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Frequency and Severity of Myasthenia Gravis Exacerbations Associated With the Use of Ciprofloxacin, Levofloxacin, and Azithromycin

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ABSTRACT

Introduction/Aims: The true frequency and severity of myasthenia gravis (MG) exacerbation associated with the usage of fluoroquinolone and macrolide antibiotics remain unknown. We aimed to investigate the association between ciprofloxacin, levofloxacin, azithromycin, and MG exacerbation.

Methods: A retrospective review was performed on MG patients seen at a single institution between 2002 and 2022, who received ciprofloxacin, levofloxacin, or azithromycin. Amoxicillin usage was chosen for comparison. The strength of association between antibiotic usage and MG exacerbation was scored using the Adverse Drug Reactions Probability Scale. A mixed-effects logistic regression model was constructed to evaluate predictors of antibiotic-associated MG exacerbation (AAMGE).

Results: 365 patients had a total of 918 episodes of antibiotic usage ($n = 339$ for ciprofloxacin, $n = 187$ for levofloxacin, $n = 392$ for azithromycin). Frequencies of MG exacerbation following antibiotic use were: 8 (2.4%) for ciprofloxacin, 3 (1.6%) for levofloxacin, 6 (1.5%) for azithromycin, and 17 (1.9%) for all. Six patients had impending crisis/crisis, and 9 required rescue therapy. MG exacerbation was associated with MG-related hospitalization or ED visit in the preceding 6 months ($p = 0.012$), female sex ($p = 0.023$) and diabetes ($p = 0.032$). Infection was the most common confounder in exacerbations (88.2%). MG exacerbation was seen in 8/603 (1.3%) episodes of amoxicillin use, without a significant difference in frequencies of AAMGE among the four antibiotics ($p = 0.68$).

Discussion: Usage of ciprofloxacin, levofloxacin, or azithromycin was associated with MG exacerbation in less than 2.5% of episodes of antibiotic use. Underlying infection may play a role in AAMGE. As AAMGE can be severe, decision-making regarding the use of these antibiotics should be individualized.

Abbreviations: AAMGE, antibiotic-associated MG exacerbation; AChR, acetylcholine receptor; ED, emergency department; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; NMJ, neuromuscular junction; NSIT, non-steroidal immunotherapy; PLEX, plasmapheresis.

1 | Introduction

Myasthenia gravis (MG) exacerbation, defined as worsening MG symptoms, can occur in up to 30% of MG patients within the first 6 years of symptom onset [1]. Myasthenic crisis requiring intubation or noninvasive ventilation to avoid intubation is the most severe form of MG exacerbation [2, 3]. MG exacerbation or crisis can be triggered by a number of etiologies including infection, surgery, medication, tapering of immunotherapy, pregnancy, and stress and can also occur in the absence of any identifiable triggers [4].

A number of medications can alter the function of the neuromuscular junction (NMJ) through different mechanisms, resulting in MG exacerbation. Immune checkpoint inhibitors, tyrosine kinase inhibitors, interferons, and penicillamine may lead to autoimmune reactions at the NMJ, resulting in the development of de novo MG or exacerbation of pre-existing MG [5]. The second general mechanism for medication-induced MG exacerbation is impaired signal transmission at the NMJ via blockade of action potential propagation, inhibition of presynaptic acetylcholine release, or degradation of acetylcholine receptor (AChR) on the postsynaptic membrane [6]. Medications belonging to this category include beta-adrenergic blockers, calcium channel blockers, antiarrhythmics, magnesium, neuromuscular blockers, anesthetics, lithium, corticosteroid, and various antibiotics [7–13].

Fluoroquinolones and macrolides are the two major classes of antibiotics that have been traditionally linked to MG exacerbation. In 2011, the U.S. Food and Drug Administration issued a black-box warning on the risk of MG exacerbation with the use of fluoroquinolones [14]. Two international MG practice guidelines advised that fluoroquinolones and macrolides be avoided or used with caution in MG patients [2, 15]. The potential risk of MG exacerbation by these commonly used antibiotics is well recognized among patients and caregivers [16]. However, the presumed antibiotic-induced MG exacerbation is not supported by data from randomized clinical trials or prospective studies, but is based on retrospective analyses or case series with conflicting observations [17–21]. The true incidence of fluoroquinolone or macrolide induced MG exacerbation and its severity currently remain unknown.

