

Guillain-Barré Syndrome and Vaccination: Usually Unrelated

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With the rapid pace of immunologic research, it is more important than ever for readers to understand rational immunodiagnosis, immunoprophylaxis, and immunotherapy. This column is intended to help you carry out proper immunologic drug use in your practice. Address suggestions to: Lt. Col. John D. Grabenstein, RPh, PhD, FASHP, Directorate of Health Care Operations, U.S. Army Medical Command, 5111 Leesburg Pike, Falls Church, VA 22041.

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Some vaccines cause specific side effects, like the rare cases of poliomyelitis after oral poliovirus vaccination. But when people talk about rare side effects related to vaccination in general, two conditions are most often mentioned: anaphylaxis and Guillain-Barré syndrome (pronounced “ghee-YAN bah-RAY”).

A previous column in this series reviewed the spectrum of severe allergic reactions known as anaphylaxis.¹ This column will address Guillain-Barré syndrome (GBS), a neuromuscular disorder, and its relationship to vaccination. Although GBS is generally acknowledged as a postinfection illness, seldom has vaccination been found to cause GBS.

PATHOLOGY AND EPIDEMIOLOGY

Guillain-Barré syndrome usually

manifests as an acute, symmetrical, lower-motor-neuron paralysis.²⁻⁵ GBS is a demyelinating disease, meaning that segments of myelin are stripped from their insulating position around nerves, reducing the propagation of electrical nerve impulses. This causes loss of reflexes, muscle weakness, and temporary paralysis (loss of muscle strength).

The main symptoms of GBS are weakness, numbness, tingling, and prickling. Muscle weakness typically begins distally in the legs and spreads proximally to the arms. It is sometimes referred to as Landry-Guillain-Barré syndrome or Landry-Guillain-Barré-Strohl syndrome, to recognize other early researchers of the condition.

GBS is usually self-limited, peaking within 2 to 4 weeks, with most people recovering fully after remyelination.³ Recuperation can take

months. In a series of 140 GBS patients in southeast England surveyed a year later, 70% had made a complete recovery, 22% were unable to run, and 8% were unable to walk unaided. The mortality rate after GBS ranges from 5% to 8%, despite modern intensive-care medicine.

With the elimination of poliomyelitis in developed countries, GBS is now the leading cause of acute flaccid paralysis there.³ GBS affects people of all ages and both genders, although males contract GBS more commonly than women, at a ratio of about 5-to-4.⁴ GBS is more common in late adolescence and young adulthood, coinciding with an increased risk of injection with cytomegalovirus and *Campylobacter jejuni*. There is a second peak in incidence among the elderly.

From 4,000 to 5,000 new GBS cases are reported each year in the US and Canada. Guillain-Barré syndrome occurs at a rate of about 1.3 to 1.9 cases per 100,000 population per year, or roughly one person per 62,000 people per year.³ Hughes and Rees listed a series of 35 GBS studies from around the world, finding an annual incidence rate ranging from 0.4 to 4 GBS cases per 100,000 people per year, with a median value of 1.3 per 100,000 per year.⁴ Scientists at the Centers for Disease Control and Prevention (CDC) have calculat-

ed the background rate of GBS as 1.5 to 3 cases per 10 million person-weeks of observation.⁶⁻⁷

Most cases of GBS are triggered by a bacterial or viral illness.³ It is likely that GBS represents a clinical spectrum of different pathological entities with distinct clinical features and probably distinct aspects of pathogenesis. About 85% to 90% of GBS cases can pathologically be described as acute inflammatory demyelinating polyradiculoneuropathy or AIDP. Delayed recovery is more likely with variants known as acute motor or acute motor-sensory axonal neuropathy.

