Managing Critically Ill Patients with AIDP: Relevance of International Guidelines to Indian Scenario

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Introduction

Guillain-Barré syndrome is the most frequent cause of acute flaccid paralysis globally.1-3 Currently available evidence supports autoimmune etiology of GBS.4 In its classic form, the disease is characterized by acute onset of weakness of the limbs or cranial nerve innervated muscles, progressive areflexic paralysis, varying degrees of sensory abnormalities, autonomic dysfunction due to damage to peripheral nerves and nerve roots, and increased protein in cerebrospinal fluid (CSF) with no pleocytosis.1-3 It is also an important life-threatening emergency requiring critical care in neurology. Contrary to the common misconception that the disease has a good prognosis, the mortality and severe disability due to GBS has been documented to be up to 5% and 20% respectively, and the disease carries a grave prognosis in a substantial number of patients.1-3

Epidemiology

In the developed countries, the median incidence of GBS has been estimated to be 1.11 per 100,000 person-years. After the first decade of life, there is an escalating increase of 20% with each passing decade of life. The male and female gender ratio has been observed to be 1.78.1 Nearly two-thirds of cases are preceded by symptoms of upper respiratory tract infection or diarrhea and rarely vaccination (e.g. A/New Jersey/1976/H1N1 "swine flu" vaccine). Studies have shown

Table 1: Various subtypes of Guillain-Barré syndrome

<table>
<thead>
<tr>
<th>Subtype of GBS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy (AIDP)</td>
<td>Facial variant: Facial diplegia and paresthesia</td>
</tr>
<tr>
<td></td>
<td>– Acute motor-sensory axonal neuropathy (AMSAN)</td>
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<tr>
<td></td>
<td>– Acute motor-sensory axonal neuropathy (AMSAN)</td>
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<tr>
<td>Acute pandysautonomia</td>
<td>Acute sensory form</td>
</tr>
<tr>
<td>Incomplete forms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Acute ophthalmoplegia (without ataxia)</td>
</tr>
<tr>
<td></td>
<td>– Acute ataxic neuropathy (without ophthalmoplegia)</td>
</tr>
</tbody>
</table>

cross-reactivity between infectious and neural epitopes especially for *Campylobacter jejuni* and certain forms, for e.g. motor axonal forms of GBS.\(^1,2,4\) Among the electrophysiological subtypes, AIDP is considered to be the most common in western countries; whereas, axonal types are more common in Asian countries.\(^1-3\) However, studies from India\(^5-8\) have yielded varying results with AIDP being more commonly described in some of the studies (Table 2).

### CLINICAL MANIFESTATIONS

Patients with AIDP present with numbness, paresthesias, weakness, pain in the limbs, or some combination of these symptoms. AIDP typically manifests as an ascending paralysis that usually begins in the feet; at presentation, nearly 60% of patients manifest symmetrical weakness in all four limbs. Generalized hyporeflexia or areflexia is common. Mild degrees of asymmetry is not uncommon, especially early in the course of the disease, and in the arms, the weakness may be worse proximally than distally. However, variants that differ from the classic AIDP are frequently encountered. About half the patients may present with facial weakness, and 5% may manifest varying degrees of ophthalmoplegia. AIDP encompasses the Miller-Fisher syndrome characterized by ophthalmoplegia, ataxia and areflexia; its incomplete forms are manifested by acute ophthalmoparesis without ataxia and acute ataxic neuropathy without ophthalmoplegia, and the more extensive form, Bickerstaff’s brainstem encephalitis.

About two-thirds of patients have one or more autonomic abnormalities. Sustained sinus tachycardia is the most common dysfunction. Postural hypotension leading to presyncope or syncope can occur. Pure pandsautonomia with minimal weakness, areflexia and autonomic failure has also been described. Diagnostic criteria for GBS have been listed in Table 3.\(^9\) Differential diagnosis of AIDP has been listed in Table 4. Presence of certain clinical features is considered inconsistent with a diagnosis of AIDP. These include weakness that remains markedly asymmetric, a sharp sensory level, and severe bladder or bowel dysfunction at the onset.

