Use of Intravenous Immunoglobulins for Prophylaxis or Treatment of Infectious Diseases

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By the advent of the era of antimicrobial drugs, passive immunization with pathogen-specific animal (usually horse, cow, or rabbit) sera for the prophylaxis or treatment of certain bacterial infections, bacterial toxin-mediated diseases such as tetanus, or serious viral infections such as rabies had become very sophisticated (13, 39, 43). Antimicrobial chemotherapy made it no longer necessary to expose patients to the serious risks posed by injection of animal sera for the treatment of pneumonia and sepsis. It is paradoxical that 60 years later, antimicrobial resistance of some bacterial and viral pathogens, new iatrogenic diseases arising from aggressive therapies for cancer or organ failure, and improved understanding of the pathogenesis and immunology of viral and bacterial infections have brought renewed interest in passive immunization for the prevention and treatment of certain infectious diseases.

Nearly 50 years have passed since Ogden C. Bruton’s report of an 8-year-old boy with recurrent Streptococcus pneumoniae bacteremia whose plasma contained little gamma globulin (immunoglobulin G [IgG]). Bruton treated the boy’s agammaglobulinemia with regular intramuscular (i.m.) injections of human-plasma-derived IgG. The treatment resulted in increased serum IgG levels and an impressive reduction in the number of serious bacterial infections he experienced (6). At the time of Bruton’s report, few appreciated the implications of his seminal observations.

Near the end of World War II, Edwin Cohn’s pooled human plasma “fraction 2” was injected intramuscularly to control outbreaks of red measles and infectious hepatitis in U.S. soldiers (7, 34, 53). Soon after, fractionated IgG became generally available for i.m. use. At that time, human IgG treatment was recommended to modify disease expression of measles and hepatitis A, but other indications for its clinical use were not fully defined. As IgG could be safely given only by the i.m. route, doses were limited to about 100 to 150 mg/kg of body weight/month. Larger doses were too painful. In the decades following Bruton’s report, the development of simple and reliable IgG assays permitted the identification of additional hypogammaglobulinemic patients. Also identified were preterm neonates, some other normal infants with transient low IgG levels in the first year of life, older infants, and occasional children and adults with congenital or acquired hypogammaglobulinemia (51). In the past 25 years, patients with lymphoid malignancies or those who were immune suppressed for organ transplantation or undergoing therapy for cancer were found to commonly experience serious infections. Might these patients also benefit from immune augmentation with IgG?

When empiric parenteral immunoglobulins were given to these patients, it remained uncertain whether they experienced significantly fewer serious infections.

An assumption underlying IgG formulations was that plasma pooled from large numbers of donors ensured that IgG lots contained comparable levels of antigen-specific antibodies. Despite this assumption, we and others demonstrated substantial lot-to-lot differences in neutralizing (NT) antibody levels for respiratory syncytial virus (RSV) and for specific opsonic antibodies to group B streptococci (GBS) (16, 18). Manufacturers were not required to quantify specific antibody content in their preparations. Hence, practitioners could not be confident of the quantities of pathogen-specific antibodies present in any given production lot of IgG.

To overcome the dosing limitations of injectable IgG, techniques were developed to prepare IgG for safe intravenous (i.v.) administration. By the early 1980s, several IgG preparations were licensed for i.v. use (IVIg), permitting as much as 10- to 20-fold increases in the amounts that could be given. (Table 1). The new technology also permitted the preparation of human hyperimmune globulins recommended for the prevention or treatment of tetanus, botulism, hepatitis B, rabies, and varicella (Table 2) (2).

Today, with more than 50 years of clinical experience with generic pooled human IgG for general treatment and/or prevention of infectious diseases, the only clear indications for use, with the exception of specific recommendations for the prevention of hepatitis A and measles, are congenital or acquired deficiencies in immunoglobulin production. Whether IgG or IVIg benefit patients with iatrogenic immunodeficiencies remains less certain.

A new era in infectious disease prevention began with the June 1998 Food and Drug Administration (FDA) licensing of palivizumab (Synagis) (9). Palivizumab is a “humanized” mouse monoclonal antibody formulated to prevent RSV pulmonary infections in high-risk patients, especially infants and young children. Human and humanized monoclonal antibodies seek to overcome several shortcomings of IVIg preparations by targeting specific viral or bacterial antigens responsible for disease pathogenesis. They improve safety by substantially reducing the amounts and diversity of proteins that must be given. As monoclonal antibodies are not derived from human blood, the risk for contamination with hepatitis B or C virus, HIV, or other blood-borne viruses is markedly reduced.

