

A retrospective observational study on characteristics, treatment patterns, and healthcare resource use of patients with myasthenia gravis in England

van Enkhuizen, Jordy; Binns, Jean; Betts, April; Hosnijeh, Fatemeh Saberi; Alexander, Myriam; McCormack, Mark; Jacob, Saiju

DOI:

[10.1177/17562864241237495](https://doi.org/10.1177/17562864241237495)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

van Enkhuizen, J, Binns, J, Betts, A, Hosnijeh, FS, Alexander, M, McCormack, M & Jacob, S 2024, 'A retrospective observational study on characteristics, treatment patterns, and healthcare resource use of patients with myasthenia gravis in England', *Therapeutic advances in neurological disorders*, vol. 17. <https://doi.org/10.1177/17562864241237495>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

A retrospective observational study on characteristics, treatment patterns, and healthcare resource use of patients with myasthenia gravis in England

Jordy van Enkhuizen¹, Jean Binns, April Betts, Fatemeh Saberi Hosnijeh, Myriam Alexander, Mark McCormack and Saiju Jacob

Ther Adv Neurol Disord

2024, Vol. 17: 1–13

DOI: 10.1177/
17562864241237495

© The Author(s), 2024.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

Background: There are limited data on the real-world healthcare resource use (HCRU) and management costs of myasthenia gravis (MG) in England.

Objective: This study aims to assess the burden of disease for patients with MG in England.

Design: A retrospective, observational cohort study of adult patients diagnosed with MG, using data from the Hospital Episode Statistics data warehouse.

Methods: Patients with a first-ever recorded diagnosis of MG between 30 June 2015 and 30 June 2020 were followed up until 30 June 2021 or death, whichever occurred first. Post-diagnosis patient characteristics, treatment patterns, HCRU, and costs were described. Costs were evaluated using National Health Service reference costs.

Results: A total of 9087 patients with a median follow-up time of 2.9 years (range, 1.7–4.3 years) were included. The mean age at diagnosis was 66.5 years and 53% of the patients were male. A large proportion of patients (72.8%) were admitted as inpatients during follow-up with a mean number of 1.3 admissions. Patients hospitalized for MG-related complications spent a mean of 9.7 days per patient-year in the hospital. During follow-up, 599 (6.6% of the total cohort) and 163 (1.8%) patients had a record of rescue therapy with intravenous immunoglobulin (IVIg) and plasma exchange (PLEX), respectively. Rituximab was administered to 81 (0.9%) patients and 268 (2.9%) patients underwent thymectomy. In those patients receiving rescue therapy or rituximab, >10% received at least three cycles of the same treatment. The average annual cost of hospital admissions across all patients treated with IVIg, PLEX, and rituximab were £907,072, £689,979, and £146,726, respectively.

Conclusion: A majority of MG patients required hospitalization or accident and emergency attendance, resulting in high HCRU and costs. A subset of patients required rescue therapy (including IVIg and PLEX), rituximab administration, ventilation, or thymectomy.

Keywords: costs, England, hospital, immunoglobulin, myasthenia gravis, resource use

Received: 27 October 2023; revised manuscript accepted: 13 February 2024.

Introduction

Myasthenia gravis (MG) is a rare, chronic autoimmune disease that affects the neuromuscular junction (NMJ).¹ MG is characterized by the production of pathogenic autoantibodies that bind to components of the NMJ, with the most common

being the acetylcholine receptor, muscle-specific tyrosine kinase (MuSK), or lipoprotein receptor-related protein 4.² The prevalence and incidence of MG in the UK have been estimated at 33.7 [confidence interval (CI): 32.7–34.7] cases per 100,000 population and 2.46 (CI: 2.34–2.59)

Correspondence to:
Jordy van Enkhuizen
UCB Pharma, 216 Bath
Road, Slough, Berkshire
SL1 3WE, UK
jordy.vanenkhuizen@
ucb.com

Jean Binns
April Betts
UCB Pharma, Slough, UK

Fatemeh Saberi Hosnijeh
Real-World Evidence,
Modelling and Meta-
Analysis, OPEN Health,
Rotterdam, The
Netherlands

Myriam Alexander
Mark McCormack
Real-World Evidence,
OPEN Health, London, UK

Saiju Jacob
Department of Neurology
and Centre for Rare
Diseases, Institute
of Immunology and
Immunotherapy,
University of Birmingham,
Edgbaston, Birmingham,
UK

cases per 100,000 person-years, respectively, and both are on the rise since 2008.³

Acetylcholinesterase inhibitors (AChEIs) are the preferred first-line symptomatic treatment, followed by corticosteroids, non-steroidal immunosuppressants, and thymectomy.⁴ In cases of myasthenic exacerbation or myasthenic crisis (a life-threatening condition due to respiratory muscle weakness and swallowing difficulties), immediate hospitalization and rescue therapy with plasma exchange (PLEX), intravenous immunoglobulin (IVIg), ventilation, or immunoadsorption may be required.⁵⁻⁷ Patients are considered to have refractory MG if they fail to respond adequately to conventional therapies, are unable to reduce immunosuppressive therapies without relapses, or have frequent myasthenic crises even while on therapy.⁶ Care of these patients places a significant burden on the healthcare system.

A recent systematic review including 16 studies found that the current body of literature on healthcare resource use (HCRU) and cost of MG management is sparse and limited to a few geographical settings and resource categories.⁸ In England, one study found that patients with refractory MG had significantly higher secondary HCRU than patients with non-refractory MG; however, the study did not include an estimation of associated costs of care.⁹ The current study aimed to evaluate the burden of MG on secondary care settings across England, and to gain a better understanding of the baseline characteristics, treatment, HCRU, and associated costs in patients with newly diagnosed MG.

