CHRONIC HEPATITIS B

MORRIS SHERMAN, MD, FRCP(C)
Assistant Professor and Acting Head
Liver Diseases Program, Division of Gastroenterology
Department of Medicine, University of Toronto
Staff Gastroenterologist
Toronto Hospital

In recent years there have been new advances in our understanding of the natural history of chronic hepatitis B. In addition, therapy has become available for some patients with this disease. These two changes have prompted a reappraisal of how patients with chronic hepatitis B should be managed.

Hepatitis B Markers

- The hepatitis B surface antigen (HBsAg) indicates active infection. The presence of antibodies to the hepatitis B surface antigen (anti-HBs) indicates a previous infection, or a previous vaccination. Occasionally both HBsAg and anti-HBs are present at the same time. When this occurs, the anti-HBs should be disregarded, and the patient should be considered to be actively infected.

- The presence of antibodies to hepatitis B core antigen (anti-HBc) has a different implication than with anti-HBs. Anti-HBc antibodies do not distinguish between active or previous infection, nor to they indicate immunity. All hepatitis B carriers and all patients who have previously been exposed to hepatitis B will be positive for total anti-HBc. Chronic hepatitis B carriers have circulating anti-Hbc IgM antibodies, but depending on the sensitivity of the assay, these may not be detected. Many laboratories test for anti-HBc when a hepatitis screen is requested, but the identification of this antibody in serum adds nothing to the management of the patient.

- The hepatitis B e antigen (HBeAg) indicates active viral replication, high levels of viremia, high infectivity, and a high likelihood of active liver disease. The corresponding antibody (anti-HBe) usually develops later in the course of the disease. Like anti-HBc, anti-HBe does not indicate immunity. However, anti-HBe is associated with low levels of viral replication and viremia, lower infectivity, and a lower likelihood of active liver disease.

The HBV DNA is a direct assay for the presence of the virus itself. There are two assays, a hybridization assay, which has a lower limit of detectability of about 10,000 virus particles, and a polymerase chain reaction assay, which is sensitive to about 100 virus particles, but is currently used only as a research tool.

Active vs. Chronic Hepatitis B. There are two forms of hepatitis B infection.

- Acute hepatitis B is a short-term illness, which usually resolves spontaneously without sequelae. Many infections (perhaps more than 50%) are asymptomatic. Fulminant liver failure causing death or requiring liver transplantation occurs in less than 1% of symptomatic acute hepatitis B. For most patients the disease is mild with minimal morbidity.

- Chronic hepatitis B is potentially a much more serious disease, although the majority of patients with the disease are asymptomatic throughout most of their lives. Depending on geographic location, up to 50% of subjects with hepatitis B may die of their disease, usually from the complications of cirrhosis, from hepatocellular carcinoma, and occasionally from liver failure due to acute or chronic hepatitis.

Hepatitis B in Canada. Hepatitis B is a notifiable disease in Canada, but most health authorities only keep statistics on acute hepatitis B. There are about 3,000-4,000 new cases of acute hepatitis B notified to the health departments each year. However, given that acute hepatitis B is often asymptomatic, there may be many more cases that are not reported. Acute hepatitis B occurs mainly in young adults, and the majority of infections are acquired sexually or by IV drug use.

The are no data on the prevalence of chronic hepatitis B in Canada. However, various estimates have put the number at 150,000-200,000 cases. Some estimates have suggested that the majority of carriers are found in immigrant communities from parts of the world where hepatitis B is common. These areas include South East

Asia, where the incidence of hepatitis B carrier state is 10-15%, Africa (10-15% of the population are carriers), and Southern and Eastern Europe (about 5% carrier rate). Other estimates have suggested that Canadians of Northern European extraction (the so-called non-ethnic Canadians) provide the largest pool of hepatitis B carriers. In the absence of epidemiological data these estimates cannot be confirmed. However, there is not doubt that the hepatitis B carrier state is common in the immigrant communities mentioned above. Furthermore, it is likely that the majority of carriers in these populations have not been identified. A case can therefore be made for testing every single individual from any of these communities for hepatitis B at least once.

Transmission of Hepatitis B. The route through which an individual acquires hepatitis B varies with the age at which infection is acquired.

- Newborn infants may acquire hepatitis B by vertical transmission from a carrier mother. The exact route of transmission is not known, but may be related to exposure to blood at birth, or by intimate contact after birth, including activities such as kissing and breast feeding. Older children may also acquire the disease by vertical transmission from either the mother or the father, again by routes not completely defined, but close personal contact is obviously important. Presumably, when an infected parent kisses the cut finger or scraped knee of their child, transmission can occur, since the organism is present in saliva. Young children in communities where hepatitis B is endemic are also at risk of acquiring the disease from other caregivers, aunts, uncles, grandparents, daycare workers. The magnitude of this risk is not known.

