Economic Costs of Myasthenia Gravis: A Systematic Review

Erik Landfeldt¹ · Oksana Pogoryelova² · Thomas Sejersen¹ · Niklas Zethraeus³ · Ari Breiner⁴ · Hanns Lochmüller^{4,5,6}

Published online: 4 May 2020

© The Author(s) 2020

Abstract

Objectives The objective of our study was to conduct a systematic literature review of economic costs (henceforth costs) associated with myasthenia gravis (MG).

Methods We searched MEDLINE (through PubMed), CINAHL, Embase, PsycINFO, and Web of Science for studies reporting costs of MG published from inception up until March 18, 2020, without language restrictions. Two reviewers independently screened records for eligibility, extracted the data, and assessed included studies for risk of bias using the Newcastle–Ottawa Scale. Costs were inflated and converted to 2018 United States dollars (\$).

Results The search identified 16 articles for data extraction and synthesis. Estimates of costs of MG were found for samples from eight countries spanning four continents (Europe, North America, South America, and Asia). Across studies, the mean per-patient annual direct medical cost of illness was estimated at between \$760 and \$28,780, and cost per hospitalization between \$2550 and \$164,730. The indirect cost of illness was estimated at \$80 and \$3550. Costs varied considerably by patient characteristics, and drivers of the direct medical cost of illness included intravenous immunoglobulin and plasma exchange, myasthenic crisis, mechanical ventilatory support, and hospitalizations.

Conclusions We show that the current body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability, both within and between countries. Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40273-020-00912-8>) contains supplementary material, which is available to authorized users.

✉ Erik Landfeldt
erik.landfeldt@ki.se

¹ Department of Women's and Children's Health, Karolinska Vägen 37A, 171 76 Stockholm, Sweden

² Absolute Antibody Ltd., Wilton Centre, Redcar TS10 4RF, UK

³ Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, Sweden

⁴ Division of Neurology, Department of Medicine, The Ottawa Hospital, and Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada

⁵ Department of Neuropediatrics and Muscle Disorders, Medical Centre-University of Freiburg, Faculty of Medicine, Freiburg, Germany

⁶ Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Canada

Key Points for Decision Makers

To our knowledge, no study has systematically reviewed the literature for costs associated with myasthenia gravis (MG).

The body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability.

Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

1 Introduction

Myasthenia gravis (MG) is an autoimmune disease in which antibodies react with structures of the neuromuscular junction, leading to impairment or failure of neuromuscular transmission [1]. Clinically, the disease results

in problems with vision, fatigable weakness, swallowing difficulties, and loss of ambulation, but may prove fatal following myasthenic crisis (i.e. paralysis of the respiratory muscles) in the absence of appropriate interventions. Acetylcholinesterase inhibitors may be sufficient to manage the mildest presentations of MG, but generalized forms usually require long-term treatment with corticosteroids and immunosuppressants, thymectomy, intravenous immunoglobulin (IVIG), or plasma exchange (PLEX) [2]. However, for a considerable proportion of MG patients, these generalized treatments lack effectiveness and/or are accompanied by non-trivial side effects [3].

In recent decades, promising treatment strategies, including immunomodulation with specific monoclonal antibodies (“biologicals”), have been explored for MG, and several clinical trials involving humans have just been completed or are still in progress [4]. Given the growing arsenal of therapy choices available to MG clinicians, there is an emerging body of literature studying the health economics of MG that has previously not been systematically reviewed. The objective of our study was to conduct a systematic review of economic costs (henceforth costs) of MG globally. Specifically, this systematic literature review sought to answer the following questions:

- In which geographical settings have costs of MG been studied?
- What types of costs have been estimated in patients with MG?
- What are the known costs of MG?

2 Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5].

2.1 Search Strategy and Selection Criteria

We searched MEDLINE (through PubMed), CINAHL, Embase, PsycINFO, and Web of Science for full-text records of studies reporting costs of MG published from inception up until March 18, 2020, without language restrictions. The search string contained a combination of the following medical subject heading terms, title/abstract, and topic field tags: “myasthenia gravis”, “cost”, “financial”, “burden”, “economic”, “monetary”, “cost of illness”, “costs and cost analysis”, “cost–benefit analysis”, “cost-effectiveness”, and “cost-utility” (full search strings available in the “Appendix”—see the electronic supplementary

material). We included all identified publications reporting costs of MG in any currency. We excluded studies based on samples comprising fewer than ten patients (to allow for meaningful inference), and also required that results were reported separately for patients with MG. No further criteria were imposed for study eligibility.

2.2 Screening, Data Extraction, and Assessment of Risk of Bias

Two independent investigators (EL and OP) initially screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. The reasons for article exclusion were recorded and disagreements were resolved by the involvement of a third investigator (HL). For all articles included in the review, the following data were extracted: author, year, setting, design, data sources, type of data, study periods, patient population, estimated costs, and cost result. For studies reporting costs for multiple time periods, we only extracted the most recent data, and we only considered estimates for subgroups comprising ten or more patients. We did not extract costs of individual resources (e.g. the cost of a specific medicine or a visit to a general practitioner) reported as part of higher-level cost categories (e.g. the direct medical cost of illness).

Result data from each article were synthesized and reported with respect to the three review questions as stated in the Sect. 1. We sought (when feasible) to structure identified estimates into the following commonly examined cost categories (based on the information in the reviewed publications): direct medical cost (i.e. the opportunity cost of medical resources directly included in the formal management of the disease), direct non-medical cost (i.e. the opportunity cost of non-medical resources directly included in the formal management of the disease), informal care cost (i.e. the opportunity cost associated with the informal management of the disease by non-professionals, typically accounted for as a direct non-medical cost), and indirect cost (typically quantified as production losses from the perspective of society due to absenteeism and presenteeism from work [6]). To facilitate comparison, identified cost estimates were inflated to 2018 values using country-specific consumer price index data from the World Bank [7] and subsequently converted to United States (US) dollars (\$) using the following rates: Colombian peso COL\$1 = \$0.00030; Canadian dollar C\$1 = \$0.747; New Taiwan dollar NT\$1 = \$0.032; Yen ¥1 = \$0.009; Euro (German) €1 = \$1.130; Indian rupee ₹1 = \$0.014; and Thai baht ฿1 = \$0.033. All reported cost estimates, extracted or derived, were rounded to the nearest ten.

