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Review of Hepatitis B for the Clinical Laboratory Scientist

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Abstract

Even 15 years after the licensure of a vaccine for Hepatitis B, this virus is still responsible for nearly 40% of the viral hepatitis cases in the United States. The high risk groups for this disease include health care professionals as well as intravenous drug users, infants born to Hepatitis B infected mothers and homosexual men. Unlike HIV, Hepatitis B has a high transmission rate, with a needle stick resulting in disease transmission in 6-24% of cases. OSHA has mandated that the employer must provide free Hepatitis B immunizations to health care workers. Many health care workers remain unimmunized, but more remain uncertain of the degree of protection conferred by the immunization that they received. Also of concern, is whether and when booster immunizations are required. This on-line presentation will present a background concerning Hepatitis B disease etiology, epidemiology, signs and symptoms, serology and laboratory analysis, prevention and vaccinology, and treatment.

Etiology

Hepatitis B is a hepatotrophic virus that causes a mild to life threatening inflammation of the liver. The disease caused by this virus was originally called serum hepatitis. The viral etiology of hepatitis was suggested in 1908, and in the 1940's the disease causative agent was shown to be a nonbacterial filterable agent (Krugman and Stevens). Epidemics of hepatitis followed early clinical use of blood products; for transfusions, as active immunization (variolation) or as passive transfer of immune globulin (measles convalescent serum) (Krugman and Stevens).

Hepatitis surface antigen was discovered in 1965 in the sera of leukemic patients (Blumberg). The discovery of this antigen facilitated the isolation and characterization of the viral particles. The hepatitis B virus is in the family Hepadnaviridae, which also contains some recently discovered hepatotrophic viruses of rodents

and birds (Robinson). Three different particles are found with Hepatitis B infection. The prominent form found in the blood is a spherical disc particle, 22nm in diameter, which is part of the filamentous form particle that is 22nm wide by 50-200nm long. The third particle (**Figure 1**) is the **Dane particle**, which is the intact virion and contains a nucleocapsid with a DNA core, and an outer lipoprotein coat (Fenner and White).

Hepatitis B virus, like all members of the Hepatovirus family, has a very small genome; smaller than most other viruses. Use of overlapping reading frames allows the production of 50% more protein then would be possible using only one reading frame with this genome size