This brief review will summarize contemporary indications for IVIg infectious diseases prophylaxis and examine recommendations for use of the recently engineered monoclonal antibody palivizumab for prevention of RSV infection (19, 36).
mented that maternally derived IgG levels in term infants
not to reduce the incidence of serious infections. Though IgG-
lactogenemia of early infancy. i.m. treatment of infants with
levels by 4 to 6 months of age. Preterm infants have less
rapidly after birth, to levels sometimes less than a quarter of
blood serum usually exceeded maternal levels. Rapid growth of
infection; if not available, IVIg is recommended,
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antibodies to affect bacterial killing and clearance. These
in vivo (16) modeling showed that for treatment of GBS in-
antibodies were present. About 20 years ago, in vitro (21) and
remia, pneumonia, soft tissue infection, and sepsis are far more

at or near the time of parturition, most other possible indica-
tions for infectious disease prophylaxis remain speculative
(50). IVIg treatment appeared to improve the outcome of an
echovirus 11 infection in a patient with agammaglobulinemia
(28), as well as in a nursery outbreak of echovirus 11 (32).
These and other studies implied that prophylaxis or treatment
with IgG might be beneficial if sufficient levels of agent-specific
antibodies were present. About 20 years ago, in vitro (21) and
in vivo (16) modeling showed that for treatment of GBS in-
fected IgG must contain sufficient quantities of specific func-
tional antibodies to affect bacterial killing and clearance. These
and complementary data led to prospective treatment trials
with IVIg or with GBS hyperimmune IVIg to reduce mortality
rates in infants at risk for perinatal GBS infection. These large
and complicated studies yielded equivocal results (54, 55). Co-
inedly, other neonatal sepsis prevention trials were con-
ducted. The National Institutes of Health-sponsored Neonatal
Research Network conducted prophylactic studies with a large
group of very-low-birth-weight infants. IVIg failed to reduce
the incidence of hospital-acquired infections in these infants
(15). Baker and associates conducted a similar large trial with
similar results (5).

Despite the discouraging results, interest in the use of IVIg
for prevention of neonatal infections continued. A November
2000 report by Sandberg and associates (42) compared infec-
tion prophylaxis results for preterm infants with cord blood
levels of ≤4 g/liter with the results for those with higher
levels. Babies received 1 g of IVIg per kg on days 0, 3, 7, 14,
and 21 (n = 40) or placebo (n = 41). Again, no significant
reduction in infectious episodes or mortality was observed in
the IVIg-treated subjects compared to placebo recipients.
H. R. Hill, in an editorial response to the Sandberg study noted
that based on “the study by Sandberg et al., and the other
controlled studies in the literature, IVIg should not be used in
an attempt to prevent nosocomial infections in premature in-
fants” (23).

Ohlsson and Lacy conducted a recent meta-analysis (33).
Data were combined from multiple randomized, placebo-con-
trolled studies of immunoglobulin for the prevention of noso-
comial infections in preterm or low-birth-weight infants.
Among the 5,054 infants included in the analysis, only a slight
reduction in sepsis (3 to 4%) and no changes in other morbid-
ities were found.

Clearly, perinatal, later-onset, and nursery-acquired bacte-
"remia, pneumonia, soft tissue infection, and sepsis are far more
complicated in their pathogenesis than just reduced levels of
IgG. The multiplicity of studies conducted during the past 20
years confirm that IVIg treatment is only marginally useful in
the prevention or treatment of these serious neonatal infec-
tions. The treatment is expensive and presents an additional
risk of exposing recipients to blood-borne pathogens. Hence,
the prophylactic use of IVIg for the prevention of neonatal
nosocomial infections should be discouraged. There remains
hope that monoclonal antibody preparations, selected for spe-
cific antigenic targets, may yet make it possible to reduce the
incidence of GBS, gram-negative enteric-pathogen, and staph-
ylococcal infections. However, any new prophylactic monoclo-
nal antibody preparation will require rigorous testing in
blinded, placebo-controlled trials.
Bacterial sepsis syndromes in adults. IVIg prophylaxis and treatment of bacterial sepsis syndromes in adults have also yielded equivocal results. Alan Cross wrote in 1995, “this form of adjunctive therapy has been implemented for infectious but also for noninfectious conditions, often in the absence of convincing data to establish its efficacy” (10). Werden’s recent report supports Cross’s analysis (56). Yet recently, Douzinas and colleagues reported that high-dose IV Ig (250 mg/kg/day infused on days 2, 3, and 6) significantly reduced the incidence of septic complications in a small group of patients hospitalized following serious trauma (12). Larger studies are required to confirm these observations. Despite such occasional reports to the contrary, neither IV Ig prophylaxis nor treatment is clearly beneficial for prevention of nosocomial bacterial infections in ill or immunocompromised adults. Whether pathogen-specific monoclonal antibodies or well-defined hyperimmune immunoglobulins will ultimately benefit sepsis-prone adults remains to be determined.

