Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature

Kamran Darabi, Omar Abdel-Wahab, and Walter H. Dzik

BACKGROUND: Intravenous immune globulin (IVIG) has been approved by the Food and Drug Administration (FDA) for use in 6 conditions: immune thrombocytopenic purpura (ITP), primary immunodeficiency, secondary immunodeficiency, pediatric HIV infection, Kawasaki disease, prevention of graft versus host disease (GVHD) and infection in bone marrow transplant recipients. However, most usage is for off-label indications, and for some of these comprehensive guidelines have been published.

STUDY DESIGN AND METHODS: We retrospectively reviewed all approved IVIG transfusions at Massachusetts General Hospital in 2004 to identify the current usage pattern and completed a literature review.

RESULTS: IVIG was most commonly used in the treatment of chronic neuropathy, which included chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy. For such patients, the annual cost of IVIG can exceed $50,000 per patient. Other common indications were the treatment of hypogammaglobulinemia, ITP, renal transplant rejection, myasthenia gravis, Guillain-Barre syndrome, necrotizing fasciitis, autoimmune hemolytic anemia, and Kawasaki disease. IVIG was administered in a variety of other indications each representing <3% of the total treated patients.

CONCLUSION: Only a few indications account for most of the usage for IVIG. Reports concerning IVIG continue to grow at a tremendous pace but few high-quality randomized controlled trials have been reported. Randomized trials are especially needed for conditions such as CIDP, which consume large quantities of product.

Intravenous immune globulin (IVIG) is a plasma protein derivative used in the treatment of a diverse variety of conditions. The cost per gram of IVIG ranges from $50 to $80. In 2004 our institution infused IVIG at an annual acquisition cost of approximately $4 million, making it the most expensive blood product dispensed by the Blood Transfusion Service (BTS). Usage of IVIG appears to be increasing.[1,2] IVIG is produced from pooled plasma of thousands of blood donors by multiple fractionation and processing steps to reduce its infectious risk and obtain its therapeutic component. As such, it contains mainly immunoglobulin G (IgG) but also traces of other immunoglobulins. Although this product has been administered in nearly 100 conditions, it has been approved by the Food and Drug Administration (FDA) for use in only 6 conditions: immune thrombocytopenic purpura (ITP), primary immunodeficiency,

ABBREVIATIONS: AIHA = autoimmune hemolytic anemia; BTS = Blood Transfusion Service; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = chronic lymphocytic leukemia; GBS = Guillain-Barre syndrome; HAART = highly active antiretroviral therapy; ITP = immune thrombocytopenia purpura; KD = Kawasaki disease; MG = myasthenia gravis; MGH = Massachusetts General Hospital; MMN = multifocal motor neuropathy; MS = multiple sclerosis; RCT = randomized controlled trial; RR-MS = relapsing-remitting multiple sclerosis; SP-MS = secondary progressive multiple sclerosis; UHC = University Hospital Consortium.

From the Harvard University Joint Program in Transfusion Medicine, Boston, Massachusetts; and the Blood Transfusion Service and the Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Address reprint requests to: Kamran Darabi, Massachusetts General Hospital, Blood Transfusion Service, GRJ 148, 55 Fruit Street, Boston, MA 02114; e-mail: kamrandarabi@yahoo.com.

Received for publication June 6, 2005; revision received September 14, 2005, and accepted September 17, 2005.

doi: 10.1111/j.1537-2995.2006.00792.x

TRANSFUSION 2006;46:741-753.

secondary immunodeficiency, pediatric human immunodeficiency virus (HIV) infection, prevention of graft-versus host disease (GVHD) and infection in bone marrow transplant (BMT) patients, and Kawasaki disease (KD). Most of the usage is for off-label indications, for which comprehensive guidelines have been published elsewhere.[2] The patterns of usage of IVIG continue to change. Despite the availability of comprehensive guidelines, clinicians occasionally request this product in circumstances where it has not been recommended, sometimes as a last resort when conventional therapies have failed. Examples from our experience include requests to treat autism, amyotrophic lateral sclerosis, antibiotic-associated colitis, paraneoplastic syndromes, and other disorders. Therefore, we began a process in 1998 whereby all requests for IVIG are evaluated by the BTS physician before issuing for use in patient care. Under the direction of the hospital transfusion committee, Massachusetts General Hospital (MGH) has developed guidelines for IVIG use. The guidelines are based on published guidelines, recent literature, and expert local opinion from an ad hoc committee composed of leadership in neurology, hematology, infectious disease, rheumatology, dermatology, nephrology, gastroenterology, transplantation, and the burn service. All requests for IVIG are reviewed by a BTS physician. Requests outside the guidelines are generally not filled although requesting physicians may appeal to the committee for an exception. We report here our current usage pattern of IVIG, which is probably influenced by the above-mentioned process, and review recent publications regarding the most common reasons for requests.

PATIENTS AND METHODS

We retrospectively reviewed all approved requests for 2004 with the centralized log for issued products. The diagnosis recorded in our database was verified with the patient chart when necessary. A small number of nine patients without clear diagnoses or limited access medical records were excluded from our analysis. Dosages were calculated by adding all issued IVIG products for individual patients and adjusted for returned products.

The literature review was performed in January 2005. To select the most relevant articles we searched the PubMed database of the National Library of Medicine with the terms IVIG, IGIV, immune globulin intravenous in combination with hypogammaglobulinemia, immune deficiency, immune-mediated thrombocytopenia, ITP, chronic inflammatory demyelinating polyneuropathy, CIDP, Guillain-Barre syndrome, multiple sclerosis, organ transplant, bone marrow transplant, pediatric HIV/AIDS, and necrotizing fasciitis. We did not limit the search based on the language of publications.

RESULTS

Usage of IVIG at the MGH for 2004 is summarized in Table 1. In this year, approximately 44,000 inpatients were admitted to MGH with approximately 32,000 surgeries

TABLE 1. The usage of IVIG at MGH, Boston, Massachusetts, in 2004

Diagnosis	Number of patients (n = 194)*	Overall amount (g)†‡	Mean usage per patient (g)
Chronic neuropathy (including CIDP, MMN)	56 (28.9)	29.850 (61.9)	530
Secondary hypogammaglobulinemia§	34 (17.5)	3205 (6.6)	90
Idiopathic thrombocytopenic (ITP)	20 (10.3)	3820 (7.9)	190
Primary hypogammaglobulinemia	18 (9.3)	3060 (6.3)	170
Renal transplantation	12 (6.2)	485 (1)	40
MG	9 (4.6)	1785 (3.7)	190
GBS	8 (4.1)	1525 (3.2)	190
Common variable immunodeficiency	8 (4.1)	1510 (3.1)	190
Necrotizing fasciitis	6 (3.1)	730 (1.5)	120
AIHA	6 (3.1)	440 (0.9)	70
Kawasaki syndrome	5 (2.6)	105 (0.2)	20
Dermatomyositis	2 (1)	985 (2)	490
HIV	2 (1)	300 (0.6)	150
Liver transplantation	2 (1)	75 (0.2)	35
Pre–heart transplantation desensitization	1 (0.5)	120 (0.2)	120
Myopathy	1 (0.5)	105 (0.2)	105
Juvenile rheumatoid arthritis	1 (0.5)	90 (0.2)	90
Parvovirus infection	1 (0.5)	20 (0.0.4)	20
Hemolytic disease of the newborn	1 (0.5)	10 (0.02)	10
Neonatal alloimmune thrombocytopenia	1 (0.5)	10 (0.02)	10

