*Neurology Asia 2014; 19(3) : 263 – 270*

# Clinical outcome of Guillain-Barré syndrome with various treatment methods and cost effectiveness: A study from tertiary care center in South India: Yashoda GBS Registry

[1]Jaydip Ray Chaudhuri *MD DM*, [2]Suvarna Alladi *DM*, [2] K Rukmini Mridula *DNB DM*, [2]Demudu Babu Boddu *MD DM*, [3]MV Rao *MD*, [3]C Hemanth *MD*, [4]V Dhanalaxmi *MD DM*, [5]J Mayurnath Reddy *MD*, [6]S Manimala Rao *MD*, [3]Banda Balaraju *MD*, [1,7]VCS Srinivasarao Bandaru *PhD*

*[1]Department of Neurology, [3]Medicine, [4]Nephrology, [5]Psychiatry, [6]Critical Care, [7]Clinical Research, Yashoda hospital, Hyderabad, India; [2]Department of Neurology, Nizams's Institute of Medical Sciences, Hyderabad, India*

### *Abstract*

*Back ground and Objective:* Both plasmapheresis and intra venous immunoglobulin (IVIG) are effective for Guillain-Barré syndrome (GBS) but differ in cost and ease of administration. The aim of this study was to evaluate and compare clinical outcome after treatment with IVIg and plasmapheresis in patients with various GBS subtypes and assess their cost effectiveness. *Methods:* Thirty seven consecutive GBS patients, recruited from May 2008 to September 2012, from Department of Neurology, Yashoda hospital Hyderabad, underwent detailed clinical and electrophysiological assessment. Patients randomly received either IVIG or plasmapheresis. Outcome was measured using change in mean motor power and Hughes grade at discharge. Effectiveness and duration of hospital stay was compared with cost effectiveness of both therapies. *Results:* Out of 37 patients; men were 23 (62.1%), mean age was 42.3 $\pm$14.1 years. Electro physiologically acute inflammatory demyelinating neuropathy (AIDP) was most common (56.7%). Nineteen patients (51.3%) received IVIG and plasmapheresis was done in 18 (48.6%). Cost of plasmapheresis was significantly lower (mean USD 2,584.5 versus USD 4,385.3) (p=0.01). At discharge, significant and similar improvement was noted in both groups although duration of hospital stay was longer in plasmapheresis group Three patients (2 in plasmapheresis and one in IVIG group) died.
*Conclusion:* In developing countries, plasmapheresis may be a better option in treatment of GBS.

## INTRODUCTION

Guillain-Barré syndrome (GBS) is an autoimmune disease of peripheral nervous system, causing progressive weakness and areflexia. It is a major cause of acute neuromuscular paralysis and causes respiratory failure requiring ventilator support in approximately 25% with a mortality rate of 4-15%.[1-3] The annual incidence of GBS is 1.3–4 per 100,000 all over the world.[1,4,5] Men are approximately 1.5 times more affected than women.[6]

The most frequent subtype in North America and Europe is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which accounts for 90% of all GBS cases in these regions.[7] In Asia, South America, and Central America, however, the axonal variants of GBS [Acute motor axonopathy (AMAN) and Acute motor sensory axonopathy (AMSAN)] account for 30% to 47% of cases.[7-9] In 1980s, plasma exchange was found to be effective[10,11] and in 1990s, efficacy was also demonstrated for intravenous immunoglobulin (IVIG) in patients with GBS.[12,13] Most studies done in the West have shown equal efficacy of both treatment modalities. The American Academy of Neurology practice guidelines has recommend either IVIG or plasmapheresis for GBS patients with severe disease who have restricted mobility.[14] In comparison to plasmapheresis, although IVIG is more expensive, it is easier to administer and is safer in patients with autonomic disturbances. The aim of the present study was to evaluate the clinical features and outcome of patients with GBS subtypes who received IVIG and plasmapheresis, and their cost effectiveness. Very limited data is available in India on this important issue.

