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Intravenous immunoglobulin and plasma exchange prescribing patterns for Guillain-Barre Syndrome in the United States—2001 to 2018

Amro M. Stino MD[1] | Evan L. Reynolds PhD[1] | Maya Watanabe MSc[2] | Brian C. Callaghan MD[1]

[1]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

[2]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA

Correspondence
Amro M. Stino, F2647 UH South, SPC 5223, 1500 E. Medical Center Dr, Ann Arbor, MI 48109, USA.
Email: amstino@med.umich.edu

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Abstract

Introduction/Aims: Randomized controlled trials show that repeat intravenous immunoglobulin (IVIG) dosing and plasma exchange (PLEX) followed by IVIG (combination therapy) have no additional therapeutic benefit in Guillain-Barre Syndrome (GBS) non-responders. Furthermore, the delineation between GBS and Acute Onset CIDP (A-CIDP) can be particularly challenging and carries therapeutic implications. We aimed to evaluate the presence of repeat IVIG, combination therapy, and diagnostic reclassification from GBS to CIDP.

Methods: We performed a retrospective study of a large healthcare database for patients with GBS in the US from 2001 to 2018. We identified individuals initially diagnosed with GBS and later re-classified as CIDP. Multivariable logistic regression models were developed to determine associations between patient factors and repeat IVIG dosing, combination therapy, and diagnostic re-classification from GBS to CIDP.

Results: We identified 2325 patients with GBS. A total of 39.7% received repeat IVIG and 6.1% received combination therapy. The proportion of individuals initially diagnosed with GBS and then re-classified as CIDP was 32.0%. Repeat IVIG, combination therapy, and diagnostic reclassification remained stable over time. Female sex (OR 0.79, 95% CI 0.65–0.96) and medium-high net worth (OR 0.64, 95% CI 0.45–0.90) associated with repeat IVIG therapy, while Asian ethnicity associated with diagnostic re-classification from GBS to CIDP (OR 1.77, 95% CI 1.09–2.86).

Discussion: Repeat IVIG dosing was quite common in GBS before newer trials suggesting harm in non-responders, and IVIG/PLEX combination therapy continues to persist despite strong evidence against use in non-responders. Further, nearly one in three patients initially diagnosed with GBS is subsequently diagnosed with CIDP, but the reasons are unclear.

KEYWORDS
Guillain-Barré Syndrome, healthcare utilization, intravenous immunoglobulin, plasma exchange, United States

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1 | INTRODUCTION

Guillain-Barré Syndrome (GBS) is an autoimmune polyradiculoneuropathy with two proven immunotherapies.[1] Despite the efficacy of both intravenous immunoglobulin (IVIG) and therapeutic plasma exchange (PLEX), up to one in five patients cannot walk at 6 months, and nearly 5% die.[2] In 1997, a pivotal randomized controlled clinical trial conclusively demonstrated not only the therapeutic equivalency of IVIG and PLEX but also determined that no additive benefit is obtained when giving PLEX followed by IVIG (combination therapy) in the initial phase.[3] In 2021, the Second Intravenous immunoglobulin Dose in individuals with GBS with poor prognosis (SID-GBS) study found that there was no therapeutic value to repeat IVIG dosing in patients with poor prognosis at baseline, as defined by a modified Erasmus GBS outcome score (mEGOS) of ≥6 at study entry.[4]

Repeat IVIG dosing[4] and combination therapy[5] both increase the risk of adverse events for patients with GBS and as a result, current expert guidelines strongly advocate against the use of repeat IVIG dosing or combination therapy in non-responders or those with poor prognosis at baseline,[6–8] as most recently codified in the 2023 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines.[9] Of note, PLEX monotherapy may be a cost-effective option in resource-constrained environments.[10]