* Data are reported as number (%).
† Data are reported as amount (% of total usage).
‡ Relative proportions of total usage were calculated based on a total usage of 48,230 g.
§ Due to hematologic malignancy/BMT.

and 3600 deliveries being performed.[3] There were approximately 1200 patients discharged from the neurology service and 800 patients discharged from the hematology-oncology ward (including the bone marrow transplantation [BMT] ward).[3] A total of 194 patients were included in our analysis and were transfused approximately 48,230 g of IVIG. The different indications are listed in Table 1.

The mean usage for the most frequent indication chronic neuropathy (n = 56; 28.9%), which included chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), was 530 g (corresponding to approx. $34,500) per patient per year. Other common indications were the treatment of hypogammaglobulinemia, ITP, renal transplant rejection, myasthenia gravis, Guillain-Barre syndrome (GBS), necrotizing fasciitis, autoimmune hemolytic anemia, and Kawasaki syndrome. A variety of other indications each representing less than 3 percent of the total treated patients are listed in Table 1.

DISCUSSION

Given the cost of IVIG, its side effect profile, and limited data about its clinical benefits in many conditions, physicians must distinguish between appropriate and inappropriate usage of this plasma product. Expert groups, such as the University Hospital Consortium (UHC) IVIG Expert Panel have raised several caveats with regard to various indications.[2]

A study conducted by the UHC in 1998 summarized the inpatient use of IVIG at 12 of its member institutions. Forty-two percent of those patients received IVIG for labeled indications. Of the remaining 58 percent of patients who received IVIG for off-label indications, only 12 percent coincided with the UHC model guidelines for acceptable use.[4] These results are in agreement with estimates from the FDA that 50 to 70 percent of IVIG is used in off-label indications.[5] Interestingly, our data show that the majority of our current use matches guidelines. The reason for this lies in the fact that previous data and a shortage of IVIG in the late 1990s prompted the MGH to institute a prerelease review process for the usage of IVIG. Every order by a clinician needs to be reviewed by a physician from the BTS and approved before release.

Our data may not be representative for the general usage of IVIG in common clinical practice, however. Patients with many chronic (e.g., demyelinating neuropathies) or life-threatening conditions (e.g., necrotizing fasciitis) are seen more frequently at referral centers like our institution and other conditions (e.g., pediatric HIV) may be less frequently encountered than at hospitals that serve patient populations where the prevalence of HIV is high. The most recent UHC technology assessment guidelines were published in 1999. At that time, much of the available evidence for the effectiveness of IVIG was anecdotal or originated from uncontrolled, open studies. Randomized controlled double-blind trials were available for only a small number of conditions.[2] Our literature review in January 2005 shows that the number of randomized controlled trials (RCTs) still remains low and many indications remain the subject of debate.

LITERATURE REVIEW

Conditions for which IVIG is FDA-approved

ITP. Imbach and coworkers[6] were the first investigators to demonstrate that IVIG can effectively increase the platelet (PLT) count in patients with ITP.[6] In this study, six children with acute ITP and seven with chronic ITP were all witnessed to have a significant increase in PLT count within 5 days of receiving 400 mg per kg per day IVIG for 5 days. Multiple studies performed since have demonstrated that IVIG effectively increases the PLT count in more than 80 percent of ITP patients.[7] Typically, the PLT count increases within days and peaks within 1 week after treatment. In the vast majority of patients, however, response is transient and lasts no longer than 4 weeks before returning to pretreatment levels.[8]

Given that ITP is generally a self-limited disorder in children and given the uncertainty regarding the actual likelihood of serious bleeding in childhood ITP, IVIG is often used as initial treatment in children who present with profound thrombocytopenia and mucosal bleeding. This recommendation is based, in part, on a RCT of IVIG, RhIG, and prednisone as the initial treatment of ITP in children with a PLT count of less than 20×10^9 per L. In this study, children randomly assigned to receive a single dose of 800 mg per kg of IVIG were found to experience a faster rate of PLT response than children randomized to receive 25 μg per kg RhIG or 4 mg per kg prednisone tapered over 21 days.[9]

In contrast to the treatment practice in children, IVIG is less often used in adults with ITP. One study found that IVIG had no advantages over oral corticosteroids as primary therapy in adults with ITP.[10] This was demonstrated in a study in which adults with ITP were randomly assigned to receive prednisone (1 mg/kg/day), high-dose IVIG (400 mg/kg/day × 5 days), or a combination of prednisone plus IVIG. The response in PLT count, time to relapse, and time to splenectomy was not significantly different between patients receiving steroids versus IVIG.[10]

Given the transient effect of IVIG on PLT count as well the expense, IVIG is generally reserved for chronic ITP 1) when there is an immediate need to increase the PLT count (e.g., serious bleeding episodes), 2) in preparation for splenectomy or other invasive procedures, 3) in pregnant women at risk of bleeding, or 4) in chronic ITP not responding to steroids or RhIG.[7,8] High-dose parenteral steroids represent an alternative medication that can be

attempted to increase PLT count in an acute setting. Godeau and colleagues[11] studied the efficacy of high-dose methylprednisolone (15 mg/kg/day × 3 days) versus IVIG (700 mg/kg/day × 3 days) in a randomized trial of untreated patients with ITP and PLT counts of less than 20×10^9/L. Although methylprednisolone significantly increased PLT counts, this trial demonstrated a slightly greater rate of increase in PLT count for those receiving IVIG. Remission rates at 1 year, however, were not affected by the initial treatment.

The optimal dose of scheduled IVIG in ITP remains to be fully examined. One current commonly used treatment regimen is 1000 mg per kg for 1 to 2 days.[7,8] This dose is based on a multicenter randomized trial of 35 patients with ITP who received either 500 or 1000 mg per kg over 1 day.[12] Nonresponders received additional IVIG on Days 4 and 5 to reach a total dose of 2000 mg per kg. Results of this study indicated that initial treatment with 1000 mg per kg IVIG was more effective than initial treatment with 500 mg per kg IVIG.

