Childhood Guillain-Barré Syndrome: Comparing Intravenous Immunoglobulin Treatment with Supportive Care

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Abstract

Objectives: Guillain-Barré Syndrome (GBS) is an acute ascending flaccid paralysis that is often preceded by a mild bacterial or viral infection. Management options include supportive care, physiotherapy, intravenous immunoglobulin (IVIG) and plasmapheresis. Our aim was to compare IVIG treatment and supportive care to supportive care alone in cases of moderate to severe GBS in children less than 16 years of age. **Methods:** Using specific keywords, the Cochrane Library and PubMed were searched. Eight relevant articles were found and appraised. The studies compared specific outcome criteria including mortality, days taken to regain independent locomotion, days taken to improve by one disability grade on Hughes' Functional Scale, days of hospitalisation and need for mechanical ventilation. **Results:** Four articles concluded definite benefits from the use of IVIG in GBS and two articles concluded that there was no difference in outcome with IVIG. One study showed statistically significant benefits with IVIG regarding death and need for mechanical ventilation. No studies showed statistically significant differences regarding recovery times or days of hospitalisation. **Conclusion:** The articles concurred with the data on GBS in adults, that timely use of IVIG reduces mortality and morbidity in a paediatric setting. However, IVIG use made no difference in the incidence of long-term sequelae of GBS. Sample sizes were small. Larger studies are needed in order to fully explore the benefits of IVIG with regard to these outcome criteria. Logistically and ethically, this would be difficult and no randomised controlled trials have been done to date for this reason. Acute relapse was a new phenomenon, which had not been previously noted in the pre-IVIG era and warrants further investigation.

INTRODUCTION

In 1916, Guillain, Barré and Strohl described a syndrome of 'radiculoneuritis' with acute flaccid paralysis and an increase in protein in the central nervous system (CNS), but without a cellular reaction. This polyradiculoneuropathy, or Guillain-Barré Syndrome (GBS) is a relatively uncommon condition affecting approximately three in 100,000 each year with an incidence in children of 0.7 to 0.9 in 100,000. It is the commonest peripheral neuropathy seen in children. Two-thirds of GBS cases are associated with an antecedent infection two to three weeks before the onset of the symptoms, most commonly with *Campylobacter jejuni* or cytomegalovirus. These infections are often trivial and may go unnoticed. 'Molecular mimicry' between the microorganism lipopolysaccharides and the host nerve ganglioside components results in an immune-mediated response, which attacks both the infectious antigen and similar epitopes in the host peripheral nervous system. This attack is thought to be mediated by anti-GM-1 and anti-GQ1b antibodies, especially IgG1 and results in demyelination of nerves in the peripheral nervous system, and the clinical syndrome of poly-neuropathy (Figure 1).

Symptoms of distal weakness and/or paraesthesia begin in the fingers and toes and ascend proximally, with progressively worsening weakness and areflexia over several to 21 days. There may also be abnormal sensory symptoms and some cases are complicated by autonomic involvement, which may cause postural hypotension, urinary retention, impaired pupillary responses and cardiac arrhythmias. In the most severe cases, involvement of the bulbar muscles causes difficulty with chewing and swallowing with an increased risk of aspiration. The initial abnormality may be a hoarse voice or a weak cry in an otherwise normal child. Involvement of the respiratory muscles necessitates mechanical ventilation.

GBS is a clinical diagnosis, confirmed by slowed conduction on electromyography and nerve conduction studies. Cerebrospinal fluid (CSF) shows a raised protein level at 1 to 3 g/L (normal = 0.3 to 1.0 g/L), with a normal cell count and glucose levels. The serum creatinine kinase (CK) may also be raised.

The differential diagnosis of GBS includes other paralytic illnesses such as botulism, poliomyelitis, cord compression and primary muscle disease such as Duchenne's Muscular Dystrophy. Other causes of polyneuropathy include chronic inflammatory demyelinating polyneuropathy,

hereditary sensory neuropathies such as Charcot-Marie-Tooth syndrome and neuropathies secondary to vitamin deficiencies, for example, vitamin B_{12} deficiency and toxins (alcohol, vincristine, and lead).[2] Variants of GBS include Miller-Fisher syndrome, characterised by ataxia, areflexia and ophthalmoplegia. Acute motor axonal neuropathy (AMAN) is another variant which involves axonal damage in addition to demyelination and carries a worse prognosis.[1]