About two-thirds of all cases of Guillain-Barré syndrome follow an acute respiratory or gastrointestinal infection.^{3-5,8} *Campylobacter* bacteria are the most frequent antecedent pathogen recognized, a finding confirmed in 14 large case-series. *Campylobacter* bacteria have also been associated with Miller-Fisher syndrome, a variant of GBS characterized by ophthalmoplegia, ataxia, and areflexia. People most frequently encounter *Campylobacter* bacteria in undercooked food. Other microbes confirmed to be associated with GBS in case-control studies or found in large number or series include: Cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, human immunodeficiency virus, and *Mycoplasma pneumoniae*. *Campylobacter*-associated GBS is a major component of the societal costs of *Campylobacter* infections.⁹

GBS is generally considered an autoimmune disease, with the immune system mistakenly attacking myelin or axons, the nerve conduits for signals to and from the brain.³ This mistake may arise because the surface of *Campylobacter* bacteria contains polysaccharides that resemble formations on nerves. This has been called cross-reactivity or "molecular mimicry."^{3,10}

While there are reports of GBS after vaccination, primarily influenza vaccination, the CDC reports that more than 99% of people with GBS do not report having received any vaccine in the weeks before developing GBS.¹¹

GBS cases need to be admitted to hospital for close observation and specialized therapy (eg, intubation, mechanical ventilation).^{3,5} GBS is treated with plasma exchange or plasmapheresis, removing plasma (including immunoglobulins) from the patient's blood, but returning red and white blood cells to the body. Another approach is to give intravenous injections of immunoglobulin G (IgG).¹²⁻¹⁴ IgG treatment is easier to administer than plasma exchange, with comparable effectiveness.³ Corticosteroids have been tried, but with less success, although methylprednisolone combined with IgG may have value. Cost-effectiveness contrasts between plasma exchange and IgG treatment are sensitive to the cost of IgG.¹⁵

IV immunoglobulin (IGIV) therapy of GBS is typically administered as 0.4 gram or more IgG per kg body-weight daily for 5 consecutive days.³ IGIV appears to work by contributing anti-idiotypic antibodies that bind and neutralize pathogenic autoantibodies. Other mechanisms may also contribute.¹²⁻¹³ Four weeks after treatment, 53% of patients treated with IGIV had functional improvement. Neurologic relapses may develop in about 10% of people treated with IGIV; most of these cases respond well to a series of repeated IGIV infusions.³

ASSOCIATION WITH VACCINATION

If the background rate of GBS is one person per year among 62,000 unvaccinated people, then we expect the rate of GBS among vaccinated people also will be one case per

62,000 per year. If the rate among vaccinated people is substantially higher than one per 62,000 per year, we have some evidence that vaccination may increase the likelihood of contracting GBS.¹⁶

Several reports of individual cases or small case series of GBS in relation to vaccination have been published, based on a mere temporal association with vaccination.^{3,17-23} But these isolated events are not alarming, given that we start with a baseline expectation of one case for every 62,000 vaccine recipients. These individual reports are not sufficient to establish a causal relationship, in part, because potentially confounding coincidental infections (eg, *Campylobacter*) were not ruled out.³

The first vaccine to be clearly associated with GBS in a proper scientific manner was the now-obsolete rabies vaccine prepared from infected brain tissues of adult animals.^{14,23-24} This association probably arose because the vaccine was contaminated with myelin antigens from the animal tissue that acted as the viral culture media. Such neural-tissue-culture rabies vaccines have not been used in the US since about 1980, although they are still used in developing countries.¹⁴

SWINE-FLU VACCINE OF 1976

The most famous, even infamous, outbreak of GBS occurred in 1976/77. Before 1976, no association between GBS and influenza vaccine had been recognized. In February 1976, a previously healthy soldier at Fort Dix, New Jersey, died of an influenza virus thought to be similar to the 1918 strain. The 1918 pandemic remains the most devastating loss of life from any cause during any 6-month period in the history of humanity.²⁵

The unusual case set in motion an intricate chain of events.²⁶⁻²⁷ In early 1976, leading infectious-disease

experts persuaded government officials that an unprecedented influenza vaccination program was needed, to prevent repetition of the 1918/19 devastation. President Gerald Ford signed Congressional legislation authorizing the National Influenza Immunization Program. Eventually, health care providers immunized 48 million Americans against "swine influenza" between October and December 1976.

