Editorial

Hepatitis B Immunization Update

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Hepatitis B virus (HBV), a 42 nm double-shelled deoxyribonucleic acid (DNA) virus, is a major cause worldwide of acute and chronic hepatitis, cirrhosis, primary hepato-cellular carcinoma and necrotizing vasculitis (polyarteritis).[1] In 1987, the Centers for Disease Control (CDC) estimated that 300,000 persons become infected each year in the United States, with 75,000 persons developing acute hepatitis, 10,000 persons requiring hospitalization and approximately 250 dying of fulminant disease.[2,3] The CDC has estimated that the United States contains a pool of 500,000 to 1,000,000 virus carriers with a high prevalence of hepatitis B surface antigen (HBsAg) being found in "high-risk" subpopulations[2] (Table).

TRANSMISSION OF HEPATITIS B IN THE HOSPITAL

The CDC has estimated that 12,000 American healthcare workers whose jobs require exposure to blood become infected with HBV each year, that 500 to 600 will require hospitalization as a result of that infection and that 250 will die (12 to 15 from fulminant hepatitis, 170 to 200 from cirrhosis and 40 to 50 from liver cancer)." Despite the fact that over 20 different infectious agents may be transmitted by needlestick,[4] HBV remains the most common infectious agent transmitted to healthcare providers by this route.

HBsAg has been detected in a variety of body fluids including blood and blood products, cord blood, tears, saliva, semen, breast milk, feces, urine, vaginal secretions, cerebrospinal fluid and synovial fluid. HBV is spread through exposure to body fluids by the parenteral route (transfusion of blood or blood products, sharing of contaminated needles or syringes, tattooing and hemodialysis), sexual contact or vertical transmission from an infected mother to her infant. Percutaneous exposure to blood via needlestick has been reported to lead to HBV infection, despite the use of immune globulin preparations in approximately 10% of healthcare workers if the source was HBsAg-positive and in 19% to 27% of recipients if the source was hepatitis B e antigen-positive.[5,6]

Studies employing molecular hybridization have suggested that detectable levels of virus in saliva (10^5 to 10^7 virus particles/ml) are 10^3- to 10^4-fold less than those simultaneously present in serum.[7] Direct oral or nasal installation of HBsAg-positive human saliva has not produced infection in susceptible primates, although infections occurred following subcutaneous injection of the same material.[8] The available data suggest that the oropharynx is a more hostile environment for an HBV inoculum than subcutaneous tissue. Horizontal transmission by salivary contamination may thus only occur in the presence of ulcers or abrasions and, because of low efficiency, require repeated exposure. This view is consistent with reports that HBV infection has not been transmitted to persons exposed to saliva of HBV carriers while sharing resuscitation manikins[9,10] or musical instruments." Transmission of HBV has followed human bites, which is further proof that saliva may be infectious when inoculated percutaneously.[12]

HBV is relatively stable in the environment, as demonstrated by its survival after drying and storage at 25°C and 42% relative humidity for one week.[13] Hence it is not surprising that indirect transmission

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Weber DJ, Rutala WA. Hepatitis B immunization update. Infect Control Hosp Epidemiol. 1989; *10(12):541-546.*

Table
Prevalence of Hepatitis B Serologic Markers in Selected Population Groups*

Population Group	Prevalence of Serologic Markers of HBV Infection: HBsAg (%)	All Markers (%)
High rlsk		
Immigrants/refugees from areas of high HBV endemicity	13	70-85
Clients in institutions for the mentally retarded	1 0-20	35-80
Parenteral drug abusers	7	60-80
Homosexually active men	6	35-80
Household contacts of HBV carriers	3-6	30-60
Patients of hemodialysis units	3-10	**20-80**
Intermedlate risk		
Healthcare workers with frequent blood contact	1-2	15-30
Prisoners (male)	1-8	1 0-80
Staff of institutions for the mentally retarded	1	1 0-25
Low risk		
Healthcare workers with no or infrequent blood contact	0.3	3-10
Healthy adults (first-time volunteer blood donors)	0 3	3-5

'Adapted from reference 2

caused by blood-contaminated instruments or other objects has been reported. Infection has been associated with a blood-contaminated jet gun injector,[14] an endoscope[15] and a multi-dose heparin vial.[16] Environmental surfaces in clinical laboratories are frequently (34%) positive for HBsAg[17] and contaminated file cards have been reported to lead to transmission among laboratory technicians.[18]

Healthcare personnel with acute HBV infection or who are asymptomatically HBsAg-positive appear to be at low risk for transmitting hepatitis B to their patients.[19] However, occasionally HBsAg-positive physicians,[20,21] dentists,[22,23] oral surgeons,[24,25] obstetric-gynecologic surgeons[26] and nurses*' have been implicated in the transmission of HBV to multiple patients.

