

III. Consensus report

Intravenous immunoglobulin consensus statement

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Intravenous immunoglobulin (IVIG) preparations are a mainstay for a number of disorders that include primary immunodeficiency, acute inflammatory conditions, hematological disorders, infections, and neuroimmunological disorders. The range of therapeutic activity is attributed to IVIG's myriad action mechanisms. IVIG can interact and bind onto complement factors, which can prevent complement-mediated tissue damage, modulate T-lymphocytes, alter cytokine profiles, and modulate the immune system. These interactions can act alone or in combination to maintain immune balance while preserving homeostasis. A consensus panel was convened in 2000 to evaluate and define new advances in IVIG therapies. (*J Allergy Clin Immunol* 2001;108:S139-46.)

Key words: *Intravenous immune globulin, fetal-neonatal alloimmune thrombocytopenia, fetal-neonatal alloimmune hemolysis, antiphospholipid syndrome, recurrent pregnancy loss, peripheral neuropathy, neuropathy, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, inflammatory neuropathy, neuroimmunology*

Intravenous immunoglobulin (IVIG) preparations have been a mainstay for the treatment of primary immunodeficiency syndromes where immunoglobulin replacement can prevent or ameliorate bacterial infections. Since its introduction, the use of IVIG has expanded to a number of other arenas, including hematological, infectious, neuroimmunological disorders, and immuno-modulation. In an era of molecular medicine, it is a surprise that a crude blood fraction can have this wide range of biological activity. Unlike other biotechnological agents, IVIG is a heterogeneous product that is derived from pooled plasma from human donors. The nature of this product has made it difficult to determine the exact mechanism of its activities. This is a tribute to the magnificence of the immune system to prevent infections, respond to foreign antigens, and yet be able to downregulate its own activity. As we understand the various action mechanisms, this may further expand the myriad biological activities and more clearly delineate the various uses of IVIG.

Abbreviations used

AHR: Acute humoral rejection
APS: Antiphospholipid syndrome
CIDP: Chronic inflammatory demyelinating polyneuropathy
DM: Dermatomyositis
GBS: Guillain-Barré syndrome
HPV: Human parvovirus
ICH: Intracranial hemorrhage
ITP: Idiopathic thrombocytopenic purpura
IVIG: Intravenous immunoglobulin
MS: Multiple sclerosis
NAIT: Neonatal alloimmune thrombocytopenia

A consensus panel was convened in 2000 to evaluate and define the therapeutic areas where IVIG has demonstrated effectiveness. This includes all of the modalities that are listed in Table I. A panel was reconvened to assess the data and revisit these issues. A major goal of this panel was to develop a current consensus of IVIG uses and its safety.

ACTION MECHANISM OF IVIG

The myriad molecular actions and interactions associated with IVIG are critical to its evaluation. Immunoglobulins can impact various immunological responses, which range from neutralizing foreign agents to immunomodulation. It stands to reason that the infusion of these immunoglobulins also would elicit an array of biological and immunological responses. Like natural immunoglobulins, IVIG can bind onto the complement factors and prevent tissue damage mediated by complement cascade.^{1,2} This action has been demonstrated in humans with dermatomyositis (DM), where serial muscle biopsies showed a C3b reduction following IVIG therapy.^{1,3}

IVIG can modulate the immune activity of both CD8+ and CD4+ cells. This has been attributed to the presence of antibodies directed against several T-cell surface molecules such as T-cell receptor, CD4, and MHC.⁴ Immunomodulatory activity also has been attributed to the presence of anti-idiotypic antibodies found in IVIG and is thought to downregulate B-lymphocyte activity.^{5,6} In addition, IVIG can regulate the expression of IL-6, a critical regulator of IgG expression and production for plasma cells.⁷

Some of the immunomodulatory activity of IVIG may be dose-dependent. At high levels of immunoglobulins,

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TABLE I. Dosage of IVIG for various disorders

