A descriptive study of patients with Guillain-Barré syndrome: Experience from an Australian tertiary level hospital

Emma Foster1, Luke Bonavia1, Ashwin Subramaniam2-4, Cameron Green1, Ernest Butler1, and Ravi Tiruvoipati2,3

1. Peninsula Health (Victoria, Australia)
2. Department of Intensive Care Medicine, Peninsula Health (Victoria, Australia)
3. Faculty of Medicine, Nursing, and Health Sciences, Monash University (Victoria, Australia)
4. Department of Medicine, Peninsula Health (Victoria, Australia)


Corresponding Author:
Emma Foster
Neurosciences Department, Alfred Health, Commercial Road, Prahran VIC 3182, Australia
Email: dr.ecfoster@gmail.com

ABSTRACT

Background
Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy characterised by progressive, symmetric muscle weakness with depressed or absent deep tendon reflexes. This is a relatively rare disorder. The long term outcomes in Australasian populations are not well described.

Aims
To describe the epidemiology of patients with GBS attending an Australian metropolitan hospital over a 10-year period, including long-term (12 months) functional outcomes.

Methods
Review of medical records of GBS patients admitted to Frankston Hospital over a ten year period (June 2004 to July 2014).

Results
Thirty seven patients were identified. Median (IQR) age of onset was 60 years (51.5–73), with a M:F ratio of 1.06:1. A seasonal trend was noted, with one-third of cases occurring in winter, and another third in spring. An antecedent event was identified in many patients, with 17 patients having a preceding viral illness, and 10 having diarrhoea. Symptoms started in the legs in the majority of patients (67.5 per cent). Peak disability occurred at admission, with only 34.3 per cent able to mobilise independently at this time. This improved to 70.8 per cent of patients by 12 months. Eleven patients required ICU admission; six of whom required mechanical ventilation, with 50 per cent of them (N=3) requiring tracheostomy. 67.6 per cent of patients required inpatient rehabilitation prior to returning home.

Conclusion
The findings are consistent with previous epidemiologic studies. The vast majority of patients were independent at 12-month follow-up.

Key Words
Guillain-Barré syndrome (GBS), Guillain-Barré syndrome disability score (GBS-DS), mobility, prognosis, intensive care unit

What this study adds:
1. What is known about this subject?
GBS can cause severe neurological deficits in the short-term; however there is relatively sparse data on long-term outcomes for GBS patients in the Australasian setting.

2. What new information is offered in this study?
Despite the severe deficits suffered at the nadir of the disease, longer-term outcomes for GBS-patients are reassuring, with most independent at 12-months.
3. What are the implications for research, policy, or practice?
In the Australasian setting, GBS patients have similar epidemiologic features and long-term outcomes compared with populations in Europe and North America.

Background
Guillain-Barré syndrome (GBS) is the most common acute areflexic polyneuropathy typically presenting with rapidly progressive ascending paralysis and areflexia. The incidence of GBS is estimated at 1.7/100,000 per year in Victoria, and world-wide the incidence is 1-2 per 100,000 per year. All age groups may be affected; however incidence of GBS increases with age, and, unusually for an autoimmune disease, there is a male predominance.

It has become widely accepted that GBS has a T-cell autoimmune pathogenesis, with various pathological subtypes triggered by preceding events, most commonly bacterial or viral infection. The most established is the relationship between Campylobacter jejuni infection and axonal-motor variant of GBS. Other antecedent infections such as CMV, EBV, hepatitis B, and mycoplasma pneumonia have also been reported.

Close monitoring and ventilatory support in an intensive care setting may be required in cases of respiratory failure and severe autonomic instability. A recent study of 106 GBS cases demonstrated that 17 per cent required mechanical ventilation. Immunoglobulin therapy and plasma exchange (PE) are the mainstay of treatment, both equally effective at improving functional outcomes. Although the majority of patients have complete return of neurologic function, some deficits persist in at least 20 per cent of cases. Rapid rate and severity of paresis, as well as requirement for mechanical ventilation, are noted to be associated with poorer outcomes. Many studies reporting outcomes on GBS have focused on in hospital outcomes and to our knowledge there are no studies reporting the long term functional outcomes of GBS is Australasian settings.

