

# 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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*Neurology*® 2020;94:1-5. doi:10.1212/WNL.0000000000009294

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## 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).

### Recommendations

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).



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Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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.

## Glossary

AAN = American Academy Neurology; AChR ab+ = acetylcholine receptor antibody–positive; CI = confidence interval; MG = myasthenia gravis; MMS = minimal manifestation status; QMG = quantitative myasthenia gravis score; VATS = video-assisted thoracoscopic thymectomy.

Reports of remission following thymectomy in patients with myasthenia gravis (MG) suggested a therapeutic benefit for patients with MG.<sup>1</sup> 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.”<sup>2</sup> A randomized controlled trial was recommended. The results of a randomized trial of thymectomy in MG were published in 2016.<sup>3</sup>

The purpose of this article is to update the 2000 AAN guideline by reviewing the evidence provided by high-quality studies relevant to the following 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.<sup>4</sup> The full-length guideline, available at [aan.com/Guidelines/home/GetGuidelineContent/994](http://aan.com/Guidelines/home/GetGuidelineContent/994), includes figures e-1 and e-2 and appendices e-1 through e-10 (including 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<sup>3</sup> in which 126 participants had acetylcholine receptor antibody–positive (AChR ab+) generalized MG that qualified as Myasthenia Gravis Foundation of America clinical classification II–IV,<sup>5</sup> 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<sup>5</sup>) and the quantitative myasthenia gravis score (QMG, a composite score ranging from 0 to 39, with higher scores indicating more severe MG<sup>6</sup>) had dropped 1 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.<sup>7</sup> 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<sup>6</sup> (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.<sup>8</sup> 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<sup>5</sup> (figure e-1, [aan.com/Guidelines/home/GetGuidelineContent/994](http://aan.com/Guidelines/home/GetGuidelineContent/994)). 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<sup>9</sup> observed 68 (61%) participants from the original Class I trial<sup>3</sup> 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 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 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; figure e-2, [aan.com/Guidelines/home/GetGuidelineContent/994](http://aan.com/Guidelines/home/GetGuidelineContent/994); table).

## 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.<sup>5</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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).

**Table** Selected secondary outcomes in the MGTX trial (Thymectomy Trial in Non-Thymomatous AChR ab+ generalized Myasthenia Gravis Patients Receiving Prednisone)

Secondary outcome	Prednisone alone	Prednisone plus thymectomy	Mean difference (95% CI)
MG-ADL, 12 months	3.33 ± 3.40	1.92 ± 2.73	1.42 (0.28 to 2.55)
MG-ADL, 24 months	3.11 ± 2.93	2.02 ± 2.78	1.1 (0.03 to 2.17)
MG-ADL, 36 months	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 months	22/60 (37)	6/66 (9)	19.2% (5.9% to 32.6%)

Abbreviations: CI = confidence interval; MG = myasthenia gravis; MG-ADL = myasthenia gravis-specific activities of daily living scale. Values are mean ± SD or n (%).

## 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.

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## 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.S.G.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

## Disclosure

G.S. Gronseth serves as an associate editor for *Neurology*<sup>®</sup> and as an editorial advisory board member of *Brain & Life* and 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. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

## Publication history

Received by *Neurology* October 18, 2019. Accepted in final form January 5, 2020.

## Appendix Authors

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<b>Gary S. Gronseth, MD</b>	University of Kansas Medical Center, Kansas City	Study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content
<b>Richard Barohn, MD</b>	University of Kansas Medical Center, Kansas City	Study concept and design, critical revision of the manuscript for important intellectual content

## Appendix (continued)

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<b>Pushpa Narayanaswami, MD, MBBS</b>	Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA	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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Gary S. Gronseth, Richard Barohn and Pushpa Narayanaswami  
*Neurology* published online March 25, 2020  
DOI 10.1212/WNL.0000000000009294

**This information is current as of March 25, 2020**

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