Comparative Analysis of Therapeutic Options Used for Myasthenia Gravis

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Objective: To compare clinical and economic outcomes following plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) in U.S. patients with primary diagnoses of myasthenia gravis (MG).
Methods: Our cohort was identified from the Nationwide Inpatient Sample database for years 2000–2005 using codes from the International Classification of Diseases, 9th edition. Multivariate regression analyses were used to identify predictors of mortality, complications, length of stay, and total inpatient cost.
Results: Among 1,606 hospitalized patients, the unadjusted mortality rate of MG crisis remained higher than those without crisis (0.44% vs 4.44%, $p < 0.001$), as well as the unadjusted complication rate (26.36% vs 11.23%, $p < 0.001$). MG crisis patients receiving PLEX had significantly more complications than those receiving IVIG (30.06% vs 14.79%, $p < 0.001$). Among the whole cohort, adjusted mortality and complication rates were not significantly different between the treatment groups ($p > 0.05$). Acute respiratory failure, major cardiac complications, and acute renal failure were associated with an increased mortality rate ($p < 0.001$). Age and respiratory failure were associated with an increased complication rate ($p < 0.001$). Length of stay was significantly longer for MG (6 vs 4 days, $p < 0.001$) and MG crisis (10 vs 5 days, $p < 0.001$) patients receiving PLEX. Inpatient costs were higher for MG ($26,662 vs $21,124, $p < 0.01$) and MG crisis ($53,801 vs $33,924, $p < 0.001$) patients receiving PLEX.
Interpretation: Compared to PLEX, IVIG appears of similar clinical (mortality and complications) and perhaps of superior economic (length of stay and total inpatient charges) outcomes in the treatment of MG. Elderly and those with complex comorbid diseases including acute respiratory failure may be better treated with IVIG.
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The national mandate to increase the rigor applied to assessment of therapies for human disease through comparative effectiveness studies has led to considerable debate of how such studies should be implemented.[1,2] The Institute of Medicine has made recommendations that prioritize areas for investigation, which highlight disorders with high prevalence and cost to society. Despite the need for a prioritization for health care assessment, patients with orphan diseases demand evaluations also be done to optimize treatment choice. By the very nature of disorders with a low prevalence, further complicated by disease heterogeneity, the gold standard, randomized, placebo-controlled clinical trials cannot be developed for all treatments. An example of this is myasthenia gravis (MG), an autoimmune neuromuscular disorder, which affects 60,000 to 80,000 Americans. Clinicians choose treatments largely based on expert recommendation and personal experience, without a rigorous evidence base.

In this investigation, we exploit a large inpatient database to evaluate plasma exchange (PLEX) or plasmapheresis, and intravenous immunoglobulin (IVIG) effectiveness for patients hospitalized with MG. Both of these therapies have been commonly utilized for MG since their first use in the 1970s.[3] PLEX has become a standard therapy for MG crisis, acute exacerbation of MG (particularly in patients with bulbar or severe generalized symptoms), and optimization of the clinical state prior to thymectomy,[4–6] despite the fact that only class III evidence exists to support the role of PLEX in the management of MG.[7] IVIG has been widely used in other neurological diseases,[8]

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Additional Supporting Information can be found in the online version of this article.

but its role in MG remains poorly defined, with only 5 small studies suggesting possible efficacy.[9–13] As the optimal dosage of IVIG remains to be determined,[14,15] Dalakas[16] recommends IVIG only as a second-line regimen once PLEX has failed, but there is currently no consensus regarding the use of IVIG in MG.

Due to the considerable confusion that exists regarding the use of PLEX and IVIG in MG and MG crisis, we chose to interrogate a sample nearly 20 times as large as any previous analysis. The objective of this observational study of U.S. patients was to compare several clinical and economic outcomes among patients treated with PLEX or IVIG with the primary diagnoses of MG and MG crisis.

