Workshop Summary and Recommendations Regarding the Development of Guillain-Barré Syndrome following Campylobacter Infection

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On the basis of the work presented and discussed at the workshop, a number of key points can be summarized, and from these, a series of recommendations can be made. These points are divided into the following categories: diagnostic aspects, epidemiology and surveillance, microbiology and pathogenesis studies, and information management.

Diagnostic Aspects

Although there is substantial immunologic evidence linking the development of Guillain-Barré syndrome (GBS) with a preceding infection with Campylobacter jejuni, microbiologic evidence is less complete. This is likely due to the brief period of excretion of C. jejuni in stools (median, 16 days) after an acute infection. Symptoms of GBS typically occur 10 days to 3 weeks after C. jejuni infection, when many patients have already cleared their stools. As such, studies of C. jejuni serotypes associated with GBS are limited to a small number of strains. If diarrheal cases were more frequently screened for C. jejuni, and if more and better typing reagents were available, the epidemiologic link between preceding infection with particular strains and the development of GBS would become better established. In addition, antibiotic resistance is emerging among Campylobacter species in both developing and developed countries. This could lead to difficulties in the treatment of human disease, and resistance enhances the need for protective vaccination of animals raised for food or of humans (or both).

The following recommendations can be made:

- Diagnostic tests sensitive for detection of a variety of Campylobacter species are needed. It is likely that a large number of Campylobacter infections go unrecognized.
- Standardized microbiologic laboratory procedures are needed to insure isolation of Campylobacter strains associated with GBS. In particular, C. jejuni and Campylobacter upsaliensis should be looked for, but other species also may play a role. The concept of viable but nonculturable Campylobacter should be examined.

Epidemiology and Surveillance

The medical costs associated with Campylobacter-induced GBS have been estimated by the US Department of Agriculture to be $57–$420 million per year in the United States. Total costs, which include days of lost productivity, are estimated to be between $247 million and $1.8 billion per year. Clearly, Campylobacter-induced GBS is a disease with a significant economic impact in this country.

Although GBS can probably result following a number of bacterial and viral infections, infection with C. jejuni is the most often recognized preceding event. However, the epidemiology of infection with the campylobacters associated with GBS is not well understood. In particular, the specific reservoirs for GBS-related strains have not been identified. Although there is a marked seasonal pattern of C. jejuni infection (summer) in some countries, there is no clear seasonal variation in the incidence of GBS. An exception has been observed in northern China, where outbreaks of GBS occur among children every summer and fall.

With the inclusion of C. jejuni and Campylobacter coli in the Centers for Disease Control and Prevention’s (CDC) FoodNet surveillance efforts, an opportunity exists to delineate the connection between prior infection with Campylobacter species and the development of GBS. It is important that strains isolated as a result of such surveillance efforts be archived, and that an analysis of the bacterial antigens related to GBS be conducted. The following recommendations are made:

- GBS (or more broadly defined acute flaccid paralysis cases) should be reportable by state health departments to the CDC (current estimates of the number of US GBS cases are 1 to 2/100,000 population per year). When combined with increased surveillance for Campylobacter as a part of FoodNet activities, a much better view of the epidemiology of the organism and of its association with GBS should become apparent.
A follow-up should be done on cases of Campylobacter infection identified through FoodNet to determine the frequency of GBS development in those cases.

There is need for better standardized case definitions of GBS-related illnesses, including acute motor axonal neuropathy, acute motor-sensory axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Miller Fisher syndrome. The definitions should be based on clinical, electrophysiologic, immunologic, and molecular data.

Surveillance for GBS in targeted populations is needed, particularly in China, where an increase in GBS is seen in the summer months and is associated with rural residence, and in Latin America, where cases of acute flaccid paralysis have not declined despite the tremendous decrease in polio cases. Surveillance efforts are underway in China but not in Latin America.

Studies should be done to try to understand the variations noted in seasonality, or lack thereof, of GBS and of the basis for the differences noted in the serotypes of C. jejuni that have been associated with the onset of GBS in different studies and in different regions of the world.

Microbiology and Pathogenesis Studies

Little is known about the pathogenesis of Campylobacter infection; it is an understudied enteric pathogen. As with other enteric pathogens, however, it is generally believed that Campylobacter colonization factors, including fimbriae and flagella, contribute to pathogenesis. The identification of immunodominant and protective antigens awaits discovery, as do the factors contributing to diarrheal symptoms. Nevertheless, as reported at the workshop, the Department of Defense has developed and is testing a formalin-inactivated, whole cell Campylobacter jejuni vaccine candidate, which is designated strain 81-176 and is a Lior type 5 (heat labile antigen–based typing system) and O type 23/36. This is the first generation of C. jejuni vaccines, and the results of clinical trials may provide insights into the important aspects of protective immunity.