Risk of bias was established with the Newcastle–Ottawa Scale (NOS) [8]. The NOS was developed to assess the quality and risk of bias of non-randomized studies in three dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Each category is attributed a score rating (maximum score: $\diamond\diamond\diamond\diamond$ for selection, $\diamond\diamond$ for comparability, and $\diamond\diamond\diamond$ for outcome). To ascertain selection, we required patients to be diagnosed with MG, that the diagnosis was confirmed via International Statistical Classification of Diseases and Related Health Problems (ICD) codes (e.g. ICD-9 358.00 and ICD-10 G70.0) in an out- or inpatient setting, and that the sample was not restricted in terms of level of fatigable weakness (or other markers limiting representativeness) (assessment of non-exposed was not applicable); to ascertain comparability, we required details of the distribution of age and sex in the

sample population, as well as MG crisis/exacerbation (as applicable); and to ascertain outcome, we required that the data were extracted from clinical charts, registries, or databases (i.e. not patient self-reported, per the scale manual), there was a minimal follow-up of 1 month for prospective studies (given the frequency of care reported), and < 25% of the total sample were lost to follow-up during the study period.

3 Results

The systematic review resulted in the identification of 848 publications (Fig. 1). Of these, 274 were duplicates, 543 were excluded following title and abstract screening, and 31 were selected for full-text review. Finally, 16 articles [9–24] were considered for data extraction and synthesis. Summary details of the included publications are presented in Table 1.

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the selection process of the included publications. MG Myasthenia gravis

Table 1 Characteristics of included studies

Author (year)	Setting	Design	Data source(s)	Type of data	Study period(s)	Patient population
Chicaiza-Becerra et al. (2012) [9]	Colombia	Modelling study (CEA)	Published literature	Clinical and economic model input data	NR	Patients with MG not associated with thymoma (<i>n</i> and distribution of age and sex NR)
Desai et al. (2020) [23]	The United States	Retrospective, observational cohort study	The NIS part of the HCUP	Claims data	2007–2014	175 patients with takotsubo syndrome secondary to MG crisis (median age: 73 years; 80% female)
Furlan et al. (2016) [10]	Canada	Retrospective, observational cohort study; modelling study (CMA)	RCT; the Toronto General Hospital (Ontario, Canada); local unit costs	RCT, hospital expense, and unit cost model input data	2007–2010	38 adults with MG treated with IVIG (mean age: 60 years; 55% female) and 32 with PLEX (mean age: 58 years; 53% female) for exacerbation of moderate to severe MG
Guptill et al. (2011) [11]	The United States	Retrospective, observational cohort study	The AHS disease management database	Claims data	2008–2010	1288 children and adults with MG (mean age: 60 years; 59% female)
Guptill et al. (2012) [12]	The United States	Retrospective, observational cohort study	The AHS disease management database	Claims data	2009	113 children and adults with MG (mean age: 60 years; 59% female)
Heatwole et al. (2011) [13]	The United States	Modelling study (CMA)	Published literature; national unit costs	Clinical and economic model input data	NR	Patients with MG crisis (<i>n</i> and distribution of age and sex NR)
Lai and Tseng (2010) [14]	Taiwan	Retrospective, observational cohort study	The NHIRD	Claims data	2000–2007	5211 children and adults with MG (distribution of age and sex NR) receiving therapeutic and surgical treatment
Mandawat et al. (2010) [15]	The United States	Retrospective, observational cohort study	The NIS part of the HCUP	Claims data	2000–2005	1606 patients hospitalized for MG or MG crisis treated with IVIG or PLEX (distribution of age and sex for each stratum reported in the article)
Mouri et al. (2019) [16]	Japan	Retrospective, observational cohort study	The Japanese Diagnosis Procedure Combination database	Claims data	2010–2016	795 adults with MG hospitalized to receive thymectomy under general anaesthesia also treated with sugammadex (mean age: 55 years; 54% female) or placebo (mean age: 54 years; 50% female)

Table 1 (continued)

Author (year)	Setting	Design	Data source(s)	Type of data	Study period(s)	Patient population
Narla et al. (2020) [24]	The United States	Retrospective, observational cohort study	The NIS part of the HCUP	Claims data	2002–2012	Patients with MG with pemphigus or pemphigoid (<i>n</i> and distribution of age and sex NR)
Ogino et al. (2017) [17]	Japan	Retrospective, observational cohort study	The JMDC	Claims data	2015–2016	Patients with MG (<i>n</i> and distribution of age and sex NR)
Omorodion et al. (2017) [18]	The United States	Retrospective, observational cohort study	The NIS part of the HCUP	Claims data	2003–2013	6394 children and adults hospitalized for MG exacerbation and discharged alive (results stratified by age categories; 58% female)
Schepelmann et al. (2010) [19]	Germany	Cross-sectional, observational study	Survey administrated to patients identified via specialized centres part of the German Network of Muscle Disorders; national unit costs	Self-reported data	2005	41 adults with MG (mean age NR; 56% female)
Sonkar et al. (2017) [20]	India	Prospective, observational cohort study	Tertiary care teaching hospital in India	Self-reported and hospital expense data	2014–2016	66 children and adults with MG (median age 42 years; 41% female) receiving conventional therapy and surgery (thymectomy)
Souayah et al. (2009) [21]	The United States	Retrospective, observational cohort study	The NIS part of the HCUP	Claims data	2001–2002	994 patients with severe MG with a primary or secondary procedure code for continuous mechanical ventilation (mean age: 65 years; 53% female)
Tiamkao et al. (2014) [22]	Thailand	Retrospective, observational cohort study	The National Health Security Office (Bangkok, Thailand)	Claims data	2009–2010	936 adult patients with MG (mean age: 45 years; 72% female)

AHS The Accordant Health Services, *CEA* cost-effectiveness analysis, *HCUP* Healthcare Cost and Utilization Project, *IVIG* intravenous immunoglobulin, *JMDC* Japan Medical Data Center, *MG* myasthenia gravis, *NHIRD* National Health Insurance Research Database, *NIS* National (Nationwide) Inpatient Sample, *NR* not reported, *PLEX* plasma exchange, *RCT* randomized controlled trial

Most articles (75%, 12 of 16) described results from retrospective, observational cohort research, and 31% (five of 16) were based on publicly accessible data from the National (Nationwide) Inpatient Sample (NIS) part of the Healthcare Cost and Utilization Project (HCUP) in the US.