*Address correspondence to:* VCS Srinivasarao Bandaru, Department of Neurology and clinical Research, Yashoda hospital, Hyderabad -500082 INDIA, Tel: 00919441266519, Fax: 9104023398667, email: rsbhandaru@gmail.com

## METHODS

The study was conducted from May 2008 to September 2012, at Department of Neurology, Yashoda Hospital, Hyderabad; a referral center from South India. This study was approved by the institutional ethics committee.

Data for the study was collected through personal interviews of patients by a trained research fellow, review of medical records, physical and neurological examination done by neuro-muscular specialist or senior neuro-physician.

Further classification into subtypes AIDP, AMAN and AMSAN, was carried out on the basis of clinical and electrophysiological criteria. Electrophysiological examinations were performed within 3 weeks of the onset of illness in all patients by a neuro muscular specialist. Nerve conduction studies with evaluation of median, ulnar, common peroneal, tibial and sural nerves were performed in all. Needle electromyogram (EMG) was done in at least two proximal and two distal limb muscles, for assessment of denervation and motor unit action potential changes, in all patients. Patients were classified as having axonal or demyelinating subtype based on the electrodiagnostic criteria given by Hadden *et al*.[15] AMSAN was diagnosed based on criteria by Rees *et al*.[16] CSF examination was done in 34 (91.8%) patients.

All patients were selected randomly to receive either IVIG or plasmapheresis in 1:1 ratio. Before starting the treatment, every patient was explained about the risks and benefits of treatment and consent was taken. Most patients with autonomic disturbances were excluded. Only patients with isolated tachycardia, persistent hypertension, fluctuations in heart rate less than 30 beats / min over 24 hours, and blood pressure fluctuations of less than 20/10 mm Hg over 24 hours were included. The plasmapheresis regimen consisted of removal of a total of 200 -250mL/kg of plasma over five to eight cycles, on daily basis. Most patients received five cycles. One patient received 8 cycles of smaller volumes of 600ml as there was initial difficulty in achieving higher plasmapheresis from the antecubital vein and on the third cycle had to be stopped intermittently as patient developed mild itching. The replacement fluid was 5% albumin in 15 patients and fresh frozen plasma in 4 patients. In many patients treatment was initiated through the antecubital veins, while few required an internal jugular venous access. The IVIG regimen was 0.4 g/kg per day for 5 consecutive days.

On admission, the muscle power was recorded using the Medical Research Council (MRC) sum score.[17] Lumbar puncture (LP) was performed in the first or second week of admission of hospital (depending on patient's condition) by a senior neurologist.

We used Hughes grade scale for assessing functional motor deficits.[18] This was as follows: 0: healthy; 1: the patient has minor symptoms and signs and is able to run; 2: the patient is able to walk 5 meters across an open space without assistance, but is unable to run; 3: the patient is able to walk 5 meters with assistance only; 4: patient is chairbound/ bed bound; 5: patient requires ventilation and 6: patient is dead.

### *Cost analysis*

We analyzed the cost of both regimens in all patients. We calculated the overall cost incurred (expenditure) during hospitalization, which included the cost of hospital stay, (including ICU care with ventilator support), other auxiliaries including urine catheter, central venous catheter, infusion pumps and medications.

### *Statistical analysis*

Statistical analysis was performed using Statistical Package for the Social Sciences, Version 16 (SPSS, Inc., Chicago, IL, USA). Mean, standard deviation and Chi-squire test were performed. p value was considered significant if less than 0.05.

## RESULTS

In this study, 21 (52.5%) patients with GBS received IVIG and 19 (47.5%) plasmapheresis. There were 13 males (61.9%) in IVIG group and 12 males (63.1%) in plasmapheresis group. Mean age and age range were comparable in both groups. Clinical features were also similar in both groups. Limb weakness was noted in all. Distal weakness, more than proximal was the most common presentation. Preceding histories of fever, cough and diarrhea were noted in 42%, 31% and 16% in plasmapheresis group and 55%, 44% and 22% in IVIG group respectively. Similar distribution of electrophysiological subtypes was seen in both IVIg and plasmapheresis groups. AIDP was most common followed by AMAN and AMSAN. CSF examination was done in 36 patients (90%) and mean CSF protein level was 110.6 ± 12.4 mg/dl (range, 18-450 mg/ dl). Mean length of stay was different in both the groups with a significantly higher number of days in

plasmapheresis group compared to IVIG group (p=0.001) (Table1).

