GENERAL GYNECOLOGY

Passive immunization: the forgotten arm of immunologically based strategies for disease containment

Bernard Gonik, MD

Passive immunization provides temporary protection in a naïve subject who has been exposed to an infectious pathogen when vaccination is unavailable or has not been given before exposure. Despite the recent attention that has been given to adult-directed vaccines, antibody-based therapeutic strategies have received little discussion yet remain an important part of infectious disease containment. This review examines some of the more common clinical situations in which an obstetrician-gynecologist may need to have expertise related to passive immunization. Potential future uses for this modality are presented.

Key words: antibody-based therapy, immunoglobulin, infectious disease, passive immunization

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Passive immunization generally is used to provide temporary protection in an unimmunized subject who has been exposed to an infectious agent when active immunization either is unavailable or has not been given before exposure. Earliest antibody or immune globulin preparations were polyclonal and made from nonhuman species such as horses. Although such therapies were effective, serious side-effects often resulted, such as serum sickness in recipients. A number of human polyclonal immune globulin preparations that have been used over the last few decades have been prepared by pooling plasma from healthy volunteers or from selected individuals with specific antibody compositions. These sterile solutions of antibodies (primarily immunoglobulin G with trace amounts of other immune globulins such as immunoglobulin M and A) are prepared by cold ethanol precipitation from large pools of human plasma. Donors have tested negative for hepatitis B surface antigen (HBsAg), antibody to human immunodeficiency virus, and antibody to hepatitis C virus.[1] Manufacturing processes are specific for viral inactivation or removal and include the addition of solvent detergent, caprylate chromatography, pasteurization, and nanofiltration. Not all immune globulin products are the same, and subtle differences in composition can be important to specific patient populations.[2]

Postexposure (and sometimes preexposure) prophylaxis with immune globulin in susceptible individuals remains an integral part of today's immunization protection protocols. Additionally, in recent years, a rebirth of interest has developed in antibody-based therapies. This is not only true for infectious disease concerns but also for adjuvant cancer therapy, neurologic disorders, and in association with organ transplantation. Most of these topics are beyond the scope of this monograph. However, within the field of infectious diseases, the recent identification of multidrug-resistant microorganisms, potential agents for bioterrorism, and immunocompromised hosts who respond poorly to traditional antimicrobial therapy have pushed the envelope related to passive antibody-based interventions. The driving force behind these advancements is the introduction of hybridoma technology in the 1970s and the development of selectively directed monoclonal antibodies (murine, natural human, and recombinant) against specific targets.

We report some of the more common recommendations that are related to passive immunization in adolescent and adult patients, with a focus on agents or circumstances that might confront the practicing obstetrician-gynecologist.

Hepatitis A virus

Until the recent availability of hepatitis A vaccines, immune globulin therapy was the mainstay of the prevention of the hepatitis A virus for people who either were likely to be exposed or had been exposed recently to this viral agent. When administered before exposure or within 2 weeks after exposure, immune globulin was >85% effective in preventing hepatitis A infection.[3] Whether immune globulin completely prevented infection or led to asymptomatic infection and the development of persistent anti–hepatitis A virus probably was a function of the amount of time that had elapsed between exposure and immune globulin administration.

In 2007, the results of a randomized, double-blind noninferiority clinical trial was published that demonstrated the efficacy of hepatitis A vaccine for postexposure prophylaxis.[4] The study included healthy individuals aged 2-40 years of age who received vaccination within 14 days after hepatitis A virus exposure. Based on these findings, the Advisory Committee on Immunization Practices (ACIP) revised its long-standing recommendations now preferentially to rec-

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI.

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ommend active vaccination over immune globulin.[3] The point estimate for hepatitis A vaccine efficacy in the prevention of clinical disease is 86% under these conditions. Patients who are <12 months old, patients who are >40 years old, patients with immunocompromised or chronic liver disease, and patients with specific vaccine contraindications should continue to receive immune globulin for hepatitis A virus prophylaxis.