Patients and Methods

Data Source and Cleansing

We conducted a cross-sectional analysis of 2000–2005 hospital discharge information from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) administrative database, a 20% stratified sample of inpatient admissions from 1,000 acute-care hospitals maintained by the Agency for Healthcare Quality and Research. International Classification of Diseases, 9th edition–Clinical Modification (ICD-9-CM) codes for primary diagnoses of MG (358.0) and MG crisis (358.01) were used to identify our initial cohort. Deidentified patients with the following secondary diagnosis were excluded: neonatal MG (775.2), Lambert-Eaton myasthenic syndrome (358.1), Guillain-Barré syndrome (357.0), chronic inflammatory demyelinating polyneuropathy (357.81), critical illness polyneuropathy (357.82), critical illness myopathy (359.81), polyneuropathy due to other diseases classified elsewhere (eg, porphyria and diphtheria) (357.4), acute poliomyelitis (with and without paralysis) (045, 045.1), acute transverse myelitis (323), acute alcohol intoxication (303.0), and poisoning by drug and biologic substances (960, 979). To avoid double representation of the same patient, we excluded those patients whose disposition or admission type indicated a transfer to or from another short-term hospital. Patients with a hospital charge of less than $100 were likely coded incorrectly and were also excluded from the analysis. Similarly, patients with a negative length of stay or length of stay exceeding 365 days were eliminated from the dataset.

We identified MG crisis by the ICD-9-CM code (358.01), or if an MG patient had a secondary diagnosis of acute respiratory failure (ICD-9-CM code 518.81), and/or required mechanical ventilation during the same admission. Mechanical ventilation included endotracheal intubation (procedure code 96.04) or continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or noninvasive mechanical ventilation (procedure code 93.90). Cases were then divided into PLEX (99.71, 99.76) and IVIG (99.14) groups based on ICD-9-CM procedure codes. Patients receiving both PLEX and IVIG in the same hospitalization were excluded from the analysis. This study was deemed exempt by the University Hospitals Case Medical Center's Institutional Review Board, as HCUP-NIS is a public database with no personal identifying information.

Independent and Outcome Variables

Independent demographic variables included patient age (grouped into $\leq$50, 51–74, and $\geq$75 years), gender, ethnicity (grouped into white, black, Hispanic, others), median household income (grouped into $\leq$\$24,999, \$25,000–\$34,999, \$35,000–\$44,999, and $\geq$\$45,000), admission source (emergency department and routine), and disposition (home, rehabilitation including skilled nursing and intermediate care facilities, and died in the hospital). Patient comorbidity was measured using the Charlson comorbidity index.[17,18] Independent hospital-provider variables included hospital region (Northeast, Midwest, South, West), hospital location (rural, urban), and hospital teaching status (teaching, nonteaching). Primary outcomes of interest were hospital mortality, inpatient complications, length of stay, and total hospital charges. Major complications were identified separately in this cohort; these are (1) cardiac complications, which included cardiac arrhythmias (427), acute myocardial infarction (410 except 410.x2), cardiac arrest during procedure (997.1), hypotension (458.8, 458.9), and fluid overloading (276.6); (2) systemic infection, which included systemic inflammatory response syndrome (995.92, 995.94, 785.52), bacteremia (790.7), septicemia (038, 999.3), and anaphylaxis (995.0, 995.2 except 995.22 and 995.23, 999.4, 999.5); (3) thrombotic events, which included ischemic stroke (433, 434), pulmonary embolism (415.1), deep vein thrombosis (453.4, 999.2), and hypercoagulable states (289.82); and (4) acute renal failure (584).