3.1 In Which Geographical Settings have Costs of MG Been Studied?

Estimates of costs of MG were found for samples from a total of eight countries across four continents (Europe, North America, South America, and Asia) (Table 1). In total, 50% (eight of 16) represented research in patients from the US [11–13, 15, 18, 21, 23, 24].

3.2 What Types of Costs have been Estimated for Patients with MG?

In total, six of 16 (38%) of identified articles estimated the direct medical costs of MG [11, 12, 14, 17, 19, 20], seven of 16 (44%) estimated cost per hospitalization [14, 16, 18, 21–24], three of 16 (19%) estimated costs of IVIG and PLEX as a treatment for MG crisis/exacerbation [10, 13, 15], two of 16 (13%) estimated indirect costs [19, 20], and one of 16 (6%) estimated costs of myasthenic crisis [9], cost per MG outpatient care service [14], and total cost of illness [19], respectively (Table 1). Schepelmann et al. [19] also estimated informal care costs of MG in Germany, accounted for as an indirect cost of illness.

3.3 What are the Known Costs of MG?

Identified costs of MG reported by the included studies are presented in Table 2. Estimates of the mean per-patient annual direct medical cost of illness ranged from \$760 in Japan [17] to \$28,780 in the US [11]. In addition, Sonkar et al. [20] estimated the median per-patient annual direct medical cost (quantified as out-of-pocket expenditures due to the lack of national healthcare insurance) in India at \$730. However, there was some variability across studies concerning included medical resources (Table 3). Two studies [19, 20] considered transportation costs, typically accounted for as a direct non-medical cost, in their calculation of direct medical cost of illness, and one [19] also included costs associated with home equipment. Guptill et al. [11] found the mean per-patient annual direct medical cost of illness in the US to vary by age, ranging from \$9100 in patients 0–19 years of age to \$23,820 in those older than 65 years.

Main drivers of the direct medical cost of illness were IVIG [11, 20] and PLEX [20], as well as myasthenic crisis [20], mechanical ventilatory support [20], and hospitalizations [12, 20]. Costs appear to also be driven by very high healthcare utilization in some patient groups. For example,

Guptill et al. [11] reported that the subset of US patients who received more than 20 infusions of IVIG in the 2-year study period (determined from the health plan payments) accounted for 62% of all MG-related pharmacy costs.

Estimates of the mean per-patient cost per hospitalization, all based on claims data, ranged between \$2550 and \$164,730 (in 2018 US dollars) (Table 2). The lowest estimate was derived from a sample of 936 Thai patients hospitalized for MG [22], and the highest for 994 US patients hospitalized for MG requiring continuous mechanical ventilation [21]. In relation to all US hospital admission that calendar year, Omorodion et al. [18] estimated the mean per-patient added cost per hospitalization for MG exacerbation in the US in 2013 at \$59,340 (\$98,800 vs. \$39,460). Looking into results from reported subgroup analyses, Omorodion et al. [18] found costs per hospitalization to be higher for males compared with females hospitalized for MG exacerbation (\$119,100 vs. \$97,330) and in the West of the US compared with the Midwest (\$55,850 vs. \$34,560), whereas Souayah et al. [21] reported higher costs for urban non-teaching compared with teaching hospitals (\$165,150 vs. \$104,980), and both recognized that the mean per-patient cost per hospitalization varied markedly by age (Table 2).

The mean per-patient indirect cost of MG was estimated at \$80 and \$3550 (Table 2). The former was based on self-reported data from 66 Indian patients and their caregivers and included production losses due to absenteeism and presenteeism estimated by valuing the number of lost work days, as well as time lost for patients and caregivers, at the daily wage, and subsequently adding caregivers' expenditure for travel, food, and stay while in the hospital [20]. In contrast, the latter estimate, based on self-reported data from 41 German patients and their caregivers, included production losses due to premature retirement and temporary sickness estimated in patients <65 years of age by valuing the number of lost work days at the daily wage, as well as estimates of informal care (defined as home care provided by family and friends) calculated by valuing the number of hours of informal care with the daily wage [19].

The mean per-patient cost of IVIG as a treatment for MG crisis/exacerbation was estimated at \$6620 in Canada [10] (including hospital costs, costs of blood products, and physician fees) and \$90,760 [13] in the US (including cost of therapy, cost of hospitalization, and cost of secondary complications). Corresponding estimates for PLEX were \$4990 [10] and \$116,470 [13], respectively. In addition, Mandawat et al. [15] estimated the median per-patient hospital cost (reflecting total hospital charges) of IVIG and PLEX in the US at \$28,080 and \$35,450 in patients with MG, and \$45,100 and \$71,520 in those with MG crisis.

