

Hepatitis B virus infection in Singapore

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Abstract

Although Singapore is in an endemic region for hepatitis B infection, the hepatitis B carriage rate of 5–6% is relatively low. The highest positivity rates for hepatitis B surface antigen (HBsAg) are found in the paediatric age group, with another peak in 40–49 year olds. Studies suggest that, although perinatal transmission is an important route of infection, most children acquire the virus through horizontal transmission between family members. Viral replication continues at a high rate in young carriers and tends to slow down with increasing age. Up to 50% of hepatitis B carriers in Singapore have chronic hepatitis, shown by raised serum ALT values and liver histology, and about 10% are infected with the precore mutant virus. About 20% of carriers have cirrhosis. Among patients with HCC, up to 75% are HBsAg positive, of whom 45% are still viraemic. Mass vaccination against hepatitis B was introduced into Singapore on a voluntary basis in 1983, with compulsory vaccination of babies born to HBeAg positive mothers since 1985. The number of cases of acute hepatitis B has fallen by 60% between 1989 and 1995 although the problems of the longterm complications of chronic hepatitis B still need to be tackled.

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Singapore is a tropical island state situated at the southern tip of the Malay Peninsular. It has an area of 626 square kilometres. Singapore is very cosmopolitan in its population and culture. At the last census count about 10 years ago, there were approximately 2.5 million people living on this island with a male:female ratio of about one. The majority of the population is Chinese in origin (77%), followed by Malays (15%) and Indians (6%). The remainder (2%) are Europeans, Euro-Asians, and Japanese.

Although Singapore is in an endemic region for hepatitis B infection,^{1,2} the hepatitis B carriage rate of 5–6% (approximately 150 000 carriers) is relatively low. The incidence of acute hepatitis B virus (HBV) infection has declined by about 63% since 1989, falling from 291 symptomatic cases to 133 in 1993 and 109 in 1994.³ About 30% of acute infections are imported.³ Cases are considered to be imported when the suspected date of contact with the disease, based on the known incubation period, corresponds with the period when

the patient was away from Singapore, usually in the surrounding countries and in the Indian subcontinent. The incidence of hepatocellular carcinoma (HCC) among men is 28 per 100 000 per year. This is a relatively high figure and reflects the cohort of hepatitis B carriers that has reached the age when cancer occurs.⁴

Epidemiology

PREVALENCE

Local data collected prior to the introduction of mass hepatitis B vaccination suggested that HBV infection starts early in life, giving rise to particularly high carrier rates, continuance of HBV infection into adult life, and a predominance of subclinical infections.⁵ Table I shows the hepatitis B surface antigen (HBsAg) carrier rates among the different ethnic groups. The carrier rates among pregnant women probably reflect the carrier rates of women generally.⁵ Figure 1 shows the age specific prevalence of HBV markers in the general population in Singapore. Sera were obtained from 569 normal adult volunteers and 272 children aged between 1 and 12 years who had been admitted to a major paediatric ward for illnesses not associated with the liver.⁴ The frequency of HBsAg positivity was highest among the paediatric age group. Numbers fell in the teenage group, and there was then a slow rise, subsequently peaking in 40–49 year olds. The frequency of antibodies against HBsAg (anti-HBs) and antibodies against hepatitis B core antigen (anti-HBc) showed a progressive increase with age, reaching about 50% in 40–49 year olds and 100% in subjects over 60 years of age.

ACUTE HEPATITIS

Acute hepatitis B is very uncommon in childhood and is predominantly a disease of male adolescents. About 20% to 30% of cases of acute HBV infection are imported and are usually the result of sexual transmission.³ Needle stick injuries probably play a minor part in HBV transmission nowadays, although they may have played a major part in the past, either through parenteral injections using non-disposable needles or through acupuncture. Outbreaks of acute hepatitis B have also been traced to tattoo parlours between 1977 and

TABLE I Hepatitis B carrier rates in different ethnic groups in Singapore⁵

	Blood donors (male)	Pregnant women
Chinese (%)	13.6	6.2
Malays (%)	7.3	2.3
Indians (%)	6.0	0.6