Statistical Analysis

Bivariate analysis of independent variables by outcomes was performed using Fisher's exact test for categorical variables and Wilcoxon signed-rank test and Mood's median test for continuous variables. The significance level was set a priori at $p < 0.05$ with no corrections for multiple testing. Stepwise multiple regression models were fitted to determine the independent association of significant variables associated with the use of IVIG over PLEX and the outcomes of in-hospital mortality, in-hospital complications, length of stay, and total hospital charge. Length of stay and total hospital charge were log-transformed to reduce skewness and meet normality assumptions. The models included basic demographics (age, gender, and ethnicity), median household income, admission source, acute respiratory failure, major complications, and hospital characteristics. These covariates were used to control for treatment choices instead of propensity scores, because as noted above, modeling treatment choice is poorly understood. In the case of variables for which data were missing for at least 10% of patients, indicator variables for the missing values were added to the models. The c-statistic, which assesses the area under a receiver operating characteristic (ROC) curve was used as a measure of discrimination for all logistic models. All statistical tests were performed using SAS 9.2 (SAS Institute, Cary, NC).

TABLE 1: Patient Demographics

	Myasthenia Gravis			Myasthenia Gravis Crisis		
	PLEX (n = 737)	**IVIG (n = 171)**	***p***	**PLEX (n = 529)**	**IVIG (n = 169)**	***p***
Age, mean (SD)	53.20 (18.36)	50.68 (23.71)	0.34	58.93 (18.45)	56.30 (22.02)	0.32
Gender (%)			0.47			0.0006
Male	34.33	37.43		45.37	29.59	
Female	65.67	62.57		54.06	69.82	
Missing	0.00	0.00		0.57	0.59	
Ethnicity (%)			0.01			0.68
White	63.09	50.29		55.58	50.30	
Black	11.13	15.20		13.99	15.38	
Hispanic	2.99	2.92		5.10	4.14	
Other	2.58	1.17		2.08	2.37	
Missing	20.22	30.41		23.25	27.81	
Income by zip code (%)			0.13			0.28
<$25,000	11.26	9.94		23.63	18.34	
$25,001–$35,000	19.13	19.88		20.04	24.26	
$35,001–$45,000	26.87	18.71		22.31	18.34	
>$45,000	41.66	50.88		31.57	37.28	
Missing	1.09	0.58		2.46	1.78	
Admission source (%)			<0.0001			0.29
Emergency department	29.44	18.71		48.77	42.60	
Routine	58.34	80.70		50.09	56.80	
Missing	12.21	0.58		1.13	0.59	
Disposition (%)			0.50			0.0004
Home	93.76	95.32		75.99	88.17	
Rehabilitation (SNF, ICF)	5.83	4.09		18.34	11.24	
Died	0.41	0.58		5.67	0.59	
Charlson comorbidity index (%)			0.39			0.22
Mild	63.77	58.48		48.96	56.80	
Moderate	34.60	39.77		46.69	39.64	
Severe	1.63	1.75		4.35	3.55	
Indications (%)[a]						
Acute respiratory failure	0.00	0.00	–	34.22	12.43	<0.0001
Endotracheal intubation	0.00	0.00	–	27.98	12.43	<0.0001
CPAP/BiPAP	0.00	0.00	–	7.37	4.73	0.29

TABLE 1. Continued

	Myasthenia Gravis			Myasthenia Gravis Crisis		
	PLEX (n = 737)	**IVIG (n = 171)**	***p***	**PLEX (n = 529)**	**IVIG (n = 169)**	***p***
Hospital size (%)			<0.0001			0.09
Small	3.12	5.26		5.67	7.10	
Medium	11.40	11.11		16.26	11.83	
Large	55.63	62.57		72.02	78.70	
Missing	29.85	21.05		6.05	2.37	
Hospital location (%)						0.002
Rural	1.09	5.26	<0.0001	0.76	4.14	
Urban	69.06	73.68		93.19	93.49	
Missing	29.85	21.05		6.05	2.37	
Hospital teaching status (%)			<0.0001			0.08
Nonteaching	21.71	17.54		31.57	28.40	
Teaching	48.44	61.40		62.38	69.23	
Missing	29.85	21.05		6.05	2.37	
Hospital region (%)			<0.0001			0.07
Northeast	14.52	11.11		17.39	20.71	
Midwest	20.22	9.36		20.23	20.12	
South	27.14	52.63		43.86	49.7	
West	8.28	5.85		12.48	7.10	
Missing	29.85	21.05		6.05	2.37	

[a]All patients with respiratory failure or needing mechanical ventilation are classified as myasthenia gravis crisis; thus, no observation was found in the myasthenia gravis group.
BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; ICF = intermediate care facility; IVIG = intravenous immune globulin; PLEX = plasma exchange; SD = standard deviation; SNF = skilled nursing facility.