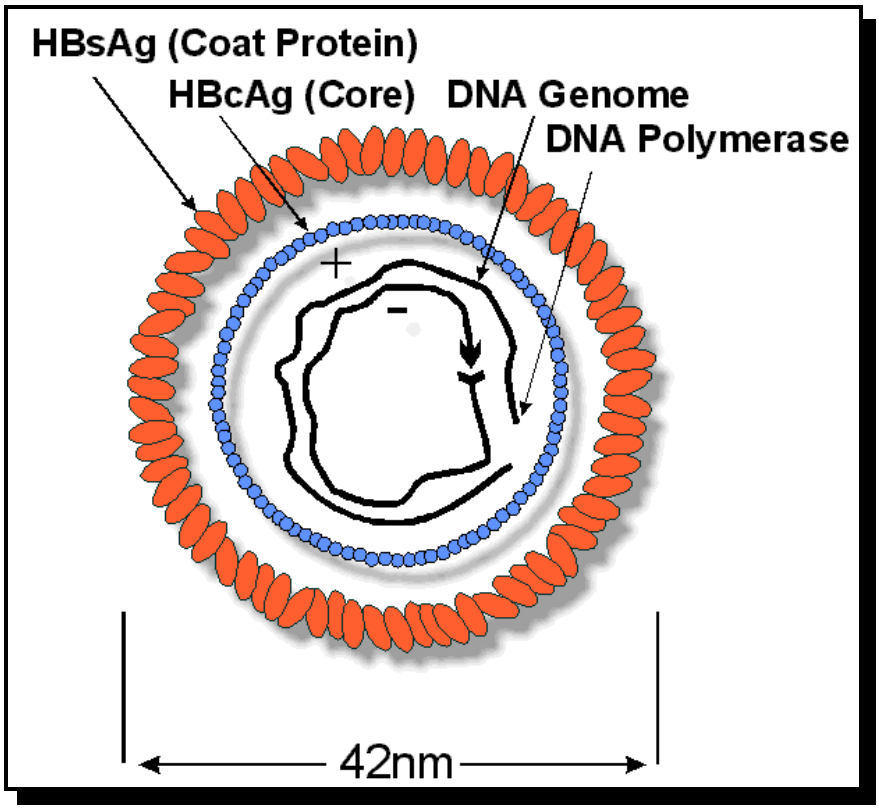

Figure 1 - The Dane Particle

(Robinson). The virus contains double stranded circular DNA with a small nick region that is single stranded. The shorter of the two strands is the + DNA and is repaired by a DNA polymerase that is packed in the virus. The negative strand of the DNA also contains a nick and the DNA at this region is attached to a protein primer. The positive strand is unusual, in that its 5' end is attached to a oligoribonucleotide primer. The positive strand is packaged at various levels of completion, and thus can be of different lengths (Robinson). It is interesting to note that the negative strand of this DNA virus is made from a longer than genome length RNA transcript using a reverse transcriptase. Thus, the Hepatovirus family and the Retrovirus family are related in this way. They are also related in genome number and in genomic nucleotide sequence homology of regions encoding proteins of similar function (Robinson).

Epidemiology

Hepatitis B is a disease of significant health importance, as more than 2 billion persons in today's worldwide population have been infected (Kane). It accounts for approximately 40% of the hepatitis cases in the United States(Larsen and Larsen). Risk factors associated with CDC reported Hepatitis B cases in the United States include 36% spread by heterosexual activity, 13% by intravenous drug use, 11% by homosexual activity, 3% by household contact, 2% healthcare employment and 33% by unknown causes (Duma). The actual percentage of each group varies in different publications, but the percentages given here show the general trends.

The commonly accepted high risk groups include health care personnel, children born to Hepatitis B positive mothers, intravenous drug users, homosexual men, institutionalized populations, hemodialysis patients, recipients of certain plasma derived products, household contacts and sexual partners of infected persons and people living in areas where the disease is endemic. In the United States, 89% of the cases of HBV occur in people aged 15-44 years old (Abbott), although, vertical transmission is common (Larsen and Larsen). Hepatitis B virus is important to the health care worker as it accounts for the death of an estimated 300 health care workers a year (Larsen and Larsen).

The typical horizontal transmission is via blood and blood products. The danger of transfusion acquired hepatitis B transmission, however, is now very low, (0.002%) due to the thorough serological screening procedures that were instituted in 1972 (Abbott), and due to the reduction of the use of paid blood donors (Turgeon). Infections can be acquired through the casual contact of an infected fluid through a trivial and even unapparent break in the skin (Turgeon). The danger of hepatitis B contaminated needle stick exposures of health care workers was seen with analysis which showed disease transmission in 6-24% of the cases. The minimum infective dose of infected sera is $1x10^{-6}$ ml. Infectious levels of the virus are also found in feces, saliva, urine, serous fluids, vaginal secretions, and semen (Larsen and Larsen).

The hepatitis B virus is resistant to many of the routine treatments in the laboratory, including repeated freezing and thawing, 37° C incubation for 60 min, desiccation, and UV light treatment. It is important to note that when the virus is in a solution which contains a high concentration of protein such as undiluted serum, it is stable to the 1:10 dilution of household bleach commonly used for bench top disinfection. For Hepatitis B Virus disinfection in serum spills, undiluted household bleach is necessary for elimination of infectivity (Escobar).