Furthermore, in the first 8 weeks of disease onset, it can be practically impossible to distinguish GBS from Acute Onset CIDP (A-CIDP).[11,12] GBS treatment-related fluctuation (TRF), defined as a worsening of one grade on the GBS disability scale or a decline in the Medical Research Council (MRC) sum score following initial stabilization or improvement, poses a unique dilemma. It occurs within the first 8 weeks after treatment and affects up to 16% of GBS patients initially treated with IVIG or PLEX.[12] Current EAN/PNS guidelines advise consideration for repeat IVIG or PLEX in such GBS-TRF patients, on the basis that A-CIDP may be indistinguishable from GBS during the acute phase.[11,12] Previous studies have shown that 16% of CIDP patients present acutely in a GBS-like fashion at disease onset[13] and that 2% of GBS patients are ultimately re-classified as CIDP.[14] In addition, according to a separate retrospective study, nearly one in four patients who have CIDP are initially mischaracterized as GBS.[15] Altogether, limited data exists regarding prescribing patterns of IVIG and PLEX in GBS and transitions in diagnoses between GBS and CIDP in the United States.

In this study, we explore the frequency of repeat IVIG dosing and combination therapy in the United States. We also evaluate the frequency of initial GBS diagnosis transitioning to CIDP diagnosis.

2 | METHODS

2.1 | Population

We conducted a retrospective cohort study using a large de-identified database that contains demographic information and detailed medical and pharmaceutical claims for over 80 million privately insured individuals from January 1, 2001 to December 31, 2018 (Optum's de-identified Data Mart Database [Clinformatics®]). The demographic characteristics of this population closely match those of privately insured individuals in the United States. We identified individuals who were diagnosed with GBS or CIDP and received at least one IVIG or PLEX treatment. For our retrospective analysis, approval was obtained from the University of Michigan Medical Campus Institutional Review Board. Participant consent was waived.

2.2 | Disease groups and treatments

We used International Classification of Diseases (ICD) 9 and 10 code definitions, to define GBS (357.0, G610, G650) and CIDP (357.81, G6181). To be eligible for study inclusion, all patients in our analyses were required to have received at least one treatment (IVIG or PLEX) in addition to their diagnoses of GBS and/or CIDP.

Demographic information included age, sex, race/ethnicity, geographic region, education level, net worth, insurance plan type, and presence of a customer-driven health plan (a high-deductible health insurance plans that allow for individuals to set aside pre-tax salary to be used for health-related costs).

We identified individuals who received IVIG using treatment brand and generic names from pharmaceutical claims and Current Procedural Terminology (CPT) codes (J1459, J1554, J1556, J1557, J1561, J1566, J1568, J1569, J1572, J1599, 36514). We identified individuals who received PLEX therapy using CPT codes (36514), and ICD-9/ICD-10 codes (99.71, 6A550Z3, 6A551Z3).[16] We defined separate IVIG treatments as those with at least 14 days between procedures. To identify separate PLEX treatments, individuals were required to have received at least five PLEX procedures at a frequency of one every other day with at least 14 days separating unique procedures. We selected a 14-day cutoff on the basis that many centers in the United States institute seven PLEX procedures given every other day (over 14 days), despite EAN/PNS guidelines strongly recommending no more than four to five exchanges given over 1–2 weeks.[9] The choice of time cutoff for IVIG was less certain, as data is conflicting regarding time to benefit, with estimates ranging from days to weeks, and it is uncertain how soon many clinicians would ascertain treatment failure and decide to re-administer IVIG (although a 7- to 9-day window was used for the SID-GBS study). Furthermore, data regarding baseline disease severity, response to initial treatment, TRF, and time to repeat IVIG dosing was not available from the database. Thus, to standardize our assessment, a 14-day cutoff was used to ascertain separate treatments for both modalities.

2.3 | Outcomes

The outcomes of interest were: (1) the proportion of individuals with GBS receiving repeat IVIG treatments (two or more) within a 3-month period; (2) the proportion of individuals with GBS receiving combination therapy within a 3-month period; and (3) the proportion of

individuals initially diagnosed with GBS who were later re-classified as CIDP. We identified the number receiving repeat IVIG treatment and combination therapy amongst individuals with only a diagnosis of GBS. We also assessed the proportion of individuals initially diagnosed with GBS who were later re-classified as CIDP amongst those with GBS only and those with GBS and then CIDP. The 3-month window was used as a cutoff for ascertaining re-treatment with IVIG or combination therapy based on median hospitalization duration data, in addition to the 8-week cutoff traditionally used for GBS treatment-related fluctuation.[12,17] Furthermore, we sought to analyze trends in practice over the last two decades from 2001 to 2018.

