

Intravenous Immunoglobulin



Consensus Statement

NIH Consensus Development Conference
May 21-23, 1990

Volume 8, Number 5

NIH Consensus Development Conferences are convened to evaluate available scientific information and resolve safety and efficacy issues related to a biomedical technology. The resultant NIH Consensus Statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public.

NIH Consensus Statements are prepared by a nonadvocate, non-federal panel of experts, based on: (1) presentations by investigators working in areas relevant to the consensus question during a 1-1/2 day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Copies of this statement and bibliographies prepared by the National Library of Medicine are available from the Office of Medical Applications of Research, National Institutes of Health, Building 1, Room 260, Bethesda, MD 20892.

For making bibliographic reference to the consensus statement from this conference, it is suggested that the following format be used, with or without source abbreviations, but without authorship attribution:

Intravenous Immuno globulin: Prevention and Treatment of Disease
NIH Consensus Dev Cent Consensus Statement 1990 May 21-23; 8(5).



Consensus Statement

NIH Consensus Development Conference
May 21-23, 1990

Volume 8, Number 5

ABSTRACT

The National Institutes of Health Consensus Development Conference on Intravenous Immunoglobulin: Prevention and Treatment of Disease brought together biomedical scientists in immunology, infectious disease, and pediatrics, as well as health care providers, patients and their families, and the public to address the safe and effective uses of intravenous immunoglobulin (IVIG) preparations. Following 11/2 days of presentations by experts and discussion by the audience, a consensus panel weighed the evidence and prepared a consensus statement.

Among their findings, the panel concluded that all currently available IVIG preparations are safe and effective in treating the conditions for which they have been licensed; however, their efficacy in treating other conditions remains to be established. Effective regimens have been developed for primary immunodeficiencies and secondary immunodeficiencies, idiopathic thrombocytopenic purpura, and Kawasaki syndrome. However, optimal dosages and treatment schedules still need to be established for patients who may benefit from IVIG therapy.

The panel also concluded that the risks of IVIG therapy are minimal, and adverse events, which are rare, can often be alleviated by reducing the rate or volume of infusion. Future research is also important, particularly studies to discern the mechanisms of action of IVIG, to compare the effectiveness of IVIG preparations, and to determine their long-term effectiveness and their effect on quality of life for patients receiving IVIG.

The full text of the consensus panel's statement follows.

INTRODUCTION

Immunoglobulins are proteins produced by cells of the B lymphocyte lineage that are the major effector molecules of the humoral immune system. Immunoglobulin molecules are antibodies that react with specific antigens, although in many circumstances, the specificity of a given immunoglobulin antibody is unknown. Immunoglobulin preparations from human blood were first used in clinical medicine in 1952 to treat immune deficiency conditions. At that time, the only available preparations required intramuscular administration. In the past decade, several immunoglobulin preparations for intravenous administration have become available. Although initially used for immune deficiency states, intravenous immunoglobulin (IVIG) has also been utilized as a prophylactic and therapeutic reagent in a variety of other conditions. The use of IVIG has undergone tremendous growth in the past several years. This rapid growth in use is the result of improvements in the preparations of IVIG, which have led to reduced morbidity and reports of its benefits in a number of unexpected circumstances. IVIG has been used in such diverse diseases as primary immunodeficiencies, pediatric AIDS, infections in low birth weight infants, bone marrow transplantation, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki syndrome, and demyelinating polyneuropathies. However, important questions regarding its use still remain. To assess the usefulness of IVIG in diseases where substantive data existed, the National Institute of Allergy and Infectious Diseases and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference on Intravenous Immunoglobulin: Prevention and Treatment of Disease on May 21-23, 1990. Cosponsors were the National Cancer Institute, National Heart, Lung, and Blood Institute, National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke, and the Food and Drug Administration.

In the various disease states in which IVIG has been used, the following questions were considered:

- What are the data to support the efficacy of IVIG in these circumstances?
- What are the appropriate dosage and treatment schedules?
- Are all IVIG preparations equally efficacious?
- What are the risks involved in the use of IVIG?
- What are the mechanisms of action?
- What are the directions for future research?

After a day and a half of presentations by experts in the field and discussion by the audience, a consensus panel drawn from specialists and generalists from the medical profession and related scientific disciplines, clinical investigators, and public representatives considered the evidence and came to the conclusions on the following pages.