This retrospective study aims to describe the demographics, clinical features, and long-term functional outcomes of patients admitted to a Metropolitan Australian hospital over a ten-year period. In addition to reviewing patient demographics, antecedent illnesses, and clinical features, this study provides an insight into long-term outcomes in GBS patients.

Method
Study setting
Peninsula Health is the major health care provider serving the metropolitan and regional areas of the Mornington Peninsula (Victoria, Australia). The catchment area encompasses approximately 900 square kilometres. The area is a prime retirement location, and there are a high proportion of older people, with age profiles over 60 years higher than the state average. (ref: http://www.peninsulalhealth.org.au/services/ Accessed 16 November 2015).

Patient identification
Patients admitted to Frankston Hospital between June 2004 and July 2014 with an admission diagnosis of GBS was identified by Health Information services of Peninsula Health, and their medical records reviewed by investigators. The diagnosis of GBS was based on the National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria. Of the 48 patients initially identified, six cases were excluded due to insufficient data, and five cases were re-classified as chronic inflammatory demyelinating neuropathy. Thirty seven GBS cases were included in the current study.

Clinical data
Patient demographics, co-morbidities, antecedent illnesses, cerebrospinal fluid (CSF) protein and white cell counts, and treatment regimens were noted. Severity of illness was assessed at admission, two weeks, four weeks, six weeks, eight weeks, six months and twelve months. These time points reflect the natural history of the disease. The nadir occurs between 2-4 weeks after onset; by definition there is no further progression beyond eight weeks; and the follow-up at six and twelve months is used to compare our data with other reports on the long-term outcomes of patients with GBS (Rajabally & Uncini, 2012). Severity was graded with the GBS-Disability Scale (GBS-DS) (Table 1). This scale was initially developed as a tool for neurologists to assess GBS patients’ response to steroids. Since then, it has continued to be used in studies to grade GBS patients’ functional status. A specific subtype of GBS was assigned where supportive electrophysiology data were available. Miller-Fisher syndrome was diagnosed based on clinical features, namely acute onset ataxia, areflexia, and ophthalmoplegia.

Statistical analysis
All descriptive statistics provided are median values and inter-quartile range (IQR) unless otherwise stated.
Non-parametric statistical tests were used to compare GBS-DS scores between groups, due to the non-normal distribution of this data. Mann-Whitney U tests were utilised to compare independent samples, with 99 per cent confidence intervals estimated using Monte-Carlo methods with 10,000 simulations.

Correlation between continuous variables was calculated using Pearson’s Correlation coefficient.

All p-values reported are two-tailed, with a threshold for statistical significance set at p<0.05.

Statistical analysis was completed using SPSS (v.20, IBM).

**Results**

A total of 37 patients were identified. The median age of diagnosis was 60 years (IQR 51.5–73 years) (Figure 1), with a M:F ratio of 1.06:1.

Symptom onset and hospital admission was most likely to occur in winter and spring (Figure 2). The median time from symptom onset to admission was four days (IQR=2.5–10 days), with a weak and non-significant correlation between time of onset to hospital admission, and GBS-DS at discharge (r=0.012, p=0.949), six months (r=0.124, p=0.539), and 12 months (r=0.09, p=0.677). The site of symptom onset was in the legs in the majority (67.5 per cent) of patients (Figure 3). A viral illness was the most commonly identified antecedent factor; others included diarrhoea and surgery (Table 2). Those with a preceding diarrhoeal illness did not have significantly worse GBS-DS scores at six months (p=0.959) and 12 months (p=0.831) compared to those without (Table 3).

