Hepatitis B virus infection in Indonesia

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Abstract
Approximately 240 million people are chronically infected with hepatitis B virus (HBV), 75% of whom reside in Asia. Approximately 60,000 deaths from HBV-related diseases or hepatocellular carcinoma (HCC) occur each year. The endemicity of hepatitis surface antigen in Indonesia is intermediate to high with a geographical difference. The risk of HBV infection is high in hemodialysis (HD) patients, men having sex with men, and health care workers. Occult HBV infection has been detected in various groups such as blood donors, HD patients, and HIV-infected individuals and children. The most common HBV subgenotype in Indonesia is B3 followed by C1. Various novel subgenotypes of HBV have been identified throughout Indonesia, with the novel HBV subgenotype C6-C16 and D6 being successfully isolated. Although a number of HBV subgenotypes have been discovered in Indonesia, genotype-related pathogenicity has not yet been elucidated in detail. The risk of HBV infection is high in hemodialysis (HD) patients, men having sex with men, and health care workers. Occult HBV infection has been detected in various groups such as blood donors, HD patients, and HIV-infected individuals and children. The most common HBV subgenotype in Indonesia is B3 followed by C1. Various novel subgenotypes of HBV have been identified throughout Indonesia, with the novel HBV subgenotypes C6-C16 and D6 being successfully isolated. Although a number of HBV subgenotypes have been discovered in Indonesia, genotype-related pathogenicity has not yet been elucidated in detail. Therefore, genotype-related differences in the prognosis of liver disease and their effects on treatments need to be determined. A previous study conducted in Indonesia revealed that hepatic steatosis was associated with disease progression. Pre-S2 mutations and mutations at C1638T and T1753V in HBV/B3 have been associated with advanced liver diseases including HCC. However, drug resistance to lamivudine, which is prominent in Indonesia, remains obscure. Although the number of studies on HBV in Indonesia has been increasing, adequate databases on HBV infection are limited. We herein provided an overview of the epidemiology and clinical characteristics of HBV infection in Indonesia.

Key words: Hepatitis B virus; Epidemiology; Prevention; Clinical characteristics; Indonesia

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The prevalence of chronic HBV infection varies greatly in different areas of the world and the prevalence of chronic HBV infection can be categorized as high, intermediate, or low endemicity. Table 1 shows the prevalence of the HBsAg in not only the general population, but also risk groups such as commercial sex workers (CSW) and men having sex with men (MSM). The prevalence of HBV in the general population in Indonesia is higher than that of HCV (2%)[12] with the highest rates being reported in Makassar (7.1%)[13] in Sulawesi Island and the lowest rates being reported in Jakarta (4.0%)[14] in Java Island; however, another study reported that the prevalence of HBV in Jakarta was 5.8% in the general population[15]. Hasan previously reported that the prevalence of HBV infection in the general population was the highest in Pontianak (9.1%) in the Kalimantan Island[5]. Furthermore, the prevalence of HBsAg was markedly higher in inhabitants in the highland of Papua (12.8%) and North Sulawesi (33.0%)[16]. The prevalence of HBsAg in pregnant women was found to be the same as that in the general population in Indonesia[17,18]. These findings demonstrated that the endemicity of HBsAg among the general population in Indonesia is intermediate to high, as reported previously[12,19].

HBV infection was not detected in children in Tahuna, North Sulawesi, and Surabaya, East Java, suggesting the efficacy of Hepatitis B (HB) vaccinations in pre-school children[11,20].

The highest risk group of HBV infection was previously reported to be hemodialysis (HD) patients (11.2%) in Yogyakarta[13], followed by MSM (9.8%)[21] in Solo in the Java Island (Table 1). The prevalence of HBV/HIV co-infection was found to be higher than that of HBV infection alone in Indonesia[22-24], as well as in neighboring countries such as Vietnam and India. The incidence of HIV and HBV burden are currently increasing in Indonesia[22,23,29]; however, no HBV/HIV co-infection cases have been identified in CSW[26]. The prevalence of HBsAg has been classified as high endemicity (8.8%) in health care workers[25] and intermediate endemicity in staff in HDU (5.7%) throughout Indonesia (Table 1). A previous study also revealed that the prevalence of HBsAg was high among medical employees in Padang (11.2%), Mataram (13.3%), and Irian Jaya (13.3%)[26].