Allergic disorders	Dosing	Reference
Asthma	2 g/kg/mo	Mazer BD. <i>Allergy Clin Immunol</i> 1991;87:976-83 Jakobsson T, et al. <i>Allergy</i> 1994;413-20 Kishiyama JL, et al. <i>Clin Immunol</i> 1999;91:126-33
Hematological		
Idiopathic thrombocytopenia	0.4 g/kg/d × 5 days	Imbach P, et al. <i>Lancet</i> 1985;2:464-8 Blanchette V, et al. <i>Lancet</i> 1994;344:703-7 Mofenson LM, et al. <i>JAMA</i> 1992;268:483-8
Chronic lymphocytic leukemia	0.4 g/kg	Boughton BJ, et al. <i>Clin Lab Haematol</i> 1995;17:75-80
Parvovirus B-19 induced anemia	0.4 g/kg every 28 days	Young N, et al. <i>J Clin Invest</i> 1989;74:2024 Frickhofen N, et al. <i>Ann Intern Med</i> 1990;113:926 Moudgil A, et al. <i>Transplantation</i> 1997;64:1847-50
Infections		
Kawasaki disease	1-2 g/kg	Durongpisitkul K, et al. <i>Pediatrics</i> 1995;96:1057-61 Burns J, et al. <i>Pediatr Infect Dis J</i> 1998;17:1144-8
Pediatric HIV	0.4 g/kg every 28 days	Calvelli TA, et al. <i>Pediatr Infect Dis</i> 1986;5:S207-10 Falloon J, et al. <i>Pediatrics</i> 1989;114:1-30
Sepsis	0.3-0.6 g/kg/d × 2 days	Jenson HB, et al. <i>Semin Perinatol</i> 1998;22:50-63 Pilz G, et al. <i>Chest</i> 1994;105:76-82
Neurological disorders		
Guillain-Barré syndrome	0.25-0.4 g/kg × 5 doses	Dalakas M, et al. <i>Ann Neurol</i> 1996;40:792-5 Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. <i>Lancet</i> 1997;349:225-30 Hahn AF, et al. <i>Brain</i> 1996;119:1067-77
Chronic inflammatory demyelinating polyneuropathy	0.4 g/kg for 5 doses	Azulay JP, et al. <i>Neurology</i> 1994;44:429-32
Multifocal motor neuropathy	0.4 g/kg for 5 doses	Muchnik S, et al. <i>Muscle and Nerve</i> 1997;20:674-8
Lambert-Eaton syndrome	0.4 g/kg for 5 doses	Basta M, et al. <i>J Clin Invest</i> 1994;94:1729-35
Dermatomyositis	0.4 g/kg for 5 doses	Jordan SC, et al. <i>Transplantation</i> 1998;66:800-5
Acute humoral rejection	1 g/kg/d for 2 doses	Stiehm ER. <i>Pediatr Infect Dis J</i> 1997;16:696-707
Primary immunodeficiency disorders	0.4-0.6 g/kg every 28 days	Valensise H, et al. <i>Prenatal Diag</i> 1995;15:509-17
Antiphospholipid syndrome	1 g/kg every 4 weeks from 5 weeks' to 33 weeks' gestation	

the Fc portion of the antibodies can compete for Fc receptor binding that is present on phagocytotic cells, thus reducing damage inflicted by inflammatory effector cells.⁸ High concentrations of immunoglobulin also can accelerate catabolism and elimination of IgG autoantibody, thus reducing the risk of developing autoimmune disorders.⁹

Anti-idiotypic antibodies recognize and attach to the antigen binding region (Fab) of other immunoglobulin molecules. A network of these anti-idiotypic antibodies may regulate or prevent the onset of autoimmunity, where the therapeutic relevance was established in SLE patients who achieved remission after receiving purified anti-idiotypic antibodies.^{6,10} This may explain why IVIG is able to produce a similar clinical response in disorders such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP).¹¹

Other biological activities attributed to IVIG include altering cytokine profiles. This biological effect has been attributed to the presence of antibodies directed against inflammatory mediators like IL-1, TNF, IL-6, and IFNs (eg, α -, β -, and γ).^{12,13} These findings may, either alone or in combination, explain why IVIGs have anti-infective activities as well as immunomodulatory activity in protecting against inflammatory cytokine-mediated cellular damage.

