Practice Advisory: Thymectomy for Myasthenia Gravis (Practice Parameter Update)

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on January 26, 2019; by the Quality Committee on November 25, 2019; and by the AAN Institute Board of Directors on January 22, 2020.

AUTHOR CONTRIBUTIONS

G. Gronseth: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

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P. Narayanaswami: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

STUDY FUNDING

This practice advisory was developed with financial support from the American Academy of Neurology (AAN). Authors who serve or served as AAN subcommittee members (P.N.) or as methodologists (G.G.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURE

G. Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Brain & Life*; he received compensation from the American Academy of Neurology (AAN) for work as its chief evidence-based medicine methodologist.

R. Barohn served as a consultant for Momenta Pharmaceuticals and Nufactor and receives research support from the government entities the Office of Orphan Products Development of the US Food and Drug Administration, the NIH, and the Patient-Centered Outcomes Research Institute (PCORI), and from the industry entities Orphazyme, PTC Therapeutics, Ra Pharma, and Sanofi Genzyme.

P. Narayanaswami serves as an associate editor for *Muscle & Nerve* and on the editorial boards of *Annals of Neurology* and *Journal of Clinical Neuromuscular Disease*; has received research support from the NIH, Agency for Healthcare Research and Quality, and PCORI; has received

funding for travel to AAN subcommittee meetings; and has received fees for consultation from Alexion, Argenx, and Momenta Pharmaceuticals.

ABSTRACT

Objective: To review updated evidence regarding the effectiveness of thymectomy for treating patients with myasthenia gravis (MG).

Methods: The practice advisory panel performed a systematic review and developed practice recommendations using methods developed by the American Academy of Neurology.

Results: One Class I study of patients younger than 65 years with nonthymomatous acetylcholine receptor antibody−positive (AChR ab+) generalized MG demonstrated better clinical outcomes in patients treated with oral prednisone and undergoing thymectomy compared with patients treated with prednisone alone, including an increased probability of attaining minimal manifestation status (no symptoms or functional limitations).

Conclusion: For patients with nonthymomatous AChR ab+ generalized MG, treatment with thymectomy plus prednisone is probably more effective than treatment with prednisone alone for increasing the chance of attaining minimal manifestation status (risk difference at 36 months, 20%; 95% confidence interval, 1.6%−37%; moderate confidence in the evidence).

Main recommendation: Clinicians should discuss thymectomy treatment with patients with AChR ab+ generalized MG (Level B). Clinicians should counsel patients with AChR ab+ generalized MG considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (Level B).

INTRODUCTION

Reports of remission following thymectomy in patients with myasthenia gravis (MG) suggested a therapeutic benefit for patients with MG.[1] However, a practice guideline regarding the efficacy of thymectomy for MG treatment published by the American Academy Neurology (AAN) in 2000 concluded that it was impossible to determine "whether the observed association between thymectomy and improved MG outcome was a result of a thymectomy benefit or was merely a result of the multiple differences in baseline characteristics between the surgical and nonsurgical groups."[2] A randomized controlled trial was recommended. The results of a randomized trial of thymectomy in MG were published in 2016.[3]

The purpose of this article is to update the 2000 AAN guideline by reviewing the evidence provided by high-quality studies relevant to the question: For patients with generalized MG, is thymectomy compared with medical therapy alone effective in improving patient-relevant outcomes? The primary audience for this guideline update is neurologists caring for patients with MG.

This practice advisory used the methods described in the 2011 edition (as amended) of the AAN's guideline development process manual.[4] Appendices e-1 through e-10 provide the methods used to develop this article, AAN guideline subcommittee information, study inclusion criteria, search strategy, and the evidence synthesis table.