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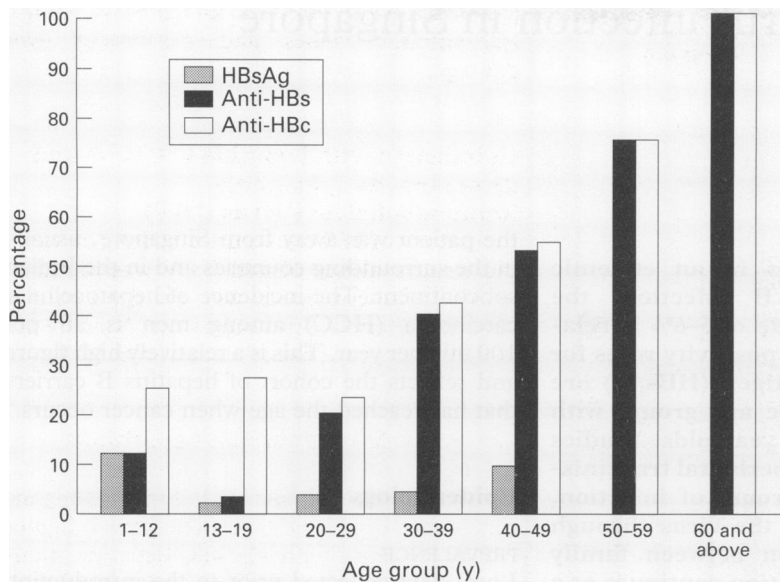


Figure 1: Age specific markers of HBV infection in Singapore.⁵

1981.⁶ Transmission of HBV infection through blood transfusion is rarely seen since the introduction of routine blood donor screening for HBsAg in the late 1970s.

TRANSMISSION

The HBV carrier pool in endemic areas is largely made up of people who acquired their infection during infancy and childhood, when the probability of developing chronic infection is the highest.⁷ Most infections transmitted from carrier mothers to their children – either at birth or shortly thereafter – are asymptomatic, and hence remain undetected. Studies from Taiwan have shown the importance of perinatal transmission in the intrafamilial spread of HBV infection in this region.⁸

Between June 1980 and June 1982, Chan and his colleagues studied the babies of 58 HBsAg carrier mothers at delivery and followed up 56 of these infants for at least one year.⁹ Overall, HBV transmission occurred in 27 of 56 (48%) infants; intrauterine infection and infection after the perinatal period each accounted for 8% of the cases. Nineteen of 56 infants remained HBsAg positive at 1 year, giving a carrier rate of 34% in the study population. The carrier rate among pregnant mothers was 4.4%. This would give a carrier prevalence of only 1.6% among Singapore infants (34% of 4.4%). However, a serological study of 458 children admitted to a major paediatric department in Singapore at around the same time showed that the prevalence of HBsAg carriers among Singapore infants was 8.9% (17 of 186).¹⁰ This was much higher than the calculated figure of 1.6% obtained above. The majority of infant HBV infection, therefore, must have occurred by horizontal transmission.

A recent serological survey performed on 270 family members of 78 hepatitis B carriers showed that the chances of children of carrier parents being HBsAg positive were similar whether the carrier parent was the father or the

mother.¹¹ The proportions of siblings and parents of HBV carriers who were HBsAg positive were also similar to those of carriers' children. Spouses were less likely to be HBsAg positive when compared with children of carrier fathers or siblings of index patients. In this study, it was also found that the hepatitis B e antigen (HBeAg) status of index subjects did not affect the proportions of parents or children who were HBsAg positive or had markers of previous HBV exposure. However, siblings of HBeAg positive index subjects were more likely to be positive for HBsAg and more likely to have markers of previous exposure when compared with siblings of HBeAg negative index cases. The above findings suggest the importance of horizontal transmission among siblings in a family group.¹¹

Natural history of childhood acquired chronic hepatitis B infection

AGE OF INFECTION

The natural history of chronic hepatitis B infection in Singapore is similar to that seen in other countries in the region. In most cases, infection starts early in life, giving rise to a high prevalence of chronic HBV carriage. Viral replication continues at a very high rate in young subjects and tends to slow down with increasing age. Young, asymptomatic HBeAg positive carriers sometimes progress to chronic hepatitis, while a proportion of them undergo spontaneous seroconversion to anti-HBe antibody positivity without developing liver disease. Viral replication is significantly reduced with the development of anti-HBe antibodies. Older hepatitis B carriers are usually asymptomatic and anti-HBe positive but those who are HBeAg positive usually have more severe liver disease.