Results

Of the 6,034 patients identified with primary diagnoses of MG or MG crisis, 20 (0.3%) were excluded for other neurological causes of weakness. The majority of this cohort, 4,093 (68.1%), had no documented immunotherapy during hospital stay, and 32 patients (0.5%) had received both PLEX and IVIG. MG crisis compared to those without crisis were more likely to receive immunotherapy during their hospital stay (36.72% vs 28.98%, $p < 0.0001$). Of the remaining 1,889 patients, 145 (7.7%) patients were transfers between hospitals, 4 (0.2%) lacked a final disposition, 63 (3.3%) were excluded for a negative length of stay or a length of stay exceeding 365 days, and 71 (3.8%) patients had a missing total hospital charges. The final study cohort comprised 1,606 patients. More than 10% of MG and MG crisis were missing ethnicity data (which was classified into 4 groups, white, black, Hispanic, others), mostly due to state suppression of this variable for privacy reasons[19]; both groups had similar missing proportions.

Among MG patients without crisis, there were no significant differences in the mean age, or the proportions by gender, median income, and Charlson comorbidity indices between the treatment groups (Table 1). MG patients receiving PLEX were more likely to be admitted through the emergency department (29.44% vs 18.71%, $p < 0.0001$), but were no more likely to be discharged to a rehabilitation facility (5.83% vs 4.09%, $p = 0.5$). Patients with a primary diagnosis of MG crisis receiving PLEX were more likely to be male (45.37% vs 29.59%, $p < 0.001$), but were no more likely to be of differing age or of differing median income than those patients receiving IVIG. Among the MG crisis group, the Charlson indices of either treatment type were similar; though those receiving PLEX had a higher

TABLE 2: Unadjusted Outcomes in Myasthenia Gravis and Myasthenia Gravis Crisis

	Myasthenia Gravis			Myasthenia Gravis Crisis		
	PLEX (n = 737)	IVIG (n = 171)	*p*	PLEX (n = 529)	IVIG (n = 169)	*p*
Mortality (%)	0.41	0.58	0.56	5.67	0.59	0.002
Complications, any (%)	11.40	10.53	0.89	30.06	14.79	<0.0001
Cardiac	9.50	7.60	0.55	22.68	11.83	0.001
Acute renal failure	0.27	1.17	0.16	4.73	1.18	0.038
Systemic infection	1.63	1.17	1.00	9.45	1.18	<0.0001
Thrombotic complications	0.27	0.58	0.46	3.40	0.59	0.05
Length of hospital stay, median (interquartile range), (d)	6 (5)	4 (3)	<0.0001	10 (11)	5 (5)	<0.0001
Total hospital charge, median (interquartile range) ($)	26,662 (24,960)	21,124 (20,947)	0.001	53,801 (65,335)	33,924 (34,840)	<0.0001

IVIG = intravenous immune globulin; PLEX = plasma exchange.

proportion of acute respiratory failure (34.22% vs 12.43%, $p < 0.001$) necessitating endotracheal intubation (27.98% vs 12.43%, $p < 0.001$). Compared to MG, patients in a crisis situation are likely to be admitted through an emergency room; however, the route of admission in those in crisis did not differ by the treatment type. MG crisis patients receiving PLEX were more likely to have been discharged to a rehabilitation facility (18.34% vs 11.24%, $p < 0.001$). We note that 28% of MG patients receiving immunotherapy had missing hospital characteristics. In contrast, 5.18% of MG crisis patients had missing information; the majority of crisis patients received treatment at large hospitals (73.64%), urban hospitals (93.27%), and academic centers (64.04%). MG crisis patients receiving PLEX were less likely to have been treated at rural hospitals (0.76% vs 4.14%, $p < 0.01$). Among MG crisis patients, hospital size, teaching status, and hospital region were not significant predictors of immunotherapy with PLEX.