WHAT ARE THE DATA TO SUPPORT THE EFFICACY OF IVIG IN THESE CIRCUMSTANCES?

Primary Immunodeficiencies

The beneficial effects of intramuscular (IM) injection of immune globulin (IG) in the prophylactic treatment of patients with primary immunodeficiency syndromes have been well established. Early studies based on small sample sizes have indicated that almost any desired blood level of IgG can be obtained by use of intravenous immunoglobulin and that infection rates are reduced by use of IVIG as compared with IM IG. IVIG has been shown to ameliorate chronic sinopulmonary disease that developed in patients on long-term IM IG. There is a suggestion that chronic enterovirus meningoencephalitis in patients with X-linked agammaglobulinemia may be less frequent in those receiving prophylactic IVIG as compared with historical data in which IM IG was used. Hence, IVIG has become the current standard in clinical practice for replacement therapy of patients with primary immunodeficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency and immunoglobulin subclass deficiency in which deficiencies of antibody production to common pathogens can be demonstrated). Studies have shown that maintenance of a trough level of 500 mg/dL is beneficial. Dose ranges of 200-800 mg/kg/mo have been shown to be effective, but dose or frequency of infusions must be tailored to the individual patient, because half life of infused IVIG varies widely.

Pediatric AIDS

Because AIDS is an acquired immunodeficiency, it is reasonable to consider the use of IVIG therapy in pediatric patients with HIV infection, given the success of IVIG in primary immunodeficiencies. To date, small, uncontrolled studies have suggested the efficacy of IVIG in pediatric AIDS by decreasing the morbidity from common bacterial pathogens, as well as measles, but no controlled studies have been completed. Currently, the National Institutes of Health (NIH) is sponsoring two large, controlled trials of IVIG with and without zidovudine (AZT) in HIV-infected children. A definitive assessment of the efficacy of IVIG in pediatric HIV infection awaits the results of these trials.

Infections in Low Birth Weight Infants

a. Prevention of infection in low birth weight infants

Premature infants have insufficient placental transfer of maternal IgG and have been demonstrated to have low levels of serum IgG. Hence, it is reasonable to consider IVIG prophylaxis in premature infants. Some pilot studies indicated a lower rate of severe infection in IVIG-treated low birth weight infants compared with placebo-treated patients. In a recently completed randomized, double-blind, placebo-controlled trial involving a large number of infants with birth weights of 500-1,500 grams, it was noted that mortality was not significantly reduced among IVIG recipients. However, the number of infections was significantly reduced among IVIG recipients. It should be noted that there was some evidence that beneficial effect may vary by birth weight category, and significantly more placebo patients were small for gestational age. Information about long-term results (greater than 56 days) is not available from this trial. Moreover, preliminary analysis of other trials indicates no significant difference in infection rates between IVIG recipients and placebo recipients. However, differences in study design make direct comparison of the various trials difficult. Further information will become available as a result of the ongoing trial sponsored by the National Institute of Child Health and Human Development Neonatal Research Network. At this time, IVIG cannot be recommended as standard prophylaxis of low birth weight infants.

b. Treatment of presumed neonatal infection

To date, small trials using primarily historical controls have yielded mixed results. Questions remain concerning dose, schedule, and patient selection. Variability in preparations and lots creates a number of difficulties in predicting results of treatment for specific organisms. There is a potential role for directed preparations containing specific antibodies. Furthermore, studies in neonatal animals have shown that in some situations survival is less with high concentrations of IVIG plus antibiotic compared with antibiotic alone. The routine use of IVIG as adjuvant therapy of neonatal infections cannot be recommended at the present time.

Bone Marrow Transplantation

In a large study of bone marrow transplant recipients, reduced rates of septicemia and local infection were noted for IVIG-treated patients (500 mg/kg weekly) compared with untreated controls. Several studies have shown a decreased rate of acute graft versus host disease (GVHD) in patients receiving IVIG, 500 milligrams to 1 gram per kilogram weekly. Results of limited trials suggest that in pediatric bone marrow recipients, reduction in infection and death but not GVHD has been associated with IVIG administration.

It has been noted that IVIG decreases the incidence of interstitial (presumably CMV) pneumonia but is ineffective in preventing CMV infections. IVIG plus ganciclovir is beneficial in treating CMV pneumonia in patients who are not ventilator dependent.

