MEDICAL EDUCATION SYSTEMS, INC

Guillain-Barre Syndrome

Medical Education Systems, Inc.

TOLL FREE 1-877-295-4719
FAX (619) 295-0252
EMAIL: Info@mededsys.com
www.mededsys.com
P.O Box 81831 San Diego, CA 92138-3939

Guillain-Barré Syndrome: An Overview

Learning Objectives

Upon successful completion of this course, you will be able to:

- Identify the meaning and clinical implications of the term Guillain-Barré syndrome
- Identify the symptoms and causes of Guillain-Barré syndrome
- Identify how Guillain-Barré syndrome is diagnosed and treated
- Identify the prognosis of persons with Guillain-Barré syndrome

Introduction

What is Guillain-Barré syndrome?

Guillain-Barré syndrome is a disorder in which the body's immune system attacks part of the peripheral nervous system. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until the muscles cannot be used at all and the patient is almost totally paralyzed. In these cases, the disorder is life-threatening and is considered a medical emergency. The patient is often put on a respiratory to assist with breathing. Most patients, however, recover from even the most severe cases of Guillain-Barré syndrome, although some continue to have some degree of weakness. Guillain-Barré syndrome is rare. Usually Guillain-Barré occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal viral infection. Occasionally, surgery or vaccinations will trigger the syndrome. The disorder can develop over the course of hours or days, or it may take up to 3 to 4 weeks. No one yet knows why Guillain-Barré strikes some people and not others or what sets the disease in motion. What scientists do know is that the body's immune system begins to attack the body itself, causing what is known as an autoimmune disease. Guillain-Barré is called a syndrome rather than a disease because it is not clear that a specific disease-causing agent is involved. Reflexes such as knee jerks are usually lost. Because the signals traveling along the nerve are slower, a nerve conduction velocity (NCV) test can give a doctor clues to aid the diagnosis. The cerebrospinal fluid that bathes the spinal cord and brain contains more protein than usual, so a physician may decide to perform a spinal tap.

Guillain-Barré syndrome can affect anybody. It can strike at any age and both sexes are equally prone to the disorder. The syndrome is rare, however, afflicting only about one person in 100,000. Occasionally surgery or vaccinations will trigger the syndrome.

What causes Guillain-Barré syndrome?

No one yet knows why Guillain-Barré - which is not contagious - strikes some people and not others. Nor does anyone know exactly what sets the disease in motion.

What scientists do know is that the body's immune system begins to attack the body itself, causing what is known as an autoimmune disease. Usually the cells of the immune system attack only foreign material and invading organisms. In Guillain-Barré syndrome, however, the immune system starts to destroy the myelin sheath that surrounds the axons of many peripheral nerves, or even the axons themselves (axons are long, thin extensions of the nerve cells; they carry nerve signals). The myelin sheath surrounding the axon speeds up the transmission of nerve signals and allows the transmission of signals over long distances.

In diseases in which the peripheral nerves' myelin sheaths are injured or degraded, the nerves cannot transmit signals efficiently. That is why the muscles begin to lose their ability to respond to the brain's commands, commands that must be carried through the nerve network. The brain also receives fewer sensory signals from the rest of the body, resulting in an inability to feel textures, heat, pain, and other sensations. Alternately, the brain may receive inappropriate signals that result in tingling, "crawling-skin," or painful sensations. Because the signals to and from the arms and legs must travel the longest distances they are most vulnerable to interruption. Therefore, muscle weakness and tingling sensations usually first appear in the hands and feet and progress upwards.

When Guillain-Barré is preceded by a viral or bacterial infection, it is possible that the virus has changed the nature of cells in the nervous system so that the immune system treats them as foreign cells. It is also possible that the virus makes the immune system itself less discriminating about what cells it recognizes as its own, allowing some of the immune cells, such as certain kinds of lymphocytes and macrophages, to attack the myelin. Sensitized T lymphocytes cooperate with B lymphocytes to produce antibodies against components of the myelin sheath and may contribute to destruction of the myelin. Scientists are investigating these and other possibilities to find why the immune system goes awry in Guillain-Barré syndrome and other autoimmune diseases. The cause and course of Guillain-Barré syndrome is an active area of neurological investigation, incorporating the cooperative efforts of neurological scientists, immunologists, and virologists.

What are symptoms of Guillain-Barré syndrome?

Symptoms of Guillain-Barré Syndrome include weakness, typically beginning in the legs and progressing upward. The weakness is accompanied by decreased feeling (paresthesia). Reflexes are lost, for example, the hammer to the front of the knee will not induce a kick. In severe cases breathing can be affected enough to require a ventilator and rarely the heart can be affected. The maximal degree of weakness usually occurs within the first 2-3 weeks.

After the first clinical manifestations of the disease, the symptoms can progress over the course of hours, days, or weeks.

How is Guillain-Barré syndrome diagnosed?

Guillain-Barré is called a syndrome rather than a disease because it is not clear that a specific disease-causing agent is involved. A syndrome is a medical condition characterized by a collection of symptoms (what the patient feels) and signs (what a doctor can observe or measure). The signs and symptoms of the syndrome can be quite varied, so doctors may, on rare occasions, find it difficult to diagnose Guillain-Barré in its earliest stages.

Several disorders have symptoms similar to those found in Guillain-Barré, so doctors examine and question patients carefully before making a diagnosis. Collectively, the signs and symptoms form a certain pattern that helps doctors differentiate Guillain-Barré from other disorders. For example, physicians will note whether the symptoms appear on both sides of the body (most common in Guillain-Barré) and the quickness with which the symptoms appear (in other disorders, muscle weakness may progress over months rather than days or weeks). In Guillain-Barré, reflexes such as knee jerks are usually lost. Because the signals traveling along the nerve are slower, a nerve conduction velocity (NCV) test can give a doctor clues to aid the diagnosis. In Guillain-Barré patients, the cerebrospinal fluid that bathes the spinal cord and brain contains more protein than usual. Therefore a physician may decide to perform a spinal tap, a procedure in which the doctor inserts a needle into the patient's lower back to draw cerebrospinal fluid from the spinal column.

How is Guillain-Barré syndrome treated?

There is no known cure for Guillain-Barré syndrome. However, there are therapies that lessen the severity of the illness and accelerate the recovery in most patients. There are also a number of ways to treat the complications of the disease.

Currently, plasma exchange (sometimes called plasmapheresis) and high-dose immunoglobulin therapy are used. Both of them are equally effective, but immunoglobulin is easier to administer. Plasma exchange is a method by which whole blood is removed from the body and processed so that the red and white blood cells are separated from the plasma, or liquid portion of the blood. The blood cells are then returned to the patient without the plasma, which the body quickly replaces. Scientists still don't know exactly why plasma exchange works, but the technique seems to reduce the severity and duration of the Guillain-Barré episode. This may be because the plasma portion of the blood contains elements of the immune system that may be toxic to the myelin.

In high-dose immunoglobulin therapy, doctors give intravenous injections of the proteins that, in small quantities, the immune system uses naturally to attack invading organisms. Investigators have found that giving high doses of these immunoglobulins, derived from a pool of thousands of normal donors, to Guillain-Barré patients can lessen the immune attack on the nervous system. Investigators don't know why or how this works, although several hypotheses have been proposed.

The use of steroid hormones has also been tried as a way to reduce the severity of Guillain-Barré, but controlled clinical trials have demonstrated that this treatment not only is not effective but may even have a deleterious effect on the disease.

The most critical part of the treatment for this syndrome consists of keeping the patient's body functioning during recovery of the nervous system. This can sometimes require placing the patient on a respirator, a heart monitor, or other machines that assist body function. The need for this sophisticated machinery is one reason why Guillain-Barré syndrome patients are usually treated in hospitals, often in an intensive care ward. In the hospital, doctors can also look for and treat the many problems that can afflict any paralyzed patient - complications such as pneumonia or bed sores.

Often, even before recovery begins, caregivers may be instructed to manually move the patient's limbs to help keep the muscles flexible and strong. Later, as the patient begins to recover limb control, physical therapy begins. Carefully planned clinical trials of new and experimental therapies are the key to improving the treatment of patients with Guillain-Barré syndrome. Such clinical trials begin with the research of basic and clinical scientists who, working with clinicians, identify new approaches to treating patients with the disease.

What is the long-term outlook for those with Guillain-Barré syndrome?

Guillain-Barré syndrome can be a devastating disorder because of its sudden and unexpected onset. In addition, recovery is not necessarily quick. As noted above, patients usually reach the point of greatest weakness or paralysis days or weeks after the first symptoms occur. Symptoms then stabilize at this level for a period of days, weeks, or, sometimes, months. The recovery period may be as little as a few weeks or as long as a few years. About 30 percent of those with Guillain-Barré still have a residual weakness after 3 years. About 3 percent may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack.

Guillain-Barré syndrome patients face not only physical difficulties, but emotionally painful periods as well. It is often extremely difficult for patients to adjust to sudden paralysis and dependence on others for help with routine daily activities. Patients sometimes need psychological counseling to help them adapt.

What research is being done on Guillain-Barré syndrome?

Scientists are concentrating on finding new treatments and refining existing ones. Researchers are also looking at the workings of the immune system to find which cells are responsible for beginning and carrying out the attack on the nervous system. The fact that so many cases of Guillain-Barré begin after a viral or bacterial infection suggests that certain characteristics of some viruses and bacteria may activate the immune system inappropriately. Investigators are searching for those characteristics. Certain proteins or peptides in viruses and bacteria may be the same as those found in myelin, and the generation of antibodies to neutralize the invading viruses or bacteria could trigger the attack on the myelin sheath.

As noted previously, neurological scientists, immunologists, virologists, and pharmacologists are all working collaboratively to learn how to prevent this disorder and to make better therapies available when it strikes.

Some recent research on Guillain–Barré syndrome:

Recurrent Guillain–Barré syndrome

ABSTRACT

Background: Guillain–Barré syndrome (GBS) is generally considered to be monophasic, but recurrences do occur in a presently undefined subgroup of patients.

Objectives: To determine which subgroup of patients develops a recurrence and to establish whether preceding infections and neurological symptoms are similar in subsequent episodes.

Methods: A recurrence was defined as two or more episodes that fulfilled the NINCDS criteria for GBS, with a minimum time between episodes of 2 months (when fully recovered in between) or 4 months (when only partially recovered). Patients with a treatment-related fluctuation or chronic inflammatory demyelinating polyneuropathy with acute onset were excluded. The clinical characteristics of recurrent GBS patients were compared with those of 476 non-recurrent patients.

Results: 32 recurrent GBS patients, who had a total of 81 episodes, were identified. The clinical symptoms in a first episode were similar to the following episodes in individual patients, being GBS or its variant Miller Fisher syndrome (MFS) but never both. While neurological symptoms in subsequent episodes were often similar, the severity of the symptoms and the nature of the preceding infections varied. Recurrent patients (mean age 34.2 years) were younger than non-recurrent patients (mean age 46.9; $p = 0.001$) and more often had MFS ($p = 0.049$) or milder symptoms ($p = 0.011$).

Conclusions: Genetic or immunological host factors may play an important role in recurrent GBS, since these patients can develop similar symptoms after different preceding infections. Recurrences occur more frequently in patients under 30, with milder symptoms and in MFS.

Guillain–Barré syndrome (GBS) is an acute polyradiculoneuropathy leading to flaccid paresis. Its annual incidence rate is 0.75 to 2 per 100 000.[1] [2] GBS is a heterogeneous disease in which approximately two-thirds of patients report a preceding incident, usually an infection, such as diarrhea or an upper-respiratory-tract infection.