The global distribution of Hepatitis B can be divided into three groups based on the percentage of the population which becomes infected with Hepatitis B. In Southeast Asia, China, the Philippines, the Middle East, Africa, the Amazon Basin, the Pacific Islands and the Arctic the percentage ever infected is >60% (Kane). In these areas, 8-15% of the people become chronically infected (Kane). The percentage of infection for Eastern and Southern Europe, Central Asia, Japan, Israel and South America is 20-60%, in these areas, 2-7% of the people become chronically infected (Kane) . In North America, Western Europe, Australia and New Zealand, the infection rate is < 20% (Kane). In these areas, less than 2% of the total population become chronically infected (Kane) (**Figure 2**)

Even though the US places in the low group of endemicity, the United States is estimated to have 750,000 to 1,000,000 HBV carriers (Abbott). The global importance of Hepatitis B in terms of morbidity and mortality is high, with the death of more than 1 million people each year attributable to this virus (Kane). The World Health Organization in 1992 endorsed a global appeal for universal rather than high risk group associated vaccination (Kane).

Signs and Symptoms

After exposure to the Hepatitis B virus, the incubation period before overt symptoms averages 90 days with a range of 60 to 180 days (Larsen and Larsen). The infection to disease ratio for Hepatitis B is thought to be 6:1 or 7:1, thus many infected individuals show subclinical symptoms only (Drew). Anorexia, malaise, fever, nausea, diarrhea, abdominal tenderness are early symptoms. Fullness in the right upper abdominal quadrant is also felt (Drew). Hepatomegaly occurs in about 70% of the patients concurrent with jaundice (Berlin). Hepatosplenomegaly occurs in most infected children (Berlin). Frequently the patient feels better for a day or two and then jaundice develops. During this period the urine is dark, and the feces may become pale and odiferous as there is increasing liver involvement. Full recovery can take 4-6 weeks, with malaise sometimes lasting longer. The above symptoms are all similar to those seen with a Hepatitis A infection, but with Hepatitis B the disease symptoms listed above can be more severe and in addition, pathology due to immune complex formation (of antibody to Hepatitis B surface antigen and Hepatitis B surface antigen) occurs. These immune complexes can deposit, causing transient polyarthralgias and serum sickness-like rashes in some patients (Fenner and White) (**Figure 3**).

The disease can manifest in three ways acute, fulminant or chronic. Most cases are acute infections with full recovery. The lesions seen in the liver during acute hepatitis include lymphoid cell infiltration, mild necrosis of liver parenchymal cells and proliferation of the liver macrophage, the Kupffer cells (Drew).