Chronic Lymphocytic Leukemia

A study in 10 centers in which 57 patients with CLL were followed for 1 year of observation has been completed. The incidence of major and moderate bacterial infections was significantly reduced in hypogammaglobulinemic CLL patients who received IVIG. The number of trivial infections was unchanged by intravenous immunoglobulin. Maintenance of serum IgG levels > 640 mg/dL tended to correlate with fewer infections, especially serious bacterial infections. The data support the conclusion that IVIG may be useful to prevent serious infections in patients with CLL with hypogammaglobulinemia.

Idiopathic Thrombocytopenic Purpura

Among children with ITP, the use of IVIG has been documented to increase platelet counts. This treatment is utilized in the rare pediatric patient with potentially life-threatening bleeding (e.g., 400 mg/kg/d x2-5 or 1 g/kg/d x1 or 2). A number of therapeutic options are available for managing the child with newly diagnosed ITP who does not have serious hemorrhage: IVIG, corticosteroids, or close observation without therapy. IVIG has been used in chronic ITP to postpone the requirement for a splenectomy. There is no firm evidence of curative effects in either acute or chronic ITP. Responses appear to be similar with different manufacturers' products licensed for this purpose.

In adult patients with ITP IVIG, at the doses indicated above, has also been used for the rapid correction of life-threatening thrombocytopenia, with or without corticosteroids. Administration every 10 to 21 days is usually required to maintain adequate platelet counts. Other indications include administration to steroid-refractory patients preoperatively. In addition, IVIG may be employed at the same dosage in patients who cannot use corticosteroids and in patients with immunodeficiency including those with HIV-associated thrombocytopenia. Although IVIG administration before scheduled splenectomy is effective, cost/benefit relationships are unclear because of the low incidence of complications during this procedure, even with extremely low platelet counts.

Kawasaki Syndrome

Studies of IVIG in Kawasaki syndrome using 400 mg/kg daily for 4 days indicate a prompt anti-inflammatory response in the acute phase and a significant decrease in the formation of coronary aneurysms compared with low/moderate aspirin administration regimens. More recently, a dosage schedule of 2 g/kg as a single administration has been shown to be at least as effective as the four-dose schedule. Complications of the larger single-dose administration were few. A smaller study using 1 g/kg as a single dose also seemed to suggest similar efficacy to the four-dose regimen.

IVIG and aspirin administration has become a standard treatment for Kawasaki syndrome. The panel agrees that on the basis of available studies, IVIG administered as a single dose of 2 g/kg is effective therapy for patients who fulfill the diagnostic criteria for Kawasaki syndrome. Treatment of patients recognized after the tenth day of the disease has not been studied systematically.

The advantages of treating patients with Kawasaki syndrome with IVIG as early as possible must be balanced against the probability that children with other inflammatory diseases will also be treated inadvertently. There is no evidence that this latter group of children will be benefitted.

Chronic Inflammatory Demyelinating Polyneuropathies

Several small studies have shown positive responses to IVIG in the majority of treated patients. Treatment needs to be periodically repeated to prevent relapse. When considered in comparison with customary treatments, IVIG may be easier to use and to be associated with fewer complications than repeated therapeutic plasma exchange and long-term glucocorticoids, respectively.

Guillain-Barré Syndrome

In a preliminary analysis of a large, randomized multicenter trial of IVIG compared with therapeutic plasma exchange, there is an indication of improved functional recovery for patients receiving IVIG. Definitive conclusions regarding the efficacy of IVIG in Guillain-Barré syndrome will need to await the final analysis of this study and other confirmatory studies.

Intractable Seizure Disorders

A number of uncontrolled studies and anecdotal reports have indicated benefit of IVIG administration in children with intractable seizures. The absence of randomized, double-blind studies does not allow specific recommendations to be made regarding such treatment. The panel emphasizes the need for controlled human studies in this area.

WHAT ARE THE APPROPRIATE DOSAGE AND TREATMENT SCHEDULES?

Effective doses of IVIG have been demonstrated in primary immunodeficiencies, ITP, and Kawasaki syndrome. Whether alterations in amount, frequency, or duration of administration will improve efficacy is not known. Specific details of dosage regimens are discussed in detail in the response to the previous question.

WHAT ARE THE RISKS INVOLVED IN THE USE OF IVIG?