There was no significant difference in the complications in both the groups. Ventilator support was needed in 9 (42.8%) patients in the IVIG group, and 7 (36.5%) patients in the plasmapheresis group. Hypotension developed in 3 (14.2%) patients in IVIG group and 5 (26%) patients in plasmapheresis group (Table 2).

Clinical outcome -- mean MRC sum score at onset and at time of discharge -- in IVIG group were 21.3± 7.83 and 42.1± 16.3 (p <0.0001); and in plasmapheresis group were 23.8 ±11.9 and 38.6 ±18.4 (p <0.0001) respectively.

Hughes grade of 0 was noted in 23.8% of plasmapheresis and 21% of IVIg groups at 30 days follow up, which improved to 66.6% of plasmapheresis and 76.4% of IVIg at 180 days follow up. There was no significant difference in outcome at discharge or at follow up at 30, 60, 180 days and 1 year between both groups (Table 3).

The cost of hospital care for plasmapheresis group at mean+2SD in USD (2,584.5± 2210.3) was significantly lower than the IVIG group (4,385.3±1971.8)(p=0.01) (Table 4)

**Table 1: Baseline data of the study subjects**

| Parameters | IVIG (n=19) | Plasmapahresis (n=18) | p value |
|---|---|---|---|
| Men | 12 (61.9%) | 11 (63.1%) | NS |
| Age range (years ) | 7-70 | 18-70 | |
| Mean age (SD) | 41.6±12.4 | 43.4±13.1 | NS |
| Hypertension | 7 (36.8%) | 3 (16.6%) | NS |
| Diabetes | 3 (15.7%) | 4 (22.2%) | NS |
| Smoker | 4 (21%) | 2 (11.1%) | NS |
| Alcoholics | 4 (21%) | 3 (16.6%) | NS |
| Mean length of staying in hospital days | 15.1 ±2.2 | 20.5 ±2.9 | 0.001 |
| **Clinical features** | | | |
| Distal>proximal | 8 (42.1%) | 7 (38.8%) | NS |
| Distal=proximal | 7 (36.8%) | 6 (33.3%) | NS |
| Distal<proximal | 4 (21%) | 5 (27.7%) | NS |
| Facial weakness | 6 (31.5%) | 7 (38.8%) | NS |
| Bulbar weakness | 6 (31.5%) | 8 (44.4%) | NS |
| Extraocular weakness | 6 (31.5%) | 3 (16.6%) | NS |
| Sensory loss | 8 (42.1%) | 10 (55.5%) | NS |
| Proprioceptive loss | 4 (21%) | 5 (27.7%) | NS |
| History of fever | 8 (42.1%) | 10 (55.5%) | NS |
| Cough | 6 (31.5%) | 8 (44.4%) | NS |
| Sore throat | 3 (15.7%) | 4 (22.2%) | NS |
| Diarrhea | 7 (36.8%) | 3 (16.6%) | NS |
| Disease progression at hospital | 1 (5.2%) | 2 (11.1%) | NS |
| **Electrophysiological grouping** | | | |
| AIDP(56.7%) | 11 (57.8%) | 10 (55.5%) | NS |
| AMAN (18.9%) | 3 (15.7%) | 4 (22.2%) | NS |
| AMSAN(24.3%) | 5 (26.3%) | 4 (22.2%) | NS |

NS, not significant; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonopathy; AMSAN, acute motor sensory axonopathy

**Table 2: Complications and outcome of Guillain-Barré syndrome syndrome in treatment groups**

| Out come | IVIG (n=19) | Plasmapheresis (n=18) | p value |
|---|---|---|---|
| Complications | | | |
| Ventilator support | 8 (42.1%) | 6 (33.3%) | NS |
| Infections | 8 (42.1%) | 9 (50%) | NS |
| Hypotension | 3 (15.7%) | 5 (27.7%) | NS |
| Death | 1 (5.2%) | 2 (11.1%) | NS |
| Clinical outcome | | | |
| Muscle strength (mean MRC sum score) at admission | 20.8± 7.4 | 22.1 ±11.1 | NS |
| Muscle strength (mean MRC sum score) at discharge | 41.5± 14.7 | 37.9 ±17.3 | NS |