CSF albuminocytologic dissociation (increased spinal fluid protein but a normal cell count) was seen in 60 per cent of cases. Five patients were diagnosed with Miller-Fisher syndrome. One patient was diagnosed with a sensory variant of GBS.

Thirty six patients received intravenous immunoglobulin (IVIg), with 33 receiving one course, and three receiving a second course. Two patients had plasma exchange after IVIg. In one case PE was used after the patient’s symptoms failed to respond to IVIg; and in the other PE was used as an adjunct to IVIg, due to the severity of the patient’s illness. Eleven patients required admission to the intensive care unit (ICU). Those requiring ICU admission were found to have significantly worse GBS-DS scores at six months [median GBS-DS=2 (1.5-25)] than those patients that did not require ICU admission [median=1 (1-2), p=0.029 (99 per cent CI=0.025-0.034)], but not at 12 months [median GBS-DS=1 (1-2) for both groups; p=0.141 (99 per cent CI=0.132-0.150)]. Six patients required mechanical ventilation, three of whom required tracheostomy. Among patients admitted to ICU, those requiring mechanical ventilation did not have significantly worse GBS-DS scores than those that did not require mechanical ventilation at 6 months (median GBS-DS=3 vs. 1; p=0.181) and 12 months (median GBS-DS=4 vs. 1; p=0.139) (Table 3).

**Patient outcomes**

Median length of acute hospital stay was eight days (IQR = 6.2-13.2). The majority of patients (67.6 per cent) required inpatient rehabilitation prior to discharge home. Around one quarter (24.3 per cent) were discharged directly home. One patient was transferred to another acute hospital. Two patients died during their acute admission, an in-hospital mortality rate of 5.4 per cent. In both cases, cause of death was due to type-II respiratory failure complicated by pneumonia, sepsis, and eventual multi-organ failure.

Only 34.3 per cent of patients were able to mobilise independently at the time of their admission (Figure 4). This figure improved over time, with 43.8 per cent of patients able to mobilise independently at the time of discharge from their acute admission. 85.2 per cent and 87.5 per cent of patients were able to mobilise independently at six- and twelve-months post-admission respectively (Figure 5). Those aged over 50 years did not have significantly worse GBS-DS scores than those aged 50 or under at six months [p=0.492 (99 per cent CI=0.479-0.504)] or 12 months [p=0.433 (99 per cent CI=0.420-0.446)].

Linear regression revealed that GBS-DS at admission was strongly associated with GBS-DS at hospital discharge [F(1)=29.79, p<0.001, r=0.829, r^2=0.687], but not at six months [F(1)=3.62, p=0.07, r=0.37, r^2=0.098] or 12 months [F(1)=3.27, p=0.086, r=0.375, r^2=0.097].

**Discussion**

We report the clinical features and long-term outcomes of 37 patients with GBS who presented to an Australian metropolitan hospital. A higher incidence in males is noted throughout the literature, with previous studies reporting a relative risk of 1.78.1 In our cohort, the incidence was approximately equal between males and females. Median age in this cohort was 60 years of age, with a peak around 70 years, which is comparable to other published Australian data.12

Two-thirds of patients were admitted in spring and winter, and this seasonal trend has been reported in a previous
Austalian study. In our cohort, this may be linked to increased incidence of viral illness during these months; with flu-like illness and gastroenteritis being the most commonly identified antecedent factors in the current study. Antecedents identified in this study are consistent with those reported in previous studies. Surgery has been previously identified as a rare risk factor for GBS, and was present in two patients in our cohort. Several patients had acute varicella zoster virus, cytomegalovirus, and Epstein-Barr virus infections, which have been linked to GBS. However, none of our patients were tested for Zika virus as it is not endemic in Australia, and to the best of our knowledge, there has not been a reported case within Australia of a Zika-virus related GBS case. No patients in our cohort had haematological or oncological malignancy, although GBS has been reported as a rare complication of lymphoma or a solid organ cancer.