The incidence of adverse events associated with the administration of IVIG is reported by the manufacturers to be in the range of 1 to 15 percent, usually less than 5 percent. Most of these reactions are mild and self-limited. Severe reactions occur very infrequently and usually do not contraindicate further IVIG therapy. Neither HIV nor hepatitis B infection has been transmitted to recipients of products currently licensed in the U.S. The various IVIGs are manufactured from large numbers of donors whose plasma has been tested and found to be negative for hepatitis B surface antigen and HIV antibody. A number of adverse events have been recognized. These include the following:

- pyrogenic reactions marked by high fever and systemic symptoms;
- minor systemic reactions with headache, myalgia, fever, chills, lightheadedness, nausea and/or vomiting;
- vasomotor and/or cardiovascular manifestations, marked by changes in blood pressure and tachycardia. These may be related to occasional reports of shortness of breath and chest tightness; and
- hypersensitivity and anaphylactic reactions.

Risk factors

Patients with primary antibody deficiency syndromes may be at increased risk for reactions. Anaphylactic reactions induced by anti-IgA can occur in individuals who have a total absence of circulating IgA and antibodies to IgA. These are extremely rare in panhypogammaglobulinemic individuals and potentially more frequent in patients with subclass deficiencies. Frequency of reactions may be correlated with volume and/or rate of infusion. Seriously ill patients with compromised cardiac function may be at increased risk of vasomotor or cardiac complications manifested by elevated blood pressure and/or cardiac failure.

Prevention and management

Adverse reactions often can be alleviated by reducing the rate or the volume of infusion. For patients with repeated severe reactions unresponsive to these measures, hydrocortisone, 1-2 mg/kg, intravenously, can be given 30 minutes before IVIG infusion. In those rare instances when reactions related to anti-IgA antibodies have occurred, use of IgA-depleted preparations will reduce the likelihood of further reactions. Avoidance of anaphylactic reactions may require the use of material completely devoid of IgA. Because the combination of the absence of IgA and the presence of anti-IgA antibodies is infrequent and reactions are rare, screening for gA-deficiency is not routinely recommended for potential recipients of IVIG.

As with any biologic or pharmacological product, the potential for new or previously unrecognized adverse events should be anticipated. With IVIG these include the following:

- transmission of blood-borne pathogens such as the newly identified hepatitis C virus.
- immunosuppression—for example, administration of IVIG has been associated with transient effects on immune response that do not appear to have clinical significance. However, with increased dosage of IVIG or new products for the treatment of specific infections, the possibility of adverse outcomes from immunosuppression should be considered.

After nearly a decade of experience, the safety of IVIG has been established. For any potential recipient, the small risk of adverse reactions must be weighed against the likelihood of significant benefit. For those patients who require repeated courses of IVIG such as those with a primary humoral immunodeficiency home infusion by the patient or a family member after adequate training has been effectively utilized and is cost effective.

WHAT ARE THE MECHANISMS OF ACTION?

At the present time, we assume that all effects of IVIG are related to the quantity and quality of IgO in the product. Various mechanisms may be important in the different therapeutic uses of IVIG, including (1) replacement therapy for primary and secondary immunodeficiencies, (2) specific passive immunotherapy, and (3) management of specific inflammatory and/or immunologic disorders.

Efficacy of IVIG infusions in primary immunodeficiency diseases is probably related to replacement of antibodies to environmental pathogens. Despite variations in the titer of specific antibodies, all licensed preparations are apparently efficacious in the treatment of these diseases. In addition, pooled antibodies may have physiologic activities other than pathogen recognition that may contribute to the beneficial effects of replacement therapy.

The effectiveness and the mechanism of action of IVIG in secondary immunodeficiencies such as indolent lymphomas is presumed to be similar to that in primary immunodeficiencies. In these diseases, a reasonable correlation between rates of systemic infection and concentrations of serum immunoglobulins supports this presumption. The benefit of prophylactic replacement of IgG in very low birth weight infants is not established. Attempts to replace antibodies may be rational in this situation. However, it is possible that administration of immunoglobulin from large donor pools could adversely affect the development of the infant's immune system, as there is substantial evidence in mice that anti-idiotypic antibodies may profoundly affect immune responsiveness. For conditions such as bone marrow transplantation and pediatric HIV infection, the complexity of immunologic abnormalities will make determination of mechanisms extremely difficult. IVIG is also being used for specific passive immunotherapy. In these instances, the titers of specific antibodies are of paramount importance. Moreover, consideration must be given to the possibility that large amounts of apparently irrelevant antibodies may block receptors on the surface of phagocytes and thus interfere with effective disposal of microbial pathogens.