ANALYSIS OF EVIDENCE

The guideline panel performed a literature search that identified 1 multicenter Class I study meeting inclusion criteria[3] in which 126 participants had acetylcholine receptor antibody−positive (AChR ab+) generalized MG that qualified as Myasthenia Gravis Foundation of America (MGFA) clinical classification II−IV,[5] in which Class I is ocular MG, Class V is MG crisis, and Classes II−IV represent mild to severe generalized MG. Participants were randomly allocated to receive thymectomy plus medical therapy (prednisone, n = 66) or medical therapy alone (prednisone, n = 60). The study design permitted participants to receive treatment with cholinesterase inhibitors with or without corticosteroids. Participants were excluded if they had thymoma or previous thymectomy, were using other immunosuppressive agents, were pregnant or lactating, were unwilling to avoid pregnancy, had contraindications to glucocorticoid use, or had substantial medical illness. Sixty of 66 participants in the prednisone plus thymectomy group and 51 of 60 participants in the prednisone group completed the required 3-year period of follow-up evaluations (dropouts 15 of 126 [12%]). Nine participants originally randomized to thymectomy did not undergo thymectomy, and 8 patients randomized to medical therapy alone underwent thymectomy outside of the protocol (crossovers). Outcomes were analyzed according to the intention-to-treat paradigm (i.e., patient outcomes were analyzed within the group to which patients were originally randomized). Although participants and treating physicians were aware of treatment assignment, primary outcome assessments were made by investigators masked to treatment assignment.

Patient characteristics

All participants enrolled had AChR ab+ generalized MG of less than 5 years in duration. The median age of participants was 32.5 years (range 18−64 years). Characteristics of participants in

both treatment groups were substantially equivalent relative to MG duration and severity at the time of enrollment.

Interventions

Participants in both treatment groups received prednisone in accordance with a standardized protocol. Prednisone was started at 10 mg on alternate days and increased by 10-mg increments to 100 mg on alternate days or to 1.5 mg/kg body weight, whichever was lower. The prednisone dose was maintained until participants attained minimal manifestation status (MMS, defined as no symptoms or functional limitations from MG[5]) and the quantitative myasthenia gravis score (QMG, a composite score ranging 0−39, with higher scores indicating more severe MG[6]) had dropped one point below baseline. Prednisone was then tapered by 10 mg every 2 weeks until a dose of 40 mg on alternate days was reached and then further tapered by 5 mg every month as long as MMS was maintained. Thymectomy was performed using an extended transsternal approach.[7] Concomitant therapies with plasma exchange, IV immunoglobulin, azathioprine, or other immunosuppressants were allowed if needed.

Outcomes

Relative to the coprimary outcomes over the 3 years of follow-up, the study demonstrated a reduction favoring thymectomy in the time-weighted average QMG scores[6] (QMG mean difference, 2.85; 99.5% confidence interval [CI], 0.47−5.22) and a 41% reduction in time-weighted average alternate-day prednisone dose (22 mg less in the prednisone plus thymectomy group; 95% CI, 12−32 mg).

The minimal clinically important change in QMG score is unknown. On the basis of a previous study, a reduction of 2.3 points in the QMG score was considered to correlate with clinical improvement.[8] Although the mean difference between thymectomy and thymectomy plus prednisone groups met this criterion for clinical improvement (2.85 points favoring thymectomy), the lower confidence limit of 0.47 is not a meaningful clinical improvement. Hence, the CI includes clinically important and unimportant effects. The average reduction of 11 mg/d in prednisone dose has the potential to reduce long-term adverse events relating to chronic steroid use, depending on the absolute daily dose.

To improve the clinical interpretability of the results, the guideline panel extracted the proportion of participants attaining MMS, that is, participants having no symptoms or functional limitations from MG[5] (figure e-1). Three years after thymectomy, 47% of participants randomized to medical therapy alone had attained MMS compared with 67% of participants randomized to thymectomy (risk difference, 20%; 95% CI, 1.6%−37%). In other words, for every 5 participants undergoing thymectomy (compared with participants receiving prednisone alone), 1 additional participant had no symptoms or functional limitations from MG at 3 years.

Safety and tolerability

There was 1 death in the prednisone group. The 1 reported complication secondary to thymectomy was paralysis of a hemidiaphragm. Overall, treatment-related adverse events were more common in the group receiving medical therapy alone (n = 93) compared with the group receiving thymectomy (n = 48).

A recently published Class III extension[9] observed 68 (61%) participants from the original Class I trial[3] for 2 years. Fifty participants completed the 60-month follow-up (prednisone, 24; prednisone plus thymectomy, 26). Outcomes were assessed by masked raters. At 60 months, lower time-weighted average QMG scores were noted for the participants receiving thymectomy plus prednisone (mean difference average time-weighted QMG score 3.87; 95% CI, 0.71−7.04) and a 24% reduction in average time-weighted prednisone dose (24 mg lower in the prednisone plus thymectomy group; 95% CI, 12−36 mg).