Primary hypogammaglobulinemia. Human immunoglobulin was first administered in the treatment of primary immunodeficiency in the form of intramuscularly injected immunoglobulin by Bruton in 1952.[13] Since then, routine administration of human immunoglobulin has become the mainstay of therapy in patients with B-cell immunodeficiencies such as X-linked agammaglobulinemia, common variable immunodeficiency, and X-linked hyper-IgM syndrome. IVIG is also utilized in the treatment of combined immunodeficiencies such as Wiskott-Aldrich syndrome, ataxia-telengiectasia and as supportive therapy in patients with severe combined immunodeficiency while they await more definitive treatment.

Although there have been no RCTs of IVIG versus placebo in the treatment of primary immunodeficiency, there is clear clinical evidence of the efficacy of IVIG in decreasing the severity and frequency of infections in these patients. For instance, Quartier and associates[14] demonstrated that the incidence of bacterial infections decreased dramatically from 0.4 per patient per year to 0.06 per patient per year ($p < 0.001$) following initiation of IVIG in 31 children with X-linked agammaglobulinemia.[14] Similarly, Busse and coworkers[15] noted a significant decrease in the number of episodes of bacterial pneumonia before versus after initiation of IVIG treatment in 50 patients with common variable immunodeficiency.[15] They found that 84 percent of their cohort experience at least one episode of bacterial pneumonia before treatment whereas only 11 percent experienced at least one episode of pneumonia after a median of 6.6 years of IVIG.

In comparison to the paucity of studies demonstrating efficacy of IVIG in primary immunodeficiency, there have been slightly more studies investigating the optimal dosing of IVIG in immunodeficient patients. A common standard guideline is that the trough IgG level should remain greater than 500 mg per dL.[16] This guideline, however, is derived from a randomized crossover study of only 12 patients with primary hypogammaglobulinemia and chronic lung disease.[17] In this study, patients received 200 or 600 mg per kg IVIG each month for 6 months followed by the alternate dose for an additional 6 months. Although the incidence of infection did not differ greatly in the high- versus low-dose group, the frequency of infection was found to be much lower when the serum IgG trough exceeded 500 mg per dL. But even above this trough level, most patients with primary hypogammaglobulinemia experience intermittent infection. Thus, Eijkhout and associates[18] investigated whether doubling the standard IVIG dose yields further reduction in infection. In this multicenter, randomized, double-blind, crossover study, patients received either standard-dose (300 mg/kg for adults, 400 mg/kg for children) or high-dose IVIG (600 mg/kg for adults, 800 mg/kg for children) every 4 weeks for 9 months. Patients receiving high-dose IVIG experience greater trough levels of IgG as well as a slightly decreased frequency and duration of infection. Given the marginal observed benefit, the authors concluded that high-dose maintenance therapy was not likely to be cost-effective care.

Based on these studies, a reasonable treatment approach to patients with primary hypogammaglobulinemia would be a maintenance dose of IVIG at 300 to 600 mg per kg every 3 weeks or 400 to 800 mg per kg every 4 weeks.[16] Since 1999, at MGH patients with primary immunodeficiency or secondary immunodeficiency (e.g., due to BMT) are maintained at trough levels more than 400 mg per dL. Residual IgG levels can be measured before IVIG infusion.[14,17,19] Dosing intervals will depend on the catabolic rate of IgG in the patient but will generally be no more frequent than every 3 to 5 weeks.

Secondary hypogammaglobulinemia due to chronic lymphocytic leukemia (CLL). Infections are the major cause of morbidity and mortality in patients with CLL.[20] These patients are at increased risk of infection due to hypogammaglobulinemia as well as defects in cell-mediated immunity and impaired opsonization. The strongest data supporting the use of IVIG as prophylactic treatment against infections come from a large randomized study by the Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia.[21] In this double-blind, placebo-controlled trial, CLL patients who received 400 mg per kg IVIG every 3 weeks for 1 year had significantly fewer bacterial infections than patients who received placebo. Further, a subset of patients continued IVIG treatment in a crossover double-blind trial. Bacterial infections were found to be less frequent during the months of IVIG therapy. But despite the overall significant decrease in frequency of bacterial infection, when bacterial infections were classified as minor, moderate, or severe, there was no significant difference in the frequency of severe bacterial infections between the IVIG

and placebo groups. Also, there was no difference in the frequency of fungal and viral infections (an expected outcome given the increased importance of cellular immunity in these infections). Finally, there was no reduction in mortality observed between patients receiving IVIG and those receiving placebo.

Later studies attempted to use lower doses of IVIG to determine if a lower dose of IVIG could still afford protection against bacterial infections. Chapel and associates[22] conducted a randomized, double-blind study to compare 500 or 250 mg per kg IVIG every 4 weeks for 1 year in CLL patients.[22] They found no significant difference in incidence of bacterial infection between the two treatment groups, supporting the use of lower doses of IVIG in CLL.

Despite the utility of IVIG as bacterial prophylaxis, studies still have not demonstrated a decrease in mortality with the use of IVIG or a decreased incidence of serious bacterial infections, and given the cheaper alternative of antibiotic prophylaxis, the cost-effectiveness of IVIG is still in question. When Weeks and coworkers[23] applied decision-analysis modeling to the results of the above RCT of IVIG versus placebo, they found that IVIG treatment yielded a gain of 0.8 quality-adjusted days per patient per year at a cost of $6 million per quality-adjusted life year gained. This means that IVIG treatment every 3 weeks for 1 year in CLL patients resulted in only a slight gain of days free from infection at a tremendous cost.

Nevertheless, some authors have continued to recommend IVIG as prophylaxis against additional episodes of bacterial infection among patients with CLL who have demonstrated prior bacterial infections.

Based on previous studies, the recommended dose is 200 to 400 mg per kg IV at 3- to 4-week intervals.[21,22] There is, however, currently no consensus for how long IVIG treatment should be continued beyond 1 year in CLL patients with hypogammaglobulinemia with a history of serious bacterial infections. At MGH, patients with CLL are not routinely given prophylactic IVIG. Prophylaxis is reserved for selected patients with hypogammaglobulinemia with a prior history of infection who are undergoing general anesthesia.

BMT. Between 1985 and 1993, several controlled trials found that prophylactic IVIG decreased the rates of cytomegalovirus (CMV) infection, interstitial pneumonia, and GVHD in allogeneic BMT recipients.[24-27] These trials, which were the basis of FDA approval for IVIG in BMT patients, were not placebo-controlled. Since the publication of these studies, prophylactic anti-CMV and antifungal medications have been incorporated into the protocols for routine care of BMT recipients with great success. Given the high cost of IVIG relative to these medications and the fact that no studies have demonstrated survival benefit of IVIG in transplantation, the use of prophylactic IVIG has been questioned in BMT.