NEUROIMMUNOLOGICAL DISORDERS

There are a number of immune-related neurological conditions in which IVIG has been shown to be effective. As previously stated, IVIG has been an established modality in the treatment of immune-mediated demyelinating disorders, in particular GBS and CIDP.^{14,15} The efficacy of IVIG for patients with GBS has been demonstrated in 2 large controlled trials. In these studies, IVIG was compared with either placebo or plasmapheresis, where IVIG was found to be as effective as, if not superior to, the paired controls. Similar outcomes were demonstrated when patients with CIDP were treated with high-dose IVIG in controlled trials.^{14,15}

Multifocal motor neuropathy is a chronic inflammatory condition that affects specifically the motor nerves. Unlike GBS, multifocal motor neuropathy is unresponsive to plasmapheresis, while treatment with corticosteroid actually can exacerbate this condition. Patients treated with 0.4 g/kg of IVIG for 5 days had similar clinical outcomes as those receiving plasmapheresis, however.¹⁶

When IVIG was given to patients with DM, an autoimmune disorder affecting muscles and skin, the disease progression was halted. DM is thought to be mediated by

complement factors attacking vascular endothelium. Patients with DM experience progressive muscle weakness and rash. High doses of IVIG have been used in patients with DM in a double-blinded, placebo-controlled, randomized, crossover study where IVIG was dosed at 1 g/kg/day for 2 doses, followed by a monthly dose for an additional 3 doses.¹⁷ Disease progression was prevented in patients treated with IVIG, and a majority of the patients achieved significant clinical improvements.

The effect of IVIG was assessed in patients with multiple sclerosis (MS); however, its efficacy was not definitively established. In 3 controlled trials using IVIG in patients with MS, positive outcomes in terms of relapse rates were shown.¹⁸ The use of low-dose IVIG (0.25-0.5 g/kg monthly for 24 months) improved clinical disability status and reduced relapse numbers as compared with controls.¹⁸ When the IVIG dose was increased to 1 g/kg/day for 2 days at 4-week intervals, 65% of patients had no exacerbation as compared with 35% in the paired controls.¹⁹ It is clear that IVIG may be active in patients with MS; however, the optimal dose must be established in this condition.

IVIG has demonstrated effectiveness in a wide variety of immune-mediated neuropathies. The efficacy of IVIG in inflammatory demyelinating disorders of the peripheral or central nervous system is well documented and has become a mainstay in treatment of such conditions.⁴

PRIMARY IMMUNODEFICIENCY DISORDERS

The use of IVIG in primary immunodeficiency patients with hypogammaglobulinemia (IgG < 400 mg/dL) is well established. Patients with these types of conditions are at a significant risk for developing serious and often life-threatening invasive infections.^{20,21} In patients with primary hypogammaglobulinemia, antibody replacement using IVIG is necessary to minimize complications associated with chronic sinusitis and bronchiectasis.^{20,22}

Although there is no question relating to the usefulness of using IVIG replacement in primary immunodeficiency disorders, its role in patients with IgG subclass deficiencies is not absolute and depends on the presence of specific antibody deficiencies. In patients with subclass deficiencies with concomitant recurrent or chronic respiratory infections, however, IVIG can provide significant benefits despite the fact that there has never been a double-blinded, placebo-controlled trial.²³ There is no question in terms of the effectiveness of IVIG replacement in patients with primary immunodeficiency; the major question that remains is the optimal dose of IVIG in such patients. A trial is necessary to establish the foundation for the optimal dose of IVIG in this patient population.

HEMATOLOGY

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is a disorder where platelet levels drop significantly. In a large portion of these patients, the condition resolves spontaneously without therapy. A small number of these

patients will require therapy, which can range from corticosteroids to splenectomy. IVIG has been shown to be effective in ITP patients who require splenectomy.²⁴ In this condition, IVIG is used as an immune modulator by blocking attack on the platelets. In a majority of patients treated with 400 mg/kg for 5 days, responses occurred within 5 days where platelet counts were above the 50,000 platelets/mm³ threshold.²⁵

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia is a B-lymphocyte malignancy where patients may develop recurrent bacterial infections that may be attributed to the B-cell dysfunction. Similar to patients with hypogammaglobulinemia, these patients are susceptible to recurrent and encapsulated bacteria. In hypogammaglobulinemia associated with chronic lymphocytic leukemia, IVIG is well established as a beneficial modality to prevent recurrent bacterial infections.²⁶

INFECTIOUS DISEASES

The role of humoral immunity is well established in the defense against pathogenic intrusion. Thus, using IVIG to treat bacterial infections, such as staphylococcal- and streptococcal-related toxic shock syndromes, stands to reason. In addition, IVIG would be beneficial in patients with altered humoral immunity, such as primary humoral immunodeficiency syndrome and pediatric HIV infections. The regulatory modulatory activity of inflammatory cytokines also has been shown to be effective in patients with sepsis. Added evidence of immunoglobulins in sepsis has been established by the landmark study using J5.²⁷

Evidence is mounting for using IVIG to treat pyogenic toxin super antigen-induced sepsis and toxic shock syndromes. IVIG can neutralize super antigens in toxic shock and Kawasaki disease.