The mean per-patient total cost of illness, including direct medical, informal care, and indirect costs, was estimated

Table 2 Costs of MG reported by included studies

Author (year)	Estimated cost(s)	Perspective of analysis	Currency; year of valuation	Cost result(s) [in 2018 US dollars [§]]	Risk of bias [‡]
Chicaiza-Becerra et al. (2012) [9]	Cost of MG crisis (including medical treatment and inpatient care)	Healthcare/payer	Colombian peso (COL\$); 2008	Mean per-patient cost of myasthenic crisis (<i>n</i> = NR): COL\$10,360 [<\$10]	Selection: ◇◇◇◇ Comparability: ◇ (age and sex NR) Outcome: ◇◇◇
Desai et al. (2020) [23]	Cost per hospitalization of takotsubo syndrome secondary to MG crisis (i.e. total hospital charge)	Healthcare/payer	US dollar (\$); year NR ^a	Median per-patient cost per hospitalization (<i>n</i> = 175): \$134,000 [\$142,130]	Selection: ◇◇◇◇ Comparability: ◇◇◇◇ Outcome: ◇◇◇
Furlan et al. (2016) [10]	Cost of IVIG and PLEX (including hospital costs, costs of blood products, and physician fees) as treatment for exacerbation of moderate to severe MG	Healthcare/payer	Canadian dollar (C\$); 2014	Mean per-patient cost of IVIG (<i>n</i> = 32): C\$8310 [\$6620] Mean per-patient cost of PLEX (<i>n</i> = 38): C\$6270 [\$4990]	Selection: ◇◇◇◇ Comparability: ◇◇◇◇ Outcome: ◇◇◇
Guptill et al. (2011) [11]	Direct medical cost	Healthcare/payer	US dollar (\$); year NR ^b	Mean per-patient annual direct medical cost (pooled sample, <i>n</i> = 1288): \$24,990 [\$28,780] Mean per-patient annual direct medical cost (age: 0–19 years, <i>n</i> = 21): \$7910 [\$9100] Mean per-patient annual direct medical cost (age: 20–39 years, <i>n</i> = 84): \$37,520 [\$43,210] Mean per-patient annual direct medical cost (age: 40–65 years, <i>n</i> = 704): \$27,610 [\$31,790] Mean per-patient annual direct medical cost (age: > 65 years, <i>n</i> = 479): \$20,690 [\$23,820]	Selection: ◇◇◇◇ Comparability: ◇◇◇◇ Outcome: ◇◇◇
Guptill et al. (2012) [12]	Direct medical cost	Healthcare/payer	US dollar (\$); year NR ^c	Mean per-patient annual direct medical cost (<i>n</i> = 113): \$20,190 [\$23,630]	Selection: ◇◇◇◇ Comparability: ◇◇◇◇ Outcome: ◇◇◇
Heatwole et al. (2011) [13]	Cost of IVIG and PLEX (including cost of therapy, cost of hospitalization, and cost of secondary complications) as a treatment for MG crisis	Healthcare/payer	US dollar (\$); year NR ^b	Mean per-patient cost of IVIG (<i>n</i> = NR): \$78,810 [\$90,760] Mean per-patient cost of PLEX (<i>n</i> = NR): \$101,140 [\$116,470]	Selection: ◇◇◇◇ Comparability: ◇◇◇◇ Outcome: ◇◇◇
Lai and Tseng (2010) [14]	Direct medical cost; cost per outpatient care service; cost per hospitalization	Healthcare/payer	New Taiwan dollar (NT\$); 2007	Mean per-patient direct medical cost (<i>n</i> = 3205): NT\$42,080 [\$1780] Mean per-patient cost per outpatient care service (<i>n</i> = 3205): NT\$1890 [\$80] Mean per-patient cost per hospitalization (<i>n</i> = 3205): NT\$107,980 [\$4560]	Selection: ◇◇◇◇ Comparability: ◇ (age and sex NR) Outcome: ◇◇◇

Table 2 (continued)

Author (year)	Estimated cost(s)	Perspective of analysis	Currency; year of valuation	Cost result(s) [in 2018 US dollars [§]]	Risk of bias [†]
Mandawat et al. (2010) [15]	Hospital cost (i.e. total hospital charge) of IVIG and PLEX as treatment for MG and MG crisis, respectively	Healthcare/payer	US dollar (\$); year NR ^d	Median per-patient hospital cost of IVIG (MG, <i>n</i> = 171): \$21,120 [\$28,080] Median per-patient hospital cost of PLEX (MG, <i>n</i> = 737): \$26,660 [\$35,450] Median per-patient hospital cost of IVIG (MG crisis, <i>n</i> = 169): \$33,920 [\$45,100] Median per-patient hospital cost of PLEX (MG crisis, <i>n</i> = 529): \$53,800 [\$71,520]	Selection: ◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇◇
Mouri et al. (2019) [16]	Cost per hospitalization (i.e. total hospital charge)	Healthcare/payer	US dollar (\$); year NR ^e	Median per-patient cost per hospitalization (sugammadex, <i>n</i> = 506): \$13,190 [\$13,800] Median per-patient cost per hospitalization (placebo, <i>n</i> = 289): \$14,120 [\$14,770]	Selection: ◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇◇
Narla et al. (2020) [24]	Cost per hospitalization (derived from hospital charges using the cost-to-charge ratio from the HCUP)	Healthcare/payer	US dollar (\$); 2014	Mean (geometric) per-patient cost per hospitalization (pemphigus, <i>n</i> = NR): \$14,970 [\$15,880] Mean (geometric) per-patient cost per hospitalization (pemphigoid, <i>n</i> = NR): \$13,300 [\$14,110]	Selection: ◇◇◇◇ Comparability: ◇ (age and sex NR) Outcome: ◇◇◇
Ogino et al. (2017) [17]	Direct medical cost	Healthcare/payer	Yen (¥); 2016	Mean per-patient annual direct medical cost (<i>n</i> = NR): ¥82,940 [\$760]	Selection: ◇◇◇◇ Comparability: ◇ (age and sex NR) Outcome: ◇◇◇

Table 2 (continued)