In the most carefully designed and recent trial of IVIG in allogeneic BMT recipients, Cordonnier and associates[28] found no benefit to the use of IVIG in this population. They performed a multicenter randomized, double-blind trial of IVIG versus placebo in 200 recipients of HLA-matched sibling marrow. Their results indicated no benefit in the incidence of interstitial pneumonia, GVHD, transplantation-related mortality, or overall survival with the use of IVIG. At MGH, prophylactic IVIG is restricted to BMT patients with demonstrated hypogammaglobulinemia (IgG concentration, <400 mg/dL).[29]

Pediatric HIV/AIDS. Although HIV infection results in profound defects in cellular immunity, there is a preponderance of evidence indicating impaired B-lymphocyte function in HIV-infected patients. This is most striking in the pediatric HIV population where serious bacterial infections, especially with encapsulated bacteria, are common in patients not receiving appropriate highly active antiretroviral therapy (HAART). In fact, the clinical definition of AIDS in HIV-infected children includes recurrent serious bacterial infections as one possible defining characteristic. As this discovery evolved, several studies of IVIG in children with AIDS were performed and noted a decreased incidence of serious bacterial infections in children treated regularly with IVIG.[30,31] The largest and best designed trial was conducted by the Intravenous Immune Globulin Study Group of the National Institute of Child Health and Human Development (NICHHD).[31] In this multicenter study, 372 children with HIV were randomly assigned to receive 400 mg per kg IVIG or placebo every 28 days. Children receiving IVIG had significantly fewer minor bacterial infections, serious bacterial infections, and hospitalization days than those receiving placebo. There was, however, no effect on mortality with IVIG treatment.

On the basis of the NICHHD trial, and several smaller studies preceding it, IVIG was approved for use in preventing bacterial infections in children with HIV infection. All of these studies, however, were performed before the era of routine use of HAART. Thus, Spector and colleagues[32] performed another randomized, double-blind study of IVIG versus placebo on HIV-infected children on zidovudine therapy. They found that IVIG only decreased the risk of serious bacterial infections in those children who were not receiving trimethropim-sulfamethazaxole prophylaxis. Thus, the utility of IVIG in preventing bacterial infections in HIV-infected children on HAART and appropriate antimicrobial prophylaxis is questionable. If IVIG is used in HIV-positive children, an infusion of 400 mg per kg every 28 days would be a reasonable dose for the goal of preventing bacterial infections.[32]

The use of IVIG in HIV-infected adults is less well characterized and appears more dubious than the case with children.[33-35] The results of studies of IVIG in adult HIV patients are inconsistent and none of the studies that

have shown benefit of IVIG in preventing serious bacterial infections in HIV-infected adults has been double-blind or placebo-controlled.

Finally, IVIG has been used to treat ITP resulting from HIV infection.[36] Guidelines for the use of ITP in HIV patients do not differ from the use of ITP in other contexts described above.

KD. KD is one of the most common vasculitides of children. Although it is typically a self-limited condition it can result in coronary artery aneurysm, myocardial infarction, congestive heart failure, and arrythmias. As such it is the most common cause of acquired heart disease in children. IVIG plus aspirin given at the first recognition of the diagnosis of KD is the current standard of care. It has been shown repeatedly that a single dose of IVIG at 2000 mg per kg within 10 days of disease onset prevents the development of coronary artery aneurysm in more than 85 percent of patients.[37-40] A Cochrane Database meta-analysis of 16 RCTs of IVIG versus placebo in KD found a definite significant decrease in new coronary artery aneurysms with the use of IVIG.[37] In addition, there is evidence from echocardiography studies that IVIG accelerates reversal of myocardial contractility depression, which results after acute KD.[41]

The initial randomized, placebo-controlled study of IVIG in KD utilized a dose of IVIG at 400 mg per kg per day for 5 consecutive days.[39] A subsequent RCT by Newburger and coworkers[38] found that a single large dose of IVIG at 2000 mg per kg resulted in decreased duration of fever, other indices of inflammation, and days of hospitalization compared with the prior conventional dose of 400 mg per kg per day for 5 days.[38] This result has been supported in further studies as well as in a Cochrane meta-analysis.[37] Thus, the current guideline for treatment of acute KD is to treat patients with a single dose of IVIG at 2000 mg per kg within 10 days of onset of symptoms or as soon as the diagnosis is made. This should be given in conjunction with high-dose aspirin (30-100 mg/kg/day in four divided doses) as documented in studies beyond the scope of this review.

Despite the effectiveness of initial IVIG therapy in preventing the cardiac complications of acute KD, 10 to 15 percent of patients will have evidence of persistent KD 48 hours after initial IVIG treatment. The proper treatment of these patients in so-called "salvage therapy" is not well characterized. Most clinicians opt to treat with repeated doses of IVIG given the evidence of a dose-response effect of IVIG in KD. In a retrospective review of 25 patients who did not respond to initial IVIG treatment of a cohort of 378, it was noted that 15 patients (85%) of the 25 initial nonresponders had a response to a second dose of IVIG.[40] Those patients who received 2000 mg per kg IVIG as the second dose were more likely to become afebrile compared with those who received smaller doses of IVIG. Because of the limitations of this study as a poorly controlled retrospective study, and the fact that there are no prospective trials of retreatment with IVIG, there are no established recommendations for treatment of patients who fail initial IVIG therapy in KD.

Off-label uses for IVIG

Low-birth-weight infants. Nosocomial infections are a major cause of morbidity and mortality in preterm (<37 weeks' gestational age) and low-birth-weight (<2500 g) infants.[42] These newborns are particularly susceptible to infections because they are prone to experience hypogammaglobulinemia after birth. This occurs because maternal transport of immunoglobulin to the fetus occurs in the latter half of the third trimester and endogenous synthesis does not begin until several months after birth. The use of IVIG to correct hypogammaglobulinemia in hopes of preventing infections and decreasing mortality in these patients has been studied extensively.[43-46] Although studies conflict as to the efficacy of IVIG to prevent serious nosocomial infections and sepsis, no study has shown a significant improvement in mortality with administration of IVIG. In fact, a 2004 Cochrane meta-analysis of 19 RCTs found that IVIG results in a 3 to 4 percent decrease in sepsis and nosocomial infections in these infants without any change in mortality.[44] This reduction in infection is not substantial enough to justify routine use of IVIG in preterm or small for gestational age infants. Treatment with IVIG is most justifiable for those infants with documented profound hypogammaglobulinemia (IgG levels, <400 mg/dL).[46] In these infants, 500 to 900 mg per kg IVIG every 14 days to achieve a trough IgG level of 500 to 700 mg per dL has been utilized in prior studies.[43,45,46]