Antibody prophylaxis and treatment of RSV infections. (i) Animal studies. Studies conducted with cotton rats in the 1980s demonstrated that parenteral administration of human IV Ig containing large quantities of RSV NT antibodies significantly reduced the incidence of bronchiolitis and/or pneumonia in vivo (22, 40, 41). NT levels were known IV Ig treatment did not significantly influence sufficient amounts of RSV antibodies might be useful for treatment and for prophylaxis of RSV infections in infants and young children (20, 36, 38).

(ii) Human studies. Despite animal evidence suggesting therapeutic efficacy, well-conducted clinical trials in which NT levels were known IV Ig treatment did not significantly shorten the duration of hospitalization of infants with RSV bronchiolitis and/or pneumonia (22, 40, 41).

Prophylaxis with high-titered human polyclonal RSV IV Ig (Respigam) does not significantly reduce the incidence of RSV infections. However, monthly prophylaxis significantly reduced the severity of RSV infections in very young high-risk patients who became infected with RSV (9, 17). Reductions in hospitalization rates and significantly shorter hospital stays compared to well-matched control patients were observed (9, 17). Yet, Respigam is expensive and requires insertion of a venous line for i.v. administration. Infusions of 750 mg of RSV IV Ig per kg are necessary at least monthly to provide sufficient protection. Production challenges, the task of finding populations of high-NT plasma donors, the cost, and the difficulty in the administration of RSV IV Ig prompted the development of a humanized mouse monoclonal antibody (palivizumab) directed against a critical neutralizing epitope located on the RSV fusion protein. As with Respigam, in the 1996–1997 (IMPact) clinical trial palivizumab, 15 mg/kg administered i.m. once each month, did not significantly reduce RSV infection rates. Rather, it resulted in significant reductions in RSV infection severity, manifested as reduction in hospitalization rate (P = 0.000004) and duration of hospitalization (P < 0.001) for high-risk infants (24). Palivizumab was licensed by the FDA in June 1998 for RSV infection prophylaxis for certain preterm infants and neonatal intensive care nursery graduates with chronic lung disease.

A retrospective follow-up analysis of palivizumab recipients from nine sites across the United States compared the results from the first year of licensed clinical use with infants enrolled in the IMPact trial (24). Data were reviewed for 1,839 children, each of whom had received at least one palivizumab injection, between September 1998 and May 1999. The investigators found a 2.9% RSV-related hospitalization rate for palivizumab recipients compared to a 4.8% rate for patients enrolled in the IMPact trial. However, since there was not a control group for this study, the results cannot be fully compared (47). Based on existing trial data and FDA approval, the American Academy of Pediatrics’ Committee on Infectious Diseases recommends palivizumab for RSV prophylaxis for “infants and children younger than two years of age with chronic lung disease (CLD) who have required medical therapy for CLD within six months before the anticipated RSV season” (3). Clinical trials are under way examining whether palivizumab may benefit transplant and cancer patients who are also at high risk for serious RSV infections.