Although GBS is considered to be monophasic, recurrences are reported in 2–5% of patients.[3] [4] It is unknown why some patients have a recurrence and whether this occurs more frequently in a distinct subgroup of patients. It is suggested that recurrent GBS patients may have similar clinical symptoms in subsequent episodes, while having the same or different triggering events.[4] It is important to distinguish between recurrent GBS patients and GBS patients with treatment-related fluctuations (GBS-TRF) or chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) especially because the treatment regimen for CIDP is different.[5]

The purpose of this study is to establish whether recurrent GBS patients have similar neurological symptoms in subsequent episodes and to determine whether these patients can be distinguished from non-recurrent patients based on their clinical characteristics. We additionally investigate whether recurrent GBS patients have similar infections prior to each episode, if the severity varies in subsequent episodes and if the interval between episodes tends to get longer or shorter. By analyzing these features, we also aim to determine the relevance of host susceptibility factors in GBS.

K Kuitwaard[1], R van Koningsveld[1,2], L Ruts[1], B C Jacobs[1,3] and P A van Doorn[1]

[1] Department of Neurology, Erasmus MC, Rotterdam, The Netherlands
[2] Department of Neurology, Elkerliek Hospital Helmond, The Netherlands
[3] Department of Immunology, Erasmus MC, Rotterdam, The Netherlands

METHODS

Subjects and methods

To determine whether the type of neurological symptoms or the type of preceding infections are similar in subsequent episodes, we studied 32 recurrent GBS patients. These patients were identified from the Erasmus MC GBS data bank, which contains information on patients enrolled in clinical studies between 1985 and 2008. Additional patients came to our attention on patient meetings organized by the Dutch Society for Neuromuscular disorders (VSN). Medical records or letters were screened, and missing or indistinct items were clarified by contacting the patients or treating doctors.

All cases were re-evaluated (by KK and PD) using the criteria of the National Institute of Neurological and Communicative Diseases and Strokes (NINCDS) for GBS.[6] Patients were also included when they fulfilled the criteria for Miller Fisher syndrome (MFS), a GBS variant characterized by areflexia, ataxia and opthalmoplegia.[1] The severity of each episode was graded according to the GBS disability scale.[7]

The GBS disability scale is a seven-point disability scale, ranging from no symptoms (zero points) to death (six points). Patients who were able to walk with or without support (GBS disability scale ≤ 3) were considered as "mildly affected," whereas patients who were bedbound (GBS disability scale ≥ 4) were categorized as "severely affected."

We defined a recurrent patient as one having two or more episodes that fulfilled the NINCDS criteria for GBS, with either a minimum interval ≥ 4 months between the episodes if the patient did not recover completely (GBS disability scale ≥ 2) or ≥ 2 months when there was a complete or near-complete recovery (GBS disability scale ≤ 1) after the previous episode.

We excluded GBS-TRF and A-CIDP patients.[5] GBS-TRF was defined as (1) improvement in the GBS disability scale of at least one grade or improvement in the MRC sum score more than five points after completion of therapy (2 g intravenous Ig/kg body weight in 2–5 days), followed by a worsening of the GBS disability scale of at least one grade or a decrease in the MRC sum score of more than five points within the first 2 months after the disease onset or (2) stabilization for more than 1 week after completion of therapy, followed by a worsening of the GBS disability scale of more than one grade or more than five points on the MRC sum score within the first 2 months after disease onset.[5 8] A-CIDP was defined as a CIDP patient in whom the nadir of the first episode was within 8 weeks of onset, and the consecutive course was chronic, as in CIDP.[9]

Information was obtained concerning age, sex, cranial nerve involvement, preceding type of infection and/or trigger, GBS disability scale at nadir, and time between recurrences. Antecedent infections were classified clinically either as upper-respiratory tract or as diarrhea/gastrointestinal. Reported flu or flu-like infections were classified as upper-respiratory-tract infections. Information was also obtained about the presence of other autoimmune or immune-mediated disease.

To investigate whether recurrent patients can be distinguished from non-recurrent patients, we compared the clinical characteristics with those of non-recurrent GBS patients admitted with a diagnosis of GBS between 1987 and 1996 in The Netherlands.[2]

We compared the groups with respect to age, sex, MFS, cranial nerve dysfunction, the need for artificial respiration, severity of the symptoms and preceding triggers.

Statistical analysis

For statistical analyses, an unpaired t test and x^2 test were performed, to compare characteristics of recurrent and non-recurrent GBS patients. If appropriate, the Fisher exact test was used. SPSS for Windows (version 15.0, SPSS, Chicago) was used for all statistical analyses and p values <0.05 were regarded as significant.

RESULTS

Forty-eight patients were considered as potentially eligible. Sixteen patients were excluded: three with GBS-TRF and six with A-CIDP; three due to missing information about clinical symptoms during one of the possible episodes, and four because they did not fulfill the diagnostic criteria for GBS.

We identified 32 recurrent patients, 21 males and 11 females, who had a total of 81 episodes of GBS. Of these 32 patients, four had recurrent MFS, and three were known with another autoimmune disease (two inflammatory bowel disease and one hyperthyroidism). In the group of non-recurrent GBS patients, 11 were known to have one of the following autoimmune disorders: rheumatoid arthritis, polyartritis nodosa, spondylitis ankylopoetica, sarcoidosis, thyroid gland disease or inflammatory bowel disease. The clinical characteristics of the recurrent GBS patients during their first episode are listed in table 1.

Table 1 Comparison of baseline characteristics of recurrent and non-recurrent Guillain–Barré syndrome (GBS) patients

	GBS patients		p Value
	Recurrent (during first episode) (n = 32)	Non-recurrent (n = 476)	
Age, years, mean (SD)	34.2 (23.9)	46.9 (21.5)	0.001
Age <30 years	44%	22%	0.006
Male	66%	60%	0.505
Cranial nerve dysfunction	38%	42% (472)	0.654
Miller Fisher syndrome	13%	4%	0.049
Sensory–motor symptoms	72%	62% (474)	0.275
Artificial respiration needed	16%	18% (472)	0.691
Mildly affected*	59%	37% (450)	0.011
Known with other autoimmune disease	9%	2%	0.051
Preceding vaccination	6%	3% (475)	0.219
Preceding gastrointestinal infection	13%	17% (475)	0.541
Preceding respiratory infection	28%	37% (475)	0.299

The number in parentheses is the number of patients on whom information was available (if different from the total).

*GBS disability scale ≤3.

Seven recurrent GBS patients had three episodes, two had four episodes, and two had five episodes. All patients with at least four episodes were female. The mean age during the first episode was 34.2 (range 1–87) and of the first recurrence 42.1 (range 5–88). The interval between recurrences ranged from 2 months to 37 years. The mean interval between all recurrences was 7 years. Most patients had a long interval between subsequent episodes, and only two patients had an interval of 2 months in between episodes with near complete recovery. The mean GBS disability score at nadir was 3.1 for the first two episodes, increasing to 3.8 for the fourth episode. The characteristics of all episodes are shown in table 2.

Table 2 Characteristics per Guillain–Barré syndrome (GBS) episode

	No of patients	Age, years, mean (SD)	Time between recurrences, years, mean (SD)	GBS disability scale nadir, mean (SD)	Mean GBS disability scale after 6–12 months
1st episode	32	34.2 (23.9)	–	3.1 (1.2)	1.0 (29)
1st recurrence	32	42.1 (23.2)	7.9 (10.8)	3.1 (1.1)	1.1 (24)
2nd recurrence	11	48.0 (25.8)	6.0 (6.3)	3.4 (1.2)	1.4 (8)
3rd recurrence	4	46.0 (24.3)	5.8 (3.1)	3.8 (1.0)	1.5 (4)
4th recurrence	2	30.0	4.0	3.0	2.0 (2)

The number in parentheses is the number of patients on whom information was available (if different from the total).

The GBS disability scale, type of preceding infection and neurological symptoms (pure motor or sensory–motor) were compared with the previous episode. The characteristics during a recurrence were compared with those during the previous episode (fig 1).

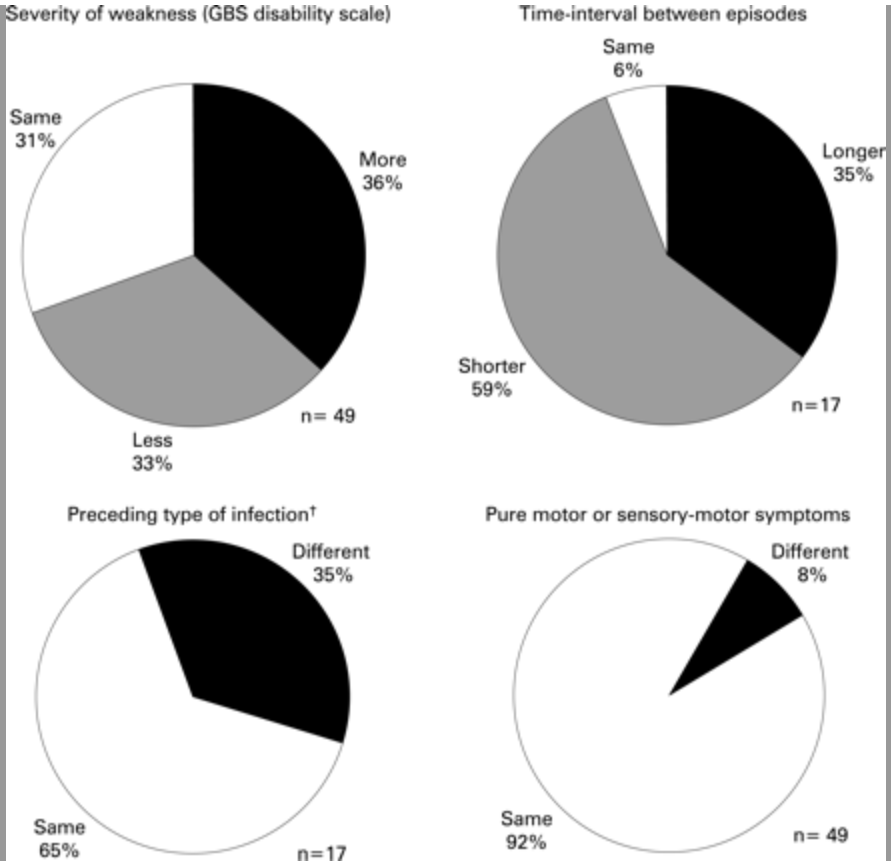

Figure 1 Recurrence characteristics, compared with the previous episode of Guillain–Barré syndrome (GBS). †Gastrointestinal or upper-respiratory-tract infection. n = number of two subsequent episodes from which information was available. For example: n = 17 means patients reported an infection 17 times before two sequential episodes. n = 49 means the GBS disability scale was reported in two sequential episodes 49 times.

In individual patients, a preceding infection in two subsequent episodes was reported 17 times. Eleven times the infections were reported as either respiratory or gastrointestinal, whereas six times a gastrointestinal infection was reported prior to one episode and a respiratory infection before the other. Two patients had an upper-respiratory-tract infection preceding three episodes and a gastrointestinal before another. Four patients had a serologically confirmed infection prior to one episode; one patient had a varicella zoster virus and a *Mycoplasma pneumoniae*, one a herpes simplex virus infection and two a *Campylobacter infection*.

One patient reported a tetanus vaccination as a trigger in two subsequent episodes. Another patient, with inflammatory bowel disease, had two episodes of GBS after starting treatment with the drug Salazopyrine. In the two patients, reporting the same trigger in subsequent episodes, neurological symptoms developed faster in the second episode. Two other patients reported a vaccination (flu virus or hepatitis virus) as a trigger prior to one of the episodes.

In 18 out of 49 successive episodes (36%) there was a more severe GBS disability scale at nadir; in 16 (33%) a less severe GBS disability scale and in 15 (31%) the GBS disability scale was equal in comparison with the previous episode.

Most patients had either pure motor or sensory–motor symptoms in subsequent episodes (fig 1). None of the patients initially had GBS in one episode followed by MFS in a subsequent episode.