The viral strain was known officially as the A/New Jersey/8/76 (swine flu). Two vaccines were marketed, a monovalent vaccine containing 200 chick-cell agglutinating (CCA) units of A/New Jersey/8/76 (Hsw1N1) strain per 0.5 mL dose and a bivalent vaccine containing 200 CCA units each of two strains per 0.5 mL: A/New Jersey/8/76 (Hsw1N1) and A/Victoria/75 (H3N2). A monovalent influenza type B vaccine (strain B/Hong Kong/5/72) was also marketed that year.²⁸⁻²⁹

From the beginning, the 1976 program was not a good example of health care marketing or risk communication.³⁰⁻³² In October 1976, three elderly people with serious heart conditions died shortly after being vaccinated at the same clinic in Pittsburgh.^{30,33} Public confidence was shaken in the face of intense media scrutiny. The deaths were quickly judged to be a statistical coincidence—likely with so many elderly people being vaccinated in so many towns in such a short period of time. After all, even unusual events will be found somewhere when the exposed population is counted in tens of millions of people.

Fortunately, influenza failed to materialize as an epidemic or pandemic.^{26-27,34-35} Unfortunately, an unexpected increase in the incidence of GBS began to appear in November among influenza vaccine recipients.^{26-27,34-37} By November 20, 1976, with CDC officials reading reports of

GBS cases among isolated vaccine recipients in Minnesota, Alabama, and New Jersey, they still could not tell if these cases were the expected background occurrences of GBS that also develop among unvaccinated people or an elevated rate of incidence. The expected frequency of GBS among unvaccinated people was not well understood in 1976. On December 16, 1976, CDC had enough information for its director to recommend the cessation of the swine-flu immunization program. Initial reports indicated that the rate of GBS among vaccinated people was seven to eight times higher than the background rate among unvaccinated people. The Department of Health, Education and Welfare (HEW) announced the decision to the public, with the agreement of President Ford.^{26-27,36}

For the 10 weeks following vaccine administration, the risk was found to be approximately 10 cases of GBS for every million recipients, an incidence rate seven times higher than that in unimmunized persons. Persons younger than 25 years of age had a lower relative risk than others and also had a lower case-fatality rate.^{26-27,31,38} GBS incidence rates did not differ among the four manufacturers of the swine-flu vaccine.³⁷ Curiously, the association between swine-flu vaccine and GBS was noted primarily because CDC had instituted a special surveillance program for adverse effects and because such an unprecedented goal of vaccine delivery had been set.

Media coverage about people with GBS who had received swine-flu vaccine, now disabled or deceased, biased the reporting of GBS cases to health officials.³⁶ With all the attention, physicians (especially neurologists) were more likely to ask about vaccination status in patients reporting muscle weakness than they ordinarily would have. Second, because GBS can be confused with other neu-

rologic disorders, the presence of swine-flu vaccination in somebody's medical history might increase the likelihood that a physician would diagnose GBS, lessening appropriate consideration of other differential diagnoses.

Before the swine-flu vaccination program began, the federal government agreed to compensate people objectively injured by the vaccine.^{26-27,36} The GBS incident triggered this provision of the law, of course, but along with GBS cases came claims totaling billions of dollars for thousands of other people. Federal judges, without juries, were to adjudicate the claims. But there were no established case definitions. Preexisting medical conditions fogged otherwise simple cause-and-effect relationships.

