerve fiber density in skin biopsy may be useful to confirm the diagnosis (see text).

NCSs = nerve conduction studies.
itly considered. When appropriate, the expert panel made changes to the document.

**Evidence.** The search yielded 1,450 references. After reviewing titles and abstracts, 61 articles were retrieved and reviewed in their entirety. After comprehensive review of these articles, 12 articles attained a grade of class I, II, or III.3-14 These articles serve as the major evidence basis for the case definition and are tabulated in table 3.

**Study characteristics.** Diabetic peripheral neuropathy, which is the most prevalent and rigorously

### Table 3 Studies meeting inclusion criteria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Target disorder</th>
<th>Predictor</th>
<th>Reference standard</th>
<th>Cases</th>
<th>Controls</th>
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PN = polyneuropathy; Ch = cohort study; B = broad spectrum of patients included; abn = abnormal; sens = sensitivity; DTRs = deep tendon reflexes; NCS = nerve conduction studies; N = narrow spectrum of patients included; ND = not described; CC = case control; CIAP = chronic idiopathic axonal polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; CIAN = chronic idiopathic axonal neuropathy; HSMN2 = hereditary motor and sensory neuropathy; NIS = Neuropathy Impairment Score; LL = lower limb.
studied type of distal symmetric polyneuropathy, was the target disorder in most studies. There is a relative lack of high-quality evidence for other varieties of distal symmetric polyneuropathy. However, three of the studies (one-fourth of the total) focused on cryptogenic sensory peripheral neuropathy. Although limited in quantity, the quality of the articles was high and allowed the development of a case definition for distal symmetric polyneuropathy.

The diagnostic predictors studied varied. Several articles described the diagnostic accuracy of single symptoms including foot numbness, foot pain, and complaints of sensory alteration. Additionally, some articles measured the accuracy of more complex composite symptom checklists. The accuracy of single examination elements was also determined. These included absent ankle reflexes, decreased distal lower extremity strength, and decreased vibration or cold detection. Some articles also measured the accuracy of composite examinations that included two or more examination elements.

The studies used different reference standards to determine the presence of a symmetric distal peripheral neuropathy. These included nerve conduction studies (NCS), a clinician’s global impression, and composite clinical examination scores.

All studies collected data prospectively. Most were cohort surveys, but some used a case control design. Four studies described measuring the presence of a polyneuropathy using the reference standard in a fashion that was masked to measurement of the diagnostic predictor. Two studies attained a grade of class I, five attained a grade of class II, and five attained a grade of class III. Diagnostic accuracy.

Diagnostic accuracy. The diagnostic accuracy of the predictors was determined by calculating their sensitivities and specificities. One way of displaying this data is to plot sensitivities against specificities in a receiver-operator-characteristics (ROC) curve (figure).

Predictors encompassing a single specific symptom such as foot numbness have low sensitivity but high specificity for the presence of polyneuropathy. Predictors incorporating the presence of any one of a number of neuropathic symptoms such as the presence of foot numbness or pain attain a greater sensitivity but have lower specificity.

Particular single examination findings such as absent ankle tendon reflexes have moderate sensitivity and high specificity for the presence of polyneuropathy. When individual examination findings are combined into a composite examination score, higher diagnostic accuracy results. The examination scores with the highest sensitivity and specificity include the screening examination used in the San Luis Valley Diabetes Study, the Neuropathy Disability Score (NDS), the Neuropathy Impairment Score in the Lower Limbs (NIS-LL), the Michigan Neuropathy Screening Instrument (MNSI), the Michigan Diabetic Neuropathy Score (MDNS), and two other well-described clinical examination scores. Notably, simple composite examination scores are as accurate as more complex examinations.

The sensitivities and specificities of quantitative sensory testing (QST) varied widely among studies. These psychophysical tests have greater inherent variability, making their results more difficult to standardize and reproduce. Reproducibility of QST varied from poor to excellent. For these reasons, QST was not included as part of the final case definition.

The sensitivities and specificities of quantitative autonomic testing are relatively high for documenting the presence or absence of autonomic dysfunction. However, these tests are not routinely performed in all medical centers. Since a usable case definition must be based upon tests that are simple, practical, and easily available, quantitative auto-
nomic testing is not included as part of the final case definition.

