

Review

Antibodies for the prevention and treatment of viral diseases

Leigh A. Sawyer *

*Virology Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, 6700B Rockledge Drive, MSC-7630, Bethesda, MD 20892-7630, USA*

Received 1 June 2000; accepted 10 June 2000

Abstract

This paper reviews current use and evolving role of polyclonal and monoclonal antibody products for the prevention and treatment of viral diseases. Antibodies continue to be indicated for prophylaxis either prior to an anticipated exposure especially in situations of travel, or more commonly following an exposure. The predominant indication for use of antibody products is to prevent infection. With the availability of vaccines for the prevention of chickenpox, hepatitis A, hepatitis B, measles, rabies and smallpox, the role of passive immunization is reserved for susceptible individuals and those at high risk for complications of infection. Risks of transmission of infections associated with use of human plasma-derived products have been reduced by improvements in donor screening and virus removal and inactivation procedures. An additional safety concern has been addressed by the removal of thimerosal as a preservative. Within the last 5 years, two antibodies have been licensed for a viral indication, RespiGam™ and Synagis™ both for prevention of respiratory syncytial virus infection. RespiGam™ is a human plasma derived antibody and Synagis™ is a humanized monoclonal antibody, the first such antibody to be licensed for an infectious disease indication. CytoGam® for prevention of cytomegalovirus infection in kidney transplant patients has recently been granted an expanded indication to include use in lung, liver, pancreas and heart transplant patients. As the use of therapeutics becomes more sophisticated, researchers may find better ways of using antibody products. © 2000 Published by Elsevier Science B.V.

Keywords: Antibodies; Monoclonal antibodies; Antiviral; Immune globulin; Therapy; Prophylaxis

1. Introduction

Animal or human sera or plasmas containing antibodies have been used worldwide for the prophylaxis and therapy of infectious diseases of known and unknown causes since the late 1800s

* Fax: +1-301-4801594.

E-mail address: lsawyer@nih.gov (L.A. Sawyer).

(Casadevall, 1999). The development of monoclonal antibodies has raised hope for new products for use in prevention and treatment of infectious diseases. Biotechnological advances have had an impact on the availability of monoclonal antibodies to address a spectrum of medical conditions including allergy, asthma, cancers, rheumatoid arthritis, and infectious diseases (Casadevall, 1999). The first and only such product to be licensed to date in the United States (US), in 1998, is Synagis™ (American Academy of Pediatrics, 1998). As basic mechanisms of antibody action continue to become elucidated antibodies may be better designed to be more effective (Krause et al., 1997; Vaughan et al., 1998). The need to produce large quantities of monoclonal antibodies and to assure safety have motivated the exploration of non-traditional production methods. This brief review will provide a status report on the current use of polyclonal and monoclonal antibody products for the prevention or treatment of viral diseases as well as other common uses.

2. Antibodies approved for the prevention or treatment of viral diseases in the US

Antibody products licensed in the US, for the prevention or treatment of viral diseases as shown in Table 1, include: monoclonal antibody for respiratory syncytial virus (RSV), human immune globulin, and pathogen-specific polyclonal human immune globulins: cytomegalovirus immune globulin, hepatitis B immune globulin, rabies immune globulin, RSV immune globulin, vaccinia immune globulin, and varicella-zoster immune globulin (<http://www.fda.gov/cber/products.htm>).

Immune globulin products consist of concentrated immune globulin G (IgG) fractions pooled from the plasmas of thousands of healthy donors to yield immune globulin mixtures with specificities for human pathogens encountered by the population at large. Immune globulin preparations must contain at least minimum concentrations of diphtheria antitoxin, and neutralizing antibodies to measles and poliomyelitis virus (US Code of Federal Regulations Title 21, part

640.104). Otherwise these products have broad reactivity. The presence and titers of antibodies to other pathogens in the pool may be influenced by the epidemiologic setting from which the plasma donors were drawn. Thus, immune globulin reactivities with particular antigens may vary by product and even among lots of the same product. Immune globulin is used in some circumstances when pathogen-specific immune globulin is in short supply or not available. Immune globulins are prepared for intravenous or for intramuscular administration.

High-titered pathogen-specific immune globulins are prepared from pools of plasma obtained from immunized donors (e.g. hepatitis B immune globulin, rabies immune globulin, and vaccinia immune globulin) or from plasma donors screened for high antibody titers against the pathogen (e.g. cytomegalovirus immune globulin, respiratory syncytial virus immune globulin, and varicella-zoster immune globulin).

Passively acquired antibodies can interfere with the immune response to measles and rubella vaccines (Siber et al., 1993) and may generally interfere with the immune responses to live viral vaccines. Health care personnel should consider the interval recommended for vaccine administration following immune globulin administration where it pertains, as it varies depending on the immune globulin dose and vaccine type (Centers for Disease Control and Prevention, 1996, 1998a, 1999d).

3. Safety of immune globulin preparations

Clinically important adverse effects of intramuscular immune globulin administration are very infrequent and are described in the package inserts. Most adverse effects associated with the use of intravenous immune globulin (IVIG) are mild, transient and related to infusion speed. A comprehensive review on the adverse effects of IVIG and their pathophysiology, treatment and prevention, divides such effects into those occurring immediately (during the infusion, e.g. anaphylactoid reactions), those delayed for hours or days (e.g. renal, pulmonary, dermatological ad-

Table 1
Immune globulins approved for prevention or treatment of viral diseases in the United States^a

Proper name	Trade name	Indication	Dose	Recommendations
Immune Globulin (Human)	BayGam	Pre-exposure prophylaxis for hepatitis A Travel <3 months Travel >3 months Post-exposure prophylaxis for hepatitis A within 2 weeks of exposure Measles prevention in susceptible persons exposed <6 days previously	0.02 ml/kg i.m. 0.06 ml/kg i.m. every 4–6 months 0.02 ml/kg i.m. 0.25 ml/kg i.m.	Centers for Disease Control and Prevention, 1999d Centers for Disease Control and Prevention, 1998a
Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV)	CytoGam	If immunocompromised Prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas and heart	0.5 ml/kg i.m. 150 mg/kg i.v. within 72 h of transplant then 2, 4, 6, 8, 12, and 16 weeks post-transplant; dose varies by type of transplant	
Hepatitis B immune globulin (human) (HBIG)	BayHep B, Nabi-HB	Infants born to HBsAg-positive mothers Acute exposure to blood containing HBsAg Sexual contact HBsAg-positive	0.5 ml i.m., initiate vaccine series 0.06 ml/kg i.m., initiate vaccine series 0.06 ml/kg i.m., initiate vaccine series	Centers for Disease Control and Prevention, 1991a
		Infants <12 months of age exposed to primary care-giver with acute HBV infection Post-exposure prophylaxis	0.5 ml i.m., initiate vaccine series 20 IU/kg i.m., initiate vaccine series	
Rabies Immune Globulin (Human) (HRIG)	BayRab, IMOGAM Rabies-HT			Centers for Disease Control and Prevention, 1999a
Respiratory Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV)	RespiGam	Prevention of serious lower respiratory tract infection caused by RSV in high risk infants and children	750 mg/kg i.v. monthly during RSV season	American Academy of Pediatrics, 1997, 1998
Palivizumab	Synagis	Prevention of serious lower respiratory tract disease caused by RSV in high risk infants and children	15 mg/kg i.m. monthly during RSV season	American Academy of Pediatrics, 1998
Vaccinia Immune Globulin (Human) (IGIV)		Therapy of complications with vaccinia vaccination	0.6 ml/kg i.m., doses may be repeated at 2–3 day intervals	Centers for Disease Control and Prevention, 1991b
Varicella-Zoster Immune Globulin (Human) (VZIG)		Post-exposure prophylaxis of highrisk persons exposed to varicella virus	125 U/10 kg i.m. up to 625 U	Centers for Disease Control and Prevention, 1996

^a See package insert for full prescribing information.

verse effects), and late appearing adverse effects (e.g. transmission of infectious agents) (Nydegger and Sturzenegger, 1999). Immune globulins prepared for intravenous administration incorporate procedures to remove IgG aggregates associated with anaphylaxis (Nydegger and Sturzenegger, 1999). Of the mild, and transient immediate adverse effects, headache remains the single most frequently reported (Nydegger and Sturzenegger, 1999). Other immediate mild non-specific reactions include myalgia, back pain, nausea, vomiting, diarrhea, fever, chills, flushing, and urticaria (Anderson, 1999; Nydegger and Sturzenegger, 1999).

Human plasma products present a small potential risk of transmission of pathogenic agents. These risks have been significantly reduced through stringent qualification and screening standards for plasma donors and the inclusion of validated virus removal and inactivation steps in the plasma production process (Nydegger and Sturzenegger, 1999). New and existing technologies continue to be examined for their application to the safe production of plasma products.

Thimerosal is a mercury-containing preservative that has been used as an additive in biologics including some blood products and vaccines since the 1930s to prevent bacterial and fungal contamination. In an effort to reduce exposure to mercury, the FDA, and other US Public Health Service agencies are collaborating to reduce the thimerosal content of vaccines (Centers for Disease Control and Prevention, 1999e). Since this issue was brought to the attention of the pharmaceutical industry, manufacturers have switched to manufacturing some blood products free of mercurial preservatives (i.e. thimerosal).

There are several manufacturers licensed for IVIG products in the US. An excellent review of IVIG products available in the US, and their characteristics and considerations for use in pediatric infectious diseases, has been published (Anderson, 1999). The manufacturing processes and the characteristics of the IVIG may vary by manufacturer. Characteristics of IVIG products that vary and which may lead to the preferential use of one product over another for a particular purpose include: pH, choice of stabilizing agent (e.g. glu-

cose, maltose, sorbitol or sucrose) and concentration (ranging from 2 to 10%), and IgA content (Anderson, 1999).

4. Indications for use of immune globulins

Labeled indications for use of IVIG include primary immunodeficiency, immunodeficiency, idiopathic thrombocytopenic purpura, adult bone marrow transplant, pediatric human immunodeficiency virus (HIV) infection, B-cell chronic lymphocytic leukemia, and Kawasaki's disease. The labeled indications for use of IVIG are not specific to anticipated antiviral effects.

IVIG 'off-label' use is not uncommon. Shortages in availability of IVIG have prompted some hospitals to develop guidelines with established priorities of use for IVIG approved indications (Gurwitsch et al., 1998). IVIG has been used in life-threatening situations for which no specific product is recommended. IVIG is administered for other clinical situations such as enterovirus infection and parvovirus-induced anemia.