Conclusion

For patients with nonthymomaous AChR ab+ generalized MG, treatment with thymectomy plus prednisone is probably more effective than treatment with prednisone alone for increasing the chance of attaining MMS (risk difference at 36 months, 20%; 95% CI, 1.6%−37%) and improving other MG-related outcomes, including decreased use of azathioprine or IV immunoglobulin rescue therapy and reduced number of hospitalizations for MG exacerbations (1 Class I study, moderate confidence in the evidence; see figure e-2, table 1).

PRACTICE RECOMMENDATIONS

Recommendation 1

Recommendation 1 rationale

Thymectomy leads to meaningful benefits for patients with nonthymomatous AChR ab+ generalized MG. In addition, transsternal thymectomy appears to be safe.[5]

Because of the moderate benefits of thymectomy and the need for a major surgical procedure with its attendant discomforts and costs, there is likely to be considerable variability in patient preferences relative to undergoing thymectomy. However, the panel anticipates that most patients would want to be aware of the availability of thymectomy as a treatment option.

Recommendation 1 statement

Clinicians should discuss thymectomy with patients who have nonthymomatous AChR ab+ generalized MG and are 18−65 years of age. The discussion should clearly indicate the anticipated benefits and risks of the procedures and uncertainties surrounding the magnitude of these benefits and risks (Level B).

Recommendation 2

Recommendation 2 rationale

There are several surgical methods of thymectomy, with the goal of removing as much thymic tissue as possible while preserving phrenic, left vagus, and recurrent laryngeal nerve function. The classical method of thymectomy is an external transsternal thymectomy, facilitating complete removal of thymic tissue and fat. A transcervical approach uses smaller incisions but is rarely used alone because of inadequate visualization of the thymus; it may be combined with the transsternal approach. Minimally invasive techniques include video-assisted thoracoscopic thymectomy (VATS) or robotic-assisted thoracoscopic surgery, both with potentially higher risk for leaving residual thymic tissue.[10] It is uncertain whether the results of a thymectomy study using an extended transsternal approach can be generalized to minimally invasive thymectomy techniques that do not involve a median sternotomy. A randomized trial with unblinded outcome

assessment comparing VATS with transsternal thymectomy demonstrated reduced blood loss, surgical times, intensive care unit stay, and hospitalization length for patients undergoing VATS but was underpowered to detect significant differences in MG clinical outcomes.[11] It seems likely, if otherwise equally efficacious in removing all thymic tissue, that patients with MG would prefer minimally invasive thymectomy techniques without a median sternotomy.

Recommendation 2 statement

Clinicians should counsel patients with nonthymomatous AChR ab+ generalized MG considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (Level B).

SUGGESTIONS FOR FUTURE RESEARCH

It seems unlikely that future adequately powered randomized controlled trials with blinded outcome assessment of thymectomy will be completed given the logistical challenges and costs associated with the recently completed trial. Much can be learned, however, from prospective cohort studies designed to identify characteristics that predict which patients with MG benefit from thymectomy. Such studies should also include pediatric and older patients with muscle-specific tyrosine kinase−positive, seronegative, and ocular types of MG. In addition, there is a need for well-designed observational studies comparing outcomes of minimally invasive thymectomy techniques with transsternal approaches. Finally, it will be informative to have

registries of patients undergoing these procedures with long-term outcome assessments using both clinician- and patient-reported outcome measures.

Figure e-1. Proportion of patients attaining minimal manifestation status (MMS) throughout the trial, by treatment group (error bars ± standard error)