NS, not significant; MRC, Medical Research Council

**Table 3: Clinical status outcome at 30 days, 60 days, 120 days, 180 days and 365 days**

| Hughes grade | 30 days (n=37) | | 60 days (n=33) | | 180 (n=33) | | 365 days (n=29) | |
|---|---|---|---|---|---|---|---|---|
| | Plasma-pheresis (n=18) | IVIG (n=19) | Plasma-pheresis (n=16) | IVIG (n=17) | Plasma-pheresis (n=16) | IVIG (n=17) | Plasma-pheresis (n=14) | IVIG (n=15) |
| 0 | 5 (27.7%) | 4 (21%) | 8 (50%) | 9 (52.9%) | 12 (75%) | 13 (76.4%) | 13 (92.8%) | 14 (93.3%) |
| 1 | 5 (27.7%) | 6 (31.5%) | 3 (18.7%) | 3 (17.6%) | 2 (12.5%) | 2 (11.7%) | 1 (7.2%) | 1 (6.7%) |
| 2 | 3 (16.6%) | 6 (31.5%) | 4 (25%) | 4 (23.5%) | 1 (6.2%) | 2 (11.7%) | 0 | 0 |
| 3 | 1 (5.5%) | 2 (10.5%) | 1 (6.2%) | 1 (5.8%) | 1 (6.2%) | 0 | 0 | 0 |
| 4 | 1 (5.5%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 1 (5.5%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 2 (11.1%) | 1 (5.2%) | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 4: Cost effectiveness of outcome**

| Parameters | IVIG | Plasmapheresis | p value |
|---|---|---|---|
| Mean Treatment cost in USD | 3,005.5±1115.8 | 1,508.6±1411.9 | 0.001 |
| Mean cost of other expenditures in USD | 1,382.6±1069.6 | 1,121.6±1058.6 | 0.82 |
| Mean total cost in USD | 4,385.3±1971.8 | 2,584.5±2210.3 | 0.01 |

## DISCUSSION

The demographic parameters of our patients are similar to previous studies. In our study men were more significantly affected with GBS. Similar results were noted in Taiwan.[19] GBS is an autoimmune disease, postulated to be caused by mechanism of molecular mimicry after an infection.[20] Prior history of infection was seen in 68% in our study which included upper respiratory tract infection in 38%, diarrhea in 27% and non specific fever in 2%. Similar prevalence of infection preceding GBS has been reported previously from India[21] and rest of the world.[7,22] The role of infections by *Campylobacter Jejuni*, Cytomagalovirus (CMV), Epstein-Barr virus (EBV) and *Mycoplasma pneumonia*e in causing

GBS is well established and the infective agent may determine the electrophysiological subtypes of GBS.[23] In our study, we observed diabetes mellitus in 30% and alcohol consumption in 25% of patients. Though they have been proposed as risk factors for GBS in previous reports[24,25], its possible associations with GBS are limited by the lack of a normal cohort.

In the present study we established that AIDP (56.7% of all patients) was the most common variant of GB syndrome. Similar reports were noted in other studies from Malaysia (74.2 %)[26], India (60%)[27], Israel (63%)[28], Pakistan (46%)[29], Japan (36%).[30] Lower proportion of AIDP have been described in China (24%)[31] and Bangladesh (24%).[32] The second most prevalent subtype was AMSAN (24.3%) in our study. Similar finding was also seen in Israel (15%)[28], and Bangladesh (11%)[32], whereas the Japanese had very low prevalence of AMSAN (1–4%).[33,34] AMAN constituted 17.5% of our patients. This prevalence is similar to studies from the West.[15,16,28,34,36] This is in contrast to China[31] and other Asian countries.[29,30,32] AMAN was the commonest subtype of GBS reported from North China.[31] The difference could be partly accounted by variations in the environmental factors, pathogenic mechanisms, genetic susceptibility, other triggering factors like different infections operating in different populations. The electrophysiological features evolve over time and may be fallacious in early stages of the disease. Serial recordings in a previous study have shown change of diagnosis in 24% of patients.[36] This may be due to the fact that in early AMAN, reversible conduction failure mimicking demyelinating neuropathy can occur which may erroneously lead to the diagnosis of AIDP.[37] These anomalies in the electrophysiological diagnosis may play a major role in false interpretation of the prevalence of subtypes in various regions of the world.