Methods

Data source and study population

Hospital Episode Statistics (HES) is a secondary care data warehouse that contains pseudonymized records of all patients admitted to the NHS hospitals in England, with data stored on hospital diagnoses, procedures, treatment, HCRU [including inpatient admissions, attendance at outpatient departments, and accident and emergency (A&E)], and associated costs for the past 10 years.¹⁰ In this retrospective, longitudinal, observational cohort study, adult patients (age ≥ 18 years) were included if they had a first-ever recorded diagnosis of MG (index date) between 30 June 2015 and 30 June 2020 (eligibility period)

in the HES. Patients were described for the 12-month period prior to the index date (baseline) and followed up from the index date until 30 June 2021 or death, whichever occurred first. Access to HES was provided under license *via* Harvey Walsh Ltd from National Health Service (NHS) Digital (Data Sharing Agreement: DARS-NIC-05934-M7V9K).

The International Statistical Classification of Diseases and Related Health Problems 10th Revision codes were used to define diagnoses including MG (G700) recorded either in inpatient or outpatient settings. Of note, as the recording of diagnosis does not form any part of the UK NHS costing system in an outpatient setting, a significant under-recording of patients receiving diagnosis in that setting is therefore likely. The Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 codes were used to classify interventions, procedures, and procurement for treatment; and Healthcare Resource Group (HRG) NHS tariff codes were used to define activity-based costs.¹¹ The HRGs were costed using Payment by Results tariffs.¹²

Data extracted included patient demographics at the index date (age, sex, ethnicity, geographic region, index of multiple deprivation), baseline pre-specified comorbidities known to be associated with MG, and baseline Charlson comorbidity index (CCI) score.^{13,14} The CCI score was calculated using the summary hospital-level mortality indicator with UK-adapted weights¹⁵ (Supplemental Table 1). The proportion of patients with mild (1–2), moderate (3–4), and severe CCI scores (≥ 5) were reported. Types and dates of rescue therapies (IVIg, PLEX), rituximab administration, ventilation, and thymectomy procedures provided in the hospital, as well as HCRU during the follow-up period (outpatient visits, inpatient hospitalizations and length of stay, A&E attendances), were extracted. This study also evaluated HCRU based on a history of rituximab treatment, as these patients are more likely to be refractory and thus are expected to require more healthcare needs/costs. Cost of treatment included all activities occurring during an inpatient spell or outpatient visit for a specific treatment, with only the relevant high-cost drugs being included, because administration of other specific treatments (e.g. AChEIs, corticosteroids, or other first-line non-steroidal immunosuppressants) is not available in HES.¹⁶

Acquisition costs of drugs were also not available.¹⁶

Statistical analysis

All analyses were descriptive. Continuous variables were analyzed using mean, standard deviation (SD), median, and interquartile range as appropriate, and categorical variables were presented using frequency counts and proportions. The number of inpatient treatments received by each patient was counted as the number of individual hospital spells, which encompassed the total duration of hospitalization from admission to discharge. To estimate the incidence of MG in the general population, a total adult population of 43 million in England was assumed.¹⁷

HCRU was summarized per patient per year for those with at least one attendance, and the frequency of non-attendances was also reported. The cumulative cost of admission for patients undergoing specific procedures (IVIg, PLEX, and rituximab) was calculated by multiplying the mean cost per patient per year by the number of patients. HCRU and treatment were summarized overall and by subgroups, including sex, age at index diagnosis (<50 and ≥50), and year of first recorded diagnosis (2015–2020). For the age subgroups, all treatments were aggregated across patients, and age at treatment administration was used rather than age at index diagnosis.

Missing data were reported, but to comply with HES guidance, frequencies estimated in less than five patients were suppressed to preserve patients' confidentiality, and other related frequencies were rounded to prevent back-calculation of the suppressed numbers.¹⁸

Results

Study participants

We identified 9087 patients with a diagnosis of MG in HES who were included in the study (Table 1). The majority of patients had their index diagnosis recorded during an inpatient stay (89.5%), with the most common departments being General Internal Medicine (23.2%) and the Neurology department (21.1%; Figure 1).

A mean of 1859 patients were diagnosed with MG each year, resulting in an estimated MG

incidence of 4.32 (95% CI: 4.13–4.52) per 100,000 population per year. The median follow-up was 2.9 years (Q1–Q3: 1.7–4.3). Of the overall cohort, 8398 (92.4%), 8098 (89.1%), and 6295 (69.3%) patients had data available for at least 6, 12, and 24 months of follow-up period, respectively.

Patients' characteristics

The mean (SD) age of patients at diagnosis was 66.5 ± 16.7 years; 53.1% were male, 77.8% were white, and 10.5% lived in the most socioeconomically deprived areas in England (Table 1). At diagnosis, 83.8% of patients were aged ≥50 years (Supplemental Table 2), and females were, on average, 6 years younger than males (mean 63.4 *versus* 69.4 years).

At baseline, nearly half of the patients (49.7%) had mild CCI scores, 19.0% had moderate scores, and 20.8% had severe scores (Table 1). The most common comorbidities during the baseline period were hypertension (16.2%), diabetes mellitus (7.5%), chronic kidney diseases (3.2%), and chronic obstructive pulmonary disease (3%) (Supplemental Table 2). Neurology and ophthalmology were the most common last specialty outpatient visits prior to MG diagnosis (Figure 1) and 3 months before MG diagnosis (Supplemental Table 2).