4.1. Use of immune globulin for prevention of hepatitis A

Immune globulin provides protection against hepatitis A virus (HAV) infection. Both immune globulin for intramuscular administration and IVIG contain anti-HAV. Anti-HAV titers differ between immune globulin lots without apparent clinical consequences (Centers for Disease Control and Prevention, 1999d). Immune Globulin (Human), BayGam™ (Bayer, Pharmaceutical Division, Elkhart, IN), is licensed for short-term pre-exposure or post-exposure protection for prevention against HAV (Table 1). BayGam™, a solution of immune globulin prepared from plasma pools from human donors, is for intramuscular administration and contains no preservatives. Prevention of hepatitis A, summarized in recommendations by the Advisory Committee on Immunization Practices (ACIP), calls for widespread active or passive immunization of appropriate susceptible populations and of those individuals at high risk for infection or its adverse

consequences (Centers for Disease Control and Prevention, 1999d). US-licensed HAV vaccines are not available as a pediatric formulation.

The ACIP recommends preexposure protection against HAV infection, preferably by HAV vaccination, for all susceptible persons traveling to or working in countries that have high or intermediate HAV endemicity (Centers for Disease Control and Prevention, 1999d). BayGam™ is recommended for travelers less than 2 years of age because the vaccine is currently not licensed for use in this age group. Because protection might not be complete until 4 weeks after vaccination, persons traveling to a high risk area less than 4 weeks after the initial dose of HAV vaccine should also receive immune globulin (0.02 ml/kg) at a different anatomic injection site. BayGam™ provides effective protection against hepatitis A for up to 3 months. For travelers not receiving HAV vaccine and who require short-term protection (1–2 months), an immune globulin dose of 0.02 ml/kg is recommended. For travelers requiring long-term protection (3–5 months), an immune globulin dose of 0.06 ml/kg is recommended with repeated dosing every 5 months if continued exposure to HAV occurs.

Post-exposure prophylaxis for recently-exposed persons not previously vaccinated with HAV vaccine, or without documented immunity to HAV, involves a single dose of BayGam™ (0.02 ml/kg) as soon as possible, but not more than 2 weeks following the most recent exposure. The extent of the exposure should be a factor in the decision to administer immune globulin (Centers for Disease Control and Prevention, 1999d).

4.2. Use of immune globulin for prevention of measles, mumps, or rubella

The ACIP recommendations for measles, mumps and rubella vaccine use include strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps (Centers for Disease Control and Prevention, 1998a). For recommendations for use of vaccines the statement should be consulted. In specific situations, The ACIP recommends the use of immune globulin (Centers for Disease Control and Prevention,

1998a). Immune Globulin (Human), BayGam™ (Bayer, Pharmaceutical Division, Elkhart, IN), is licensed for use as prophylaxis in susceptible persons exposed to measles (Table 1). BayGam™, a solution of immune globulin prepared from plasma pools from human donors is for intramuscular administration and contains no preservatives. If administered within 6 days of exposure, BayGam™ can prevent or modify measles in a susceptible person. The usual recommended dose of BayGam™ is 0.25 ml/kg of body weight, intramuscular (maximum dose = 15 ml).

The ACIP recommends immune globulin for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e. infants aged less than or equal to 12 months, pregnant women, or immunocompromised persons). Severely immunocompromised patients and other symptomatic HIV-infected patients who are exposed to measles should receive immune globulin prophylaxis regardless of vaccination status because the vaccine may not protect them (Centers for Disease Control and Prevention, 1998a). For patients receiving IVIG therapy, a standard dose of 100–400 mg/kg should be sufficient to prevent measles infection after exposures occurring within 3 weeks after administration of IVIG; for patients exposed to measles greater than 3 weeks after receiving a standard IVIG dose, an additional dose should be considered. Immune globulin should not be used to control measles outbreaks.

Immune globulin is not recommended for routine prophylaxis following rubella or mumps exposures. Administration of immune globulin should be considered only if a pregnant woman who has been exposed to rubella will not consider termination of pregnancy (Centers for Disease Control and Prevention, 1998a).

Immune globulin and measles vaccine should not be given at the same time. Passively acquired measles antibodies can interfere with the immune response to measles vaccine (Siber et al., 1993). To avoid such interference in patients recently receiving immune globulin prophylaxis (e.g. IVIG therapy for HIV infection, immune globulin for hepatitis A, immune globulin for measles, hepatitis B immune globulin, rabies immune globulin,

respiratory syncytial virus immune globulin, varicella zoster immune globulin) health care providers may wish to consult this ACIP statement for the recommended time interval before administration of vaccines containing live measles virus (Centers for Disease Control and Prevention, 1998a).

4.3. Prevention of cytomegalovirus infections

Cytomegalovirus (CMV) remains the single most important pathogen in organ transplantation. Prior to the availability of specific CMV prophylaxis or therapeutic intervention in the form of antivirals such as ganciclovir and acyclovir, CMV immune globulin, CMV immune plasma and IVIG were used in patients receiving bone marrow transplants and reported to prevent or modify clinical disease (Winston et al., 1982, 1987; Meyers et al., 1983). Randomized controlled studies of CMV immune globulin for the prevention of CMV infection in solid organ transplant populations followed.

Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV, CytoGam[®]) is manufactured by Massachusetts Public Health Biologic Laboratories, Boston, MA and marketed by MedImmune, Gaithersburg, MD. CMV-IGIV is prepared from pooled adult human plasma selected for high titers of antibodies for CMV. Initially, CMV-IGIV was indicated for use in renal transplant recipients who were seronegative for CMV (R –) and who received kidney transplants from CMV seropositive donors (D +) (Nightingale, 1990). This indication has been expanded to include the prophylaxis of CMV disease associated with transplantation of kidney, lung, liver, pancreas and heart (CytoGam[®] package insert, 1998). The maximum recommended total dosage per infusion is 150 mg/kg administered in a multi-dose regimen (Table 1). The package insert includes a statement to the effect, that, for transplants of those organs other than kidney from CMV seropositive donors into seronegative recipients (D + /R –), prophylactic use of CMV-IGIV in combination with ganciclovir should be considered. Many transplant centers use CMV-IGIV routinely for all high-risk

(D + /R –) solid organ or bone marrow transplantations. Use of CMV-IGIV has also been influenced by the introduction of ganciclovir and, in some centers, acyclovir.

In separate clinical trials, CMV-IGIV provided effective prophylaxis in renal transplant recipients at risk for primary CMV disease. The first of these was a prospective randomized placebo-controlled trial of CMV-IGIV for the prevention of primary CMV disease in renal transplant recipients. The incidence of virologically confirmed CMV-associated syndromes was significantly reduced from 60% in 35 controls to 21% in 24 recipients of CMV-IGIV (Snydman et al., 1987). Data from this and other studies supporting the efficacy of CMV-IGIV in preventing CMV disease in D + /R – kidney transplant recipients were used in support of licensure of CMV-IGIV for that indication (Nightingale, 1990; reviewed by DesJardin and Snydman, 1998). In a study of similar design in liver transplant patients the incidence of severe CMV disease was reduced from 26% in 72 control patients to 12% in 69 patients receiving CMV-IVIG ($P = 0.02$) (Snydman et al., 1993). In a separate study CMV-IGIV prophylaxis was associated with increased survival in liver transplant recipients (Falagas et al., 1997).

The use of CMV-IGIV and antivirals for prophylaxis of CMV disease has been recently reviewed and the extensive literature on treatment trials using immune globulin, antivirals, or combinations to prevent CMV disease in transplant recipients summarized (DesJardin and Snydman, 1998; King, 1999). Uncertainty about benefits of various antiviral and immunoprophylactic regimens for the prevention of CMV infection and disease is evident in this literature. DesJardin and Snydman conclude that immunoglobulins are efficacious in preventing CMV disease in solid organ transplantation, with CMV-IGIV more beneficial than IVIG. They further conclude that combination therapy with CMV-IGIV plus an antiviral agent is more effective than monotherapy. King suggests that in all transplant settings, ganciclovir is the most effective anti-CMV agent and in almost all situations, ganciclovir alone is more effective than IVIG alone for the prevention of CMV infection or disease. IVIG is beneficial in

reducing other complications of CMV infection, such as graft-versus-host disease post-BMT (Desjardins and Snyderman, 1998; King, 1999).

At a recent symposium, the appropriate uses of CMV-IGIV and IVIG for prevention of CMV infection in solid organ transplantation were considered to be somewhat restricted (Oestreicher, 1999). Although several agents have proven effective for CMV prophylaxis in kidney transplant recipients, these experts agreed that long-term ganciclovir therapy appears to be the most consistently effective for preventing CMV disease, particularly in patients receiving antilymphocyte therapy (Keay, 1999). However, for some very high risk transplant patients, such as lung transplant recipients, ganciclovir alone appears to be incompletely effective. Some transplant centers use CMV-IGIV in combination with ganciclovir, especially in D + /R – lung transplant recipients (Avery, 1999). Nonetheless, there are no published data that demonstrate benefit with this combination. CMV-IGIV or IVIG in combination with ganciclovir is considered the treatment of choice for established CMV pneumonia in bone marrow and stem cell transplant recipients (Nichols and Boeckh, 2000).

Many of the manifestations attributed to CMV infection, as well as long-term mortality and/or development of opportunistic infections, could be due to other herpes viruses such as HHV-6 and HHV-7 (Paya, 1999). Perhaps, beneficial effects of CMV-IGIV prophylaxis resulted from antiviral effects of CMV-IVIG on other herpes-related viruses. A better understanding of the contribution of CMV-IGIV to the management of indirect complications following transplantation may reveal targets for more specific prophylactic and therapeutic interventions (Paya, 1999).

With regard to cost-effectiveness, a recently published analysis comparing different strategies of CMV chemoprophylaxis in a hypothetical cohort of liver transplant recipients suggests that oral ganciclovir may be the single best intervention of those compared (Das, 2000). Another recent cost effectiveness analysis based on the use of CMV-IGIV in the absence of other anti-CMV prophylaxis, suggests routine prophylaxis with CMV-IGIV is an appropriate use of resources (Arbo et al., 2000).