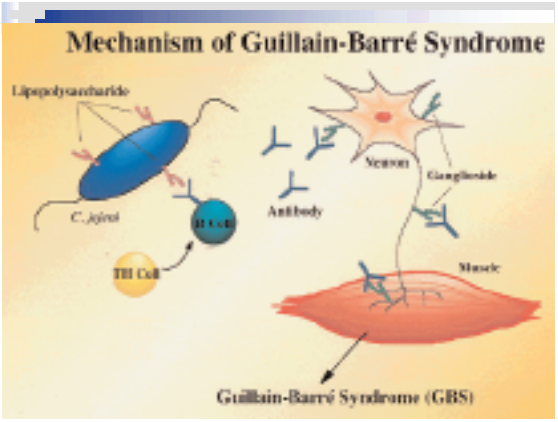

Figure 1. *Mechanism of Guillain-Barré Syndrome: Adapted from the Gifu University Website: http://www.gifu-u.ac.jp/~kassei/guillain.html.*

Current management centres on supportive care, provided by a multidisciplinary team of doctors, nurses, physiotherapists, speech and language therapists, occupational therapists and clinical psychologists. Vital signs, respiratory capacity and urine output of the patient should be monitored. Physiotherapy and splints are used to maintain muscle strength and flexibility, both in the acute and recovery stages and to clear respiratory secretions. As much activity as can be tolerated should be encouraged. Adequate hydration is maintained with intravenous fluids and nutrition with nasogastric feeding or total parenteral nutrition, if there is bulbar muscle involvement. Bladder and bowel problems may be managed using laxatives and urinary catheterisation, whether suprapubic or intermittent. Corneal exposure should be avoided. Low molecular weight heparin and thromboembolic deterrent stockings are used to avoid venous thrombo-embolism. Neuropathic pain, muscle cramps and backache can be very distressing and can be treated with analgesics and muscle relaxants. Light sedation may also be used if children are distressed. Complications such as urinary tract infections and pneumonia are detected and treated. Monitoring of pulse oximetry and peak expiratory flow rate will detect the development of respiratory involvement and the need for mechanical ventilation.[3] If mechanical ventilation is required for more than a week, a tracheostomy may be conducted.

Children may be managed at home with outpatient physiotherapy in the recovery stages or in mild GBS. Indications for admission would include difficulty with mobility, significant paralysis, difficulty breathing and complications such as pneumonia or cardiac arrythmias. Parents must be educated regarding warning signs, such as shortness of breath, gagging or coughing on eating. [3]

Reassurance and encouragement to both the children and their parents is also vital as the overall prognosis is generally very good. Clearly, the illness may be extremely frightening for children who, though paralysed, are still aware of their surroundings. Familiar voices and objects are reassuring and devices to aid communication will help the most severely affected. Children may continue to be moody and tearful for some time after resolution of the acute symptoms. Parents may find contact with a support association such as the GBS Support Group helpful.[4]

The prognosis of childhood GBS is excellent, with 95 percent of children making a complete recovery, though this may take up to two years. There is a three to five percent mortality rate and up to 10 percent of children have a permanent disability, ranging from subtle weakness of the lower extremities to being wheelchair dependant.

While the vast majority of children make a full recovery with only supportive care, a number of interventions have been shown to hasten recovery and improve outcome in children with more severe GBS. Corticosteroids had been used for many years but have been shown to be of no value. More recently, intravenous immunoglobulin (IVIG) and plasmapharesis have been shown to be of benefit in shortening the course of the illness and decreasing morbidity.

Specific indications for IVIG include a diarrhoeal prodrome, Miller Fisher Syndrome, autonomic instability and poor venous access.[5]

Generally, IVIG is well tolerated and there were no reports of adverse effects in the cases described below from Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland (OLHSC). Mild adverse effects such as headache, flushing, low backache, nausea and wheeze, are often associated with a fast infusion rate and respond rapidly on slowing the infusion. Rare episodes of

life-threatening anaphylaxis may occur, especially in IgA deficient patients. Patients should therefore be screened for IgA deficiency before treatment and if deficient should receive IgA depleted preparations of IVIG. IVIG is a blood product and there is anxiety about transmission of viruses such as hepatitis C and HIV, however there have been no reports of HIV transmission with IVIG and the introduction of specific anti-viral measures in the manufacture of IVIG should relieve concern. Where very high doses of IVIG are administered, for example for immunomodulatory purposes, Coomb's test positive haemolytic anaemia, aseptic meningitis and renal profile disturbances have been reported.[6]