In this study, we aimed to investigate the association between the use of two fluoroquinolones (ciprofloxacin and levofloxacin) and one macrolide (azithromycin) and the occurrence of MG exacerbation, and to identify predictors of antibiotic-associated MG exacerbation (AAMGE) in a large group of myasthenic patients.

2 | Methods

This was a retrospective study using electronic medical record data of patients evaluated at the Cleveland Clinic between 2002 and 2022. Patients were included if they met all the following criteria: (1) confirmed diagnosis of MG; (2) use of ciprofloxacin, levofloxacin, or azithromycin based on prescription and/or pharmacy/clinician documentation following the establishment of MG diagnosis; and (3) availability of clinical information for at least 6 months prior to and 3 months after the use of the antibiotic of interest, for the purpose of evaluating the baseline disease status and subsequent clinical outcomes. Amoxicillin usage was determined as a control for comparison. MG patients who had a single visit at our neuromuscular center without subsequent follow-up were excluded. The use of antibiotics prior to the establishment of MG diagnosis was excluded from data analysis. MG diagnosis was based on the presence of a compatible clinical syndrome plus one of the following findings: positive antibody testing, electrodiagnostic studies, or edrophonium test, and a documented improvement with MG-specific treatment. This study was approved by the Institutional Review Board, and informed consent for participants was waived.

AAMGE was defined as worsening myasthenic symptoms or signs within 14 days following the use of target antibiotics. Only patients with worsening signs that are specific for MG and/or supported by objective findings on exam were considered as having an MG exacerbation, and those with reported generalized weakness or fatigue were excluded. The cutoff of 14 days was chosen based on a previous review showing that most quinolone-associated exacerbations occurred within 10 days of initial antibiotic administration [22]. A previously developed Adverse Drug Reaction Probability Scale was used to categorize AAMGE as being definite, probable, or possible based on the following features: clinical descriptions of symptoms and signs, temporal relationship between antibiotic initiation and symptom worsening, clinical improvement after drug discontinuation, positive rechallenge, alternative causes of exacerbation, prior exacerbations with the same drug, and any objective evidence of exacerbation (Table S1) [23]. This scoring system has been used to estimate the association between MG exacerbation and selected medications, as well as other diseases [24–26]. The strength of AAMGE was determined based on a review of medical records, including treating clinicians' judgment and multiple potential factors contributing to an MG exacerbation, including the contribution of infections. All exacerbation episodes and the strength of association were reviewed and agreed upon by two investigators (S.P.U. and Y.L.).

Demographic and historical data that were collected included the following: sex, ethnicity, age at time of antibiotic use, duration of MG at time of antibiotic use, antibody status, MG type (generalized versus ocular), Myasthenia Gravis Foundation of America (MFGA) classification [27] based on the patient's examination findings at the most recent visit prior to antibiotic usage, history of thymoma, prior thymectomy, comorbidities, MG-related hospitalization or emergency department (ED) visit in the 6 months prior to the first antibiotic dose, use of rituximab, intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX) in the preceding 6 months, type of infection treated (respiratory, genitourinary, other infection, or none [prophylactic use prior to procedures]). Baseline was determined as being prior to the initiation of antibiotics or the first treatment episode of antibiotics if multiple courses were administered successively. The clinical features of AAMGE were collected as follows: timing of exacerbation from first antibiotic dose, nature of exacerbation symptoms (ocular, bulbar, respiratory, limb), objective physical examination findings, laboratory or

test findings supportive of MG exacerbation, presence of confounding factors for MG exacerbation, progression to impending crisis or crisis, change in MG treatment, and use of rescue therapies.