In the treatment of ITP there may be multiple mechanisms of IVIG action. The platelet count increase occurring within several days of the initiation of therapy appears to be caused by diminished sequestration of autoantibody-sensitized platelets. This may be caused by interference with Fc receptors on the cells of the monocyte-macrophage system. A similar mechanism may operate in other autoimmune and alloimmune cytopenias. Sustained responses to IVIG may represent spontaneous remissions or may be related to an immunosuppressive effect of IVIG.

There are several possible mechanisms by which the infusion of large concentrations of immunoglobulins may have an immunosuppressive effect. The presence of IgG dimers in immunoglobulin preparations, a result of pooling samples from a large number of individual donors, likely represents the occurrence of idiotype-anti-idiotype complexes. There is evidence that anti-idiotype antibodies in IVIG react with epitopes on the autoantibodies in patients with thyroiditis or spontaneous factor VIII inhibitors. Alterations of T-cell subsets and of in vitro B cell function, both spontaneous and mitogen driven, have been reported in patients treated with IVIG. It is unknown if these observations are related to a mechanism of therapeutic effect.

A striking anti-inflammatory effect of IVIG has been observed. This phenomenon is most apparent in Kawasaki syndrome, where reductions in fever, neutrophil counts, and acute phase reactants regularly occur within a day or so of initiation of treatment. This effect is not unique to Kawasaki syndrome but has been seen in other inflammatory disorders. The mechanisms are unknown but may be distinct from those that mediate immunosuppression. One possible mechanism demonstrated in experimental animals is the inhibition of complement-dependent tissue damage caused by binding of IVIG to active C3 fragments.

There is a great need for an understanding of the mechanisms of IVIG in the various conditions in which it is used. A variety of mechanisms have been suggested but none proven. Mechanistic hypotheses such as the provision of anti-idiotype antibodies, Fc receptor blockade, and alteration of reticuloendothelial cell system function should be rigorously tested. Utilization of appropriate animal models would provide an efficient way to test these hypotheses.

ARE ALL IVIG PREPARATIONS EQUALLY EFFICACIOUS?

Seven IVIG preparations have been licensed in the U.S.: all seven for use in primary immunodeficiencies, five for idiopathic thrombocytopenia, and one for chronic lymphocytic leukemia. For these disease groups, the limited comparative data available reveal no differences in efficacy among the licensed preparations. For the other uses of IVIG, there is insufficient information to choose one product over another or to know whether each has comparable activity. Given the large number of conditions for which IVIG may have potential value, the prescribing physician should be aware of the demonstrated efficacy of each IVIG preparation to treat a specific disorder. The products and their quality are under the control of commercial firms who must meet general regulatory guidelines of the Center for Biologics Evaluation and Research of the Food and Drug Administration. These include tests for sterility, pyrogenicity, purity, and safety. It is required also to measure antibody levels against polio, measles, hepatitis B, and diphtheria. At the present time, there is no requirement to identify hepatitis C virus in IVIG preparations. Epidemiologic data support the quality and safety of current products. However, guidelines and monitoring methods must be developed as information about transmission of hepatitis C virus and other infectious diseases becomes better defined. Consideration should be given to screening donors for hepatitis C. Confidence in the capacity of a given preparation to accomplish the desired end result would be enhanced if a more rigorous procedure were established for using IVIG to prevent or treat infections caused by specific microorganisms. The availability of antibody titers to a wider range of pathogens would permit a more rational basis for the choice of a specific product in situations where immunotherapy is directed to a restricted number of infectious agents. Because the factor essential for the effectiveness of IVIG in a number of disorders, such as ITP and Kawasaki syndrome, is unknown, it is not possible to predict efficacy of a given preparation of IVIG for any of these disease processes.

WHAT ARE THE DIRECTIONS FOR FUTURE RESEARCH?

The effects of IVIG in the various disease states can probably be accounted for by the presence of one or more specific antibodies. These may be directed against microbial pathogens or their toxins, common idiotypes, cellular components, receptors, or regulatory proteins. The need for massive doses of IVIG to achieve therapeutic effects suggests that many of these antibodies are present at very small concentrations in immunoglobulin pools. One of the major directions of future research therefore should be to identify and isolate these particular antibodies or prepare supplementary monoclonal antibodies so that more specific therapeutic interventions can be designed.