Some progress has been reported in recent years for monoclonal antibodies under clinical development for CMV therapy (Paar and Pollard, 1996). Human anti-CMV monoclonal antibodies have been evaluated in small clinical trials as prophylaxis for CMV disease in bone marrow transplant recipients (Aulitzky et al., 1991), for treatment of retinitis and other CMV infections in AIDS patients, and as therapy for asymptomatic congenital CMV infection (reviewed by Paar and Pollard, 1996). Human CMV monoclonal antibody MSL 109 was shown not to be effective in slowing the progression of CMV retinitis in AIDS patients (McCarthy, 1996). In fact, highly active antiretroviral therapy has had a major impact on the treatment of CMV disease in HIV-infected individuals, and current treatment regimens do not include the use of anti-CMV antibody (Nichols and Boeckh, 2000). The study of MSL 109 for treatment of asymptomatic congenital CMV infection was closed because the product was no longer made available to complete the study (personal communication, Richard Whitley, Birmingham, AL).

4.4. Prevention of hepatitis B virus infections

Two Hepatitis B Immune Globulin (Human) (HBIG) products are currently licensed for use in the US (Table 1), BayHep B™ (Bayer, Pharmaceutical Division, Elkhart, IN) and Nabi-HB™ (Nabi, Boca Raton, FL). Both products are solutions containing hepatitis B hyperimmune globulin prepared from human plasma donations by individuals with high titers of antibody to the hepatitis B surface antigen (anti-HBs). Both HBIG preparations are for intramuscular administration and contain no preservative. HBIG has been shown to be efficacious in the prevention of transmission of hepatitis B virus (HBV) post-exposure. It should always be used in regimens that include hepatitis B vaccine.

The current ACIP recommendations for prevention of HBV transmission in the US include a comprehensive hepatitis B vaccination strategy and selective use of HBIG (Centers for Disease Control and Prevention, 1991a, 1999b). The post-exposure regimen used to prevent the transmis-

sion of HBV depends not only on the type of exposure, but also on the consideration of several factors. For infants born to mothers who are hepatitis B surface antigen (HBsAg) positive, the immunoprophylaxis regimen includes concurrent administration of the first dose of hepatitis B vaccine and HBIG (0.5 ml) within 12 h of birth. HBIG should be administered by intramuscular injection at an anatomical site different from that used for the vaccine (Centers for Disease Control and Prevention, 1991a). Subsequent doses of vaccine should be administered according to the recommended schedule (Centers for Disease Control and Prevention, 1991a). If the HBsAg status of the mother is not known, the infant should receive hepatitis B vaccine within 12 h of birth, at the same dose as for infants born to HBsAg-positive mothers. If the mother is subsequently determined to be HBsAg positive, the infant should receive HBIG for additional protection, within 7 days of birth.

The ACIP recommendations for post-exposure prophylaxis in circumstances outside of the perinatal period involve consideration of such factors as: the type of exposure to hepatitis B; the HBsAg status of the source of the exposure; the hepatitis B vaccination history of the exposed person, and their response to the hepatitis vaccine. Generally, the treatment of choice to prevent transmission of HBV from a confirmed source to a non-immune recipient, is a regimen of HBIG given in a single dose (0.06 ml/kg) intramuscular injection concurrently with the first dose of hepatitis B vaccine administered at a separate site. More specific guidelines are available and should be consulted (Centers for Disease Control and Prevention, 1991a).

Prevention of recurrent hepatitis B in liver transplant recipients currently utilizes high dose HBIG, usually administered intravenously. A recent publication of the American Liver Foundation Program on Hepatitis B and Liver Transplantation provides expert opinion on treatment strategies for liver transplant patients with hepatitis B infection (Vierling and Teperman, 2000a). Polyvalent HBIG is the current 'gold standard' for preventing hepatitis B recurrence following liver transplantation for HBV-related

liver disease (Vierling and Teperman, 2000b), although it is not labeled for use in this indication. Lifetime passive immunization with intravenous HBIG, to achieve and maintain anti-HBs in serum, is the accepted standard of care (Colquhoun et al., 2000). It is recommended that the frequency of dosing be adjusted to maintain serum levels of anti-HBs at > 500 IU/l during the first 2 weeks after transplantation and > 100 IU/l thereafter (Dickson, 1998; Sawyer et al., 1998; Dodson et al., 1999b; Colquhoun et al., 2000; Vierling and Teperman, 2000b). Patients at high risk for reinfection (i.e. those positive for either HBeAg or HBV-DNA before transplantation) may require higher target level (e.g. > 500 IU/l) maintenance HBIG therapy (Lake, 1995; Dodson et al., 1999b).

Although HBIG has become the standard of care for prevention of recurrent hepatitis B in the liver transplant setting, several concerns remain. HBIG products available in the US have been approved for intramuscular administration only, and intravenous administration of high dose HBIG for hepatitis B prophylaxis has been associated with side-effects (Lake, 1995; Al-Hemsi et al., 1996; McGory et al., 1996; Terrault et al., 1996). The side-effects are those seen with other preparations of antibodies given intravenously (discussed above). In general, using a slow infusion rate and pre-medicating with analgesics and/or antihistamines controls the side-effects.

The high cost associated with long-term (life-long) intravenous HBIG administration is a concern. Alternative regimens have been proposed including intramuscular rather than intravenous HBIG for maintenance therapy (Lake, 1995). Alternatively, enhanced potency preparations of HBIG may allow longer dosing intervals, thereby reducing the number of doses required and the associated costs (Adler et al., 1999).

Studies have been conducted to evaluate the use of HBIG to prevent recurrent HBV infection due to the emergence of resistance to nucleoside analogue therapy following hepatic transplantation. Lamivudine, an orally administered nucleoside analogue treatment for chronic hepatitis B virus infection, has been studied for its ability to prevent reinfection associated with transplantation

(Grellier et al., 1996), and for treatment of recurrent infection after transplantation (Perrillo et al., 1999). The development of drug resistant mutants limits the usefulness of this monotherapy (Perrillo et al., 1999, 2000). Combination therapy with lamivudine and HBIG prevented hepatitis B recurrence following liver transplantation at a median 1.1 years of follow-up (Markowitz et al., 1998). Passive immunization with HBIG alone, or in combination with nucleoside analogues, is now considered the treatment of choice to delay or prevent reinfection in transplant patients known to be HBV DNA-positive (Colquhoun et al., 2000). Clinical trials are necessary to establish the optimum drug combinations, regimens and strategies (Perrillo et al., 2000; Peters et al., 2000). Clinical trials investigating these issues are now beginning.

A majority (~86%) of post-transplantation de novo hepatitis B infections may be attributable to the use of livers from anti-hepatitis B core antigen (anti-HBc) positive donors (Dickson et al., 1997). There is limited experience with prophylactic regimens to prevent de novo HBV infection in recipients of livers from anti-HBc-positive donors. Vaccination of HBV-negative transplant candidates is recommended but may not always be successful due to the immunocompromised status of these patients (Peters et al., 2000). Combination prophylaxis with HBIG and lamivudine in anti-HBs-negative, HBsAg-negative patients receiving hepatic allografts from donors positive for anti-HBc appears promising (Dodson et al. 1999a).

Some attention has been given to the emergence of viral escape mutants during HBIG use. Mutations in the S-gene have been found in virus isolates from patients who developed re-infection of HBV after liver transplantation while receiving HBIG (Ghany et al., 1998; Protzer-Knolle et al., 1998; Carman et al., 1999). These S-mutants are rare.

Clinical experience with anti-HBV monoclonal antibodies is limited. Three patients with chronic hepatitis B infections receiving liver transplants were treated with an anti-HBV monoclonal antibody (SDZ OST 577, Sandoz Research Institute, East Hanover, NJ). All three patients became negative after liver transplantation and antibody

therapy. However HBV escape mutants were isolated within 252 days of transplantation (McMahon et al., 1992).

4.5. *Prevention of hepatitis C virus infections*

The administration of current preparations of immune globulin for post-exposure prophylaxis of hepatitis C is not effective and is therefore not recommended (Centers for Disease Control and Prevention, 1998b). Interest in the development of an anti-hepatitis C virus (HCV) product as a therapeutic intervention for HCV — analogous to HBIG for HBV — has been encouraged by demonstration in chimpanzees of high-titer anti-HCV neutralizing antibodies capable of neutralizing HCV (Farci et al., 1994, 1996; Krawczynski et al., 1996). Indirect support for this approach is provided by the results of a single-mask, randomized, controlled trial of 899 anti-HCV negative steady heterosexual partners of anti-HCV-positive patients. The anti-HCV negative partners received placebo or immune globulin by intramuscular injection. (The immune globulin was prepared prior to the mandatory screening for anti-HCV.) The treatment was repeated every 2 months for the duration of the study. Of the 884 partners completing the study, six in the comparison group versus one in the immune serum globulin group became infected ($P=0.03$; Piazza et al., 1997), suggesting that the use of immune globulin prepared from unscreened donors was associated with a reduction in risk of HCV infection in partners. Similarly, the results of retrospective studies of patients who had liver transplantation for HCV-related liver disease and were co-infected with HBV and received HBIG (in particular, HBIG prepared before mandatory screening for anti-HCV) were protected against recurrent hepatitis C (Feraý et al., 1998, 1999). An immune globulin preparation enriched for HCV antibody by screening plasma pools for anti-HCV has been developed (Civacir™, Nabi, Boca Raton, FL) and a Phase I clinical trial for its use in patients with HCV infection receiving liver transplants is in development (National Institute of Allergy and Infectious Diseases, National Institutes of Health, Collaborative Antiviral Study Group).

4.6. Prevention of rabies

Two Rabies Immune Globulin (Human) (RIG) products are currently licensed for use in the US (Table 1). BayRab™ (Bayer, Pharmaceutical Division, Elkhart, IN) and Imogam® Rabies-HT (Aventis-Pasteur, Pasteur-Merieux Serum et Vaccins, Connaught Laboratories, Swiftwater, PA). Both products are a solution of antirabies hyperimmune globulin prepared from plasma of human donors hyperimmunized with rabies vaccine. Both are for intramuscular administration and contain no preservative. Preparation of Imogam® Rabies-HT includes a prolonged heat treatment step (58–60°C, 10 h) to inactivate viruses (Lang et al., 1998). Occasionally, the availability of RIG has been restricted prompting the consideration of the emergency substitution of a new-generation purified equine rabies immune globulin (ERIG) under US Investigational New Drug Application. ERIG is currently available in some other countries (Hanlon et al., 1999). Although considered essential in standard rabies post-exposure prophylaxis, HRIG and ERIG are not readily available throughout much of the developing world (Wilde et al., 1999), where human rabies is more common than in the US.

