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Hepatitis B Infection - a Systematic Review with a Bird's Eye View on Pre and Post Exposure Prophylaxis

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Abstract: In the field of health care, numerous diseases are emerging as a day to day challenge to the health care professionals and most of these newly emerging diseases are deadly. Among the new diseases, there are also other common diseases that spread through occupational exposure which are prevalent among us for many years and still pose a challenge. Prevention of transmission of infection due to occupational exposure has to be inculcated right from their recruitment into every health care provider. Ever since its inception, in the field of dentistry, dentists are frequently exposed to blood and body fluids like saliva in their routine dental practice. As dental professionals, we continuously getting exposed to blood and body fluids should have an updated knowledge about hepatitis B infection, its effective vaccination schedules and management of exposure with post exposure prophylaxis.

Key words: Hepatitis B Virus · Hepatitis B Infection · Pre Exposure Prophylaxis · Post Exposure Prophylaxis

INTRODUCTION

AIDS, Hepatitis B and Hepatitis C infections are those among the occupational infections that alarm us need for the knowledge of these diseases and prevention [1, 2]. Hepatitis B infection is a disease caused by the hepatitis B virus (HBV), which is transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. Hepatitis B virus (HBV) infection remains a global public health challenge that causes significant morbidity and mortality and the burden of disease is especially high in less-developed countries. HBV has infected more than 2000 million persons alive today and 350 million persons are infected and result in chronic infections, jaundice, cirrhosis of the liver, hepatocellular carcinoma, hepatic failure to even death [3].

Hepatitis B vaccination is the most effective measure to prevent HBV infection and its consequences. Recommendations for hepatitis B vaccination were first issued in 1982; a comprehensive strategy to eliminate HBV transmission has evolved. This strategy includes 1) universal vaccination of infants beginning at birth, 2) prevention of perinatal HBV infection through routine screening of all pregnant women for hepatitis B surface antigen (HBsAg) and postexposureimmunoprophylaxis of infants born to HBsAg-positive women or to women with unknown HBsAg status, 3) vaccination of all children and adolescents who were not vaccinated previously and 4) vaccination of previously unvaccinated adults at risk for HBV infection [4].

Although vaccination offered is high among adults, the low adult vaccination coverage reflects the lack of

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hepatitis B vaccination services in settings in which a high proportion of adults have risk factors for HBV infection. Although hepatitis B incidence among adults is expected to continue to decline during the next decade as successive cohorts of persons vaccinated in infancy, childhood and adolescence reach adulthood, new implementation strategies are needed to protect unvaccinated adults at risk for HBV infection [5].

Epidemiology: The rates of HBV infection vary by sex, race and ethnicity. The rate of acute hepatitis B was higher in men than in women between 2002 and 2010. Males are also much more likely to become chronic carriers than females and the course in males is more likely to be complicated or fulminant than in females. Of those who progress to hepatocellular carcinoma, 76% are male [6].

High endemicity areas account for approximately 45% of the world's population include most of Asia and Africa. The lifetime risk of HBV infection is 60% and most of these infections are acquired during infancy or early childhood. Intermediate endemicity areas account for approximately 43% of the world's population which include India and most of northern Africa, the Middle East and Eastern Europe. The lifetime risk of HBV infection is 20% to 60% and infections occur at all ages. Low endemicity areas account for only 12% of the world's population which include most of North America, Western Europe andAustralia.The lifetime risk of HBV infection is less than 20% [6].

Structure of Hepatitis B Virus: Hepatitis B virus is a DNA virus with a remarkably compact genomic structure; despite its small, circular, 3200-bp size, HBV DNA codes for four sets of viral products with a complex, multiparticle structure.HBV achieves its genomic economy by relying on an efficient strategy of encoding proteins from four overlapping genes: S, C, P and X. HBV is recognized as one of a family of animal viruses, hepatotropic DNA viruses and is classified as hepadnavirus type 1 [7]. This hepadna virus mainly relies on the reverse transcription of minus strand DNA from a “progenomic” RNA intermediate. HBV is very difficult to cultivate. Several cells that have been transfected with HBV DNA support viral replication of the intact virus and its component proteins. This virus is found abundantly in blood and certain body fluids [8]. There are three particulate form of HBV, 42nm virions form, tubular, spherical 22nm form (most abundant).