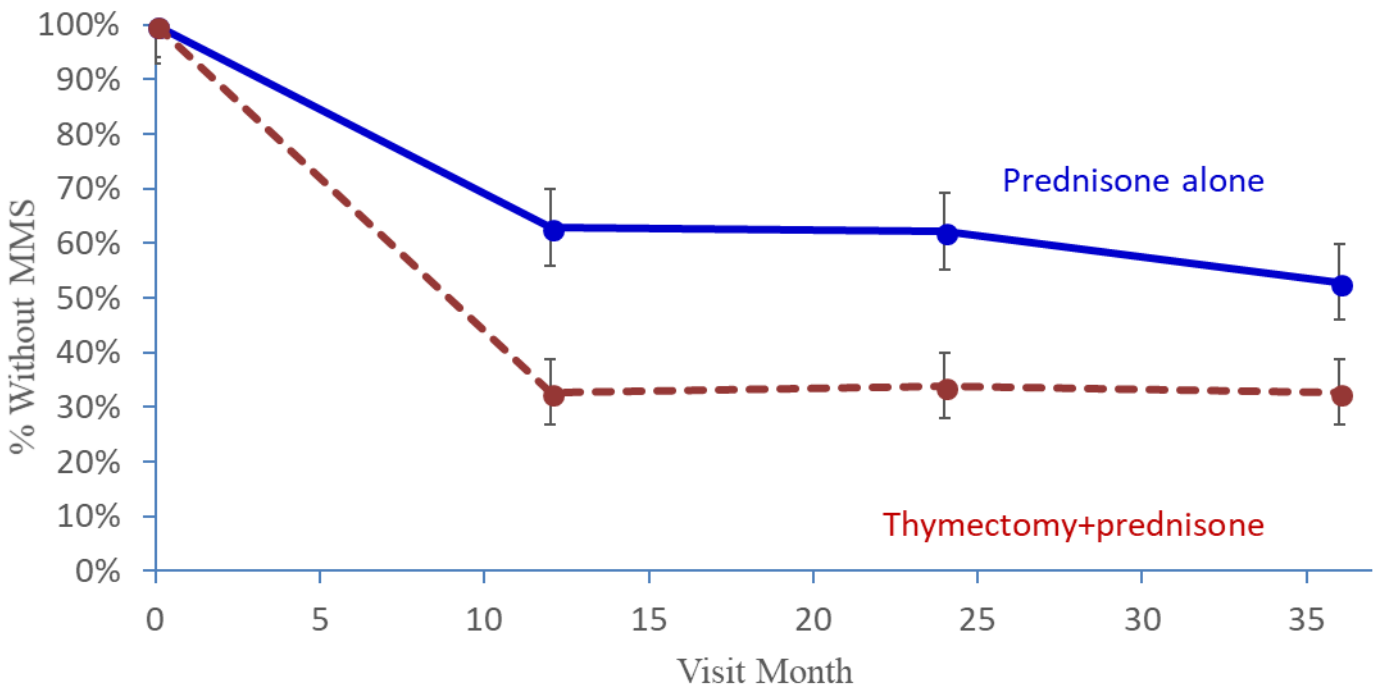
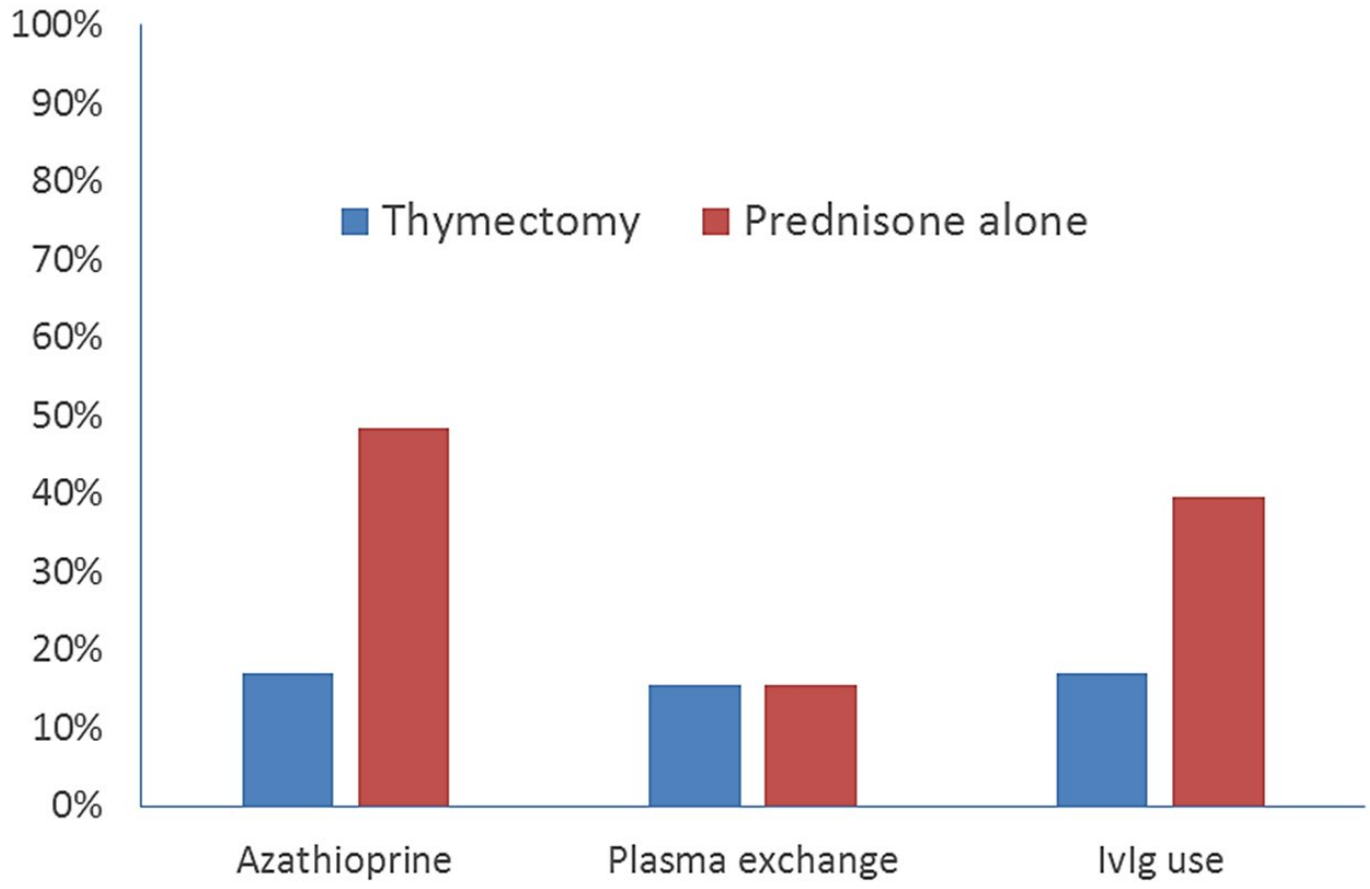