GBS. GBS is an acute inflammatory demyelinating polyneuropathy that can lead to quadraparesis and respiratory muscle paralysis. The exact cause of GBS is unknown but the leading hypothesis states that it is due to an autoimmune response against antigens on peripheral nerves triggered by a preceding infection. As such, a number of immunomodulatory treatments have been utilized in GBS. In the 1980s, therapeutic plasma exchange (PE) became standard treatment of GBS based on the results of multiple randomized trials that demonstrated that PE hastens recovery of neurologic function compared with supportive therapy.[47] Then, in the late 1980s, several small studies revealed some benefit in the use of IVIG in patients with GBS who could not receive PE.[48] This led to six randomized trials of IVIG versus PE in patients with GBS. A meta-analysis of five of these trials involving a total of 536 patients with GBS for no more than 2 weeks revealed equal efficacy between PE and IVIG in time to neurologic recovery.[49] There have been no trials of IVIG versus placebo in GBS because PE was considered the

standard treatment by the time of the first studies of IVIG in treatment of GBS.

The largest trial of IVIG in GBS was a trial of 383 patients randomized to receive IVIG, PE, or PE followed immediately by IVIG within 2 weeks of GBS diagnosis.[50] Patients receiving IVIG were treated with 400 mg per kg per day IVIG for 5 days. Patients were followed for 48 weeks after treatment and the primary outcome was functional disability qualified by a 7-point disability scale. Treatment with IVIG, PE, and PE plus IVIG all yielded similar improvements in disability.

Based on the above data, the current consensus is that IVIG treatment within 2 weeks of diagnosis of GBS is of similar efficacy to PE. The combination of PE plus IVIG has never been shown to be superior to either treatment alone.

CIDP. In contrast to the acute inflammatory demyelinating polyneuropathy of GBS, CIDP is an insidious illness that leads to the slow development of neurologic disability, and unlike trials of IVIG in GBS, studies of IVIG in CIDP have included small numbers of patients and have had conflicting results. For example, Hahn and associates[51] conducted a double-blind, placebo controlled, crossover study of IVIG versus placebo in 30 patients with CIDP.[51] Based on quantitative assessment of neurologic function and electrophysiology studies, they found significant differences in favor of IVIG 28 days after treatment. In contrast, another double-blind placebo-controlled study of IVIG in 28 CIDP patients found no benefit in IVIG versus placebo.[52]

Currently, there are no definitive data regarding the use of IVIG in CIDP. This is because patients with varying courses of CIDP (i.e. continuous progression vs. stepwise progression) may respond differently to IVIG treatment[51] and studies have utilized different measures of outcome at different times after treatment making interpretation of results difficult.[51-53] Although there is no consensus dosing recommendation, the majority of studies examining use of IVIG in CIDP utilize a high-dose treatment schedule of 400 mg per kg per day for 5 consecutive days.[52,53] Patients on maintenance therapy may not require such high-dose treatment.

MMN. MMN is an immune-mediated neuropathy that is in the differential diagnosis of CIDP. MMN is characterized by a slowly progressive, asymmetric weakness of the limbs without sensory loss. The symptoms usually begin distally, travel proximally, and are most common in the upper extremities.[54] The electrophysiologic hallmark feature of MMN in nerve conduction studies is the presence of a conduction block that is a failure of neural impulse to travel through a structurally intact axon.[54] In addition, 30 to 50 percent of patients have detectable IgM antibodies to GM_1 ganglioside.[54]

In contrast to CIDP, corticosteroids and PE are ineffective in the treatment of MMN.[55] Since the description of MMN in 1985, anecdotal reports and case series have noted that IVIG is the only effective therapy for MMN, other than cyclophosphamide.[54] Thus far, there have been four double-blind, placebo controlled studies of IVIG in MMN.[56-59] The largest study investigated the use of IVIG (500 mg/kg/day for 5 consecutive days) every month for 3 months in 19 patients with MMN.[56] Subjective and objective evaluation of muscle function at 4 and 7 months found significant improvement in muscle strength and ability to perform motor activities of daily living.

The downside to treatment with IVIG is that therapy may need to be repeated at a minimum of every 2 to 3 months for sustained improvement of motor function.[60] An observational study of 11 patients with MMN receiving IVIG every 2 to 3 months for 4 to 8 years found that IVIG did not induce remission in any patient and cessation of IVIG treatment resulted in progression of weakness in affected muscle groups.[60] Unfortunately, at the present time there is no known alternative treatment in MMN that is more efficacious than IVIG.

Multiple sclerosis. A number of immunomodulatory medications have been studied in multiple sclerosis (MS) to halt disease progression and to attempt to reverse neurologic disability. There is evidence from basic science studies that IVIG may contain anti-idiotypic antibodies, which may protect myelin by binding myelin-destructive autoantibodies,[61] circulating cytokines,[62] and Fc receptors on immune cells.[63] IVIG has been studied in the clinical setting to treat relapsing-remitting MS (RR-MS) and secondary progressive MS (SP-MS). In short, there is some evidence that IVIG reduces attack rate in RR-MS[64-66] but there is little convincing evidence that IVIG has any utility in SP-MS.[67-69] The American Academy of Neurology describes the treatment of RR-MS with IVIG as a "Class C" recommendation, meaning that it is possibly effective.[70] In contrast, treatment of SP-MS with IVIG is stated as being supported by inadequate and conflicting data.

The most convincing evidence to support the use of IVIG in RR-MS comes from a randomized, placebo-controlled, multicenter study performed by the Austrian Immunoglobulin in Multiple Sclerosis Study Group.[64] In this study, 150 patients with MS were randomized to receive monthly IVIG infusions or placebo for 2 years. The primary outcome measure in this study, as in most MS trials, was the effect on clinical disability as measured by Kurtzke's expanded disability status scale. This study found significant beneficial effect on the functional status of patients receiving monthly IVIG infusions for RR-MS. These results must be interpreted with caution because most of the long-term disability of MS occurs over many years. Thus, the true effect of IVIG on long-term disability may not be fully evident after only 2 years of follow-up.[70]

The largest and most well-controlled trial of IVIG in SP-MS revealed no utility in use of IVIG in these patients.[67] This study randomly assigned 318 patients to IVIG

(1000 mg/kg/month for 27 months) or placebo. There was no significant effect of IVIG infusion on expanded disability status scale score or on the quantity of MRI lesions at any point within 2 years of treatment. All of the trials that show evidence to support the use of IVIG in SP-MS were smaller and of questionable design.