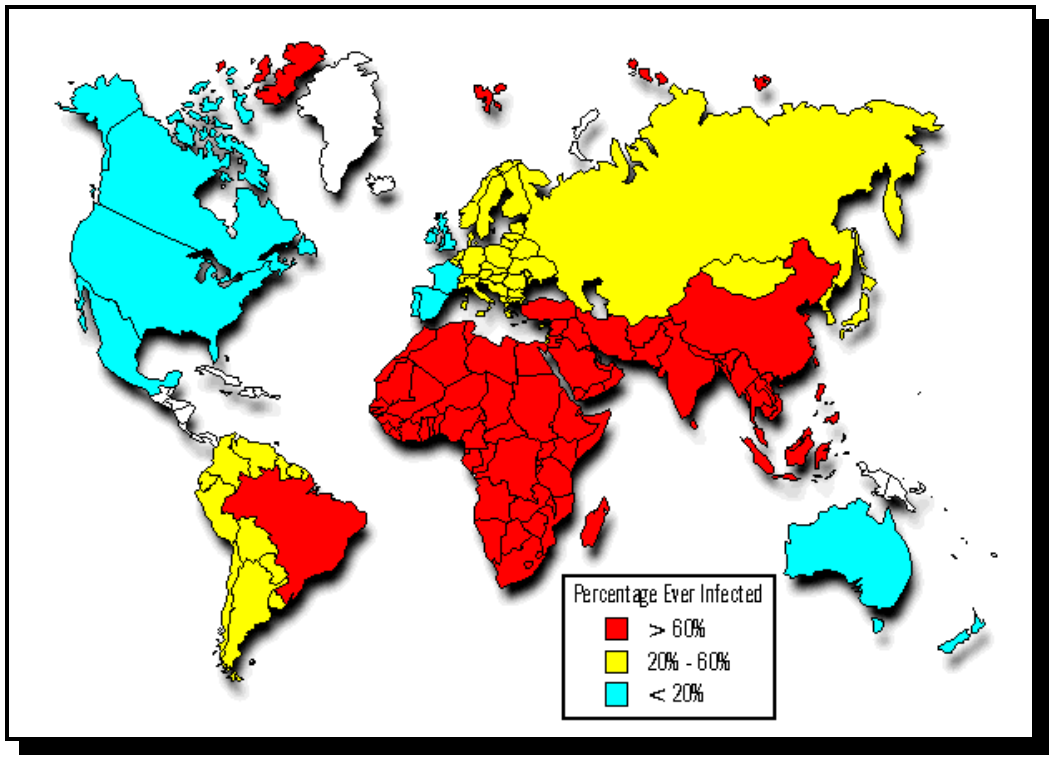

Figure 2 - Global distribution of Hepatitis B

Fulminant infections cause massive liver necrosis, cerebral function changes, hepatic failure and often death. These infections are rare, occurring in less than 1% of the cases (Drew) (Berlin). In these individuals, the disease onset is sudden, and may result in a sudden

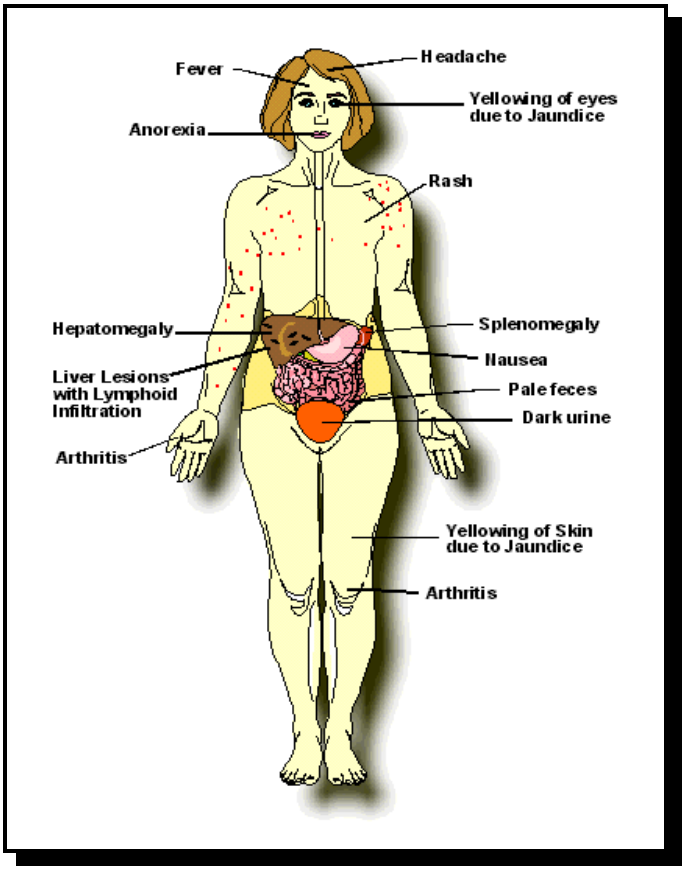

Figure 3 - Physical symptoms

collapse from fatigue. Additional symptoms are rapid onset of jaundice and hepatomegaly (http://libertynet.org/~hep-b/info.html#symptoms).

Chronic infections occur in 5-10% of the hepatitis cases, and is typically linked to development of liver cirrhosis and hepatoma (Larsen and Larsen). Infants, children under 6 years of age and immunocompromised patients show the greatest risk of development of chronic hepatitis B (Hyams). Chronic infection is defined as the presence of the HBsAg in the serum of the patient for 6 months or longer after the preliminary laboratory finding (http://www.hepnet.com/update6.html). In chronic hepatitis the virus is not cleared due to the absence of the development of a sufficient protective immune response. The liver pathology may increase and increased liver necrosis, collapse of the reticular framework and fibrosis may occur (Drew). Hepatocytes may appear abnormal due to cytoplasmic HBsAg, and are called ground glass hepatocytes (http://www.hepnet.com/update6.html) This syndrome is called post-necrotic liver necrosis (Drew). A small percentage of patients with chronic hepatitis become HBsAg negative and HBeAg negative, and this is thought to be a cure from chronic infection (http://www.hepnet.com/update6.html). This percentage can be increased with interferon treatment and this therapy will be discussed in a later section.