Treatments administered in secondary care

During the full follow-up period, 599 (6.6% of the total cohort) and 163 (1.8%) patients were prescribed IVIg and PLEX, respectively (Table 2). Rituximab was administered to 81 (0.9%) patients, and 480 (5.3%) patients were ventilated. In those treated, the mean number of treatment cycles per patient was 2.3 for IVIg, 2.0 for PLEX, 1.7 for rituximab, and 1.3 for ventilation during the follow-up period (Table 3). The majority of patients receiving PLEX required it as an acute short-term treatment (American Society for Apheresis category I; Table 3). In total, 2.9% ($n=268$) of patients underwent thymectomy. For all calendar years between 2015 and 2020, IVIg was the most frequently prescribed treatment (Supplemental Figure 1). Although not tested statistically, we observed a decreasing proportion of patients received IVIg treatment by calendar year; 62.8% of all patients received high-cost treatment and procedures in 2015 *versus* 43.5%

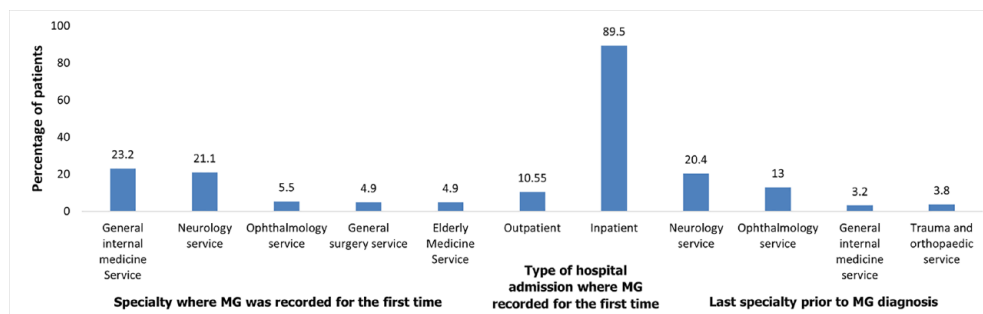


Figure 1. Referral pathways in patients diagnosed with MG.

of those in 2020, and similarly for thymectomy; 25.5% of all patients received high-cost treatment and procedures in 2015 *versus* 12.6% of those in 2020 (Supplemental Figure 1). Few patients received both IVIg and PLEX ($n=70$) during follow-up; rituximab and PLEX ($n=25$); or IVIg, PLEX, and rituximab ($n=16$); however, a considerable subset of those who did receive ≥ 3 treatments (32/70, 16/25, and 14/16 patients, respectively) (Table 3).

Equal proportions of males and females received IVIg and PLEX, while approximately twice as many females received rituximab ($n=55$ *versus* $n=26$ for males; Table 2) or thymectomy ($n=174$ *versus* 94 for males). IVIg and PLEX treatments occurred in equal proportions across age groups (at treatment time), whereas 12% of all treated patients aged <50 years received rituximab and 5% of those ≥ 50 years. Equally, thymectomy occurred more at a younger age (45% of all treated patients aged <50 years *versus* 15% of those aged ≥ 50 years; Supplemental Table 3).

Healthcare resource utilization

The proportion of patients with ≥ 1 attendance at 6 months was 85.6% for outpatient visits, 42.5% for inpatient admissions, 4.2% for critical care admissions, and 26.8% for A&E attendances; and for all follow-up was 92.4% outpatient, 72.8% inpatient, 9.7% critical care, and 51% A&E (Table 4).

In those with ≥ 1 attendance, the mean \pm SD number of attendances for all patients' follow-up was: 7.1 \pm 10.5 outpatient visits per patient-year, 1.3 \pm 4.0 inpatient admissions per patient-year, 0.4 \pm 1.8 critical care admissions, and 0.9 \pm 2.7 A&E attendances (Table 4). Mean \pm SD of HCRU in those attending hospital was highest at

6 months follow-up and decreased afterward: at 6 months, there were on average 12.0 \pm 13.7 outpatient visits (9.9 at 12 months and 8.4 at 24 months follow-up), 4.5 \pm 5.9 inpatient admissions (2.8 at 12 months and 1.8 at 24 months follow-up), 3.6 \pm 4.3 A&E attendances per patient-year (2.3 at 12 months and 1.5 at 24 months follow-up), and 2.3 \pm 2.2 critical care admissions (Table 4).

The distribution of outpatient visits during the follow-up period is shown in Supplemental Table 4. Neurology service (a mean of 6.6 visits per patient) and ophthalmology service (a mean of 5.7 visits per patient) were the most frequently visited outpatient departments in the all-follow-up period in patients with ≥ 1 attendance. Myasthenia, gastroenterological, and cardiovascular complications were the most common primary diagnoses in inpatient admissions for patients with MG (Supplemental Table 5).

Patients hospitalized for MG-related complications stayed in the hospital for a mean \pm SD of 9.7 \pm 29.2 days per patient-year (Table 4) and the most common related complications were myopathy and neuropathy (Supplemental Table 5).

The mean number of A&E attendances, inpatient admissions, or outpatient visits did not differ considerably by sex or age group (Table 5)—.

Costs

The mean \pm SD cost of inpatient hospitalization for patients who incurred HCRU was £3226 \pm 13,142 per patient-year in all follow-up periods, with the lowest cost incurred by A&E attendance (£140 \pm 475 per patient-year; Table 4). The mean \pm SD cost per patient-year associated with the treatment administration based on the

Table 1. General characteristics of patients diagnosed with MG.