Rabies is a disease for which effective control measures are known, resulting in few human rabies cases in the US and most industrialized countries. Human rabies cases continue to occur in greatest numbers in developing countries. The high cost of post-exposure prophylaxis, the lack of effective canine rabies control in some countries, and the inconsistent availability of rabies biologics, remain major obstacles to the control of rabies worldwide (Meltzer and Rupprecht, 1998; Wilde et al., 1999). Pre-exposure and post-exposure issues for rabies vaccine and passive immunoprophylaxis, in the context of rabies in the US are described in the recommendations of the ACIP for Human Rabies Prevention (Centers for Disease Control and Prevention, 1999a). The ACIP statement and additional information are available at the National Centers for Disease Control and Prevention web site (<http://www.cdc.gov/ncidod/dvrd/rabies>). The decision to give pre-exposure prophylaxis and booster doses

of vaccine is based on assessment of risk of exposure. The decision to give post-exposure prophylaxis is based upon type of exposure, the animal rabies epizootiology and evaluation of the involved species, the circumstances of the biting or exposure incident, and the vaccination status of the exposing animal. The post-exposure regimen is based on previous rabies vaccination history of the exposed person (Centers for Disease Control and Prevention, 1999a).

RIG is recommended as part of the rabies post-exposure regimen for persons not previously immunized against rabies, and includes concurrent administration of rabies vaccine (Centers for Disease Control and Prevention, 1999a). RIG is administered once, to provide immediate antibodies until the patient responds to rabies vaccine. The recommended dose of human RIG (20 IU/kg body weight) provides maximum circulating antibody with minimum interference of active immunization by rabies vaccine. After thorough washing with soap and water, the full dose of RIG, if feasible, should be thoroughly infiltrated in the area around and into the wound(s). Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. There are no reported cases in which rabies developed in persons given the appropriate complete post-exposure regimen.

4.7. Antibody preparations for prevention of respiratory syncytial virus infections

Two products are currently available in the US for the prevention of serious lower respiratory tract respiratory syncytial virus (RSV) infection in children at high risk of developing severe RSV disease (Table 1). Respiratory Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV, RespiGam™) is a solution of immune globulin G enriched in neutralizing antibodies to RSV. RSV-IGIV is prepared from pooled human plasma selected for high titers of neutralizing antibody against RSV and contains no preservative. Licensed in 1996, RespiGam™ was the first intervention with demonstrated safety and efficacy in the prevention of RSV infections in high-risk children (Groothuis et al., 1993; The PREVENT

Study Group, 1997). Prophylaxis with RespiGam™ in high-risk infants reduced the incidence of RSV hospitalization by 41% and the duration by 53% (The PREVENT Study Group, 1997). RespiGam™ is manufactured by Massachusetts Public Health Biologic Laboratories (Boston, MA) and is marketed in the US by MedImmune (Gaithersburg, MD). RespiGam™ 750 mg/kg is given monthly during the RSV season by intravenous infusion over a 4-h period. RespiGam™ is indicated for the prevention of serious lower respiratory tract infections caused by RSV in children under 24 months of age with bronchopulmonary dysplasia, or a history of premature birth (≤ 35 weeks gestation) (RespiGam™ package insert, 1996).

Licensed in the US in 1998, Synagis™ (palivizumab, MEDI-493, MedImmune, Gaithersburg, MD), a humanized monoclonal antibody (IgG1k), is the first and only monoclonal antibody yet licensed for an infectious disease indication. The antibody was humanized (95% human, 5% murine antibody sequences) using recombinant DNA technology and is directed against a neutralizing epitope on the RSV F glycoprotein (Johnson et al., 1997). Administered to high-risk-infants once a month during the RSV season and given intramuscularly at a dose of 15 mg/kg, Synagis™ resulted in a 55% reduction in hospital admissions for RSV illness compared to placebo ($P < 0.001$) (The IMPact-RSV Study Group, 1998). For several reasons, including the ease of administration (intramuscular versus intravenous route), lack of interference with childhood live viral vaccines, and absence of theoretical risks associated with the administration of human blood products, Synagis™ is the preferred of the two available licensed products for most situations (American Academy of Pediatrics, 1998).

The most appropriate use of these products is of considerable debate among pediatricians (Moler et al., 1999). Advantages and disadvantages of each product have recently been reviewed (Meissner et al., 1999b) however no direct comparison of the two products has been conducted. Neither product is approved for the prophylaxis of RSV infection in patients with cyanotic congenital heart disease. Likewise, neither product is

approved for the treatment of RSV infection. Recommendations for the use of RSV-IGIV (RespiGam™) (American Academy of Pediatrics, 1997) were recently updated and include recommendations for the use of palivizumab (Synagis™) (American Academy of Pediatrics, 1998). A consensus opinion on the most appropriate use for palivizumab followed (Meissner et al., 1999b). Estimates of the RSV-related health care expenditures for prophylaxis with palivizumab are based on assumptions that may not be applicable to all geographic locations (Storch, 1998; Joffe et al., 1999; Marchetti et al., 1999; Moler et al., 1999; Stevens et al., 2000) and may not be justified (Moler, 1999). A method for establishing local guidelines based on the local cost of RSV prophylaxis and geographic variables associated with rehospitalization rates for premature infants with RSV infection is being utilized to identify when it is appropriate to use these products (Hall et al., 1999). As more data become available through publications on the impact of these products in clinical practice (Redding et al., 1999) recommendations may be refined.

Another humanized monoclonal antibody, RSHZ19 (SB 209763) has also been tested in clinical trials and has not been shown to be effective in reducing hospitalization for RSV-induced disease (Meissner et al., 1999a). RSHZ19 is directed against a neutralizing epitope on the RSV F glycoprotein that is distinct from the epitope recognized by palivizumab, and in a direct comparison study, palivizumab had consistently greater antigen binding, RSV neutralizing, and fusion inhibiting activities compared to RSHZ19 activities, which may account for the difference in clinical efficacy (Johnson et al., 1999).

RSV initiates infection in the nasopharynx, an accessible site for direct application of antibody. Theoretically, application of antibodies on mucosal surfaces could provide better protection than systemic administration of antibodies (Hemming et al., 1995). A purified murine RSV F-specific monoclonal IgA antibody, HNK-20 (Oravax, Cambridge, MA), has been produced. Results of murine experiments suggest that nasal instillation of HNK-20 was no better than an IgG monoclonal antibody reactive with the same RSV epi-

tope in reducing RSV titers in the lung, and was less effective than systemically-administered IgG monoclonal antibody in protecting against RSV infection following challenge (Fisher et al., 1999). In contrast, Weltzin and Monath, report the results of a controlled trial of prophylactic nasal instillation of HNK-20 conducted in several hundred infants at risk for severe RSV, in which beneficial trends were noted as a decrease in RSV hospitalizations among infants younger than 4 months receiving treatment, although their data has not been reported in publication (Weltzin and Monath, 1999).

Once RSV infection is established in the lower respiratory tract therapeutic passive immunization may not be effective in reducing disease. Aerosolized IVIG administered by inhalation therapy to infants at high risk for severe RSV disease on the first day of hospitalization for RSV lower respiratory tract infection did not show benefit (Rimensberger et al., 1996). The negative results are not definitive, however, since the IVIG used had low titers of RSV neutralizing activity (Rimensberger et al., 1996). RSV-IGIV administered as one infusion (1500 mg/kg) to previously healthy infants and young children hospitalized for RSV lower respiratory tract infection resulted in beneficial trends for those with more severe disease, but did not reduce duration of hospitalization or ICU stay in the entire group randomized to the treatment arm of the study (Rodriguez et al., 1997a). Efficacy was not demonstrated in a study of RSV-IGIV administered as one infusion (1500 mg/kg) to infants and young children at high risk for severe RSV infection hospitalized with RSV lower respiratory tract infections (Rodriguez et al., 1997b). Synagis™, administered as one 15-mg/kg intravenous dose to infants hospitalized with RSV infection requiring intubations and mechanical ventilation, significantly reduced RSV concentrations in tracheal aspirates but had no measurable clinical efficacy (Malley et al., 1998).

Effective therapy of RSV infection developing in adults and children following bone marrow transplant, organ transplant, or chemotherapy for leukemia, has not been established (Englund et al., 1997). Ribavirin solution for inhalation (VI-

RAZOLE®, ICN Pharmaceuticals, Costa Mesa, CA) is an antiviral approved in the US for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV infection. The clinical effectiveness of ribavirin therapy for RSV has been questioned, and the American Academy of Pediatrics limits recommendations of ribavirin use to selected infants and young children at high risk for serious RSV disease (American Academy of Pediatrics, 1996). Those with underlying immunosuppressive disease or therapy are included among them.

RSV infection is often a fatal complication of bone marrow transplantation, thus research into the optimum therapy continues. RSV immune globulin given prophylactically and therapeutically to immunosuppressed cotton rats challenged with RSV had an effect on viral replication reducing the titer to nearly undetectable levels (Ottolini et al., 1999). Encouraging results have also recently been published in which the use of aerosolized ribavirin and RSV-IGIV (RespiGam™) administered under a compassionate-use protocol for the treatment of RSV pneumonia in several pediatric patients undergoing bone marrow transplantation was associated with increased survival suggesting the combination may increase survival above that in such patients treated with ribavirin alone (De Vincenzo et al., 2000). Other promising results include those of a pilot trial in adult bone marrow transplant patients, using aerosolized ribavirin and IVIG for the treatment of RSV upper respiratory tract illness suggesting that the combination may be useful in preventing progression of RSV upper respiratory tract infection to RSV pneumonia and death (Ghosh et al., 2000). Controlled clinical trials are necessary to establish whether aerosolized ribavirin alone or in combination with IVIG, RSV-IGIV or Synagis™ is most effective in preventing and/or treating RSV disease in immunocompromised patients.