Chronic hepatitis is strongly linked to the development of hepatocellular carcinoma (HCC). The hepatitis B virus is not known to contain an oncogene. The association of Hepatitis B with hepatocellular carcinoma may be indirect, in that the liver necrosis is followed by intense proliferation of hepatocytes during healing, and this rapid proliferation may be related to aberrant cell development (Drew). In areas where Hepatitis B is endemic, hepatocellular carcinoma is the leading cancer cause of death (Terrault, Wright). People that were infected via maternal to neonatal transmission show the highest risk of hepatocellular carcinoma (http://www.hepnet.com/update6.html).

Hepatitis D or the delta agent is a defective virus that can not infect by itself, but occurs as a co-infection with Hepatitis B. It is increasingly associated with those cases of Hepatitis B that become fulminant or chronic (Turgeon). Laboratory tests show elevated liver enzymes and a variety of serologic markers which are associated with each manifestation, and will be discussed in the next section.

Serology and Other Laboratory Analysis

The important serologic tests for hepatitis B viral infection include screening for Hepatitis surface antigen (HBsAg) during the incubation period and during acute clinically apparent disease, screening for antibody to Hepatitis core antigen (anti-HBc) during acute disease and during early convalescence, and screening for antibody to Hepatitis B surface antigen (anti-HBsAg) during late convalescence (Turgeon). In addition, PCR is being performed as a diagnostic test for Hepatitis viral particles during the incubation period after known exposure (Turgeon). Hepatitis Be antigen (HBeAg) is an additional marker that has clinical utility, as it appears to be an antigen related to the presence of the viral core and therefore correlates well with infectivity of the serum (Turgeon). When measurable levels of HBeAg are present HBsAg is almost always also present (Turgeon).

Hepatitis B surface antigen is the first viral antigen

detectable in the sera of infected individuals. This is the marker used to screen blood for use by the American Red Cross. This antigen is a major constituent of the coat protein of Dane particles and is also a constituent of the 2 other forms of the virus. After infection, the titer of HBsAg in the patient's sera rises to a peak at about 3 months post infection, near this time the patient's diagnostic tests also show elevation in serum liver enzyme levels (Turgeon). The reason for the apparent decrease in HBsAg levels at approximately 3 months is not due to a decrease in infective particles, or in circulating coat protein, but appears to be due to the development of anti-HBsAg and thus the presence of HBsAg in immune complexes which are not detectable as HBsAg in current serologic assays (Turgeon). During this time the anti-HBsAg is also not detectable and anti-HBcAg may become the only marker which reveals the infection, and the presence of IgM to HBcAg may become important (Turgeon). Anti-HBsAg is important to the clinical recovery of the patient and is the major protective antibody in this disease. The presence of antibody to this marker has been used to determine protective ability of Hepatitis immune globulin and to determine the protective effect of the various vaccines (Krugman, Stevens).

Diagnostic tests for the presence or absence of these antigens and antibodies most commonly involve radioimmunoassays or enzyme immunoassays (Turgeon). An immune response acquired as the result of infection will include measurable antibody to HBcAg and HBsAg, whereas antibody response acquired as a result of vaccination will only include anti-HBsAg (Turgeon) (**Table 1**).

Clinical State	Acute	Chronic	Prior Exposure, no current infection	Recovery	Vaccination
Ags: HBsAg	+	+	-	-	-
HBeAg	+ marker of infectivity	- or + marker of infectivity	-	-	-
Abs: anti-HBsAg	- early	-	+	+	+ may become - while patient may still be immune
anti-HBeAg	- early, + indicates good outcome	-	-	+	-
anti-HBcAg	+ IgM	+	+ IgG	+	-
anti-delta	+ or -	+ or -	+ or -	+ or -	-
DNA: HBV	+	+	-	-	-
serum ALT	increased or normal	increased, or normal	normal	normal	normal

TABLE 1: Serologic and Molecular Biology Markers Involved in Hepatitis B (Larsen and Larsen, Abbott learning guide, Mahon)

Prevention and Vaccination

Careful screening of blood donors and blood products has considerably decreased the spread of Hepatitis B. Screening of blood donors for high risk of infection includes questions concerning intravenous drug use, sexual activity and country of origin. Screening of blood products includes screening for HBsAg and for anti-HBc.

