Passive Immunity in Prevention and Treatment of Infectious Diseases

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INTRODUCTION

Antibodies have been used for a century for the prevention and treatment of infectious diseases (Table 1). In bacterial disease, antibodies neutralize toxins, facilitate opsonization, and, with complement, promote bacteriolysis; in viral disease, antibodies block viral entry into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation of complement.

Prior to the use of antibiotics, antibodies were the only specific agents for the treatment of certain infections. Although this role has largely been supplanted by antibiotics, there still remains a crucial role for antibody in the treatment of certain infectious diseases (Table 1). Since several excellent reviews are available, this article will emphasize new developments (30, 31, 101, 164, 165).

Antibodies can be administered as human or animal plasma

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or serum, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, as high-titer human IVIG or IG from immunized or convalescing donors, and as monoclonal antibodies (MAb) (30, 164, 178). The therapeutic use of MAb is increasing dramatically, but only one (palivizumab for respiratory syncytial virus [RSV]) has been licensed for prophylaxis of an infectious disease.

BACTERIAL INFECTIONS

Respiratory Infections

It is well recognized that respiratory tract infections secondary to group A *Streptococcus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and to a lesser extent *Neisseria meningitidis* are more frequent in patients with primary antibody deficiencies and that these infections can be markedly reduced by regular administration of immunoglobulin (101, 125). Further, specific animal antisera to these organisms were used in the early 1930s for treatment of severe infections (e.g., meningitis), even after the introduction of sulfonamides (4). The efficacy varied, but antiserum treatment was clearly better

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Infection	Prophylaxis	Treatment
Bacterial infections		
Respiratory infections (streptococcus, Streptococcus pneumoniae, Neisseria meningitis, Haemophilus influenzae)	Proven (NR) ^{<i>a,b</i>}	Proven $(NR)^b$
Diphtheria	Unproven (NR)	Proven
Pertussis	Unproven (NR)	Unproven (NR)
Tetanus	Proven	Proven
Other clostridial infections		
C. botulinum	Proven	Proven
C. difficile	Unproven (NR)	Probable benefit
Staphylococcal infections	• • • •	
Toxic shock syndrome	Unproven (NR)	Probable benefit
Antibiotic resistance	Unproven (NR)	Possible benefit
S. epidermidis in newborns	Possible benefit	Not studied
Invasive streptococcal disease (toxic shock syndrome)	Unproven (NR)	Probable benefit
High-risk newborns	Possible benefit (NR)	Probable benefit
Shock, intensive care, and trauma	Possible benefit (NR)	Unproven
Pseudomonas infection		
Cystic Fibrosis	Unproven (NR)	No benefit
Burns	Unproven (NR)	No benefit
Viral diseases		
Hepatitis A	Proven	No benefit
Hepatitis B	Proven	No benefit
Hepatitis C	Unproven (NR)	No benefit
HIV infection	Unproven (NR)	Unproven (NR)
RSV infection	Proven	Unproven (NR)
Herpesvirus infections		
CMV	Proven	Possible benefit
EBV	Unproven (NR)	Unproven (NR)
HSV	Unproven (NR)	Unproven (NR)
VZV	Proven	Unproven (NR)
Parvovirus infection	Unproven (NR)	Proven $(NR)^b$
Enterovirus infection	Proven $(NR)^b$	Proven $(NR)^b$
In newborns	Unproven	Possible benefit
Ebola	Possible benefit	Unproven
Rabies	Proven	No benefit
Measles	Proven	No benefit
Rubella	Unproven (NR)	No benefit
Mumps	Unproven (NR)	No benefit
Tick-borne encephalitis	Possible benefit	No benefit
Vaccinia	Proven	Proven

TABLE 1. Summary of the efficacy of antibody in the prevention and treatment of infectious diseases

^a NR, not recommended.

^b Except for immunodeficient patients.

than no treatment at all, and a combination of sulfonamides and antibody seemed to be synergistic (4).

More recently, Santoshan et al. (149) administered a human IG prepared from the sera of donors immunized with pneumococcal, meningococcal, and *H. influenzae* type b polysaccharide vaccines (termed bacterial polysaccharide immune globulin [BPIG]) to Apache Native American infants living on reservations in Arizona. The 222 infants in the study group received 80 mg of BPIG per kg at 2, 6, and 10 months of age, while the 218 infants in the control group received saline injections at the same ages. During the period of the study, seven cases of invasive *H. influenzae* type b disease and four cases of invasive pneumococcal disease occurred in the control group compared with one and two cases, respectively, in the BPIGtreated group, a significant difference (P < 0.05).

BPIG was also shown to reduce the number of episodes of pneumococcal otitis media in these high-risk Native American infants (155). It did not, however, decrease the total number of otitis media episodes. Large doses of IVIG (400 mg/kg monthly) reduced the frequency of otitis media (and serious bacterial infections) in children with human immunodeficiency virus (HIV) infection (112, 120), while even larger doses of RSV IVIG (750 mg/kg monthly) reduced the frequency of non-RSV otitis in young infants (157). Ishizaka et al. (80) successfully used IVIG to treat seven children with recurrent pneumococcal otitis media.

Diphtheria

Many of the adverse consequences of diphtheria result from the action of its potent toxin on the heart, central nervous system, and other organs (165). The prompt use of equine diphtheria antitoxin is indicated in all infections, in addition to antibiotics (5). The dose is dependent on the severity and site of infection (5): for pharyngeal or laryngeal disease of 48 h duration, 20,000 to 40,000 U is given; for nasopharyngeal lesions, 40,000 to 60,000 U is given; and for extensive disease of more than 72 h duration or with neck edema, 80,000 to 120,000 U is given intravenously. Since the antitoxin is of equine origin, skin testing for hypersensitivity and possible desensitization (6) may be necessary. The product is available through the Centers for Disease Control and Prevention, Atlanta, Ga.