Descriptive statistics were utilized to present data as mean with standard deviations or median with range for continuous variables, and count with percentage for categorical variables. Continuous variables were compared between episodes with versus without AAMGE using *t*-tests or Wilcoxon rank sum tests. Categorical variables were compared using chi-square tests or Fisher's exact tests. Specifically, we conducted *t*-test for age at time of antibiotic use and Wilcoxon rank sum test for duration of MG at time of antibiotic use. Chi-square tests were conducted for sex, duration of MG at antibiotic use (≤ 5 years vs. > 5 years), diabetes at time of antibiotic use, and use of immunotherapy, prednisone and non-steroidal immunotherapy (NSIT) at time of antibiotic use. Fisher's exact tests were conducted for race, age group (< 50 vs. ≥ 50 years), antibody status, MG type, prior thymectomy, history of thymoma, hospitalization or ED visit in the preceding 6 months, rituximab, IVIG, or PLEX in the preceding 6 months, and MGFA classification of disease severity prior to antibiotic use.

We used univariate logistic regression models to evaluate the predictors of AAMGE, where the dependent variable was the occurrence of AAMGE. In addition, a multivariable mixed-effects logistic regression model was constructed. The dependent variable was the occurrence of AAMGE, and the independent variable was the type of antibiotic, adjusting for significant variables in univariate analyses as well as variables determined a priori based on clinical considerations (sex, antibody status, prior thymectomy). A subject random effect was included in the model to account for repeated measures.

Fisher's exact test was used to compare the frequencies of AAMGE across antibiotic groups. Antibiotic dosage was summarized and compared between episodes with versus without AAMGE using Wilcoxon rank sum tests, within each antibiotic group. A p value of < 0.05 was considered statistically significant. Due to the exploratory nature of our study, we did not correct for multiple testing.

3 | Results

Of the 1105 MG patients (531 females and 574 males) who were screened from our neuromuscular database, a total of 365 patients met the inclusion criteria, and their characteristics are summarized in Table 1. There was a total of 918 episodes of azithromycin ($n = 392$), ciprofloxacin ($n = 339$) or levofloxacin ($n = 187$) usage. The most common indications for ciprofloxacin, levofloxacin, and azithromycin use were respiratory infections (49.2%), followed by genitourinary infections (24.6%) (Table S2).

Clinical characteristics related to episodes of antibiotic use are summarized in Table 2, stratified based on the presence or absence of AAMGE. A total of 17 AAMGE episodes occurred, constituting 1.9% of all episodes of antibiotic use. Specifically, the use of ciprofloxacin was associated with MG exacerbation in 8 (2.4%) episodes, levofloxacin in 3 (1.6%), and azithromycin in 6 (1.5%).

TABLE 1 | Baseline clinical features of all included patients ($N = 365$).

Clinical features	Number (%)
Female sex	179 (49.0)
Race	
Caucasian	304 (83.3)
Non-Caucasian	55 (15.1)
Unknown	6 (1.6)
Antibody status	
AChR antibody	274 (75.1)
MuSK antibody	20 (5.5)
LRP4 antibody	1 (0.3)
Seronegative	64 (17.5)
Unknown	6 (1.6)
MG type	
Generalized	275 (75.3)
Ocular	90 (24.7)
Prior thymectomy	96 (26.3)
History of thymoma	42 (11.5)
Diabetes at time of antibiotic usage	106 (29.0)

Abbreviations: AChR, acetylcholine receptor; LRP4, low-density lipoprotein receptor–related protein 4; MG, myasthenia gravis; MuSK, muscle-specific kinase; *N*, number.

The baseline characteristics of the patients with AAMGE are summarized in Table 3. Patients with AAMGE were predominantly female and had generalized MG. Eleven (85%) of those with generalized MG had bulbar-predominant symptoms. Infection was the indication for antibiotic use in 15 (88.2%) patients, and 2 patients had prophylactic antibiotic use related to surgical procedures.

The clinical features pertinent to each episode of AAMGE are presented in Table S3. MG exacerbation was confirmed in 11 patients by examination, and in the remaining 6 patients, worsening of MG-specific symptoms was described. Exacerbation symptoms included ocular involvement in 7 (41.2%), bulbar in 8 (47.1%) and respiratory in 7 (41.2%) of patients.