US Judge Sherman Finesilver, in Denver, invoked the little-used Federal Rule of Evidence number 706 to appoint a panel of three scientific experts to examine plaintiffs, review documents, and decide whether plaintiffs' injuries should be considered caused by the swine-flu vaccine.³⁶ Of 126 swine-flu cases on Judge Finesilver's docket, all but four settled out of court. In many respects, the swine-flu vaccine/GBS incident of 1976 set the stage for the Vaccine Injury Compensation Program adopted by the US 10 years later.³⁹

Curiously, contradictory information was also found. The United States Armed Forces reported that Guillain-Barré syndrome occurred at basically the same rate in 1976 as in previous years, even though military personnel received two doses of the A/New Jersey/8/76 influenza vaccine.^{3,36,38} This study may have been flawed by looking at too wide a time interval. Other countries, such as the Netherlands and the United Kingdom, manufactured their own swine-flu vaccine, but found no elevation in the rate of GBS.^{10,36,38} The health of

residents of Olmsted County, Minnesota, home of the Mayo Clinic, is more intensively scrutinized than other areas of the country. In that setting, 40,000 people were vaccinated, but only one neurologic case of questionable diagnosis was identified.^{36,38} In Europe and Olmstead County, too few people may have been studied to evaluate the association adequately.

With the luxury of more time, additional and more detailed analyses were performed. Published analyses found that swine-flu-vaccinated people were 4 to 7.6 times as likely to develop GBS in the 6 to 8 weeks after vaccination as unvaccinated people.^{26-27,31,37-38,40-42} About 532 people had been vaccinated shortly before the onset of their GBS symptoms. Of these, 211 to 246 cases could be attributed to the vaccine over a 6-week period. The difference between 532 and 211 or 246 consists of the people who would have contracted GBS regardless of influenza vaccination. Which of the 532 people contracted GBS due to the vaccine and which would have contracted GBS anyway cannot be known. The attributable risk of vaccine-related GBS in adults ranged from 5 to 12 cases per million vaccinations.

In the end, most scientists who have studied the data conclude that the 1976 influenza vaccine and GBS were linked in a cause-and-effect manner. Most also conclude that had an influenza epidemic materialized, this level of Guillain-Barré syndrome may well have been considered acceptable, in exchange for a lower death rate from influenza. But the elevated rate of GBS was not acceptable when the threatened pandemic did not materialize. The swine-flu vaccination program was abruptly terminated in mid-December 1976.

The 1976 swine-flu crisis provides an interesting case-study in decision-making and public policy.^{26-27,31,37} Independent analyses have

suggested that, confronted with similar circumstances, public policy makers would make largely the same decisions again, as the next HEW Secretary acknowledged during the Carter administration.^{27,31} Analysis of the 1976 policy decision makes an excellent subject for students of government, management, scientific communication, and health policy.

Guillain-Barré syndrome in association with influenza vaccine in 1976 offers an interesting opportunity to illustrate the differences among relative risks, risk differences, and attributable risk. A newspaper headline could truthfully trumpet that the risk of GBS in 1976 was seven times higher among vaccinated people, compared with the baseline rate in unvaccinated people. That is the relative risk. It is an assessment on a relative or multiplicative scale.

The other way of assessing the risk is on an absolute or additive scale. If 48 million people were vaccinated in 1976 and 300 cases of GBS resulted from those vaccinations, then the vaccine did not cause GBS in 47,999,700 vaccinated people. This is a risk difference.

The attributable risk was one case of GBS for every 110,000 recipients of the 1976 influenza vaccine. Is that a lot? Is it too much? Society's answer, as well as a vaccine recipient's answer, depends on the likelihood and severity of the disease being avoided. Again, in the absence of the morbidity and mortality due to infection, the 1976 vaccine's risks outweighed its benefits. This judgment is applied in retrospect. The situation easily could have been reversed under other circumstances.

OTHER INFLUENZA VACCINES

An active surveillance system for GBS was initiated in 1978 and data were collected for 3 years, but a statistically significant excess risk of contracting GBS after influenza vacci-

nation was not found.⁴³⁻⁴⁴ For a recipient of the 1978/79 influenza vaccine formulation, the relative risk was 1.4; for the 1979/80 and 1988/81 formulations, the relative risk was 0.6 to 1.4. These values were not statistically significantly elevated above the background risk of GBS in unvaccinated people.