Pertussis

Pertussis antiserum was used in the 1930s for treatment of pertussis (27), but subsequent studies could not confirm a protective effect (20, 113). Antibodies have largely been abandoned in pertussis prevention or treatment, although Granström et al. (63) used an experimental, human hyperimmune serum from subjects immunized with a two-component acellular vaccine to treat 33 children, while an equal number received an albumin placebo. The treated children had decreased coughing and whooping, particularly if treatment was started early. Ichimaru et al. (76) successfully used a high-titer human IVIG preparation to treat a severely ill 1-year-old child. Bruss et al. (27a) studied a 4% high-titer human pertussis immune globulin in 26 children with pertussis and found that the product was safe at three dose levels (250, 750, and 1,500 mg/kg), and provided good pertussis immunoglobulin G (IgG) levels in serum with a half-life of 38 days. Little antibody appeared in the nasal secretion. Efficacy was not evaluated in this study. Further evaluation (27b) did show that this product was efficacious in the treatment of aerosol-induced pertussis in mice.

Tetanus

Antibody for the prevention and treatment of tetanus dates from 1890, when serum prepared from immunized horses was used in the treatment of severe tetanus since toxin neutralization is a crucial part of the treatment (7, 165). Extensive studies were done to determine the optimal dose of antitoxin and the possible benefit of intrathecal antitoxin, particularly in tetanus neonatorum, a common problem in developing countries (68). Since 1960, a human tetanus immune globulin (TIG) has been available in the United States, but in some areas of the world only equine antitoxin is available.

Current recommendations are to use TIG in unimmunized or incompletely immunized patients who sustain other than a clean minor wound, including contaminated wounds, those associated with devitalized tissues, and deep puncture wounds (7). The recommended prophylactic dose is 250 IU intramuscularly, and active immunization should be initiated. In countries where human TIG is not available, 3,000 to 5,000 U of equine antitoxin can be used. Human polyvalent IVIG can also be used, but it contains variable levels of tetanus antitoxin, and thus a minimal dose of 100 mg/kg is suggested for tetanus prophylaxis (100).

TIG is also indicated in the treatment of tetanus (3,000 to 6,000 IU or 50,000 to 100,000 U of equine tetanus antitoxin), and a portion of it can be used to infiltrate a wound site (7). TIG is also indicated in the treatment of tetanus neonatorum. Intrathecal TIG in tetanus neonatorum has been recommended (68), but its efficacy is not proven (26).

Other Clostridial Infections

Botulism is a severe paralytic disease resulting from ingestion or absorption of the potent neurotoxin produced by *Clostridium botulinum*. Three clinical variants include food poisoning from ingestion of contaminated canned food, wound botulism from a contaminated soft tissue injury, and infant botulism from ingestion of spores, sometimes from honey, and multiplication within the gastrointestinal tract (153).

Food-borne and wound botulism are treated with a trivalent (types, A, B, and E) equine antitoxin available through the Centers for Disease Control and Prevention (8, 153). Antitoxin can also be given to individuals known to have ingested contaminated food. An investigational equine heptavalent botu-

lism immune globulin fragment $F(ab')_2$ for treatment is also under study (74).

Equine antitoxin is not indicated in the treatment of infant botulism, but a trial of human botulinum IG for treatment of infant botulism has been completed in California with encouraging results. This product is available from the Infant Botulism Treatment and Prevention Program of the California Department of Health Services under a treatment IND protocol [telephone, (510) 540-2646] (8).

Clostridium difficile infection of the gastrointestinal tract may result in pseudomembranous colitis and antibiotic-associated diarrhea (187). Two toxins, A and B, have been identified. The disease can be severe, particularly in immunocompromised subjects, and is usually treated with metronidazole or vancomycin. A few patients with refractory *C. difficile* colitis have been treated successfully with human IVIG (200 to 400 mg/kg). IVIG contains significant titers of *C. difficile* antitoxin, and immunocompromised subjects often lack these antibodies in their sera (71, 102, 144). Preliminary studies with an oral anti-*C. difficile* bovine immunoglobulin for both treatment and prevention are under way (187).

Staphylococcal Infections

Staphylococcal infections are ubiquitous and of varying severity, ranging from superficial skin infections to deep-seated cellulitis, osteomyelitis, and overwhelming toxic shock. Antibiotics are usually effective in controlling the infections, but in some instances the organism is antibiotic resistant or the disease is rapidly progressive with toxin production. IVIG may be of adjunctive benefit in some of these situations (36).

In staphylococcal toxic shock syndrome, often associated with tampon use in menstruating women, there is rapid onset of fever, shock, macular desquamating rash, and multisystem organ failure (36, 109). The pathogenesis of the disorder is infection with a strain that releases the toxin, toxic shock syndrome toxin 1. This toxin is a potent superantigen, which activates the immune system directly with the release of multiple cytokines and a clinical picture of rapidly progressive illness (36).

IVIG contains antibodies to staphylococcal and streptococcal superantigens and has been used successfully both in animal models of toxic shock syndrome (36) and in several patients (23, 127, 131). Although there have been no clinical trials, most authorities recommend the use of large IVIG doses, at least 400 mg/kg, in addition to antibiotic treatment and circulatory support (36). IVIG also downregulates cytokine synthesis and action and inhibits immune activation, providing nonspecific beneficial effects in addition to toxin neutralization (21).

Higuchi et al. (75) reported a large family who had recurrent episodes of staphylococcal toxic shock syndrome associated with normal immunoglobulin levels but low serum antibody titers to staphylococcal superantigens; two boys in the family were given successfully prophylaxis with regular IVIG infusions.

A second situation where antibody may be of value is in the prevention of *Staphylococcus epidermidis* infection in the newborn, particularly in premature infants (19). This organism is a common cause of serious neonatal infections such as sepsis, and IVIG containing *S. epidermidis* opsonizing antibodies may be effective in its prevention. Fischer et al. (50) have studied IVIG in the treatment of *S. epidermidis* infections in suckling rats and have demonstrated a potential benefit. A further discussion of IVIG in the newborn is provided below.