One patient had right-sided oculomotor nerve dysfunction in four subsequent episodes, and another patient had three episodes with right-sided oculomotor nerve and abducens nerve palsy, accompanied by dysphagia. One patient had acute motor axonal neuropathy (AMAN) with moderate recovery five times over a period of 14 years.

In the recurrent group, patients more often had MFS (13% vs. 4%, $p = 0.049$) and were more frequently <30 years (44% vs. 22%, $p = 0.006$) and more often had a mild course (59% vs. 37%, $p = 0.011$) compared with the non-recurrent group. The mean age was lower in the recurrent group than in the non-recurrent group (34.2 vs. 46.9, 95% CI –20.4 to –4.9, $p = 0.001$). The clinical characteristics of recurrent and non-recurrent patients are listed in table 1.

DISCUSSION

The patients with a recurrent GBS in our study showed similar signs and symptoms during every episode despite having different types of symptoms of a preceding infection. This may indicate that genetic and immunological host factors partly determine the clinical phenotype irrespective of the preceding infection. The recurrent patients were younger and more often had MFS and a milder course of disease, which suggests that a distinct subgroup of patients has a higher susceptibility of recurring.

To our knowledge, this is the largest group of recurrent GBS patients described so far, and a comparison with non-recurrent patients has not been documented before. We excluded GBS-TRF and A-CIDP patients. One study reported 12 "recurrent" patients with a progressive phase of less than 8 weeks, therefore not excluding the possibility that some of these patients had A-CIDP or subacute GBS.[3] Distinguishing between recurrent GBS, GBS-TRF and A-CIDP can be difficult but is clinically relevant because treatment may differ. In a previous study, we found that nine out of 11 patients with GBS-TRF had their TRF within 9 weeks from onset, and most patients having an exacerbation after 9 weeks eventually developed CIDP.[5]

Whether clinical symptoms and preceding infections differ in recurrent patients has already been addressed in other case studies and is controversial.[10–12] Two studies have reported different antecedent events in individual recurrent GBS patients.[10 11] In contrast, another study described similar antecedent illnesses in individual recurrent GBS patients.[12] Unfortunately, infection serology in this group of patients was not always testable since serum was not systematically obtained. Two of our patients appeared to have had recurrences after the same specific triggers, one after the drug Salazopyrine and one after a tetanus vaccination; both showed a shorter time between trigger exposure and symptom onset the following episode. Tetanus toxoid vaccination as a trigger for GBS with a shorter symptom onset in subsequent episodes has been reported previously.[13] The drug Salazopyrine has not previously been described as a trigger for GBS, but ulcerative colitis has.[14] We cannot exclude that these events occurred coincidental or that there had not been a subclinical preceding infection in this patient.

In subsequent episodes, most of the recurrent GBS patients had either pure motor or sensory–motor symptoms. Some patients had very specific symptoms during subsequent episodes, such as unilateral cranial nerve palsy at the same site. We cannot explain this specific finding, but it could be related to a local susceptibility of neural tissue-related epitopes, as replicated laterality of cranial nerve dysfunction has been described before in MFS.[15 16]

Our observations identify a trend towards shorter intervals between subsequent recurrences, and a more severe deficit with each recurrence. The GBS disability scale is not a linear scale, but a tendency to accumulate neurological deficits after each episode has been reported previously.[4] It has been established that patients over 50 years of age are more likely to have a worse recovery, which may explain that disability becomes worse after each subsequent recurrence.[17] Recurrent patients are more likely to have MFS than non-recurrent patients. The presence of anti-GQ1b antibodies in almost all MFS patients highlights the importance of immunological factors in this disorder. Since females are more susceptible to autoimmune diseases, it is of interest that the recurrent patients with at least four episodes were all female. Three of the recurrent GBS patients were known with another autoimmune disease, which suggests that genetic host factors are relevant.

The mean age was significantly lower in the recurrent group compared with non-recurrent GBS patients. Age as a risk factor for a recurrent GBS has not been described before, but it has for CIDP. The mean age of relapsing CIDP patients (27 years) is reported to be significantly lower compared with CIDP patients with a non-relapsing course (51 years).[18]

Due to the retrospective nature of our study, we cannot estimate unbiased the exact incidence of recurrent GBS, but as there were 32 recurrent patients out of a total of 524, the crude estimated prevalence will be around 6%.

We cannot exclude the fact that some non-recurrent GBS patients have developed a recurrence outside the geographic boundary of the study area or after the 10-year study period. It is possible that some "non-recurrent" patients had their first GBS episode just before the end of the study period, which would have limited the chance of recording a recurrence.

Individual patients developed either GBS during all episodes or MFS, never both. Because recurrent GBS patients were significantly younger, more mildly affected and more often had MFS, neurologists should be aware that these patients are more prone to recurrences. Since similar neurological symptoms can occur after different infections, this study further indicates that immunological and genetic host factors play a role in determining the clinical phenotype in recurrent GBS.

REFERENCES

1. Ropper AH. The Guillain–Barré syndrome. *N Engl J Med* 1992;**326**:1130–6.[Medline]

2. van Koningsveld R, van Doorn PA, Schmitz PI, *et al*.. Mild forms of Guillain–Barré syndrome in an epidemiologic survey in The Netherlands. *Neurology* 2000;**54**:620–5.[Abstract/Free Full Text]

3. Grand'Maison F, Feasby TE, Hahn AF, *et al*.. Recurrent Guillain–Barré syndrome. Clinical and laboratory features. *Brain* 1992;**115**:1093–1106.[Abstract/Free Full Text]

4. Das A, Kalita J, Misra UK. Recurrent Guillain–Barré syndrome. *Electromyogr Clin Neurophysiol* 2004;**44**:95–102.[Medline]

5. Ruts L, van Koningsveld R, van Doorn PA. Distinguishing acute-onset CIDP from Guillain–Barré syndrome with treatment related fluctuations. *Neurology* 2005;**65**:138–40.[Abstract/Free Full Text]

6. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. *Ann Neurol* 1990;**27**:21–4S.[CrossRef]

7. Hughes RA, Newsom-Davis JM, Perkin GD, *et al*.. Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978;**2**:750–3.[CrossRef][Medline]

8. Kleyweg RP, van der Meché FG. Treatment related fluctuations in Guillain–Barré syndrome after high-dose immunoglobulins or plasma-exchange. *J Neurol Neurosurg Psychiatry* 1991;**54**:957–60.[Abstract/Free Full Text]

9. Anon. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. *Neurology* 1991;**41**:617–18.[Medline]

10. Taly AB, Gupta SK, Anisya V, *et al*.. Recurrent Guillain Barré Syndrome: a clinical, electrophysiological and morphological study. *J Assoc Physicians India* 1995;**43**:249–52.[Medline]

11. Hayashi H, Park-Matsumoto YC, Yuki N, *et al*.. A case of recurrent Guillain–Barré syndrome preceded by different infections. *J Neurol* 1993;**240**:196–7.[Medline]

12. Wijdicks EF, Ropper AH. Acute relapsing Guillain–Barré syndrome after long asymptomatic intervals. *Arch Neurol* 1990;**47**:82–4.[Abstract/Free Full Text]

13. Pollard JD, Selby G. Relapsing neuropathy due to tetanus toxoid. Report of a case. *J Neurol Sci* 1978;**37**:113–25.[CrossRef][Medline]

14. Roca B, Moreno I, Meneu E. Ulcerative colitis and acquired demyelinating neuropathy (Guillain–Barré syndrome). *Neth J Med* 1999;**54**:129–30.[CrossRef][Medline]

15. Uchihara T, Ikeda M, Tsukagoshi H. Recurrent Fisher's syndrome with immunological abnormalities and replicated laterality. *Eur Neurol* 1991;**31**:270–2.[CrossRef][Medline]

16. Orr CF, Storey CE. Recurrent Miller–Fisher syndrome. *J Clin Neurosci* 2004;**11**:307–9.[CrossRef][Medline]

17. Chiò A, Cocito D, Leone M, *et al*.. Guillain–Barré syndrome: a prospective, population-based incidence and outcome survey. *Neurology* 2003;**60**:1146–50.[Abstract/Free Full Text]

18. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyneuropathy. A clinical and electrophysiological study of 92 cases. *Brain* 1987;**110**:1617–30.[Abstract/Free Full Text]

Immunotherapy for Guillain-Barré syndrome: a systematic review

Summary

Guillain-Barré syndrome (GBS) is an acute inflammatory disorder of the peripheral nervous system thought to be due to autoimmunity for which immunotherapy is usually prescribed. To provide the best evidence on which to base clinical practice, we systematically reviewed the results of randomized trials of immunotherapy for GBS. We searched the Cochrane Library, MEDLINE and EMBASE in July 2006 and used the methods of the Cochrane Neuromuscular Disease Group to extract and synthesize data. Almost all trials used a 7-point disability grade scale. In four trials with altogether 585 severely affected adult participants, those treated with plasma exchange (PE) improved significantly more on this scale 4 weeks after randomization than those who did not, weighted mean difference (WMD) –0.89 (95% confidence interval (CI) –1.14 to –0.63). In five trials with altogether 582 participants, the improvement on the disability grade scale with intravenous immunoglobulin (IVIg) was very similar to that with PE, WMD –0.02 (95% CI –0.25 to 0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. In one trial with 148 participants, following PE with IVIg did not produce significant extra benefit. Limited evidence from three open trials in children suggested that IVIg hastens recovery compared with supportive care alone. Corticosteroids were compared with placebo or supportive treatment in six trials with altogether 587 participants.

There was significant heterogeneity in the analysis of these trials which could be accounted for by analysing separately four small trials of oral corticosteroids with altogether 120 participants, in which there was significantly less improvement after 4 weeks with corticosteroids than without, WMD –0.82 (95% CI –0.17 to –1.47), and two large trials of intravenous methylprednisolone with altogether 467 participants, in which there was no significant difference between corticosteroids and placebo WMD –0.17 (95% CI 0.06 to –0.39). None of the treatments significantly reduced mortality. Since ~20% of patients die or have persistent disability despite immunotherapy, more research is needed to identify better treatment regimens and new therapeutic strategies.

Richard A. C. Hughes[1], Anthony V. Swan[1], Jean-Claude Raphaël[2], Djillali Annane[2], Rinske van Koningsveld[3] and Pieter A. van Doorn[3]
[1]Department of Clinical Neuroscience, King's College London, Guy's Campus, London, UK, [2]Service de Réanimation Médicale, Hôpital Raymond Poincaré, Garches, France and [3]Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Key Words: Guillain-Barré syndrome; treatment; systematic review; plasma exchange; intravenous immunoglobulin; corticosteroid

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; PE, plasma exchange; RR, relative rate; WMD, weighted mean difference

Introduction

Guillain-Barré syndrome (GBS) is the major cause of acute neuromuscular paralysis with an annual incidence of 1.3–2 per 100 000 throughout the world (Van Koningsveld *et al.*, 2000; Govoni and Granieri, 2001). It is a clinical syndrome whose pathological substrate may be acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or acute axonal motor or motor and sensory axonal neuropathy (Griffin *et al.*, 1995). AIDP is much more common than axonal forms in the Western world. Experimental evidence implicates autoantibodies to gangliosides as the cause of the axonal subgroups of GBS and of Fisher syndrome (Willison and Yuki, 2002). These autoantibodies may be generated by the immune response to an infective organism, such as *Campylobacter jejuni*, cross-reacting with epitopes on the axon (Yuki *et al.*, 2004). The resemblance of AIDP to experimental autoimmune neuritis suggests pathogenetic mechanisms involving T-cell induced macrophage-associated demyelination (Hughes and Cornblath, 2005).