Three (17.6%) AAMGE patients had a crisis and an additional three patients (17.6%) experienced an impending crisis. Fifteen (88.2%) patients required a treatment change, of which 9 (52.9%) required rescue therapy with PLEX or IVIG (Table S3). In 3 (17.6%) of 17 patients, the same antibiotic was re-challenged subsequently, without recurrence of MG exacerbation.

The occurrence of AAMGE was associated with a shorter median duration of MG at the time of antibiotic use, a higher rate

TABLE 2 | Clinical features of the study sample, stratified by presence versus absence of MG exacerbation associated with ciprofloxacin, levofloxacin, or azithromycin usage.

Clinical features	Total episodes of antibiotic use (*N*, %)	Episode of antibiotic use with MG exacerbation (*N*, %)	Episode of antibiotic use without MG exacerbation (*N*, %)	*p*	OR (95% CI)
Sex				0.089[a]	
Male	402 (43.8)	4 (23.5)	398 (44.2)		Reference
Female	516 (56.2)	13 (76.5)	503 (55.8)		2.57 (0.83, 7.95)
Race				0.34[b]	
Caucasian	743 (80.9)	12 (70.6)	731 (81.1)		Reference
Non-Caucasian	166 (18.1)	5 (29.4)	161 (17.9)		1.99 (0.72, 5.53)
Unknown	9 (0.98)	0 (0.00)	9 (1.00)		3.08 (0.15, 64.98)
Age at time of antibiotic use (years, mean ± SD)	62.4 ± 16.8	59.6 ± 16.1	62.4 ± 16.9	0.49[c]	0.99 (0.96, 1.02)
Older age at time of antibiotic use (50 years or higher)	716 (78.0)	14 (82.4)	702 (77.9)	0.99[b]	1.32 (0.38, 4.65)
Duration of MG in months at time of antibiotic use (range)	87.0 (0, 1405)	34.0 (0, 276)	88.0 (0, 1405)	**0.016[d]**	0.99 (0.99, 1.00)
Duration of MG exceeding 5 years at time of antibiotic use (%)	562 (61.2)	7 (41.2)	555 (61.6)	0.087[a]	0.44 (0.17, 1.16)
Antibody status				0.12[b]	
AChR	635 (69.2)	13 (76.5)	622 (69.0)		Reference
MuSK	37 (4.0)	2 (11.8)	35 (3.9)		2.74 (0.59, 12.59)
Other	246 (26.8)	2 (11.8)	244 (27.1)		0.39 (0.09, 1.75)
MG type				0.99[b]	
Generalized	692 (75.4)	13 (76.5)	679 (75.4)		Reference
Ocular	226 (24.6)	4 (23.5)	222 (24.6)		0.94 (0.30, 2.92)
MGFA classification of disease severity (0–5) prior to antibiotic use*				0.40[b]	1.33 (0.88, 2.00)
0 (no MG symptoms or signs)	344 (38.4)	4 (23.5)	340 (38.7)		
1 (pure ocular)	204 (22.8)	4 (23.5)	200 (22.8)		
2 (mild generalized)	264 (29.5)	6 (35.3)	258 (29.4)		

(Continues)

TABLE 2 | (Continued)

Clinical features	Total episodes of antibiotic use (*N*, %)	Episode of antibiotic use with MG exacerbation (*N*, %)	Episode of antibiotic use without MG exacerbation (*N*, %)	*p*	OR (95% CI)
3 (moderate generalized)	65 (7.3)	3 (17.6)	62 (7.1)		
4 (severe generalized)	14 (1.6)	0 (0.00)	14 (1.6)		
5 (intubation/myasthenic crisis)	4 (0.45)	0 (0.00)	4 (0.46)		
Prior thymectomy (%)	260 (28.3)	4 (23.5)	256 (28.4)	0.79[b]	0.78 (0.25, 2.40)
History of thymoma (%)	136 (14.8)	1 (5.9)	135 (15.0)	0.49[b]	0.36 (0.05, 2.70)
Diabetes at time of antibiotic usage (%)	276 (30.1)	9 (52.9)	267 (29.6)	**0.038**[a]	2.67 (1.02, 7.00)
Hospitalization or ED visit in the preceding 6 months	63 (6.9)	6 (35.3)	57 (6.3)	**< 0.001**[b]	8.08 (2.88, 22.63)
Rituximab, IVIG or PLEX within preceding 6 months (%)	105 (11.4)	5 (29.4)	100 (11.1)	**0.036**[b]	3.34 (1.15, 9.67)
Use of immunotherapy at time of antibiotic use (%)	581 (63.3)	11 (64.7)	570 (63.3)	0.90[a]	1.07 (0.39, 2.91)
Use of prednisone at time of antibiotic use (%)	423 (46.1)	8 (47.1)	415 (46.1)	0.93[a]	1.04 (0.40, 2.72)
NSIT at time of antibiotic use (%)	306 (33.3)	6 (35.3)	300 (33.3)	0.86[a]	1.09 (0.40, 2.98)