A final use of IVIG in staphylococcal infection is in the

treatment of antibiotic-resistant chronic staphylococcal infection in addition to antibiotics. In 1957, Waisbren (180) treated 13 such patients, including 5 with osteomyelitis, with antibiotics and gamma globulin, and 11 of them recovered. One of us (E.R.S.) successfully treated a woman with antibiotic-resistant dissecting cellulitis of the scalp by using a combination of high dose IVIG and antibiotics. Animal studies have supported such a combined approach; for example, Fisher increased the survival of mice given *S. aureus* intraperitoneally from 20% with chloramphenicol treatment to 93% with chloramphenicol and gamma globulin treatment (52).

Invasive Streptococcal Infection

Invasive group A streptococcal infections, including septicemia, toxic shock syndrome, and necrotizing fasciitis or myositis, are increasing in severity and frequency (15). Streptococcal superantigens such as the pyrogenic exotoxins (e.g., SPE A, B, and C) may be implicated in the pathogenesis of these disorders by activating lymphocytes and releasing multiple proinflammatory cytokines.

Since IVIG contains variable titers of antibodies to these antigens, its administration may rapidly neutralize streptococcal toxins and down-regulate immune activation (124). Several reports (99, 135) suggest its clinical benefit in invasive streptococcal disease when given in large doses (1 to 2 g/kg), in addition to antimicrobial and supportive therapy.

Infection in High-Risk Newborns

Newborns, particularly premature newborns with birth weights of <2,000 g, are potential candidates for antibody treatment, in view of the frequency and severity of infections (189). All newborns have very low levels of IgM and IgA and, if premature, a deficiency of transplacental maternal IgG. In addition, they have slow antibody responses, neutrophil mobilization and killing defects, opsonic defects associated with complement activation abnormalities, and variably deficient cellular immune responses (189).

Accordingly, several studies have been conducted to determine the value of IVIG in the prevention or early treatment of infection in newborn infants (85, 86, 98). Although these studies differ as to entry criteria, dose and brand of IVIG, and outcome end points, a recent meta-analysis of 12 prophylaxis studies showed a modest protective effect (P = 0.0193). For the most part, the infants treated were 20 to 37 weeks of gestation with birth weights of 1,300 to 2,000 g and were given IVIG at doses of 400 mg/kg at weekly or biweekly intervals until discharge at 1 to 3 months of age. However, only 5 of the 12 studies showed a beneficial effect, 6 were inconclusive, and 1 showed a detrimental effect (i.e., increased incidence of sepsis).

For treatment of neonatal sepsis, a meta-analysis of three controlled studies (86) showed a clear beneficial effect (a sixfold decrease in mortality). There were 3 deaths among 52 IVIG-treated infants (5.7%) compared to 13 deaths among 42 untreated infants (31%), a highly significant difference (P = 0.007). IVIG may be particularly valuable for the neutropenic infant since it may help to mobilize leukocytes from the storage pool (37).

In summary, IVIG is not indicated routinely for the prevention of neonatal infections, but it may be of some value in the infected newborn not responding to antibiotics, particularly in the presence of neutropenia.

Shock, Intensive Care, and Trauma

Patients undergoing severe stress associated with trauma, extensive surgery, or intensive care have profound exposure and susceptibility to infection and develop a spectrum of immune deficiencies including cutaneous anergy, phagocytic dysfunction, hypogammaglobulinemia, and transiently impaired antibody function (61, 148). Bowel stasis and hypotension may promote gram-negative bacterial sepsis, endotoxemia, or both, with development of severe and often irreversible shock (88, 148). Ziegler et al. (196) and Baumgartner et al. (25) reduced the incidence and severity of severe shock in such patients by using human antisera to a mutant J5 *Escherichia coli* endotoxin with anti-lipid A activity.

Calandra et al. (29), using a human IVIG to J5 E. coli in 71 patients with gram-negative bacterial infections and shock, could not confirm these results, since the anti-J5 E. coli antibody showed no benefit compared to regular IVIG. Just et al. (88) gave antibiotics and IVIG to 50 intensive care patients and compared their outcome to that in 54 control patients who received antibiotics alone. Although there was no difference in survival, the IVIG-plus-antibiotic group had a shortened intensive care unit stay, a shorter period in which respirator therapy was necessary, improved renal function, and a decreased number of deaths from infection. A large multicenter study of 352 postsurgical patients (77) confirmed the observation that polyvalent IVIG (400 mg/kg/week) reduced the incidence and shortened the intensive care unit stay compared to placebo-treated or hyperimmune core lipopolysaccharide IGtreated patients.

MAb preparations to endotoxin have been tested in clinical trials of septic shock patients, but none were of proven efficacy (119, 184). MAb to tumor necrosis factor alpha also has shown no efficacy in the treatment of adults with septic shock (1, 39). MAb to interleukin-6, interleukin-1 receptor, and bacterial permeability factor are under investigation for the treatment of shock (56). In summary, there are no compelling data to suggest that antibody, either polyclonal or monoclonal, is of benefit in the acutely ill patient with shock.

Pseudomonas Infection

Severe Pseudomonas infections occur in a number of disorders in which systemic or local host defense is compromised, notably cutaneous burns, illnesses requiring intensive care, and cystic fibrosis (115, 177, 190). Animal studies show that antibodies to Pseudomonas aeruginosa polysaccharide protect against experimental infection (115). There was suggestive clinical benefit in burn patients given a human Pseudomonas IVIG or burn plasma, but subsequent studies could not prove clinical efficacy (40, 89). In a more recent study, Donta et al. (43) gave an experimental human IVIG (at 100 mg/kg) derived from donors immunized with an octavalent Pseudomonas polysaccharide toxin A conjugate and a 24-valent Klebsiella polysaccharide conjugate to alternative patients (n = 1,497) admitted to a Veterans Administration hospital intensive care unit. There was no statistically significant benefit in the rate or severity of infection in these patients.