Author (year)	Estimated cost(s)	Perspective of analysis	Currency; year of valuation	Cost result(s) [in 2018 US dollars [§]]	Risk of bias [†]
Omorodion et al. (2017) [18]	Cost per hospitalization (i.e. total hospital charge)	Healthcare/payer	US dollar (\$); 2013	<p>Mean per-patient cost per hospitalization (pooled sample, $n = 5535$): \$98,800 [\$106,490]</p> <p>Mean per-patient cost per hospitalization (age: 1–7 years, $n = 145$): \$66,860 [\$72,070]</p> <p>Mean per-patient cost per hospitalization (age: 18–44 years, $n = 1195$): \$82,790 [\$89,240]</p> <p>Mean per-patient cost per hospitalization (age: 45–64 years, $n = 1705$): \$93,030 [\$100,280]</p> <p>Mean per-patient cost per hospitalization (age: 65–84 years, $n = 2165$): \$117,000 [\$126,110]</p> <p>Mean per-patient cost per hospitalization (age: ≥ 85 years, $n = 320$): \$83,710 [\$90,240]</p> <p>Mean per-patient cost per hospitalization (males, $n = 2380$): \$110,490 [\$119,100]</p> <p>Mean per-patient cost per hospitalization (females, $n = 3150$): \$90,290 [\$97,330]</p>	<p>Selection: $\diamond\diamond\diamond\diamond$</p> <p>Comparability: $\diamond\diamond$</p> <p>Outcome: $\diamond\diamond\diamond$</p>
Schepelmann et al. (2010) [19]	Direct medical cost; indirect cost (production losses due to absenteeism and presenteeism, as well as informal care, estimated using the HCA); and total cost of illness	Societal	Euro (€); 2009	<p>Mean per-patient annual direct medical cost ($n = 41$): €11,840 [\$15,050]</p> <p>Mean per-patient annual indirect cost (including informal care) ($n = 41$): €2790 [\$3550]</p> <p>Mean per-patient annual informal care cost ($n = 41$): €910 [\$1160]</p> <p>Mean per-patient annual total cost of illness ($n = 41$): €14,950 [\$19,000]</p> <p>Mean per-patient annual total cost of illness (ADL assistance, $n = \text{NR}$): €44,690 [\$56,800]</p> <p>Mean per-patient annual total cost of illness (no ADL assistance, $n = \text{NR}$): €11,360 [\$14,440]</p>	<p>Selection: $\diamond\diamond\diamond\diamond$</p> <p>Comparability: $\diamond\diamond$</p> <p>Outcome: $\diamond\diamond$ (self-reported data)</p>

Table 2 (continued)

Author (year)	Estimated cost(s)	Perspective of analysis	Currency; year of valuation	Cost result(s) [in 2018 US dollars [§]]	Risk of bias [†]
Sonkar et al. (2017) [20]	Direct medical cost (i.e. out-of-pocket expenditures incurred during the management of MG and associated co-morbidities ^b); indirect cost (i.e. production losses due to absenteeism and presenteeism) estimated using the HCA ^g	Societal	Indian rupee (₹); 2016	Median per-patient annual direct medical cost ($n=66$): ₹48,570 [₹730] Median per-patient annual indirect cost ($n=66$): ₹5100 [₹80] Median per-patient annual total cost of illness ($n=66$): ₹61,390 [₹920]	Selection: ◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇ (self-reported data)
Souayah et al. (2009) [21]	Cost per hospitalization (i.e. total hospital charge)	Healthcare/payer	US dollar (\$); 2002	Mean per-patient cost per hospitalization (pooled sample, $n=994$): \$118,000 [\$164,730] Mean per-patient cost per hospitalization (age: <50 years, $n=196$): \$113,100 [\$157,890] Mean per-patient cost per hospitalization (age: ≥50 years, $n=798$): \$119,100 [\$166,260] Mean per-patient cost per hospitalization (urban teaching hospital, $n=NR$): \$75,200 [\$104,980] Mean per-patient cost per hospitalization (urban non-teaching hospital, $n=NR$): \$118,300 [\$165,150]	Selection: ◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇◇◇
Tiankao et al. (2014) [22]	Cost per hospitalization (i.e. total hospital charge)	Healthcare/payer	Thai baht (฿); 2010	Mean per-patient cost per hospitalization ($n=936$): ฿68,730 [฿2550]	Selection: ◇◇◇◇ Comparability: ◇◇ Outcome: ◇◇◇◇

Costs were rounded to the nearest ten

Details of resources included in estimates of direct medical costs are presented in Table 3

ADL activities of daily living, *HCA* human capital approach, *HCUP* Healthcare Cost and Utilization Project, *IVI* intravenous immunoglobulin, *MG* myasthenia gravis, *NR* not reported, *PLEX* plasma exchange

[§]Converted to United States (US) dollars (\$) [Colombian peso COL\$1 = \$0.00030; Canadian dollar C\$1 = \$0.747; New Taiwan dollar NT\$1 = \$0.032; Yen ¥1 = \$0.009; Euro (German) €1 = \$1.130; Indian rupee ₹1 = \$0.014; and Thai baht ฿1 = \$0.033] and inflated to 2018 values using consumer price index data from the World Bank [7]

[†]Assessed with the Newcastle–Ottawa Scale. Maximum score: ◇◇◇◇ for selection, ◇◇◇◇ for comparability, and ◇◇◇◇ for outcome (see “Methods” section for details)

^aIn the absence of data, year of valuation was assumed to be 2014

^bIn the absence of data, year of valuation was assumed to be 2010

^cIn the absence of data, year of valuation was assumed to be 2009

^dIn the absence of data, year of valuation was assumed to be 2005

^eIn the absence of data, year of valuation was assumed to be 2016

^fIncluding costs of transportation to the hospital, subsequent hospitalization, over-the-counter medications, laboratory tests, and the food consumed during the waiting period

^gIndirect cost of illness also included time lost for the patient and caregivers (valued at the daily wage), as well as caregivers’ expenditure for travel, food, and stay while in hospital

Table 3 Resources included in identified estimates of the direct medical cost of MG

Author (year)	Inpatient care	Outpatient care	Prescription drugs	OTC drugs	IVIG/PLEX	Co-payments
Ogino et al. (2017) [17]	×	×	×		NR	
Sonkar et al. (2017) [20]	×	×	×	×	×	NA ^a
Guptill et al. (2011) [11]	×	×	×	×	×	
Guptill et al. (2012) [12]	×	×	×	×	×	
Lai et al. and Tseng (2010) [14]	×	×			NR	
Schepelmann et al. (2010) [19]	×	×	×	NR	NR	×

IVIG intravenous immunoglobulin, MG myasthenia gravis, NA not applicable, NR not reported (i.e. the information was not provided, but the specific resource category could have been included in the estimation, for example, as part of higher level cost categories), OTC over-the-counter, PLEX plasma exchange

^aThe direct medical cost was estimated based on patients' out-of-pocket expenditure

^bExcluding inpatient IVIG costs

at \$19,000 in Germany [19]. Patients who required assistance with activities of daily living were found to have significantly higher costs than those who did not (\$56,800 vs. \$14,440), and there was a trend of higher costs for older patient groups. Additional details of identified costs are presented in Table 2.