Evidence based conclusions for the case definition. Using the Definitions for Strength of Recommendation (Appendix 3), the following conclusions and recommendations can be supported from formal analysis and classification of the literature:

1. Symptoms alone have relatively poor diagnostic accuracy in predicting the presence of polyneuropathy. Multiple neuropathic symptoms are more accurate than single symptoms and should be weighted more heavily. (Level B)

2. Signs are better predictors of polyneuropathy than symptoms and should be weighted more heavily. (Level B)

3. A single abnormality upon examination is less sensitive than multiple abnormalities in predicting the presence of polyneuropathy; therefore, an examination for polyneuropathy should look for a combination of signs. (Level B)

4. Relatively simple examinations are as accurate in diagnosing polyneuropathy as complex scoring systems; therefore, the case definition can use simple examinations without compromising accuracy. (Level B)

5. There is too much inconsistency among the studies describing the accuracy of quantitative sensory testing (QST) to incorporate QST in the case definition. (Level U)

Consensus-based principles. The concept of distal symmetric polyneuropathy requires a clear definition of distal and symmetric in the context of polyneuropathy. Distal refers to those parts most distant from the center of the body. The polyneuropathy must begin in the feet. Symmetric indicates that the symptoms and signs are the same on both sides of the body. Persistent or striking asymmetry of symptoms or signs is inconsistent with the case definition. The case definition must encompass a description of symptoms and signs with an easily recognizable phenotype.

Symptoms. Symptoms may be primarily sensory, primarily motor, or both.4,7,10,12 Symptoms begin distally in the feet. Sensory symptoms are either persistent or intermittent alterations of sensation initially involving the toes or feet. Occasionally, an isolated digital sensory neuropathy affecting one or more toes may be difficult to distinguish from an early polyneuropathy. The differentiation may be discernible only with time. Frequently described sensory symptoms include numbness, burning, prickling paresthesias, dyesthesias, and allodynia. When motor symptoms are the first manifestation of polyneuropathy, the patient may note weakness in the distal legs. Distal symmetric polyneuropathy may be asymptomatic, especially in its early stage. An asymptomatic presentation is more likely when positive sensory symptoms such as dyesthesias or par-
The protocol for performing NCSs was determined by the structured consensus process described previously. There are many previous recommendations regarding NCS criteria for the diagnosis of polyneuropathy, but no formal consensus exists. The recommendations that follow are based on electrophysiologic principles that combine both the highest sensitivity and specificity as well as the highest efficiency for the diagnosis of distal symmetric polyneuropathy.

Recommended protocol for nerve conduction studies. The following set of sensory and motor NCSs should be performed if patients are entering a clinical research trial in which NCSs will be tracked longitudinally. This protocol includes unilateral studies of sural sensory, ulnar sensory, and median sensory nerves, and peroneal, tibial, median, and ulnar motor nerves with F waves. Other NCSs may be necessary as determined by clinical judgment. The minimum case definition criterion for electrodiagnostic confirmation of distal symmetric polyneuropathy is an abnormality (≥99th or ≤1st percentile) of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve. Electrodiagnostic studies should follow rigorous guidelines such as those set by the AAEM. Variables such as skin temperature, age, height, sex, and weight should be measured and accounted for when reporting a NCS as normal or abnormal.

A simplified NCS protocol may be used for the purpose of defining the presence of distal symmetric polyneuropathy. However, the abbreviated protocol is not sufficient to determine the subtype or severity of the polyneuropathy. For these purposes as well as for clinical trials in which electrodiagnostic measures will be tracked serially, the more comprehensive set of NCSs is recommended.

The simplified NCS protocol is as follows:

1. Sural sensory and peroneal motor NCSs are performed in one lower extremity. Taken together, these NCSs are the most sensitive for detecting a distal symmetric polyneuropathy. If both studies are normal, there is no evidence of typical distal symmetric polyneuropathy. In such a situation, no further NCSs are necessary.