Because hepatitis A infection cannot be diagnosed reliably based on clinical findings alone, serologic confirmation by immunoglobulin M anti–hepatitis A virus testing of the index case is recommended before the treatment of unvaccinated contacts is initiated. Household and sexual contacts of patients with hepatitis A should receive active vaccination or immune globulin as soon as possible, but not >2 weeks after exposure. Casual contacts, such as school classmates or coworkers, who have not had close physical contact usually do not require prophylaxis. More aggressive use of prophylaxis is indicated to control hepatitis A outbreaks in child care centers where a child or staff member is diagnosed with hepatitis A and in other settings (eg, hospitals, institutionalized individuals) when outbreaks occur. When a food handler is identified with hepatitis A, vaccine or immune globulin should be administered to other food handlers at the same establishment. Because common-source transmission is unlikely under these circumstances, patrons generally do not require prophylaxis for hepatitis A. However, if repeated exposures have occurred when the food handler was likely to be infectious, if poor hygienic practices are suspected, and if the patron can be identified within the 2 week postexposure window, vaccination or immune globulin prophylaxis should be considered.[3]

Hepatitis A vaccine or immune globulin is also recommended for preexposure prophylaxis to persons who are traveling to areas with high or intermediate hepatitis A endemicity. These endemic areas can be identified through Centers for Disease Control and Prevention sources (www.cdc.gov) or through healthcare providers who specialize in travel-related medical care.[3]

The usual dose of immune globulin for preexposure prophylaxis is a single intramuscular injection of 0.02 or 0.06 mL/kg. The lower dose is adequate to provide protection for up to 3 months, and the higher dose is effective for up to 5 months. Repeat administration every 5 months is necessary for extended trips beyond 5 months if active vaccination has not been initiated. Intramuscular preparations of immune globulin should never be given intravenously, and the intravenous preparations of immune globulin are not intended for hepatitis A prevention strategies. An appropriate muscle mass (deltoid or gluteal muscle) should be used to accommodate the relatively large immune globulin volume. Serious adverse events from intramuscularly administered immune globulin are rare. Because anaphylaxis has been reported after repeated doses to persons with immunoglobulin A deficiency, these individuals should not receive immune globulin. Pregnancy or breast feeding is not a contraindication to immune globulin administration.[3]

Hepatitis B virus

The recognition that passively acquired antibodies to hepatitis B virus (HBV) were protective against acute and chronic infection led to the use of standard immune globulin for postexposure HBV prophylaxis. However, because all current blood donor screening programs specifically exclude HBV antibody–positive individuals, this would be a poor approach to modern-day prophylaxis. With the development of hepatitis B immune globulin (HBIG), which is a specific preparation that contains high titers of anti–hepatitis B surface–directed antibody, pre- and postexposure prophylaxis became a useful strategy in combating HBV infection. Now, with several efficacious HBV vaccines on the market, the current recommendations are only for postexposure prophylaxis with HBIG. This is recommended frequently in combination with active HBV vaccination. HBIG should be used in the following postexposure settings: perinatal exposure for an infant who is born to an HBsAg-positive mother, percutaneous or mucous membrane exposure to HBsAg-positive blood, and sexual exposure to an HBsAg-positive person.[5]

Transmission of HBV from mother to infant during the perinatal period represents a significant postexposure concern. Infants who are born to surface antigen–positive and "e" antigen–positive mothers have a 70-90% chance of becoming infected. Eighty to ninety percent of these infected infants will become chronic HBV carriers, with many experiencing primary hepatocellular carcinoma or cirrhosis of the liver years later.[6] A regimen of 3 doses of HBIG, started within 48 hours of birth, has been shown to be approximately 75% effective in the prevention of chronic infection in infants.[5] However, because the child continues to live in a household with an infected mother, it is common for infection to occur after the first year of life. Therefore, HBIG administration alone is not sufficient for long-term protection. With the introduction of the hepatitis B vaccine, it has been shown that immunoprophylaxis with HBIG in combination with hepatitis B vaccine increases the efficacy of the prevention of perinatal HBV transmission to 85-95% and provides long-term protection.[5] In fact, recent studies have suggested that vaccine alone, when started at birth and at appropriate doses, provides protection similar to the HBIG/vaccine combination.[7] Current recommendations are that HBIG (0.5 mL) be given as a single intramuscular dose after stabilization of the at-risk infant, preferably within 12 hours of delivery.[5] The efficacy of HBIG decreases markedly if the administration is delayed to >48 hours.[5] The first dose of the hepatitis B vaccine series should be given concurrently with the HBIG, but at a separate injection site.

For percutaneous or mucus membrane exposures in susceptible individuals to infectious body fluids that contain HBsAg, HBIG is indicated for postexposure prophylaxis. Although data are limited, the timely administration of HBIG is estimated to be approximately 75% effective in the prevention of transmission and clinical disease.[5] If the exposed individual is unvaccinated against HBV, a single dose (0.06 mL/kg) of HBIG should be administered intramuscularly, with consideration given to the initiation of the HBV vaccine series concomitantly. If