Bivariate Analyses of Clinical and Economic Outcomes

The unadjusted mortality rates in MG and MG crisis patients receiving immunotherapy were 0.44% and 4.44%, respectively ($p < 0.001$). While unadjusted mortality rates were similar between the treatment groups in MG patients, MG crisis patients who received PLEX had significantly higher unadjusted mortality rate than those who received IVIG (5.67% vs 0.59%, $p < 0.01$) (Table 2). Variables associated with higher mortality included disease in crisis, PLEX, older age, more severe comorbidity index, and admission source through the emergency department (all $p < 0.05$) (Supporting Information Table S1). Acute respiratory failure and endotracheal intubation led to increased mortality rates ($p < 0.001$) but not the use of CPAP/BiPAP ($p = 0.08$). Cardiac complications, acute renal failure, and systemic inflammatory responses led to increased mortality (all $p < 0.001$). No specific hospital characteristic was associated with mortality. Eleven percent of MG patients experienced at least 1 complication, while 26.36% of MG crisis patients did so ($p < 0.001$). Unadjusted complication rates were similar between the treatment groups in MG patients, but those in crisis treated with PLEX had a significantly higher unadjusted complication rate (30.06% vs 14.79%, $p < 0.0001$) (see Table 2). Disease, type of immunotherapy, patient age, ethnicity, admission source, Charlson comorbidity index, acute respiratory failure, endotracheal intubation, CPAP/BiPAP, and hospital teaching status were all associated with higher complication rates ($p < 0.05$).

The median length of stay for MG and MG crisis were 5 and 9 days, respectively ($p < 0.001$). Length of stay was significantly longer in those treated with PLEX in the MG (6 vs 4 days, $p < 0.001$) and MG crisis (10 vs 5 days, $p < 0.001$) groups. Total hospital charges for MG and MG crisis were $25,829 and $49,152, respectively ($p < 0.001$). Hospital charges were higher in patients treated with PLEX in both MG groups (see Table 2). Characteristics associated with a longer length of stay and higher hospital charges are shown in Supporting Information Table S2.

Adjusted Clinical and Economic Outcomes

All variables associated with outcomes on bivariate analysis except endotracheal intubation (colinear with acute

TABLE 3: Multivariate Logistic Regression Models for Outcomes of Hospital Mortality and Hospital-Associated Complication

	Odds Ratio (95% Confidence Interval)	*p*
Effect: mortality		
IVIG vs PLEX	0.39 (0.09–1.72)	0.21
Acute respiratory failure	8.25 (3.75–18.18)	<0.0001
Cardiac complications	4.22 (1.97–9.03)	<0.0001
Acute renal failure	10.88 (4.07–29.04)	<0.0001
Effect: any complications		
IVIG vs PLEX	0.71 (0.48–1.03)	0.07
Age (yr)		
51–74 vs ≤50	3.58 (2.49–5.14)	0.0019
≥75 vs ≤50	5.26 (3.56–7.78)	<0.0001
Acute respiratory failure	4.89 (3.51–6.84)	<0.0001

IVIG = intravenous immunoglobulin; PLEX = plasma exchange.

respiratory failure) were included in the multiple logistic regression analyses. The adjusted analysis included all patients in this cohort. Acute respiratory failure, cardiac complications, and acute renal failure were associated with an increased mortality rate (Table 3). Older age and respiratory failure were associated with increased complication rate (see Table 3). Among all patients and after accounting for all significant covariates, adjusted mortality rates after IVIG therapy were not significantly different from that after PLEX (odds ratio [OR] = 0.40; 95% confidence interval [CI] = 0.09–1.72). Treatment with IVIG showed a trend toward decreased adjusted complication rates (OR = 0.70; 95% CI = 0.48–1.02), but was not statistically significant. Variables associated with a longer hospital stay were MG crisis, admissions through the emergency department, moderate Charlson index, acute respiratory failure, and cardiac complications (Table 4). MG crisis, Hispanic ethnicity, admissions through the emergency department, a moderate Charlson index, acute respiratory failure, systemic infection, and Western hospitals were associated with higher hospital charge (see Table 4). Treatment with IVIG was associated with a shorter length of stay and lower hospital charge.