2.4 | Statistical analysis

Descriptive statistics were used to characterize demographic, socioeconomic, and insurance plan information for individuals with GBS. We also calculated the proportion of individuals that received repeat IVIG treatment and combination therapy, and that were initially diagnosed with GBS and later reclassified as CIDP, stratified by year. To investigate whether demographic, socioeconomic, and insurance plan characteristics are associated with each outcome, we fit a series of multivariable logistic regression models. Specifically, for each outcome of interest (repeat IVIG, combination therapy, GBS to CIDP diagnosis), we fit a logistic model as a function of the year of GBS diagnosis and adjusted for demographic/socioeconomic information (race, sex, age, region, education, net worth) and insurance plan type. Available case analysis was used to handle missing demographic/socioeconomic and insurance plan information.

Statistical significance was determined using a *p*-value threshold of .05. We did not correct for multiple statistical comparisons.

3 | RESULTS

3.1 | Patient characteristics

We identified 2325 patients with only a diagnosis of GBS and who received at least one immunotherapy. The mean age was 49.9 with a slight male predominance (Table 1). We also identified 1092 individuals with an initial diagnosis of GBS and a later diagnosis of CIDP.

3.2 | Prescribing trends (amongst patients with only a GBS diagnosis)

Amongst individuals with only a GBS diagnosis, 66.0% received IVIG only, 28.0% received PLEX only, and 141 (6.1%) received combination therapy. Repeat IVIG dosing was observed in 923 patients with GBS (39.7%), and of these, 345 (37.4%) received two IVIG doses and 578 (62.6%) received three or more IVIG doses. Of patients receiving combination therapy, 103/141 (73.1%) received IVIG before PLEX. Proportions of both combination therapy and repeat IVIG therapy remained stable from 2001 to 2018 (Figure 1A).

3.3 | Predictors of repeat IVIG dosing or combination therapy (amongst patients with only a GBS diagnosis)

Amongst individuals with only a GBS diagnosis, adjusted logistic regression models found that female patients had reduced odds of repeat IVIG dosing (OR 0.79, 95% CI 0.65–0.96). In addition, patients with a high-medium net worth ($250,000–$499,000) (OR 0.64, 95% CI 0.45–0.90) had reduced odds of repeat IVIG compared with patients with a low net worth (<$25,000) (Table 2). Race, age, year of diagnosis, insurance plan information, and education level did not affect the odds of receiving repeat IVIG dosing.

Adjusted logistic regression models revealed that no demographic, socioeconomic, or insurance plan characteristics were significantly associated with the odds of combination therapy.

3.4 | Reclassification from GBS to CIDP (amongst patients with only a GBS diagnosis or with an initial GBS diagnoses and eventual CIDP diagnosis)

There were 1092 (32.0%) patients that were initially classified as GBS and later re-classified as CIDP (Figure 1B). This proportion remained relatively stable over time. Adjusted logistic regression revealed that older age (OR 1.01, 95% CI 1.01–1.02) and Asian ethnicity resulted in increased odds of being re-classified as CIDP (reference group = White, OR 1.77, 95% CI 1.09–2.86). No other demographic, socioeconomic, or insurance plan characteristics factored into the odds of diagnostic re-classification into CIDP.

4 | DISCUSSION

We found that repeat IVIG dosing was much more prevalent than combination therapy, but that both practices persisted without change over the last two decades. Furthermore, there was a much higher than expected diagnostic re-classification of cases from GBS to CIDP.