Kawasaki disease

Kawasaki disease is an acute vasculitis of unknown etiology that occurs predominantly in infants and young children. Without treatment with high-dose intravenous IVIG, coronary artery ectasia or aneurysms develop in about 15% to 25% of afflicted patients.²⁸ The administration of IVIG during the acute phase can reduce the prevalence of coronary dilation to less than 5% and that of giant coronary aneurysms to less than 1%.²⁹ It is well established that patients with Kawasaki disease can be treated effectively with aspirin and IVIG at 1-2 g/kg.³⁰ Furthermore, patients in the United States and Canada with persistent or recrudescent fever 48 to 72 hours after initial IVIG therapy often are given a second IVIG treatment (2 g/kg).³¹

Sepsis

Sepsis, an exaggerated immunological disorder, is a consequence of the presence of infectious agents found in the blood. Despite advances in molecular medicine, sepsis accounts for 100,000 deaths yearly.³² The pathophysiology of sepsis is well documented where the pres-

ence of the infectious organism induces cytokine expression and elaboration in response to the infection. Immune activation will result in cellular expansion and recruitment to the affected site, leading to vascular damage, hypotension, and poor organ perfusion, thereby causing morbidity and mortality associated with sepsis.

As stated earlier, IVIG is a crude immunological product that contains neutralizing and opsonizing antibodies. This may increase antibactericidal activity while stimulating phagocytotic activity of leukocytes. The IgG-IVIG-mediated modification and specific suppression of cytokine release from activated mediator cells deserves particular attention. This emphasizes the role of mediators, especially cytokines, as a common pathway of both sepsis and systemic inflammatory response syndrome. While the beneficial effects of IVIG in *in vitro* and *in vivo* animal sepsis models are well documented, the use of IVIG in the treatment of sepsis remains controversial.^{33,34}

Sepsis patients often have low serum levels of immunoglobulin; thus, replacement using IVIG for the prophylaxis and treatment of severe infection and sepsis can be justified. Similar to other therapeutic agents for the management of sepsis, the use of IVIG in this arena continues to be controversial. Criticism continues despite a number of studies suggesting the effectiveness of IVIG in sepsis. More studies are necessary to delineate the efficacy of IVIG in sepsis.

Human immunodeficiency virus

Immunologic and clinical abnormalities in pediatric patients infected with HIV differ from those seen in adult patients with HIV. In pediatric patients, impaired B-cell activity is an early and prominent manifestation of HIV infection where HIV-positive infants do not develop the antigen-specific B- and T-cell clones required for immunologic memory, amplification, and production of specific antibodies. B-lymphocyte defects are more common among HIV-infected infants and children than adults with HIV where defects in B cells can predispose patients to serious bacterial infections.^{35,36} HIV glycoproteins can induce 2 contrasting effects on B cells: (1) polyclonal expansion of activated B lymphocyte resulting in high levels of nonspecific antibodies and (2) a decreased production of specific antibodies to both new and recall antigens.³⁷⁻⁴⁰ Recurrent bacterial infections also often are correlated with low levels of antibodies, which is a consequence of B-cell defect.

A number of studies have been conducted to determine the efficacy of IVIG to prevent serious bacterial infections in this population.³⁷⁻⁴⁰ Despite these studies, IVIG therapy in HIV-infected pediatric patients is based on evidence of impaired antibody function, although this use remains controversial. One large-scale, double-blind, placebo-controlled study showed that IVIG administered at a rate of 400 mg/kg every 28 days can decrease the morbidity associated with serious bacterial infections in HIV-infected children with CD4 cell counts of less than 200 cells/mm³. Another study involving HIV-infected children

who received concurrent zidovudine demonstrated that IVIG helped prevent serious bacterial infections in children who were not concurrently receiving trimethoprim-sulfamethoxazole. These benefits were not observed in patients who were receiving trimethoprim-sulfamethoxazole prophylaxis. Despite these findings, IVIG has not been shown to alter mortality in these patients. Rather, the benefits of IVIG appear to decrease bacterial infection morbidity associated with pediatric HIV.