VIRAL MARKERS

In a report from the National University Hospital in Singapore, 404 consecutive hepatitis B carrier patients aged 3–85 years were studied over a five year period.¹² At presentation, 177 (44%) patients were HBeAg positive and 217 (54%) patients were anti-HBe positive. The remaining 10 (2%) patients were negative for both e markers. HBV-DNA was detected in the serum of 169 (42%) patients, including 85% of HBsAg positive patients and 9% of HBeAg negative patients. Figure 2 shows the frequencies of HBsAg positivity according to age. There was a tendency for patients to lose their HBeAg with increasing age. HBeAg positive patients were generally found to have higher mean serum ALT values (75 IU/l) compared with those who were HBeAg negative (46 IU/l) ($p < 0.001$).

HISTOLOGY

Liver histology was available in 135 patients in the above study.¹² Minimal changes were found in 53 patients (39%). Chronic hepatitis (chronic persistent hepatitis, chronic lobular

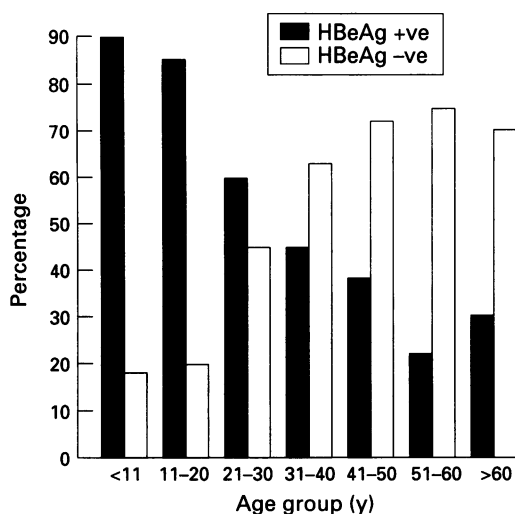


Figure 2: Frequency of HBeAg positive/negative status according to age groups in Singapore.¹²

hepatitis, and chronic active hepatitis) was seen in 61 (45%) patients, and 21 (16%) had liver cirrhosis.

LONGTERM FOLLOW UP

Two hundred and fifty eight patients were followed up for a mean duration of two years (range 3–108 months).¹² Of these, 101 were HBeAg positive. The cumulative probability of clearing HBeAg at the end of the first, second, and third years of follow up was 14%, 16%, and 18%, respectively. Among those who lost HBeAg, the cumulative probability of developing anti-HBe over one, two, and three years was 8%, 9%, and 11%, respectively. Reappearance of HBeAg occurred in 1.5% of patients who were HBeAg negative at presentation and in 1% of HBeAg positive patients who had cleared HBeAg during follow up. HBV-DNA was detected intermittently in 9% patients with anti-HBe. Four (1.5%) patients underwent HBsAg seroconversion to anti-HBs within five to 30 months (mean 15 months) of follow up, all of whom were over 40 years of age.

Precore mutant infection

About 10% of patients with chronic hepatitis B infection in Singapore harbour the HBeAg negative HBV variant resulting from a mutation in the precore region of the viral genome.¹² Most infections with this variant are asymptomatic. They have been found to occur even before seroconversion to anti-HBe has occurred. Precore mutant infection becomes clinically significant in the older HBeAg positive hepatitis B carrier, and is usually

TABLE II Histological features of 135 chronic hepatitis B patients¹²

	Total	HBeAg+ve	HBeAg-ve
Minimal changes (%)	53 (39)	31 (36)	22 (46)
Chronic hepatitis (%)	61 (45)	44 (50)	17 (35)
Cirrhosis (%)	21 (15)	12 (14)	9 (19)
Total (%)	125 (100)	87 (64)	48 (36)

associated with episodic increases in serum transaminase values and continuing liver damage.