Originally it was only recommended that persons in the high risk groups get vaccinated, and this included newborn children of HBV infected mothers, household contacts of chronic carriers, health care workers, intravenous drug users, homosexuals, heterosexuals with multiple partners, and travelers to high risk countries; where over 8% of the population are carriers (Asia, Africa, South America, and Eastern and Mediterranean Europe). Although the first vaccine was licensed in 1982, the incidence rate continued to increase, with a fall in incidence in 1985 that was probably more attributable to HIV inspired behavioral changes (Kane). One difficulty in high risk group targeting was the repeated failures in getting patient compliance in obtaining all 3 necessary immunizations (Kane, Hallauer). A study was performed using immunizations of high risk people in one town, and in infants and adolescents in another town in Brazil. A greater drop in prevalence was seen in the town where infant and adolescent immunization was done, although both groups did show a drop in prevalence in HBsAg and anti-HBcAg (Da Villa). In summary, studies using high risk pool targeted immunization either did not reduce incidence, or were less effective then infant and adolescent immunization.

Considering these studies, the Center for Disease Control and the American Academy of Pediatrics now recommend that all infants receive the HBV vaccine at birth. The World Health Organization (WHO) recommends that Hepatitis B vaccination should now be included in the national universal vaccine programs, and that immunization of infants and adolescents (middle school aged) should receive priority (Hallauer). The Hepatitis B Foundation recommends that in addition to the above, all school age children, adolescents and college students receive the vaccine (www.libertynet.org/~hep-b/vaccine.html). A recent article was published which suggested that although the public vaccination policy now suggests that infants and adolescents should be targeted, the high riskgroups should not be left out. This group advocates that vaccination funding be extended to include high risk adults (Sharfstein).

The first vaccine to receive licensure for the development of a protective immune response to Hepatitis B was a plasma derived vaccine (PDV). This was made using purified Hepatitis B surface antigen obtained from the plasma of chronic carriers (Andre). After purification, the preparation was treated by 2 different viral inactivation protocols to insure the inactivation of any intact HB virus that may have inadvertently co-purified with the surface antigen (Deinhardt,Jilg). Despite the safety of this vaccine, many patients were concerned about receiving blood product derived material.

Recombinant vaccines were developed using expression of the Hepatitis B surface antigen in a yeast cell. The recombinant yeast produced 20nm particles expressing the surface antigen in a similar form as that expressed in the sera of chronic carriers. The vaccine contains these particles absorbed onto Alum (Andre). The use of molecular biology has allowed for the production of large quantities of a very safe vaccine. Recombivax HB (Merck) and Energix-B (SmithKline Beecham) are the 2 recombinant vaccines currently licensed in the US (Lawrence). The vaccination schedule that is recommended is 3 intramuscular injections, with the second injection 1 month after the first and the third injection six months after the first injection of vaccine (www.libertynet.org/~hep-b/vaccine.html). A shorter waiting period of 1 month before the third immunization was attempted, but significantly lower titers resulted in adults (West, Calandra). A time point 12 months after the first immunization was attempted, and the titer was improved over the 5 month titer in adults. The scheduling regime used is a compromise which allows for suitable titer while allowing for scheduling convenience in children to coincide to times when they receive other vaccinations. (West,Calandra).

Recombivax HB and Energix-B were compared for production of a protective immune response in infants. The vaccines had similar efficacy as the plasma derived vaccines. The response of the infants was quicker after the SmithKline Beecham vaccine than after the Merck vaccine, but the final efficacy after three doses was the same (Greenberg). For infants that did not complete the 3 immunizations, those that received the SmithKline Beecham vaccine were more likely to be protected (Greenberg). This difference in immunogenicity may be due to the different recommended doses of the 2 vaccines, 20 micrograms per dose for the SmithKline Beecham and 10 microgram per dose for the Merck vaccine (Greenberg). Analysis of the seroconversion rate after the required doses of either the plasma derived vaccine or the recombinant vaccine was 99% for infants up to 2 years of age, 96 percent for 13 year

old children and 86% for adults up to 60 years of age (Da Villa).