Despite the theoretical basis for the use of IVIG, its use remains controversial. The IVIG action mechanism is characterized poorly in pediatric HIV infection because of the complexity of the immunologic abnormalities involved in these patients.^{41,42} IVIG also may provide anti-idiotypic antibodies, which can produce negative feedback to B cells, resulting in a decrease in immunoglobulin production.⁴³ Reduction in bacterial infections possibly may slow progression of the HIV disease itself; antigenic stimulation resulting from bacterial infection may lead to lymphocyte and T-cell activation and thus potential progression of HIV disease since HIV can lie dormant in T cells.^{36,37}

Parvovirus

Human parvovirus (HPV) B19 is an icosahedral, nonenveloped, single-stranded DNA virus with tropism for human erythroid precursor cells. Viral proliferation will induce host erythroblast lysis that is found in the bone marrow.^{44,45} The clinical manifestation is significant anemia accompanied by profound reticulocytopenia.⁴⁶ In immunocompetent subjects, B19-associated anemia generally is transient and mild; however, sickle cell anemia patients may develop clinical manifestation.⁴⁶ Patients infected with HPV B19 with concomitant immunosuppression often present with persistent and severe anemia because of the lack of immune-mediated viral suppression.^{47,48}

In immunocompetent patients, anemia usually is mild and often has little clinical impact. Anemia may be severe in patients with a pre-existing chronic hemolysis process such as sickle cell anemia, however.⁴⁶ In infected patients with immunosuppression or on immunosuppressive therapy, this viral infection can cause a persistent and severe anemia and reticulocytopenia as a result of inadequate humoral immune response.^{47,49-51}

Immune recovery may be adequate in the management of HPV infection. In patients with persistent immunosuppression, however, the use of IVIG to treat HPV B19-mediated anemia may be necessary.^{50,51} Recipients of IVIG demonstrated a hematocrit recovery greater than 40% with resolution of all symptoms and with an elevated IgG titer, suggesting immunity. In addition, IVIG has been shown to be effective in recurrent infection.⁵²

The advisory panel suggests that IVIG may be useful in patients with HPV B19. This is in accordance with the 1995 consensus statement. Although there are no definitive clinical trials demonstrating the efficacy of HPV B19-induced anemia, IVIG has become the standard of care based on the evidence available.

ORGAN TRANSPLANTATION

Hyperacute rejection and acute humoral rejection (AHR) are conditions without effective treatments. Since both types of rejection are mediated by antibodies directed against the vasculature, plasmapheresis has been shown to remove HLA-specific antibody. Similarly, IVIG has been shown to suppress alloantibodies and modulate immune responses.⁵²

One study combined both plasmapheresis and IVIG therapy to preemptively desensitize organ transplant recipients cross-matched with the live donors. This study evaluated 7 live donor kidney transplant recipients who have experienced AHR and had donor-specific antibodies for 1 or more mismatched donor HLA antigens. The combination of plasmapheresis and IVIG was successful in reversing established AHR in 3 of 7 patients.⁵²

Another study showed that IVIG was effective in patients experiencing antibody-mediated allograft rejection. In this study, 10 patients receiving either kidney or heart transplants complicated with severe allograft rejection were treated with IVIG. Nine of 10 patients treated did not experience recurrent rejection.⁵³

OBSTETRICS-GYNECOLOGY

Patients who are pregnant may experience a number of conditions above, including fetal-neonatal alloimmune thrombocytopenia and alloimmune hemolysis. IVIG also has been evaluated in patients with antiphospholipid syndrome (APS) and recurrent miscarriages. IVIG is the standard of care for neonatal alloimmune thrombocytopenia, while the effectiveness of IVIG in neonatal alloimmune hemolysis remains limited. Thus, no conclusive recommendation can be made with the absence of a controlled trial. Similarly, experience with IVIG in both recurrent miscarriage and APS continues to be limited to small trials. Clinical trials in patients with these conditions will be necessary to ascertain the effectiveness of IVIG.