Discussion

We used a population-based analysis to determine contemporary short-term clinical and economic outcomes following PLEX and IVIG in MG and MG crisis patients. Multivariate analysis of mortality implied that prognosis is dependent only upon the presence of acute respiratory failure, major cardiac complications, and acute renal failure. Older age and acute respiratory failure led to a higher incidence of complications, after adjusting for other significant independent predictors. A lower but insignificant adjusted complication rate was observed in the IVIG treatment group. This suggests that some patients, especially the elderly and those with complex comorbid diseases, may be better served by IVIG therapy than PLEX. The trials which compared PLEX to IVIG in the treatment of MG and MG crisis are generally consistent with our results that IVIG has a lower complication rate but its efficacy is similar to PLEX. A retrospective study of 54 patients in MG crisis found a lower complication rate with IVIG, but functional outcomes at 2 weeks and 30 days were better in patients treated with PLEX.[20] Twelve MG patients in a controlled cross-over study showed similar clinical responses after both PLEX and IVIG treatments, but adverse events were higher during and after IVIG treatment.[13] The largest single experience with PLEX and IVIG in MG of 87 patients found similar improvement rates of about 65% with PLEX and IVIG. Complications occurred in 8 patients receiving PLEX and 1 patient receiving IVIG ($p < 0.01$).[9] Qureshi and colleagues[20] confirmed a better tolerability of IVIG, but found superior ventilatory function and less disability in those patients receiving PLEX. None of the studies evaluated mortality, which is a challenging endpoint given the overall low hospital mortality rate of MG and the small number of subjects in these trials (2.40%).[19] Also, no studies of MG have analyzed length of hospital stay or total hospital charges of MG stratified by the type of immune therapy. We found a significantly shorter length of stay for patients receiving IVIG, and IVIG was less costly than PLEX. We therefore conclude that IVIG may be a better treatment choice for hospitalized MG patients. Controlled trials are not likely to be developed to address the question of the overall benefit of IVIG vs PLEX because of their technical difficulty in a rare disease and the potential ethical concerns. Therefore, we would advocate that continued monitoring of large patient data bases would be a means to evaluate real-life safety and efficacy of IVIG and PLEX for MG.

Alshekhlee and colleagues[19] reported a shift in treatment for MG toward IVIG and away from PLEX over a 5-year period in the last decade. The reasons for this may lie with IVIG being easier to administer; IVIG also appears to have a better adverse effect profile compared with PLEX.[21] Consistent with previous reports,[22–24] we found a 7.6% to 22.7% rate of major cardiac complications, depending on diagnosis of MG or

TABLE 4: Multivariate Logistic Regression Models for Outcomes of Length of Hospital Stay and Total Hospital Charge

	β Coefficient (95% Confidence Interval)	p
Effect: length of stay		
Intercept	5.07 (4.77–5.38)	<0.0001
Myasthenic crisis	1.00 (0.53–1.36)	<0.0001
Intravenous immunoglobulin	−5.07 (−5.38 to −4.77)	<0.0001
Admission source		
Emergency department	1.31 (0.82–1.90)	<0.0001
Missing	−3.13 (−3.19 to −3.01)	<0.0001
Charlson index		
Moderate	1.54 (1.03–2.14)	<0.0001
Severe	1.10 (−0.04 to 2.67)	0.06
Acute respiratory failure	5.17 (3.83–6.81)	<0.0001
Cardiac complications	1.26 (0.61–2.04)	<0.0001
Effect: total hospital charges		
Intercept	22,128 (20,738–23,612)	<0.0001
Myasthenic crisis	9,840 (6,930–13,260)	<0.0001
Intravenous immunoglobulin	−4,912 (−5,930 to −3,593)	<0.0001
Race		
Hispanic	8,840 (3,443–16,044)	0.0003
Others	15,545 (7,216–27,160)	<0.0001
Admission source		
Emergency department	6,993 (4,574–9,895)	<0.0001
Missing	−14,220 (−14,363 to −13,802)	<0.0001
Charlson index		
Moderate	4,166 (2,176–6,561)	<0.0001
Severe	3,236 (−1,531 to 9,882)	0.20
Acute respiratory failure	22,228 (16,013–29,929)	<0.0001
Systemic inflammatory response	20,956 (12,873–31,615)	<0.0001
Western hospitals	9,010 (5,119–13,892)	<0.0001