Nearly one in three patients with GBS in our study received repeat IVIG dosing. These results are important in light of findings from the landmark 2021 SID-GBS randomized controlled trial that conclusively found no added benefit to repeat IVIG dosing (as compared with one-time dosing) in those with poor prognosis at presentation.[4] A previous non-randomized trial also showed no added benefit to repeat dosing in poor responders.[18] Before the SID-GBS study, it was thought that repeat IVIG dosing could potentially help a subset of refractory cases, but current data strongly suggests otherwise. Internationally, a 2019 International GBS Outcome Study (IGOS) study found that a quarter of patients with GBS who do not clinically improve get re-dosed with IVIG.[19] Of note, our study did not specifically separate non-responders from TRF patients, for whom the current EAN/PNS guidelines advocate consideration for re-treatment. Nevertheless, it must be noted that consideration for re-treatment of TRF patients is based only on observational data.[20,21]

TABLE 1 Sociodemographic, insurance, and treatment information for patients with GBS ($N = 2325$).

Age (years), mean (SD)	49.9 (19.4)
Sex, *N* (%)	
Male	1304 (56.1%)
Race, *N* (%)	
Asian	52 (2.6%)
Black	200 (10.0%)
Hispanic	208 (10.4%)
White	1548 (77.1%)
Missing	317
Division, *N* (%)	
East North Central	294 (12.7%)
East South Central	98 (4.2%)
Middle Atlantic	190 (8.2%)
Mountain	220 (9.5%)
New England	94 (4.0%)
Pacific	203 (8.7%)
South Atlantic	643 (27.7%)
West North Central	253 (10.9%)
West South Central	328 (14.1%)
Missing	2 (0.1%)
Education level (%)	
<12th Grade	21 (1.0%)
High School Diploma	527 (25.6%)
Less than bachelor's degree	1093 (53.1%)
Bachelor's degree Plus	418 (20.3%)
Missing	266
Net worth (%)	
<$25 K	358 (19.6%)
$25 K–$149 K	401 (22.0%)
$150 K–$249 K	223 (12.2%)
$250 K–$499 K	346 (19.0%)
$500 K+	496 (27.2%)
Missing	501
Insurance type (%)	
Exclusive Provider Organization	199 (8.6%)
Health Maintenance Organization	599 (25.8%)
Indemnity	27 (1.2%)
Point of Service	994 (42.8%)
Preferred Provider Organization	223 (9.6%)
Other	283 (12.2%)
Customer driven health plan type (%)	
Health Reimbursement Arrangement (HRA)	86 (5.4%)
Health Savings Account (HSA)	161 (10.2%)
No HRA/HSA	1336 (84.4%)
Missing	742
Treatment administered, *N* (%)	
IVIG only	1534 (66.0%)
PLEX only	650 (28.0%)
IVIG and PLEX	141 (6.1%)

Abbreviations: HAS, health savings account; HRA, health reimbursement arrangement; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

The lack of significant patient-level factors may indicate that provider and/or healthcare system-level factors may be the primary drivers of high repeat IVIG therapy use in this privately insured population. In short, it is unclear why female patients and those of high socioeconomic status were less likely to receive repeat IVIG, as shown in our study. Future studies should attempt to replicate these results and determine the underlying pathways to inform potential interventions. It is also quite probable that patients with TRF were more likely to receive repeat IVIG dosing. Our study database did not include detailed provider or healthcare system level information, nor data regarding baseline disease severity, initial IVIG responder status, nor the presence or absence of TRF, thus precluding a more detailed analysis of prescribing practices for GBS patients with poor baseline prognosis and GBS patients with TRF. Nevertheless, future studies are needed to determine the factors driving the non-evidence-based practice of repeat IVIG dosing in non-responders (or those with poor baseline prognosis) who do not have TRFs, with the goal of informing provider and/or healthcare system-level interventions and curbing this potentially harmful practice.