In cystic fibrosis patients, both an experimental human hyperimmune *Pseudomonas* immune globulin and regular IVIG have been used with very modest clinical benefit and without eradicating the organism (177, 190); thus, IVIG is not indicated.

VIRAL DISEASES

Hepatitis A

IG has been used extensively for prevention of hepatitis A, both following exposure and prior to travel to an area of endemic infection (169). Its use for these indications has decreased since the introduction of hepatitis A vaccines. Proof of the value of IG for the prevention of hepatitis A dates from 1945 in studies of epidemics in summer camps, institutions for mentally handicapped children, and in the Mediterranean battle front (57, 72, 182).

When administered before or within 2 weeks after exposure, IG is 85 to 90% effective in preventing clinical hepatitis, but efficacy varies with the severity of exposure and the delay in administering IG (182). IG may not prevent the disease, but passive-active immunity seems to occur, in which the IG prevents early clinical disease but subclinical viremia results in a long-lived protective antibody response (9).

The usual postexposure dose of IG is 0.02 ml/kg given as soon as possible after exposure but no later than 2 weeks (9). This dose can also be used in susceptible travelers to areas of endemic infection who will be gone for less than 3 months. For longer stays, a dose of 0.06 ml/kg is recommended. (These doses do not interfere with the antibody response to simultaneously administered vaccine.) Travelers are better protected by vaccine administration. Infants born to hepatitis A-infected mothers should also receive IG.

Hepatitis **B**

In contrast to its value in hepatitis A prophylaxis, IG does not prevent hepatitis B in exposed subjects because of its low titer of anti-HBSAg antibody. However, hepatitis B immune globulin (HBIG), prepared from donors with high anti-HBSAg titers, is a highly effective prophylactic agent (32, 33). Studies in institutionalized subjects, patients exposed by needle sticks, patients and staff of renal dialysis units, and sexual partners of hepatitis B-infected subjects all indicate that HBIG is 80 to 90% effective in preventing infection when given before or shortly after needle stick, sexual exposure, or mucous membrane exposure (33). The usual HBIG dose is 0.06 ml/kg given within 24 h of exposure. Hepatitis B vaccine should also be started after acute exposure, for durable immunity.

Hepatitis B can also be transmitted from mothers to infants at the time of birth, and this transmission can be markedly reduced by the immediate postpartum administration of HBIG (0.5 ml) to the infant either alone or, as currently recommended, with commencement of hepatitis B vaccine (10). Prompt use of HBIG and vaccine does not prevent all cases of maternal-fetal transmission, since transmission may also occur during the prepartum period.

An increasingly important use of HBIG is to prevent hepatitis B recurrence in hepatitis B-seropositive liver transplantation recipients, many of whom are transplanted because of complications of hepatitis B infection (64, 114, 145, 173). These individuals have at least a 50% risk of developing hepatitis B in the transplanted liver within 3 years (114). Recurrence can be reduced (up to 50%) with the use of HBIG given either intravenously or intramuscularly starting immediately posttransplantation and continuing indefinitely (64, 114, 145, 146, 173). In one retrospective study, the recurrence rate was 74% among 67 patients not given HBIG, 74% among 83 patients given HBIG for 2 months, and 36% among 209 patients given HBIG for 6 months or longer (146). Other studies show similar results, using different schedules of HBIG administration (64, 173). The use of antiviral agents (e.g., lamivudine and alpha interferon) given pretransplantation to patients with a high viral burden may enhance the effectiveness of the HBIG, since less virus must be neutralized (172).

The use of HBIG after liver transplantation is still experimental, and no standard dose or route of administration is recommended. An intravenous form of HBIG is under development. The use of HBIG may permit many patients to receive a liver transplant who were previously considered ineligible.

Hepatitis C

Although no antibody preparation is available for the prevention of hepatitis C, past studies suggested that polyvalent immune globulin or HBIG provided some protection against acquisition of non-A, non-B hepatitis (presumably hepatitis C) following heart surgery or hemodialysis (94, 147, 159).

Hepatitis C was transmitted by IVIG in the mid-1990s, shortly after hepatitis C-seropositive donors were excluded from the donor pools used in the manufacture of IVIG (150). A plausible explanation for the lack of transmission prior to this Food and Drug Administration policy is that the hepatitis C antibodies neutralized trace amounts of hepatitis C virus not eliminated during the fractionation. New manufacturing processes (solvent-detergent and pasteurization) have seemingly eliminated hepatitis C virus from IVIG, and no new cases of hepatitis C transmission have been reported.

Two recent studies also provide some evidence for a prophylactic effect of IG. Piazza et al. (136) gave polyvalent IG (from pools containing antibodies to hepatitis C virus) or placebo monthly for 4 to 20 months to the seronegative sexual partners of 884 hepatitis C virus-seropositive subjects. One of the 450 (representing 506 subject-years) in the IG group became infected compared to 6 of the 449 (500 subject-years) in the placebo group (P = 0.03; relative risk, 10.7). The authors conclude that sexual transmission of hepatitis C occurs and that IG has a protective effect.

Feray et al. (48) conducted a retrospective review of 210 patients who were hepatitis C seronegative prior to liver transplantation. Among the 68 patients who postoperatively received HBIG containing antibodies to hepatitis C, 18 (26%) acquired hepatitis C infection posttransplantation, while 40 of 86 patients (47%) not receiving HBIG developed hepatitis C, indicating a significant protective effect (P < 0.001).

There also is a great need to prevent a recurrence of hepatitis in hepatitis C-seropositive patients undergoing liver transplantation. Studies are under way to determine if an experimental immunoglobulin preparation enriched in hepatitis C antibodies can be used for this purpose. As noted, current lots of IVIG or IG contain no hepatitis C antibodies.