This proposed autoimmune aetiology led to the introduction of immunotherapy. Before its introduction, 10% of patients died and 20% were left seriously disabled (Winer *et al.*, 1988). Plasma exchange (PE) was introduced as a possible treatment in 1978 (Brettle *et al.*, 1978) and was shown to offer significant benefit by a randomized trial published in 1985 (The Guillain-Barré Syndrome Study Group, 1985). It became the gold standard against which other treatments were measured (Consensus Conference, 1986). Intravenous immunoglobulin (IVIg) was introduced for GBS in 1988 (Kleyweg *et al.*, 1988). In 1992, the first randomized trial comparing IVIg and PE showed similar effects from each treatment (van der Meché *et al.*, 1992). Corticosteroids were introduced for GBS in the early 1950s (Stillman and Ganong, 1952; Hughes, 1990).

The first randomized trial, of ACTH, published in 1976 did not show a significant effect (Swick and McQuillen, 1976) but the most recent trial reported possible minor short-term benefit when high dose intravenous methylprednisolone was combined with IVIg (Van Koningsveld *et al.*, 2004). The significance of this benefit has been debated (Hughes, 2004). This review is based on the individual Cochrane systematic reviews of PE, IVIg and corticosteroid treatment for GBS (Raphaël *et al.*, 2002; Hughes *et al.*, 2006*a*, *b*). Cochrane systematic reviews are updated regularly and the Cochrane Library should be consulted for the latest version of each review. We systematically review the evidence on which to base immunotherapy and indicate areas for further research.

Material and methods

Data acquisition

We used the search strategy of the Cochrane Neuromuscular Disease Group (Annane *et al.*, 2004). We searched the Cochrane Library and the trials register of the Group, MEDLINE and EMBASE for randomized trials using Guillain-Barré syndrome or acute polyradiculoneuritis and plasma exchange or plasmapheresis or intravenous immunoglobulin or corticosteroid or adrenocorticotrophic hormone or treatment or therapy as the search terms. We also searched for quasi-randomized trials, which are those which use methods such as alternate allocation and are not truly randomized. We checked the bibliographies in reports of the randomized trials and contacted their authors and other experts to identify additional published or unpublished data. We updated these searches on July 13, 2006. Two reviewers checked titles and abstracts identified from these sources and obtained the full text of all potentially relevant studies for independent assessment. Two reviewers decided which trials fitted the inclusion criteria and extracted data independently onto specially designed forms. Disagreements were resolved by reference to the original reports and discussion. Some missing data were obtained from the authors.

Efficacy end points and populations

In most trials disability had been measured with a simple 7-point scale, the GBS disability scale (Table 1) (Hughes *et al.*, 1978). For patients with such severe disease that they could not walk independently (GBS disability grade 3 or more), we considered mean improvement in disability grade 4 weeks after randomization as the primary outcome measure. As secondary outcome measures, we considered the number of participants improved by one or more grades after 4 weeks, duration of ventilation, time needed to recover independent walking, death and residual disability and death. For patients who could still walk without aid (GBS disability grade 2 or less), we used time to the onset of motor recovery as the outcome, defined by improvement of at least two items of a muscle strength score or one item and improvement in cranial nerve function or trunk or respiratory involvement. We have also reported other relevant outcomes which had been selected as important in individual trials.

Table 1 Guillain-Barré syndrome disability scale

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work/*capable of running*
2. Able to walk without support of a stick (*5 m across an open space*) but incapable of manual work/*running*
3. Able to walk with a stick, appliance or support (*5 m across an open space*)
4. Confined to bed or chair bound
5. Requiring assisted ventilation (*for any part of the day or night*)
6. Death

The original scale is shown in regular print (Hughes *et al.*, 1978) and subsequent modifications in *italics* (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).

Statistical analysis

We calculated a weighted treatment effect across trials using the Cochrane statistical package RevMan 4.2 with a fixed effect model when the results were homogeneous and a random effects model when they were not. Results were expressed as relative risks (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean difference (WMD) with 95% CIs for continuous outcomes. In two instances, the standard deviation of the change in disability grade after 4 weeks was not available and, to calculate the WMD of the improvement in disability grade, we imputed the largest values of the standard deviation for any of the other trials with that intervention (Bril *et al.*, 1996; Diener *et al.*, 2001). Coefficients from logistic regression analyses, representing the odds ratio of relative recovery rates from different studies on a logarithmic scale, were combined using a weighted average with weights inversely proportional to their variances. This was achieved using the Generic Inverse Variance facility in RevMan.

Results

Characteristics of trials included

We included eight trials comparing PE with supportive treatment or differing amounts of PE (Table 2). A ninth trial, mentioned in the table for completeness, could not be included in our analyses because the patients randomized to PE also received prednisone, whereas the control group received neither (Mendell *et al.*, 1985) (Table 2).

Six trials had adequate randomization and allocation concealment but in two allocation was alternate (Osterman *et al.*, 1984; Farkkila *et al.*, 1987). None of the trials compared PE with sham exchange which was considered unethical in patients who were acutely ill. We included 10 trials comparing IVIg with supportive care, PE or immunoabsorption and one trial comparing IVIg 1.0 g/kg given over 2 days with IVIg 2.0 g/kg given over 5 days (Table 3). Eight trials had adequate randomization and allocation concealment but two used alternate or block sequential randomization (Gürses *et al.*, 1995; Haupt *et al.*, 1996) and one used randomization but had unclear allocation concealment (Wang *et al.*, 2001). We included eight trials of corticosteroids (Table 4). Four had adequate concealment and randomization, one had adequate randomization but unclear allocation concealment (Shukla *et al.*, 1988) and three had alternate allocation (García *et al.*, 1985; Singh and Gupta, 1996; Bansal *et al.*, 2004). Four small trials of other treatments have been mentioned in the discussion.

Table 2 Characteristics of included studies of plasma exchange

Study	Trial design (RCT unless stated)	Participants	Treatment	Results
Greenwood *et al.*, 1984	Multicentre Open Parallel group	*n* = 29 All ages No mild forms	PE versus supportive care, 5 PE in 5 days, 55 ml/kg per PE	7/14 in the treated group improved by ≥1 disability grade at 4 weeks, compared to 6/15 in the control group (NS)
The Guillain-Barré Syndrome Study Group, 1985	Multicentre Open Parallel group	*n* = 245 All ages No mild forms	PE versus supportive care, 3 to 5 PE in 5 days, 40 ml/kg per PE	39% of control and 59% of treated participants improved ≥1 grade at 4 weeks ($P < 0.01$)
Mendell *et al.*, 1985	Multicentre Open Parallel group	*n* = 25	PE daily for 5 days and on days 8, 11, 15 and 22 and prednisone 100 mg daily for 10 days and then 100 mg on alternate days for 20 days and then tailed off over 21 days versus supportive care	No significant differences in muscle strength, functional tasks and FVC weekly for 4 weeks and then at 8, 12 and 24 weeks

Farkkila *et al.*, 1987	Single centre Open Parallel group	*n* = 29 Adults No mild forms	PE versus supportive care, 3 to 5 PE, 3 l per PE, diluted albumen	Isometric hand-grip force increased faster in the treated group and was significantly greater than in the control group throughout 3-week follow-up period ($P < 0.001$)
Osterman *et al.*, 1984	Multicentre Open Parallel group	*n* = 38 Adults No mild forms	PE versus supportive care, 3 to 8 PE in 7 to 10 days, 3 l per PE	6/20 patients in the control group compared to 14/18 in the treated group improved by ≥1 Osterman disability grade at 4 weeks ($P < 0.025$)
French Cooperative Group in plasma exchange in Guillain-Barré syndrome, 1987	Multicentre Open Parallel group	*n* = 220 Adults All forms	PE versus supportive care, 4 PE in 8 days, 3 l per PE, diluted albumen or fresh frozen plasma	The time to recover walking with assistance was significantly faster improvement in the plasma exchange group [median, 44 versus 30 days ($P < 0.01$)]
French Cooperative Group on plasma exchange in Guillain-Barré syndrome, 1997	Multicentre Open Parallel group	*n* = 91 Adults Mild forms	PE versus supportive care, 2 PE every other day, 3 l per PE, diluted albumen + gelatin	In the treated group, the median time to onset of motor recovery was significantly shortened compared to the control group (8 versus 4 days, $P = 0.0002$)
French Cooperative Group on plasma exchange in Guillain-Barré syndrome, 1997	Multicentre Open Parallel group	*n* = 304 Adults Moderate forms	2 PE versus 4 PE, 3 l per PE, diluted albumen + gelatin, PE every other day	In the 4-PE group, the median time to recover walking with assistance was significantly shortened compared to the 2-PE group (24 versus 20 days, $P =$

				0.04)
French Cooperative Group on plasma exchange in Guillain-Barré syndrome, 1997	Multicentre Open Parallel group	*n* = 161 Adults Ventilated forms	4 PE versus 6 PE, 3 l per PE, diluted albumen + gelatin, PE every other day	No significant difference in time to recover walking with assistance
Wollinsky *et al.*, 2001	Two centres Open Parallel group	*n* = 37 Adults Cannot walk >5 m unassisted	CSF filtration 150 to 300 ml daily for 5 to 15 days versus PE daily or every other day for 7 to 14 days	No significant differences in any outcome. Mean change in disability grade at 4 weeks was –0.82 with CSF filtration (*n* = 17) and –0.80 with PE (*n* = 20)

Table 3 Characteristics of included studies of intravenous immunoglobulin

Study	Trial design (RCT unless stated)	Participants	Treatment	Results
Bril *et al.*, 1996	Single centre Parallel group	*n* = 50 Adults	IVIg 0.5 g/kg daily for 4 days versus PE 40–50 ml/kg daily for 5 days	No significant differences in multiple outcomes
Diener *et al.*, 2001	Multicentre Parallel group	*n* = 67 Adults and possibly children	IVIg 0.4 g/kg daily for 5 days versus PE 40–50 ml/kg on five occasions within 14 days versus immune absorption on five occasions (4 l on two occasions and then 2 l on three occasions) within 14 days	16/20 IVIg and 15/21 PE improved by ≥1 disability grade after 4 weeks (NS)
García *et al.*, 1985	Alternate allocation	20 Mostly adult	Intravenous methylprednisolone	No significant difference in

	Single centre Parallel group		1500 mg daily for 5 days versus supportive care	time to recovery
Gürses *et al.*, 1995	Alternate allocation Single centre Parallel group	*n* = 18 Children	IVIg 1 g/kg daily for 2 days versus supportive care	After 4 weeks 7/9 in the IVIg group but only 2/9 in control group recovered full strength (*P* = 0.057)
Haupt *et al.*, 1996	Block sequential design Single centre	*n* = 34 Adults and possibly children	Immunoabsorption followed by IVIg 0.4 g/kg daily for 5 days versus immunoabsorption	No significant differences in multiple outcomes
Korinthenberg *et al.*, 2005	Multicentre Parallel group	*n* = 21 Children able to walk without aid	IVIg 0.5 g/kg daily for 2 days versus supportive care	No significant difference in maximum disability score the primary outcome but median disability grade after 4 weeks 1 (0–3) in the IVIg and 2 (1–5) in the controls (*P* = 0.025)
Korinthenberg *et al.*, 2005	Multicentre Parallel group	*n* = 50 Children able to walk without aid	IVIg 1 g/kg daily for 2 days versus 0.4 g/kg daily for 5 days	Median time to regain unaided walking 19 days with 2-day and 13 days with 5-day regimen, not significantly different (*P* = 0.94). Also no significant difference in change in disability grade after 4 weeks, mean difference