In contrast to repeat IVIG therapy, we found that the prevalence of combination therapy was much less common and remained stable at around 6% over the preceding two decades. The 1997 randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in GBS (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial)[3] showed that combination therapy did not confer a therapeutic advantage. Since this trial, numerous position statements have advocated against combination therapy.[6–9] In the United States, a 2000–2005 study of 1657 patients with GBS found that 2.9% of individuals received combination therapy.[5] In that study, individuals receiving combination therapy had higher mortality rates as compared with those receiving IVIG monotherapy or PLEX monotherapy as well as higher hospital costs. Globally, a retrospective multicenter nationwide study of 1300 patients using the IGOS dataset found an overall combination therapy prevalence of 10%–15%, mainly directed at patients who did not improve with initial treatment or those who experienced treatment-related fluctuation.[19] Other global estimates range from 3% to 25%.[22–24] Despite 26 years of clear evidence that this practice does not benefit GBS patients with poor baseline prognosis, a small unchanging proportion of patients continues to receive both IVIG and PLEX without change over nearly two decades, although our study could not definitively separate this subset from those with TRF.

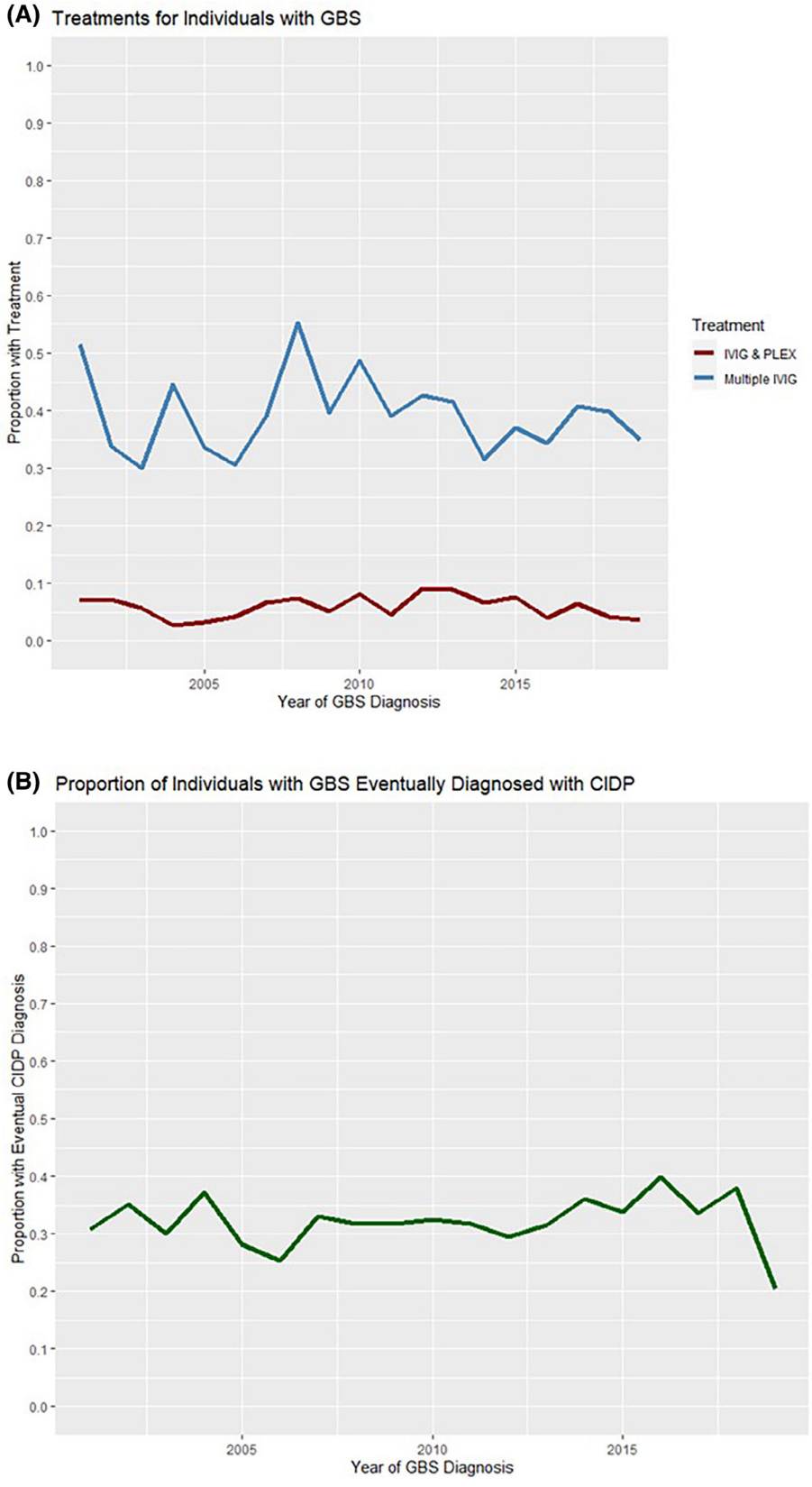


FIGURE 1 (A) Proportion of individuals with GBS who are treated with repeat IVIG treatments within 90 days (blue) or both IVIG and PLEX treatments (combination therapy) (red) within 90 days, over year of GBS diagnosis. (B) Proportion of individuals with GBS who are later diagnosed with CIDP over year of GBS diagnosis. Numerator (1092) = # individuals with CIDP after GBS in each year; denominator (3417) = # individuals with GBS who do not have a CIDP diagnosis or do not have a CIDP diagnosis before GBS diagnosis.

