The economic and quality of life burden that myasthenia gravis has on patients: A US targeted literature review

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INTRODUCTION

- Myasthenia gravis (MG) is a rare chronic neuromuscular autoimmune disorder (Gilhus 2016; Carr 2010; Grob 2008) mediated by pathogenic immunoglobulin G (IgG) autoantibodies (Behin 2018; Rodgaard 1987; Hoch 2001; Shen 2013), which causes debilitating and potentially life-threatening muscle weakness (Jacob 2018).
- Patients suffer with debilitating muscle weakness leading to difficulties in mobility, speech, swallowing, and vision; impaired respiratory function; and extreme fatigue (Grob 2008; Lee 2018). Up to 20% of patients experience potentially life-threatening MG, with respiratory failure requiring mechanical ventilation (Grob 2008; Wendell 2011).
- MG also has a profoundly negative impact on patients' quality of life (QoL) as a result of physical impairments, poor psychological well-being, and treatment-related side-effects (Lee 2018; Boldingh 2015; Twork 2010; Wendell 2011). Further, there is a major socioeconomic impact associated with MG in terms of health resource utilization in the United States (US), with higher healthcare costs than many other chronic neurological diseases (Guptill 2011).

OBJECTIVE

- The goal of this targeted literature review was to understand the economic and humanistic burden attributed to MG.

METHODS

Search Strategy

- A review of the literature was conducted in the biomedical database Embase (including Medline) for articles published from January 2009 to April 2019.
- Included studies were English language observational studies, including retrospective database evaluations, and administrative healthcare claims analyses, as well as cohort, registry, case-control, and cross-sectional studies, evaluating adult patients with MG in the US.
- Terminology used to identify relevant studies included cost; fees; expenditures; resource use; healthcare utilization; absenteeism; presenteeism; employment; hospitalization; medical leave; QoL; activities of daily living; patient-reported outcomes; caregiver burden; humanistic burden; and disability.

RESULTS

Included studies

- After reviewing titles and abstracts of identified references, followed by the full-text publications, 15 studies assessing the economic and humanistic burden of MG were included in this review.

Economic burden of MG

- Overall, there were 9 articles reporting the economic burden of MG (See **Table 1** for study design, data sources, and study timeframe). Economic burden was assessed by 5 studies using national datasets (Alshekhleee 2009, Souayah 2009; Mandawat 2010; Alshaikh 2016, Omorodion 2017) and 3 studies using disease management or claims data (Guptill 2011; Guptill 2012; Engel-Nitz 2018). One study reported a cost model using multiple data sources (Heatwole 2011).
- Studies reporting specifically on hospital length of stay (LOS) in patients with MG can be found in **Table 2**.
  - Median hospital LOS in patients with MG ranged from 2 days to 8 days using National Inpatient Sample (NIS) data (Alshekhlee 2009; Omorodion 2017).
  - Studies evaluating hospital LOS in differing years suggest that LOS has not changed over time (Souayah 2009; Omorodion 2017).
  - Some factors were associated with a greater burden of disease. Patients receiving plasma exchange (PE) had longer LOS compared to patients receiving intravenous immunoglobulin (IVIG) in those with MG and MG crisis (*P*<0.001 for both) (Mandawat 2010).
    - In addition, MG crisis and the presence of respiratory failure worsened the burden, increasing LOS from a median of 4 to 6 days to 6 to 10 days (Alshekhlee 2009; Mandawat 2010).
- Studies reporting on the costs related to MG can be found in **Table 3**.
  - The mean (± standard error of the mean [SEM]) annual direct costs per MG patient was $20,190 ($4,763), with pharmacy costs comprising approximately 45% and non-pharmacy costs comprising 55%, of annual costs (Guptill 2012). Additionally, Guptill 2012 included information on control patients (propensity-score matched non-MG patients in the same healthcare claims database) who had direct costs of $4,515 ($457), meaning the mean per-patient costs attributable to the treatment of MG were $15,675.
  - Total charges per hospital admission were driven largely by the year of the study and the criteria for patient selection. Using 2000-2005 NIS hospitalizations, the median charge of MG and MG crisis were $16,000 and $38,000, respectively (Alshekhlee 2009). Another study of NIS hospitalizations showed that in 2003 the median charges for all MG hospitalizations were $48,024, increasing to $98,795 in 2013 (Omorodion 2017).
  - Patient factors, including MG crisis, age, male gender, and treatment with PE (vs IVIG) increased hospital and total costs, and thus increased the economic burden associated with MG (Alshekhlee 2009; Mandawat 2010; Guptill 2011; Heatwole 2011; Omorodion 2017).