4.8. *Antibody preparations for vaccinia*

Vaccinia vaccination has lead to the eradication of natural smallpox virus transmission. In May 1983, Wyeth Laboratories, Lancaster, PA, then the only active US licensed producer of vaccinia

virus vaccine, discontinued distribution of the vaccine. ACIP guidelines, updated in 1991, reflect the current recommendations for limited distribution of vaccinia vaccine to laboratory and health-care workers occupationally exposed to vaccinia, recombinant vaccinia viruses or other orthopoxviruses that can infect humans (Centers for Disease Control and Prevention, 1991b). Vaccinia Immune Globulin (Human), VIG, prepared by Baxter Healthcare, from plasma pools donated by recipients of vaccinia vaccine must be immediately available when the vaccine is administered to treat unexpected complications (Table 1). VIG is the only product shown to be effective for treatment of adverse events resulting from live vaccinia virus immunization, including: eczema vaccinatum, vaccinia necrosum, ocular vaccinia, some cases of progressive vaccinia, and severe generalized vaccinia. The VIG is distributed by the CDC in the case of medical emergency. CDC is the only source of vaccinia vaccine and VIG for civilians. The possibility that smallpox (variola virus) could be used as a biological warfare agent has prompted renewed interest in the development of treatment and prevention strategies (Henderson et al., 1999). Such research requires access to variola virus. The stocks of vaccinia vaccine and VIG will need to be replenished in order to meet the needs of the investigators for research and development in this infectious disease area.

4.9. Prevention of varicella-zoster virus infections

Varicella-Zoster Immune Globulin (Human) (VZIG) for use in the US is produced by the Massachusetts Public Health Biologic Laboratories and is distributed by American Red Cross regional distribution centers and service areas. VZIG is a solution of human immune globulin prepared from plasma obtained from blood donors identified by routine screening to have high antibody titers to varicella-zoster virus. VZIG is for intramuscular use and contains no preservatives VZIG package insert, 1996. Varicella vaccine (Varivax; Merck, West Point, PA) was licensed in the US in 1995. Recommendations for prevention of primary varicella infection (chickenpox) emphasize the use of varicella virus

vaccine (American Academy of Pediatrics, 1995; Centers for Disease Control and Prevention, 1996, 1999c; American Academy of Pediatrics, 2000). Recommendations for the use of VZIG have not been specifically updated since an ACIP statement published in 1996 (Centers for Disease Control and Prevention, 1996). VZIG is recommended for passive immunization of susceptible, immunocompromised children (< 13 years of age) after substantial exposure to varicella or herpes zoster; neonates whose mothers have signs or symptoms of varicella within 5 days before or 2 days after delivery, and some premature infants who have substantial postnatal exposure (Centers for Disease Control and Prevention, 1996). VZIG is recommended for susceptible immunocompromised, and some healthy adolescents (≥ 13 years of age) and adults who have had substantial exposure to varicella. VZIG should be strongly considered for susceptible pregnant women who have been exposed to varicella virus, to prevent complications of varicella in the mother. The recommended dose of VZIG is 125 U per 10 kg body weight up to a maximum of 625 U, administered intramuscularly (Table 1). Maximum benefit is obtained when administered as soon as possible and within 96 h of exposure. The appropriate dose for prophylaxis in adults has not been established, however 625 U is considered a sufficient dose of VZIG to modify or prevent infection in healthy adults (Centers for Disease Control and Prevention, 1996). VZIG is expensive and provides only temporary protection (i.e. ~ 3 weeks) and it is not recommended for treating clinical varicella or herpes zoster or for preventing disseminated zoster (Centers for Disease Control and Prevention, 1996).

4.10. HIV infection

Studies have been conducted to evaluate the potential use of anti-HIV antibodies to prevent HIV infection pre- or post-exposure. A significant concern regarding the potential for success in this area has been the realization that human sera do not easily neutralize viruses transmitted between humans, so-called primary viruses. Animal models have been helpful in testing the concept of passive protection and providing evidence that passive

antibody may be protective (reviewed recently by Haigwood and Zolla-Pazner, 1998). Significant results have been obtained in the hu-PBL-SCID mouse model in which severe combined immunodeficient (SCID) mice are populated with human peripheral blood mononuclear cells (PBMCs). After receiving a potent neutralizing murine monoclonal antibody SCID mice were protected against primary virus challenge (Gauduin et al., 1997). Recent studies in the HIV-1/simian immunodeficiency virus (SIV) chimeric virus (SHIV) macaque model have provided encouraging results. Purified immunoglobulin from chimpanzees infected with several different HIV-1 isolates was used to passively immunize macaques. The antibody was shown to have HIV neutralizing activity and to block infection following intravenous challenge with a chimeric simian-HIV (SHIV) derived from a primary virus isolate (Shibata et al., 1999). In a separate study, macaques were protected against vaginal transmission of a pathogenic SHIV by passive infusion of anti-HIV-1 neutralizing monoclonal antibodies with or without HIV immune globulin (Mascola et al., 2000). These results are particularly interesting because the vaginal challenge model as opposed to the intravenous challenge route might be more relevant as a model of human exposure. These results seem to indicate that antibodies may protect against HIV infection. However, clinical trials to demonstrate efficacy have been difficult (Lambert and Moye, 1999) and in a hospital exposure setting are not possible due to the large sample size requirements.

Limited studies have been done to evaluate the use of antibodies for treatment of established HIV infection. Poignard et al., 1999 evaluated high serum concentrations of HIV neutralizing monoclonal antibodies, alone or as a cocktail of monoclonals for treatment of established HIV-1 infection in hu-PBL-SCID mice. They observed little sustained effect on viral load. Neutralization escape occurred after a few days of treatment. These results suggest that the use of anti-HIV antibodies to treat established HIV-1 infection in humans might not be feasible.

4.11. *Enterovirus*

Enterovirus infection of neonates and of antibody-deficient patients may result in serious disease and death. Reviewed recently (DesJardin and Snyderman, 1998; Rotbart et al., 1998), immune globulin used prophylactically and therapeutically in these populations has been of variable success and has not been evaluated in sufficient numbers of patients in controlled clinical trials to establish efficacy. Because there are 68 recognized enteroviruses that circulate in unpredictable patterns each immune globulin preparation differs in antibody reactivity to the various enterovirus serotypes. On theoretical grounds, it would be expected that preparations with high neutralizing antibody specific for the infecting serotype would be more likely to be beneficial. However, it is not currently possible to assess potency to guide use at the bedside.

4.12. *Parvovirus*

Parvovirus B19 infection of persons unable to mount an effective humoral immune response results in chronic infection and anemia. The evidence for effective use of intravenous immunoglobulin for the treatment of chronic parvovirus B19 infection is limited to small-uncontrolled clinical trials and case reports, including patients with acquired immune deficiency syndrome, congenital immunodeficiencies, and leukemia patients undergoing chemotherapy, reviewed briefly by DesJardin and Snyderman, 1998. Commercial lots of IVIG have been shown to contain variable titers of parvovirus B19 antibodies (Schwarz et al., 1990). In the absence of data from controlled trials, the therapeutic titer of parvovirus B19 antibodies and the optimum regimen of immune globulin for effective intervention are not established. Monoclonal antibodies with parvovirus B19 neutralizing activities have been described. Among these, human monoclonal antibodies with potent *in vitro* parvovirus B19 neutralizing activity may be appropriate candidates for further development as immunotherapeutics for chronically infected patients and acutely infected pregnant women (Gigler et al., 1999).

4.13. Viral hemorrhagic fevers

Treatment of viral hemorrhagic fevers has been evaluated in animal models and in limited numbers of people; however, at this time there is insufficient clinical data to support the use of any particular antibody preparation in humans. Human monoclonal antibodies may hold greater promise than immune globulin preparations prepared in the past. Using current technology, antibodies to a number of viral hemorrhagic fevers are being developed. As an example, a panel of recombinant human monoclonal antibodies to Ebola virus antigens has been isolated from phage display libraries constructed from RNA from donors who recovered from infection (Maruyama et al., 1999). Antibodies derived using these methods may be useful for passive immunization and vaccine development.

5. Mucosal passive immunization

Prevention of transmission of epidemic infectious diseases via passive immunization of mucosal surfaces is of great public health interest (Zeitlin et al., 1999). Application of antibodies to respiratory mucosal surfaces as nose drops, aerosol, or nasal spray have been evaluated in limited numbers of patients, for prevention of several common respiratory tract viral infections including Coxsackie, influenza, rhinovirus and RSV (reviewed recently by Weltzin and Monath, 1999). Oral administration of antibody has been studied for the prevention or treatment of rotavirus infection. Human immune globulin, bovine colostrum and bovine antibodies from hyperimmunized cows have been used for this purpose on an experimental basis; however, routine use of such products is not an established practice. Antibodies delivered to the vaginal mucosa of mice protect against vaginal transmission of genital herpes infection, but other species have not been studied (Whaley et al., 1994; Zeitlin et al., 1996). Advances in monoclonal antibody technology, e.g. antibody production in transgenic plants, may substantially reduce production costs and thereby assure the availability of large quantities of spe-

cific antibodies for safe and effective use worldwide.

6. Recent advances in recombinant antibody technology

Strategies to overcome the limitations of murine monoclonal antibodies as human therapeutics include the generation of mouse-human chimeras (retaining ~30% of the murine sequences), and of humanized monoclonal antibodies (retaining ~5% of the murine sequences). These modifications have successfully minimized the post-administration human anti-mouse antibody response to these products. Hybridoma technology is being replaced by newer methods including the use of in vitro phage-display of combinatorial antibody libraries, and techniques such as chain shuffling, to generate novel antibodies as reagents, and as diagnostic and therapeutic molecules (Hayden et al., 1997; Rader and Barbas, 1997; Hudson, 1999). Recently, this technology has been used to select and humanize antibodies from immune rabbits (Rader et al., 2000). Possibly, one of the most promising research advances has been the creation of transgenic mice that produce a highly diverse human antibody response with high affinity for specific antigens (Mendez et al., 1997).

Significant progress has been made in the expression of recombinant antibodies in plants (see recent review by Fischer et al., 1999). The use of plants as bioreactors for large-scale production of clinical grade pharmaceuticals requires the development of a production system that meets the rigorous requirements of the current FDA standards for pharmaceutical products. A discussion of the issues with regard to the feasibility of such an undertaking is the subject of a recent publication (Russell, 1999). In the first human trial of a monoclonal secretory IgA antibody produced in transgenic tobacco plants, investigators were able to demonstrate protection against oral *Streptococcus mutans* colonization (Ma et al., 1998). Pre-clinical studies of a humanized anti-HSV glycoprotein B monoclonal antibody produced in transgenic soybean plants showed that when ap-

plied to the vaginal mucosa, the monoclonal antibody prevented transmission of HSV-2 infection in mice (Zeitlin et al., 1998). These results suggest potential promise for the use of this technology.

Acknowledgements

I would like to thank Gary Davis, Thelma Gaither, Michael Gerber, David Morens and Carlos Paya for their comments and constructive discussions during preparation of this manuscript.