Patients' characteristics	All MG patients, N = 9087
Age at diagnosis, mean (SD)	66.5 (16.7)
Sex, N (%) ^a	
Male	4824 (53.1)
Female	4262 (46.9)
Index of multiple deprivation, N (%)	
Least deprived (≤10%)	689 (7.6)
Less deprived (10–50%)	4223 (46.5)
More deprived (50–90%)	2882 (31.7)
Most deprived (>90%)	953 (10.5)
Missing	340 (3.7)
Ethnicity, N (%)	
White	7073 (77.8)
Asian	285 (3.1)
Black	211 (2.3)
Mixed	51 (0.6)
Other	157 (1.7)
Missing	1310 (14.4)
Charlson comorbidity index, mean (SD)	3.23 (5.8)
Mild (0–2), N (%)	4517 (49.7)
Moderate (3–4), N (%)	1727 (19.0)
Severe (≥5), N (%)	1891 (20.8)
No score, N (%)	952 (10.5)
Calendar year, N (%)	
2015 ^b	937 (10.3)
2016	1783 (19.6)
2017	1871 (20.6)
2018	1954 (21.5)
2019	1829 (20.1)
2020 ^{b,c}	713 (7.9)
Follow-up duration, years, mean (SD)	3 (1.6)
Median (Q1–Q3)	2.9 (1.7–4.3)
^a Sex was missing for one patient.	
^b Data for 6 months	
^c Less patients due to the initiation of the COVID-19 pandemic.	
MG, myasthenia gravis; SD, standard deviation; Q, quartile.	

HRG recorded was highest for PLEX (£4233 ± 8928; Table 6). The cumulative costs of admissions for patients treated with IVIg ($n = 599$), PLEX ($n = 163$), and rituximab ($n = 81$) were £907,072, £689,979, and £146,726, respectively. In patients with a history of rituximab treatment, the mean cost related to all HCRU per patient-year for IVIg, ventilation, and PLEX was substantially higher than in those without a history of rituximab treatment (Supplemental Table 3).

Discussion

We performed a retrospective analysis of treatment patterns and HCRU for a large cohort of patients with MG diagnosed in secondary care settings in England, using HES data collected between 2014 and 2021. We found that myasthenic crisis and disease exacerbation in MG incur high HCRU and associated costs, with a subset of patients requiring rescue therapy beyond first-line medication.

This study found an estimated annual incidence for MG of 4.32 per 100,000 population. Limitations exist regarding the precision of this estimate due to the absence of direct denominator data in secondary healthcare settings. Notably, certain MG patients, particularly those with ocular or mild MG, may never require hospitalization, potentially leading to a skew toward patients with more severe MG. The lack of mandatory recording of outpatient diagnosis in HES may have led to an underestimate of the true incidence of MG and an over-representation of recorded inpatient MG diagnosis. Our findings align with a recent German study using anonymized insurance claims data, which reported an MG incidence of 4.6 cases per 100,000 individuals between 2015 and 2019.¹⁹ A previous UK study based on primary care data, however, reported a lower incidence rate ratio of 2.46 (CI: 2.34–2.59) per 100,000 person-years,³ though imprecision may arise from the absence of validated diagnoses in primary care records.

MG diagnoses were primarily documented in neurology or general medicine departments. However, a significant proportion of patients had previously visited neurology and ophthalmology outpatient departments, particularly within 3 months before MG diagnosis (index date). These outpatient visits likely aimed at obtaining a

Table 2. Patients' characteristics by type of rescue treatments or rituximab received at least once during follow-up.

Patients' characteristics	Treatment received (N cohort = 1057)			
	Rescue therapy		Ventilation, n = 480 (45.4%)	Rituximab, n = 81 (7.7%)
	IVIg, n = 599 (56.7%)	PLEX, n = 163 (15.4%)		
Age at diagnosis, mean (SD)	59.5 (17.7)	57.6 (16.8)	66.6 (14.8)	51.1 (16.4)
Sex, N (%)				
Male	299 (49.9)	85 (52.2)	282 (58.6)	26 (32.1)
Female	300 (50.1)	78 (47.9)	198 (41.3)	55 (67.9)
Charlson comorbidity index, mean (SD)	2.4 (5.0)	2.8 (5.9)	3.6 (5.3)	2.4 (4.6)
Mild (0–2), N (%)	366 (61.1)	100 (61.4)	229 (47.7)	49 (60.5)
Moderate (3–4), N (%)	100 (16.7)	25 (15.3)	109 (22.7)	17 (21)
Severe (≥5), N (%)	87 (14.5)	28 (17.2)	117 (24.4)	10 (12.5) ^a
No score, N (%)	46 (7.7)	10 (6.1)	25 (5.2)	<5
Follow-up duration, years, mean (SD)	3.5 (1.5)	3.3 (1.5)	2.8 (1.7)	3.9 (1.4)
Median (Q1–Q3)	3.6 (2.4–4.8)	3.3 (2.0–4.6)	2.7 (1.4–4.1)	4.0 (2.9–5.0)

^aNumber was rounded.
IVIg, intravenous immunoglobulin; PLEX, plasma exchange; Q, quartile; SD, standard deviation.

Table 3. Treatments administered in secondary care during follow-up in patients with MG who had a treatment record in HES.