				–0.27 (95% CI –0.94 to 0.40) more improvement with 5-day regimen
Nomura *et al.*, 2000	Multicentre Parallel group	*n* = 47 Adults	IVIg 0.4 g/kg daily for 5 days versus PE total 200–250 ml/kg in up to seven sessions over 4 weeks	No significant differences in multiple outcomes
Plasma Exchange/ Sandoglobulin Guillain- Barré Syndrome Trial Group, 1997	Multinational Multicentre Parallel group	*n* = 383 Adults	IVIg 0.4 g/kg daily for 5 days versus PE 250 ml/kg over 8–13 days versus PE followed by IVIg	Mean change in disability grade after 4 weeks – 0.9 (SD 1.3) in PE group and – 0.8 (SD 1.3) in IVIg group, difference 0.10 (95% CI –0.22 to 0.42), and – 1.1 (SD 1.14) in PE and IVIg group, difference from PE group – 0.20 (95% CI – 0.54 to 0.14)
Raphaël *et al.*, 2001	Multicentre Parallel group	*n* = 39 Adults with contraindications to PE	IVIg 0.4 g/kg daily for 3 days versus 6 days	Median (range) time to walk with aid 84 (23 to 121) days in 6-day group and 131 (51 to 120) days in 3-day group ($P = 0.08$)
van der Meché *et al.*, 1992	Multicentre Parallel group	*n* = 150 Adults and children	IVIg 0.4 g/kg daily for 5 days versus PE 200–250 ml/kg over 7–14 days	53% of IVIg group improved ≥1 disability grade versus 34% in the PE group, difference 19% (95% CI –2 to 39%)

Wang *et al.*, 2001	Number of centres unclear Parallel group	*n* = 54 Children	Dexamethasone 5–10 mg daily for 5 or 6 days and then tailed over 7 to 10 days versus IVIg 0.2 to 0.3 g/kg daily for 5 or 6 days and dexamethasone 5 mg daily for 5 or 6 days and then tailed over 7 days versus PE 500–1500 ml over 5 to 10 days and dexamethasone 5 mg daily for 5 or 6 days and then tailed over 7 days	Time to partial recovery or improvement by one muscle strength grade or time to complete recovery of cranial and respiratory nerves and two grades of improvement in muscle mean 17.1 days in the IVIg and 24.8 days in the corticosteroid group, difference 7.7 days ($P <$ 0.01).

Table 4 Characteristics of included studies of corticosteroids

Study	Trial design (RCT unless stated)	Participants	Treatment	Results
Bansal *et al.*, 2004	Alternate allocation Single centre Open Parallel group	*n* = 20	Prednisolone 15 mg 4 times daily for 4 days, 10 mg 3 times daily for 3 days, 10 mg 3 times daily for 10 days and then tapered or no treatment	No significant differences in changes in GBS disability grade after 1, 2, 3, and 4 weeks and 3 months; disease duration; residual disability; death; relapse
García *et al.*, 1985	Alternate allocation Single centre Open Parallel	*n* = 20	Intravenous methylprednisolone 1500 mg daily for 5 days or supportive	No significant difference in time to recovery. After 6 months 7/10

	group		care	treated with corticosteroid had returned to work compared with 3/10 treated without
Guillain-Barré Syndrome Steroid Trial Group, 1993	Multinational Double blind Parallel group	*n* = 242 Adult Unable to run Disease onset <15 days	Intravenous methylprednisolone 500 mg daily for 5 days or placebo infusions	Mean improvement after 4 weeks 0.80 grade in corticosteroid group and 0.73 in placebo group, difference 0.07 (95% CI –0.27 to 0.13). Also no significant differences in disability grade difference after 12 weeks, reduction of times to cease artificial ventilation and to recover ability to walk unaided
Hughes *et al.*, 1978	Multicentre Observer blind Parallel group	*n* = 40 Adults and children	Prednisolone 15 mg 3 times daily for 1 week, 10 mg 3 times daily for 4 days, 5 mg 4 times daily for 3 days followed by treatment at discretion or no corticosteroid treatment	No significant differences in change in GBS disability grade after 1, 3 and 12 months, time to onset of improvement, time to recover ability for manual work, and proportion with residual disability
Shukla *et al.*, 1988	Single centre Double blind Parallel group	*n* = 14	Prednisolone 60 mg daily in divided doses for 1 week, 40 mg daily for 1 week, 30 mg daily for 2 weeks and then at discretion	No significant differences in change in GBS disability grade after 1, 4 and 6 weeks

			or identical appearing placebo tablets	
Singh and Gupta, 1996	Alternate allocation Single centre Parallel group	*n* = 46	Prednisolone 40 mg twice daily for 2 weeks and thereafter gradually tapered or identical appearing placebo tablets	No significant differences in GBS disability grade after 2, 4 and 24 weeks
Swick and McQuillen, 1976	Single centre Parallel group	*n* = 16 Patients requiring artificial ventilation or with contraindications to corticosteroids were excluded	Active treatment for adults 100 units and children 2 units/kg aqueous ACTH intramuscularly daily for 10 days or equal volumes of diluent as placebo	No significant differences in duration of hospitalization, time to complete recovery
Van Koningsveld *et al.*, 2004	Multicentre Parallel group	*n* = 225	All patients received IVIg 0.4 g/kg daily for 5 days and also either intravenous methylprednisolone 500 mg daily for 5 days or placebo infusions	76/112 corticosteroid and 63/113 placebo participants improved ≥1 disability grade after 4 weeks, relative risk 1.14 (95% CI 0.97–1.34). No significant differences in ability to walk unaided after 8 weeks or time to walk independently

Efficacy results

Plasma exchange

There was significantly more improvement in disability, the primary outcome in this review, after 4 weeks in the PE-treated participants than the untreated controls. For the 585 participants in the four trials with available data (Greenwood *et al.*, 1984; The Guillain-Barré Syndrome Study Group, 1985; French Cooperative Group in Plasma Exchange in Guillain-Barré Syndrome, 1987; French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997), the WMD in improvement was –0.89 of grade (95% CI –1.14 to –0.63) more improvement in those who received PE than those who did not, $P < 0.00001$.

Other secondary outcome measures including the relative rate of improving one disability grade, median time to recover independent walking and being dead or disabled after 1 year also significantly favoured the treated participants compared with those who only received supportive care (Tables 5 and 6). The relative rate of full muscle strength recovery was 1.24 (95% CI 1.07–1.45) times more with PE than without. The mortality was similar, ~5%, in the treated and untreated arms of the studies (Table 5).

Table 5 Secondary outcomes

Comparison	Number of trials	Numbers (%)	RR (95% CI)
Improvement by one or more disability grades after 4 weeks			
PE versus supportive care only	4	162/290 (56%) versus 104/295 (35%)	1.58 (1.32–1.90)***
IVIg versus PE	5	159/273 (58.2%) versus 134/253 (53%)	1.09 (0.94–1.27)
PE + IVIg versus PE	1	77/127 (61%) versus 70/121 (58%)	1.05 (0.85–1.29)
Oral corticosteroids versus control	3	24/51 (47.1%) versus 29/49 (59.2%)	0.80 (0.55–1.16)
IV corticosteroids versus placebo	2	143/236 (60.6%) versus 123/231 (53.0%)	1.14 (0.97–1.34)
Death or disability after 1 year			
PE versus supportive care only	6	35/321 (10.9%) versus 55/328 (16.8%)	0.65 (0.44–0.96)*
IVIg versus PE	1	21/129 (16.3%) versus 19/114 (16.7%)	0.98 (0.55–1.72)
PE + IVIg versus PE	1	17/122 (13.9%) versus 19/114 (16.7%)	0.84 (0.46–1.53)
Oral corticosteroids versus control	1	2/21 (9.5%) versus 2/19 (10.5%)	0.90 (0.14–5.81)
IV corticosteroids versus placebo	2	33/231 (14.3%) versus 20/220 (9.1%)	1.57 (0.93–2.66)
Death			

PE versus supportive care only	6	15/321 (4.7%) versus 18/328 (5.5%)	0.86 (0.45–1.65)
IVIg versus PE	1	7/296 (2.4%) versus 9/286 (3.1%)	0.78 (0.31–1.95)
PE + IVIg versus PE	1	8/128 (6.3%) versus 5/121 (4.1%)	1.51 (0.51–4.50)
Oral corticosteroids versus control	5	8/72 (11.1%) versus 7/66 (9.1%)	1.04 (0.41–2.63)
IV corticosteroids versus placebo	2	11/236 (4.7%) versus 7/231 (3.0%)	1.55 (0.61–3.94)
Relapse			
PE versus supportive care only	6	13/321 (4%) versus 4/328 (1.2%)	2.98 (1.06–8.39)*
IVIg versus PE	1	12/227 (5.2%) versus 13/218 (6.0%)	0.89 (0.42–1.89)
PE + IVIg versus PE	1	9/128 (7.0%) versus 7/121 (5.8%)	1.22 (0.47–3.16)
Oral corticosteroids versus control	1	3/21 (14.3%) versus 0/19 (0%)	6.36 (0.35–115.7)
IV corticosteroids versus control	2	15/230 (6.5%) versus 15/220 (6.8%)	0.96 (0.48–1.91)

***$P = 0.00001$, *$P < 0.05$. Note that the numbers and percentages have been obtained by adding the results for each trial. The RRs are the pooled RRs for the trials from which the significance has been computed. Thus for the first row the pooled relative rate of improving one or more disability grades after 4 weeks is 1.58 times more with PE than with supportive treatment.

Table 6 Median time in days to recover independent walking

Comparison	Treatment 1[a]		Treatment 2		Median difference 95% CI
	n	median	*n*	median	
PE versus supportive care only					
The Guillain-Barré Syndrome Study Group, 1985	108	53	120	85	32 (11.2–

					52.8)**
French Cooperative Group in plasma exchange in Guillain-Barré syndrome, 1987; French Cooperative Group on plasma exchange in Guillain-Barré syndrome, 1992	101	70	107	111	41 (17.5–64.5)**
IVIg versus PE					
Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997	130	51	121	49	–2 (–28.2–24.2)
van der Meché *et al.*, 1992	74	55	73	69	14 (–15.0–43.0)
PE + IVIg versus PE					
Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997	127	40	121	49	9 (–16.5–34.5)
Oral corticosteroids versus control					
Hughes *et al.*, 1978	21	29	19	34	5 (–95–105)
IV corticosteroids versus placebo					
Guillain-Barré Syndrome Steroid Trial Group, 1993	124	38	118	50	12 (–21.3–45.3)
Van Koningsveld *et al.*, 2004	112	28	113	56	28 (–6.0–62.0)

**$P < 0.001$. [a] Treatment 1 is the first and Treatment 2 the second in each row.

One trial was confined to people with mild GBS, who were able to walk unaided at randomization (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997♦). Participants were randomized to receive either two sessions of PE in 3 days, or supportive care. The number of patients with one or more grades of improvement at 1 month was significantly greater, 26/45, in the treated group compared to the control group, 13/46 (RR 3.47, 95% CI 1.45–8.31, $P < 0.001$).

In most studies, the amount of PE was arbitrarily set at the equivalent of five single plasma volume exchanges undertaken over up to 2 weeks. The French studies used larger exchanges of 1.5 plasma volumes. Two trials have investigated the amount of PE. In one trial, patients who could not stand unaided and who did not need respiratory assistance were randomized to either two or four 1.5 plasma volume exchanges (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997♦). Significantly more participants (93/155, 64%) treated with four PEs recovered full muscle strength after a year than those treated with two PEs (67/149, 48%), RR 1.35 (95% CI 1.09–1.67, $P = 0.006$).

In a parallel trial, 161 ventilator-dependent GBS patients were randomized to receive either six PEs or four PEs. There was no significant difference between the two regimens in the same measure of recovery (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997). In most studies, the replacement fluid has been a mixture of albumen and saline. In one study, 57 patients were randomly allocated to receive PE with albumen and gelatin as replacement fluids, and 52 received PE with fresh frozen plasma as the replacement fluid. There was no significant difference between the two groups in any measure of recovery (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997).