The protective effect of vaccination has been analyzed in infants and children. For 5 to 10 years after immunization, the patients showed detectable antibody, but then the Ab is no longer detectable. The fact that, even after the Ab is gone, none of the children developed clinically apparent disease seems to indicate that immunity lasts longer than detectable antibody (Kane). Immune memory lasts for at least 10 years after the successfully completed vaccination series (Kane). Krugman et al. analyzed the ability to form an amnestic (secondary) response in 52 persons that had received the plasma derived vaccine 5 to 7 years previously. Ninety percent of the people responded to the recombinant derived vaccine with a secondary response, even though many of them had less than 10 IU/ml of anti-Hepatitis B antibody before the booster dose. Trivello et al. performed a similar study and found that 97-99% of the patients that received a booster dose formed an anamnestic response (Trivello). The conclusion from these studies is that these people would be protected from infection, because of the shortened time of their antibody response would allow for production of a protective response before the incubation time for the virus was completed.

The World Health Organization recommends for adults that a post vaccination titer be performed to insure seroconversion. A protective titer is assumed to be greater than 10 IU/ml after vaccination. If this value is not reached after 3 immunizations, a fourth immunization is suggested. Individuals that do not respond after 4 doses may respond if given a combination of alpha interferon with the hepatitis vaccination (S. Iwarson). The CDC does not suggest titration analysis for adolescents since the seroconversion rate of this group is so high (Lawrence, Goldstein). It is important to understand how the testing lab is determining a positive titer after immunization, as test kits are available with a sensitivity of 1 IU/ml and this is not considered a protective level.

Some reports indicate that patients that are not immunized but receive needle sticks should receive Hepatitis B immune globulin (Kane), whereas others suggest immediate immunization with vaccine (within 48 hrs) followed by a second vaccination at 2 weeks, and a third at 6 weeks, with no concomitant immune globulin given (Iverson). Infants born to infected mothers should receive Hepatitis B immune globulin and HBV vaccine within 12 hours of birth (Kane). An analysis of the literature done by SmithKline Beecham Biologicals (Andre) suggests that infant immunization with 10-20 micrograms of plasma derived vaccine allows for protective efficacy without the concomitant use of hepatitis B immune globulin. Lower doses of vaccine require concomitant use of hepatitis B immune globulin for maximum protective effect. Patients on hemodialysis do not seroconvert as readily as healthy adults, and vaccine trials have shown better efficacy for protection if higher doses of antigen is used in these immunizations (Andre).

A study was done in British Columbia which documented every case of reported side effects for over 134,000 vaccinations. Sixty nine cases with side effects were reported, 16 local reactions at injection site, 14 episodes of fainting after the injection, 3 cases with fever over 39.5, 12 cases with a rash, 4 with arthritis, 1 with anaphylaxis, 19 with a variety of other complaints. The authors suggest that about 59% of these cases were indeed vaccine related. This is a very low incidence rate for a vaccine, and in general the vaccination is well tolerated (Bell).

The current cost per 3 injection course of Hepatitis B recombinant vaccine is between $25 and $55 per dose, thus it is $75 to $165 for the series for a child (http://www.libertynet.org/~hep-b/Vaccine.html), and $150-$200 for the series for an adult. Lower concentrations of the vaccines are used in earlier age groups and this is the reason for the difference in cost (Lawrence). Higher volumes of sales and the licensure of new vaccines may lower price in the near future (Lawrence).

Treatment

Treatment for Hepatitis B primarily concerns therapeutic attempts to end chronic hepatis. These attempts are aimed either at increasing the patients immune response to the Hepatitis B virus, or are anti-viral agents which will prevent viral replication. The morbidity and mortality caused by chronic Hepatitis B infection includes cirrhosis and hepatocellular carcinoma, so the importance of effective therapy for this manifestation of Hepatitis B infection is apparent. This importance is highlighted in the view that 5% of the world's total population have chronic hepatitis B (Larsen).