Treatment	Number of patients ^a	≥3 treatments received in those receiving ≥1 treatment, for each treatment separately	The mean number of treatment spells/cycles per patient	Treatment received, by sex	
				Male, N = 564	Female, N = 493
Rescue therapy					
IVIg, N	599	83 (13.9%)	2.3	299 (53.0%)	300 (60.9%)
PLEX, N	163	17 (10.4%)	2.0 ^b	85 (15.1%)	78 (15.8%)
Rituximab, N	81	10 (12.3%)	1.7	26 (4.6%)	55 (11.2%)
Ventilation, N	480	27 (5.6%)	1.3	282 (50.0%)	198 (40.2%)
Multiple treatments in follow-up					
IVIg/PLEX, N	70	32 (45.7%)	4.7	35 (6.2%)	35 (7.1%)
Rituximab/PLEX, N	25	16 (64%)	7.4	8 (1.4%)	17 (3.4%)
IVIg/Rituximab/PLEX, N	16	14 (87.5%)	13.4	<5	10 (2.0%) ^c
Thymectomy, N	268	–	–	94	174

^aWith ≥1 administration of specified treatments.
^b85.9% of patients receiving PLEX had 1 (67.5%), 2 (12.3%), or 3 (6.1%) records of PLEX during the entire follow-up period.
^cNumber was rounded.
HES, hospital episode statistics; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange.

Table 4. HCRU and associated costs in MG patients who had HCRU record, during follow-up period.

Category	Number of patients with ≥1 visit/admission	HCRU per patient-year in patients with ≥1 visit/admission	
		Mean (SD)	Median (Q1–Q3)
Outpatient visits			
All follow-up	8395 (92.4%)	7.1 (10.5)	5.8 (3.0–10.3)
At 6 months post-diagnosis	7781 (85.6%)	12.0 (13.7)	8.0 (4.0–16.0)
Inpatient admissions			
All follow-up	6617 (72.8%)	1.8 (5.4)	1.2 (0.6–2.6)
All follow-up, MG related ^a	6617 (72.8%)	1.3 (4.0)	0.7 (0.3–1.5)
At 6 months post-diagnosis	3858 (42.5%)	4.9 (7.3)	4.0 (2.0–6.0)
At 6 months post-diagnosis, MG related ^a	3858 (42.5%)	4.5 (5.9)	2.0 (2.0–6.0)
LOS, all-cause, days	–	13.6 (34.2)	2.1 (0.2–10.3)
LOS, MG related ^a , days	–	9.7 (29.2)	1.8 (0.0–6.9)
Critical care admissions			
All follow-up	878 (9.7%)	0.4 (1.82)	0.3 (0.2–0.7)
At 6 months post-diagnosis	381 (4.2%)	2.3 (2.2)	2.0 (2.0–2.0)
A&E attendances			
All follow-up	4633 (51%)	0.9 (2.7)	0.7 (0.4–1.5)
At 6 months post-diagnosis	2433 (26.8%)	3.6 (4.3)	2.0 (2.0–4.1)
Cost of HCRU, £			
Outpatient visits	–	£454 (870)	£356 (161–704)
Inpatient admissions	–	£3226 (13,142)	£1981 (637–5607)
A&E attendances	–	£140 (475)	£108 (54–243)
Total cost	£81,337,574	–	–

^aMG-related inpatient admissions were defined as admissions with a recorded diagnosis of MG.

A&E, accident and emergency; HCRU, healthcare resource use; LOS, length of stay; MG, myasthenia gravis; Q, quartile; SD, standard deviation.

diagnosis, as they occurred in the period leading up to the confirmation of MG.

Among the observed cohort, a subset (11.6%, $n = 1057$) required additional treatment and procedures, including rescue therapies for myasthenic exacerbation or crisis, as well as rituximab. Only 2.9% ($n = 268$) of patients were recorded to have undergone thymectomy, similar to 2.6% of MG patients in a previous study of MG patients in England.⁹ In a recent study in Germany,¹⁹

29.9% of incident patients experienced exacerbations, and 6.7% experienced myasthenic crises during the follow-up period (mean \pm SD: 846.5 ± 528.5 days), most occurring within the first year after diagnosis. The high reported rate of exacerbations and crises in the German study may be attributed to the inclusion criteria, which required patients to have received at least one inpatient and/or two confirmed outpatient diagnoses of MG in the period, or to differences in the healthcare system. In our study, 6.6% of patients

Table 5. HCRU in patients diagnosed with MG by sex and age.

HCRU category	Number of patients with ≥ 1 visit/admission	HCRU per patient-year in patients with ≥ 1 visit/admission	
		Mean (SD)	Median (Q1–Q3)
Outpatient visits			
Male	4521	7.1 (9.9)	6.0 (3.1–10.3)
Female	3951	7.0 (10.9)	5.5 (2.7–10.2)
Age <50	1370	5.7 (11.2)	7.0 (3.5–14.0)
Age ≥ 50	7208	7.2 (13.8)	9.0 (4.7–16.5)
Inpatient admissions, all cause			
Male	3518	1.7 (6.1)	1.2 (0.6–2.7)
Female	3100	1.8 (4.6)	1.2 (0.6–2.4)
Age <50	950	1.8 (6.8)	1.5 (0.5–3.0)
Age ≥ 50	5727	1.7 (7.1)	2.0 (1.0–4.0)
Inpatient admissions, MG-related			
Male	3518	1.0 (4.7)	0.6 (0.3–1.4)
Female	3100	1.5 (3.1)	0.7 (0.4–1.6)
Age <50	950	1.8 (7.3)	1.0 (0.5–3.0)
Age ≥ 50	5727	1.0 (4.8)	1.0 (0.5–2.0)
A&E attendances			
Male	2359	0.9 (3.0)	0.7 (0.4–1.6)
Female	2251	1.0 (2.4)	0.7 (0.4–1.4)
Age <50	703	0.9 (3.0)	1.0 (0.5–2.0)
Age ≥ 50	3964	0.9 (3.0)	1.2 (0.5–2.5)

A&E, accident and emergency; HCRU, healthcare resource use; MG, myasthenia gravis; Q, quartile; SD, standard deviation.

received IVIg, 1.8% received PLEX, and 0.9% received rituximab treatment, consistent with a recent real-world HCRU study in the United States.²⁰ Among the small subset of patients who received multiple therapies during follow-up (i.e. IVIg, PLEX, and rituximab), a significant proportion (87.5%; 14 out of 16) received ≥ 3 treatments. These patients likely experience frequent and significant relapses, have an ‘explosive’ disease onset, are unresponsive to conventional rescue treatments, or have inadequate response or intolerance to other immunosuppressive drugs.