Figure e-2. The proportion of patients with MG receiving azathioprine, plasma exchange, or IVIg during the trial, by treatment group[a]



[a] Patients could have received more than one of these treatments

IVIg = IV immunoglobulin.

Table 1: Selected secondary outcomes in the MGTX trial

Secondary outcome	Prednisone alone	Prednisone plus thymectomy	Mean difference (95% CI)
	Mean ± SD or N, (%)		
MG-ADL, 12 mo	3.33 ± 3.40	1.92 ± 2.73	1.42 (0.28 to 2.55)
MG-ADL, 24 mo	3.11 ± 2.93	2.02 ± 2.78	1.1 (0.03 to 2.17)
MG-ADL, 36 mo	2.69 ± 2.80	2.14 ± 2.92	0.55 (-0.53 to 1.63)
Azathioprine use	28/58 (48%)	11/65 (17%)	31.4% (15.6% to 47%)
Plasma exchange use	9/58 (16%)	10/65 (15%)	0.1% (-12.7% to 12.9%)
IV immunoglobulin use	23/58 (40%)	11/65 (17%)	22.7% (7% to 38%)
Hospitalization for MG exacerbation, 0−36 mo	22/60 (37%)	6/66 (9%)	19.2% (5.9% to 32.6%)

Abbreviation: MG-ADL = Myasthenia Gravis-specific Activities of Daily Living scale.

DISCLAIMER

Practice guidelines, practice advisories, comprehensive systematic reviews, focused systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines (CPGs) and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships for this

practice advisory were conducted in compliance with the 2011 AAN process manual section titled, "Revealing Conflicts of Interest."[4]

Appendix e-1. Description of the analytic process

This practice advisory used the methods described in the 2011 version of the AAN's guideline development process manual, as amended to include the following changes: introduction of the practice advisory document type, an update to the classification of evidence scheme for therapeutic studies, introduction of the topic nomination form for guidelines and other evidence-based documents, and the change in steps for the guideline external review process.[4]

After reviewing conflicts of interest, the AAN's Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) selected an author panel to develop this update (appendices e-2 and e-3). The process for managing conflicts of interest is described in appendix e-4. Two panel members (G.G., P.N.) performed a literature search and independently selected potentially relevant articles (appendix e-5).

Studies were independently rated for their risk of bias using the AAN 4-tiered classification of evidence scheme for therapeutic studies (appendix e-6). After anchoring to the risk of bias rating, the panel rated the overall confidence in evidence using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) process (appendices e-7 and e-8). Subsequently, the panel developed the wording of actionable recommendations and the strength of recommendations after considering the strength of evidence and deductive inferences, risks and benefits, cost, feasibility, and patient preferences (appendices e-9 and e-10).

Before journal submission for peer review, the panel sent a draft of the guideline to the AAN member reviewer network for comment. When appropriate, the manuscript was modified to address the comments.