Antiphospholipid syndrome

IVIG use in patients with APS focused on the prevention of recurrent pregnancy loss.⁵⁴ APS is an autoimmune condition where patients may experience venous or arterial thrombosis, fetal death, or thrombocytopenia.^{55,56} The conventional pharmacological management of patients with APS is heparin and low-dose aspirin to reduce the rate of maternal thromboembolic events.⁵⁷⁻⁶⁰

In one study of 16 female patients, 7 patients received IVIG and 9 patients were given placebo. The groups were similar with respect to age, gravidity, number of previous pregnancy losses, and gestational age at the initiation of treatment. Fewer cases of fetal growth restriction were seen (0% vs 33%, IVIG group vs placebo, respectively). A reduction in ICU admissions also was seen with IVIG as compared with placebo (20% vs 44%, respectively).⁶¹

Neonatal alloimmune thrombocytopenia

The frequency of neonatal alloimmune thrombocytopenia (NAIT) is 1 in 1000-2000 live births. This is due primarily to the incompatibilities between positive fetal and negative maternal epitopes for platelet specific antigen-1.^{62,63} Approximately 20% of NAIT cases are complicated with the presence of intracranial hemorrhage (ICH) where one half of the hemorrhage is thought to occur antenatally.^{64,65} The estimated perinatal mortality is 15% where neurological impairment is thought to be 25%.^{66,67} The consequence of this incompatibility will continue with subsequent pregnancies where 75% to 90% of infants will suffer thrombocytopenia and the severity will increase following each pregnancy.⁶⁴

The management of thrombocytopenia and ICH can occur antepartum and intrapartum where the primary pharmacotherapy is high-dose steroids, in utero platelet transfusions, and early elective cesarean delivery.⁶⁷⁻⁷² Neither steroids nor cesarean delivery are able to prevent antenatal ICH, however, whereas serial in utero transfusions pose substantial risk to the fetus.

IVIG has been employed in a series of patients with complications of NAIT.⁶⁸ All 7 infants from the prior pregnancies had been born with platelet counts greater than $30 \times 10^9/L$ and 3 patients developed ICH. Fetal platelet counts rose substantially as compared with baseline. When cord platelet counts were measured at delivery, platelets were substantially higher than those seen in untreated older siblings. In addition, there were no cases of ICH reported in the IVIG-treated pregnancies.⁶⁸

IVIG also was used in 12 additional patients, with 10 of 12 fetuses experiencing a rise in platelet counts. Similar to other studies, there was no report of ICH in any of the treated patients. Two patients did not respond to therapy, one of whom was treated with a lower dose (0.5 g/kg/wk) of IVIG.⁷²

Immune thrombocytopenic purpura

Autoimmune thrombocytopenic purpura (ITP) is thought to be caused by autoantibody directed against platelet glycoproteins IIb/IIIa and Ib/IX, causing platelet sequestration and elimination from the circulation. Autoantibody directed against platelet surface antigen can be detected in the plasma in 75% of patients, while 58% have persistent levels of the autoantibody.^{73,74}

The primary treatment of ITP is corticosteroids and splenectomy. Steroid use during pregnancy can have significant impact on mother and fetus.⁷⁵ IVIG treatment for pregnancy-associated ITP normally begins at 32 weeks' gestation.⁷⁶ Similar to other immune thrombocytopenias, 400 mg/kg/day of IVIG is infused for 5 days.

CONCLUSION

The consensus panel focused on a number of issues, which are listed below. These topics were classified as follows: primary immunodeficiency diseases, vascular biology, infectious diseases, transplantation, and obstetrics-gynecology.

Primary immunodeficiency disease

IVIG first was approved for patients with primary immunodeficiency diseases, and its use improved the health of these patients. Despite these remarkable improvements, patients continue to suffer from recurrent infections, progressive end organ damage, and chronic enteroviral meningitis. Although IVIG has provided remarkable advances in treating these disorders, the optimization of IVIG has not been investigated.

Currently, there are no double-blind, placebo-controlled trials evaluating the effect of IVIG in primary immunodeficiency diseases. A number of studies have compared different doses in these patients. In all of the studies the higher dose has been shown to have greater therapeutic benefit, whether assessed as number of hospitalizations, as number of hospital days, or as incidence of specific infections such as pneumonia. Yet there is no study where 2 dosages have been compared and where patients receiving higher doses have been reported to have significantly improved outcomes. In an attempt to establish an upper limit of therapeutic benefit, therefore, the panel recommends a double-blind, controlled trial comparing the current upper dose of IVIG with doses above the conventional 400 mg/kg every 28 days.