HEPATITIS B IMMUNIZATION

Three hepatitis B vaccines are currently available in the United States: "Heptavax-B" (Merck, Sharpe and Dohme, Rahway, New Jersey, licensed November 1981), "Recombivax-HB" (Merck, Sharpe and Dohme, Rahway, New Jersey, licensed July 1986), and "Engerix-B" (Smith Kline & French Laboratories, Philadelphia, Pennsylvania, licensed September 1989). Heptavax-B is a suspension of alum-adsorbed HBsAg particles purified from the plasma of HBsAg carriers. Inactivation is accomplished by treatment with pepsin at pH 2, 8M urea and 1:4,000 formalin. Recombivax-HB is a recombinant hepatitis B vaccine produced by inserting a plasmid containing the gene for HBsAg subtype adw into *Saccharomyces cerevisiae* (common baker's yeast).[28] The HBsAg is harvested by lysing the yeast cells and is separated from the yeast components by hydrophobic interaction and size-exclusion chromatography. After filtration, the purified HBsAg is adsorbed with alum followed by treatment with formaldehyde and preservation with thimerosal. Engerix-B is also a recombinant hepatitis B vaccine that differs from Recombivax-HB in that it is not subject to a treatment process with formalin. The significance of this difference is unknown. The only detectable differences between the recombinant and plasma-derived vaccine is that the recombinant vaccines have, on the average, a higher lipid content and are nonglycosylated. Neither of these differences appear to affect the efficacy or toxicity of the product.

Vaccine Efficacy

Initial studies of Heptavax-B revealed that three doses resulted in seroconversion of 85% to 97% of homosexual men[29-31] and high-risk healthcare workers.[32-33] Vaccine responders were shown to have significantly less hepatitis B during follow-up periods. Older age, heavy smoking, higher body-mass indices, injection into the buttock and genetic factors have been associated with lower rates of seroconversion.[34-37] Hemodialysis,[38,39] chronic renal failure[40] and human immunodeficiency virus (HIV)-1-infected patients[41-43] exhibit both lower seroconversion rates and lower geometric mean titers among responders than normal hosts. The administration of immune-globulin preparations simultaneous with hepatitis B vaccine does not affect the development of antibody to HBsAg (anti-HBs).[44,45] Since its introduction, the method of preparing Recombivax-HB has been altered twice, resulting in improved immunogenicity.[46] Currently Heptavax-B is being phased out and soon will no longer be available.

Long-term follow-up studies demonstrated that HBV vaccines were efficacious in preventing HBV infection[29,32,42,47] and antibody levels greater than 10 sample ratio units (SRU) provided protection.[29,48] Despite marked reduction of antibody levels with time, vaccine responders have generally not developed clinical illness.[47]

Currently available recombinant vaccines have resulted in the development of protective antibody levels in greater than 95% of immunologically normal recipients.[49-57] Some but not all studies comparing the immunogenicity of the recombinant vaccine to the plasma-derived vaccine have revealed similar high rates of seroconversion but induction of a lower geometric mean titer of anti-HBs. As with the plasma-derived vaccine, immunologically impaired persons respond less well[57,58] and titers decline with time.[59] Either of the recombinant vaccines may be used to complete a course of primary immunization or as a

booster regardless of the vaccine initially employed.

HBV vaccines are administered by intramuscular injection into the deltoid. Currently recommended doses are as follows: Heptavax-B-40 μg for adult dialysis patients, 20 μg for adults and 10 μg for children; Recombivax-HB-10 μg for adults and 5 μg for children; and Engerix-B-40 μg for adult dialysis patients, 20 μg for adults and 10 μg for children. Whether or not the increased dose of antigen present in Engerix-B versus Recombivax-HB leads to higher antibody levels requires additional study.

Vaccine Safety

Side effects with all currently licensed vaccines are similar. Fifteen percent to 20% of recipients will experience soreness at the injection site and approximately 15% experience one or more mild systemic symptoms (fever, headache, nausea and fatigue). Postlicensure surveillance of the plasma-derived vaccine conducted between 1982 and 1985 revealed a borderline significant risk for Guillain-Barre syndrome. However, the risk for this event was insignificant compared to the morbidity and mortality associated with HBV infection.[60] Other serious side effects have not been reported. Concerns that HIV-l may be transmitted by the plasma-derived vaccine have proved to be unfounded.