We observed that mean CSF protein levels were elevated in all patients with GBS (mean CSF 110.6± 12.4). The results were comparable with other studies by Corston *et al*,[38], Chio *et al*.[39] and Khan.[40] Several reports have attributed the increase in CSF protein concentration in GBS from the breakdown of the blood CSF barrier.[41-46] Alternatively an inflammatory reaction might occur in the choroid plexus and disturb the transport processes.[47-51]

In both IVIG and plasmapheresis groups, the outcomes were similar in the improvement of muscle strength and Hughes grade, which is in agreement with previous reports.[52,53] However some studies have found that in children with GBS on mechanical ventilator, plasmapheresis is better than IVIg.[54]

In our study we found no difference in the complications between the two groups, in contrast to other studies where risk of infections and hypotension were more in plasmapheresis group.[55-57] In our study, one patient had difficulty in maintaining venous access in the plasmapheresis group and had developed an allergic reaction. The use of fresh frozen plasma carries a risk of developing infections and allergic / immune reactions with increased risk of developing transfusion related lung injury (TRALI), acute respiratory distress syndrome (ARDS) and death.[58] In the present study, there was no TRALI seen. However, our sample size was small, and hence the low risk of complications in plasmapheresis may be by chance.

In our study we noted plasmapheresis group had a significant longer hospital stay compared to IVIG group. This was attributed to the hospital working system. Our transfusion medicine team preferred to start plasmaphersis in the morning after all the investigations were obtained and venous access was achieved. Hence the treatment usually started after 2-3 days of hospital stay, as compared to IVIG group. There were two patients in the plasmaphersis group who had other reasons for prolonged stay. One patient was given 8 cycles of small volume plasmapheresis over 10 days, and the other patient developed sepsis and had a prolonged hospital stay of more than one month.

In the present study, mortality rate was 8.1% (two patients in plasmapheresis group and one patient in IVIG group). All the mortalities required ventilator support and developed sudden cardiac arrhythmias. Similar reports were noted from Iran[59], and Taiwan.[60] Dias-Tosta and Kuckelhaus[61] reported a mortality of 5.4% in pediatric GBS. However, in most studies from the West, the mortality rate was reported as 3%.[11, 62]

On evaluation of the cumulative cost, IVIG was more expensive than plasmapheresis. The treatment cost for IVIG was USD 4,250-5,300, and it was USD 2,600-4,100 for plasmaphersis, which was similar to the West.[63, 64] This evaluation included the cost of the procedure, but also the hospital cost including the treatment for co-morbid infections and intensive unit care. However, IVIG is easier to administer and is associated with fewer days of hospital stay in our patients. There was no difference between the two groups in effectiveness or rate of improvement.

In conclusion, this is the first randomized study from India assessing efficacy and cost effectiveness of the two treatment groups, IVIG and plasmaphersis. AIDP was the most common subtype of GBS. Men were slightly more affected. CSF in most patients showed elevated protein. Mortality rate was 8.1%. Both IVIG and plasmapheresis were equally effective. In plasmapheresis group, although mean duration of hospital stay increased, both had similar complications. However a small sample size may have precluded this study from identifying all the complications associated with plasmaphersis, such as line related sepsis and autonomic disturbances. IVIG was more expensive than plasmapheresis in our study. Due to cost effectiveness, plasmapheresis can be a preferred treatment option for GBS in low socioeconomic countries like India. A larger study in the future can confirm the findings.

## ACKNOWLEDGEMENT

We would like to thank Dr.G.S Rao, Managing Director, Yashoda group of hospitals and Dr.A.Lingaih, Director of Medical services for their generous support to carry out this study in the Yashoda Hospital, Hyderabad.