Many unique animals exist in Indonesia because of its specific ecosystem. Gibbons in Kalimantan were previously reported to be infected with HBV having their own genotype[28].

**OCCULT HBV INFECTION**

Occult HBV infection (OBI) is defined as the presence of HBV DNA in the serum and/or liver tissue of individuals with HBV core antibodies (anti-HBc) without HBsAg[29]. Several studies have been conducted on OBI in Indonesia. OBI was detected in 8.1% of blood donors with amino acid mutations (T123A, M133L, and T143M) in the a determinant of HBsAg, which
resulted in changes in predicted antigenicity\textsuperscript{[30]}. Several OBI cases were detected among school children with the variant T126I, which may be one of the viral mechanisms helping the virus to escape from current HB vaccines in Indonesia\textsuperscript{[31]}. In Banjarmasin, Kalimantan, OBI was identified in healthy young adults with 13 amino acid substitutions\textsuperscript{[32]}. Awareness of the reactivation of OBI has increased in Indonesia, especially in HBV endemic areas\textsuperscript{[33]}. A total of 27.1% and 14.7% of HIV-infected individuals and HD patients, respectively, were considered to have OBI\textsuperscript{[12,22]}; suggesting that the prevalence of HBV infection regardless of HBsAg was high in immunosuppressive patients.

**HBV GENOTYPES/SUBGENOTYPES IN INDONESIA**

HBV is currently grouped into at least 9 genotypes (A through H and J, with I still being controversial)\textsuperscript{[34]}. The HBV sequence is characterized by more than 8% nucleotide (nt) differences for genotypes and 4%-8% for subgenotypes. The most common HBV subgenotype in Indonesia is HBV/B3, followed by HBV/C1\textsuperscript{[35,36]} (Table 1), with various novel subgenotypes of HBV being identified throughout Indonesia. Ten

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence (%)</th>
<th>Subject</th>
<th>Main genotype</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Java</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandung</td>
<td>4.7</td>
<td>Pregnant women</td>
<td></td>
<td>Reniers et al\textsuperscript{[37]}, 1987</td>
</tr>
<tr>
<td>Jakarta</td>
<td>4.0</td>
<td>General population</td>
<td></td>
<td>Akbar et al\textsuperscript{[38]}, 1997</td>
</tr>
<tr>
<td>Jakarta</td>
<td>5.8</td>
<td>General population</td>
<td></td>
<td>Budihusodo et al\textsuperscript{[39]}, 1991</td>
</tr>
<tr>
<td>Jakarta</td>
<td>2.2</td>
<td>Parturient women</td>
<td></td>
<td>Gunardi et al\textsuperscript{[40]}, 2014</td>
</tr>
<tr>
<td>Solo</td>
<td>4.0</td>
<td>CSW</td>
<td></td>
<td>Kotski et al\textsuperscript{[41]}, 2013</td>
</tr>
<tr>
<td>Solo</td>
<td>9.8</td>
<td>MSM</td>
<td></td>
<td>Prasetyo et al\textsuperscript{[42]}, 2014</td>
</tr>
<tr>
<td>Four prisons in Central Java\textsuperscript{1}</td>
<td>3.2</td>
<td>Drug abuser inmates in prisons</td>
<td>B3, C1</td>
<td>Prasetyo et al\textsuperscript{[42]}, 2013</td>
</tr>
<tr>
<td>Yogyakarta</td>
<td>11.2</td>
<td>HD patients</td>
<td>B3</td>
<td>Rinonce et al\textsuperscript{[43]}, 2013</td>
</tr>
<tr>
<td>Surabaya</td>
<td>5.7</td>
<td>Staff in HDU</td>
<td>B3</td>
<td></td>
</tr>
<tr>
<td>Solo</td>
<td>7.1</td>
<td>Pregnant women</td>
<td>C1, B3</td>
<td>Siburian et al\textsuperscript{[44]}, 2013</td>
</tr>
<tr>
<td>Banjarmasin</td>
<td>4.6</td>
<td>General population</td>
<td>B, C</td>
<td>Darmawan et al\textsuperscript{[45]}, 2015</td>
</tr>
<tr>
<td>Sulawesi</td>
<td>4.9</td>
<td>General population</td>
<td>C5</td>
<td>Achwan et al\textsuperscript{[46]}, 2007</td>
</tr>
<tr>
<td>Makassar</td>
<td>7.1</td>
<td>General population</td>
<td></td>
<td>Amirudin et al\textsuperscript{[47]}, 1991</td>
</tr>
<tr>
<td>Bali\textsuperscript{1}</td>
<td>1.9</td>
<td>Pregnant women</td>
<td></td>
<td>Surya et al\textsuperscript{[48]}, 2005</td>
</tr>
<tr>
<td>Papua</td>
<td>4.6</td>
<td>General population</td>
<td>C6, D6, B3</td>
<td>Lusida et al\textsuperscript{[49]}, 2008</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Exact place is not mentioned. MSM: Men having sex with men; CSW: Commercial sex workers; HD: Hemodialysis; HDU: Hemodialysis unit.