Note: p values: a = Pearson's chi-squared test; b = Fisher's Exact test; c = *t*-test; d = Wilcoxon's Rank Sum test. *Data not available for all subjects. Number of patients with documented MGFA classification of disease severity: overall = 895; patients with no MG exacerbation due to antibiotic use = 878; and patients with MG exacerbation due to antibiotic use = 17. *P* values in bold indicate statistical significance (< 0.05).

Abbreviations: AChR, acetylcholine receptor; ED, emergency department; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; *N*, number; NSIT, non-steroidal immunotherapy; PLEX, plasmapheresis; SD, standard deviation.

TABLE 3 | Clinical features of 17 patients with MG exacerbation after antibiotic use.

Clinical features	Number (%)
Female sex	13 (76.5)
Race	
Caucasian	12 (70.6)
African-American	5 (29.4)
Antibody status	
AChR antibody	15 (88.2)
Seronegative	2 (11.8)
MG type	
Generalized	13 (76.5)
Ocular	4 (23.5)
MGFA classification (median, range)	2 (0, 3)
MG-related admission or ED visit in prior 6 months	6 (35.3%)
Antibiotic use	
Azithromycin	6 (35.3%)
Ciprofloxacin	8 (47.1%)
Levofloxacin	3 (17.6%)
Probability of exacerbation due to medication	
Probable	3 (17.6%)
Possible	14 (82.4%)
Changes in MG treatment (rescue therapy/other)	
No	2 (11.8%)
Yes	15 (88.2%)
IVIG	6/15 (40%)
PLEX	3/15 (20%)
Other	6/15 (40%)

Abbreviations: ED, emergency department; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; PLEX, plasmapheresis.

TABLE 4 | Multivariable mixed-effects model for MG exacerbation associated with antibiotic use.

	OR (95% CI)	*p*
Antibiotic group		
Azithromycin only	Reference	
Ciprofloxacin only	1.22 (0.36, 4.15)	0.75
Levofloxacin only	1.15 (0.25, 5.25)	0.85
Female	4.68 (1.24, 17.74)	**0.023**
Duration of MG at antibiotic use (months)	0.99 (0.99, 1.00)	0.12
MGFA classification of disease severity (0–5) prior to antibiotic use	0.91 (0.54, 1.54)	0.74
Antibody status (AChR as reference)		
MuSK	1.20 (0.17, 8.21)	0.86
Other	0.48 (0.09, 2.63)	0.40
Prior thymectomy	0.67 (0.17, 2.62)	0.56
Diabetes at time of antibiotic usage	3.32 (1.11, 9.91)	**0.032**
Hospitalization or ED visit in the preceding 6 months	13.61 (1.78, 104.20)	**0.012**
Rituximab, IVIG or PLEX in the preceding 6 months	0.36 (0.04, 2.99)	0.34

Note: P values in bold indicate statistical significance (< 0.05).
Abbreviations: AChR, acetylcholine receptor; CI, confidence interval; ED, emergency department; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MuSK, muscle-specific kinase; OR, odds ratio; PLEX, plasmapheresis.

of diabetes, a higher frequency of rituximab, IVIG, or PLEX use, and more hospitalizations or ED visits in the preceding 6 months (Table 2). There was no significant association between antibiotic dosage and AAMGE (Table S4). Among the factors analyzed in the multivariable mixed-effects logistic regression model, a history of hospitalization or ED visit in the preceding 6 months, female sex, and diabetes were identified as predictors of AAMGE (Table 4). There was no difference between patients with and without AAMGE in terms of antibody status, prior thymectomy, or MGFA disease severity at baseline.