## DISCLOSURE

Conflict of interest: None

## REFERENCES

1. van Koningsveld R, van Doorn PA, Schmitz PI, Ang CW, Van der Meche FG . Mild forms of Guillain-Barre syndrome in an epidemiologic survey in The Netherlands. *Neurology* 2000; 54:620-5.
2. Prevots DR, Sutter RW. Assessment of Guillain-Barre syndrome mortality and morbidity in the United States: Implications for acute flaccid paralysis surveillance. *J Infect Dis* 1997; 175:S151-S155.
3. Rees JH, Thompson RD, Smeeton NC, Hughes RA. An epidemiological study of Guillain-Barre syndrome in south east England. *J Neurol Neurosurg Psychiatry* 1998; 64:74-7.
4. Govoni V, Granieri E. Epidemiology of the Guillain-Barre syndrome. *Curr Opin Neurol* 2001; 14:605-13.
5. Hughes RA, Rees JH. Clinical and epidemiological features of Guillain- Barre syndrome. *J Infect Dis* 1997; 176:S92-S98.
6. Bogliun G, Beghi E. Incidence and clinical features of acute inflammatory polyradiculoneuropathy in Lombardy, Italy, 1996. *Acta Neurol Scand* 2004; 110:100-6.
7. Hughes RA, Cornblath DR. Guillain-Barre syndrome. *Lancet* 2005; 366:1653-66.
8. Hung KL, Wang HS, Liou WY, *et al*. Guillain-Barré syndrome in children: a cooperative study in Taiwan. *Brain Dev* 1994; 16:204-8.
9. Cheng Q, Wang DS, Jiang GX, *et al*. Distinct pattern of age-specific incidence of Guillain-Barre syndrome in Harbin, China. *J Neurol* 2002; 249:25-32.
10. Efficiency of plasma exchange in Guillain-Barre syndrome: role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain-Barre Syndrome. *Ann Neurol* 1987; 22:753-61.
11. The Guillain-Barre Syndrome Study Group. Plasmapheresis and acute Guillain-Barre syndrome. *Neurology* 1985; 35:1096-104.
12. van der Meche´ FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain- Barre´ Study Group. *N Engl J Med* 1992; 326:1123-9.
13. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange / Sandoglobulin Guillain-Barre Syndrome Trial Group. *Lancet* 1997; 349:225-30.
14. Hughes RA, Wijdicks EF, Barohn R, *et al*. Practice parameter: immunotherapy for Guillain-Barré syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; 61:736-40.
15. Hadden RD, Cornblath DR, Hughes RAC, *et al*. Electrophysiological classification of Guillain- Barre syndrome: clinical associations and outcome. *Ann Neurol* 1998; 44:780-8.
16. Rees JH, Gregson NA, Hughes RAC. Anti-ganglioside GM1 antibody in Guillain–Barré syndrome and their relationship to Campylobacter jejuni infection. *Ann Neurol* 1995; 38:809-16.
17. Kleyweg RP, van der Mechè FGA, Schmitz PIM. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barrè syndrome. *Muscle Nerve* 1991; 14:1103-9.
18. Hughes RAC, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. *Lancet* 1978; 2:750-3.
19. Lyu RK, Tang LM, Cheng SY, Hsu WC, Chen ST. Guillain-Barre syndrome in Taiwan: a clinical study of 167 patients. *J Neurol Neurosurg Psychiatry* 1997; 63: 494-500.
20. Yu RK, Usuki S, Ariga T. Ganglioside molecular mimicry and its pathological roles in Guillain-Barré syndrome and related diseases. *Infect Immun* 2006; 74(12):6517-27.
21. Sarkar UK, Menon L, Sarbapalli D, *et al*. Spectrum of Guillain-Barré syndrome in tertiary care hospital at Kolkata. *J Nat Sci Biol Med* 2011; 2:211-5.
22. Shui IM, Rett MD, Weintraub E, *et al*. Guillain-Barré syndrome incidence in a large United States cohort (2000–2009). *Neuroepidemiology* 2012; 39:109-15.
23. Hahn AF. Guillain-Barré syndrome. *Lancet* 1998; 352:635-41.
24. Flax H, Matthew DR. Diabetes associated with Guillain-Barre syndrome. *Diabetes Res* 1990; 14:47-50.
25. Pastena L, Chiodi F Cedia A. Guillain-Barre syndrome in Chronic alcoholism. *Drug Alchol Depend* 1988; 21:153-6.