Next, surveillance studies of mass influenza vaccination programs in the US Army were reported for the interval from 1980 to 1989. This analysis found no elevated incidence of hospital admission with a diagnosis of GBS in November, compared with other calendar months.⁴⁵

For the 1990/91 influenza season, CDC scientists found a slightly elevated rate of GBS among vaccinated people 18 to 64 years of age. But the rate among people 65 years or older was not elevated.^{7,46}

The number of GBS cases reported to the Vaccine Adverse Event Reporting System (VAERS) doubled from 37 reports for the 1992/93 influenza vaccination season to 74 reports for the 1993/94 influenza vaccination season. Based on this, CDC scientists coordinated a cohort study in four states.⁷ Within 6 weeks after influenza vaccination, vaccinated people had a GBS incidence rate 2.4 times higher than unvaccinated people (95% CI: 1.5 to 3.8) during those years. Adjusting for the effects of age group, season, and gender the relative risk was 1.7, still statistically significantly elevated (95% CI: 1.0 to 2.8).

In this study, the background incidence of GBS among unvaccinated adults was 0.87 cases per million people per 6-week period.⁷ Given a relative risk of 1.7, the authors calculated that the risk of Guillain-Barré syndrome attributable to the 1992/92 and 1993/94 influenza vaccines was 0.61 case per 1 million vaccinations. The authors' adjustments for other aspects of the study design raise the

attributable risk to 1.1 cases per million influenza vaccinations during 1992/93 and 1993/94.

Similarly, a short publication from the United Kingdom reported an elevated rate of GBS, primarily related to influenza vaccine in 1992 to 1994.²¹ This finding was not statistically significant, perhaps due to the small sample size of a study.

GBS AND OTHER VACCINES

Case reports of Guillain-Barré syndrome after administration of several other vaccines have been published. For most vaccines, the incidence of cases appeared to be no higher than the background rate of GBS incidence expected in an unvaccinated population. This includes vaccines against anthrax,⁴⁷ *Haemophilus influenzae* type b,^{19,23} measles,^{3,21-22} rabies,²³ rubella,²¹ or tetanus-diphtheria.¹⁸

Postlicensure spontaneous reports for hepatitis B vaccine identified 41 cases of neuromuscular disorders (including nine GBS cases) during an interval when 850,000 people received the vaccine.⁴⁸ The authors found that GBS was reported significantly more often than expected in some analyses. But they concluded that no conclusive epidemiologic association was found, because the reports were not clinically confirmed and for other methodologic reasons.

An elevated incidence of GBS was reported after a national oral poliovirus vaccination campaign in Finland.^{3,49} This finding has not been replicated in any other study and may be confounded by a coincidental exposure to wild-type poliovirus or an influenza epidemic.

Two exceptional patients have been identified who developed demyelinating polyneuropathy or polyradiculoneuropathy after each of several repeated doses of tetanus toxoid.^{19,23,50} A population-based study of vaccines containing tetanus toxoid

found no increased risk of GBS above baseline for adults and children in the United States.⁶

Reviewing the world's literature, a committee of the Institute of Medicine (IOM) found there to be insufficient evidence to accept or reject a causal relationship between GBS and *Haemophilus influenzae* type b, hepatitis B, measles, or inactivated poliovirus vaccines.^{19,51} The IOM committee considered the evidence to favor acceptance of a causal relationship between GBS and tetanus toxoid (based on the two rechallenge-positive patients) and oral poliovirus vaccine (based on the Finnish data). The IOM committee did not categorize any vaccine as having an established cause-and-effect relationship with GBS.

Guillain-Barré syndrome is not mentioned in the Vaccine Injury Table (VIT) for any covered vaccine.^{16,39} Under the no-fault provisions of the Vaccine Injury Compensation Program (VICP), inclusion in the VIT is presumptive evidence of a vaccine's causal relationship to an adverse event. Influenza vaccine is not covered under the VICP, for which the Vaccine Injury Table is maintained.