2. If sural sensory or peroneal motor NCSs are abnormal, the performance of additional NCSs is recommended. This should include NCS of at least the ulnar sensory, median sensory, and ulnar motor nerves in one upper extremity. A contralateral sural sensory and one tibial motor NCS may also be performed according to the discretion of the examiner. Caution is warranted when interpreting median and ulnar studies since there is a possibility of abnormality due to compression of these nerves at the wrist or ulnar neuropathy at the elbow.

3. If a response is absent for any of the nerves studied (sensory or motor), a NCS of the contralateral nerve should be performed.

4. If a peroneal motor response is absent, an ipsilateral tibial motor NCS should be performed.

Minimal criteria for the electrodiagnostic confirmation of distal symmetric polyneuropathy are the same as listed previously.

Combining evidence and consensus: case definition of distal symmetric polyneuropathy. The best approach to defining distal symmetric polyneuropathy is an ordered set of definitions ranked by likelihood of disease. The likelihood of distal symmetric polyneuropathy was rated on an ordinal scale from highest likelihood (+++++) to lowest likelihood (+). Since diagnostic certainty for polyneuropathy follows a continuum of probability, this manner of definition is the most sensible. In each set of case definitions, a hierarchy of parameter combinations was established to provide the most relevant combinations for the diagnosis of distal symmetric polyneuropathy. Combinations of parameters that were considered clinically unusual and not appropriate for research studies were not included. For these reasons not every possible combination of parameters is presented.

The essential characteristics of the case definition are contained in tables 1 and 2. Important aspects of the case definition that warrant emphasis are the following:

1. The combination of neuropathic symptoms, signs, and abnormal electrodiagnostic studies provides the most accurate diagnosis of distal symmetric polyneuropathy (see table 1).

2. Electrodiagnostic studies are recommended as part of the clinical research case definition (see table 1) since they are objective and validated tests of peripheral nerve function. Abnormal electrodiagnostic studies increase the likelihood of the presence of distal symmetric polyneuropathy and provide a higher level of specificity to the case definition. Electrodiagnostic studies should not be used alone to make the diagnosis since their sensitivity and specificity are not perfect.

3. Electrodiagnostic studies are not required for field or epidemiologic studies (see table 2), but the likelihood of diagnosis must be downgraded accordingly.

4. For research studies enrollment should be limited to cases that are most likely to have distal symmetric polyneuropathy (i.e., those that achieve the highest specificity for the diagnosis). For clinical research studies, this consists of cases with an ordinal likelihood of +++++ (see table 1). For epidemiologic studies, this consists of cases with an ordinal likelihood of ++ (see table 2).

Limitations and future research. This case definition is heavily weighted toward distal symmetric...
polyneuropathy with predominant involvement of large fibers, and it is not intended to emphasize the subset of distal symmetric polyneuropathy termed small-fiber polyneuropathy. Since this type of polyneuropathy may present with only pain and numbness in the feet accompanied by few signs and normal NCSSs, a formal case definition restricted to small-fiber polyneuropathy is difficult to develop at this time. This is especially true since there is no widely available method to confirm the diagnosis. Determination of intraepithelial nerve fiber density in punch biopsies of skin is a promising technique.23-26 Inclusion of small-fiber polyneuropathy in a formal case definition must await further studies.

Another limitation of the case definition is that most of the available best evidence is restricted to diabetic peripheral neuropathy. The reason that diabetic neuropathy figures so prominently in the analysis is that it is the most common and rigorously studied variety of distal symmetric polyneuropathy. The other studies that were included in the analysis focused on cryptogenic sensory peripheral neuropathy. Thus, some uncertainty exists with respect to the generalization of the case definition to distal symmetric polyneuropathy associated with other etiologies.

The process described above represents an attempt to develop formal criteria for a case definition of distal symmetric polyneuropathy. The principal purpose of the case definition is the identification of cases for clinical research and epidemiologic studies. The criteria were formulated using a nominal group process in addition to the best available scientific evidence. Validation and refinement of these criteria in future studies is encouraged. Specifically, additional studies are needed before conclusions can be made regarding the role of QST and skin biopsy in the diagnosis of distal symmetric polyneuropathy. As quantitative autonomic testing becomes more routinely available, these tests could easily be incorporated into the case definition. Future studies should also compare the criteria delineated in this article with evolving new criteria. A major aim of the AAN, AAEM, and AAPM&R is that the case definition will be modified and refined as new evidence accumulates.