26. Goh KJ, Ng WK, Vaithailingam M, Tan CT. A clinical and electrophysiological study of Guillain-Barre syndrome in Malaysia. *Neurol J Southeast Asia* 1999; 4:67-72.
27. Sharma A, Lal V, Modi M, Vaishnavi C, Prabhakar S. Campylobacter jejuni infection in Guillain-Barré syndrome: a prospective case control study in a tertiary care hospital. *Neurol India* 2011: 59:717-21.
28. Kushnir M, Klein C, Pollak L, Rabey JM. Evolving pattern of Guillain–Barre syndrome in a community hospital in Israel. *Acta Neurol Scand* 2008; 117:347-50.
29. Shafquat S, Khealani A, Awan F, Abedin E. Guillain–Barre syndrome in Pakistan:similarity of demyelinating and axonal variants. *Eur J Neurol* 2006; 13:662-5.
30. Ogawara K, Kuwabara S, Mori M, Hattori T, Koga M, Yuki N. Axonal Guillain–Barré syndrome: relation to anti-ganglioside antibodies and Campylobacter jejuni infection in Japan. *Ann Neurol* 2000; 48:624-31.
31. Ho TW, Mishu B, Li CY, *et al*. Guillain-Barre syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. *Brain* 1995; 118:597-605.
32. Islam Z, Jacobs BC, van Belkum A, *et al*. Axonal variant of Guillain–Barré syndrome after Campylobacter infection in Bangladesh. *Neurology* 2010; 74:581-7.
33. Kuwabara S. Guillain–Barré syndrome. *Curr Neurol Neurosci Rep* 2007; 7:57-62.
34. Nachamkin I, Arzarte Barbosa P, Ung H, *et al*. Patterns of Guillain–Barré syndrome in children. Results from a Mexican population. *Neurology* 2007; 69:1665-71.
35. Paradiso G, Tripoli J, Galicchio S, Fejerman N. Epidemiological, clinical and electrodiagnostic findings in childhood Guillain-Barré syndrome: A reappraisal. *Ann Neurol* 1999; 46:701-7.
36. Uncini A, Manzoli C, Notturno F, Capasso M. Pitfalls in electrodiagnosis of Guillain–Barré syndrome subtypes. *J Neurol Neurosurg Psychiatry* 2010; 81:1157-63.
37. Uncini A, Kuwabara S. Electrodiagnostic criteria for Guillain–Barrè syndrome: A critical revision and the need for an update. *Clinical Neurophysiology*2012; 123:1487-95.
38. Corston RN, Mc GaleEH, Stronier C, Aber GM, Hutchinson EC. Abnormalities of cerebrospinal fluid amino acids in patients with the Guillain-Barre syndrome. *J Neurol Neruosurg Psychiatry* 1981; 44:86-9.
39. Chio A, Cocito D, Leone M, *et al*. Register for Guillain-Barre Syndrome. Guillain-Barre syndrome A prospective, population-based incidence and outcome survey. *Neurology* 2003; 60:1146-50.
40. Khan F.Rehabilitation in Guillian Barre syndrome. *Australian Family Physician* 2004; 33:1013-7.
41. Okuyama H. A study of the mechanism of high protein content of cerebrospinal fluid (CSF) in the Guillain-Barre syndrome. RISA diffusion within CSF cavity and transport from CSF to circulating plasma. *Clin Neurol (Tokyo)* 1975; 15:817-26.
42. Miyazaki M, Fujita M, Genba H, Shimazaki K, Ogawa M. Study on the blood-cerebrospinal fluid barrier (III). Permeability in normal state and in polyradiculoneuritis. *Clin Neurol (Tokyo)* 1975; 15:843-50.
43. Schliep G, Felgenhauer K. Serum-CSF protein gradients, the blood-CSF barrier and local immune response. *J Neurol* 1978; 218:77-96.
44. Jensen K. Cerebrospinal fluid proteins in neurological diseases. Studies on agar gel electrophoresis protein profiles. *Acta Neurol Scan* 1978; 58 (Suppl):1-268.