Intravenous immunoglobulin

Only three trials have compared IVIg with no treatment or placebo and all concerned children. One trial allocated 18 children alternately to IVIg or supportive treatment alone (Gürses *et al.*, 1995). After 4 weeks, seven of the nine patients in the IVIg group but only two of the nine untreated patients had recovered full strength. The other trial randomized children into three groups: dexamethasone alone in a dose of 5–10 mg daily for 5 or 6 days and then tailed over 7–10 days, or the same dose of dexamethasone and either IVIg or PE (Wang *et al.*, 2001). This trial included 20 children treated with IVIg and corticosteroids and 16 with corticosteroids alone who could be used to investigate the efficacy of IVIg. The children who received IVIg recovered muscle strength significantly faster than those treated without. The third trial (Korinthenberg *et al.*, 2005) was a randomized open study which compared IVIg in a dose of 1.0 g/kg (half the usual dose) with supportive treatment in 21 mildly affected children who could still walk unaided. The authors made available the detailed results from which we were able to compute the change in the disability grade scale used in this review after 4 weeks. The mean improvement in the IVIg group was significantly more than in the untreated participants (mean difference –1.42; 95% CI –2.57 to –0.27, $P = 0.02$). No meta-analysis was performed because this outcome used was not available for the other two trials.

Five trials including 582 participants compared IVIg with PE (Table 3) (van der Meché *et al.*, 1992; Bril *et al.*, 1996; Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997; Nomura *et al.*, 2000; Diener *et al.*, 2001). The weighted mean disability grade improvement was almost identical, being –0.02 more with IVIg than with PE (95% CI –0.25 more improvement to 0.20 less improvement) (Fig. 1B). There was also no significant difference between the treatments for any of the available outcome measures (Tables 5 and 6).

Immunoabsorption is an alternative to PE for removing plasma constituents. One trial with 41 participants found no difference in any outcome between those treated with IVIg and those treated with immunoabsorption (Diener *et al.*, 2001).

Two trials compared different doses or regimens of IVIg. One, in adults, randomized 39 patients with GBS of any severity and contraindications for PE to 3 or 6 days of IVIg 0.4 g/kg (Raphaël *et al.*, 2001). The mean improvement in disability grade after 4 weeks was greater in the 6- than the 3-day dose group but not significantly so, mean difference –0.5 (95% CI –1.26 to 0.26). There were no significant differences in the time to walk without assistance, duration of ventilation, adverse events or mortality. Full recovery of strength was non-significantly greater in the 6-day group (11 out of 16) compared with the 3-day group (6 out of 15), RR 1.72 (95% CI 0.85–3.47).

The other, in 50 children, compared the standard regimen of 0.4 g/kg daily for 5 days with same total dose of 2.0 g/kg given as 1.0 g/kg daily for 2 days (Korinthenberg *et al.*, 2005). There were no significant differences in the primary or secondary outcome measures reported by the authors (Table 3) except that early relapses were significantly more common after the 2-day (5/23) than the 5-day regimen (0/23, $P = 0.049$). There was no significant difference in the primary outcome measure for this review. The mean difference in change in disability grade after 4 weeks was –0.27 less improvement with the 2-day than the 5-day regimen but the 95% CIs were wide, –0.94 to 0.40, so that there is uncertainty about this conclusion.

Combination of PE or immunoabsorption with intravenous immunoglobulin

One trial compared PE alone with PE followed by IVIg (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). After 4 weeks the WMD in disability grade was not significant, being 0.20 (95% CI –0.14 to 0.54) of a grade more improvement in the 128 patients who received both treatments than in the 121 patients who received PE alone. There were also no significant differences in the secondary outcome measures: number improved after 4 weeks, time to independent walking, duration of ventilation, death or death and disability 12 months later (Tables 5 and 6).

One non-randomized trial compared immunoabsorption followed by IVIg in 24 patients with immunoabsorption alone in 13 patients. There was no significant difference in improvement after 4 weeks. The mean difference was 1.10, 95% CI 0.36–1.84, more improvement in the immunoabsorption followed by IVIg group than in the group treated with immunoabsorption alone (Haupt *et al.*, 1996). There were also no significant differences in any other outcome.

Corticosteroids

Eight trials randomized altogether 623 participants to corticosteroids or placebo or supportive care (Table 4). Six trials with 587 participants had information about our primary outcome measure: there was no significant difference in the mean improvement in disability after 4 weeks between those who received corticosteroids and those who did not (Fig. 1C). The WMD of change in grade was –0.36 (95% CI –0.88 to 0.16), indicating less improvement in the corticosteroid-treated participants. There was significant heterogeneity in this analysis so that a random effects model was used for the computation. Inspection of the forest plot suggested more benefit from the intravenous regimens so that we undertook a separate analysis of the trials which used oral and intravenous regimens. In the four small trials which used oral corticosteroids (Shukla *et al.*, 1988; Singh and Gupta, 1996; Bansal *et al.*, 2004), there were in total 120 participants and there was significantly less improvement with corticosteroids than without, WMD –0.82 of a grade (95% CI –0.17 to –1.47, $P < 0.0001$). In the two large trials which used intravenous methylprednisolone (Guillain-Barré Syndrome Steroid Trial Group, 1993; Van Koningsveld *et al.*, 2004), there were 467 participants and the change in grade was not significantly different in the corticosteroid from the placebo allocated participants, WMD –0.17 of a grade (95% CI 0.06 to –0.39) more improvement in the corticosteroid-treated patients.

When we analysed the number of patients who improved one or more disability grades after 4 weeks, information was only available for five trials with 567 participants. The same trends were observed but there was no significant heterogeneity and the differences were less significant.

The relative rate of improving by one or more grades was 1.08 (95% CI 0.93–1.24) more in the corticosteroid treated than the control participants, a non-significant difference. In the three small oral corticosteroid trials there were 100 participants and the relative rate of improvement was less in the corticosteroid-treated participants but not significantly less, 0.8 (95% CI 0.5–1.16). When this analysis was confined to the two large trials which used intravenous methylprednisolone, the relative rate of improvement did not quite achieve significance, being 1.14 (95% CI 0.97–1.34) of a grade more in the corticosteroid-treated patients. The effects of two known important prognostic variables, age (less than 50 years and 50 years or more) and initial disability, on the relative rate of improving one or more grades in 4 weeks, were tested using logistic regression and an inverse variance weighted meta-analysis for these two trials. The result gave an adjusted log odds ratio of 1.41 (95% CI 0.95–2.07, $P = 0.08$) which was in favour of corticosteroids but not quite significant. Assuming that in the controls the probability of recovering one or more grades is the average of those observed in the two studies, i.e. 53.2%, then these adjusted log odds ratio results are equivalent to a RR of 1.16 (95% CI 0.98–1.32, $P = 0.08$) for improving one or more grades comparing corticosteroids with placebo.

In the two intravenous methylprednisolone trials the median time from randomization to discontinuation of ventilation ranged from 18 to 30 days in those treated with corticosteroids and 26 to 27 days in the placebo group (Guillain-Barré Syndrome Steroid Trial Group, 1993; Van Koningsveld *et al.*, 2004).

The median time to regain independent walking and relative risks of death or death and disability after a year were not significantly different in the corticosteroid and the control subjects (Tables 5 and 6).

Relapses

Relapses occurred in 13/321 PE-treated participants and only 4/328 of those who did not receive PE, a significant difference, RR 2.89 (95% CI 1.05–7.93, $P = 0.04$). There were no significant differences in the frequency of relapses in PE-treated compared with IVIg-treated or in corticosteroid-treated compared with control subjects (Table 5).

Safety results

In three trials with altogether 556 participants comparing PE with supportive care, details of complications were available. The RRs of serious adverse events (severe infections, blood pressure instability, pulmonary embolus or cardiac arrhythmias) were not significantly greater in the treated than the untreated participants. In the trial that compared albumen and gelatin with fresh frozen plasma as the replacement fluid there were adverse events in 46% of 135 sessions using fresh frozen plasma and 32% of 208 sessions using albumen (RR 1.40, 95% CI 0.86–2.26). In three trials with 347 participants comparing PE with IVIg (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997; Nomura *et al.*, 2000; Diener *et al.*, 2001), the number of patients with adverse events was not significantly different between the treatments (RR 0.84, 95% CI 0.45–1.59, less in the IVIg-treated patients). In one of the large trials (van der Meché *et al.*, 1992), significantly less patients treated with IVIg had multiple complications than with PE: only 5 of 74 IVIg had multiple complications compared with 16 of 73 PE patients, RR 0.31, 95% CI 0.12–0.80.

Subgroups
Limited information was available about the relative merits of the treatments in different subgroups of patients. Patients requiring ventilation have a worse prognosis. Three trials of PE described the outcome of a total of 198 participants who were ventilated at randomization (The Guillain-Barré Syndrome Study Group, 1985; Farkkila *et al.*, 1987; French Cooperative Group in Plasma Exchange in Guillain-Barré Syndrome, 1987). The outcomes were better in the PE treated than the untreated patients, significantly so in two of the trials, but the measures reported did not permit meta-analysis. For patients randomized early, within 7 days, the two trials of PE reporting the appropriate information found significantly better outcomes for those receiving PE.

Outcomes were also better with PE and for those treated between 7 and 14 (French Cooperative Group in Plasma Exchange in Guillain-Barré Syndrome, 1987) or 28 days (The Guillain-Barré Syndrome Study Group, 1985) after onset compared with those treated later. Older age is an adverse prognostic factor but age did not have a significant influence on the treatment effect in either of the large trials comparing IVIg with PE. There was also no influence of the presence or absence of sensory deficit on the response to treatment in either of those trials. The occurrence of a previous diarrhoeal illness had been a significant adverse prognostic factor in some series. The effect of a previous diarrhoeal illness had opposite interactions with treatment in the two large trials that provided this information: patients with previous diarrhoea had significantly more improvement in disability grade after 4 weeks when treated with IVIg than with PE in one trial (van der Meché *et al.*, 1992) and with PE than with IVIg in the other (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).

Discussion

This synthesis of the results of all the randomized trials confirms that PE hastens recovery and shows that it also improves the outcome at 1 year without a significant effect on mortality or increase in adverse events. Although the outcomes of the PE trials were not conducted in a blinded fashion, the reported benefits were large and considered robust. The evidence from randomized trials comparing IVIg with no treatment is inadequate. However, the synthesis of the evidence shows that IVIg and PE have similar effects and the confidence limits are so narrow that an important clinical difference is unlikely to have been missed. One trial found no significant difference between the combination of PE followed by IVIg with either treatment alone but the sample sizes were not large enough to rule out a small beneficial effect of the combination treatment. Oral corticosteroids given for two or more weeks significantly slowed recovery. When the results of two trials were synthesized intravenous methylprednisolone did not produce significant long- or short-term benefit. When a correction for prognostic factors was taken into account, a minor synergistic effect on short-term outcome of IVIg combined with intravenous methylprednisolone could not be excluded (Van Koningsveld *et al.*, 2004). The explanation for the lack of more obvious benefits from corticosteroids is unclear but they might have harmful effects on denervated muscle or inhibit macrophage repair processes.

Only limited information is available concerning dosage. The standard dose of PE used in the American and PSGBS trials was the equivalent of five plasma volumes. The French trials used one and a half plasma volume exchanges and showed that four such exchanges were superior to two for moderately affected patients, while six were no better than four for ventilated patients (French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997). The usual IVIg regimen is 0.4 g/kg for 5 days. In a French trial, 3 days of 0.4 g/kg daily was slightly, but not significantly, less effective than 6 days (Raphaël *et al.*, 2001). A 5-day course of intravenous methylprednisolone showed a trend towards more rapid recovery, whereas oral corticosteroids for four or more weeks delayed recovery.