Humanistic burden of MG

- Six articles representing the results from 4 studies evaluated the QoL and humanistic burden in patients with MG. Three studies reported on results from a single study population (the MG Composite and MG-QOL15 Study Group; Burns 2010; Burns 2011; Muppidi 2011), and 2 reports evaluated data from the Myasthenia Gravis Foundation of America MG Patient Registry (Boscoe 2019; Lee 2018). Three were prospective, 2 were retrospective, and 1 was a cross-sectional study (**Table 4**).
- The MG Composite and MG-QOL15 Study Group evaluated several outcomes instruments to assess how different measures translated to both clinical improvement in MG patients and improvement in their QoL.
  - Newly diagnosed MG patients were evaluated at 2 consecutive visits (with a mean of 4.7 months between visits) for improvement in QoL measures supporting clinical improvement (**Table 5**).
  - A 3-point improvement in the Myasthenia Gravis Composite (MGC) score was an optimal measure of clinical improvement. Among 138 patients with MGC data at both visits, 49 (35.5%) had ≥3-point improvement, and 90% of these patients had an improvement in the MG-QOL15 score (Burns 2010).
  - A mean improvement of −5.0 on the 15-item MG Quality of Life Scale (MG-QOL15) corresponded to a 2-point improvement in MGC score (Burns 2011).
    - Better improvement in MG-QOL15 scores (larger reductions) were significantly correlated with higher initial MGC scores (correlation = −0.25; *P*=0.003).
  - An older scale, the Myasthenia Gravis Activities of Daily Living (MG-ADL), evaluates patient symptoms and activities in MG using 8 items related to daily activities, including chewing, swallowing, and getting up from a chair.
    - Among 76 patients evaluated at both study visits, a 2-point improvement on the MG-ADL scale best predicted clinical improvement, and was also significantly correlated with changes in QoL (Muppidi 2011).
- Three studies reported on humanistic outcomes and potential predictors in MG (**Table 6**).
  - Among patients treated with multiple immunosuppressants, presence of continued functional disability contributed to a worse QoL (Boscoe 2019).
  - Smoking was associated with worse QoL (Gratton 2016).
    - Current smokers had higher MG-ADL total (*P*=0.003) and ocular subscores (*P*=0.031), while never smokers had the lowest (*P*=0.031).
  - QoL, fatigue, and depression were all worse in women than men across several measures of humanistic burden (*P*<0.00001 for all scales assessed) (Lee 2018).
    - Across different variables potentially influencing QoL, thymectomy was associated with improved QoL in women, compared to women without a thymectomy; for men, thymectomy status did not impact QoL scores.

Table 1. Studies Reporting on the Economic Burden of MG

Publication	Study Design	Data Source	Timeframe
Alshekhlee 2009	Retrospective	NIS	2000-2005
Souayah 2009	Retrospective	NIS	1991-1992; 2001-2002
Mandawat 2010	Retrospective	NIS	2000-2005
Guptill 2011	Retrospective	Accordant Health Services disease management database (includes US health plan data)	2008-2010
Heatwole 2011	Cost model	Multiple data sources including primary studies, the University of Rochester (NY) Billing Office, and Lexi-comp	NA
Guptill 2012	Retrospective	Accordant Health Services disease management database (includes US health plan data)	2009
Alshaikh 2016	Retrospective	American College of Surgeons National Surgical Quality Improvement Program database	2005-2012
Omorodion 2017	Retrospective	NIS	2003-2013
Engel-Nitz 2018	Retrospective	Optum Research Database and Impact National Benchmark Database (pharmacy and medical claims data)	1999-2015

Key: NIS – National Inpatient Sample; NA – not applicable; NY – New York; US – United States.