The association of GBS with particular serotypes of C. jejuni implies that lipopolysaccharide (LPS) is an important contributor to the pathology of GBS. The structures of LPS are complex and unique in C. jejuni and differ markedly from those of the Enterobacteriaceae. These unique structures are evident in O side chains and core oligosaccharides. Often, portions of these structures resemble mammalian tissue gangliosides (molecular mimicry) and suggest a mechanism of immune damage to nerve fibers. There is an association of GBS and infection with C. jejuni of the O serotypes 19 and 41. The strongest association has been with O19. For example, in the United States, the risk of developing GBS following C. jejuni infection has been estimated as 1 in 1058; however the risk increases to 1 in 158 following infection with serotype O19.

The development of GBS is rare in children <2 years of age despite their susceptibility to Campylobacter infection. This may indicate that particular maturation of the immune system or neural antigens or receptors are needed for GBS to manifest itself.

The mechanism of immune-mediated nerve damage is poorly understood. The nature of the initial antigen-antibody reaction(s) that leads to damaging immune reactions, which may involve cell-mediated immunity, complement fixation, cytokine production, lymphocyte and macrophage infiltration, and breach of the blood-nerve barrier, needs to be better defined. Why gangliosides on nerves are particularly targeted or more sensitive than the same molecules found on other tissues is not known. The following recommendations are made:

- A more complete LPS typing system that will include more of the strains now classified as ‘‘untypeable’’ is needed. LPS typing should be complemented with a molecular typing system based on DNA restriction fragment length polymorphism, rRNA gene polymorphism (ribotyping), or by polymorphism of other genes.
- Continuing effort is warranted to determine the LPS structures associated with the development of GBS. Identification of specific epitopes would be helpful. Since sialylated polysaccharides are suspect, a probe to detect the presence of sialyl transferase may be helpful in identifying GBS-associated strains.
- There is a need for standardized reagents, particularly monoclonal antibodies, that can be used to identify bacterial epitopes and that can be tested for their ability to react with different neural ‘‘targets.’’ Well-characterized reagents also could be distributed to researchers from a National Institute of Allergy and Infectious Diseases (NIAID) repository.
- There should be a Campylobacter strain bank established in which bacterial strains isolated from patients who develop GBS (or variants) can be deposited. These strains should be available to researchers in the field. NIAID could play a role in the storage and distribution of strains from the proposed repository.
- Studies should be done on HLA typing of clinically well-defined cases of GBS and the related neurologic conditions and of matched controls to determine whether there is a genetic component to host susceptibility to these diseases.
- An animal model for Campylobacter enteritis with ensuing GBS is urgently needed. A recently described ferret model for Campylobacter-induced enteritis may be useful. Mouse, rat, primate, chicken, and rabbit models for immune neuropathies are being examined and show promise, but they need to be developed further, perhaps by examining specific pathogen-free animals. The development of relevant transgenic mice should also be considered.
- The mechanism of intravenous immunoglobulin amelioration of GBS symptoms is not known. More clinical research is needed, with the aim of developing improved therapies.
Information Management

After the workshop, it was evident that a forum such as this, which provided an opportunity for communication between scientists from diverse disciplines, would be helpful. The groups concerned with *C. jejuni* (mostly microbiologists) and with GBS (mostly neurologists) normally have little chance for interaction with each other at their respective national scientific meetings. In an effort to increase the dialog between the groups and to make more rapid progress toward our understanding of *Campylobacter* infections and the development of GBS, the following recommendations are made:

- Periodic international conferences attended by the diverse group of scientists and physicians studying GBS and its preceding infectious etiologies are needed for sharing and disseminating information as well as providing a forum for the generation of new ideas and hypotheses.
- A mechanism to share preliminary information among scientists studying *Campylobacter* or associated GBS (or both) would be helpful in keeping this worldwide research community in contact. The ability to send such information to an Internet address, for example, that would be widely accessible was discussed. Posting of interesting new observations, information, or questions would facilitate research efforts by all involved. Information on DNA sequences, availability of new strains or reagents, new techniques, reservoirs of infection, structures of LPS or proteins, new typing methods, antibiotic resistance patterns, frequency of isolation of particular serotypes associated with GBS, epidemiology, and more could be included in such an exchange.