- Horizontal transmission can also occur between siblings and between young children at play. Again, the exact routes of transmission are not known, and the magnitude of the risk is uncertain.

- Young adults are most at risk for hepatitis B because of sexual activity. The risk increases as the number of sexual partners increases. Transmission is not particularly related to homosexuality, rather to promiscuity within this community. Thus homosexual males, promiscuous heterosexuals, including street kids, and prostitutes are at risk for hepatitis B. Young adults may also acquire the disease by sharing needles while using intravenous street drugs.

- Older adults may also acquire the disease by sexual transmission or by IV drug use, but professional risks also become important at this stage. Professions associated with an increased risk of hepatitis B include doctors, nurses, medical laboratory technicians, ambulance paramedics, police, firefighters and morticians. Exposure to blood and blood products are the major factors causing the risk. Workers in mental health institutions, particularly for children, are also at risk, although the routes of transmission have not been defined.

Risk of Developing Chronic Hepatitis B. Whether or not an individual infected with hepatitis B becomes a chronic carrier depends largely on the age at which the infection was acquired.

- In infancy more than 90% of infected babies become carriers.

- When hepatitis B is contracted in childhood about 40-60% of subjects develop chronic hepatitis B.

- When the disease is contracted in adulthood less than 5%, and perhaps less than 1%, go on to become chronic carriers.

There are several important corollaries stemming from this information.

- First, most chronic carriers are likely to have been infected in childhood. They are also therefore likely to have acquired the infection from a close relative. Thus, when a hepatitis B carrier is identified, the entire extended family should also be screened for the disease.

- Second, since infection in childhood is more important in the development of the chronic carrier state than infection in adulthood, it follows that the ideal vaccination policy would be to immunize all newborns. This is the strategy that has been recommended by almost all official bodies that have considered the problem, which has been adopted in parts of the world where hepatitis B is common. In Canada, only British Columbia has adopted a universal vaccination policy. In B.C. the hepatitis B vaccine is offered to all children in grade 6. This policy has two main flaws. This policy will decrease the incidence of acute hepatitis B in young sexually active adults, and to the extent that a small proportion of these people will become carriers, this will decrease the carrier rate somewhat. However, since most carriers are infected in childhood it is unlikely that this strategy will have a major effect on the overall carrier rate. The second problem is that delaying vaccination until the teenage years means that a proportion of this population will already

have become carriers. Depending on the demographic makeup of the B.C. population, 1-2% of children will be hepatitis B carriers by the time that they are in grade 6. (The overall carrier rate in Canada is about 1%.) These children will have been vaccinated and will no doubt believe that they are immune to hepatitis B, whereas they are really chronic carriers. These people may still pass the infection on to their sexual partners or to their children.

The Natural History of Chronic Hepatitis B. The natural history of chronic hepatitis B has now been well described and is somewhat different from what is written in textbooks. The disease can be divided into three more or less overlapping phases.

- The first phase is characterized by a normal or near-normal liver, within minimal or no liver damage. the liver enzymes (AST or ALT) are minimally elevated or are normal. However, the virus load is high, as demonstrated by the presence of HBeAg and high levels of HBV DNA in serum. In this phase the host exhibits immune tolerance to the virus. In those infected in childhood this phase lasts until the teens or early twenties. In those infected in adulthood this phase may be very brief.

- The second phase is characterized by intermittent or continuous bouts of hepatic inflammation (hepatitis). The levels of viremia fluctuate, as do the liver enzymes. Episodes of moderately to markedly elevated liver enzymes are interspersed with periods in which the liver enzymes are normal or only minimally elevated. The HBeAg and HBV DNA levels are variable. A liver biopsy may show mild, moderate, or severe viral hepatitis, and fibrosis or even cirrhosis may be present. (The terms "chronic active" and "chronic persistent hepatitis" are no longer used. Rather, the histologic picture is described as mild, moderate, or severe chronic hepatitis.) Most episodes of hepatitis resolve spontaneously within a few weeks. Sometimes the inflammation may persist or may be severe, leading to liver failure and death. This occurs in less than 1% of all carriers.

  The intermittent flares of hepatitis may or may not be associated with changes in the e antigen status. A flare of acute or chronic hepatitis may occur when a hepatitis B carrier seroconverts from HBeAg-positive to anti-HBe positive. The seroconversion is heralded by loss of HBV DNA from serum, followed by a flair in inflammatory activity and an elevation of liver enzymes. Either during the flare, or some weeks to months after the flare has subsided, HBeAg is lost, and anti-HBe develops. However, non-seroconversion flares can occur in either HBeAg-positive or anti-HBe-positive individuals, with no change in the e antigen status. About 10% of chronic carriers older than about 20 years of age lose HBeAg each year.