To further analyze the possible role of infection as a factor for MG exacerbation, the use of amoxicillin was screened in the same group of 365 MG patients. Among the 603 episodes of usage of amoxicillin, a total of 8 (1.3%) episodes of possible AAMGE were identified. MG exacerbation associated with amoxicillin usage led to a change in MG treatment in most patients, including IVIG/PLEX administration in 2 episodes (25.0%). Comparison of frequencies of AAMGE among all four antibiotics showed no significant difference (Table S5).

4 | Discussion

In this study, analysis of a large group of MG patients demonstrated that the use of ciprofloxacin, levofloxacin, or azithromycin resulted in MG exacerbation in less than 2.5% of episodes. This frequency of AAMGE was found to be similar among these three antibiotics and no different from that associated with the use of amoxicillin in the same group of MG patients. Our findings indicate that although MG exacerbations may occur after the use of ciprofloxacin, levofloxacin, or amoxicillin, this risk is relatively small in the overall MG population.

Despite the concern for potential MG worsening, fluoroquinolones and macrolides are frequently prescribed for MG patients in the clinical setting. For example, in one study of 127 MG patients treated at a university hospital, 31 (24.4%) were given azithromycin and 49 (38.6%) were given quinolones [28]. Prescription of fluoroquinolone and macrolide antibiotics for MG patients

may be due to unawareness of existing warnings or overriding them when weighing risks versus benefits for treating severe infections.

Jones et al. [22] analyzed 27 patients with fluoroquinolone-associated MG exacerbation for whom respiratory and urinary tract infections were the most common indications for antibiotic use, similar to our study. Upon fluoroquinolone discontinuation, the majority of patients demonstrated clinical improvement, although this was confounded by the concomitant escalation of MG therapies. Two retrospective analyses also studied the risk of AAMGE in groups of MG patients, with mixed results. The study by Gummi et al. [28] revealed that azithromycin, but not fluoroquinolones, had a higher odds ratio of MG exacerbation. Nguyen et al. [29] evaluating MG exacerbation from healthcare claims of 1556 MG patients, found the use of fluoroquinolones to be a risk factor for AAMGE, but not macrolides. The differences between our findings and previous studies could possibly be explained by the method of retrospective data collection. In our study, we reviewed electronic medical records of a large group of MG patients whose clinical information preceding and following antibiotic usage were documented in detail and readily available, which allowed us to obtain more comprehensive and patient-specific information compared to the use of a healthcare administrative database.

Through further mixed model analyses, MG patients with MG-related hospitalization or ED visit in the preceding 6 months, female sex, and diabetes were found to be at higher risk of AAMGE. MG-related hospitalization or ED visit in the preceding 6 months as a predictor of AAMGE suggests that suboptimally controlled MG disease at baseline portends a lower threshold for exacerbation when exposed to triggering factors. This finding also indicates that stable MG disease has a lower risk of MG exacerbation, which is in line with previous studies that explored risk factors for MG exacerbation or crisis [30, 31]. A retrospective cohort study with 815 MG patients found that minimal manifestation status at 12 months after diagnosis had a lower risk of MG crisis or disease exacerbation [32]. Therefore, it appears reasonable to consider the usage of these antibiotics in stable MG patients.

We also found female sex to be a predictor of AAMGE, which could indicate an inherent difference in MG disease severity influenced by sex-related alterations. Similar to our study, Jones et al. [22] reported female predominance (80%) in a group of 37 MG patients with exacerbation after fluoroquinolone use. It is known that female MG patients tend to have a more refractory course, and female sex serves as a risk factor for the occurrence of exacerbation in patients with generalized MG or post-thymectomy [33–36].