There are several variants of GBS. The majority of our patients (83.8 per cent) presented with features consistent with acute inflammatory demyelinating polyneuropathy (AIDP), a form seen in 85–90 per cent of GBS cases in the United States and Europe. This included progressive, symmetric muscle weakness, with absent or depressed tendon reflexes. Five patients (13.5 per cent) had Miller-Fisher variant, presenting with ophthalmoplegia, ataxia and areflexia. One patient (3 per cent) had pure sensory GBS, with significant sensory ataxia and absent reflexes. Other GBS subtypes not represented in our cohort include acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) which are seen more commonly in Japan and China; Bickerstaff encephalitis, which is characterised by encephalopathy, hyperreflexia, ophthalmoplegia and ataxia; and the milder ‘paraparesis’ variant.

CSF albuminocytologic dissociation was found in 60 per cent of our patients. This is lower than previously reported, with other series reporting incidence of >90 per cent at two-weeks post admission. This may be due to CSF collection occurring within the first two weeks of symptom onset in 92.9 per cent of our cohort, and we note that a normal CSF protein is found in one-third to one-half of patients within the first week after symptom onset. The presence of albuminocytologic dissociation increases to more than 75 per cent of patients in the third week after symptom onset. It is therefore recommended that CSF samples should be collected at least two weeks after symptom onset in order to be used to support a diagnosis of GBS.

Non-contrast magnetic resonance imaging (MRI) in GBS tends to be normal, and so contrast is required to identify pathological changes. These pathological changes include surface thickening and contrast enhancement of the conus medullaris and cauda equina nerve roots, with anterior nerve roots more involved than posterior nerve roots.

A recent Cochrane meta-analysis concluded that there was no significant difference between plasma exchange and intravenous immunoglobulin therapy in improving functional outcomes in patients with GBS. The majority of patients in our cohort were treated with immunoglobulin therapy, in keeping with other Australian data. This may relate to its wide-spread availability and ease of administration. Previous studies have also reported a significant difference in length of hospital stay favouring immunoglobulin in mild cases of GBS, compared with plasma exchange. Although there is no evidence to support the use of any known therapeutic options in poor responders, within our cohort five patients went on to receive further treatment; three underwent another course of immunoglobulin therapy, and two received plasma exchange.

Respiratory failure is reported to occur in 20-30 per cent of cases of GBS. Six patients in our cohort required mechanical ventilation and 50 per cent of these patients went on to have tracheostomies. Other studies report up to 30 per cent of patients with GBS develop neuromuscular respiratory failure requiring mechanical ventilation.

A recent review associates a poor prognosis in GBS with increased age; preceding diarrhoeal illness; greater disability at time of admission; short interval between symptom onset and admission; and need for mechanical ventilation. Among our cohort, preceding diarrhoeal illness, age >50 years, and time from symptom onset to hospital admission were not associated with worse long-term outcomes. GBS-DS score at admission was found to be strongly related to GBS-DS at hospital discharge, but not at six months or 12 months. Patients requiring ICU admission had significantly worse GBS-DS scores at six months, but not at 12 months post-discharge.

GBS carries a mortality of 4–5 per cent at one year, despite best supportive care, and mortality increases to 20 per cent for patients who become ventilator-dependent. Deaths arise from complications including acute respiratory distress syndrome, sepsis, pulmonary emboli, and unexplained cardiac arrest which may be due to GBS-induced autonomic instability. One study found that death after GBS occurs most commonly in the elderly and most severely affected patients. Two-thirds of patients died during the recovery
phase, after neurologic improvement, most frequently from respiratory or cardiovascular complications. With regards to our cohort, the two deaths occurred in elderly patients (aged 84 and 87 years) during the acute admission phase, and cause of death was respiratory failure in the setting of pneumonia, in-keeping with previous study findings.