In our study, the administration of IVIg was more frequent than PLEX, which is consistent with clinical practice trends.⁴ IVIg is often preferred due to its availability and lower risk of adverse events, such as hypotension, coagulopathy, and sepsis, compared to PLEX.^{21,22} The 599 patients with recorded IVIg use during all follow-ups appear underreported as the National Immunoglobulin Database Report²³ estimates 666 MG patients annually receive IVIg [or 189,534 g, the equivalent of £13 m (based on an average price of £70/g)²⁴]. However, despite its preferred use over

Table 6. Costs of selected treatment among patients with MG.

Treatment ^a		Cost per treated patients ^b	Male	Female
IVIg (N=599)	Mean (SD)	£1514 (13,375)	£1418 (4440)	£1604 (19,001)
	Median (Q1–Q3)	£202 (123–520)	£653 (237–1595)	£676 (257–1828)
PLEX (N=163)	Mean (SD)	£4233 (8928)	£3181 (8262)	£5281 (11,162)
	Median (Q1–Q3)	£1583 (294–3895)	£2113 (236–5510)	£3639 (1377–6713)
Rituximab (N=81)	Mean (SD)	£1811 (6556)	£2995 (11,371)	£1278 (3973)
	Median (Q1–Q3)	£170 (110–336)	£330 (256–2333)	£386 (241–933)
Ventilation (N=480)	Mean (SD)	£1426 (10,033)	£1409 (16,189)	£1451 (9183)
	Median (Q1–Q3)	£283 (0–1780)	£283 (0–2470)	£645 (0–3051)
Thymectomy (N=268) ^c	Mean (SD)	£1155 (1428)	£1309 (1953)	£1075 (1021)
	Median (Q1–Q3)	£1067 (637–1730)	£1314 (719–2107)	£1017 (632–1656)

^aPatients with ≥ 1 administration of specified treatments.
^bThe reported treatment cost is related to all healthcare resources used during an inpatient spell or outpatient visit for a specific treatment, with only the relevant high-cost drug treatments or procedure being included, as administration of other treatments (e.g. AChEIs, corticosteroids, or other first-line non-steroidal immunosuppressants) is not recorded in HES and presented as cost per patient-year.
^cCost of thymectomy presented as per patient-year.
AChEIs, acetylcholinesterase inhibitors; HES, hospital episode statistics; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange; Q, quartile; SD, standard deviation.

PLEX, the use of IVIg has its limitations: it is a human blood product that may be subject to supply issues and there is a risk of passing infections.²⁵ We observed a slight decrease in the rates of IVIg treatment between 2015 and 2020, which may be due to the introduction of rituximab as an alternative to IVIg for the treatment of refractory MG in the UK in 2018²⁶ as well as stricter regulation for IVIg treatment. Previous studies showed that rituximab may be used in new-onset MG, MuSK-MG patients, and early treatment initiation.^{22,27} The higher utilization of rituximab in female patients (11.2%) compared to male patients (4.6%) observed here aligns with the higher prevalence of MuSK-MG in females.²²

The observed decline in thymectomy rates (from 24.5% of patients treated in 2015 to 12.6% in 2020) could be due to reluctance from clinicians to undertake the procedure due to relatively weak evidence of effectiveness; the practice guideline by the Association of British Neurologists published in 2018⁶ states thymectomy *may* induce remission, *may* prevent generalization of ocular myasthenia, and *may* reduce corticosteroid requirements. Similar to our study, a recent German study¹⁹ reported a low rate of thymectomy (4.4% of the total MG incident cohort), which the authors interpreted as likely being

caused by the refusal of procedures due to older age and the presence of comorbidities. Notably, the rate of thymectomies in the early-onset MG subgroup was higher at 13.3%.¹⁹

A majority of patients were admitted during follow-up (72.8% inpatient admissions and 51.0% A&E attendances), indicating that patients with MG incur significant HCRU. A minority of these attendances are directly linked to rescue therapy treatment. Due to the complexity of MG pathology, a new diagnosis of MG may prompt intervention to address existing symptoms, partially accounting for this healthcare burden. Moreover, a high proportion of patients presenting at the A&E department may suggest the occurrence of acute comorbidities related to MG treatment (e.g. infections and hyperglycemia due to steroids/immunosuppressants) or exacerbations and crises following diagnosis. In addition, due to the lack of outpatient diagnosis recording and the fact that over 80% of patients were included *via* an inpatient index diagnosis, our study is likely to have an over-representation of severe MG patients; therefore, these findings may not be generalizable to the entire population of MG patients. However, the rate of MG-related hospitalization in our study (1.3 ± 4.0 inpatient admissions per patient-year) aligns with a previous UK study

using linked data from the Clinical Practice Research Datalink and HES.²⁸ The costs incurred by inpatient admissions may be driven by the length of MG-related hospital stays (mean: 9.7 days in the current study), but further investigation of specific cost drivers is required. The reported HCRU patterns, except for inpatient hospitalization, are also consistent with findings from a US study.²⁰ In those attending the hospital, mean HCRU was highest in the first 6 months after MG diagnosis and decreased during follow-up, in line with previous findings in England, where proportions of patients with myasthenic crises and exacerbations were highest in the first year after the index date,²⁸ and the United States.^{20,29}