Table 2. LOS in Patients With MG

Publication	HCRU Results
Alshekhlee 2009	• LOS, median (IQR) days – MG: 4 (2,7) – MG Crisis: 6 (4,12) *P*<0.0001
Souayah 2009	• LOS, mean (SD) days – 1991–1992: 21 (16) – 2001–2002: 22 (19) Not statistically significantly different
Mandawat 2010	• LOS for MG, median (IQR) days – PE = 6 (5) – IVIg = 4 (3) *P*<0.0001 • LOS for MG Crisis, median (IQR) days – PE = 10 (11) – IVIg = 5 (5) *P*<0.0001
Alshaikh 2016	• LOS, median (IQR) days: 4.0 (2.5–5.0)
Omorodion 2017	• LOS, days – 2003: 7.4 – 2013: 8 Statistical significance not reported

Key: ED – emergency department; HCRU – healthcare resource utilization; ICU – intensive care unit; IQR – interquartile range; IVIg – intravenous immunoglobulin; LOS – length of stay; MG – myasthenia gravis; PE – plasma exchange; SD – standard deviation.

Table 3. Economic Costs of MG per Patient, USD

Publication	HCRU Results
Alshekhlee 2009	• Total hospital charge, median (IQR) – MG: $16,009 ($8,239–$30,527) – MG crisis: $37,784 ($17,484–$74,355) *P*<0.0001
Souayah 2009	• Hospitalization charges (mean per patient) – 1991–1992: $84,100 – 2001–2002: $118,000 *P*<0.05
Mandawat 2010	• Total hospital charge for MG, median (IQR) – PE: $26,662 ($24,960) – IVIG: $21,124 ($20,947) *P*=0.001 • Total hospital charge for MG Crisis, median (IQR) – PE: $53,801 (6$5,335) – IVIg: $33,924 ($34,840) *P*<0.0001
Guptill 2011	• Average total annual claims-based cost for MG patients: $24,988 (SD: $48,208) (median: $9,023) • Annualized mean healthcare costs (pharmacy and medical) per patient by age: *0–19 years* – Pharmacy: $1,196 – Medical: $6,710 *20–39 years* – Pharmacy: $19,573 – Medical: $17,949 *40–65 years* – Pharmacy: $12,498 – Medical: $15,112 *≥65 years* – Pharmacy: $8,089 – Medical: $12,597
Heatwole 2011 (cost model)	• Mean short-term treatment utilization cost per patient – PE: $101,140 – IVIg: $78,814
Guptill 2012	• MG – Mean annual total cost (± SEM): $20,190 ($4,763) – Mean annual pharmacy cost (± SEM): $9,012 ($3,723) – Mean annual non-pharmacy cost (± SEM): $11,178 ($2,751)
Omorodion 2017	• Mean charges per hospital admission – 2003: $48,024 – 2013: $98,795 • By age group, 2013: – <1 year: unavailable – 1–7 years: $66,862 – 18–44 years: $82,793 – 45–64 years: $93,028 – 65–84 years: $116,997 – 85+ years: $83,714 • By sex, 2013 – Men: $110,491 – Women: $90,294 Statistical significance not reported

Key: IQR – interquartile range; IVIG –intravenous immunoglobulin; MG – myasthenia gravis; PE – plasma exchange; SD – standard deviation; SEM – standard error of the mean; USD – US dollars.

Table 4. Studies reporting on the humanistic burden of MG

Publication	Study Design	QoL Scale/Tool
Burns 2010	Prospective	MGC MG-ADL MG-QOL15 MG-MMT Choose 2
Burns 2011	Prospective	MG-QOL15
Muppidi 2011	Prospective	MGC MG-ADL MG-QOL15
Gratton 2016	Cross-sectional	MG-ADL MG-ADL ocular subscore
Lee 2018	Retrospective	MG-QOL15 MG-ADL UEADL LEADL Fatigue Scale Depression Scale
Boscoe 2019	Prospective	MG-ADL, total score NeuroQoL Lower Extremity score NeuroQoL Upper Extremity score NeuroQoL Fatigue score Depression score

Key: Choose 2 – Component of the MGC; LEADL – Mobility/Lower Extremity Function; MGC – Myasthenia Gravis Composite; MG-ADL – Myasthenia Gravis Activities of Daily Living Scale; MG-MMT –Myasthenia Gravis Manual Muscle Testing; MG-QOL 15 – 15-item MG Quality of Life Scale; QoL – quality of life; UEADL – Fine Motor Activity of Daily Living/Upper Extremity Function.