Coinfection with hepatitis C (HCV) and delta virus and the human immunodeficiency virus (HIV)

In a survey of 188 consecutive HBsAg carriers, the seroprevalence of anti-HCV was found to be 3%.¹³ Superinfection with the delta virus is virtually absent in this island state. No data are available on the coinfection rate with HIV.

Complications of chronic hepatitis B infection

The frequency of hepatitis B surface antigenaemia has been found to be significantly higher among patients with chronic hepatitis, non-alcoholic cirrhosis, and HCC compared with the normal local population.⁵

CHRONIC HEPATITIS

Up to 50% of hepatitis B carriers have chronic hepatitis, confirmed by raised serum ALT values and liver histology.¹² These patients are usually asymptomatic but may present with lethargy. The diagnosis is usually suspected as a result of persistently raised serum transaminase values.

CIRRHOSIS

Cirrhosis is seen in about 20% of HBV carriers locally. Macronodular cirrhosis occurs after a few years in patients with hepatitis B e antigenaemia and continuing liver disease activity (as shown by persistently raised transaminase values) and in those subjects with multiple attempts at seroconversion to anti-HBe. Not all patients with cirrhosis have decompensated disease, although no figures are available. About 1% of patients with cirrhosis develop HCC yearly.⁴

HEPATOCELLULAR CARCINOMA

HCC is a late complication of chronic hepatitis B infection. HBsAg is present in up to 75% of patients with HCC in Singapore^{5 14} and up to 97% of patients with HCC have been found to have evidence of previous HBV infection.^{15 16} In a recent study in 60 HBsAg positive patients with HCC, 45% were still viraemic.¹⁶ This was a significantly higher rate than that found in HBsAg positive age and sex matched controls, indicating the possible role of continuing HBV activity in the pathogenesis of HBV related HCC. Exposure to aflatoxin is not an important factor in the pathogenesis of HCC locally.^{17 18}

A review of 104 cases of HCC seen at the National University Hospital over a two year period, from January 1988 to December 1989, showed that most patients were over 60 years of age.¹⁵ Hepatomegaly with features of cirrhosis was the main physical finding and pain the main symptom. Many patients were not

suitable for curative resection at presentation and all of these died within two years of diagnosis. Chemotherapy did not seem to improve survival. Ten patients underwent successful resections, but two of them died one year later – one from liver failure and the other from disease recurrence. Four patients were still alive and had been followed up for a mean duration of 18 months (range 7–34 months) when the study was published.

Because of the unresectable nature of the lesion at clinical presentation, attempts have been made at early detection of HCC in high risk patients by frequent measurements of serum α fetoprotein and liver ultrasound, and this has resulted in increased numbers of resectable tumours. It is, however, an expensive measure and may not be cost effective.^{19 20}

Treatment

The aim of treatment of patients with chronic HBV infection is to eliminate viral replication and hence to prevent liver damage. Elimination of HBV with successful treatment is rare in this part of the world. Treatment in the early stages of chronic infection, when liver histology does not show any inflammatory activity, has been uniformly dismal using the usual treatment regimens practised in the West.^{21–23} The reasons for the relative insensitivity of this group of patients to treatment are not entirely known. It has been suggested that the failure to respond to the presently available modality of treatment (alpha interferon) is because of immunotolerance of the body to the virus.²¹ Cell mediated immunity has been found to be normal in asymptomatic HBV carriers locally,^{24 25} with no reduction in the ability of their peripheral blood mononuclear cells to produce alpha or gamma interferon.²⁶ Nevertheless, patients with chronic hepatitis B and raised liver transaminase values do respond to interferon therapy in the same manner as patients in the West.²⁷ Patients with precore mutant infections can be easily treated with small doses of interferon. Furthermore, the problem of relapse is not as common in Singapore as in the West.