Finally, our study found that nearly a third of patients initially diagnosed with GBS were ultimately re-classified as CIDP. Despite year-to-year fluctuations, there was no consistent trend in our study. It is almost certain that a subset of those patients had A-CIDP,[12] which, in its relapsing phase, can present like GBS. A-CIDP clinically resembles GBS, especially GBS with TRF,[25] and a relapsing–remitting

TABLE 2 Association between patient characteristics and odds of receiving IVIG + PLEX, multiple IVIG, or transition from GBS and CIDP.

Variable	Amongst GBS patients: IVIG + PLEX (within 90 days) ($n = 1764$) Odds ratio (95% CI)	Amongst GBS patients: Multiple IVIG (within 90 days) ($n = 1764$) Odds ratio (95% CI)	Amongst GBS and GBS + CIDP patients: Transition from GBS to CIDP ($n = 2616$) Odds ratio (95% CI)
Year of GBS diagnosis	0.98 (0.93, 1.02)	1.00 (0.97, 1.02)	0.98 (0.97, 1.00)
Race (reference = White)			
Asian	0.35 (0.05, 2.62)	1.12 (0.60, 2.09)	1.77 (1.09, 2.86)*
Black	1.36 (0.69, 2.65)	1.32 (0.93, 1.86)	0.80 (0.59, 1.09)
Hispanic	1.83 (0.96, 3.48)	1.28 (0.91, 1.81)	0.74 (0.54, 1.02)
Sex = Female (reference = Male)	1.05 (0.70, 1.56)	0.79 (0.65, 0.96)*	1.11 (0.94, 1.32)
Age	1.00 (0.99, 1.02)	1.00 (0.99, 1.00)	1.01 (1.01, 1.02)*
Commercial Plan (reference = Medicare plan)	1.53 (0.64, 3.68)	1.14 (0.77, 1.69)	0.87 (0.63, 1.20)
Insurance Plan Type (reference = Preferred provider organization)			
Exclusive provider organization	1.91 (0.68, 5.34)	1.04 (0.64, 1.69)	1.26 (0.83, 1.92)
Health maintenance organization	1.08 (0.44, 2.68)	0.80 (0.54, 1.17)	0.94 (0.68, 1.31)
Indemnity	Not estimable	2.37 (0.91, 6.17)	1.48 (0.72, 3.06)
Other	2.72 (0.89, 8.28)	0.76 (0.47, 1.26)	0.91 (0.61, 1.36)
Point of service	1.59 (0.67, 3.79)	1.25 (0.85, 1.84)	1.10 (0.79, 1.53)
Net worth (reference = <$25 K)			
$25 K–$149 K	1.30 (0.69, 2.46)	0.85 (0.63, 1.15)	0.91 (0.69, 1.18)
$150 K–$249 K	1.95 (0.97, 3.90)	0.75 (0.52, 1.08)	0.78 (0.56, 1.08)
$250 K–$499 K	0.89 (0.43, 1.88)	0.64 (0.45, 0.90)*	1.19 (0.90, 1.58)
$500 K+	1.23 (0.60, 2.51)	0.91 (0.65, 1.28)	0.94 (0.70, 1.26)
Education (reference = Less than 12th Grade)			
High School Diploma	0.53 (0.11, 2.58)	2.67 (0.82, 8.69)	0.97 (0.35, 2.66)
Less than Bachelor Degree	0.54 (0.11, 2.68)	2.31 (0.71, 7.52)	1.14 (0.84, 1.55)
Bachelor Degree Plus	0.67 (0.13, 3.55)	2.86 (0.86, 9.55)	1.13 (0.88, 1.44)