IV Ig and CMV infections in transplant patients. Cytomegalovirus (CMV) infection emerged as a serious problem for patients immunocompromised by treatment for malignancies or organ transplantation. In 1983–1984 Meyers and coworkers (29) and Condie and O’Reilly (8) reported that serious CMV infections may be attenuated or prevented by passive immunization with “cytomegalovirus immune globulin.” Cytomegalovirus immunoglobulin (CIg) was licensed in 1991 and has regularly been utilized to reduce CMV morbidity and mortality. Treatment is expensive and does not always prevent serious CMV disease in severely immunocompromised patients. For these patients, it is imperative that other preventive strategies also be employed. These include serologic matching of patients and donors, screening of blood and plasma for CMV antibodies to confirm prior infection, and where possible, reducing transplantation of organs from CMV-positive donors to CMV-negative recipients. Several studies demonstrate that CIg infusion moderately reduces serious CMV infections associated with renal and liver transplants and improves survival of infected patients (14, 44, 45, 46). Efforts to further reduce infection rates or improve survival of CMV-infected patients by adding prophylactic ganciclovir only slightly improved clinical outcomes (25). In summary, CIg prophylaxis is indicated for patients at risk for CMV infections following solid organ and perhaps bone marrow transplantation. For patients receiving organs from CMV-positive donors, prophylaxis may be improved by concomitant ganciclovir therapy.

IV Ig or hyperimmune IV Ig in prevention and treatment of mother-infant HIV infection. (i) Transmission. Infants and children with AIDS benefit from IV Ig therapy together with antiviral therapy if they are also hypogammaglobulinemic (IgG < 250 mg/dl) or have had two or more serious bacterial infections in the previous year. Other indications for passive immunization with IV Ig include parvovirus B19 infection, failure to make specific antibodies after immunization, immunemediated thrombocytopenia, and adjunctive therapy for HIV-infected children with bronchiectasis (2, 30, 48).

A hyperimmune IV Ig preparation has also been prepared (11, 26). Hyperimmune IV Ig administered with zidovudine appeared to reduce mother-infant transmission compared to a control group receiving zidovudine and IV Ig (52). The low HIV transmission rates in both arms of this study confirmed that zidovudine prophylaxis is highly effective, even for women with advanced HIV disease, but could not address whether
passive immunization diminishes perinatal transmission of HIV. Much remains to be learned about the role of NT antibody in HIV infection. Recent studies with macaques (4, 27) showed that passive immunization and maintenance of high titers of NT antibodies protect mucosal surfaces from infection when they are challenged with substantial doses of HIV (31). The relevance of these observations to the prevention of HIV infection in humans remains to be studied.

SUMMARY

Prophylactic polyclonal human IVIg is indicated for infectious disease prophylaxis for patients of all ages with primary or secondary agammaglobulinemia. Such treatment has markedly reduced infectious morbidity and mortality for these patients. The use of IVIg in immunocompromised patients, such as preterm infants, or those undergoing cancer chemotherapy, bone marrow transplantation, or transplantation of solid organs, has not significantly reduced the incidence of bacterial sepsis syndromes in these patients. Their general use should be discouraged.

IVIg and pathogen-specific hyperimmune IVIg prophylaxis are indicated to modify or prevent certain viral syndromes including hepatitis A, hepatitis B, measles, varicella, and rabies. Specific immunoglobulins may be indicated for prevention of tetanus and botulism for patients at risk. They also appear to be useful in treatment of enteral or central nervous system infections in patients with agammaglobulinemia and in reducing infectious morbidities during enteroviral nursery epidemics. CIG appears to reduce CMV disease severity for some severely immunocompromised transplant patients. Whether Respigran or palivizumab is efficacious in preventing or reducing the morbidity of RSV pneumonias in transplant patients remains to be determined. The evidence is compelling that palivizumab prophylaxis reduces RSV disease severity in preterm infants and neonatal intensive care graduates with chronic lung disease. A season's treatment is expensive and debate continues over whether general use is cost-effective. Still, for some patients, the prevention of hospitalization justifies the great expense.

IgG or IVIg efficacy for preventing or modulating bacterial toxin-mediated diseases such as tetanus, botulism, and diphtheria is undisputed. Less clear is whether they might be used in mediating the physiological consequences of certain streptococcal or staphylococcal infections. It is evident, however, that preparations must contain the requisite kinds and amounts of antigen-specific antibodies to be effective.

The success of palivizumab and other monoclonal antibody preparations will encourage the development of monoclonal antibodies that may prevent other serious bacterial and viral infections that afflict high-risk patients. One can imagine the development of such antibodies for the prevention of nosocomial staphylococcal and antibiotic-resistant-enterococcus infections. Monoclonal antibodies should also be developed and studied for acute prophylaxis of influenza and parainfluenza virus infections for high-risk patients, such as infants, transplant patients, the elderly, persons with cystic fibrosis or other chronic pulmonary diseases, and perhaps some patients with AIDS.

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