Myasthenia gravis. Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and fatigability of voluntary muscles. In 80 to 90 percent of patients with MG, IgG autoantibodies to the nicotinic acetylcholine receptor (anti-AchRAb) are detectable in the blood.[71] In a proportion of the remaining patients without anti-AchRAb, antibodies to the neuromuscular junction antigen MuSK may be found.[72]

The use of IVIG in MG treatment has been reported in many different clinical scenarios. The only evidence for effectiveness of IVIG in MG has been the use of IVIG in patients experiencing exacerbations of MG not responsive to other medications.[73] There is no sufficient placebo-controlled evidence for the use of IVIG in stable MG, as a steroid-sparing agent in MG, or before thymectomy.[73] There are multiple case reports, however, to suggest that IVIG may be effective in such contexts.[74-76]

The single published randomized trial of IVIG in MG exacerbation found that IVIG was as effective as PE in improving symptoms of MG exacerbation.[77] On the basis of this study, IVIG (at a dose of 400-600 mg/kg/day for 3-5 consecutive days) appears to be a reasonable treatment option in the management of myasthenic crisis. Further controlled studies of IVIG in the management of MG at other stages are clearly needed.

Solid organ transplantation. IVIG has been studied in the context of solid organ transplantation to decrease anti-HLA alloantibody titers before transplantation,[78] to prevent humoral rejection of organs after transplantation,[79-82] in the routine use as immunomodulatory medication after retransplantation,[81] and as an alternative immunosuppressant to more widely used immunosuppressive medications.[80] In none of these instances has there been a placebo-controlled multicenter trial.

The most frequently studied use of IVIG in organ transplantation has been use of IVIG to reduce HLA alloantibody titers. Glotz and coworkers[78] were the first to report that in some patients repeated infusions of IVIG led to a significant and prolonged reduction in HLA alloantibody titers.[78] In this uncontrolled pilot study, five dialysis patients awaiting renal transplantation for more than 1 year with greater than 25 percent panel-reactive antibodies (PRAs) received IVIG (400 mg/kg) after four consecutive dialysis treatments. This resulted in a decrease in mean PRA that was sustained for more than 3 months in four of five patients. Subsequent studies investigated the use of IVIG to decrease HLA alloantibody titers after transplantation in hopes of controlling antibody-mediated rejection episodes.[79,82,83] Although several selected cases of improvement in acute humoral rejection have been associated with infusion of IVIG, all reports are poorly controlled and have combined IVIG therapy with an assortment of immunosuppressive regimens, making generalizable conclusions difficult.

The best designed trial of IVIG in the context of solid organ transplantation was performed by Peraldi and coworkers[81] in routine administration of IVIG in retransplanted patients. In this study, 41 patients undergoing a second cadaveric renal transplant were randomly assigned to receive IVIG or no treatment in addition to a standard immunosuppressive protocol. Patients randomized to receive IVIG were found to have a significantly higher 5-year survival rate compared to those not receiving IVIG. In addition, it was noted that patients receiving IVIG experienced a significantly shorter delay in graft function. This study suggests that administration of IVIG in the first 5 days after retransplantation may improve graft function as well as patient survival.

Finally, IVIG has been studied as an alternative means of controlling steroid-resistant rejection episodes. In a study by Casadei and associates,[80] 30 patients undergoing steroid-resistant rejection of kidney allografts were randomly assigned to receive the anti-CD3 antibody OKT3 (14 days) or IVIG (500 mg/kg/day for 7 days).[80] Patient survival and the incidence of rejection were essentially the same in both treatment groups. This result implies that IVIG could be used as an alternative to antilymphocyte medications in controlling steroid-resistant rejection. This study is worthwhile repeating in a larger study as IVIG has fewer unwanted side effects than antilymphocyte immunosuppressants such as OKT3.

Further prospective studies with larger patient samples are needed to more fully determine the role of IVIG in decreasing humoral rejection before transplantation, controlling humoral rejection after transplantation, and affecting patient survival after transplantation.

Autoimmune hemolytic anemia. Given the relatively large experience and success with the use of IVIG in the treatment of ITP, IVIG has been used to treat other autoimmune cytopenic disorders, such as autoimmune hemolytic anemia (AIHA). Published literature on the treatment of AIHA with IVIG, however, is limited to small retrospective studies and case series. Furthermore, all published studies evaluating the effectiveness of IVIG in AIHA have examined use of IVIG in treatment of AIHA due to heterogeneous causes.[84-86]

Based on initial case reports, it is believed that treatment of AIHA requires larger doses of IVIG than are conventionally used in ITP.[85,86] Furthermore, it has been shown that IVIG, like corticosteroids, is much more likely to be effective in the treatment of warm-antibody AIHA than in cold-antibody AIHA.[87] In the largest retrospective study of the use of IVIG in warm-antibody AIHA, however, it was determined that IVIG yielded a response in only

about one-third of the 73 total patients.[84] Furthermore, response was transient in almost all patients who did respond unless IVIG was given repeatedly every 3 weeks. On this basis, IVIG is not recommended as standard therapy of AIHA. The role of IVIG in AIHA is believed to be in cases where AIHA is refractory to conventional therapy with corticosteroids and as a possible temporizing measure to perform splenectomy.[88]

Thus, IVIG likely has some benefit in warm-antibody AIHA. No controlled trials have been performed, however, and in most patients who do respond to IVIG, improvement in hemolysis is transient. Clinical experience from published reports of IVIG use in AIHA note that a dose as high as 400 to 1000 mg per kg per day for 5 days is necessary for successful treatment of AIHA.[85-87]

Necrotizing fasciitis. Necrotizing fasciitis is a rapidly progressive, tissue-destroying invasive infection caused by *Streptococcus pyogenes* (group A *Streptococcus*). Group A *Streptococcus* causes a spectrum of invasive diseases including septicemia, toxic shock syndrome, and necrotizing fasciitis. All of these are mediated by a streptococcal exotoxin, which behaves as a superantigen. A superantigen bypasses the normal route of antigen processing and presentation and, instead, directly cross-links the constant portion of the T-cell receptor and the HLA Class II molecule. Superantigens thus quickly result in massive production of inflammatory cytokines.

Takei and coworkers[89] were first to discover that IVIG contains antibodies that inhibit superantigen elicited T-cell activation.[89] In this in vitro study, it was determined that IVIG contains antibodies that bind several staphylococcal superantigens and prevent their stimulation of peripheral blood T cells. In a later in vivo study, Norrby-Teglund and colleagues[90] examined plasma samples from 15 patients with invasive streptococcal infections before and after IVIG treatment. They noted that plasma treated with IVIG inhibited the activity of streptococcal antigens to elicit cytokine production. This suggested that treatment with IVIG confers inhibition against streptococcal superantigens.