The most common adverse effect associated with plasmapharesis is hypotension, which may cause syncope, blurred vision, diaphoresis or abdominal cramps. Bleeding secondary to anti-coagulant drugs used may also occur. Perioral and distal paraesthesia, muscle cramps, seizures and cardiac arrhythmias can also occur. Anaphylaxis with pruritis, wheeze and rash is the most serious adverse consequence of this treatment.

Practically, plasmapharesis is difficult. Each session takes several hours during which the patient is restriced to the bedside due to the large bore cannulae in each arm. Several sessions may be needed before improvement is seen. It is generally performed only in the intensive care unit.

The role of immunotherapy in GBS is accepted and it has been shown that IVIG and plasmapharesis are equally effective in reducing morbidity and mortality in adult GBS.[7] However, there is a higher rate of relapse in adults treated with plasmapharesis compared to those treated with IVIG.[1] Though studies have compared each with placebo in childhood GBS, no studies have compared IVIG with plasmaphoresis in childhood disease. Due to practical reasons, notably the ease of administration, IVIG is currently the first line immunotherapy in childhood GBS.

This study aims to determine if there is a benefit in the use of IVIG in children with moderate to severe GBS in addition to standard supportive care, by analysing the data on previous similar studies according to a predetermined set of criteria.

REVIEW OF AVAILABLE LITERATURE ON THE TREATMENT OF GBS

This research was conducted during a two-month attachment in the National Children's Hospital attached to the Adelaide and Meath Hospital (AMNCH), Dublin, Ireland. Seven members of the group combined to collect research data and articles. Some recent case histories of childhood GBS were also obtained from the OLHSC, three of which were presented in June 2004 as part of a final year paediatrics project.[8]

The study population included all children with moderate or severe GBS under the age of 16 years. The severity of the GBS was graded according to internationally accepted diagnostic criteria: grade three, four and five in the American National Institute of Neurological Disease and Stroke (ANINDS) criteria for GBS, as well as those children over grade five on the Asbury Cornblath Criteria for GBS. The study also restricted the population to those children who received treatment within one month of the onset of symptoms. Children who had had prior treatment with plasmapheresis or who had a contraindication to IVIG were excluded from the study.

The intervention studied was IVIG at a standard dose of 400 mg/kg over five days or at a single dose of IVIG 2g/kg, with supportive care. This was compared to supportive care alone. The cases receiving only supportive care (the controls) included cases from the pre-IVIG era, late referrals and in one, controls from their own study. The outcomes measured and compared were days to regain independent locomotion, days taken to improve by one grade on Hughes Function Disability Scale, days of hospitalisation needed, need for mechanical ventilation and deaths.

Search engines used included the Cochrane Library, PubMed, Medline, the Evidence Based Medicine website with its links to the British Medical Journal, Lancet and various other paediatric journals.

The keywords used were Guillain Barré Syndrome, polyradiculoneuropathy, polyradiculoneuritis, children, paediatric, paediatric, treatment, flaccid paralysis, intravenous immunoglobulins.

Trials and studies of children under the age of 16 years, with moderate to severe GBS were included. Moderate to severe GBS was defined as grades three to five on the ANINDS criteria or grade five or higher on the Asbury Cornblath criteria for GBS. Exclusions were children who

had received prior treatment with plasmapharesis, who had a contraindication to IVIG or those who presented more than one month after the onset of symptoms.

Hughes Functional Disability Scale (HFDS)
O=normal
1=minor symptoms, capable of running
2=able to walk up to 10 meters without assistance but unable to run
3=able to walk 10 meters with assistance of one person, a walker or a cane
4=unable to walk
5=requires assisted ventilation
6=death

Figure 2. *Table to show the Hughes Functional Disability Scale.*[9]

Eight articles that fulfilled these criteria were found and all were included. Follow-up varied from one month to five years after the onset of symptoms. Each article investigated different potential benefits of IVIG compared with supportive therapy and other variables, including early IVIG treatment compared with late treatment.