References

- Adler, R., Safadi, R., Caraco, Y., Rowe, M., Etzioni, A., Ashur, Y., Shouval, D., 1999. Comparison of immune reactivity and pharmacokinetics of two hepatitis B immune globulins in patients after liver transplantation. *Hepatology* 29, 1299–1305.
- Al-Hemsi, B., McGory, R.W., Shepard, B., Ishitani, M.B., Stevenson, W.C., McCullough, C., Pruett, T.L., 1996. Liver transplantation for hepatitis B cirrhosis: clinical sequelae of passive immunization. *Clin. Transplant.* 10, 668–675.
- American Academy of Pediatrics, Committee on Infectious Diseases, 1995. Recommendations for the use of live attenuated varicella vaccine. *Pediatrics* 95, 791–796.
- American Academy of Pediatrics, Committee on Infectious Diseases, 1996. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. *Pediatrics* 97, 137–140.
- American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn, 1997. Respiratory syncytial virus immune globulin intravenous: indications for use. *Pediatrics* 99, 645–650.
- American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn, 1998. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics* 102, 1211–1216.
- American Academy of Pediatrics, Committee on Infectious Diseases, 2000. Varicella vaccine update. *Pediatrics* 105, 136–141.
- Anderson, M.S., 1999. Intravenous gammaglobulin for pediatric infectious diseases. *Pediatr. Ann.* 28, 499–506.
- Arbo, M.D.J., Snyderman, D.R., Wong, J.B., Goldberg, H.S., Schmid, C.H., Pauker, S.G., 2000. Cytomegalovirus immune globulin after liver transplantation: a cost-effectiveness analysis. *Clin. Transplant.* 14, 19–27.
- Aulitzky, W.E., Schulz, T.F., Tilg, H., Niederwieser, D., Larcher, K., Ostberg, L., Scriba, M., Martindale, J., Stern, A.C., Grass, P., Mach, M., Dierich, M.P., Huber, C., 1991. Human monoclonal antibodies neutralizing cytomegalovirus (CMV) for prophylaxis of CMV disease: report of a phase I trial in bone marrow transplant recipients. *J. Infect. Dis.* 163, 1344–1347.
- Avery, R.K., 1999. Special considerations regarding CMV in lung transplantation. *Cytomegalovirus in the transplant population: current issues and future directions. Transplant. Infect. Dis.* 1 (suppl. 1), 13–18.
- Carman, W.F., Owsianka, A., Wallace, L.A., Dow, B.C., Mutimer, D.J., 1999. Antigenic characterisation of pre- and post-liver transplant hepatitis B surface antigen sequences from patients treated with hepatitis B immune globulin. *J. Hepatol.* 31, 195–201.
- Casadevall, A., 1999. Short analytical review. Passive antibody therapies: progress and continuing challenges. *Clin. Immunol.* 93, 5–15.
- Centers for Disease Control and Prevention, 1991a. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). *Morbidity and Mortality Weekly Rep.* 40 (RR-13), 1–25.
- Centers for Disease Control and Prevention, 1991b. Vaccinia (smallpox) vaccine: recommendations of the Immunization Practices Advisory Committee (ACIP). *Morbidity and Mortality Weekly Rep.* 40 (RR-14), 1–10.
- Centers for Disease Control and Prevention, 1996. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Rep.* 45 (RR-11), 1–36.
- Centers for Disease Control and Prevention, 1998a. Measles, mumps, and rubella — vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Rep.* 47 (RR-8), 1–57.
- Centers for Disease Control and Prevention, 1998b. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *Morbidity and Mortality Weekly Rep.* 47 (RR-19), 1–39.
- Centers for Disease Control and Prevention, 1999a. Human rabies prevention — United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Rep.* 48 (RR-1), 1–21.
- Centers for Disease Control and Prevention, 1999b. Notice to readers update: recommendations to prevent hepatitis B virus transmission — United States. *Morbidity and Mortality Weekly Rep.* 48, 33–34.
- Centers for Disease Control and Prevention, 1999c. Prevention of varicella updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Rep.* 48 (RR-6), 1–5.
- Centers for Disease Control and Prevention, 1999d. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Rep.* 48 (RR-12), 1–37.

- Centers for Disease Control and Prevention, 1999e. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. *Morbidity and Mortality Weekly Report* 48, 996–998.
- Colquhoun, S.D., Belle, S.H., Samuel, D., Pruett, T.L., Teperman, L.W., 2000. Transplantation in the hepatitis B patient and current therapies to prevent recurrence. *Hepatitis B and liver transplantation: proceedings of an American Liver Foundation program. Semin. Liver Dis.* 20 (suppl. 1), 7–12.
- Das, A., 2000. Cost-effectiveness of different strategies of cytomegalovirus prophylaxis in orthotopic liver transplant recipients. *Hepatology* 31, 311–317.
- DesJardin, J.A., Snyderman, D.R., 1998. Antiviral immunotherapy — a review of current status. *Biodrugs* 9, 487–507.
- De Vincenzo, J.P., Hirsch, R.L., Fuentes, R.J., Top, F.H. Jr, 2000. Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation — a compassionate use experience. *Bone Marrow Transplant.* 25, 161–165.
- Dickson, R.C., 1998. Management of posttransplantation viral hepatitis — hepatitis B. *Liver Transplant. Surg.* 4 (suppl. 1), S73–S78.
- The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database, Dickson, R.C., Everhart, J.E., Lake, J.R., Wei, Y., Seaberg, E.C., Wiesner, R.H., Zetterman, R.K., Pruett, T.L., Ishitani, M.B., Hoofnagle, J.H., 1997. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. *Gastroenterology* 113, 1668–1674.
- Dodson, S.F., Bonham, C.A., Geller, D.A., Cacciarelli, T.V., Rakela, J., Fung, J.J., 1999. Prevention of de novo hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. *Transplantation* 68, 1058–1061.
- Dodson, S.F., Issa, S., Bonham, A., 1999. Liver transplantation for chronic viral hepatitis. *Liver transplantation: current management. Surg. Clin. North Am.* 79, 131–145.
- Englund, J.A., Piedra, P.A., Whimbey, E., 1997. Prevention and treatment of respiratory syncytial virus and parainfluenza viruses in immunocompromised patients. *Proceedings of a symposium. Community respiratory viral infections in the immunocompromised host. Am. J. Med.* 102 (3A), 61–70.
- The Boston Center for Liver Transplantation CMVIG Study Group, Falagas, M.E., Snyderman, D.R., Ruthazer, R., Griffith, J., Werner, B.G., Freeman, R., Rohrer, R., 1997. Cytomegalovirus immune globulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. *Clin. Transplant.* 11, 432–437.
- Farci, P., Alter, H.J., Wong, D.C., Miller, R.H., Govindarajan, S., Engle, R., Shapiro, M., Purcell, R.H., 1994. Prevention of hepatitis C virus infection in chimpanzees after antibody-mediated in vitro neutralization. *Proc. Natl. Acad. Sci. USA* 91, 7792–7796.
- Farci, P., Shimoda, A., Wong, D., Cabezon, T., De Gioannis, D., Strazzer, A., Shimizu, Y., Shapiro, M., Alter, H.J., Purcell, R.H., 1996. Prevention of hepatitis C virus infection in chimpanzees by hyperimmune serum against the hypervariable region 1 of the envelope 2 protein. *Proc. Natl. Acad. Sci. USA* 93, 15394–15399.
- Feray, C., Gigou, M., Samuel, D., Ducot, B., Maisonneuve, P., Reynes, M., Bismuth, A., Bismuth, H., 1998. Incidence of hepatitis C in patients receiving different preparations of hepatitis B immunoglobulins after liver transplantation. *Ann. Intern. Med.* 128, 810–816.
- The European Concerted Action on Viral Hepatitis (EURO-HEP) Group, Feray, C., Caccamo, L., Alexander, G.J.M., Ducot, B., Gugenheim, J., Casanovas, T., Loinaz, C., Gigou, M., Burra, P., Barkholt, L., Esteban, R., Bizollon, T., Lerut, J., Minello-Franza, A., Bernard, P.-H., Nachbaur, K., Botta-Fridlund, D., Bismuth, H., Schalm, S.W., Samuel, D., 1999. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. *Gastroenterology* 117, 619–625.
- Fischer, R., Liao, Y.-C., Hoffmann, K., Schillberg, S., Emans, N., 1999. Review. Molecular farming of recombinant antibodies in plants. *Biol. Chem.* 380, 825–839.
- Fisher, R.G., Crowe, J.E. Jr, Johnson, T.R., Tang, Y.-W., Graham, B.S., 1999. Passive IgA monoclonal antibody is no more effective than IgG at protecting mice from mucosal challenge with respiratory syncytial virus. *J. Infect. Dis.* 180, 1324–1327.
- Gauduin, M.-C., Parren, P.W.H.I., Weir, R., Barbas, C.F., Burton, D.R., Koup, R.A., 1997. Passive immunization with a human monoclonal antibody protects hu-PBL-SCID mice against challenge by primary isolates of HIV-1. *Nat. Med.* 3, 1389–1393.
- Ghany, M.G., Ayola, B., Villamil, F.G., Gish, R.G., Rojter, S., Vierling, J.M., Lok, A.S.F., 1998. Hepatitis B virus S mutants in liver transplant recipients who were reinfected despite hepatitis B immune globulin prophylaxis. *Hepatology* 27, 213–222.
- Ghosh, S., Champlin, R.E., Englund, J., Giralt, S.A., Rolston, K., Raad, I., Jacobson, K., Neumann, J., Ippoliti, C., Mallik, S., Whimbey, E., 2000. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant.* 25, 751–755.
- Gigler, A., Dorsch, S., Hemauer, A., Williams, C., Kim, S., Young, N.S., Zolla-Pazner, S., Wolf, H., Gorny, M.K., Modrow, S., 1999. Generation of neutralizing human monoclonal antibodies against parvovirus B19 proteins. *J. Virol.* 73, 1974–1979.
- Grellier, L., Mutimer, D., Ahmed, M., Brown, D., Burroughs, A.K., Rolles, K., McMaster, P., Beranek, P., Kennedy, F., Kibbler, H., McPhillips, P., Elias, E., Dusheiko, G., 1996. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 348, 1212–1215.