Table 5. Humanistic/QoL Improvement Supporting Clinical Improvement in MG

Publication	Humanistic/QoL Results
Burns 2010	• Percentage of patients with defined improvement in MCG scores between 2 consecutive visits: – ≥3 point improvement: 35.5% – 0–2 point improvement: 37.7% – Worsening: 26.8% • A 3-point improvement in MGC score was an optimal measure of clinical improvement
Burns 2011	• Mean (SD) change in MG-QOL15 between 2 consecutive visits: – All patients: −5.0 (11.16) – Patients without clinical improvement (defined as ≥3 points in the MGC and an initial MG-QOL15 score ≥4): −3.44 (9.51)
Muppidi 2011	• Mean (SD) change in QOL scores between 2 consecutive visits: – MG-ADL: −1.22 (3.0) – MGC: −2.61 (6.25) – MG-QOL15 total: −5.32 (11.7) • A 2-point improvement in MG-ADL score was an optimal measure of clinical improvement

Key: MGC – Myasthenia Gravis Composite; MG-ADL – Myasthenia Gravis Activities of Daily Living Scale; MG-MMT – Myasthenia Gravis Manual Muscle Testing; MG-QOL 15 – 15-item MG Quality of Life Scale; QoL – quality of life; SD – standard deviation.

Table 6. Humanistic/QoL Outcomes and Potential Predictors of MG

Publication	Humanistic/QoL Results
Gratton 2016	• Mean (SD) MG-ADL score by smoking status (*P*<0.003): – Current smoker: 5.6 (4.5) – Former smoker: 2.9 (3.1) – Never smoker: 1.4 (2.5) • Mean (SD) MG-ADL ocular subscore by smoking status (*P*=0.031) – Current smoker: 3.4 (2.6) – Former smoker: 1.8 (2.1) – Never smoker: 1.1 (1.5)
Boscoe 2019	• Mean (SD) scale score in Men: – MG-QOL15: 24.53 (14.74) – MG-ADL: 6.72 (3.95) – UEADL: 36.38 (4.74) – LEADL: 31.74 (6.80) – Fatigue Scale: 19.03 (7.03) – Depression Scale: 1.31 (1.19) • Mean (SD) scale score in Women: – MG-QOL15: 18.44 (13.65) – MG-ADL: 5.02 (3.57 – UEADL: 38.23 (3.35) – LEADL: 34.86 (5.88) – Fatigue Scale: 14.57 (7.98) – Depression Scale: 0.96 (1.09) • All scores were significantly different for men vs women (*P*<0.00001)
Boscoe 2019	• MG-ADL, total score: – Refractory: 9.4 (2.8) – Non-refractory: 5.7 (4.0) *P*<0.0001 • NeuroQoL Lower Extremity score: – Refractory: 28.6 (6.6) – Non-refractory: 33.1 (6.5) *P*<0.0001 • NeuroQoL Upper Extremity score: – Refractory: 35.0 (4.3) – Non-refractory: 37.2 (4.3) *P*=0.0004 • NeuroQoL Fatigue score: – Refractory: 29.6 (5.7) – Non-refractory: 24.9 (8.2) *P*<0.0001 • NeuroQoL Fatigue score: – Refractory: 1.7 (1.2) – Non-refractory: 1.1 (1.2) *P*=0.0011

Key: LEADL – Mobility/Lower Extremity Function; MG-ADL – Myasthenia Gravis Activities of Daily Living Scale; MG-QOL 15 – 15-item MG Quality of Life Scale; QoL – quality of life; SD – standard deviation; UEADL – Fine Motor Activity of Daily Living/Upper Extremity Function.

LIMITATIONS

- Included results were from observational studies, which may suffer from biases, including selection bias and reporting bias.
- Results from studies were heterogeneous, which limited the ability to synthesize and summarize across studies. No studies reported MG severity other than as measured by specific MG-related instruments, thus limiting the ability to consider different outcomes by severity in the evaluations.

CONCLUSIONS

- The economic burden associated with MG is considerable, particularly for patients with severe complications, including MG crisis. Median LOS in patients with MG ranged from 2 days to 8 days and was longer for patients receiving PE during hospitalization. While LOS did not increase over calendar year, the charges per-patient hospitalization doubled from $48,000 in 2003 to $99,000 in 2013.
- Patients with MG also experience a humanistic burden with the presence of continued functional disability and smoking contributing to a worse QoL. Women may fare worse than men, with lower QoL and more fatigue and depression.
- Understanding the risk factors associated with MG-related complications, and the potential impact on treatment modalities, is crucial to advancing the medical management of these patients.
- Additionally, the QoL impact and costly hospitalizations among patients with MG suggest a continuing need for new treatment options to improve disease course and prevent complications.