In total, 56% (nine of 16) of included studies were judged to have low risk of bias as assessed using the NOS (see Table 1). Reasons for increased risk of bias included limited comparability due to inadequate description of the distribution of age and sex in the studied samples [9, 13, 14, 17, 20, 24], and self-reported data [19, 20].

4 Discussion

In this study, we systematically reviewed the literature for estimates of costs associated with MG. Our findings, spanning eight countries across four continents, show that specific components of the cost burden are relatively well-described in some settings (e.g. the direct medical cost in the US), but also reveal that up-to-date data are lacking for many resource categories and countries. Our synthesis of data also demonstrates that resource use and accompanying costs associated with MG appear to be sensitive to geographic variation in healthcare systems, as well as the medical management of the disease. This is true both within and between countries. We also noted that costs depend heavily on demographic and clinical characteristics of the underlying patient populations.

We identified six estimates of the mean per-patient annual direct medical cost of illness of MG. As expected, due to differences in the organization, provision, and utilization of healthcare and currency purchasing power (among other factors), costs for the US (\$28,780 [11] and \$23,630 [12]) were notably higher than estimates derived from samples from India (\$730) [20] and Taiwan (\$1780) [14], but also

Germany (\$15,050) [19] and in particular Japan (\$760) [17]. One reason for this heterogeneity, in addition to actual differences across countries in the medical management of MG, includes variability in resources included in the analysis (as illustrated in Table 3). For example, US estimates included parts of costs associated with IVIG and PLEX (which have, in a separate US study [15], been estimated at \$28,080 and \$35,450 in patients with MG, respectively), whereas the Japanese study did not. In addition, it is worth noting that, according to the Organisation for Economic Co-operation and Development (OECD) [25], purchasing power parity-adjusted health expenditure per capita is more than twice as large in the US compared with Japan. Observed differences in costs could also be a function of the employed perspective of analysis (e.g. healthcare/payer vs. societal) and valuation of included resources. Interestingly, to further analyse the added direct medical costs associated with MG in the US, Gupta et al. [12] included a matched control group comprising non-MG members of the general population. The mean per-patient annual cost attributable to the medical management of MG was \$15,680 (\$18,350 in 2018 values), making up 78% of the total direct medical cost recorded. This indicates that MG typically dominates over other medical co-morbidities, as costs associated with the disease formed the majority of healthcare expenditures.

Our review also shows that published data of the mean per-patient cost per hospitalization vary substantially across studies, settings, and sample characteristics. Similar to estimates of direct medical costs, this variability is due to inter-study differences pertaining to the disease severity and morbidity profile of the hospitalized patients, the inpatient care of MG, and included resources and their valuation, among other factors. Although not part of the data extraction, two studies reported that costs cost per hospitalization associated with MG had risen over time in the US. Souayah et al. [21] found that the mean charge for patients hospitalized for MG requiring continuous mechanical ventilation had

increased by 40% (\$84,100 vs. \$118,000) from 1991–1992 to 2001–2002. However, the increase was only seen in patients admitted to urban non-teaching hospitals. Conversely, for urban teaching hospitals, total charges during the same 10-year period decreased. Given the data in the article, it is not possible to directly investigate reasons for this development. The second study [18] that examined costs over time found that the total mean per-patient charge per hospital admission for MG exacerbation in the US increased by 135% (\$48,020 vs. \$98,800) from 2003 to 2013. The authors suggest that this increase might be attributed to changes in the underlying practice pattern of the disease, a rise in the prevalence of MG among the elderly (a subpopulation that on average has higher resource needs and costs compared with younger individuals), and/or increased utilization and costs of IVIG and PLEX over time. Interestingly, in the same study, the mean per-patient cost per hospitalization of multiple sclerosis also rose by an almost identical proportion (106%) from 2003 to 2013 [18], indicating that the increase may be related to more general (non-disease-specific) factors within the healthcare system.

We identified a total of four studies that reported stratified cost estimates by patient age and/or disease status/severity. Guptill et al. [11] found that patients incurred the highest total direct medical costs during their second and third decade of life (possibly due to a higher frequency of thymectomy and/or non-steroidal immunosuppressive agents in this age group, according to the authors). In contrast, Omorodion et al. [18] found that the mean cost per hospitalization was highest in the oldest patients (i.e. 65–84 years of age), in line with findings reported by Souayah et al. [21] for patients ≥ 50 years of age versus < 50 years (Table 2). Finally, Schepelmann et al. [19] estimated the mean per-patient annual total cost of illness in patients requiring assistance with activities of daily living at \$56,800, markedly higher than estimates for those without assistance (\$14,440). This surprisingly wide range in costs is indicative of the heterogeneous presentation of the disease between patients and across the varying disease evolution, and clearly illustrates the importance of appropriately stratifying estimates of costs of MG to allow for meaningful interpretation.