### CRITICAL CARE CONCERNS

The disease progresses for up to 1–3 weeks after the onset of symptoms and nearly 40% of patients may present with oropharyngeal or respiratory muscle weakness. About 25–35% develop acute respiratory failure requiring assisted mechanical ventilation.\(^1,2,10-12\) Important complications observed in critically ill patients with AIDP include unexplained cardiac arrest, perhaps

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**TABLE 2 | Prevalence of various subtypes of Guillain-Barré syndrome* in some recent studies from India**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kalita et al. (2008)(^5)</th>
<th>Gupta et al. (2008)(^6)</th>
<th>Alexander et al. (2011)(^7)</th>
<th>Vengamma (2011)(^8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of study</td>
<td>Lucknow</td>
<td>Thiruvananthapuram</td>
<td>Vellore</td>
<td>Tirupati</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>51</td>
<td>142</td>
<td>115</td>
<td>59</td>
</tr>
<tr>
<td>AIDP</td>
<td>86.3%</td>
<td>85.2%</td>
<td>38.2%</td>
<td>76.2%</td>
</tr>
<tr>
<td>Axonal variants</td>
<td>AMAN in 7.8% and AMSAN in 5.9%</td>
<td>AMAN in 10.6%</td>
<td>51 (44.3%)</td>
<td>AMAN in 3.4%, AMSAN in 12%</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>-</td>
<td>4.2%</td>
<td>17.4%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

* Miller-Fisher syndrome was also observed in 5%

**Abbreviations: AIDP, Acute inflammatory demyelinating polyneuropathy; AMAN, Acute motor axonal neuropathy; AMSAN, Acute motor-sensory axonal neuropathy**

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**TABLE 3 | Diagnostic criteria for typical GBS**

**Features required for diagnosis**

- Progressive weakness in both arms and legs (might start with weakness only in the legs)
- Areflexia (or decreased tendon reflexes)

**Features that strongly support diagnosis**

- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain (often present)
- High concentration of protein in CSF

**Typical electrodiagnostic features**

Features that should raise doubt about the diagnosis of GBS include presence of the following manifestations at the onset, such as fever, severe pulmonary dysfunction with limited limb weakness at onset, severe sensory signs with limited weakness, bladder or bowel dysfunction, a sharp sensory level, slow progression with limited weakness without respiratory involvement (subacute inflammatory demyelinating polyneuropathy or CIDP likely), marked persistent asymmetry of weakness, persistent bladder or bowel dysfunction, increased number of mononuclear cells in CSF (＞50 x 10^6/L) and presence of polymorphonuclear cells in CSF.

**Abbreviations: GBS, Guillain-Barré syndrome; CSF, Cerebrospinal fluid; CIDP, Chronic inflammatory demyelinating polyneuropathy**

related to dysautonomia, pneumonia, sepsis, pulmonary embolism, gastrointestinal bleeding, among others (Table 5).

**UTILITY OF INTERNATIONAL GUIDELINES ON DIAGNOSIS**

Till 2009, several case definitions of GBS existed like the Asbury-Cornblath case definition\(^8\) (Table 3), which required ancillary diagnostic testing including electrophysiological studies. Subsequently, Brighton criteria (Table 6)\(^13\) based on purely clinical case definition have been introduced for use in resource limited countries. In a study conducted from India,\(^14\) the sensitivity of the Brighton Working Group case definitions for GBS was evaluated using a population-based cohort from the National Polio Surveillance Unit of India (that actively collects all cases of acute flaccid paralysis in children under 15 years old). During the period 2002–2003, 79 cases with GBS were selected, in which the diagnosis of GBS was based on clinical history, neurological examination findings, CSF and nerve conduction studies (NCS) results. The sensitivity of the Brighton GBS criteria (Table 6) for level 3 of diagnostic certainty (which requires no clinical laboratory testing), level 2 (which employs CSF or NCS) and level 1 (which employs both) was computed. The majority of cases (86%) fulfilled Brighton level 3 (86%), level 2 (84%), and level 1 (62%) diagnostic certainty suggesting that these criteria are potentially useful with a moderate to high sensitivity in resource limited settings like India.\(^14\)

**TREATMENT**

**General Measures**

Ideally, all patients with AIDP should remain hospitalized until it is certain that there is no evidence of clinical progression of the disease. Patients with AIDP should be ideally treated in a neurological intensive care unit, where adequate resources for continuous cardiac and respiratory monitoring are available. The key principles underlying the general care and monitoring of patients with AIDP have been listed in Table 7 and Flow chart 1. Early assessment and careful monitoring of swallowing will identify patients at risk for aspiration, necessitating the placement of a nasogastric tube.