Note: Models also adjusted for geographical division. * indicates statistical significance.

course occurs in up to one-third of patients with CIDP.[13] Our study contrasts with a 2003 Japanese study that found a much lower frequency of diagnostic reclassification of only 2%.[14] Underlying the unexpectedly high proportion of diagnostic re-classification in our study could be several factors, including, for one, lack of accurate ascertainment of time to nadir, which is fundamental in discriminating GBS from CIDP. It is quite possible that many of these patients were misdiagnosed with CIDP because of persistent GBS symptoms or misdiagnosed initially with GBS because of a lack of familiarity with CIDP on the part of the evaluating clinician. It is uncertain why Asian ethnicity conferred an increased likelihood of diagnostic reclassification from GBS to CIDP. It is worth noting that young age appears to be associated with A-CIDP, although there was no age association in our study with diagnostic re-classification.[13] Future prospective studies are needed to determine why such a large proportion of patients initially diagnosed with GBS are eventually diagnosed with CIDP, including whether these are appropriate diagnostic changes.

Our study faced certain limitations, namely its claims-based nature, which precluded our ability to establish diagnostic certainty for GBS or CIDP, using the Brighton criteria or EAN/PNS guidelines, respectively. A 2019 Danish study found that primary GBS diagnostic codes, using the Danish National Patient Registry, were highly accurate, however, with a positive predictive value of 83.8%, with Brighton level 1–3 certainty established in 99% of cases.[26] In addition, we did not evaluate uninsured patients, thus limiting study generalizability. Separately, our study did not include data after the SID-GBS study of 2021, which may have impacted subsequent GBS treatment prescribing patterns. Also, detailed clinical information regarding baseline disease severity, disease outcome at discharge (including mortality), electrodiagnostic testing, and cerebrospinal fluid (CSF) protein level

were not available as part of the dataset and thus could not be analyzed. Finally, and most importantly, we could not distinguish between GBS patients with and without TRF who received repeat IVIG treatment, although it is worth noting that the rate of repeat IVIG dosing in our study (40%) far exceeded the published rate of TRF in GBS (16%), suggesting that the majority of repeat IVIG dosing in our study was administered for poor prognosis/non-responder patients, and thus non-evidence based.

In conclusion, we found that the prevalence of repeat IVIG dosing was substantial at 39.7%, whereas combination therapy was less common at 6.1%. The prevalence of these treatment patterns remained largely stable over the course of the study. Patient characteristics were not consistently associated with these outcomes; therefore, provider and/or healthcare system-facing interventions are likely needed to reduce unnecessary treatment of GBS non-responders. Furthermore, initial GBS diagnoses were frequently transitioned to CIDP diagnoses, but the accuracy of these transitions is unclear and warrants further study.

AUTHOR CONTRIBUTIONS

Amro M. Stino: Writing – review and editing; writing – original draft; formal analysis; investigation. **Evan L. Reynolds:** Investigation; conceptualization; methodology; data curation; formal analysis; software; writing – review and editing. **Maya Watanabe:** Investigation; methodology; data curation; formal analysis; writing – review and editing. **Brian C. Callaghan:** Conceptualization; supervision; writing – review and editing; methodology.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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.

ORCID

Amro M. Stino https://orcid.org/0000-0002-7793-6662
Evan L. Reynolds https://orcid.org/0000-0002-0138-8436

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