Pre-IVIG era compared to post-IVIG era

A prospective study by Koul *et al.* followed 42 cases of GBS for 10 years from 1990 and compared the outcomes of the patients with one retrospective study and 10 other case studies from the pre-IVIG period (Figure 3).[10] The study concluded a reduced time to recovery and a favourable duration of hospital stay with IVIG treatment, compared to outcomes described during the pre-IVIG era. There were several deaths in the pre-IVIG era studies, but none in the post-IVIG era.

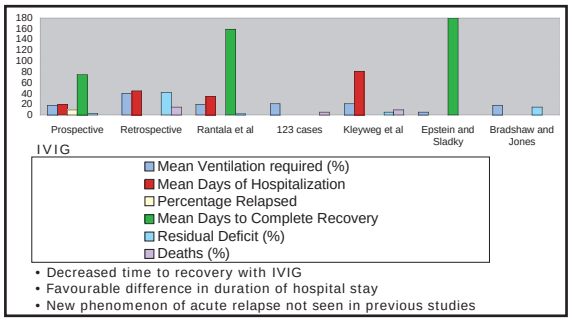

Figure 3. *Comparison of patient outcome with GBS Pre-IVIG and Post IVIG.*[10]

Long-term benefits of IVIG

Another recent article by Vajsar *et al.* assessed 31 children for evidence of motor and functional deficits on an average of five years after the onset of GBS symptoms.[11] Twenty-four of these children had moderate or severe GBS and were given IVIG. Of the children who received IVIG, 27 percent reported fatigue and 46 percent had mild motor or sensory abnormalities on examination. Findings included foot drop, pes cavus and tremor. The findings were compared to a pre-IVIG 1978 study, which found that 24 percent of children had long-term motor deficits five years after the acute episode of GBS. The conclusion was that there was no significant difference in the long-term motor sequelae of childhood GBS treated with IVIG compared to supportive care alone.

IVIG in early GBS and late GBS

A study performed in India, by Shanbag *et a1.*, also reported definite benefits with the use of IVIG.[2] The study compared IVIG use in 17 elective early admissions with IVIG use in eight children whose presentation to hospital was delayed and who, in some cases, were already in respiratory distress.

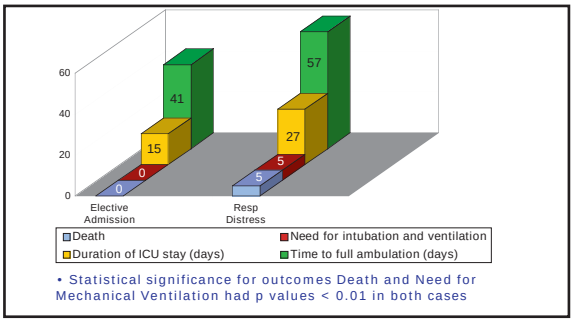

Figure 4. *Comparison of IVIG use in early severe GBS to late severe GBS.*[12]

There were five deaths (62.5 percent) in the late admission group, all of whom had needed artificial ventilation. The duration of stay in the intensive care unit (ICU) was 27 days, compared with 15 days in the children who received IVIG early. The surviving three children also took a longer time to regain full ambulation, indicating that timely use of IVIG significantly improved outcome.

Single dose IVIG compared with a five-day infusion of IVIG

A 1997 study followed nine consecutive cases where a single dose of IVIG 2g/kg was given within 10 days of onset of paralysis.[13] This was found to be as effective as a five-day infusion in preventing further progression of symptoms, thus, shortening the clinical course of GBS. Though the study involved only nine children and was intended to be a pilot study for a more comprehensive prospective controlled trial, single-dose treatment, with possibly a shorter hospital stay, has obvious benefits from an economic and resource point of view.

IVIG with supportive care compared to supportive care alone

Another study by Graf *et al.* of 20 children with moderate or severe GBS found no evidence of IVIG improving outcome or shortening the duration of illness when compared with supportive care alone (Figure 5).[14] This was a well designed study, comparing outcome in 12 children who received only supportive care with eight who received supportive care and IVIG at the standard dose of 0.4g/kg/day for five days. Three children were lost to follow-up and one who had received plasma exchange was excluded from the study. As seen in Figure 5, the addition of IVIG to supportive care did not impact substantially on the time taken to recover from the highest severity score to a score of two on the Hughes Functional Disability Scale, though some benefit was seen. However, the authors pointed out several potential sources of confounding bias, including the timing of the immunotherapy and the more benign natural history of the illness in children.