Human Immunodeficiency Virus Infection

Antibody therapy has been used for two purposes in the management of HIV infection. Regular IVIG has been used to prevent concomitant infection, and HIV-specific antibody has been used to provide a specific antiviral effect. IVIG decreases the number of serious bacterial and respiratory infections in HIV-infected children with moderately compromised immune systems, particularly if they were not receiving prophylactic antimicrobials (120, 162).

More relevant to this review are the studies that have used specific HIV antibodies in an attempt to ameliorate the course of the primary HIV infection. These studies have employed human immune plasma or hyperimmune immunoglobulin (HIVIG) from asymptomatic HIV-seropositive patients (168). Two of three controlled studies in adults with advanced AIDS suggested a modest clinical benefit as judged by decreased opportunistic infections, a slight increase in CD4 cell counts, and improved survival; however, there were no striking decreases in the viral burden (81, 103, 179).

In a recent double-blind, placebo-controlled multicenter study, HIV-seropositive pregnant women receiving zidovudine were given HIVIG during the last trimester of pregnancy and one HIVIG dose was given to their newborns at birth; there was no effect on the rate of maternal-fetal HIV transmission compared to that in a similar group given regular IVIG (167). Because the rate of transmission in both groups was unexpectedly low (less than 5%), the study was discontinued after 800 patients had been enrolled, since the study was not statistically powered to detect a slight reduction in transmission rates.

Another recent study (166) examined the antiviral effect of large doses of HIVIG in 30 children with moderately advanced HIV infection who were on stable antiviral treatment and who showed a measurable viral burden. No striking beneficial effect was observed as indicated by HIV RNA levels in plasma, cellular viral culture titers, or immunologic assays.

MAb against HIV epitopes or against coreceptors are under study as a means of controlling infection or preventing transmission following needle stick or sexual exposure.

Respiratory Syncytial Virus Infection

RSV infection is the leading cause of hospitalization of young children with respiratory tract disease. Since there is no vaccine, passive antibody therapies are used in high-risk infants to prevent and modify RSV infection.

RSV-IGIV is derived from plasma donors with high RSV neutralizing antibodies. In 1995, a prospective, blinded, randomized study conducted at five centers (66) with 162 premature infants, 102 of whom had bronchopulmonary dysplasia, reported that prophylaxis with RSV-IGIV (750 mg/kg monthly) significantly decreased intensive care unit stays (P =0.05) and severe RSV infection (7 versus 24%; P = 0.01). A subsequent, double-blind, placebo-controlled trial of RSV-IGIV, conducted at 54 centers (175) with 510 infants and children with bronchopulmonary dysplasia or prematurity without lung disease, confirmed its efficacy; RSV-IGIV (750 mg/kg every 30 days) decreased RSV hospitalizations from 13.5 to 8.0%, a 41% reduction (P = 0.047).

In 1997, the American Academy of Pediatrics (17) recommended considering RSV-IGIV (Respigam) prophylaxis during RSV season for infants younger than 2 years with bronchopulmonary dysplasia requiring oxygen therapy in the past 6 months and for high-risk premature infants. Patients with cyanotic congenital heart disease were excluded from these recommendations due to increased side effects (65, 158).

Palivizumab, an RSV MAb, was next studied in a randomized, double-blind, placebo-controlled, trial at 139 centers in the prophylaxis of RSV in 1,502 high-risk infants (174). Children younger than 24 months with bronchopulmonary dysplasia requiring medical treatment in the past 6 months or premature infants received 15 mg of palivizumab or placebo per kg intramuscularly monthly. The infants who received palivizumab had a 55% reduction in RSV hospitalizations (4.8 versus 10.6%; P < 0.001), a 42% reduction in total RSV hospital days (36.4 versus 62.6 days; P < 0.001), and a 40% reduction in days requiring supplemental oxygen (30.3 versus 50.6 days; P < 0.001). Licensed in 1998, palivizumab is the first MAb commercially available for the prevention of an infectious disease. It is a humanized mouse IgG1 MAb against the RSV surface F glycoprotein (60, 170).

Although the indications for RSV-IGIV and palivizumab

are similar, palivizumab is preferred because of its lower cost and its ease of administration (intramuscular versus intravenous for RSV-IGIV). Further, palivizumab does not interfere with measles and varicella vaccines and is less likely to transmit an infectious agent since it is not prepared from plasma. There is the theoretical risk that palivizumab will elicit an antibody response in recipients, with resultant reaction or resistance to treatment.

The American Academy of Pediatrics (16) recommends that palivizumab or RSV-IGIV be considered during RSV season for children younger than 2 years with chronic lung disease who have required treatment within the prior 6 months and for premature infants of less than 32 weeks gestation at birth. Palivizumab is preferred. Patients with congenital or acquired immunodeficiency may also benefit. For immunodeficient patients, RSV-IGIV may be substituted for IVIG since IVIG does not contain sufficient anti-RSV antibodies.

Treatment of established RSV infection with either polyclonal antibodies or MAb has not been successful. Rodriguez et al. (142) found that RSV-IGIV at a single dose of 1,500 mg/kg was not effective in the treatment of RSV in previously healthy children. High-risk children with RSV also did not benefit from treatment, although the titer of RSV in the nasopharyngeal secretions was decreased (141). Similarly, palivizumab reduced the tracheal concentration of RSV in 35 mechanically ventilated children but did not decrease disease severity (104).

The combined use of RSV-IGIV and ribavirin has been studied in a small number of adult bone marrow transplant recipients with RSV pneumonia and has shown a possible benefit (185). Aerosolized antibody has also been used for treatment of infants with severe RSV disease (140). A single treatment with polyclonal immunoglobulin aerosol (not RSV-IGIV) had no effect on the clinical course of RSV bronchiolitis.