45. Snodgrass SR, Lorenzo AV. Transport of Gaba from the perfused ventricular system of the cat. *J Neurochem* 1973; 20:761-9.
46. Rieder HP, Kaeser HE, Nusselt L. Ligmer-proteinveranderungen bei Polyneuritis. *Schweiz Med Wschr* 1972; 102:766-72.
47. Haymaker W, Kernohan JW. The Landry- Guillain-Barre syndrome, a clinico-pathological report of fifty fatal cases and a critique of the literature. *Medicine* (Baltimore) 1949; 28:59-141.
48. Cutler RWP, Lorenzo AV. Transport of 1-aminocyclo-pentanecarboxylic acid from feline cerebrospinal fluid. *Science* 1968; 161:1363-4.
49. Lorenzo AV, Cutler RWP. Amino acid transport by choroid plexus in vitro. *J Neurochem* 1969; 16:577-85.
50. Snodgrass SR, Cutler RWP, Kang ES, Lorenzo AV. Transport of neutral aminco acids from feline cerebrospinal fluid. *Am J Physiol* 1969; 217:974-80.
51. Cutler RWP. Transport of lysine from cerebrospinal fluid of the cat. *J Neurochem* 1970; 17:1017-27.
52. Bril V, Ilse WK, Pearce R, Dhanani A, Sutton D, Kong Kl. Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barre syndrome. *Neurology* 1996; 46:100-3.
53. Normura T, Hamaguchi K, Hattori T, *et al*. A randomized controlled trial comparing intravenous immunoglobulin and plasmpheresis in Guillain Barre syndrome. *Neurol Therapeutics* 2000; 18:69-81.
54. EI-Bayoumi MA, El-Refaey AM, Abdelkader AM, Assmy MM, Alwakeel AA, El-Tahan HMl. Comparison of intravenous immunoglobulin and plasma exchange in treatment of mechanically ventilated children with Guillain Barré syndrome: a randomized study. *Crit Care* 2011; 15:R164.
55. Wing, EJ, Bruns, FJ, Fraley, DS, Segel DP, Adler S. Infectious complications with plasmapheresis in rapidly progressive glomerulonephritis. *JAMA* 1980; 244:2423.
56. Pohl, MA, Lan, SP, Berl, T.Plasmapheresis does not increase the risk for infection in immunosuppressed patients with severe lupus nephritis. *Ann Intern Med* 1991; 114:924.
57. Chen WH, Yeh JH, Chiu HC. Experience of double filtration plasmapheresis in the treatment of Guillain-Barré syndrome. *J Clin Apher* 1999; 14:126-9.
58. Watson GA, Sperry JL, Rosengart MR, *et al*. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009; 67(2):221-7.
59. Aram MA, Yazdchi M, Khandaghi R. Epidemiology and characteristics of Guillain-Barre syndrome in the northwest of Iran. *Annals of Soudi Medicine* 2006; 26:22-7.

60. Yuan CL, Tsou HK, Wang YJ, Tsai CP. Guillain –Barre syndrome: a retrospective, hospital-based study. *Zhonghua Yi Xue Za Zhi* (Taipei) 2002; 65:540-7.
61. Dias-Tosta E, Kuckelhaus CS. Guillain Barre syndrome in a population less than 15 years old in Brazil. *Arq Neuropsiquiatr* 2002; 60:367-73.
62. Ramírez-Zamora M, Burgos-Ganuza CR, Alas-Valle DA, Vergara- Galan PE, Ortez-Gonzalez CT. Guillain-Barre syndrome in the paediatric age: epidemiological, clinical and therapeutic profile in a hospital in El Salvador. *Rev Neurol* 2009; 48:292-6.
63. Nagpal S, Benstead T, Shumak K, Rock G, Brown M, Anderson DR. Treatment of Guillain-Barré syndrome: a cost-effectiveness analysis. *J Clin Apher* 1999; 14:107-13.
64. Winters JL, Brown D, Hazard E, Chainani A, Andrzejewski C Jr. Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain- Barre syndrome. *BMC Health Serv Res* 2011; 11:101.