- There is a great need for an understanding of the mechanisms of action of IVIG in the various conditions in which it is employed. Without knowledge of specific mechanisms, progress in this area will be slow. This should be a major focus of future efforts.
- Appropriate objective outcome measures, including long-term outcome measures, should be established that can be applied in clinical trials. Cost-effectiveness and objective measures of quality of life should be included in this analysis. Without such outcome measures, results of additional clinical trials will be difficult to interpret.
- Controlled clinical trials in pediatric intractable recurrent seizures, chronic inflammatory demyelinating polyneuropathies, and Guillain-Barré' syndrome are warranted in the U.S. In addition, consideration should be given to clinical trials in areas where compelling biologic reasons or experimental data suggest potential efficacy. There is no justification for clinical trials in areas without strong biologic rationales.
- Serious neonatal infections continue to be a major problem. Development of appropriate hyperimmune preparations of IVIG should be undertaken for this purpose.

Comparative efficacy of various preparations of IVIG should be established, if possible.

- Surveillance for long-term positive and adverse effects should be carried out.

CONCLUSIONS

In answer to the question, "What are the data to support the efficacy of IVIG in various clinical circumstances?" the consensus panel concludes the following:

- IVIG is a safe and effective means of replacement therapy in patients with primary humoral immunodeficiency syndromes in which deficiencies of antibody production to common pathogens can be demonstrated. The ideal dosage of IVIG has not been established, although the monthly administration of 200-800 mg/kg appears to be adequate to maintain trough Ig levels at approximately 500 mg/dL in most patients.
- The usefulness of IVIG in pediatric AIDS has not been documented. Results are not yet available from two ongoing NIH-supported multicenter placebo-controlled double-blind trials being carried out to evaluate this issue in more detail.
- The use of IVIG in the prevention of late onset infections in preterm neonates has a rational basis. However, the data indicate that this is of no value in neonates of birth weight of more than 1,500 grams. In neonates under 1,500 grams, the results are conflicting. Thus, the currently available data do not support the routine use of IVIG in this group either. Although there may be an impact of IVIG on the rate of bacterial infections in this group and the length of hospitalization, there is no effect on mortality. The use of IVIG as adjuvant therapy in neonates with infections is not supported by the current data. Additional clinical trials, especially involving the use of hyperimmune preparations, would be useful to delineate this issue.
- In immunosuppressed bone marrow transplant recipients, IVIG is useful to treat interstitial (CMV) pneumonia, in combination with ganciclovir. IVIG may be protective against gram-negative septicemia and development of local infections in these patients. In addition, IVIG may suppress GVHD in some patient groups.
- In hypogammaglobulinemia associated with chronic lymphocytic leukemia, IVIG can decrease the number of infections significantly. Although it has no effect on mortality, there is a decrease in the number of days per year spent in a hospital or convalescing.

- The comparative efficacy of IVIG versus corticosteroids or other approaches has not been clearly delineated in either adults or children with ITP. IVIG is useful in the treatment of pediatric acute ITP where it usually increases the platelet count rapidly. In adult ITP it can also induce increases in the platelets. In adults, it is most useful in special circumstances requiring acute increases in the platelet count such as immediately before surgery.
- IVIG in conjunction with aspirin is the current standard of care for children during the first 10 days of Kawasaki syndrome to prevent the development of coronary aneurysms.
- IVIG shows some promise in the treatment of chronic inflammatory demyelinating polyneuropathies, and Guillain-Barré' syndrome, and therefore additional clinical trials are warranted.
- There is the preliminary suggestion that IVIG might be useful in certain childhood intractable seizure disorders. Therefore, clinical trials are warranted.

In response to the question, "What are the appropriate dosage and treatment schedules?" the consensus panel concludes that in most circumstances this has not been established. For primary and secondary immunodeficiencies, ITP, and Kawasaki syndrome, effective regimens have been developed, but there is no evidence about whether these schedules are optimal.

In response to the question, "Are all IVIG preparations equally efficacious?" the consensus panel concludes that the preparations are efficacious for the indications for which each has been licensed. Although it is possible that they can be used for other conditions interchangeably, the comparability of the various preparations of IVIG for these purposes has not been documented.

In response to the question, "What are the risks involved in the use of IVIG?" the consensus panel concludes that they are minimal. However, appropriate means to monitor IVIG for contamination with potential pathogens should be developed. In response to the question, "What are the mechanisms of action of IVIG?" the panel concludes that in most circumstances present hypotheses are speculative and not proven. In response to the question, "What are the directions of future research?" the panel concludes information concerning

mechanism of action is critically needed. Deriving information concerning mechanisms of action or other potential uses of IVIG from clinical experiments and trials is costly and inefficient. Without knowledge concerning anticipated objective physiologic end points, trials to establish effective therapeutic regimens are empiric and new initiatives largely exercises in serendipity.