Polyclonal RSV-IGIV for prophylaxis also decreased total respiratory infection hospitalizations (16 versus 27%; P = 0.005) (175). Not surprisingly, the MAb had no such effect (174). Similarly, as mentioned above, there was a decrease in otitis media in polyclonal antibody recipients but not in MAb recipients.

Herpesvirus Infections

The *Herpesviridae* family of viruses, including herpes simplex virus (HSV), varicella zoster virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV), can cause significant human disease. All are enveloped DNA viruses that produce lifelong latent infection which can be reactivated if the host becomes immunodeficient. Thus, immunoglobulin has been used to both prevent and treat reactivation in these situations.

Cytomegalovirus. The use of CMV immune globulin (CMVIG) (prepared from the plasma of individuals with high titers of anti-CMV antibodies) or IVIG for prophylaxis of posttransplantation CMV disease has been studied for over a decade. Studies include the use of CMVIG or standard IVIG (which contains CMV antibody) with or without antiviral therapy in different patient populations and with differing CMV seropositivity status of the patients. With regard to the latter, it is now agreed that the seronegative recipient receiving a transplant from a seronegative donor has the highest risk of serious CMV disease while a seronegative recipient receiving a transplant from a seronegative donor and receiving CMV-negative blood products has an extremely low risk.

Initial studies evaluated CMVIG or IVIG as single prophylactic agents, but later they were evaluated as adjuncts to antiviral prophylaxis with acyclovir or ganciclovir. The most convincing studies for a beneficial role for antibody prophylaxis come from studies in renal transplant patients (28, 53, 161; G. H. Wirnsberger, A. Mauric, and H. Holzer, Letter, Nephron **81:**368–369, 1999) and to a lesser extent in liver transplant patients (45, 70, 137). The combination of antibody and antivirals has also been used in heart transplantation (55) and lung transplantation (69).

The efficacy of CMVIG or IVIG is difficult to assess because of variable concurrent antiviral regimens (acyclovir, oral ganciclovir, and intravenous ganciclovir), variable CMV serologic status of the donor and recipient, and variable immunosuppression during the treatment period. In the situation of a CMV-seropositive donor and a CMV-seronegative recipient, the need for antiviral prophylaxis is established, but whether CMV antibody should also be given is not established (84, 133). Jassal et al. (84) recommend ganciclovir prophylaxis for all CMV-seropositive kidney transplant recipients or seronegative recipients receiving a transplant from a seropositive donor if these recipients are receiving intensive immunosuppression. No recommendation was made for CMVIG in these 1998 consensus guidelines.

The meta-analysis of Wittes et al. (192) suggested that CMVIG prophylaxis decreased CMV mortality and severe CMV disease, including prevention of pneumonia in bone marrow transplant and solid-organ transplant recipients. The 1994 meta-analysis of Glowacki and Smaill (62) supported the use of either IVIG or CMVIG to prevent symptomatic CMV disease, CMV pneumonia, and CMV-mediated death in solid-organ and bone marrow transplant recipients. Similar analyses of bone marrow transplantation have shown a benefit of either CMVIG or IVIG in preventing CMV disease (24, 67, 110, 156), but a recent study (143) demonstrated no significant clinical benefit or enhanced survival in seronegative bone marrow transplant recipients. Zikos et al. (197) also could not demonstrate a beneficial effect of high-dose IVIG versus CMVIG in allogeneic hematopoietic stem cell transplant patients.

In summary, CMVIG or IVIG is added to antiviral prophylaxis for high-risk transplant patients at some centers. The value of CMVIG in the treatment of severe CMV disease including pneumonitis is unproven, although some recommend combined antiviral-antibody therapy (130, 134, 139, 195).

CMVIG may be of value for in utero CMV infection. Negishi et al. gave CMVIG intraperitoneally to a CMV-infected fetus at 28 weeks gestation (122). Although the infant was born with CMV infection and central nervous system calcification, there was no evidence of neurologic symptoms at the age of 1 year. Subsequently, Nigro et al. (123) treated a pregnant woman who had primary CMV infection and intrauterine infection of one twin fetus with intravenous CMVIG at 30 weeks gestation. The fetus was also treated with CMVIG injected into the amniotic sac fluid. Response to therapy was suggested by the twin's growth and decreased placental thickening and cord edema. The infant was born with mild hepatosplenomegaly and CMV infection, but the child was clinically normal at 2 years of age.

Epstein-Barr virus. EBV infects B cells via the CD21 receptor and usually causes infectious mononucleosis in normal patients. In boys with X-linked lymphoproliferative syndrome and in immunocompromised patients, it can cause severe and often progressive lymphoproliferative syndrome. IVIG prophylaxis has been used in patients with X-linked lymphoproliferative syndrome to prevent EBV infection, but patients have died of EBV infection despite this therapy (49). Feranchak et al. (47) successfully treated a patient with fulminant EBV hepatitis by liver transplantation, antiviral therapy, and

EBV antibody (using CMVIG, which contains high titers of anti-EBV antibodies). CMVIG or IVIG (containing anti-EBV antibodies) has been used, in addition to antiviral therapy and alpha interferon, to successfully treat posttransplantation EBV-induced lymphadenopathy, lymphoproliferative syndrome, or hepatitis (42, 126, 171). However, IVIG and alpha interferon were not successful in a patient with X-linked lymphoproliferative syndrome (129).

In summary, the EBV antibodies in IVIG or CMVIG have been used with unproven benefit to prevent EBV infection in X-linked lymphoproliferative syndrome. EBV antibodies may be beneficial in the treatment of posttransplantation lymphoproliferative syndrome and hepatitis.

Herpes simplex virus. The 10-fold-lower risk of a neonate acquiring HSV infection during passage through an HSV-infected birth canal of a seropositive mother than from a sero-negative mother indicates that transplacental maternal antibody prevents infection (12). IVIG is not recommended, since acyclovir is effective in this situation. The use of HSV human MAb, humanized MAb, or hyperimmune immunoglobulin for treatment of neonatal disseminated infection has been proposed by Whitley (186). MAb are currently under development, including a human recombinant MAb against a highly conserved group Ib antigenic site of glycoprotein D (41).