Appendix e-2. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-3. AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it was superseded by the Guideline Subcommittee in May 2019. At the time this guideline was approved to advance beyond subcommittee development, the GDDI subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-4. Conflicts-of-interest management

Potential panel members completed a form detailing potential conflicts of interest. This form was reviewed by members of the AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI).

The subcommittee considered one panel member (R.B.) potentially conflicted (see disclosures) and disallowed that member's participation in the systematic review process. That member was permitted to participate in the recommendation development process and provided input in drafting the document. Final decisions regarding the wording of the document's conclusions and recommendations were made by the nonconflicted authors and the GDDI, the AAN Quality Committee, and the AAN Institute Board of Directors.

Appendix e-5. Complete search strategies and flow of article selection process

On October 7, 2016, MEDLINE and the Cochrane Databases of Systematic Reviews and Controlled Clinical trials were searched for relevant articles published after February 1998 (the last date of the search used for the previous AAN guideline). The search was updated on January 16, 2019, and again on March 24, 2019.

Relevance was determined according to the following prespecified inclusion criteria:

- The study enrolled patients of any age with autoimmune myasthenia gravis (MG).
- Patients were randomly or pseudo-randomly (e.g., every other patient) allocated to thymectomy plus medical therapy or medical therapy alone.
- Patients were observed for a minimum of 6 months.
- Patient relevant outcomes were compared between thymectomy and nonthymectomy groups.
- Outcome assessments were masked (blinded).
- The panel accepted any patient relevant outcomes, including remission rates (i.e., minimal manifestation status), quantitative MG outcome scores, quality of life determinants, Medical Research Council scale scores, or steroid dosages.

The specific search strategies used are as follows:

MEDLINE

Therapy/Narrow[filter] AND (("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields]) AND ("thymectomy"[MeSH Terms] OR "thymectomy"[All Fields]))

Cochrane search (CENTRAL and DARE)

Myasthenia gravis and Thymectomy

A secondary search of the references of selected and reviewed articles was performed to identify studies missed by the panel's search strategy:

Review articles reviewed: Cea G, Benatar M, Verdugo RJ, Salinas RA. Thymectomy for non-thymomatous myasthenia gravis. Cochrane Database Syst Rev 2013;(10):CD008111.

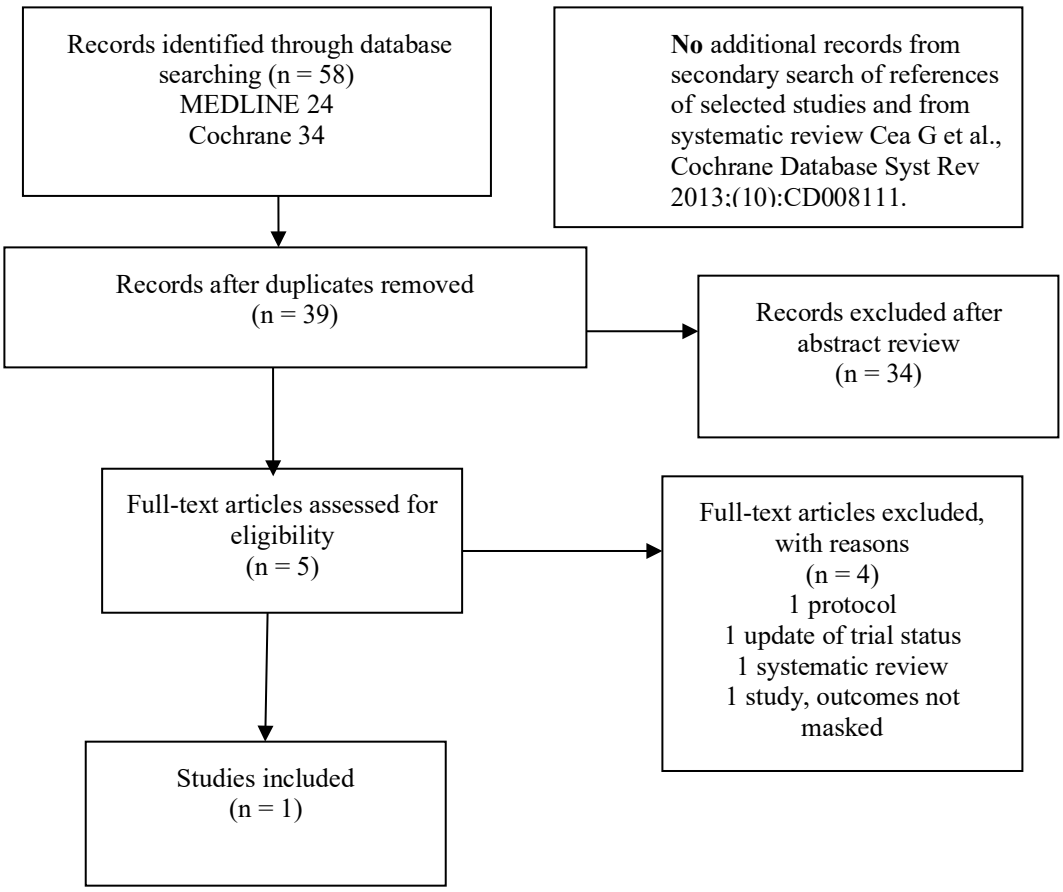
Selected articles reviewed:

1. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375:511−522.
2. Lorenzana P, Casallas A, Vega D, Aguirre C, et al. Misatenia gravis IIa. Timectomia vs tratamiento medico. Acta Med Colomb 1999;24:151−158.

The titles and abstracts of the identified citations were reviewed for relevance to the clinical question. The full text of potentially relevant articles was retrieved and included in the analysis if the studies met inclusion criteria. Two authors (G.G. and P.N.) independently reviewed articles and classified studies for their risk of bias. Discrepancies were resolved through discussion. One study (Wolfe et al.) was included. Lorenzana et al. was excluded because it did not meet the inclusion criterion of masked outcomes.

The following diagram documents the flow of the article selection process:

Evidence review flow diagram



Appendix e-6. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-7. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
    - High confidence: highly likely or highly probable
    - Moderate confidence: likely or probable
    - Low confidence: possibly
    - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
    - High: requires 2 or more Class I studies
    - Moderate: requires 1 Class I study or 2 or more Class II studies
    - Low: requires 1 Class II study or 2 or more Class III studies
    - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
    - Consistency
    - Precision
    - Directness
    - Publication bias
    - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
    - Magnitude of effect
    - Dose response relationship
    - Direction of bias

Appendix e-8. Summary of factors used to determine the overall confidence in the evidence, with completed modified GRADE table

Because of the high risk of bias in observational studies of the efficacy of thymectomy, the conclusions of this update are based solely on this single randomized controlled trial.

On the basis of a single Class I study, the panel's confidence in the evidence is anchored at moderate.

Biological plausibility

The biological plausibility of a benefit of thymectomy in patients with generalized myasthenia gravis (MG) is judged to be good.

Residual bias

Although this study is rated Class I because of internal validity, some residual sources of bias remain. Patients were aware of treatment assignment, and thus some improvement might be expected from a placebo effect. However, given the relatively short duration of the placebo effect,[12] it seems unlikely that the effect would explain a benefit of thymectomy persisting for 3 years (appendix e-8). Treating providers were also aware of treatment assignment, raising the possibility of performance bias—an apparent treatment benefit of thymectomy might result solely from more aggressive collateral MG therapies for patients undergoing thymectomy. However, an analysis of collateral MG treatments—plasma exchange, immunoglobulin, steroid-sparing agents—indicates that patients undergoing thymectomy were as likely or less likely to receive such treatments than patients randomized to medial therapy alone (appendix e-9).

Directness

The panel judged that the patients enrolled, interventions employed, and outcomes measured were sufficiently generalizable as not to substantially influence the effect sizes reported.

Precision

An absolute (risk difference) effect of greater than 10% was considered clearly important and an effect of less than 1% clearly unimportant. The width of the 95% confidence intervals for the difference in patients attaining minimal manifestation status ranged from 1.6% to 37%. It is possible, therefore, that from random error alone the magnitude of benefit of thymectomy is actually larger (number needed to treat [NNT] = 3) or smaller (marginal at NNT > 50).

Other factors

No other factors influenced the panel's confidence in the evidence.

The final confidence in evidence is moderate.