The virus is divided into four major serotypes (adr, adw, ayr, ayw) based on antigenic epitopes presented on its envelope proteins and into eight genotypes (A-H) according to overall nucleotide sequence variation of the genome. The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus. Differences between genotypes affect the disease severity, course and likelihood of complications and response to treatment and possibly vaccination [9]. Percutaneous inoculation has long been recognized as a major route of hepatitis B transmission, but the outmoded designation "serum hepatitis" is an inaccurate label for the epidemiologic spectrum of HBV infection recognized today [10]. Hepatitis B virus (HBV) is found in highest concentrations in blood, serum and wound exudates and in lower concentrations in semen, vaginal secretions and saliva. Saliva can be a vehicle of transmission through bites; however, other types of exposure to saliva, including kissing, are unlikely modes of transmission. There appears to be no transmission of HBV via tears, sweat, urine, stool, breast milk, or droplet nuclei [11].

The Virus Is Transmitted Through One or More of the Following Modes

Percutaneous Transmission: Inoculation via the skin with infected blood or blood products, such as needle-stick injury, shared IV/IM needle use, ear or body piercing, tattooing, acupuncture, inadequate sterilization of medical equipment, contaminated needles and other sharps, such as broken glass contaminated with blood. Other breaks in the skin such as fresh cutaneous scratches, abrasions, burns or other lesions may also serve as routes for entry [12].

Permucosal Transmission: Contamination with infective serum and plasma via mucous membranes such as the eyes, nose, or mouth. This may occur from mouth pipetting, eye splashes, or hand-to-mouth or hand-to-eye direct contact when contaminated with infective blood or serum [13].

Sexual Transmission: Absorption of HBV into mucosal surfaces through sexual activity. Infection by sexual transmission has been associated with increased number of sex partners, number of years of sexual activity, history of sexually transmitted disease and receptive anal intercourse among homosexual men. In studies of sexual partners of persons with acute HBV, infection developed in 18%- 30%. Among sex partners of persons with chronic HBV, infection developed in 25% -59%. Recent studies have demonstrated that sexual activity accounts for 61% of HBV transmission [14].

Perinatal Transmission: Acquisition of HBV by infant from an infected mother. Ninety-five percent of perinatal transmissions occur during birth. In utero transmission is rare and accounts for about 5% of all infections acquired perinatally. Data indicate that mode of delivery (vaginal versus caesarean) does not affect the risk of perinatal transmission [15].

Horizontal Transmission: Acquisition of HBV in situations and settings such as shared toothbrushes, razors and combs, or passed child-to-child by biting, shared objects, oozing cuts, etc. In follow up studies of the susceptible household contacts of children with chronic HBV infection, new HBV infections developed in 14% - 60% of contact [16].

Risk Factors associated with Hepatitis B [17]:

Many populations are at high risk of acquiring the disease, including:

- Persons with multiple sex partners (24%);
- Persons diagnosed with a sexually transmitted disease (17%);
- Men who have sex with men (13%);
- Injection drug users (20%);
- Household contact with an infected person (3%);
- Haemodialysis patients & Health care workers (23%);

Pathogenesis: In HBV, the existence of inactive hepatitis B carriers with normal liver histology and function suggests that the virus is not directly cytopathic. The fact that patients with defects in cellular immune competence are more likely to remain chronically infected rather than to clear HBV is cited to support the role of cellular immune responses in the pathogenesis of hepatitis B–related liver injury [18]. The model that has the most experimental support involves cytolytic T cells sensitized specifically to recognize host and hepatitis B viral antigens on the liver cell surface. Laboratory observations suggest that nucleocapsid proteins (HBcAg and possibly HBeAg), present on the cell membrane in minute quantities, are the viral target antigens that, with host antigens, invite cytolytic T cells to destroy HBV-infected hepatocytes [10]. Differences in the robustness of CD8+ cytolytic T cell responsiveness and in the elaboration of antiviral cytokines by T cells have been invoked to explain differences in outcomes between those who recover after acute hepatitis and those who progress to chronic hepatitis or between those with mild and those with severe (fulminant) acute HBV infection [18].