Our observation that diabetes serves as a risk factor for AAMGE is consistent with several prior observations. Firstly, higher rates of myasthenic crises and a refractory course have been reported in MG patients with diabetes [37–39]. Secondly, comorbid diabetes has been shown to be associated with the development and recurrence of infection in MG patients, and this can contribute to exacerbation [40, 41]. Furthermore, diabetes can lead to worsening MG symptoms through an increased risk of drug–drug interactions in MG patients [42]. Finally, in experimental autoimmune MG rats, diabetes was shown to exacerbate MG by promoting both adaptive and innate immunity [43].

Infections were the most common indication for antibiotic use (88.2%) in our patient population and pose a major confounding factor for AAMGE. Several studies showed that various types of systemic infections are the most common causes of MG exacerbation [44–46]. Infections are associated with 30%–50% of myasthenic crisis occurrences [3]. Almost all AAMGE cases, including those following the use of amoxicillin, occurred in the setting of an infection. We failed to find a significant difference in the frequencies of AAMGE among all antibiotics analyzed. This may be due to the low number of AAMGE, but it may also suggest that infection, rather than antibiotics, could be the main contributor to AAMGE. In two patients without infection, ciprofloxacin prophylactic usage led to MG exacerbation following skin removal and thymectomy procedures. Similar to infection, procedures could give rise to significant physical and/or emotional stress, serving as exacerbating factors.

It is important to note that AAMGE is not always trivial, as most of our patients required escalation in MG treatment. In a significant portion of the AAMGE patients, hospitalization for close monitoring and rescue therapy was needed, where three patients required intubation and an additional three were in impending crisis. As a result, it is valuable to isolate additional factors that can precisely predict AAMGE.

Limitations of our study included the single-center study design, retrospective analyses, and small number of exacerbation cases which could hinder generalizability. As a natural consequence of retrospective data review, it cannot be definitively ascertained if most patients actually took the prescribed medications; however, clinical notes from inpatient and outpatient settings were utilized when available to confirm compliance. We were unable to use specific outcome measures to define or quantify AAMGE. We relied on a thorough review of medical record documentation and treating physicians' opinions for identifying factors contributing to MG exacerbation, which is prone to judgment bias. We did not collect information on the severity of infection that could lead to differences in the development of AAMGE. Finally, the three antibiotics of interest were chosen as representatives of their drug class, given that NMJ dysfunction is thought to be a class effect; however, there may be innate differences between individual antibiotics in terms of side effect profiles.

5 | Conclusion

The use of fluoroquinolones and macrolides can be associated with MG exacerbations. However, the overall exacerbation risk appears to be low. Stable MG patients appear likely to tolerate these antibiotics without a high risk of MG worsening. Patients with recent MG-related hospitalization or ED visit, female sex, and comorbid diabetes are at higher risk of AAMGE. When caring for a female MG patient with diabetes and/or recent hospitalization or ED visit, the use of fluoroquinolones or macrolides should be avoided or used with caution. However, it is important to realize that AAMGE can be severe, leading to crisis/near crisis and escalation in MG treatment. When considering the use of these antibiotics, there is always a need to consider many

factors on an individual basis, including patient demographics, history of MG, status of MG, severity of the infection, as well as the availability of alternative safer antibiotics to provide the optimal care for MG patients.

Author Contributions

Sanem Pinar Uysal: conceptualization, investigation, writing – original draft, writing – review and editing, methodology, formal analysis. **Yadi Li:** conceptualization, methodology, formal analysis, writing – review and editing. **Nicolas R. Thompson:** conceptualization, methodology, writing – review and editing, formal analysis. **Yuebing Li:** supervision, formal analysis, methodology, writing – review and editing, investigation, conceptualization, writing – original draft.

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The authors have nothing to report.

Ethics Statement

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.

Conflicts of Interest

Dr. Yuebing Li served as a consultant for Advisory Board Meeting by Alexion, Amgen, Argenx, Catalyst, Immunovant, and UCB Pharma and received grant support from Argenx. The other authors declare no conflicts of interest.

Data Availability Statement

Anonymized data not published within this article will be made available by request from any qualified investigator.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.