Acute relapses

Several other studies remarked on the recurrence of symptoms in children who had previously shown clinical improvement, usually two to three

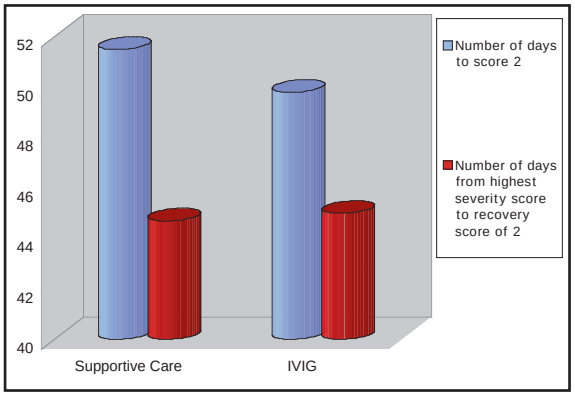

Figure 5. *Outcome in severe childhood GBS after IVIG with supportive care or supportive care alone.* [15]

weeks after IVIG administration. This is a seemingly new phenomenon, which was not described in the pre-IVIG era. One study of nine consecutive cases saw one child relapse after five months.[13] Another Japanese study found that three patients out of a group of 11 previously treated with IVIG had recovered and subsequently deteriorated, but who subsequently made a full recovery with re-treatment with IVIG.[15]

CLINICAL CASES

Three recent cases that presented to OLHSC are illustrated below. These cases demonstrate varying clinical presentations of GBS, all at the severe end of the spectrum with varying progression and prognosis of the illness. This also allows comparison of cases in which treatment with IVIG was commenced immediately on presentation (Case 1), in which treatment of IVIG was commenced only when no clinical improvement was seen with supportive care alone (Case 2), and one case which was managed with supportive care alone (Case 3).

These examples illustrate the relatively benign course of GBS in children and the excellent prognosis enjoyed by the vast majority of children affected by GBS. They also demonstrate the inherent variation in the prognosis and duration of illness in childhood GBS that is such a confounding factor when objective comparisons of treatments are being made: is a fast recovery the result of a specific intervention or would recovery have occurred even without the treatment?

Case 1

S.F. is a 14 year-old girl who was transferred to OLHSC from Louth County Hospital, Ireland, with an eight-day history of discomfort and weakness in her legs and a one-day history of left-sided facial weakness. She had a history of a flu-like illness and otitis media three weeks prior to the onset of symptoms, which had been treated by her general practitioner with oral antibiotics.

On examination S.F. was well and her vital signs were normal. There was marked unsteadiness of gait, proximal myopathy in both upper and lower limbs and a left-sided facial weakness that spared the forehead. Reflexes in both upper and lower limbs, including plantar reflexes, were absent. Sensation was normal. A lumbar puncture was performed showing raised protein in her CSF. There was also a raised CK and liver transaminases. Nerve conduction studies confirmed a demyelinating neuropathy.

S.F. was treated with a five-day course of IVIG 0.4g/kg/day and physiotherapy. Her CK levels returned to normal and she was discharged back to Louth County Hospital 10 days later. She had improvement in her facial weakness, but still retained significant disability. She was scheduled for follow-up nerve conduction studies six to eight weeks later.

Case 2

K.P. is an 18-month-old girl who was referred

from Portiuncula Hospital, Ballinasloe, Ireland, where she presented with a sudden onset of reduced lower limb movement, inability to bear weight or walk. Her birth history, motor and cognitive development had all been normal up to this point.

On examination K.P. was alert but irritable on handling. There was truncal weakness and she was unable to sit without support. There was bilateral facial weakness and upper and lower limb power and tone were reduced bilaterally. Her reflexes were absent. Sensation appeared intact in the upper and lower limbs and she had no sphincter disturbances or other signs of autonomic neuropathy.

A diagnosis of GBS was made on clinical grounds, confirmed by nerve conduction studies and a CSF protein level of 1.54mmols/L.

She was admitted for supportive care and physiotherapy, but no change was observed. On day three of admission, a five-day course of IVIG 0.4g/kg/day was started. K.P. showed rapid improvement and was discharged home when the course of IVIG was finished. She was scheduled for ongoing physiotherapy and follow-up two months later.