Although a robust cytolytic T cell response occurs and eliminates virus-infected liver cells during acute hepatitis B, >90% of HBV DNA has been found in experimentally infected chimpanzees to disappear from the liver and blood before maximal T cell infiltration of the liver and before most of the biochemical and histologic evidence of liver injury. This observation suggests that components of the innate immune system and inflammatory cytokines, independent of cytopathic antiviral mechanisms, participate in the early immune response to HBV infection; this effect has been shown to represent elimination of HBV replicative intermediates from the cytoplasm and covalently closed circular viral DNA from the nucleus of infected hepatocytes [19]. Ultimately, HBV-HLA-specific cytolytic T cell responses of the adaptive immune system are felt to be responsible for recovery from HBV infection. Debate continues over the relative importance of viral and host factors in the pathogenesis of HBV-associated liver injury and its outcome. As noted above, pre-core genetic mutants of HBV have been associated with the more severe outcomes of HBV infection (severe chronic and fulminant hepatitis), suggesting that, under certain circumstances, relative pathogenicity is a property of the virus, not the host [20].

Although the precise mechanism of liver injury in HBV infection remains elusive, studies of nucleocapsid proteins have shed light on the profound immunologic tolerance to HBV of babies born to mothers with highly replicative (HBeAg-positive), chronic HBV infection. In HBeAg-expressing transgenic mice, in utero exposure to HBeAg, which is sufficiently small to traverse the placenta, induces T cell tolerance to both nucleocapsid proteins. This, in turn, may explain why, when infection occurs so early in life, immunologic clearance does not occur and protracted, lifelong infection ensues [21]. Extra hepatic pathogenesis include immune complex–mediated tissue damage appears to play a pathogenetic role in the extrahepatic manifestations of acute hepatitis B. The occasional prodromal serum sickness–like syndrome observed in acute hepatitis B appears to be related to the deposition in tissue blood vessel walls of HBsAg-anti-HBs circulating immune complexes, leading to activation of the complement system and depressed serum complement levels [22].

Clinical Manifestations: After a susceptible person is exposed, the virus enters the liver via the bloodstream; no evidence exists indicating that the virus replicates at mucosal surfaces. HBV infection can produce either asymptomatic or symptomatic infection [7].

Clinical signs and symptoms of hepatitis B virus occur more often in adults than in infants or children, who usually have an asymptomatic acute course. However, approximately 50% of adults who have acute infections are asymptomatic. When symptoms occur in acute HBV infection, they may occur in the following patterns [18]:

- The preicteric or prodromal phase from initial symptoms to onset of jaundice usually lasts from 3 to 10 days. It is nonspecific and is characterized by an insidious onset of malaise, anorexia, nausea, vomiting, abdominal pain in the right upper quadrant, fever, headache, myalgias, skin rashes, dark urine, beginning one to two days before the onset of jaundice. A serum sickness–like syndrome characterized by arthralgia or arthritis, rash, angioedema and rarely hematuria and proteinuria may develop in 5–10% of patients. This syndrome occurs before the onset of clinical jaundice and these patients are often diagnosed erroneously as having rheumatologic diseases. The diagnosis can be established by measuring serum aminotransferase levels, which are almost invariably elevated and serum HbsAg [10].
- The icteric phase is variable, but usually lasts from one to three weeks, characterized by jaundice, light or gray stools, hepatic tenderness and hepatomegaly (splenomegaly is less common)[10].
- Convalescence phase: malaise and fatigue may persist for weeks or months, while jaundice, anorexia and other symptoms disappear. The term fulminant hepatitis is used when encephalopathy and hepatic failure suddenly occur, usually during the first eight weeks of illness [10].