\textsuperscript{\textit{Figure 1 Map of Indonesia. Indonesia is the largest archipelago in the world, consisting of five major islands and approximately 30 smaller groups.}}
novel HBV subgenotypes (HBV/C7-C16) were isolated in Indonesia between 2008 and 2012\[^{[37-41]}\]. HBV/C6, HBV/C11, and HBV/D6 were identified in a Papuan population\[^{[36,40,42]}\]. Genotype J (HBV/J) was detected in a Japanese patient with HCC who was thought to have been infected in Kalimantan, Indonesia, during World War II \[^{[28,43]}\]. HBV isolates from subjects from Sulawesi clustered within the HBV/C5, together with known isolates from the Philippines and Vietnam\[^{[11]}\]. The distribution of genotypes/subgenotypes varies even in different regions of a country, which may partly be related to the ethnic origin of the infected patients.

**PREVENTION**

The most significant achievement in the prevention of HB is the implementation of a universal infant vaccination for HB. The HB universal vaccination was introduced in Indonesia in 1997, with the Indonesian government attempting to ensure that every newborn was vaccinated against HBV infection during the first 7 d of life. The immunization project in Lombok decreased the prevalence of HBsAg from 6.2% to 1.4% among children less than 5 years old\[^{[44]}\]. In Surabaya and North Sulawesi, the prevalence of HBsAg in preschool children was reported to be 0%\[^{[11,20]}\], a result that was attributed to the universal HB vaccination. Although the prevalence of HBsAg among children varies by region, for example, 3.1% in Lamongan in East Java\[^{[31]}\] and 4.2% in Papua, the HB vaccination history is obscure. Since the HB vaccination is one of the Expanded Program on Immunization projects being run by the government, communication with the local government is of great importance for better practices.

**CHARACTERISTICS OF CHRONIC HBV INFECTION IN INDONESIA**

Previous studies revealed that the clinical characteristics of chronic HB (CHB) differed among genotypes, and the prognosis of genotype B was better than that of genotype C\[^{[45-47]}\]. However, most studies in Asia were conducted in Taiwan, China, Hong Kong, and Japan. The main subgenotype in Indonesia is HBV/B3, which is different from the subgenotypes HBV/B1 and HBV/B2 mainly analyzed in other Asian countries\[^{[48]}\]. Furthermore, HBV/C in Indonesia is mainly HBV/C1 in Java and HBV/C6 in Papua, and is different from HBV/C, which is spreading in East Asian countries such as China and Japan\[^{[36,42]}\]. Since most clinical studies conducted in Indonesia involved patients with HBV/B, the clinical course of HBV/C in Indonesia currently remains unclear. Although HCC is prevalent in Indonesia, further studies are needed to determine clinical characteristics in relation to the genotypes in Indonesia.