Other issues to consider include the specific antibodies that provide protection. This would include the specific level of these antibodies to provide benefits.

Vascular biology

IVIG has been used for ITP; however, the panel suggests that there is evidence supporting the use of IVIG in ITP associated with immune complex such as in HIV thrombocytopenia. The panel also suggests that IVIG be considered in patients sensitized to platelet transfusions. In addition, the panel questions whether IVIG can be used to reduce the use of steroids in the management of ITP. Other issues to consider include studies to determine optimal dosage for IVIG and to define the duration of therapy.

Infectious diseases

The panel reviewed the literature and found 2 major points of discussion. The first is the evidence supporting the use of polyclonal IVIG for the treatment of pyogenic toxin superantigen-induced sepsis and toxic shock syndromes. Despite improvements in supportive therapies, new antibiotics, and increasingly sophisticated critical care measures, mortality rates for adult patients with sepsis remain high at 40% to 60%.

Information presented by Schlievert (see article in this issue on p S107) provided additional evidence of polyclonal IVIG's use in neutralizing superantigens in toxic shock syndrome and Kawasaki disease. Data from clinical trials suggest that polyclonal IVIG significantly reduces mortality and is a useful adjuvant treatment for sepsis or septic shock. With these data, the infectious diseases subgroup supported a statement that IVIG may be useful in these situations.

Secondly, the issue of interchangeability between various IVIG products may need to be revisited. Information

presented at this meeting demonstrated that different IVIG products have varying capacities to neutralize the toxic shock syndrome antigen. Further clinical trials are warranted, looking specifically at pathogen-specific antibodies, lot-to-lot variability, and differences between preparations from various manufacturers.

Transplantation

The subgroup evaluating IVIG in the organ transplantation setting addressed several issues, but focused on viral infections. Post-transplantation IVIG is effective for a number of infections, including HPV B-19, polyomaviruses, Epstein-Barr virus, and cytomegalovirus.

The ability of IVIG to inhibit proliferation of these viruses also may prevent the onset of graft rejections. Both cytomegalovirus and Epstein-Barr virus are stimulators of B-cell responses and can induce chronic rejection. In addition, IVIG can downregulate immune response towards these viruses.

Obstetrics-gynecology

IVIG is approved for use in a number of conditions that may occur in obstetrical patients, including ITP and immune deficiency syndromes. IVIG also is used widely in obstetrics for non-approved indications, however, such as fetal-neonatal alloimmune thrombocytopenia, fetal-neonatal alloimmune hemolysis (erythroblastosis fetalis), APS, and recurrent miscarriage. The obstetric advisory panelists, all of whom are perinatologists, critically reviewed the use of IVIG for these indications based on the best available studies and concluded that the use of maternal IVIG in the management of fetal-neonatal alloimmune thrombocytopenia is effective.

This group also supports the thought that maternal IVIG is promising treatment for fetal-neonatal alloimmune hemolysis (erythroblastosis fetalis). The use of IVIG in antierythrocyte alloimmunized pregnancies may be beneficial by inhibiting maternal antibody synthesis, blocking Fc-mediated antibody transport across the placenta, or limiting fetal red blood cell destruction. Though published trials have yielded mixed results, most groups have reported some benefit when IVIG is administered maternally.

The advisory panel recommends appropriate pilot studies and, most importantly, a multicenter randomized trial to determine the use of IVIG in the management of alloimmune-mediated erythroblastosis fetalis.

IVIG also has been studied as a treatment for pregnancy loss. The data supporting the use of IVIG in the treatment of recurrent miscarriage are limited to one well-designed study, while several other well-designed studies suggest no benefit. The advisory panel concluded that the use of IVIG in the treatment of recurrent miscarriage should be abandoned unless a properly designed multicenter trial of sufficient size finds evidence of benefit.

For APS, a specific cause of pregnancy loss, a prospective, randomized trial suggests that IVIG may be no more beneficial than heparin. This trial was of limited size, however. Case studies have suggested IVIG may benefit women with APS who have failed heparin treatment in a

prior pregnancy. The advisory panel recognizes that a randomized trial of IVIG treatment in these cases is justified.

All of the working groups had one consistent recommendation, which was a call for studies to establish the optimal dosing of IVIG in the various settings. The panelists agree that IVIG is an effective immune modulator with significant anti-infective properties. As data and experience increase, the use of these agents also will broaden.

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APPENDIX

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