Incubation Period: The average incubation period is 90 days (range: 60-150 days) from exposure to onset of jaundice, 60 days (range: 40-90 days) from exposure to onset of abnormal serum alanine aminotransferase (ALT) levels and 30 days (range: 6-60 days) from exposure to detection of hepatitis B surface antigen (HbsAg) [23].

Period of Communicability: All persons who are HBsAg-positive are considered to be infectious. The HBsAgmay be present several weeks before the onset of illness and last for several weeks (for those who are acutely infected) or years (for those who are chronically infected). If chronic infection develops, patients will most likely remain HBsAg-positive and infective for their lifetime. HBV infection can produce either asymptomatic or symptomatic infection (Figure 1). The onset of acute disease is usually insidious. Infants and young children (aged <10 years) are typically asymptomatic 10. When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain and jaundice. Extrahepatic manifestations of disease (e.g., skin rashes, arthralgias and arthritis) also can occur [23].

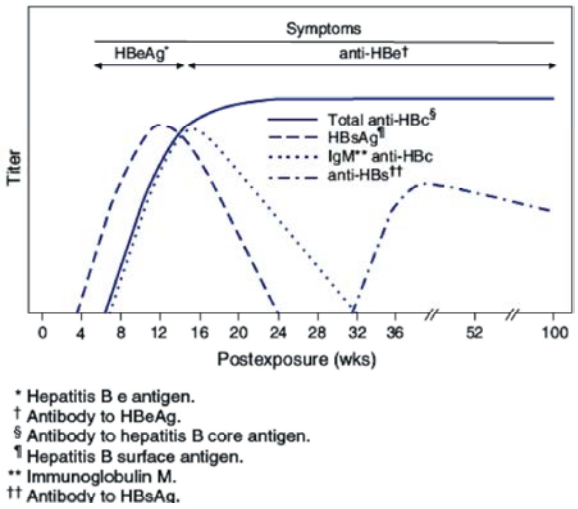

Fig. 1: Typical Serological course in Hepatitis B infection

Three Phases of Chronic HBV Infection Have Been Recognized [23]: The immune tolerant phase (HBeAg-positive, with high levels of HBV DNA but absence of liver disease) The immune active or chronic hepatitis phase (HBeAg-positive, HBeAg-negative, or anti-HBe-positive, with high levels of HBV DNA and active liver inflammation) and The inactive phase (anti-HBe positive, normal liver aminotransferase levels and low or absent levels of HBV DNA).

Patients can evolve through these phases or revert from inactive hepatitis B back to immune active infection at any time. Testing can be performed to assess the presence and concentration of circulating HBV DNA. At least one serologic marker is present during each of the different phases of HBV infection. Serologic assays are available commercially for all markers except HBcAg, because no free HBcAg circulates in blood [23] (Table 1).

Pre and Post Exposure Prophylaxis

Hepatitis B Vaccine: Hepatitis B vaccine is available as a single-antigen formulation and also in fixed combination with other vaccines. Two single-antigen vaccines are available are the Recombivax HB and Engerix-B. There are three licensed combination vaccines; Twinrix is used for

Table 1: Serological pattern in hepatitis B virus infection & their interpretation [24]

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B, high infectivity
+	–	IgG	+	–	Chronic hepatitis B, high infectivity
+	–	IgG	–	+	1. Late acute or chronic hepatitis B, low infectivity
					2. HBeAg-negative ("precore- mutant") hepatitis B (chronic or, rarely, acute)
+	+	+	+/–	+/–	1. HBsAg of one subtype and heterotypic anti-HBs (common)
					2. Process of seroconversion from HBsAg to anti-HBs (rare)
–	–	IgM	+/–	+/–	1. Acute hepatitis B
					2. Anti-HBc "window"
–	–	IgG	–	+/–	1. Low-level hepatitis B carrier
					2. Hepatitis B in remote past
–	+	IgG	–	+/–	Recovery from hepatitis B
–	+	–	–	–	1. Immunization with HBsAg (after vaccination)
					2. Hepatitis B in the remote past (?)
					3. False-positive