**Mechanical Ventilation**

Even in the absence of clinical respiratory distress, mechanical ventilation may be required in patients with at least one major criterion or two minor criteria. The major criteria are hypercarbia (partial pressure of arterial carbon dioxide > 48 mm Hg), hypoxemia (partial pressure of arterial oxygen while the patient is breathing ambient air < 56 mm Hg) and a vital capacity less than 15 mL/kg of body weight. The minor criteria are inefficient cough, impaired swallowing and atelectasis.\(^1\)
### TABLE 6 | Brighton Working Group clinical case definitions: GBS

**Level 1 of Diagnostic Certainty**
Presence of:
1. Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs with or without involvement of respiratory or cranial nerve innervated muscles
2. Decreased or absent deep tendon reflexes at least in affected limbs
3. Monophasic illness pattern with weakness nadir reached between 12 hours and 28 days, followed by clinical plateau and subsequent improvement or death
4. Electrophysiologic findings consistent with GBS
5. Presence of albuminocytologic dissociation (elevation of CSF protein level above laboratory normal value and CSF total white cell count < 50 cells/mm$^3$)
6. Absence of an alternative diagnosis for weakness

**Level 2 of Diagnostic Certainty**
Presence of:
1. Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs with or without involvement of respiratory or cranial nerve innervated muscles
2. Decreased or absent deep tendon reflexes at least in affected limbs
3. Monophasic illness pattern, with weakness nadir reached between 12 hours and 28 days, followed by clinical plateau and subsequent improvement or death
4. CSF with a total white cell count < 50 cells/mm$^3$ (with or without CSF protein elevation above laboratory normal value) or if CSF not collected or results not available, and electrodiagnostic studies consistent with GBS
5. Absence of an alternative diagnosis for weakness

**Level 3 of Diagnostic Certainty (clinical case definition)**
Presence of:
1. Acute onset of bilateral and relatively symmetric flaccid weakness/paralysis of the limbs with or without involvement of respiratory or cranial nerve innervated muscles
2. Decreased or absent deep tendon reflexes at least in affected limbs
3. Monophasic illness pattern, with weakness nadir reached between 12 hours and 28 days, followed by clinical plateau and subsequent improvement or death
4. Absence of an alternative diagnosis for weakness

**Abbreviations:** GBS, Guillain-Barré syndrome; CSF, Cerebrospinal fluid

### TABLE 7 | General care and monitoring of patients with AIDP

- Regular monitoring of pulmonary function (vital capacity, respiration frequency), initially every 2–4 hours; in stable phase, every 6–12 hours
- Regular check for autonomic dysfunction (at initial presentation: blood pressure, heart rate, pupils, ileus; preferably continuous monitoring of ECG, pulse and blood pressure; if logistically difficult, check every 2–4 hours; in stable phase, every 6–12 hourly)
- Careful check for swallowing dysfunction
- Recognition and treatment of pain: acute nociceptive pain (preferably avoid opioids), chronic neuropathic pain (amitriptyline or antiepileptic drugs)
- Prevention and treatment of infections and pulmonary embolism
- Prevention of corneal ulceration due to facial weakness
- Prevention of decubitus ulcers and contractures

In studies from India, factors independently associated with the need for mechanical ventilation included elderly age ($p = 0.014$), simultaneous motor weakness in both upper and lower limbs as the initial symptom ($p = 0.02$), upper limb power less than grade 3/5 (Medical Research Council grade) at nadir ($p = 0.013$), presence of bulbar weakness ($p < 0.001$), autonomic dysfunction ($p = 0.002$) and pulmonary complications ($p = 0.011$). 10-12

### Immunotherapy

#### Plasma Exchange

Plasma exchange eliminates circulating immunoglobulins and immune complexes directed at components of the central and peripheral nervous system. This was the first therapeutic intervention found to be effective in hastening recovery in patients with GBS, especially if it was started within the first 2 weeks after disease onset in patients who were unable to walk. Plasma exchange nonspecifically removes antibodies and complement, and appears to be associated with reduced nerve damage and faster clinical improvement as compared with supportive therapy. 15

As per the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, plasma exchange is established as effective, and should be offered in severe AIDP/GBS severe enough to impair the ability to walk independently or to require mechanical ventilation (Class I studies, Level A). It is probably effective and should be considered for mild AIDP/GBS in which amelioration is preserved. The usual empirical regimen is five exchanges over a period of 2 weeks with a total exchange of five plasma volumes. One trial showed that patients who could walk with or without aid but could not run benefited from two exchanges of 1.5 plasma volumes, but more severely affected patients required at least four exchanges.
if infrastructural facilities exist, plasma exchange is a cheaper option. However, huge initial investment is required to setup plasma exchange. Furthermore, there is need for procuring, and periodically renewing permissions and licenses from regulatory authorities for providing plasma exchange. Although IVIg is more widely available, the cost is prohibitive. These factors influence the utilization of these treatment options in patients with AIDP in hospitals across India.

**REFERENCES**

Section 16

Chapter 122 Managing Critically Ill Patients with AIDP