	Evidence Synthesis	Model: Random Effects		Scale: Linear			Effect values less than 0 favor Comparator			
	Population **I**ntervention **C**omparator **O**utcome Important effect size Unimportant effect size	patients with generalized myasthenia gravis, thymectomy plus prednisone prednisone alone increasing the chance of attaining minimal manifestation status. 10% 1%					Setup Insert Row Sort		Forest Plot Funnel Plot Bubble Plot	
1	Biological Plausibility (prior)	Yes		1	0.00001	10000				
Include	Study (Author Year)	Class	Indirectness	Effect	LCL	UCL	Sig. Dose Response	Bias favors	Consist.	Pub. Bias (p)
1	Wolfe *et al* 2016	I	Minor	20.0%	1.6%	37.0%				
	Summary (Rand. Effects)	1; I	Minor	20.0%	1.6%	37.0%	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	For patients with generalized myasthenia gravis, thymectomy plus prednisone is probably more effective than prednisone alone in increasing the chance of attaining minimal manifestation status.								

Appendix e-9. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- ≥ 80% agreement on dichotomous judgments
- ≥80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
    - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
        - Level A: High confidence
        - Level B: Moderate confidence
        - Level C: Low confidence
        - Level U: Very low confidence
    - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
        - Level A: 100%
        - Level B: ≥ 80% to < 100%

        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
        - Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
    - Magnitude relative to harm rated on 4-point ordinal scale
        - Large benefit relative to harm: benefit judged large, harm judged none
        - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none

        - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
        - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
    - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
        - Level A: large benefit relative to harm
        - Level B: moderate benefit relative to harm
        - Level C: small benefit relative to harm
        - Level U: too close to call
    - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains
    - Importance of the outcome: critical, important, mildly important, not important
    - Expected variation in patient preferences: none, minimal, moderate, large
    - Financial burden relative to benefit expected: none, minimal, moderate, large
    - Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-10 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-10. Rationale profile of factors considered in developing the practice recommendation

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

Practice recommendations

Recommendation 1

Recommendation 1 rationale

Thymectomy leads to meaningful benefits for patients with AChR ab+ generalized MG. In addition, transsternal thymectomy appears to be safe (EVID).[7]

Because of the moderate benefits of thymectomy and the need for a major surgical procedure with its attendant discomforts and costs, there is likely to be considerable variability in patient preferences relative to undergoing thymectomy (PRIN). However, the panel anticipates that most patients would want to be aware of the availability of thymectomy as a treatment option (PRIN).

Recommendation 1 statement

Clinicians should discuss thymectomy with patients who have AChR ab+ generalized MG and are younger than 65 years of age. The discussion should clearly indicate the anticipated benefits and risks of the procedures and uncertainties surrounding the magnitude of these benefits and risks (Level B).

Domain	Ratings				Consensus
Confidence in Inference (& Evidence)	Very low	Low	Moderate	High 3	Yes
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 0	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 3	Critically Important 0	Yes
Variation in preferences	Large 0	Moderate 0	Modest 0	Minimal 3	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 3	Always 0	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 0	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Recommendation 2

Recommendation 2 rationale

There are several surgical methods of thymectomy, with the goal of removing as much thymic tissue as possible safely while preserving phrenic, left vagus, and recurrent laryngeal nerve function. The

classical method of thymectomy is an external transsternal thymectomy, facilitating complete removal of thymic tissue and fat (RELA).[11] A transcervical approach uses smaller incisions but is rarely used alone because of inadequate visualization of the thymus; it may be combined with the transsternal approach (RELA).[11] Minimally invasive techniques include video-assisted thoracoscopic thymectomy (VATS) or robotic-assisted thoracoscopic surgery, both with potentially higher risk for leaving residual thymic tissue (RELA).[11] It is uncertain whether the results of a thymectomy study using an extended transsternal approach can be generalized to minimally invasive thymectomy techniques that do not involve a median sternotomy (INFER). A randomized trial with unblinded outcome assessment comparing VATS with transsternal thymectomy demonstrated reduced blood loss, surgical times, intensive care unit stay, and hospitalization length for patients undergoing VATS but was underpowered to detect significant differences in MG clinical outcomes (RELA).[12] It seems likely, if otherwise equally efficacious in removing all thymic tissue, that patients with MG would prefer minimally invasive thymectomy techniques without a median sternotomy (INFER).

Recommendation 2 statement

Clinicians should counsel patients with AChR ab+ generalized MG considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (Level B).

Domain	Ratings				Consensus
Confidence in Inference (& Evidence)	Very low	Low	Moderate 3	High 0	Yes
Benefit relative to Harm	Harm ≥ Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 0	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 3	Critically Important 0	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 0	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 3	Always 0	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 3	Small 0	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

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