vaccination of adults. Comvax and Pediarix are used for vaccination of infants and young children. Twinrix contains recombinant HbsAg and inactivated hepatitis A virus [24] Comvax contains recombinant HBsAg and Haemophilusinfluenzae type b (Hib) polyribosylribitol phosphate conjugated to Neisseria meningitidis outer membrane protein complex. Pediarix contains recombinant HbsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP) and inactivated poliovirus (IPV) [25]. HBsAg is the antigen used for hepatitis B vaccination. Vaccine antigen can be purified from the plasma of persons with chronic HBV infection or produced by recombinant DNA technology [26].

Hepatitis B vaccine should be administered IM in the deltoid muscle and may be administered simultaneously with other vaccines. For adolescents and adults, the needle length should be 1–2 inches, depending on the recipient's weight (1 inch for females weighing <70 kg), 1.5 inches for males weighing <120 kg; and 2 inches for males weighing >120 kg and females >100 kg). A 22- to 25-gauge needle is recommended. If the vaccine series is interrupted after the first or second dose of vaccine, the missed dose should be administered as soon as possible. The series does not need to be restarted after a missed dose [27].

Preexposure Vaccination Schedule: Recommendations & Implementation Strategies for Hepatitis B Vaccination of Adults [1]:

- Hepatitis B vaccination is recommended for all unvaccinated adults at risk for HBV infection and for all adults requesting protection from HBV infection. Acknowledgment of a specific risk factor should not be a requirement for vaccination.
- Providers should select the vaccine schedule they consider necessary to achieve completion of the vaccine series.
- Public health programs and primary care providers should adopt strategies appropriate for the practice setting to ensure that all adults at risk for HBV infection are offered hepatitis B vaccine.

Primary vaccination consists of >3 intramuscular doses of hepatitis B vaccine. The 3-dose vaccine series administered intramuscularly at 0, 1 and 6 months produces a protective antibody response in approximately 30%--55% of healthy adults aged <40 years after the first dose, 75% after the second dose and >90% after the third dose [28]. After age 40 years, the proportion of persons who have a protective antibody response after a 3-dose vaccination regimen declines below 90% and by age 60 years, protective levels of antibody develop in only 75% of vaccinated persons. Alternative vaccination schedules (e.g., 0, 1 and 4 months or 0, 2 and 4 months) have been demonstrated to elicit dose-specific and final rates of seroprotection similar to those obtained on a 0-, 1-, 6-month schedule [29].

Post-Exposure Prophylaxis (PEP): PEP is defined as any prophylactic treatment started immediately after exposure to a pathogen (such as a disease- causing virus). It is the drug therapy immediately following exposure to an infectious organism in an attempt to prevent the infection from taking hold in the body and is designed to protect an individual against a disease agent to which the individual has been recently exposed [30].

Significance of PEP: The risk of transmission of Hepatitis B from an infected individual through a needle stick is less than 1% [31]. However the risk of transmission from

Table 2: Guidelines for postexposure hepatitis B immunoprophylaxis [33]

Cause of Exposure		
Discrete exposure to an HBsAg*-positive source	Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids that contain blood	Administer hepatitis B vaccine and hepatitis B immune globulin (HBIG)†
	Sexual or needle-sharing contact of an HbsAg-positive person	Administer hepatitis B vaccine and HBIG†
	Victim of sexual assault/abuse by a perpetrator who is HBsAg-positive	Administer hepatitis B vaccine and HBIG†
Discrete exposure to a source with unknown HBsAg status	Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine†
	Percutaneous (e.g., bite or needlestick) or mucosal exposure to blood or body fluids that contain blood from a source with unknown HBsAg status	Administer hepatitis B vaccine†

• *- Hepatitis B surface antigen (HBsAg); †-Immunoprophylaxis should be administered as soon as possible, preferably within ≤24 hours.

exposure to infected fluids or tissues is much lower than the infected blood. It is believed that the availability of PEP for health workers will serve to increase staff motivation to work with people infected with hepatitis B.