The mean cost of total secondary HCRU for MG patients in our study was £3820 per patient-year (equal to \$4849 in 2023), which was lower compared to those reported in a US study. However, a broader definition in terms of healthcare settings was used, and US healthcare costs are generally higher.²⁰ Published data suggest that IVIg utilization is a major contributor to the total annual cost of MG^{20,30} and patients receiving chronic IVIg for MG experience a significant economic burden,³¹ which aligns with our findings (though IVIg acquisition costs were not included in this study). Recent evidence suggests that PLEX is more cost-effective than IVIg in the treatment of autoimmune neurological conditions like MG, supporting the need for PLEX centers in regional neurology units, particularly considering the constrained supplies of IVIg.²⁵ However, with limited PLEX centers available and a burdensome treatment administration over several days, a preference to use IVIg may remain. The cumulative cost of admission for IVIg and PLEX was higher compared to rituximab alone, highlighting the unmet need in this subpopulation. It is worth noting that the variability of costs observed was very high, suggesting a small number of extremely high-cost patients. We found that patients with a history of rituximab treatment had higher costs for IVIg, ventilation, and PLEX compared to those without prior rituximab treatment.

A notable strength of this study is the inclusion of a large cohort of MG patients. In addition, the HES data encompass all newly diagnosed MG patients treated within the NHS in England.

However, there are several limitations to our study. First, only high-cost drug treatments are recorded in HES, excluding data on non-high-cost MG drugs such as AChEIs, corticosteroids, and non-steroidal immunosuppressant drugs. Second, the current analysis is limited to secondary care settings, omitting information on MG diagnosis, treatment, and HCRU in primary care settings. It is possible that patients were initially diagnosed by their general practitioner, but their diagnosis was only recorded in HES during their first hospital visit, introducing a time lag that may affect estimates of time from diagnosis to end of follow-up. In real-world practice, outpatient visits, particularly in ophthalmology and neurology, often involve suspected MG cases, which may later lead to hospitalization for further investigations or treatment initiation upon confirmation. Consistently, our findings indicate that neurology and ophthalmology departments were the most common specialties visited prior to MG diagnosis. In addition, in certain hospitals, neurology falls under the umbrella of general medicine either as a directorate or due to neurologists practicing within a general internal medicine department. Consequently, reported neurology referrals and subsequent diagnoses may be underestimated. Third, the CCI and baseline comorbidities may have been underestimated as these measures include conditions that can be diagnosed in primary care settings. Fourth, MG patients exclusively treated in private hospitals were not captured in this study. However, since HES covers 98% of the population in England,¹⁰ the number of missed MG patients with inpatient admissions is expected to be minimal. Lastly, HES does not capture clinical outcomes and the coding system for treatments and procedures primarily serves reimbursement purposes, potentially introducing bias in estimates for certain treatments (e.g. low number of patients undergoing thymectomy).

In conclusion, a majority of patients with MG required hospitalization or attending A&E departments, resulting in a significant burden in terms of HCRU and cost. A subset of patients required rescue therapy (including IVIg and PLEX), rituximab administration, ventilation, or thymectomy. Overall, these findings highlight the burden of MG on secondary care settings across England and may help policymakers manage costs and treatment decisions in MG.

Declarations

Ethics approval and consent to participate

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Because the database used in this study consists of de-identified data compliant with the US Health Insurance Portability and Accountability Act of 1996, no ethics committee approval or separate patient consent was required.

Consent for publication

Not applicable.

Author contributions

Jordy van Enkhuizen: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Jean Binns: Conceptualization; Methodology; Writing – review & editing.

April Betts: Conceptualization; Methodology; Writing – review & editing.

Fatemeh Saberi Hosnijeh: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Myriam Alexander: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Mark McCormack: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Saiju Jacob: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors thank the patients, the investigators, and their teams who took part in this study.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was sponsored by UCB Pharma.

Competing interests

JvE, JB, and AB are employees of UCB Pharma, the study sponsor. FSH and MM are current employees of OPEN Health and MA is a former OPEN Health employee; Open Health received payment from UCB Pharma for work on this

study and medical writing support. SJ has served as an international advisory board member for Alexion, Alnylam, Argenx, Immunovant, Janssen, Regeneron, and UCB Pharma, and is currently an expert panel member of myasthenia gravis consortium for Argenx pharmaceuticals and VitAccess. He has received speaker fees from Argenx, Eisai, Terumo BCT, and UCB Pharma. He is also a board member (trustee) of the UK myasthenia patient charity, Myaware.

Availability of data and materials

This work uses data provided by patients and collected by the NHS as part of their care and support. The pseudonymized patient data that were used for this study can be accessed by contacting NHS Digital (see <https://digital.nhs.uk/services/data-access-request-service-dars>) or Harvey Walsh Ltd (part of OPEN Health Group Ltd.) (Data Sharing Agreement: DARS-NIC-05934-M7V9K; Copyright© 2023 Re-used with the permission of NHS Digital. All rights reserved.) Access to these data is subject to a data sharing agreement (DSA) containing detailed terms and conditions of use following protocol approval from NHS Digital.

ORCID iD

Jordy van Enkhuizen  <https://orcid.org/0000-0002-8344-7750>

Supplemental material

Supplemental material for this article is available online.