Only a single potential adverse reaction, a severe local reaction (type 1) to yeast-derived proteins, has been reported among recipients of the recombinant vaccines.[61] Furthermore, rises in IgE antibodies against *S cerevisiae* or IgG antibodies against *Candida albicans* have not been found.[56,57,61,62] Thimerosal (mercury derivative) is present in the vaccine preparations as a preservative. Local reactions and rarely anaphylaxis have been reported in thimerosal-allergic patients who are exposed to this agent.[63] There is no evidence that hepatitis B vaccine is not efficacious nor safe in pregnancy. Fetal toxicity has not been reported. However, toxicity studies in pregnant animals or humans have not been performed.

CONTROVERSIES IN HEPATITIS B IMMUNIZATION

Management of Vaccine Nonresponders

Administration of two to three booster doses to persons who fail to develop a protective antibody level following primary immunization in the deltoid has resulted in approximately 80% to 100% of initial hyporesponders (maximal SRU 2.1-10) and 41% to 50% of nonresponders developing protective antibody levels.[35,47,64] However, geometric mean titers ate considerably lower than titers found in initial responders. Attempts to identify and re-immunize hyporesponders or nonresponders are unlikely to be cost-effective, as most healthy persons will develop protective antibody levels following immunization. Additionally, re-immunization will not be successful in a significant number of hyporesponders and nonresponders, and even if the hyporesponder or nonresponder develops protective antibody levels following re-immunization, the levels of antibody have been shown to be low and of short duration.

Duration of Protection and Need for Booster Doses

Following immunization, anti-HBs levels decline in a nonlinear way, with levels falling more rapidly in the immediate period postimmunization.[47,65,66] After four to five years, approximately 35% to 50% of vaccine recipients no longer demonstrate protective antibody levels (SRU>10).[47,48,66] Several studies have suggested that the persistence and titer of antibody have been directly related to the maximal level of anti-HBs achieved after immunization.[47,48,66,67] However, a recent study by Nommensen and co-workers found that the rate of antibody decline was unrelated to the height of postvaccination antibody titer and varied widely.[68] Administration of a booster dose in initial vaccine responders has induced an anamnestic response in 78% to more than 95% of persons.[34,38,48,69-71]

Options for the maintenance of immunity against hepatitis B include:

- Not providing booster doses and relying on immunologic memory to protect against serious complications of HBV infection;
- Testing all vaccine recipients at periodic intervals and boosting those with low antibody titers;
- Providing booster doses of HBV vaccine to all persons at a set interval; or
- Determining the antibody response of all vaccine recipients within six months of completing primary immunization and providing boosters at an interval determined by the initial antibody response and use of published nomograms.[65,66]

The first strategy, relying on immunologic memory, is currently advised by the Immunizations Practices Advisory Committee (ACIP) and CDC. However, this strategy will continue to raise concerns until additional evidence accumulates that immunologic memory provides sufficient protection against clinically important disease when antibody titers fall below 10 SRU. The third strategy, routine booster doses at set intervals, is simple and would be similar to the booster-dose strategies devised for other inactivated vaccines. Strategies that involve testing of antibody levels and administration of boosters on the basis of the results are likely to be costly, administratively complex and likely to present difficulties in the interpretation of commercially-available antibody tests.[47] Issues involved in the cost-effectiveness of the above alternatives include duration of protection against clinically significant disease by immunologic memory, vaccine cost that is likely to drop and ability to accurately determine antibody titers and assure appropriate booster intervals.

Determination of Postimmunization Titers

Determination of postimmunization titers has been suggested for a number of reasons. First, it would identify hyporesponders and nonresponders. Hypo-

responders could then be boosted by an additional two to three vaccine doses. Nonresponders would be counseled and could receive hepatitis B immune globulin (HBIG) in the event of parenteral exposure to HBsAg. Second, vaccine responders would be reassured as to their protection against hepatitis B. Finally, determination of antibody levels following primary immunization could lead to an individualized schedule of booster doses. Because neither detection of hyporesponders nor the use of an individualized booster dose schedule are likely to be cost-effective, determination of antibody titers postimmunization is of limited value.

Postimmunization testing is advisable only for individuals in whom a suboptimal response may be anticipated (e.g., buttock injection) or for persons whose subsequent management depends on knowing their immune status (e.g., dialysis patients). Determination of antibody levels more than six months after primary immunization is of value only following parenteral exposure to HBsAg or a high-risk source.