Although the above studies demonstrated a mechanism of activity of IVIG in treating invasive staphylococcal and streptococcal diseases, studies examining clinical outcome with use of IVIG in these illnesses have been very limited. All of the studies are uncontrolled case series or poorly controlled case-control studies.[91-94] Thus, currently there are no strong data to support or refute the use of IVIG to improve clinical outcome in staphylococcal and streptococcal superantigen-mediated illnesses. Dosing of IVIG in studies examining IVIG use in these toxin-mediated illnesses has ranged from 200 to 800 mg per kg per day for 1 to 5 days.[93] At MGH, patients are candidates for IVIG if they are sufficiently ill to require critical care unit support and have documented evidence of fasciitis and microbiologic data consistent with invasive streptococcal infection (culture or Gram stain). The dose used is 1000 mg per kg with up to two repeat doses of 500 mg per kg on Days 2 and 3 if the patient remains pressor-dependent.

CONCLUSION

Our data indicate that only a few indications account for most of the $4 million annual expenditure for IVIG in 2004 at MGH. Nearly all of the usage is consistent with hospital review guidelines. Our literature review demonstrated that published reports concerning IVIG continue to grow at a tremendous pace, but that few high-quality RCTs have been reported. Even in some conditions where IVIG is FDA-approved for use, IVIG therapy may be outdated or not cost-effective. Such is the case with use of IVIG to prevent infection in BMT patients and pediatric HIV patients as studies showing efficacy of IVIG did not use alternative treatments relevant to current clinical practice. Despite the success of IVIG in the treatment of some conditions (e.g., primary hypogammaglobulinemia), there seem to be few indications where IVIG is essential therapy. Better quality clinical trials are needed to understand the proper value of IVIG therapy, especially for conditions such as CIDP that consume large quantities of product.

REFERENCES

1. Knezevic-Maramica I, Kruskall MS. Intravenous immune globulins: an update for clinicians. Transfusion 2003;43: 1460-80.
2. Ratko T. Technology assessment: intravenous immunoglobulin preparationos. Oak Brook (IL): University HealthSystem Consortium; 1999.
3. Facts and Figures [database on the Internet]. Boston: Massachusetts General Hospital; c2004. Available from: http://www.massgeneral.org/news/for_reporters/facts_and_figures.htm
4. Chen C. Result of the UHC intravenous immunoglobulin multicenter drug surveillance study. Oak Brook (IL): University HealthSystem Consortium; 1998.
5. IVIG trials for off-label uses recommended by HHS committee on blood safety. In: The Pink Sheet. Chevy Chase (MD): FDC Reports; 1998.
6. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981;1:1228-31.
7. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002;346:995-1008.
8. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc 2004;79:504-22.
9. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and

oral prednisone in childhood acute immune thrombocytopenic purpura. Lancet 1994;344:703-7.
10. Jacobs P, Wood L, Novitzky N. Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: a prospective randomized clinical trial. Am J Med 1994;97: 55-9.
11. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. Lancet 2002;359:23-9.
12. Godeau B, Caulier MT, Decuypere L, et al. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0.5 and 1 g/kg b.w. Br J Haematol 1999;107: 716-9.
13. Bruton OC. Agammaglobulinemia. Pediatrics 1952;9:722-8.
14. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 1999;134:589-96.
15. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002;109:1001-4.
16. Bonilla FA, Geha RS. 12. Primary immunodeficiency diseases. J Allergy Clin Immunol 2003;111(2 Suppl):S571-81.
17. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987;1:1075-7.
18. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: a randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001;135:165-74.
19. Lee ML, Gale RP, Yap PL. Use of intravenous immunoglobulin to prevent or treat infections in persons with immune deficiency. Annu Rev Med 1997;48:93-102.
20. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP. Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 2000;75:1039-54.
21. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988;319:902-7.
22. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol 1994;88:209-12.
23. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. N Engl J Med 1991;325:81-6.
24. Abdel-Mageed A, Graham-Pole J, Del Rosario ML, et al. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. Bone Marrow Transplant 1999;23:929-32.
25. Winston DJ, Antin JH, Wolff SN, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. Bone Marrow Transplant 2001;28:187-96.
26. Winston DJ, Ho WG, Lin CH, et al. Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med 1987;106:12-8.
27. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 1990;323:705-12.
28. Cordonnier C, Chevret S, Legrand M, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. Ann Intern Med 2003;139:8-18.
29. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep 2002;51(RR-8):1-52.
30. Mofenson LM, Moye J Jr, Bethel J, et al. Prophylactic intravenous immunoglobulin in HIV-infected children with CD4+ counts of, 0.20 x 10(9)/L or more: effect on viral, opportunistic, and bacterial infections. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. JAMA 1992;268:483-8.
31. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. N Engl J Med 1991;325:73-80.
32. Spector SA, Gelber RD, McGrath N, et al. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. Pediatric AIDS Clinical Trials Group. N Engl J Med 1994;331:1181-7.
33. Kiehl MG, Stoll R, Broder M, et al. A controlled trial of intravenous immune globulin for the prevention of serious infections in adults with advanced human immunodeficiency virus infection. Arch Intern Med 1996;156: 2545-50.
34. Schrappe-Bacher M, Rasokat H, Bauer P, et al. High-dose intravenous immunoglobulins in HIV-1-infected adults with AIDS-related complex and Walter-Reed 5. Vox Sang 1990; 59(Suppl 1):3-14.