- The Respiratory Syncytial Virus Immune Globulin Study Group, Groothuis, J.R., Simoes, E.A.F., Levin, M.J., Hall, C.B., Long, C.E., Rodriguez, W.J., Arrobio, J., Meissner, H.C., Fulton, D.R., Welliver, R.C., Tristram, D.A., Siber, G.R., Prince, G.A., Van Raden, M., Hemming, V.G., 1993. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *New Engl. J. Med.* 329, 1524–1530.
- Gurwitsch, K.D., Goldwire, M.A., Baker, C.J., 1998. Intravenous immune globulin shortage: experience at a large children's hospital. *Pediatrics* 102, 645–647 (commentary).
- Haigwood, N.L., Zolla-Pazner, S., 1998. Humoral immunity to HIV, SIV, and SHIV. *AIDS* 12 (suppl. A), S121–S132.
- Hall, C.B., Stevens, T.P., Swantz, R.J., Sinkin, R.A., McBride, J.T., 1999. Development of local guidelines for prevention of respiratory syncytial viral infections. *Pediatr. Infect. Dis. J.* 18, 850–853.
- The National Working Group on Rabies Prevention and Control, Hanlon, C.A., Olson, J.G., Clark, C.J., 1999. Recommendations of a national working group on prevention and control of rabies in the United States. Article I: prevention and education regarding rabies in human beings. *J. Am. Vet. Med. Assoc.* 215, 1276–1280.
- Hayden, M.S., Gilliland, L.K., Ledbetter, J.A., 1997. Antibody engineering. *Curr. Opin. Immunol.* 9, 201–212.
- Hemming, V.G., Prince, G.A., Groothuis, J.R., Siber, G.R., 1995. Hyperimmune globulins in prevention and treatment of respiratory syncytial virus infections. *Clin. Microbiol. Rev.* 8, 22–33.
- The Working Group on Civilian Biodefense, Henderson, D.A., Inglesby, T.V., Bartlett, J.G., Ascher, M.S., Eitzen, E., Jahrling, P.B., Hauer, J., Layton, M., McDade, J., Osterholm, M.T., O'Toole, T., Parker, G., Perl, T., Russell, P.K., Tonat, K., 1999. Consensus Statement. Smallpox as a biological weapon. Medical and public health management. *J. Am. Med. Assoc.* 281, 2127–2137.
- Hudson, P.J., 1999. Recombinant antibody constructs in cancer therapy. *Curr. Opin. Immunol.* 11, 548–557.
- Joffe, S., Ray, G.T., Escobar, G.J., Black, S.B., Lieu, T.A., 1999. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics* 104, 419–427.
- Johnson, S., Oliver, C., Prince, G.A., Hemming, V.G., Pfarr, D.S., Wang, S.-C., Dormitzer, M., O'Grady, J., Koenig, S., Tamura, J.K., Woods, R., Bansal, G., Couchenour, D., Tsao, E., Hall, W.C., Young, J.F., 1997. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J. Infect. Dis.* 176, 1215–1224.
- Johnson, S., Griego, S.D., Pfarr, D.S., Doyle, M.L., Woods, R., Carlin, D., Prince, G.A., Koenig, S., Young, J.F., Dillon, S.B., 1999. A direct comparison of the activities of two humanized respiratory syncytial virus monoclonal antibodies: MEDI-493 and RSHZ19. *J. Infect. Dis.* 180, 35–40.
- Keay, S., 1999. CMV infection and disease in kidney and pancreas transplant recipients. Cytomegalovirus in the transplant population: current issues and future directions. *Transplant. Infect. Dis.* 1 (suppl. 1), 19–24.
- King, S.M., 1999. Mini review. Immune globulin versus antivirals versus combination for prevention of cytomegalovirus disease in transplant recipients. *Antiviral Res.* 40, 115–137.
- Krause, R.M., Dimmock, N.J., Morens, D.M., 1997. Summary of antibody workshop: the role of humoral immunity in the treatment and prevention of emerging and extant infectious diseases. *J. Infect. Dis.* 176, 549–559.
- Krawczynski, K., Alter, M.J., Tankersley, D.L., Beach, M., Robertson, B.H., Lambert, S., Kuo, G., Spelbring, J.E., Meeks, E., Sinha, S., Carson, D.A., 1996. Effect of immune globulin on the prevention of experimental hepatitis C virus infection. *J. Infect. Dis.* 173, 822–828.
- Lake, J.R., 1995. Should liver transplantation be performed for patients with chronic hepatitis B? Yes!. *Liver Transplant. Surg.* 1, 260–265.
- Lambert, J.S., Moye Jr., J., 1999. Review. Current issues in the immunoprophylaxis of vertical transmission of HIV. *Biodrugs* 11, 31–41.
- Lang, J., Gravenstein, S., Briggs, D., Miller, B., Froeschle, J., Dukes, C., Le Mener, V., Lutsch, C., 1998. Evaluation of the safety and immunogenicity of a new, heat-treated human rabies immune globulin using a sham, post-exposure prophylaxis of rabies. *Biologicals* 26, 7–15.
- Ma, J.K.-C., Hikmat, B.Y., Wycoff, K., Vine, N.D., Chargelegue, D., Yu, L., Hein, M.B., Lehner, T., 1998. Characterization of a recombinant plant monoclonal secretory antibody and preventive immunotherapy in humans. *Nat. Med.* 4, 601–606.
- Malley, R., De Vincenzo, J., Ramilo, O., Dennehy, P.H., Meissner, H.C., Gruber, W.C., Sanchez, P.J., Jafri, H., Balsley, J., Carlin, D., Buckingham, S., Vernacchio, L., Ambrosino, D.M., 1998. Reduction of respiratory syncytial virus (RSV) in tracheal aspirates in intubated infants by use of humanized monoclonal antibody to RSV F protein. *J. Infect. Dis.* 178, 1555–1561.
- Marchetti, A., Lau, H., Magar, R., Wang, L., Devercelli, G., 1999. Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings. *Clin. Ther.* 21, 752–766.
- Markowitz, J.S., Martin, P., Conrad, A.J., Markmann, J.F., Seu, P., Yersiz, H., Goss, J.A., Schmidt, P., Pakrasi, A., Artinian, L., Murray, N.G.B., Imagawa, D.K., Holt, C., Goldstein, L.I., Stribling, R., Busuttill, R.W., 1998. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology* 28, 585–589.
- Maruyama, T., Rodriguez, L.L., Jahrling, P.B., Sanchez, A., Khan, A.S., Nichol, S.T., Peters, C.J., Parren, P.W.H.I., Burton, D.R., 1999. Ebola virus can be effectively neutralized by antibody produced in natural human infection. *J. Virol.* 73, 6024–6030.
- Mascola, J.R., Stiegler, G., VanCott, T.C., Katinger, H., Carpenter, C.B., Hanson, C.E., Beary, H., Hayes, D., Frankel, S.S., Birk, D.L., Lewis, M.G., 2000. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat. Med.* 6, 207–210.

- McCarthy, M., 1996. CMV retinitis monoclonal antibody trial halted. *Lancet* 348, 603.
- McGory, R.W., Ishitani, M.B., Oliveira, W.M., Stevenson, W.C., McCullough, C.S., Dickson, R.C., Caldwell, S.H., Pruett, T.L., 1996. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 61, 1358–1364.
- McMahon, G., Ehrlich, P.H., Moustafa, Z.A., McCarthy, L.A., Dottavio, D., Tolpin, M.D., Nadler, P.I., Ostberg, L., 1992. Genetic alterations in the gene encoding the major HBsAg: DNA and immunological analysis of recurrent HBsAg derived from monoclonal antibody-treated liver transplant patients. *Hepatology* 15, 757–766.
- Meissner, H.C., Groothuis, J.R., Rodriguez, W.J., Welliver, R.C., Hogg, G., Gray, P.H., Loh, R., Simoes, E.A.F., Sly, P., Miller, A.K., Nichols, A.I., Jorkasky, D.K., Everitt, D.E., Thompson, K.A., 1999. Safety and pharmacokinetics of an intramuscular monoclonal antibody (SB 209763) against respiratory syncytial virus (RSV) in infants and young children at risk for severe RSV disease. *Antimicrob. Agents Chemother.* 43, 1183–1188.
- Meissner, H.C., Welliver, R.C., Chartrand, S.A., Law, B.J., Weisman, L.E., Dorkin, H.L., Rodriguez, W.J., 1999. Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. *Pediatr. Infect. Dis. J.* 18, 223–231.
- Meltzer, M.I., Rupprecht, C.E., 1998. Review. A review of the economics of the prevention and control of rabies. Part 1: global impact and rabies in humans. *Pharmacoeconomics* 14, 365–383.
- Mendez, M.J., Green, L.L., Corvalan, J.R.F., Jia, X.-C., Maynard-Currie, C.E., Yang, X.-d., Gallo, M.L., Louie, D.M., Lee, D.V., Erickson, K.L., Luna, J., Roy, C.M.-N., Abderrahim, H., Kirschenbaum, F., Noguchi, M., Smith, D.H., Fukushima, A., Hales, J.F., Finer, M.H., Davis, C.G., Zsebo, K.M., Jakobovits, A., 1997. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nat. Genet.* 15, 146–156.
- Meyers, J.D., Leszczynski, J., Zaia, J.A., Flournoy, N., Newton, B., Snyderman, D.R., Wright, G.G., Levin, M.J., Thomas, E.D., 1983. Prevention of cytomegalovirus infection by cytomegalovirus immune globulin after marrow transplantation. *Ann. Intern. Med.* 98, 442–446.
- Moler, F.W., 1999. RSV immune globulin prophylaxis: is an ounce of prevention worth a pound of cure? *Pediatrics* 104, 559–560 (commentary).
- Moler, F.W., Brown, R.W., Faix, R.G., Gilsdorf, J.R., 1999. Comments on palivizumab (Synagis). *Pediatrics* 103, 495–497 (commentary).
- Nichols, W.G., Boeckh, M., 2000. Review. Recent advances in the therapy and prevention of CMV infections. *J. Clin. Virol.* 16, 25–40.
- Nightingale, S.L., 1990. From the Food and Drug Administration. *J. Am. Med. Assoc.* 264, 168.
- Nydegger, U.E., Sturzenegger, M., 1999. Adverse effects of intravenous immunoglobulin therapy. *Drug Safety* 21, 171–185.
- Oestreicher, A., 1999. Cytomegalovirus in the transplant population: current issues and future directions. *Transplant. Infect. Dis.* 1 (suppl. 1), 1–41.
- Ottolini, M.G., Porter, D.D., Hemming, V.G., Zimmerman, M.N., Schwab, N.M., Prince, G.A., 1999. Effectiveness of RSVIG prophylaxis and therapy of respiratory syncytial virus in an immunosuppressed animal model. *Bone Marrow Transplant.* 24, 41–45.
- Paar, D.P., Pollard, R.B., 1996. Immunotherapy of CMV infections. *Adv. Exp. Med. Biol.* 394, 145–151.
- Paya, C.V., 1999. Indirect effects of CMV in the solid organ transplant patient. Cytomegalovirus in the transplant population: current issues and future directions. *Transplant. Infect. Dis.* 1 (suppl. 1), 8–12.
- The Lamivudine Transplant Group, Perrillo, R., Rakela, J., Dienstag, J., Levy, G., Martin, P., Wright, T., Caldwell, S., Schiff, E., Gish, R., Villeneuve, J.P., Farr, G., Anschuetz, G., Crowther, L., Brown, N., 1999. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 29, 1581–1586.
- Perrillo, R.P., Krueger, M., Sievers, T., Lake, J.R., 2000. Posttransplantation: emerging and future therapies. Hepatitis B and liver transplantation: proceedings of an American Liver Foundation program. *Semin. Liver Dis.* 20 (suppl. 1), 13–17.
- Peters, M.G., Shouval, D., Bonham, A., Vierling, J.M., Lok, A.S.F., 2000. Posttransplantation: future therapies. Hepatitis B and liver transplantation: proceedings of an American Liver Foundation program. *Semin. Liver Dis.* 20 (suppl. 1), 19–24.
- Piazza, M., Sagliocca, L., Tosone, G., Guadagnino, V., Stazi, M.A., Orlando, R., Borgia, G., Rosa, D., Abrignani, S., Palumbo, F., Manzin, A., Clementi, M., 1997. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin. *Arch. Intern. Med.* 157, 1537–1544.
- Poignard, P., Sabbe, R., Picchio, G.R., Wang, M., Gulizia, R.J., Katinger, H., Parren, P.W.H.I., Mosier, D.E., Burton, D.R., 1999. Neutralizing antibodies have limited effects on the control of established HIV-1 infection in vivo. *Immunity* 10, 431–438.
- Protzer-Knolle, U., Naumann, U., Bartenschlager, R., Berg, T., Hopf, U., zum Buschenfelde, K.-H.M., Neuhaus, P., Gerken, G., 1998. Hepatitis B virus with antigenically altered hepatitis B surface antigen is selected by high-dose hepatitis B immune globulin after liver transplantation. *Hepatology* 27, 254–263.
- Rader, C., Barbas, C.F. III, 1997. Phage display of combinatorial antibody libraries. *Curr. Opin. Biotechnol.* 8, 503–508.
- Rader, C., Ritter, G., Nathan, S., Elia, M., Gout, I., Jungbluth, A.A., Cohen, L.S., Welt, S., Old, L.J., Barbas, C.F. III, 2000. The rabbit antibody repertoire as a novel source for the generation of therapeutic human antibodies. *J. Biol. Chem.* 275, 13668–13676.