References

1. Hehir MK and Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. *Neurol Clin* 2018; 36: 253–260.
2. Mantegazza R, Bernasconi P and Cavalcante P. Myasthenia gravis: from autoantibodies to therapy. *Curr Opin Neurol* 2018; 31: 517–525.
3. Carey IM, Banchoff E, Nirmalanathan N, *et al.* Prevalence and incidence of neuromuscular conditions in the UK between 2000 and 2019: a retrospective study using primary care data. *PLoS One* 2021; 16: e0261983.
4. Sussman J, Farrugia ME, Maddison P, *et al.* Myasthenia gravis: association of British

- Neurologists' management guidelines. *Pract Neurol* 2015; 15: 199–206.
5. Sieb JP. Myasthenia gravis: an update for the clinician. *Clin Exp Immunol* 2014; 175: 408–418.
 6. Sussman J, Farrugia ME, Maddison P, *et al.* The association of British Neurologists' myasthenia gravis guidelines. *Ann N Y Acad Sci* 2018; 1412: 166–169.
 7. Farmakidis C, Pasnoor M, Dimachkie MM, *et al.* Treatment of myasthenia gravis. *Neurol Clin* 2018; 36: 311–337.
 8. Landfeldt E, Pogoryelova O, Sejersen T, *et al.* Economic costs of myasthenia gravis: a systematic review. *Pharmacoeconomics* 2020; 38: 715–728.
 9. Harris L, Graham S, MacLachlan S, *et al.* Healthcare resource utilization by patients with treatment-refractory myasthenia gravis in England. *J Med Econ* 2019; 22: 691–697.
 10. National Health Service. Hospital episode statistics (HES). *NHS England*. <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics> (2023, accessed September 2023).
 11. National Health Service. National cost collection for the NHS. *NHS England*. <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/> (2020, Accessed September 2023).
 12. National Health Service. A simple guide to payment by results. *NHS England*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf (2012, Accessed September 2023).
 13. Quan H, Sundararajan V, Halfon P, *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130.
 14. Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; 173: 676–682.
 15. National Health Service. About the summary hospital-level mortality indicator (SHMI). *NHS England*. <https://digital.nhs.uk/data-and-information/publications/ci-hub/summary-hospital-level-mortality-indicator-shmi> (2023, accessed September 2023).
 16. National Health Service. High-cost drugs commissioning list. *NHS England*. <https://www.england.nhs.uk/publication/nhs-england-drugs-list/> (2023, accessed September 2023).
 17. Office for National Statistics. Population and household estimates, England and Wales: census 2021, unrounded data. *GOV.UK*. <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/populationandhouseholddestimatesenglandandwales/census2021unroundeddata> (2021, accessed September 2023).
 18. National Health Service. Disclosure control methodology for Hospital Episode Statistics (HES) and Emergency Care Data Set (ECDS). *NHS England*. <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/disclosure-control-methodology-for-hospital-episode-statistics-and-emergency-care-data-set> (2018, accessed September 2023).
 19. Mevius A, Jöres L, Biskup J, *et al.* Epidemiology and treatment of myasthenia gravis: a retrospective study using a large insurance claims dataset in Germany. *J Neuromuscul Dis* 2023; 33: 324–333.
 20. Phillips G, Abreu C, Goyal A, *et al.* Real-world healthcare resource utilization and cost burden assessment for adults with generalized myasthenia gravis in the United States. *Front Neurol* 2021; 12: 809999.
 21. Qureshi AI, Choudhry MA, Akbar MS, *et al.* Plasma exchange *versus* intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 1999; 52: 629–632.
 22. Farrugia ME and Goodfellow JA. A practical approach to managing patients with myasthenia gravis – opinions and a review of the literature. *Front Neurol* 2020; 11: 604.
 23. National Health Service. Immunoglobulin database: annual report 2021/2022. *NHS England*. https://igd.mdsas.com/wp-content/uploads/Igd_DataReport_202122.pdf (2023, accessed September 2023).
 24. National Institute for Health and Care Excellence. British National Formulary (BNF). NICE. <https://www.nice.org.uk/drugs/normal-immunoglobulin/medicinal-forms/> (2023, accessed September 2023).
 25. Klemencic Kozul T, Yudina A, Donovan C, *et al.* Cost-minimisation analysis of plasma exchange *versus* IVIg in the treatment of autoimmune neurological conditions. *BMC Health Serv Res* 2022; 22: 904.

26. National Health Service, England. Clinical commissioning policy statement: rituximab biosimilar for the treatment of myasthenia gravis (adults). Version 2; Reference: 170084P. *NHS England*. <https://www.england.nhs.uk/wp-content/uploads/2021/04/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf> (2021, accessed September 2023).
27. Brauner S, Eriksson-Dufva A, Hietala MA, *et al.* Comparison between rituximab treatment for new-onset generalized myasthenia gravis and refractory generalized myasthenia gravis. *JAMA Neurol* 2020; 77: 974–981.
28. Harris L, Graham S, MacLachlan S, *et al.* A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. *BMC Neurol* 2022; 22: 172.
29. Mahic M, Bozorg A, Rudnik J, *et al.* Healthcare resource use in myasthenia gravis: a US health claims analysis. *Ther Adv Neurol Disord* 2023; 16: 17562864221150327.
30. Guptill JT, Sharma BK, Marano A, *et al.* Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle Nerve* 2012; 45: 363–366.
31. Ting A, Story T, Lecomte C, *et al.* A real-world analysis of factors associated with high healthcare resource utilization and costs in patients with myasthenia gravis receiving second-line treatment. *J Neurol Sci* 2023; 445: 120531.

Visit Sage journals online
[journals.sagepub.com/
home/tan](https://journals.sagepub.com/home/tan)

 Sage journals