35. Williams PE, Thompson C, Yap PL, Brettle RP. Controlled study of intravenous IgG therapy for HIV-infected adults with recurrent bacterial infections. Vox Sang 1991;60:126-7.
36. Yap PL. Does intravenous immune globulin have a role in HIV-infected patients? Clin Exp Immunol 1994;97(Suppl 1):59-67.
37. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2003;(4): CD004000.
38. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633-9.
39. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;2:1055-8.
40. Burns JC, Capparelli EV, Brown JA, et al. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. Pediatr Infect Dis J 1998;17:1144-8.
41. Newburger JW, Sanders SP, Burns JC, et al. Left ventricular contractility and function in Kawasaki syndrome: effect of intravenous gamma-globulin. Circulation 1989;79: 1237-46.
42. Stoll BJ, Gordon T, Korones SB, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1996;129:63-71.
43. Fanaroff AA, Korones SB, Wright LL, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 1994;330:1107-13.
44. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Cochrane Database Syst Rev 2004;(1):CD000361.
45. Baker CJ, Melish ME, Hall RT, et al. Intravenous immune globulin for the prevention of nosocomial infection in low-birth-weight neonates. The Multicenter Group for the Study of Immune Globulin in Neonates. N Engl J Med 1992;327:213-9.
46. Clapp DW, Kliegman RM, Baley JE, et al. Use of intravenously administered immune globulin to prevent nosocomial sepsis in low birth weight infants: report of a pilot study. J Pediatr 1989;115:973-8.
47. The utility of therapeutic plasmapheresis for neurological disorders. NIH Consensus Development. JAMA 1986; 256:1333-7.
48. Kleyweg RP, van der Meche FG, Meulstee J. Treatment of Guillain-Barre syndrome with high-dose gammaglobulin. Neurology 1988;38:1639-41.
49. Hughes RA, Raphael JC, Swan AV, Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev 2004;(1):CD002063.
50. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Lancet 1997;349:225-30.
51. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, cross-over study. Brain 1996;119:1067-77.
52. Vermeulen M, van Doorn PA, Brand A, et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 1993;56:36-9.
53. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 1994;36:838-45.
54. Van Asseldonk JT, Franssen H, Van den Berg-Vos RM, et al. Multifocal motor neuropathy. Lancet Neurol 2005;4:309-19.
55. Pestronk A, Adams RN, Kuncl RW, et al. Differential effects of prednisone and cyclophosphamide on autoantibodies in human neuromuscular disorders. Neurology 1989;39:628-33.
56. Leger JM, Chassande B, Musset L, et al. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain 2001; 124:145-53.
57. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 1995;59:248-52.
58. Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. Neurology 2000;55:1256-62.
59. Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology 1994;44(3 Pt 1):429-32.
60. Van den Berg LH, Franssen H, Wokke JH. The long-term effect of intravenous immunoglobulin treatment in multifocal motor neuropathy. Brain 1998;121:421-8.
61. Rossi F, Dietrich G, Kazatchkine MD. Anti-idiotypes against autoantibodies in normal immunoglobulins: evidence for network regulation of human autoimmune responses. Immunol Rev 1989;110:135-49.
62. Andersson UG, Bjork L, Skansen-Saphir U, Andersson JP. Down-regulation of cytokine production and interleukin-2 receptor expression by pooled human IgG. Immunology 1993;79:211-6.
63. Jungi TW, Brcic M, Kuhnert P, et al. Effect of IgG for intravenous use on Fc receptor-mediated phagocytosis by human monocytes. Clin Exp Immunol 1990;82:163-9.
64. Fazekas F, Deisenhammer F, Strasser-Fuchs S, et al. Randomised placebo-controlled trial of monthly

intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. Austrian Immunoglobulin Multiple Sclerosis Study Group. Lancet 1997;349:589-93.
65. Achiron A, Gabbay U, Gilad R, et al. Intravenous immunoglobulin treatment in multiple sclerosis: effect on relapses. Neurology 1998;50:398-402.
66. Sorensen PS, Wanscher B, Jensen CV, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. Neurology 1998;50:1273-81.
67. Hommes OR, Sorensen PS, Fazekas F, et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. Lancet 2004;364:1149-56.
68. Noseworthy JH, O'Brien PC, Weinshenker BG, et al. IV immunoglobulin does not reverse established weakness in MS. Neurology 2000;55:1135-43.
69. Sorensen PS, Haas J, Sellebjerg F, et al. IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. Neurology 2004;63:2028-33.
70. Goodin DS, Frohman EM, Garmany GP Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002;58: 169-78.
71. Illa I. IVIg in myasthenia gravis, Lambert Eaton myasthenic syndrome and inflammatory myopathies: current status. J Neurol 2005;252(Suppl 1):i14-i8.
72. Hoch W, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 2001;7:365-8.
73. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2003; (2):CD002277.
74. Hilkevich O, Drory VE, Chapman J, Korczyn AD. The use of intravenous immunoglobulin as maintenance therapy in myasthenia gravis. Clin Neuropharmacol 2001;24: 173-6.
75. Arsura E. Experience with intravenous immunoglobulin in myasthenia gravis. Clin Immunol Immunopathol 1989;53(2 Pt 2):S170-9.
76. Ronager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artif Organs 2001;25:967-73.
77. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol 1997;41:789-96.
78. Glotz D, Haymann JP, Sansonetti N, et al. Suppression of HLA-specific alloantibodies by high-dose intravenous immunoglobulins (IVIg): a potential tool for transplantation of immunized patients. Transplantation 1993;56: 335-7.
79. Glotz D, Antoine C, Julia P, et al. Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). Am J Transplant 2002;2:758-60.
80. Casadei DH, del C Rial M, Opelz G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation 2001;71:53-8.
81. Peraldi MN, Akposso K, Haymann JP, et al. Long-term benefit of intravenous immunoglobulins in cadaveric kidney retransplantation. Transplantation 1996;62: 1670-3.
82. Jordan SC, Quartel AW, Czer LS, et al. Posttransplant therapy using high-dose human immunoglobulin (intravenous gammaglobulin) to control acute humoral rejection in renal and cardiac allograft recipients and potential mechanism of action. Transplantation 1998;66:800-5.
83. Luke PP, Scantlebury VP, Jordan ML, et al. IVIG rescue therapy in renal transplantation. Transplant Proc 2001;33:1093-4.
84. Flores G, Cunningham-Rundles C, Newland AC, Bussel JB. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. Am J Hematol 1993;44:237-42.
85. Bussel JB, Cunningham-Rundles C, Abraham C. Intravenous treatment of autoimmune hemolytic anemia with very high dose gammaglobulin. Vox Sang 1986;51:264-9.
86. Majer RV, Hyde RD. High-dose intravenous immunoglobulin in the treatment of autoimmune haemolytic anaemia. Clin Lab Haematol 1988;10: 391-5.
87. Bjorkholm M. Intravenous immunoglobulin treatment in cytopenic haematological disorders. J Intern Med 1993; 234:119-26.
88. Ritch PS, Anderson T. Reversal of autoimmune hemolytic anemia associated with chronic lymphocytic leukemia following high-dose immunoglobulin. Cancer 1987;60: 2637-40.
89. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens [see comment]. J Clin Invest 1993;91:602-7.
90. Norrby-Teglund A, Kaul R, Low DE, et al. Plasma from patients with severe invasive group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal superantigen-induced T cell proliferation and cytokine production. J Immunol 1996;156:3057-64.
91. Yong JM. Necrotising fasciitis. Lancet 1994;343: 1427.
92. Lamothe F, D'Amico P, Ghosn P, et al. Clinical usefulness of intravenous human immunoglobulins in invasive group A streptococcal infections: case report and review. Clin Infect Dis 1995;21:1469-70.

93. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis 1999;28:800-7.

94. Haywood CT, McGeer A, Low DE. Clinical experience with 20 cases of group A streptococcus necrotizing fasciitis and myonecrosis: 1995 to 1997. Plast Reconstr Surg 1999;103: 1567-73.