Consensus Development Panel

Peter E. Lipsky, M.D.

Conference and Panel Chairperson; Professor, Departments of Internal Medicine and Microbiology; Director, Harold C. Simmons Arthritis Research Center University of Texas Southwestern Medical Center, Dallas, Texas

Robert J. Beall, Ph.D.

Executive Vice President for Medical Affairs
Cystic Fibrosis Foundation
Bethesda, Maryland

Diana S. Beardsley, M.D., Ph.D.

Assistant Professor of Pediatrics, Department of Pediatrics, Yale University School of Medicine
New Haven, Connecticut

James D. Cherry, M.D.

Professor, Department of Pediatrics, Division of Infectious Diseases, University of California at Los Angeles School of Medicine
Los Angeles, California

Daniel Em, M.D.

Clinical Professor of Medicine
George Washington University School of Medicine; Private Practice of Allergy, Washington Allergy Associates PC
Washington, D.C.

Patricia Ferrieri, M.D.

Professor Departments of Laboratory Medicine and Pathology and Pediatrics
University of Minnesota Medical School and Hospital
Minneapolis, Minnesota

James George, M.D.

Professor of Medicine
Department of Cell Biology
University of Miami
School of Medicine
Miami, Florida

Welton M. Gersony, M.D.

Professor of Pediatrics
Director, Division of Pediatric Cardiology, College of Physicians and Surgeons of Columbia University, Columbia Presbyterian Medical Center Baby's Hospital
New York, New York

M. Douglas Jones, Jr., M.D.

Professor of Pediatrics
Associate Professor of Obstetrics, Associate Professor of Anesthesiology/Critical Care Medicine, Department of Pediatrics, The Johns Hopkins University School of Medicine
Baltimore, Maryland

Alexander Lawton, M.D.

Professor of Pediatrics and Microbiology, Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Vanderbilt University School of Medicine
Nashville, Tennessee

Georges Peter, M.D.

Professor of Pediatrics
Brown University
Director Division of Pediatric Infectious Diseases
Rhode Island Hospital
Providence, Rhode Island

George W. Williams, Ph.D.

Chairman, Department of Biostatistics and Epidemiology
Cleveland Clinic Foundation
Cleveland, Ohio

John N. Whitaker, M.D.

Professor and Chairman
Department of Neurology
University of Alabama at Birmingham
Birmingham, Alabama

Speakers

Carol J. Baker, M.D.

"Intravenous Immunoglobulin in Low Birth Weight Infants: Prevention"

Karyl S. Barron, M.D.

"Treatment of Kawasaki Syndrome: A Comparison of Two Dosage Regimens of Intravenous Immune Globulin"

James B. Bussel, M.D.

"Outline of the Use of IVIG in Immune Cytopenias"

Helen Chapel, M.D.

"Intravenous Immunoglobulin Therapy Prevents Bacterial Infection in Patients With Secondary Hypogammaglobulinemia Due to Low-Grade B Cell Tumors"

Charlotte Cunningham-Rundles, M.D., Ph.D.

"Intravenous Immunoglobulin: Development as a Therapy and Unresolved Issues"

Av Fanaroff, M.D.

"Preterm Infants: Intravenous Immunoglobulin to Prevent Nosocomial Infection"

Ralph D. Feigin, M.D.

"Kawasaki Syndrome: An Overview"

Gerald W. Fischer, M.D.

"Use of Intravenous Immunoglobulin During the Treatment of Infection in Low Birth Weight Infants"

Erwin W. Gelfand, M.D.

"Dosing Regimens for Replacement Therapy in Primary/Secondary Antibody Deficiency"

William J. Harrington, M.D.

"Idiopathic Thrombocytopenic Purpura"

Harry R. Hill, M.D.

"The Role of IVIG in the Treatment of Bacterial Infection in Low Birth Weight Infants"

Winston O. Ho, M.D.

"The Role of Intravenous Immunoglobulin in Bone Marrow Transplantation"

Paul Imbach, M.D.

"Intravenous Immunoglobulin Treatment of Immune Thrombocytopenic Purpura (ITP) in Children"

Roger J. Kurlander, M.D.