Post Exposure Measure [32]: What to do after exposure?

- Do not panic.
- Do not put cut /pricked finger into your mouth.
- Wash hands with soap and water after patient contact. Flush mucous membranes with water. No added advantage of bleach or antiseptic.
- Determine the risk of exposure:

Type of fluid (i.e. blood, body fluids with visible blood, other potentially infectious fluid or tissue and concentrated virus).

Type of exposure (i.e. percutaneous injury, mucous membrane or nonintact skin exposure and bites resulting in blood exposure).

- It is necessary to determine the source of the exposure before starting the PEP.
- Test known sources for HBsAg.
- For known sources assess the risk of exposure to HBV infection.
- Give HBIg and/or HBV vaccine for exposure posing risk of infection transmission.
- Perform follow up testing and provide counseling.
- Advice exposed persons to seek medical evaluation for any acute illness during follow- up.
- Perform follow-up anti-HBs testing in persons who receive hepatitis B vaccine.
- Post- exposure treatment should begin as soon as possible preferably within two hours.
- Late PEP? May be YES.
- Is PEP needed for all type of exposures? NO

Guidelines for postexposure hepatitis B immunoprophylaxis (Table 2) and Post-exposure Prophylaxis Regime [33]:

Unvaccinated Individual:

Source Positive : HBIg single dose and HB vaccine series (0,1,6 months)
Source negative : HB vaccine series (0,1,6 months)
Source unknown : HB vaccine series (0, 1,6 months).

Vaccinated Individual:

Known responder : No PEP indicated.
Known non-responder : HBIg single dose and HB vaccine series (0,1,6 months)

Management: Although progression to cirrhosis is more likely in severe than in mild or moderate chronic hepatitis B, all forms of chronic hepatitis B can be progressive and progression occurs primarily in patients with active HBV replication. Moreover, in populations of patients with chronic hepatitis B who are at risk for hepatocellular carcinoma, the risk is highest for those with continued, high-level HBV replication. Therefore, management of chronic hepatitis B is directed at suppressing the level of virus replication [34]. To date, five drugs have been approved for treatment of chronic Hepatitis B: injectable interferon (INF)-α; pegylated interferon [long-acting IFN bound to polyethylene glycol (PEG), known as PEG IFN]; and the oral agents lamivudine, adefovirdipivoxil and entecavir. Several other drugs, including emtricitabine, tenofovir, telbivudine, pradefovir and clevudine, are in the process of efficacy testing in clinical trials [18].

Antiviral therapy for hepatitis B has evolved rapidly since the mid-1990s, as has the sensitivity of tests for HBV DNA. When IFN and lamivudine were evaluated in clinical trials, HBV DNA was measured by insensitive hybridization assays with detection thresholds of 105-106 virions/mL; when adefovir, entecavir and PEG IFN were studied in clinical trials, HBV DNA was measured by sensitive amplification assays (polymerase chain reaction [PCR]) with detection thresholds of 102-103 virions/mL [35].

CONCLUSION

The dental personnel are at a frequent risk of exposure to blood and body fluids in routine dental practice. It is an irony that the dentist becomes a victim in an attempt of treating the patient. Hence, a thorough and an updated knowledge should be present on prevention and prophylactic measures to deadly diseases like HIV, HBV infections, thus ensuring that treating these patients is not denied as well as effectively safeguarding the health care personnel. Our current level of understanding, towards hepatitis B infection should always be refreshed so that we can face the difficulties in their diagnosis and management. Clinicians and researchers are in a paradoxical situation where the quest for knowledge and understanding is hampered by our intrinsic lack of understanding. The positive aspect is that hepatitis B infection does have an effective vaccine and also a formulated post-exposure prophylaxis algorithm.

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