References in Targeted Literature Review:

- Alshaikh JT, Anstur R, Sidawy A, Trachiotis G, Kaminski HJ. Thymectomy is safe for myasthenia gravis patients: analysis of the NSQIP database. *Muscle Nerve*. 2016;53(3):370-374.
- Alshekhlee A, Miles JD, Katirji B, Preston DC and Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009;72(18):1548-1554.
- Ashfaq, A, Bernes, SM, Weidler, EM and Notrica, DM. Outcomes of thoracoscopic thymectomy in patients with juvenile myasthenia gravis. *J Pediatr Surg*. 2016;51(7):1078-1083.
- Boscoe AN, Haichang X, L'Italien GJ, Harris LA, Cutter GR. Impact of refractory myasthenia gravis on health-related quality of life. *J Clin Neuromuscul Dis*. 2019;20(4):173-181.
- Burns TM, Conaway M, Sanders DB; MG Composite and MG-QOL15 Study Group. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology*. 2010;74(18):1434-1440.
- Burns TM, Grouse CK, Wolfe GI, Conaway MR, Sanders DB; MG Composite and MG-OL15 Study Group. The MG-QOL15 for following the health-related quality of life of patients with myasthenia gravis. *Muscle Nerve*. 2011;43(1):14-18.
- Engel-Nitz NM, Boscoe A, Wolbeck R, Johnson J and Silvestri NJ. Burden of illness in patients with treatment refractory myasthenia gravis. Muscle and Nerve. 2018; 58(1): 98-105.
- Gratton SM, Herro AM, Feuer WJ and Lam BL. Cigarette smoking and activities of daily living in ocular myasthenia gravis. *J Neuroophthalmolog*. 2016;36(1):37-40.
- Guptill JT, Marano A, Krueger A, Sanders DB. Cost analysis of myasthenia gravis from a large U.S. insurance database. *Muscle Nerve*. 2011;44(6):907-911.
- Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A and Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle Nerve*. 2012;45(3):363-366.
- Hartwich J, Tyagi S, Margaron F, Oltcica C, Teasley J, Lanning D. Robot-assisted thoracoscopic thymectomy for treating myasthenia gravis in children. *J Laparoendosc Adv Surg Tech A*. 2012;22(9):925-929.
- Heatwole C, Johnson N, Holloway R, Noyes K. Plasma exchange versus intravenous immunoglobulin for myasthenia gravis crisis: an acute hospital cost comparison study. *J Clin Neuromuscul Dis*. 2011;13(2):85-94.
- Jeong A, Min JH, Kang YK, et al. Factors associated with quality of life of people with Myasthenia Gravis. *PLoS One*. 2018;13(11):e0206754.
- Lee I, Kaminski HJ, Xin H, Cutter G. Gender and quality of life in myasthenia gravis patients from the Myasthenia Gravis Foundation of America Registry. *Muscle Nerve*. 2018;58(1):90-98.
- Mandawat A, Kaminski HJ, Cutter G, Katrji B and Alshekhlee A. Comparative analysis of therapeutic options used for myasthenia gravis. *Ann Neurology*. 2010;68(6):797-805.
- Muppidi S, Wolfe GI, Conaway M, Burns TM; MG Composite and MG-QOL15 Study Group. MG-ADL: still a relevant outcome measure. *Muscle Nerve*. 2011;44(5):727-731.
- Omorodion JO, Pines JM and Kaminski HJ. Inpatient cost analysis for treatment of myasthenia gravis. *Muscle Nerve*. 2017;56(6):1114-1118.
- Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12:1756286419832242.
- Souayah N, Nasar A, Suri MF, Kirmani JF, Ezzeddine MA, Qureshi AI. Trends in outcomes and hospitalization charges among mechanically ventilated patients with myasthenia gravis in the United States. *Int J Biomed Sci*. 2009;5(3):209-214.
- Tracy MM, McRae W and Millichap GJ. Graded response to thymectomy in children with myasthenia gravis. *J Child Neurol*. 2009;24(4):454-459.

Please contact Xcenda co-authors for a complete list of references.

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