Minor side-effects from IVIg occur commonly but serious adverse events such as stroke and renal failure are rare: its main disadvantages are expense and theoretical risk of transmission of infection by viruses, prions or other agents (Dalakas and Clark, 2003; Dalakas, 2004). In experienced centres adverse events occur in ~4% of PE procedures and serious adverse events, usually complications of central venous catheter insertion, are rare (Kiprov *et al.*, 2001). Since PE is less available, less convenient and less comfortable for the patient, IVIg is the usual treatment of choice in many centres. Although long-term treatment with corticosteroids causes numerous serious side-effects (Bromberg and Carter, 2004), short-term treatment did not result in more serious adverse events than supportive treatment or placebo in the trials reviewed here. In both trials of intravenous methylprednisolone, there was a highly significant, but unexplained, reduction in the occurrence of hypertension.

Independent adverse prognostic factors in each of two large trials were previous diarrhoea, older age, disease severity and rapid disease onset (van der Meché *et al.*, 1992) (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). In neither trial did multivariate analysis show a significant interaction with treatment, except for diarrhoea which was associated with a better response to IVIg in one (van der Meché *et al.*, 1992) and to PE in the other (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997). Unfortunately neither these nor other randomized trials included sufficient participants with axonal forms of GBS to permit conclusions about whether they respond differently to treatment than people with AIDP. In children, who have a better prognosis than adults, the available trial evidence is not of primary quality but consistently points to a beneficial effect of IVIg, which is supported by a good quality observational study (Kanra *et al.*, 1997). A randomized study compared 20 children who received IVIg with 18 who received PE (Wang *et al.*, 2001). Both groups received dexamethasone. The children who received IVIg recovered bulbar or respiratory function, or made a two-grade improvement in muscle strength, in a mean (SD) of 17 (6 days) compared with 30 (7 days) in the PE group ($P < 0.0001$). In retrospective studies, patients with antibodies to ganglioside GM1 or GM1b treated with IVIg recovered faster than those treated with PE (Jacobs *et al.*, 1996; Yuki *et al.*, 2000; Kuwabara *et al.*, 2001).

The only other acute immunotherapy treatments tested in randomized trials have been the Chinese medicine herbal medicine tripterygium polyglycoside compared with dexamethasone (Zhang *et al.*, 2000), cerebrospinal fluid filtration compared with PE (Table 2) (Wollinsky *et al.*, 2001) and, as treatments in addition to IVIg, brain derived neurotrophic factor (Bensa *et al.*, 2000) or beta-interferon (Bensa *et al.*, 2000; Pritchard *et al.*, 2003) compared with placebo. None of these trials were large enough to detect even moderate treatment effects.

It has been possible to synthesize the results of studies performed over 30 years because the diagnostic criteria are clinical and reasonably robust and because most studies and all the large ones used or could provide results measured with the GBS disability scale (Table 1). This scale has the virtues of simplicity, face validity and reproducibility but it is non-linear and its large steps may be insufficiently sensitive to detect some clinically meaningful differences (Kleyweg *et al.*, 1991). The disease is heterogeneous and the speed and extent of recovery are variable. We chose change in the GBS disability scale after 4 weeks as being the most powerful statistical test, arguing that changes in the scale were sufficiently normally distributed to justify the assumptions of parametric tests. Even so, in order to detect statistically significant differences in short-term outcomes with this scale, sample sizes of about 120 patients in each of two groups are necessary to detect differences with a power of 80% at the 5% significance level (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).

In the randomized trials neither PE nor IVIg improved mortality, which ranged from 2.4% to 6.3% (Table 5). Since the introduction of these treatments, the mortality in hospital and population-based studies has not changed, ranging from 5% to 15% (Hughes and Cornblath, 2005). The greater mortality in the observational studies than in the trials might reflect the exclusion of patients with co-morbidity from the trials, more effective intensive care facilities in specialist centres or other factors.

Death or severe residual disability in the trials ranged between 9 and 17% despite a 6% risk reduction with PE (Table 5). The comparisons of IVIg and PE showed no difference in long-term outcome. Lesser degrees of disability and fatigue are common in survivors. The persistent mortality and residual symptoms in the survivors emphasize the need for continued efforts to design new treatments. Other areas of uncertainty needing more research are the identification of patients at greatest risk of a poor outcome, the long-term effects of initial immunotherapy and clarification of the value of IVIg in adults with mild disease, Fisher syndrome, axonal forms and other conditions related to GBS. Information is also lacking about how to treat patients who worsen or fail to improve after being treated with IVIg or PE. It is common practice to treat patients who improve and then relapse with IVIg or PE again. Some centres treat patients again if they fail to improve after about 2 or 3 weeks but evidence is needed to test the effectiveness of this practice. Advances in understanding the immunopathogenesis of GBS should eventually lead to the design of novel treatments which will enhance recovery or remyelination and regeneration.

This systematic review not only confirms that PE hastens recovery from GBS and improves its long-term outcome in severely affected adult patients, but also provides the best quantitative estimates of these effects. In adult patients, the effect of IVIg is equivalent. Because of its greater convenience and availability, IVIg is, appropriately, usually used. Following PE with IVIg did not produce significant extra benefit. In mildly affected patients, PE may be beneficial but there is no direct evidence about the efficacy of IVIg. By collecting evidence from several small trials, this review was able to draw conclusions which could not have been drawn from individual trials. Thus, three trials in children consistently showed a beneficial effect from IVIg compared with supportive care alone. Similarly, meta-analysis of the evidence from all the available trials showed that oral corticosteroids significantly slowed recovery, whereas intravenous methylprednisolone alone did not produce significant long- or short-term benefit. Despite these treatments, between 9% and 17% of patients in these trials died or remained severely disabled.

No other treatments have been adequately tested and improved therapeutic strategies are urgently needed.

Guillain-Barre Syndrome Glossary of Terms

Abnormal: Not normal. Deviating from the usual structure, position, condition, or behavior. In referring to a growth, abnormal may mean that it is cancerous or premalignant (likely to become cancer).

Arms: An appendage in anatomy and in clinical trials.

Autoimmune: Pertaining to autoimmunity, a misdirected immune response that occurs when the immune system goes awry and attacks the body itself.

Autoimmune disease: An illness that occurs when the body tissues are attacked by its own immune system . The immune system is a complex organization within the body that is designed normally to "seek and destroy" invaders of the body, including infectious agents. Patients with autoimmune diseases frequently have unusual antibodies circulating in their blood that target their own body tissues.

Axon: A long fiber of a nerve cell (a neuron) that acts somewhat like a fiber-optic cable carrying outgoing (efferent) messages.

Bacteria: Single-celled microorganisms which can exist either as independent (free-living) organisms or as parasites (dependent upon another organism for life).

Bacterial: Of or pertaining to bacteria. For example, a bacterial lung infection.

Blood pressure: The blood pressure is the pressure of the blood within the arteries. It is produced primarily by the contraction of the heart muscle. It's measurement is recorded by two numbers. The first (systolic pressure) is measured after the heart contracts and is highest. The second (diastolic pressure) is measured before the heart contracts and lowest. A blood pressure cuff is used to measure the pressure. Elevation of blood pressure is called "hypertension".

Brain: That part of the central nervous system that is located within the cranium (skull). The brain functions as the primary receiver, organizer and distributor of information for the body. It has two (right and left) halves called "hemispheres."

Breathing: The process of respiration, during which air is inhaled into the lungs through the mouth or nose due to muscle contraction, and then exhaled due to muscle relaxation.

Cerebrospinal fluid: CSF. A watery fluid, continuously produced and absorbed, which flows in the ventricles (cavities) within the brain and around the surface of the brain and spinal cord.

Clinical trials: Trials to evaluate the effectiveness and safety of medications or medical devices by monitoring their effects on large groups of people.

Cure: 1. To heal, to make well, to restore to good health. Cures are easy to claim and, all too often, difficult to confirm.
2. A time without recurrence of a disease so that the risk of recurrence is small, as in the 5-year cure rate for malignant melanoma .
3. Particularly in the past, a course of treatment. For example, take a cure at a spa.

Diagnosis: 1 The nature of a disease ; the identification of an illness. **2** A conclusion or decision reached by diagnosis. The diagnosis is rabies . **3** The identification of any problem. The diagnosis was a plugged IV.

Gastrointestinal: Adjective referring collectively to the stomach and small and large intestines.

Hammer: The malleus.

Heart: The muscle that pumps blood received from veins into arteries throughout the body. It is positioned in the chest behind the sternum (breastbone; in front of the trachea, esophagus, and aorta; and above the diaphragm muscle that separates the chest and abdominal cavities. The normal heart is about the size of a closed fist, and weighs about 10.5 ounces. It is cone-shaped, with the point of the cone pointing down to the left. Two-thirds of the heart lies in the left side of the chest with the balance in the right chest.

Heart rate: The number of heart beats per unit time, usually per minute. The heart rate is based on the number of contractions of the ventricles (the lower chambers of the heart). The heart rate may be too fast (tachycardia) or too slow (bradycardia). The pulse is bulge of an artery from the wave of blood coursing through the blood vessel as a result of the heart beat. The pulse is often taken at the wrist to estimate the heart rate.

Immune: Protected against infection. The Latin immunis means free, exempt.

Immune system: A complex system that is responsible for distinguishing us from everything foreign to us, and for protecting us against infections and foreign substances. The immune system works to seek and kill invaders.

Immunoglobulin: A protein produced by plasma cells and lymphocytes and characteristic of these types of cells. Immunoglobulins play an essential role in the body's immune system. They attach to foreign substances, such as bacteria, and assist in destroying them. Immunoglobulin is abbreviated Ig. The classes of immunoglobulins are termed immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin D (IgD) and immunoglobulin E (IgE).

Infection: The growth of a parasitic organism within the body. (A parasitic organism is one that lives on or in another organism and draws its nourishment therefrom.) A person with an infection has another organism (a "germ") growing within him, drawing its nourishment from the person.

Intensive care: See critical care.

Knee: The knee is a joint which has three parts. The thigh bone (the femur) meets the large shin bone (the tibia) to form the main knee joint. This joint has an inner (medial) and an outer (lateral) compartment. The kneecap (the patella) joins the femur to form a third joint, called the patellofemoral joint. The patella protects the front of the knee joint.

Limb: The arm or leg.

Low blood pressure : Any blood pressure that is below the normal expected for an individual in a given environment. Low blood pressure is also referred to as hypotension.

Muscle: Muscle is the tissue of the body which primarily functions as a source of power. There are three types of muscle in the body. Muscle which is responsible for moving extremities and external areas of the body is called "skeletal muscle." Heart muscle is called "cardiac muscle." Muscle that is in the walls of arteries and bowel is called "smooth muscle."

Myelin: The fatty substance that covers and protects nerves. Myelin is a layered tissue that sheathes the axons (nerve fibers). This sheath around the axon acts like a conduit in an electrical system, ensuring that messages sent by axons are not lost en route. It allows efficient conduction of action potentials down the axon. Myelin consists of 70% lipids (cholesterol and phospholipid) and 30% proteins. It is produced by oligodendrocytes in the central nervous system.

Nerve: A bundle of fibers that uses chemical and electrical signals to transmit sensory and motor information from one body part to another.

Neurological: Having to do with the nerves or the nervous system.

NIH: The National Institutes of Health. The NIH is an important U.S. health agency. It is devoted to medical research. Administratively under the Department of Health and Human Services (HHS), the NIH consists of 20-some separate Institutes and Centers. NIH's program activities are represented by these Institutes and Centers.

NINDS: Stands for the National Institute of Neurological Disorders and Stroke, one of the National Institutes of Health in the U.S., whose mission is to "support and conduct research and research training on the normal structure and function of the nervous system and on the causes, prevention, diagnosis, and treatment of more than 600 nervous system disorders including stroke, epilepsy, multiple sclerosis, Parkinson's disease, head and spinal cord injury, Alzheimer's disease, and brain tumors."

Onset: In medicine, the first appearance of the signs or symptoms of an illness as, for example, the onset of rheumatoid arthritis . There is always an onset to a disease but never to the return to good health. The default setting is good health.