Prevention

Before the availability of hepatitis B vaccine, prevention and control were based entirely on sanitary precautions and personal health education. These included routine screening of blood donors for HBsAg, introduction of disposable syringes and needles, sterilisation of medical and dental equipment, and surveillance of tattoo parlours and acupuncture clinics. There was a significant decline in the proportion of chronic hepatitis B cases with a history of parenteral exposure from 62% in 1977 to 29% in 1988. Post-transfusion and tattoo associated acute hepatitis B were virtually eliminated. Mass hepatitis B vaccination was introduced into Singapore on a voluntary basis in 1983, starting with health care workers.²⁸ Compulsory vaccination of babies born to HBsAg positive mothers since 1985 has reduced the number of new carriers.²⁹

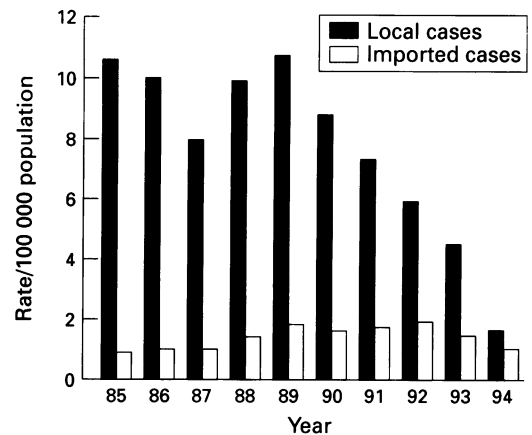


Figure 3: Morbidity rate of reported acute hepatitis B cases in Singapore.³

Hepatitis B vaccination is now being recommended for the following groups of people: health care workers, inmates of homes for the intellectually impaired, and people at risk from direct contact with infected people.

Due to the initial high cost of the vaccine, studies using reduced doses of vaccine were performed both in infants and adults. These studies showed that the reduced doses were as effective as the manufacturer's recommended dose.^{30 31} Antibody values, however, were much lower than those achieved using the manufacturer's recommended regimen. Despite this, persistence of antibodies was similar to that achieved using the recommended doses.^{29 32}

No local figures are available on the number of people vaccinated with the hepatitis B vaccine. In view of the prevalence of hepatitis B infection locally, it is recommended that hepatitis B serology be performed before vaccination is given. Vaccinating a carrier is harmless but wasteful and gives a false sense of security, although a recent study in France has shown that vaccination of such individuals may have therapeutic implications.³³ On the one hand, vaccination would boost anti-HBs values in those already immune. On the other hand, however, vaccination is been shown to give rise to vaccine escape mutants.^{34 35} In 1990, Carmen and colleagues reported a point mutation in residue 145 (predicting a change from glycine to arginine) in the second loop of the 'a' determinant of the surface genome in an infant from southern Italy.³⁴ Four similar cases were later identified in Singapore and Japan.³⁵ All these infants were born of HBeAg positive mothers and all had vaccination together with immunoprophylaxis. Horizontal transmission of these mutants has not been proved.

Figure 3 shows the impact of hepatitis B vaccination on the incidence of chronic hepatitis B infection in Singapore. The number of acute cases has fallen by 60% between 1989 and 1995.³ The impact of vaccination on the incidence of HCC will not be evident until about 20 years' time.

Conclusion

Hepatitis B vaccination is preventing mother to child transmission of hepatitis B infection

and stemming the source of the carrier pool locally. The problem of the longterm complications of chronic hepatitis B infection – notably cirrhosis and HCC – still needs to be tackled. To date, the only effective treatment for chronic hepatitis B infection is alpha interferon, and this is appropriate in only about 30–40% of chronic hepatitis B infections locally. Clinical trials using nucleoside analogues seem promising. Both these agents reduce HBV replication and therefore the infectivity of the affected person and the disease activity in the liver. Complete elimination of HBV is not always possible with the currently available therapeutic agents. New classes of drugs are urgently needed, especially for those patients in the early stages of the disease.

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