Investigational vaccines to prevent *Campylobacter* infections are currently in human clinical trials. With *Campylobacter* infection implicated as one of the major causes of Guillain-Barré syndrome, any *Campylobacter* vaccine will undergo extra scrutiny to assess that vaccine's propensity to induce GBS itself.⁵²⁻⁵³

IMPLICATIONS FOR PHARMACISTS

Some members of the public have a vague understanding that something went wrong with the 1976 swine influenza vaccination program, causing side effects among vaccine recipients. A larger number believe that influenza vaccine can

cause serious side effects, without understanding the historical details. Far fewer people probably know that the nation's best scientists found that the side effects amounted to fewer than 300 excess cases of Guillain-Barré syndrome among 48 million vaccine recipients in 1976, with most of those 300 people eventually recovering.

Influenza vaccine was recognized as one of the minor causes of GBS in 1976 and again in 1992-94, but not in other years. The risk of GBS in vaccine recipients increased by about one case per 100,000 vaccinations above the expected background rate in 1976 or about one case per million vaccinations in 1992-94. This is called the "attributable risk," the amount of disease caused by the vaccine above the baseline risk.

From both the societal and individual perspectives, the risk of GBS after a flu shot pales in comparison to the risk of serious adverse events if infected with the influenza virus: 60 to 70 cases of GBS vs. 20,000 deaths from influenza.⁷ Keeping things on the same scale, people over 65 years of age can choose from a risk of 1 case of GBS per million people or 10,000 cases of hospitalization and 1500 deaths due to influenza among 1 million people.⁵

Should people who have recovered from Guillain-Barré syndrome receive a flu shot in subsequent years? One rule-of-thumb is to wait a year after the neurologic illness subsides, and then consider the value of the vaccine to the individual person.^{5,10} Increased risk of a second adverse episode may occur with GBS, but not necessarily with chronic inflammatory demyelinating polyneuropathy (CIDP). On the other hand, it may be appropriate to avoid immunologic stimuli in people with CIDP unless the probability and consequences of infection are substan-

tial. Helping the patient reach a carefully considered decision, based on a personal risk-benefit ratio, is probably the most prudent course.

What about vaccines other than influenza? The Advisory Committee on Immunization Practices (ACIP) noted that administration of tetanus toxoid to a person who developed GBS after a previous dose of tetanus toxoid may be justified for people whose primary immunization schedules are incomplete (ie, they received fewer than three doses), but that routine booster immunization probably is not indicated for adults who received three or more doses.⁵¹ The ACIP did not comment about vaccination decisions in people who contract tetanus-prone wounds, in whom the personal risk-benefit ratio may be more likely to favor vaccination. The number of people for whom these decision guidelines apply is extremely small.

If the theory of molecular mimicry is valid, then the vaccine antigen and the corresponding microbe might both be able to trigger GBS in a susceptible person.¹⁰ In other words, it is possible that people who develop GBS after vaccination might also have developed GBS after natural exposure to the corresponding microbe, which might tend to lessen the degree of philosophical "blame" attributable to vaccination. As Ropper and Victor note: "Even if one is destined to contract the Guillain-Barré syndrome, however, it seems sensible to avoid or ameliorate the affliction of influenza."

Numerous other authors join in affirming the merit of vaccination, while recognizing the low risk of GBS.^{5,11,19,23,48,54} For reasons arising in human nature, some people avoid vaccines in order to avoid adverse events after vaccination, even when their personal risk of death or disability due to infection is greater.^{16,55-56} Persuading them to be vaccinated

remains an important clinical responsibility.

More information is available at the CDC website www.cdc.gov/nip/vacsafe/vaccinesafety/hottopics/gbs.htm, which also notes that there is no information to suggest that receiving multiple vaccines simultaneously increases the risk of GBS.¹¹

Resources for patients with GBS and their families are available from the Guillain-Barré Syndrome Foundation International: www.webmast.com/gbs/, gbint@ix.netcom.com, 610-667-0131.⁵

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