- Redding, G.J., Braun, S., Mayock, D., 1999. Impact of respiratory syncytial virus immune globulin in 1996–1997. A local controlled comparison. *Arch. Pediatr. Adolesc. Med.* 153, 503–507.
- Rimensberger, P.C., Burek-Kozłowska, A., Morell, A., Germann, D., Eigenmann, A.K., Steiner, F., Burger, R., Kuenzli, M., Schaad, U.B., 1996. Aerosolized immunoglobulin treatment of respiratory syncytial virus infection in infants. *Pediatr. Infect. Dis. J.* 15, 209–216.
- The RSV-IGIV Study Group, Rodriguez, W.J., Gruber, W.C., Groothuis, J.R., Simoes, E.A.F., Rosas, A.J., Lepow, M., Kramer, A., Hemming, V., 1997. Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics* 100, 937–942.
- The Respiratory Syncytial Virus Immune Globulin Study Group, Rodriguez, W.J., Gruber, W.C., Welliver, R.C., Groothuis, J.R., Simoes, E.A.F., Meissner, H.C., Hemming, V.G., Hall, C.B., Lepow, M.L., Rosas, A.J., Robertsen, C., Kramer, A.A., 1997. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections. *Pediatrics* 99, 454–461.
- Rotbart, H.A., O'Connell, J.F., McKinlay, M.A., 1998. Mini review. Treatment of human enterovirus infections. *Antiviral Res.* 38, 1–14.
- Russell, D.A., 1999. Feasibility of antibody production in plants for human therapeutic use. *Curr. Top. Microbiol. Immunol.* 240, 119–138.
- Sawyer, R.G., McGory, R.W., Gaffey, M.J., McCullough, C.C., Shephard, B.L., Houlgrave, C.W., Ryan, T.S., Kuhns, M., McNamara, A., Caldwell, S.H., Abdulkareem, A., Pruett, T.L., 1998. Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. *Ann. Surg.* 227, 841–847.
- Schwarz, T.F., Roggendorf, M., Hottentrager, B., Modrow, S., Deinhardt, F., Middeldorp, J., 1990. Immunoglobulins in the prophylaxis of parvovirus B19 infection. *J. Infect. Dis.* 162, 1214 (correspondence).
- Shibata, R., Igarashi, T., Haigwood, N., Buckler-White, A., Ogert, R., Ross, W., Willey, R., Cho, M.W., Martin, M.A., 1999. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat. Med.* 5, 204–210.
- Siber, G.R., Werner, B.G., Halsey, N.A., Reid, R., Almeida-Hill, J., Garrett, S.C., Thompson, C., Santosham, M., 1993. Interference of immune globulin with measles and rubella immunization. *J. Pediatr.* 122, 204–211.
- Snydman, D.R., Werner, B.G., Heinze-Lacey, B., Berardi, V.P., Tilney, N.L., Kirkman, R.L., Milford, E.L., Cho, S.I., Bush, H.L. Jr, Levey, A.S., Strom, T.B., Carpenter, C.B., Levey, R.H., Harmon, W.E., Zimmerman, C.E. II, Shapiro, M.E., Steinman, T., LoGerfo, F., Idelson, B., Schroter, G.P.J., Levin, M.J., McIver, J., Leszczynski, J., Grady, G.F., 1987. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. *New Engl. J. Med.* 317, 1049–1054.
- The Boston Center for Liver Transplantation CMVIG Study Group, Snydman, D.R., Werner, B.G., Dougherty, N.N., Griffith, J., Rubin, R.H., Dienstag, J.L., Rohrer, R.H., Freeman, R., Jenkins, R., Lewis, W.D., Hammer, S., O'Rourke, E., Grady, G.F., Fawaz, K., Kaplan, M.M., Hoffman, M.A., Katz, A.T., Doran, M., 1993. Cytomegalovirus immune globulin prophylaxis in liver transplantation. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 119, 984–991.
- Stevens, T.P., Sinkin, R.A., Hall, C.B., Maniscalco, W.M., McConnochie, K.M., 2000. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier. Hospitalization and economic implications of prophylaxis. *Arch. Pediatr. Adolesc. Med.* 154, 55–61.
- Storch, G.A., 1998. Humanized monoclonal antibody for prevention of respiratory syncytial virus infection. *Pediatrics* 102, 648–651 (commentary).
- Terrault, N.A., Zhou, S., Combs, C., Hahn, J.A., Lake, J.R., Roberts, J.P., Ascher, N.L., Wright, T.L., 1996. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 24, 1327–1333.
- The Impact-RSV Study Group, 1998. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 102, 531–537.
- The PREVENT Study Group, 1997. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* 99, 93–99.
- Vaughan, T.J., Osbourn, J.K., Tempest, P.R., 1998. Review. Human antibodies by design. *Nat. Biotechnol.* 16, 535–539.
- Vierling, J.M., Teperman, L.W., 2000. Hepatitis B and liver transplantation: proceedings of an American Liver Foundation program. *Semin. Liver Dis.* 20 (suppl. 1), 1–35.
- Vierling, J.M., Teperman, L.W., 2000. Introduction to hepatitis B transplantation. Hepatitis B and liver transplantation: proceedings of an American Liver Foundation program. *Semin. Liver Dis.* 20 (suppl. 1), 1–2.
- Weltzin, R., Monath, T.P., 1999. Intranasal antibody prophylaxis for protection against viral disease. *Clin. Microbiol. Rev.* 12, 383–393.
- Whaley, K.J., Zeitlin, L., Barratt, R.A., Hoen, T.E., Cone, R.A., 1994. Passive immunization of the vagina protects mice against vaginal transmission of genital herpes infections. *J. Infect. Dis.* 169, 647–649.
- Wilde, H., Tipkong, P., Khawplod, P., 1999. Review. Economic issues in post exposure rabies treatment. *J. Travel Med.* 6, 238–242.
- Winston, D.J., Pollard, R.B., Ho, W.G., Gallagher, J.G., Rasmussen, L.E., Huang, S. N.-Y., Lin, C.-H., Gossett, T.G., Merigan, T.C., Gale, R.P., 1982. Cytomegalovirus

- immune plasma in bone marrow transplant recipients. *Ann. Intern. Med.* 97, 11–18.
- Winston, D.J., Ho, W.G., Lin, C.-H., Bartoni, K., Budinger, M.D., Gale, R.P., Champlin, R.E., 1987. Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. *Ann. Intern. Med.* 106, 12–18.
- Zeitlin, L., Whaley, K.J., Sanna, P.P., Moench, T.R., Bastidas, R., De Logu, A., Williamson, R.A., Burton, D.R., Cone, R.A., 1996. Topically applied human recombinant monoclonal IgG₁ antibody and its Fab and F(ab')₂ fragments protect mice from vaginal transmission of HSV-2. *Virology* 225, 213–215.
- Zeitlin, L., Olmsted, S.S., Moench, T.R., Co, M.S., Martinell, B.J., Paradkar, V.M., Russell, D.R., Queen, C., Cone, R.A., Whaley, K.J., 1998. A humanized monoclonal antibody produced in transgenic plants for immunoprotection of the vagina against genital herpes. *Nat. Biotechnol.* 16, 1361–1364.
- Zeitlin, L., Cone, R.A., Whaley, K.J., 1999. Using monoclonal antibodies to prevent mucosal transmission of epidemic infectious diseases. *Emerg. Infect. Dis.* 5, 54–64.