In effort to improve the patients' immune response to HBV, interferon therapy has been employed. Alpha-2b interferon was approved as therapy for chronic hepatitis B by the FDA in 1992 (AbbottEd Services 1995). The efficacy of treatment is shown through loss of HBeAg and HBV DNA (Fried). Less than 50% of chronic hepatitis patients respond to alpha interferon treatment. The patient must be immunologically reactive to Hepatitis B antigens for the interferon therapy to work,

so this doesn't work in most neonatally infected patients as they are tolerant to the hepatitis antigens, and it also doesn't work in immunocompromised patients (Regenstein). In the chronic hepatitis patients that are successfully treated, 90 to 95% remain seronegative for HBeAg after therapy (AbbottEd Services 1995). Side effects depend on the dose of interferon being used, and include fever, chills, myalgias and headaches (Fried). Usually side effects can be prevented by use of acetaminophen before the interferon injection. Long term therapy can also result in fatigue, nausea, anorexia, weight loss, depression, anxiety and irritability. Autoimmunity can develop with prolonged use. Thyroid autoimmune disease occurs in 2-5% of patients treated with alpha interferon (Fried). In general all these side effects are mild, resolve when therapy is discontinued and can be easily treated. Alpha interferon is the only drug approved for the treatment of chronic hepatitis (Fried).

Thymosin, another immunomodulatory agent, which is a partially purified extract of bovine thymus, is being evaluated (Regenstein) for immunomodulation in patients with chronic hepatitis B. Thymosin augments T cell function, and in a preliminary study appeared to decrease HBV viral load. This drug has particular promise because it causes very few side effects (Regenstein).

A therapeutic lipopeptide vaccine has been developed to stimulate cytotoxic T cell activity in patients with chronic hepatitis B. The vaccine is called Theradigm-HBVF™ (Cytel,San Diego, Ca). It contains HBcAg peptide, tetanus toxoid peptide and 2 palmitic acid molecules (Vitiello). Clinical trials of this vaccine are currently being performed (Fried).

Anti-viral drugs used for Hepatitis B therapy either inhibit DNA polymerase or inhibit the function of the reverse transcriptase. These drugs will have some side effects because they can also inhibit synthesis of host DNA (Regenstein). In general these drugs are nucleoside analogs. The first nucleoside analogs to be used were adenine arabinoside and adenine monophosphate arabinoside. The use of these drugs did not result in permanent responses, and did result in some toxicity problems so their use was discontinued (Regenstein).

Famiciclovir, a relative of ganciclovir, is a purine analog of thymidine which is used as an anti-viral drug in the treatment of herpes and varicella zoster. Recent studies have shown that famiciclovir decreases HBV-DNA levels in patients with chronic hepatitis and in patients post liver transplantation. Since this drug is already clinically used with the other viruses mentioned, the toxicity studies of long term treatment have already been performed. The study included only eleven patients, but 6 of the eleven show a dramatic decrease in HBV DNA levels, so this shows promise and warrants future studies (Cirelli). Other nucleoside analogs that have been used including acyclovir, ddI, fialuridine, 3TC but have not been found to be effective (Regenstein).

Combination therapy with anti-virals combined with immunomodulatory agents need to be studied to improve the current response rate (Regenstein).

The only currently used therapy that does not fall into either of the above categories is liver transplantation for individuals with fulminant or chronic hepatitis B. Although this therapy does allow for replacement of lost liver functions, difficulties arise with the infection of the new liver.

Research areas of importance for hepatitis B include development of better therapy for individuals with fulminant or chronic hepatitis and development of a vaccine that would require only one immunization. The final and most currently important area concerning hepatitis is developments in education that would increase compliance rate for vaccinations. In conclusion, a message to clinical laboratory scientists and all others that work with human blood or blood products, hepatitis B infection is highly contagious, but easy to prevent. Receive your immunizations and have your titer checked!

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