Pain: An unpleasant sensation that can range from mild, localized discomfort to agony. Pain has both physical and emotional components. The physical part of pain results from nerve stimulation. Pain may be contained to a discrete area, as in an injury, or it can be more diffuse, as in disorders like fibromyalgia . Pain is mediated by specific nerve fibers that carry the pain impulses to the brain where their conscious appreciation may be modified by many factors.

Paralysis: Loss of voluntary movement (motor function). Paralysis that affects only one muscle or limb is partial paralysis, also known as palsy; paralysis of all muscles is total paralysis, as may occur in cases of botulism.

Paresthesia: An abnormal sensation of the skin, such as numbness, tingling, pricking, burning, or creeping on the skin that has no objective cause. Paresthesia is the usual American spelling and paraesthesia the preferred English spelling.

Peripheral: Situated away from the center, as opposed to centrally located.

Peripheral nervous system (PNS): That portion of the nervous system that is outside the brain and spinal cord.

Physical therapy: A branch of rehabilitative health that uses specially designed exercises and equipment to help patients regain or improve their physical abilities. Physical therapists work

with many types of patients, from infants born with musculoskeletal birth defects, to adults suffering from sciatica or the after- effects of injury, to elderly post-stroke patients.

Plasma: The liquid part of the blood and lymphatic fluid, which makes up about half of its volume. Plasma is devoid of cells and, unlike serum, has not clotted. Blood plasma contains antibodies and other proteins. It is taken from donors and made into medications for a variety of blood-related conditions. Some blood plasma is also used in non-medical products.

Plasmapheresis: A procedure designed to deplete the body of blood plasma (the liquid part of the blood) without depleting the body of its blood cells. Whole blood is removed from the body, the plasma is separated from the cells, the cells are suspended in saline, a plasma substitute or donor plasma), and the reconstituted solution may be returned to the patient. The procedure is used to remove excess antibodies from the blood in lupus, multiple sclerosis, multiple myeloma, etc. Plasmapheresis carries with it the same risks as any intravenous procedure. The risk of infection increases with the use of donor plasma, which may carry viral particles despite screening procedures. The procedure is done in a clinic or hospital.

Pneumonia: Inflammation of one or both lungs with consolidation. Pneumonia is frequently but not always due to infection. The infection may be bacterial, viral, fungal or parasitic. Symptoms may include fever, chills, cough with sputum production, chest pain, and shortness of breath.

Protein: A large molecule composed of one or more chains of amino acids in a specific order determined by the base sequence of nucleotides in the DNA coding for the protein.

Proteins: Large molecules composed of one or more chains of amino acids in a specific order determined by the base sequence of nucleotides in the DNA coding for the protein.

Relapse: The return of signs and symptoms of a disease after a patient has enjoyed a remission . For example, after treatment a patient with cancer of the colon went into remission with no sign or symptom of the tumor, remained in remission for 4 years, but then suffered a relapse and had to be treated once again for colon cancer.

Residual: Something left behind. With residual disease, the disease has not been eradicated.

Respiratory: Having to do with respiration, the exchange of oxygen and carbon dioxide. From the Latin re- (again) + spirare (to breathe) = to breathe again.

Sensory: Relating to sensation , to the perception of a stimulus and the voyage made by incoming (afferent) nerve impulses from the sense organs to the nerve centers.

Spinal cord: The major column of nerve tissue that is connected to the brain and lies within the vertebral canal and from which the spinal nerves emerge. Thirty-one pairs of spinal nerves originate in the spinal cord: 8 cervical , 12 thoracic , 5 lumbar, 5 sacral, and 1 coccygeal. The spinal cord and the brain constitute the central nervous system (CNS). The spinal cord consists of nerve fibers that transmit impulses to and from the brain. Like the brain, the spinal cord is covered by three connective-tissue envelopes called the meninges . The space between the outer and middle envelopes is filled with cerebrospinal fluid (CSF), a clear colorless fluid that cushions the spinal cord against jarring shock. Also known simply as the cord.

Spinal tap: Also known as a lumbar puncture or "LP", a spinal tap is a procedure whereby spinal fluid is removed from the spinal canal for the purpose of diagnostic testing. It is particularly helpful in the diagnosis of inflammatory diseases of the central nervous system, especially infections, such as meningitis. It can also provide clues to the diagnosis of stroke , spinal cord

Stage: As regards cancer , the extent of a cancer, especially whether the disease has spread from the original site to other parts of the body. See also: Staging .

Steroid: A general class of chemical substances that are structurally related to one another and share the same chemical skeleton (a tetracyclic cyclopenta[a]phenanthrene skeleton).

Stroke : The sudden death of some brain cells due to a lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain. A stroke is also called a cerebrovascular accident or, for short, a CVA.

Surgery: The word "surgery" has multiple meanings. It is the branch of medicine concerned with diseases and conditions which require or are amenable to operative procedures. Surgery is the work done by a surgeon. By analogy, the work of an editor wielding his pen as a scalpel is s form of surgery. A surgery in England (and some other countries) is a physician's or dentist's office.

Syndrome: A set of signs and symptoms that tend to occur together and which reflect the presence of a particular disease or an increased chance of developing a particular disease.

Therapy: The treatment of disease .

Trigger: Something that either sets off a disease in people who are genetically predisposed to developing the disease, or that causes a certain symptom to occur in a person who has a disease. For example, sunlight can trigger rashes in people with lupus.

Ventilator: A ventilator is a machine which mechanically assists patients in the exchange of oxygen and carbon dioxide (sometimes referred to as artificial respiration).

Viral: Of or pertaining to a virus. For example, "My daughter has a viral rash ."

Viral infection: Infection caused by the presence of a virus in the body. Depending on the virus and the person's state of health, various viruses can infect almost any type of body tissue, from the brain to the skin. Viral infections cannot be treated with antibiotics; in fact, in some cases the use of antibiotics makes the infection worse. The vast majority of human viral infections can be effectively fought by the body's own immune system , with a little help in the form of proper diet, hydration, and rest. As for the rest, treatment depends on the type and location of the virus, and may include anti-viral or other drugs.

Virus: A microorganism smaller than a bacteria, which cannot grow or reproduce apart from a living cell. A virus invades living cells and uses their chemical machinery to keep itself alive and to replicate itself. It may reproduce with fidelity or with errors (mutations)-this ability to mutate is responsible for the ability of some viruses to change slightly in each infected person, making treatment more difficult.

Viruses: Small living particles that can infect cells and change how the cells function. Infection with a virus can cause a person to develop symptoms. The disease and symptoms that are caused depend on the type of virus and the type of cells that are infected.

EXAM

1. Guillain-Barré syndrome is a disorder in which _____ attacks part of the peripheral nervous system.

a. a neurological virus
b. a bacterial virus
c. the body's immune system
d. None of the above

2. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the _____.

a. arms
b. legs
c. feet
d. None of the above

3. These symptoms can increase in intensity until the muscles cannot be used at all and the patient is _____. In these cases, the disorder is life-threatening and is considered a medical emergency.

a. in tremendous pain
b. in a coma
c. almost totally paralyzed
d. None of the above

4. Usually Guillain-Barré occurs a few days or weeks after the patient has had symptoms of a respiratory or _____. Occasionally, surgery or vaccinations will trigger the syndrome. The disorder can develop over the course of hours or days, or it may take up to 3 to 4 weeks.

a. gastrointestinal viral infection
b. headaches
c. leg pain
d. None of the above

5. Guillain-Barré is called a syndrome rather than a disease because it is not clear that a specific disease-causing agent is involved.

a. True
b. False

6. Guillain-Barré syndrome can affect anybody. It can strike at any age and both sexes are equally prone to the disorder. The syndrome is rare, however, afflicting only about one person in _____.

a. 1,000
b. 10,000
c. 100,000
d. 1,000,000

7. No one yet knows why Guillain-Barré - which is not contagious - strikes some people and not others. Nor does anyone know exactly what sets the disease in motion.What scientists do know is that the body's immune system begins to attack the body itself, causing what is known as an autoimmune disease.

a. True
b. False

8. When Guillain-Barré is preceded by a viral or bacterial infection, it is possible that the virus has changed the nature of cells in the nervous system so that the _____treats them as foreign cells.

a. body’s nervous system
b. immune system
c. brain
d. None of the above

9. The cause and course of Guillain-Barré syndrome is an active area of neurological investigation, incorporating the cooperative efforts of neurological scientists, immunologists, and virologists.

a. True
b. False

10. In Guillain-Barré patients, the cerebrospinal fluid that bathes the spinal cord and brain contains more _____ than usual. Therefore a physician may decide to perform a spinal tap, a procedure in which the doctor inserts a needle into the patient's lower back to draw cerebrospinal fluid from the spinal column.

a. calcium
b. density
c. protein
d. None of the above

11. The signs and symptoms of the syndrome can be quite varied, so doctors may, on rare occasions, find it difficult to diagnose Guillain-Barré in its earliest stages.

a. True
b. False

12. Guillain–Barré syndrome (GBS) is generally considered to be monophasic, but recurrences do occur in _____.

a. women
b. a presently undefined subgroup of patients
c. the elderly
d. None of the above

13. Guillain–Barré syndrome (GBS) is an acute polyradiculoneuropathy leading to_____. Its annual incidence rate is 0.75 to 2 per 100 000.

a. aphasia
b. dementia
c. flaccid paresis
d. None of the above

14. There is no known cure for Guillain-Barré syndrome. However, there are therapies that lessen the severity of the illness and accelerate the recovery in most patients. There are also a number of ways to treat the complications of the disease.

a. True
b. False

15. Currently, plasma exchange (sometimes called _____) and high-dose immunoglobulin therapy are used. Both of them are equally effective, but immunoglobulin is easier to administer.

a. apheresis
b. plasmapheresis
c. pheresis
d. None of the above

16. The use of steroid hormones has also been tried as a way to reduce the severity of Guillain-Barré, but controlled clinical trials have demonstrated that this treatment not only is not effective but may even have a deleterious effect on the disease.

a. True
b. False

17. The recovery period for this syndrome may be as little as a few weeks or as long as a few years. About 30 percent of those with Guillain-Barré still have a residual weakness after 3 years. About 3 percent may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack.

a. True
b. False

18. Scientists are concentrating on finding new treatments and refining existing ones. Researchers are also looking at the workings of the immune system to find which cells are responsible for beginning and carrying out the attack on the nervous system.

a. True
b. False

19. The GBS disability scale is a _____-point disability scale, ranging from no symptoms to death. Patients who were able to walk with or without support (GBS disability scale ≤3) were considered as "mildly affected," whereas patients who were bedbound (GBS disability scale ≥4) were categorized as "severely affected."

a. three
b. seven
c. nine
d. None of the above

20. Three trials in children consistently showed a beneficial effect from IVIg compared with supportive care alone. Similarly, meta-analysis of the evidence from all the available trials showed that oral corticosteroids significantly slowed recovery, whereas intravenous methylprednisolone alone did not produce significant long- or short-term benefit.

a. True
b. False

MEDEDSYS
PO BOX 81831, San Diego, CA, 92138-3939
TOLL FREE 1-877-295-4719
FAX: 619-295-0252
info@mededsys.com
www.mededsys.com

How to Complete Your Test and Print Your Certificate Online

If you chose to receive your order by postal mail, you have been mailed the printed course material(s) and the printed test(s). To take a test, simply complete the mailed test and send it back. Upon successful completion of a test, a certificate will be mailed or faxed to you. If you don't wish to mail the test back, customers who chose to have the course material(s) mailed may also follow the steps below to complete a test and print a certificate online.

INSTRUCTIONS

1. Go to www.mededsys.com
2. Login and go to "My Account".
3. On the page that opens, select an option from the "My Courses" menu.
4. Select the test you wish to complete.
5. After completion of test, print your certificate online by clicking on the "Continue" button. Alternatively, you may return to the "My Courses" section and select the option to print a certificate.