Masci et al. (107) gave monthly IVIG to 11 patients with recurrent genital HSV infection and compared them to patients treated with acyclovir. They had fewer recurrences, less severe lesions, and reduced duration of lesions. However, such use of IVIG is not considered standard management.

Varicella-zoster virus. Varicella-zoster immune globulin (VZIG), available since 1978, is prepared from plasma with high titers to VZV. If given shortly after exposure, VZIG can prevent or modify varicella (51). VZIG should be given as soon as possible after exposure but must be given within 96 h for maximum efficacy (14). VZIG may modify disease if given for up to 10 days following exposure (128). The dose is 125 U/10 kg intramuscularly, with 125 U as a minimum dose and 625 U as a maximum dose.

Immunocompromised adults, adolescents, and children, who are susceptible to VZV, are candidates for VZIG (14, 18, 128). Patients receiving IVIG at 400 mg/kg may be protected for 3 weeks (14). Newborns whose mothers develop varicella within 5 days prior to delivery or within 2 days after delivery may develop severe varicella due to transplacental infection prior to development and transfer of maternal antibody, and these newborns should receive VZIG. Varicella-exposed premature infants of less than 28 weeks gestation or <1,000 g birth weight should receive VZIG, regardless of the mother's varicella history or seropositivity, because of incomplete transfer of maternal antibody (14). Newborn infants of >28 weeks of gestation exposed in the nursery are also given VZIG if the mother is seronegative or has no history of varicella (14).

Because of the availability of acyclovir, VZIG is not indicated for healthy exposed adults. However, exposed seronegative pregnant women are candidates for VZIG because of the increased risk of varicella pneumonia (160).

VZIG is ineffective in preventing the dissemination of zoster or in the treatment of severe postherpetic neuralgia (163).

Parvovirus B19 Infection

Parvovirus B19 is a DNA virus that causes fifth disease, a common exanthem of childhood. Parvovirus B19 infects bone marrow erythroid progenitors through the P-antigen receptor (194). Since the immune response to parvovirus includes the development of neutralizing antibodies, immunodeficient pa-

tients may become chronically infected, usually manifested by pure red cell aplasia. Patients with congenital or acquired immunodeficiencies, including HIV-infected individuals (38, 95, 194), organ transplant recipients (105), and patients receiving cytotoxic or immunosuppressive therapy (194), may develop chronic parvovirus infection. IVIG is an excellent source of parvovirus B19-specific IgG (151), and many case reports attest to its value in the treatment of parvovirus infection. Doses from 400 mg/kg/day for 5 to 10 days (54) to 2 g/kg over 2 days (95) are used. Dosing for chronic suppressive therapy has been less extensively studied, but a dose of 400 mg/kg each month has been reported (95).

IVIG has been used successfully in a 24-week-old hydropic fetus by giving intravenous treatment to the mother (152). Fetal ascites and pericardial effusion both resolved.

The detection of parvovirus by DNA PCR tests permits diagnosis in patients unable to develop an antibody response. AIDS patients are particularly susceptible to chronic parvovirus infection, and IVIG can be used to successfully treat these subjects. MAb are also under development (59).

Enterovirus Infections

Two groups of patients are particularly susceptible to severe enteroviral disease, neonates (79) and immunodeficient patients, especially those with X-linked agammaglobulinemia. The latter may develop chronic central nervous system enteroviral disease (108) or vaccine-associated poliomyelitis (125). The routine use of high-dose IVIG to treat X-linked agamaglobulinemia has dramatically reduced the occurrence of chronic enteroviral meningoencephalitis. In a review by McKinney et al. (108) of 42 patients with chronic enteroviral meningoencephalitis (predominantly echovirus, with two coxsackie A virus and two coxsackie B virus infections), 12 patients received intraventricular IVIG therapy in addition to IVIG. Six patients substantially improved. IVIG plus intraventricular IVIG has cleared infection in some but not all patients (44, 96, 111).

Neonates are also at risk for disseminated enteroviral infection (138). Intramuscular immunoglobulin containing echovirus 11 antibody was used prophylactically in a nursery outbreak (117). Others (78, 93) have questioned its benefit. A therapeutic benefit of IVIG has also been suggested for neonates with disseminated coxsackie B virus (79), echovirus 11 (87), and coxsackie B_1 virus (176) infections.

Infants with neonatal enterovirus treated with IVIG at 750 mg/kg (2) had decreased viremia and viruria when the neutralization titer of the IVIG was greater than 1:800 for the patient's isolate. There was no effect on clinical outcome in this study of nine infants. Pasic et al. (132) gave 21 asymptomatic neonates IVIG at 400 mg/kg (neutralization titer, 1:32) during an echovirus 6 nursery outbreak; the treatment did not prevent viral transmission within the nursery, but there was some decrease in disease severity.

Despite the lack of controlled trials, infants with severe disseminated enterovirus disease may be candidates for IVIG containing a significant titer against the outbreak serotype.

Ebola

Ebola virus, a filovirus first described in 1976, causes severe and often fatal hemorrhagic fever. Outbreaks have occurred in Africa since 1995, and since air travel can cause spread, it poses a significant public health problem. There is currently no effective prevention or treatment.

The value of hyperimmune goat or equine sera for prophylaxis and treatment has been reviewed by Kudoyarova-Zubavichene et al. (97). Goat hyperimmune serum had maximal prophylactic benefit in guinea pigs if given 24 h or less before virus exposure, but there was some benefit for up to 72 h after viral challenge. This preparation was first given to seven normal human volunteers and was then used in Russia for emergency prophylaxis of four patients exposed by laboratory accidents. The one patient who definitely received a significant dose of virus developed only a mild infection, but he was also given interferon and hemosorption therapy. An equine antiserum was used successfully to protect baboons challenged with a low dose of virus, but it only delayed the onset of illness in cynomolgus monkeys receiving a high dose of virus (82). Treatment of Ebola virus-infected cynomolgus monkeys on the day of infection and again on day 5 with equine serum only delayed clinical signs and death (83), suggesting that antibody alone will not be an effective therapy.