Postexposure Prophylaxis

Following percutaneous exposure to HBsAg, healthcare personnel who have received HBV vaccine should be tested for anti-HBs, and if their antibody titer is inadequate (i.e., <10 SRU) they should receive HBIG immediately plus an HBV vaccine booster dose.[2,72,73]

Dosing Schedule

Most studies have employed the standard dosing schedule of 0, 1 and 6 months. Recent reports suggest that a short dosing schedule (0, 2 and 6 weeks or 0, 4 and 8 weeks) results in a more rapid attainment of protective levels.[74] A more prolonged dosing schedule (0, 1 and 12 months) will result in higher long-term antibody levels.[75] Based on current evidence, it is reasonable to use a short dose schedule for postexposure prophylaxis in unimmunized persons. In such cases a fourth dose should be given at 12 months. Whether or not such a schedule in fact provides better protection should be investigated. In medical personnel who will be exposed to blood only in the future (i.e., medical, dental and nursing students) it may be reasonable to use a more prolonged dosing schedule (i.e., 0, 1 and 12 months).

Intradermal Administration

Intradermal administration of 2 μg of plasma-derived HBV vaccine in normal subjects using a 0-, 1- and 6-month dosing schedule has resulted in seroconversion in 83% to 96% of recipients in several small studies.[76-81] Approximately 30% to 60% of patients developed an erythematous macule that was occasionally pruritic and rarely painful at the site of injection. These skin lesions gradually faded over weeks to months.

Several concerns about intradermal administration have been raised.[82] First, intradermal injection requires skill, and subcutaneous injection into fat results in a poor immune response. Second, several studies have reported lower geometric mean titers with intradermal compared to intramuscular injection.[80,83-85] This would mean a faster rate of disappearance of immunity. Finally, intradermal injection frequently leads to the development of an erythematous macule that may persist for weeks to months.

The main advantage of intradermal administration is that one tenth of the normal vaccine dose is usually employed, resulting in a substantial cost saving. Because of these concerns, primary immunization by the intradermal route should be avoided until such time as large comparative trials demonstrate similar rates of seroconversion, geometric means titers and safety comparable with intramuscular injection. Intradermal vaccination in a small study has been shown to result in a similar anamnestic response as intramuscular vaccination when used as a booster dose.[34] Use of the intradermal route to provide routine boosters should be further investigated.

Implementation of an Employee Vaccination Program

Most hospitals currently have hepatitis B vaccination programs.[86] Unfortunately, significant numbers of healthcare personnel continue to refuse immunization.[87-89] Reasons for refusals include:

- Concern regarding vaccine safety, including unknown low-frequency side effects or fear of acquiring HIV-l infection;
- The need for more information about vaccine;
- Vaccine cost;
- Possible effects on present or future pregnancies; and
- Not considering oneself to be at risk.

Improved education of healthcare personnel about the safety of HBV vaccines, disease transmission and complications and indications for vaccination can improve immunization coverage. Mandating "high-risk" personnel to sign "informed refusal" forms can lead to a 90% vaccine acceptance rate."')

The CDC[89] currently recommends hepatitis B vaccine for all healthcare personnel with substantial blood or needlestick exposure. This recommendation is based on studies that have demonstrated an increased risk of HBV infection among healthcare workers with substantial exposure to blood.[91-93] Current proposed rules of the Occupational Safety and Health Administration (OSHA)[94] require that hepatitis B vaccine be offered to all employees who incur occupational exposures to blood an average of one or more times per month. Occupational exposure is defined as reasonably anticipated skin, eye, mucous membrane or parenteral contact with blood or other potentially infectious materials that may result from the performance of an employee's duties. We were unable to find a scientific basis for the premise that one occupational exposssure as defined above per month leads to an increased risk of HBV infection.

CONCLUSIONS

HBV infection remains a major hazard for hospital personnel. In addition to use of hepatitis B immunization, prevention of HBV transmission in the hospital should involve the following: implementation of universal blood and body fluid precautions,[95] proper disinfection of all semi-critical items and efforts to reduce needlestick injuries. The latter is particularly important as studies continue to demonstrate frequent needlestick injuries, many of which are preventable.

An aggressive immunization program should be used for all hospital personnel with substantial blood exposure. Booster doses at set intervals or an individualized booster schedule based on initial postimmunization titers is likely to be necessary to prevent transmission of HBV infection and the subsequent development of clinical disease in immunized healthcare workers whose antibody titers fall with time. Routine booster doses may prove to be the most cost-effective method of maintaining immunity, although the optimal time for providing booster doses has not yet been defined.

Based on the current data, it appears that available recombinant vaccines are safe and provide comparable protection against hepatitis B. The choice of manufacturer should be based mainly on cost, unless subsequent studies demonstrate that one vaccine produces a substantially higher geometric mean antibody titer and consequently provides a longer duration of immunity to HBV.

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