"The Use of Intravenous Gamma Globulin in Treating Adult ITP"

Jane W. Newburger, M.D., M.P.H.

"Use of IVIG in Kawasaki Syndrome"

Hans D. Ochs, M.D.

"Intravenous Immunoglobulin (IVIG) in Primary Immunodeficiencies"

James M. Oleske, M.D.

"Historical Approach of the Use of IVIG in Pediatric AIDS"

Fred S. Rosen, M.D.

"Overview of Issues"

William T. Shearer, M.D., Ph.D.

"Review of Clinical Trials in the Literature"

Keith M. Sullivan, M.D.

"Immunomodulatory and Antimicrobial Efficacy of Intravenous Immunoglobulin in Bone Marrow Transplant Recipients"

Donald L. Tankersley, A.B., M.S.

"Intravenous Immunoglobulins: Past, Present, and Future"

Alberto C. Ugazio, M.D.

"Childhood Recurrent Seizures"

**Frans G.A. van der Mech,
M.D., Ph.D.**

“The Effect of High-Dose Immunoglobulins in Acute and Chronic Inflammatory Demyelinating Polyneuropathy”

Anne D. Willoughby, M.D., M.P.H.

“NICHHD Clinical Trial of IVIG in HIV Infection in Children”

Planning Committee

Howard B. Dickler, M.D.

Planning Committee Chairperson
Acting Deputy Director
Division of Allergy, Immunology,
and Transplantation
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Marinos Dalakas, M.D.

Chief, Neuromuscular Diseases
Section, National Institute of
Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

Jerry M. Elliott

Program Analyst
Office of Medical Applications
of Research
National Institutes of Health
Bethesda, Maryland

Ralph D. Feigin, M.D.

Chairman and J.S.
Abercrombie Professor
Department of Pediatrics
Baylor College
of Medicine
Houston, Texas

John H. Ferguson, M.D.

Director, Office of Medical
Applications of Research
National Institutes of Health
Bethesda, Maryland

John S. Finlayson, Ph.D.

Associate Director for Science
Division of Blood and Blood
Products, Center for Biologics
Evaluation and Research
Food and Drug Administration
Bethesda, Maryland

Erwin W. Gelfand, M.D.

Chairman, Department of
Pediatrics, National Jewish
Center for Immunology and
Respiratory Medicine
Denver, Colorado

William H. Hall

Director of Communications
Office of Medical Applications
of Research
National Institutes of Health
Bethesda, Maryland

Carole Heilman, Ph.D.

Acting Chief
Respiratory Diseases Branch
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

James G. Hill

Chief, Office of Science
Policy and Analysis
National Institute of Child
Health and Human Development
National Institutes of Health
Bethesda, Maryland

Peter E. Lipsky M.D.

Conference and Panel
Chairperson; Professor,
Departments of Internal
Medicine and Microbiology
Harold C. Simmons Arthritis
Research Center, University
of Texas Southwestern
Medical Center
Dallas, Texas

Paul R. McCurdy, M.D.

Special Assistant for Clinical Hematology, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Madelaine Morgan

Conference Coordinator
Prospect Associates
Rockville, Maryland

David L. Nelson, M.D.

Chief, Immunophysiology Section
Division of Cancer Biology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Dina Rice

Conference Coordinator
Prospect Associates
Rockville, Maryland

Rachel E. Solomon, M.H.S.

Clinical Trials Administrator
Cardiac Diseases Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Mary Jane Walker

Public Affairs Specialist
Office of Communications
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Sumner J. Yaffe, M.D.

Director, Center for Research for Mothers and Children
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Conference Sponsors

National Institute of Allergy and Infectious Diseases

Anthony S. Fauci, M.D., Director

NIH Office of Medical Applications of Research

John H. Ferguson, M.D.,
Director

National Cancer Institute

Samuel Broder, M.D., Director

National Heart, Lung, and Blood Institute

Claude Lenfant, M.D., Director

National Institute of Child Health and Human Development

Duane F. Alexander, M.D.,
Director

National Institute of Neurological Disorders and Stroke

Murray Goldstein, M.D., Director

Food and Drug Administration

James Benson,
Acting Commissioner



U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health
Office of Medical Applications of Research
Building 1, Room 260
Bethesda, MD 20892

Official Business
Penalty for private use \$300

BULK RATE
Postage & Fees
PAID
PHS/NIH/OD
Permit No. G291