We identified one publication that reported estimates of costs associated with informal care of patients with MG. Schepelmann et al. [19] quantified annual costs associated with informal care by family and friends (based on the number of hours of informal care provided) in Germany at \$1160, markedly lower than estimates from the same study for amyotrophic lateral sclerosis (\$17,170) and facioscapulohumeral muscular dystrophy (\$9230), as well as published estimates for German patients with Duchenne muscular dystrophy (DMD) (\$20,266) [26]. Additionally, the indirect costs of MG, quantified as production losses due to patient absenteeism and presenteeism estimated using the

human capital approach, were investigated by Schepelmann et al. [19] and Sonkar et al. [20]. Given that informal care accounts for the majority of the day-to-day long-term care of many chronic illnesses, in particular for chronic diseases with onset in childhood, further research of this cost category in MG is warranted. In particular, to avoid underestimating the monetary burden of the disease, future studies should aim to assess patient and caregiver indirect (productivity) costs and informal care costs as separate mutually exclusive subsets of total costs [6].

There are several implications of our review for health policy and future research. First, it is important to underscore that the outcomes do not provide any direct guidance of the cost-effectiveness of current or forthcoming health technologies targeting MG (as such economic evaluations compare both costs and benefits from alternative uses of resources). That being said, our results do show that, based on the existing body of evidence, it may prove challenging to conduct economic evaluations of treatments for MG considering the lack of comprehensive cost data in many settings. Indeed, for most evaluations and countries, depending on the complexity of the underlying cost-effectiveness model and the analysis, it will likely be necessary to conduct new cost studies. Second, considering the relatively high inter-patient variability in costs observed in our review, it appears essential to appropriately stratify costs (and related health economic outcomes) in future research, and also carefully document employed study criteria to ensure adequate interpretation of validity, both internal and external. Third, due to the relatively high costs associated with the treatment and management of the disease, it is not obvious that an intervention significantly improving prognosis for survival in MG would be cost-effective. This phenomenon, which was recently discussed in the context of DMD [27], emerges when the annual direct medical cost of illness is greater than the willingness to pay (WTP) for the effect outcome of interest [e.g. quality-adjusted life-years (QALYs), constructed by multiplying every life-year with a quality weight reflecting health-related quality of life] as applied in the evaluation. For example, using data from Guptill et al. [12], extending life by 1 year for a US patient with MG would, on average, be associated with a direct medical cost of \$23,250 (not accounting for the cost of the intervention). This cost can then be related to the benefit, which is 1 life-year, or 0.69 QALYs (using recently published SF-6D utility data for MG from Barnett et al. [28]), resulting in an incremental cost-effectiveness ratio (ICER) of $\$23,250/0.69 \approx \$35,000$. Considering that prices for orphan drugs in many cases exceed \$100,000 per annum [29], the total cost per QALY would be \$135,000, higher than commonly employed WTP thresholds for QALYs in most jurisdictions. Accounting for additional disease-related costs, such as direct non-medical and indirect costs, this estimate would increase considerably.

That being said, future treatments may be associated with significant cost offsets (e.g. from avoiding hospitalizations), which would alter the distribution of costs and evaluation outcomes. Fourth, and last, from our review it is evident that any measures that help reduce the need for IVIG/PLEX (e.g. careful compliance to care guidelines, timely discontinuation of treatments for non-responders, and alternative/new therapies) would have a major impact on the individual cost burden of MG.

A limitation with our review is related to the fact that we, due to considerable inter-study heterogeneity, were unable to perform a proper meta-analysis [30]. Given that our search strategy limited the review to publications indexed in five principal bibliographic databases, studies published in local journals were not covered, which could potentially help explain the low number of studies for some geographical settings and regions. Concerning our findings, it is also worth noting that the costs identified in this review would not be expected to be directly transferable to other settings (because of, e.g., local/national prices and healthcare systems). Additionally, older point estimates (e.g. from Souayah et al. [21], Mandawat et al. [15], and Schepelmann et al. [19]) should be interpreted with some caution, as they may not be representative of the current medical management of the disease, and because opportunity costs of the underlying resources may have developed differently than inflation. Finally, despite being attributed a relatively low risk of bias as assessed using the NOS, all of the included studies were observational in nature, which means that they may still lack quality (due to, e.g., selection, confounding, and/or information bias). That being said, it should be noted that intervention-specific costs reported by Furlan et al. [10] were derived based on clinical data from a randomized controlled trial, which would imply a lower risk of confounding with respect to treatment allocation and associated outcomes.

5 Conclusion

We show that the current body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability, both within and between countries. Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

Acknowledgements Open access funding provided by Karolinska Institute.

Author Contributions Dr. Landfeldt conceptualized and designed the study, conducted the literature review and the analysis, led the interpretation of findings, drafted the manuscript, critically reviewed the manuscript for important intellectual content, and approved the final

manuscript version as submitted. Dr. Pogoryelova conducted the literature review, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Sejersen interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Zethraeus interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Dr. Breiner interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Lochmüller conceptualized and designed the study, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted.

Data Availability Statement All data analysed as part of this study are included in this published article (and its supplementary information files).

Compliance with Ethical Standards

Funding None.

Conflict of interest Dr. Landfeldt is an employee of ICON plc (Stockholm, Sweden), outside the submitted work. Dr. Pogoryelova is an employee of Absolute Antibody (Red Car, UK), outside the submitted work. Professor Sejersen, Professor Zethraeus, Dr. Breiner, and Professor Lochmüller declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. Konecny I, Herbst R (2019) Myasthenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. *Cells*. <https://doi.org/10.3390/cells8070671>.
2. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: association of British Neurologists' management guidelines. *Pract Neurol*. 2015;15(3):199–206. <https://doi.org/10.1136/practneurol-2015-001126>.
3. Silvestri NJ, Wolfe GI. Treatment-refractory myasthenia gravis. *J Clin Neuromusc Dis*. 2014;15(4):167–78. <https://doi.org/10.1097/cnd.0000000000000034>.
4. Cai XJ, Li ZW, Xi JY, Song HZ, Liu J, Zhu WH, Guo Y, Jiao Z. Myasthenia gravis and specific immunotherapy: monoclonal antibodies. *Ann N Y Acad Sci*. 2019. <https://doi.org/10.1111/nyas.14195>.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the

- PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.
6. Landfeldt E, Zethraeus N, Lindgren P. Standardized questionnaire for the measurement, valuation, and estimation of costs of informal care based on the opportunity cost and proxy good method. *Appl Health Econ Health Policy.* 2019;17(1):15–24. <https://doi.org/10.1007/s40258-018-0418-2>.
 7. The World Bank. <https://www.worldbank.org/>. Accessed 13 Sep 2019.
 8. Wells G, Shea B, O'Connell J, Robertson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 5 Jan 2019.
 9. Chicaiza-Becerra LA, Garcia-Molina M, Gamboa O, Castaneda-Orjuela C. The cost-effectiveness of open or thoracoscopic thymectomy compared to medical treatment in managing myasthenia gravis without thymomas. *Revista de salud publica (Bogota, Colombia).* 2012;14(2):260–70. <https://doi.org/10.1590/s0124-00642012000200007>.
 10. Furlan JC, Barth D, Barnett C, Bril V. Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis. *Muscle Nerve.* 2016;53(6):872–6. <https://doi.org/10.1002/mus.24960>.
 11. Guptill JT, Marano A, Krueger A, Sanders DB (2011) Cost analysis of myasthenia gravis from a large U.S. insurance database. *Muscle Nerve.* 44 (6):907–911. <https://doi.org/10.1002/mus.22212>.
 12. Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB (2012) Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle Nerve* 45(3):363–366. <https://doi.org/10.1002/mus.22327>.
 13. 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 Neuromusc Dis.* 2011;13(2):85–94. <https://doi.org/10.1097/CND.0b013e31822c34dd>.
 14. Lai CH, Tseng HF. Nationwide population-based epidemiological study of myasthenia gravis in Taiwan. *Neuroepidemiology.* 2010;35(1):66–71. <https://doi.org/10.1159/000311012>.
 15. Mandawat A, Kaminski HJ, Cutter G, Katirji B, Alshekhlee A. Comparative analysis of therapeutic options used for myasthenia gravis. *Ann Neurol.* 2010;68(6):797–805. <https://doi.org/10.1002/ana.22139>.
 16. Mouri H, Jo T, Matsui H, Fushimi K, Yasunaga H. Effect of sugammadex on postoperative myasthenic crisis in myasthenia gravis patients: propensity score analysis of a Japanese nationwide database. *Anesth Analg.* 2019. <https://doi.org/10.1213/ane.0000000000004239>.
 17. Ogino M, Okamoto S, Ohta H, Sakamoto M, Nakamura Y, Iwasaki K, Yoshida M, Hiroi S, Kawachi I. Prevalence, treatments and medical cost of multiple sclerosis in Japan based on analysis of a health insurance claims database. *Clin Exp Neuroimmunol.* 2017;8(4):318–26. <https://doi.org/10.1111/cen3.12411>.
 18. Omorodion JO, Pines JM, Kaminski HJ. Inpatient cost analysis for treatment of myasthenia gravis. *Muscle Nerve.* 2017;56(6):1114–8. <https://doi.org/10.1002/mus.25624>.
 19. Schepelmann K, Winter Y, Spottke AE, Claus D, Grothe C, Schroder R, Heuss D, Vielhaber S, Mylius V, Kiefer R, Schrank B, Oertel WH, Dodel R. Socioeconomic burden of amyotrophic lateral sclerosis, myasthenia gravis and facioscapulohumeral muscular dystrophy. *J Neurol.* 2010;257(1):15–23. <https://doi.org/10.1007/s00415-009-5256-6>.
 20. Sonkar KK, Bhoi SK, Dubey D, Kalita J, Misra UK. Direct and indirect cost of myasthenia gravis: a prospective study from a tertiary care teaching hospital in India. *J Clin Neurosci.* 2017;38:114–7. <https://doi.org/10.1016/j.jocn.2016.11.003>.
 21. 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 IJBS.* 2009;5(3):209–14.
 22. Tiamkao S, Pranboon S, Thepsuthammarat K, Sawanyawisuth K. Prevalence of factors associated with poor outcomes of hospitalized myasthenia gravis patients in Thailand. *Neurosciences (Riyadh, Saudi Arabia).* 2014;19(4):286–90.
 23. Desai R, Abbas SA, Fong HK, Lodhi MU, Doshi R, Savani S, Gangani K, Sachdeva R, Kumar G. Burden and impact of takotsubo syndrome in myasthenic crisis: a national inpatient perspective on the under-recognized but potentially fatal association. *Int J Cardiol.* 2020;299:63–6. <https://doi.org/10.1016/j.ijcard.2019.09.054>.
 24. Narla S, Silverberg JJ. Associations of pemphigus or pemphigoid with autoimmune disorders in US adult inpatients. *J Am Acad Dermatol.* 2020;82(3):586–95. <https://doi.org/10.1016/j.jaad.2019.07.029>.
 25. Organisation for Economic Co-operation and Development. OECD.Stat Extracts. Available at: <http://stats.oecd.org>. Accessed June 2019.
 26. Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, Lochmuller H, Bushby K. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. *Neurology.* 2014;83(6):529–36. <https://doi.org/10.1212/wnl.0000000000000669>.
 27. Landfeldt E. Extending life in Duchenne muscular dystrophy: implications for appraisals of cost-effectiveness. *Pharmaco-Econom Open.* 2019;3(3):279–80. <https://doi.org/10.1007/s41669-018-0107-y>.
 28. Barnett C, Bril V, Bayoumi AM. EQ-5D-5L and SF-6D health utility index scores in patients with myasthenia gravis. *Eur J Neurol.* 2019;26(3):452–9. <https://doi.org/10.1111/ene.13836>.
 29. Picavet E, Morel T, Cassiman D, Simoons S. Shining a light in the black box of orphan drug pricing. *Orphanet J Rare Dis.* 2014;9:62. <https://doi.org/10.1186/1750-1172-9-62>.
 30. Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Effect Resour Alloc C/E.* 2003;1(1):8. <https://doi.org/10.1186/1478-7547-1-8>.