The nadir of disease occurred at admission, compared to other studies which have reported the nadir occurring between 2 to 4 weeks, with the majority reaching the nadir by two weeks. Patients in this cohort were admitted to hospital a median of 4 days after symptom onset, with only 34.3 per cent of patients able to walk independently at this time. This improved to 43.8 per cent at time of discharge. Our data extends to 12 months, at which time 87.5 per cent of patients were able to walk independently. This is in line with previous studies, which have reported that >80 per cent and 84 per cent of patients are able to walk independently at six and 12 months respectively.

With regards to prognosis, the literature reports that even after treatment, up to 20 per cent of patients have persistent neurologic symptoms. A qualitative study reports that the recovery process may be ongoing two years after GBS onset, with a survey revealing GBS patients experienced limitations in everyday life and reduced function in several parts of the body. One study found that GBS impaired the function and social life of patients beyond one year, with nearly 40 per cent changing their work, and 40 per cent having persistent pain. Although the results of this investigation appear to suggest that the majority of survivors of GBS have a reasonable return to function following discharge from hospital, further studies should aim to investigate the long-term psychosocial outcomes of survivors of GBS.

Limitations
This study is a retrospective investigation of patients admitted to a single centre. Due to our small sample size, the likelihood of detecting a significant effect for associations between antecedent events and the development of GBS, as well as features predictive of poor outcome, is low. For this reason, care should be taken in interpreting this data. As this is a retrospective study, information about long-term outcomes was not available for all patients.

Conclusion
This study indicates that the long-term outcomes for patients with GBS may be largely positive, with a large proportion being independently mobile at 12 months. Other findings are consistent with previously described characteristics of GBS, including increasing incidence with increasing age and a higher frequency during winter and spring.

References

PEER REVIEW
Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

ETHICS COMMITTEE APPROVAL
This study was reviewed and approved as an audit by the Research Governance of Peninsula Health (ref: QA/14/PF/45).
Table 1: The Guillain-Barre syndrome disability scale (R. A. Hughes et al., 1978)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Minimal signs and symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Able to walk without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Able to walk with assistance for 5 metres</td>
</tr>
<tr>
<td>4</td>
<td>Bed or chair bound</td>
</tr>
<tr>
<td>5</td>
<td>Requiring ventilatory support</td>
</tr>
<tr>
<td>6</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Figure 1: Incidence of GBS**

![Incidence of GBS](image)
Figure 2: Season of symptom onset

![Season of Symptom Onset](image)

Figure 3: Site of initial symptoms

![Site of initial symptoms](image)
Table 2: Antecedent factors

<table>
<thead>
<tr>
<th>Present (%)</th>
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<tbody>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
</tr>
<tr>
<td>Flu-like Symptoms</td>
</tr>
<tr>
<td>Viral infection</td>
</tr>
<tr>
<td>Cancer</td>
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<tr>
<td>Hodgkin’s</td>
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<tr>
<td>Hepatitis</td>
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<tr>
<td>HIV/AIDS</td>
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<tr>
<td>Bacterial Pneumonia</td>
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<tr>
<td>Surgery</td>
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<td>Sepsis</td>
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Table 3: Association between various factors GBS-DS scores at 6 months and 12 months

<table>
<thead>
<tr>
<th></th>
<th>GBS-DS at 6 Months</th>
<th>GBS-DS at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (total)</td>
<td>N (valid)</td>
</tr>
<tr>
<td>Aged &gt; 50 years</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Aged ≤ 50 years</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Preceding diarrheal illness</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>No diarrheal illness</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>Required ICU admission</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>No ICU admission</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Requiring Mechanical Ventilation</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>ICU admission without Mechanical Ventilation</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 4: Proportion of patients at each time point that were independently mobile (with a GBS-DS score ≤ 2)

Figure 5: GBS-DS plotted at admission, 2, 4, 6 and 8 weeks, and 6 and 12-months, post-admission