Recent studies revealed that hepatic steatosis was associated with disease progression\[^{[49]}\]. Steatosis was identified as an independent risk factor for HCC and the progression of hepatitis was found to be more rapid in HCV patients with steatosis\[^{[50,51]}\]. However, a meta-analysis revealed that hepatic steatosis was not related to the clinical course of HBV patients\[^{[52]}\]. A previous study reported that hepatic steatosis was more strongly associated with genotype C (37.9%) than with genotype B (24.0%)\[^{[53]}\]. Lesmana et al\[^{[54]}\] examined 179 CHB patients in Jakarta and found the prevalence of hepatic steatosis to be approximately 30%. Obesity is a serious social issue in Indonesia, as in other countries\[^{[55]}\]. However, studies on steatosis in Indonesia are still limited, and, as such, further investigations are warranted.

Although the prevalence of HB and HCV infections in Southeast Asia including Indonesia is high, clinical studies remain limited. Lamivudine, adefovir, and telbivudine, therapeutic drugs for CHB, are currently covered by health insurance in Indonesia. Although drug resistance to lamivudine has not yet been examined, it is common for the cheapest drug, lamivudine, to be prescribed or antiviral therapy to be discontinued due to economic reasons. Therefore, the prevalence of lamivudine-resistant HBV may increase. Telbivudine, which was recently approved in Indonesia, was found to be effective for Indonesian HBV carriers. Sulaiman et al\[^{[56]}\] reported that HBeAg loss and the seroconversion rate for HBeAg-positive patients were 28.8% and 14.1% at week 52 of telbivudine therapy, respectively. Furthermore, undetectable HBV DNA (PCR negativity) was 51.8% at week 24 and 62.7% at week 52 of this therapy. However, a large-scale study has not yet been conducted on interferon therapy for CHB and, thus, its effectiveness currently remains unknown.

Previous studies revealed a hepatitis virus co-infection among HIV patients. Anggorowati et al\[^{[23]}\] examined 126 HIV patients in Yogyakarta city and found that 8% had the HBsAg and were considered to be co-infected with HBV. Utsumi et al\[^{[22]}\] examined 118 HIV patients in Surabaya City, and reported that 15.3% were HBsAg-positive while 27.1% were positive for HBV-DNA regardless of being HBsAg-negative and were considered to have OBI. These findings suggested that HBV co-infection including OBI was frequent among HIV patients and serological examinations were sometimes insufficient for detecting co-infections because of a compromised immune system. Fibriani et al\[^{[24]}\] recently examined 616 HIV patients in Bandung city in West Java, found HBV co-infection in approximately 7% of these patients, and identified the clinical characteristics of co-infection as being male and having a history of injection drug use.

HBV infection was examined in HD patients. Rinonce et al\[^{[12]}\] examined 161 HD patients in Yogyakarta, and revealed that the prevalence of HBsAg positivity was 11.8% and also that the viral...
HBV INFECTION AND HOST FACTORS

Recent technological advances revealed that various kinds of genetic factors are associated with cancers. The genome-wide association study showed that a large number of single nucleotide polymorphisms (SNPs) were related to various kinds of cancers. In case-control and retrospective studies on liver cancers, numerous candidate genes for SNPs were found to be associated with HCC. In 2009, Kamatani et al. examined 188 Japanese CHB patients and 934 controls and was the first to show that SNPs in the human leukocyte antigen (HLA)-DP region were associated with HCC. In 2009, Kamatani et al. examined 188 Japanese CHB patients and 934 controls and was the first to show that SNPs in the human leukocyte antigen (HLA)-DP region were associated with HCC.

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