In a 1995 Ebola outbreak in the Congo, eight patients were treated with whole blood from convalescent patients, which contained anti-Ebola antibody (116). The mortality was 12.5% (1 of 8), compared to the expected 80%, suggesting that the antibody contributed to survival. However, Jahrling et al. (82) found only low anti-Ebola virus titers (by enzyme-linked-immunosorbent assay or fluorescent-antibody assay) in plasma from convalescent Ebola virus patients compared to the level in goat or equine hyperimmune sera. Human MAb to Ebola virus are under development (106) for emergency prophylaxis and treatment, but an effective antiviral treatment will probably be necessary to control this infection.

Rabies

Optimal prevention of rabies following exposure requires both vaccine and immunoglobulin administration in addition to wound cleansing. In the United States, two human rabies immune globulin (RIG) products are available, BayRab and Imogam Rabies-HT, both prepared from the plasma of hyperimmunized donors. The recommended dose is 20 IU/kg, and the importance of infiltrating the full dose around all of the wounds is now stressed (35). Administration of one of the three licensed vaccines should be started at the same time, but RIG and vaccine must not be mixed in the same syringe. The RIG dose must be precise, since excessive antibody may decrease the antibody response to vaccine.

Wilde et al. (188) recognized the difficulty in infiltrating multiple wounds on the face, head, arms, and hands with a small volume of immune globulin and recommended dilution to ensure infiltration around every wound. The World Health Organization recommendations state that sterile saline can be used to dilute RIG two- to threefold to permit thorough infiltration (193).

Current recommendations are to use RIG for up to 7 days after exposure if it is not given immediately. In developing countries where RIG is not available, purified equine RIG is used.

Measles, Rubella, and Mumps

Although the principal means of preventing measles is the use of live-attenuated measles vaccine, passive immunoprophylaxis can be used to prevent or modify measles if it is given within 6 days of exposure. Since infants younger than 1 year, unimmunized pregnant women, and immunocompromised patients are at risk for severe measles infection, they should receive IG following exposure (58). IG can also prevent or modify transmission to other susceptible contacts (11), but administration of measles vaccine within 72 h of exposure will provide some protection and is used in school or day care outbreak situations. The dose of IG is 0.25 mg/kg for healthy

subjects and 0.5 mg/kg for immunocompromised subjects. Immunocompromised patients receiving IVIG at 100 to 400 mg/kg are protected for 3 weeks from a measles exposure (11).

Postexposure prophylaxis of rubella with IG in pregnancy is usually not recommended. A dose of 0.55 mg/kg can be given when the pregnancy will not be terminated. The efficacy of such a practice is debatable since infected infants with congenital rubella syndrome have been born to exposed pregnant women despite IG prophylaxis (13).

Mumps immune globulin is not available.

Tick-Borne Encephalitis

Tick-borne encephalitis, caused by a flavivirus, is endemic in central Europe. An effective vaccine is available, but hyperimmune human immunoglobulin can be used following a tick bite. Severe disease following prophylaxis has been reported, suggesting the occurrence of antibody-dependent enhancement of infection (181). Although its use has been questioned (3) due to the lack of definitive efficacy trials, von Hedenstrom et al. (179a) recommended that postexposure hyperimmune globulin be given along with vaccine.

Vaccinia and Smallpox

Since 1977, smallpox has been eradicated worldwide, but it has tremendous biologic warfare potential because routine vaccination has been discontinued. The two major viruses of the *Orthopoxvirus* genus, variola virus (causing smallpox) and vaccinia virus (which may be derived from cowpox virus and is used for the vaccine), are very closely related (121). Smallpox vaccine is still available from the Centers for Disease Control and Prevention and is recommended (34) for laboratory personnel working with vaccinia virus or related viruses.

Vaccination may lead to serious complications, such as encephalitis in immunocompromised patients and eczema vaccinatum in patients with eczema. When vaccination must be given despite an obvious contraindication, human vaccinia immunoglobulin (VIG) can be used to prevent serious complications (46, 118, 154).

Kempe et al. (91) used VIG to prevent the spread of smallpox to contacts during a 1953 outbreak in Madras, India. VIG has also been used to treat complications of immunization (22, 46, 90, 154). Recently, Kesson et al. (92) used VIG and ribavirin to treat a severely immunocompromised patient who inadvertently received a vaccinia melanoma oncolysate vaccination.

VIG is available from the Centers for Disease Control and Prevention for treatment of vaccination complications including eczema vaccinatum, severe generalized vaccinia, and ocular vaccinia. A dose of 0.6 ml/kg is given intramuscularly; in adults this dose is divided and given over 24 to 36 h. Repeat doses are given at intervals of 2 to 3 days (34).

LOOK TO THE FUTURE

The use of human MAb or humanized MAb to key epitopes of infectious pathogens may further define the humoral responses with significant therapeutic potential. Since many infections are now caused by bacteria resistant to antibiotics (e.g., *S. aureus, Enterococcus* species, and *S. pneumoniae*), the development of immune therapy for such resistant microorganisms may potentially provide a new lifesaving strategy.

The use of MAbs may lead to more effective postexposure prophylaxis including their use intranasally in viral disease (183). A major question is whether such prophylaxis can be effective at an acceptable cost and treatment frequency. Treatment of established viral infections with antibody is rarely successful, but there are important exceptions (parvovirus, vaccinia virus, and enterovirus). As MAb recognizing key epitopes are developed, they may have enhanced therapeutic potential.

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