Case 3

J.A. is a four-year-old boy who was admitted to OLHSC with a one-month history of muscle weakness. The weakness began with difficulty climbing stairs, which progressed to an inability to run and then to walk. At presentation he was dragging himself with his arms in order to move around. J.A. is a known asthmatic and uses Becotide and Ventolin inhalers daily. He had a history of an upper respiratory illness two weeks before the onset of his symptoms. He had no significant medical or family history.

On examination J.A. had grade one to two out of five power in the upper and lower limbs bilaterally and Gower's sign was positive. There was also a tremor in his hands and reflexes were absent in all his limbs. The muscle bulk and sensation was normal and there were no signs of autonomic neuropathy. There was no abnormality detected on cranial nerve examination.

A CT scan of J.A.'s brain was normal. The diagnosis of GBS was confirmed after CSF results revealed an increased CSF protein and nerve conduction studies showed delayed nerve conduction, along with a raised CK. J.A. was treated with physiotherapy and had improved significantly on his discharge 10 days after admission.

DISCUSSION

There was a paucity of data on childhood GBS. Some articles found were inaccessible or were not in English. In the end, a relatively small number of articles were available for appraisal that fit the inclusion criteria for the review. Two of these articles concluded that IVIG made no difference to outcome and four studies concluded a definite benefit with IVIG. Only one study provided statistically significant evidence for deaths and the need for ventilation within the clinical criteria.[12] A study by Graf *et al.* indicated that a sample size of 370 patients would be needed to show statistical significance in improvement in time to recovery with IVIG. There were no randomised controlled trials or systematic reviews available and overall sample sizes were small. Childhood GBS is an uncommon condition and ethical and logistic barriers prevent the study of a large sample size.

While the commonly accepted benefits of IVIG in adult GBS cannot be automatically extrapolated to the paediatric population it has been shown that IVIG has the potential to significantly reduce the mortality and morbidity arising from this syndrome. Koul *et al.* found that IVIG treatment reduced the time taken to recovery and the time spent in hospital. Shanbag *et al.* reported statistically significant benefits with IVIG regarding time to recovery, the need for mechanical ventilation, and reduced mortality. Though Graf *et al.* found no convincing evidence of the benefits of IVIG the authors enumerated several confounding factors that may have affected this data. IVIG has not been found to have an impact on the long term sequelae of GBS, for example, the presence of fatigue and motor or sensory deficits. Acute relapse after apparent recovery is a new phenomenon which had not been previously noted in the pre-IVIG era and warrants further investigation. The administration of IVIG as a single dose of 2g/kg merits further study also. This approach could enhance the usefulness of IVIG as a treatment for GBS, which not only reduces its morbidity and mortality, but also enables discharge from hospital earlier, benefiting both the patient and the hospital from an economic point of view.

IVIG and plasmaphoresis are the two most

commonly used immunotherapies in GBS. The practicalities and expense of administering plasmaphoresis makes IVIG the immunotherapy most used in practice. Though expensive, IVIG is simple to administer, whether over five days or a single day. As demonstrated in the case studies above, IVIG is not in routine use as a first-line therapy in clinical practice in Ireland today and would generally be administered only in a tertiary care centre, such as OLHSC. In the case of J.A., recovery occurred with supportive care alone and in the case of K.P., IVIG was only commenced when no clinical improvement was seen with supportive care alone. It is well recognised that GBS in children runs a more benign course than in adults. Recovery usually occurs spontaneously even without specific intervention. As mentioned, this is a major confounding factor in the study of its management.

The natural history of GBS in children has a gradual onset associated with milder symptoms and a faster recovery compared with the disease in adults. GBS has the potential, however, to cause significant disability and disruption to children's lives, education and development for up to and beyond five years after an acute episode. Its acute phase can be extremely traumatic for both child and parents. In particular, pain is more characteristic of GBS in children than in adults and may be severe. Therapies that shorten the course of the illness not only allow the child to return to normal life sooner, but also reduce the risk of complications of immobility, for example, pneumonia and allow the inevitable trauma experienced to be minimised. In addition, it cannot be forgotten that the illness carries a mortality rate of three to five percent, which has been shown to be reduced by the adequate and timely use of IVIG. The use of IVIG can be seen to have considerable benefits in this context and with time the full potential of this treatment in the management of childhood GBS will undoubtedly come to light.

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