MG crisis and choice of therapy. Cardiac complications were less frequent in MG crisis patients treated with IVIG compared to PLEX. Major thrombotic complications were nonsignificantly higher in MG patients receiving IVIG, consistent with its established prothrombotic properties, but rose dramatically in MG crisis patients given PLEX therapy. The reason may be a consequence of a hypercoagulable state acquired after large-volume PLEX.[25,26] The requirement for in-dwelling catheters to receive PLEX treatment almost certainly contributed to their higher sepsis rate in MG crisis patients treated with PLEX.[27] While MG crisis patients receiving PLEX had higher rates of renal failure, this is likely related to the associated sepsis complication. PLEX is an established therapy for immune-mediated disorders causing acute renal failure[28] and may be a preferable option to IVIG for MG patients with concurrent renal failure.

The limitations of this study include those inherent to any study using an administrative database. Disease severity assessment by clinical classification and serum

concentrations of acetylcholine receptor and muscle-specific kinase autoantibodies, and specific treatment regimens are unknown. The additional administration of corticosteroids and other immune suppressives could not be determined using this database. In addition, more than 10% of patients had missing race, admission source, and hospital characteristics variables, but exclusion of these patients from the analysis would have been inappropriate, with the possibility of introducing a biased evaluation, as outcomes were dissimilar between these patients and the remaining study population (Supporting Table S3). Indicator variables more appropriately adjust analyses for missing data by assuming that unwillingness or inability to report certain types of information may not be independent of the outcome measure under study.[29,30] Errors in ICD-9 coding and documentation are possible, but they have been shown to be limited (http://www.hcup-us.ahrq.gov/db/nation/nis/nisrelatedreports). In addition, patients with MG treated in an outpatient setting with PLEX and IVIG are not captured by our analysis, but these patients are likely to represent a very different population with different disease severity and treatment indications. Information for each patient was limited to a single hospitalization, and longitudinal analysis with review of long-term outcomes such as rates of readmission and survival cannot be measured. Last, this study is observational and selection bias for treatment choice could not be excluded. The decision-making by the clinicians at these 1,000 hospitals could not be characterized via propensity scores, but we used the variables available in direct adjustment for patient differences.

To date, therapeutic decisions for MG have been based widely on results from small institutional series. Twenty times as large as previous studies, this evaluation is the first to report mortality, length of hospital stay, and total hospital charge for PLEX and IVIG in the treatment of MG and MG crisis. With the limited clinical information available in the NIS datasets, IVIG appears comparable to PLEX with regard to the clinical outcomes (mortality and complications), and IVIG may be superior with regard to the economic outcomes (length of stay and total hospital charges) in the treatment of both MG and MG crisis. Some patients, especially the elderly, those with complex comorbid disease, and those in acute respiratory failure, may be better served by IVIG therapy than PLEX. The analysis offers insight into real-world outcomes of treatments for a rare disease; however, the results should be interpreted with caution as the dataset lacks information on the clinical characteristics for patients in the study. The basic approach should prove useful for comparative-effectiveness evaluations of other disorders, whether they are rare or common. The results of such analyses can then serve to focus specific controlled trials for interventions already in practice.

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Potential Conflict of Interest

Nothing to report.

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