Disclaimer. The diagnosis of polyneuropathy is complex. The case definition is not intended to replace the clinical judgment of experienced physicians in the diagnosis of polyneuropathy since none of the criteria have perfect diagnostic accuracy.

This statement is provided as an educational service of the AAN, the AAEM, and the AAPM&R. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN, AAEM, and AAPM&R recognize that specific care decisions are the prerogative of the patient and physician caring for the patient, based on all of the circumstances involved.

Appendix 1: Glossary of terms

Predictor. (Diagnostic predictor.) A symptom, examination finding, or test result potentially predicting the presence of a distal symmetric polyneuropathy.

Target disorder. The condition or disease being sought. In the current context, the target disorder was a specific type of distal symmetric polyneuropathy (e.g., diabetic peripheral neuropathy).

Reference standard. (The gold standard.) The test or procedure (or series of tests or procedures) performed to determine the actual presence or absence of a distal symmetric polyneuropathy.

Nominal group process. A formalized, iterative method for achieving consensus from a group of experts that attempts to maximize group reasoning while preserving individual input.

ROC. (Receiver-operator-characteristic) curve. A standardized graph of sensitivity (true positive rate) by specificity (true negative rate) designed to depict diagnostic accuracy and the trade-off between increasing sensitivity and decreasing specificity.

Appendix 2: Definitions for strength of evidence

Diagnostic evidence. Class I. Evidence provided by a prospective study of a broad spectrum of persons with the suspected condition. The study measures the diagnostic accuracy of the test using an acceptable independent reference standard for case definition. The test, if not objective, is applied in an evaluation that is masked to the persons’ clinical presentations and the reference standard is applied in an evaluation that is masked to the test result.

Class II. Evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or by a retrospective study of a broad spectrum of persons with the condition compared with a broad spectrum of control subjects. The study measures the diagnostic accuracy of the test using an acceptable independent reference standard for case definition. The test is applied in an evaluation that is masked to the reference standard.

Class III. Evidence provided by a retrospective study when either the persons with the condition or the control subjects are of a narrow spectrum. The study measures the diagnostic accuracy of the test using an acceptable independent reference standard for case definition.

Class IV. Evidence provided by expert opinion or case series without control subjects. Any study not measuring the diagnostic accuracy of the test using an acceptable independent reference standard for case definition.

Appendix 3: Definitions for strength of recommendations

Level A. Established as effective, ineffective, or harmful for the given condition in the specified population. Usually a Level A recommendation requires that the pooled result from two or more distinct Class I studies demonstrates a consistent, significant, and important effect.

Level B. Probably effective, ineffective, or harmful for the given condition in the specified population. Usually a Level B recommendation requires that a single Class I study demonstrates a significant and important effect or the pooled result from two or more distinct Class II studies demonstrates a consistent, significant, and important effect.

Level C. Possibly effective, ineffective, or harmful for the given condition in the specified population. Usually a Level C recommendation requires that a single Class II study demonstrates a significant and important effect or the pooled result of two or more distinct Class III studies demonstrates a consistent, significant, and important effect.

Level U. Data inadequate or conflicting. Given current knowledge the intervention is unproven and an evidence-based recommendation cannot be made.

Appendix 4

AAN Quality Standards Subcommittee members: Gary Franklin, MD, MPH (co-chair); Gary Gronseth, MD (co-chair); Milton Alter, MD, PhD; Charles Argoff, MD; Stephen Ashwal, MD; Christopher Bever, MD; Jody Carey-Bloom, MD; Richard Dubinsky, MD; John England, MD; Jacqueline French, MD; Gary Friday, MD; Michael Glantz, MD; Deborah Hirtz, MD; Donald Iverson, MD; Robert G. Miller, MD; David Thurman, MD; Samuel Wiebe, MD; William Weiner, MD; and Catherine Zahn, MD.

Appendix 5

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**Note.** Strength of evidence is indicated for references used to formulate case definition.

**References**

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