- The third period, as with the first, is characterized by low or normal liver enzymes and minimal hepatic inflammation. However, cirrhosis or fibrosis may be present. In this phase HBeAg is usually negative, and anti-HBe is positive. The HBV DNA levels are low. Disease progression in phase three, if it occurs at all, is very slow.

  The severity of cirrhosis in phase III is roughly proportional to the total amount of inflammation that occurred during the phase II. If there were only a few sporadic bouts of hepatitis, the likelihood of cirrhosis is small. If the middle phase was characterized by many repeated bouts of moderate hepatitis, or if the period of hepatitis was prolonged, then cirrhosis is more likely.

  This is the phase in which hepatocellular carcinoma develops.

  About 1% of carriers in phase III lose HBsAG each year. This probably does not affect the risk or hepatocellular carcinoma, but there are no data to confirm this.

One important consequence of this natural history is that we now realize that there is no such thing as a "safe" hepatitis B carrier. All HBV carriers are at risk for the development of liver disease, including cirrhosis and hepatocellular carcinoma. A second consequence is that all hepatitis B carriers need lifelong follow-up. During the active phase of the disease patients should be seen at approximately six monthly intervals, to have their liver enzymes measured. If the enzymes remain normal the patient can return in another six months, but if the enzymes are high the patient should be followed more closely. In most instances the enzymes will return to normal spontaneously with 2-3 months, but if the elevation persists, the patient should be evaluated for treatment.

Prognosis. Despite the presence of chronic hepatitis B,the prognosis for carriers as a group is good. There are several prospective studies with more than five years of follow-up. Unfortunately, the data is incomplete, because most studies have included mainly men, or have not reported results for women separately from men, or the studies were not performed in an urban North

American population. Therefore, it is not certain that the data are applicable to Canada, for example. These studies have shown that in patients diagnosed as having chronic active hepatitis (using the old terminology) the 5-year survival is in excess of 80%, those diagnosed with chronic persistent hepatitis have a slightly higher survival, at about 90% at five years. However, when cirrhosis is present the 5-year survival is about 60%. This study does not provide the life-time risk of death for hepatitis B and its complications. Another study, from Taiwan, predicted that 55% of male hepatitis B carriers will die from liver disease, either the complications of cirrhosis, or from hepatocellular carcinoma. This study did not indicate the yearly death rate. However, it was estimated that most of the deaths would be from hepatocellular carcinoma and that about 1% per year would die from this disease. The only comparable study from North America is in a cohort of "les enfants du Du plessis," children brought up in orphanages in Quebec dating from the 1950's when illegitimate children were placed in state institutions. About 400 of these children who were hepatitis B carriers were followed, and as recently as two years ago none had developed hepatocellular carcinoma, nor died of liver disease. This cohort may be too young to have developed these complications.

Women are known to have less severe and less frequent cirrhosis and to develop hepatocellular carcinoma less often than male hepatitis B carriers, but there are no good data to quantitate this.

Therapy for Hepatitis B. The recent introduction of interferon for the treatment of hepatitis B has provided us with the first drug that is effective in this disease. Interferon is indicated for hepatitis B carriers with liver enzymes which are at least twice normal, who are HBeAg positive and HBV DNA positive, and who have chronic viral hepatitis on liver biopsy. Those who fit this profile have about a 40% chance of responding to treatment, by which is meant that the liver enzymes normalize permanently, the HBV DNA disappears from serum, and the patient loses HBeAg. Long term follow-up studies show that responders may also lose HBsAg in significant numbers (up to 60%). However, there is as yet no data to indicate that the prognosis in treated patients is better than in non-treated patients.

Sixty percent of properly selected patients will not respond to interferon. There are several characteristics that allow us to identify those who have a higher likelihood of response. Women respond better than men. Cirrhosis decreases the response rate. The more active the inflammation, the better the response. The lower the HBV DNA (below 200 picograms) the better the response. HIV positive individuals with low CD4 counts also respond less well.

Interferon has several side effects. A flu-like illness, consisting of fever, rigors, myalgia, headache, chills and dry cough commonly follows the first few injections, but these symptoms become less troublesome as the course of treatment proceeds. Patients are advised to take the injection in the evening and to take Tylenol and go to bed early.

Interferon suppresses the bone marrow, and therefore the blood count needs to be watched carefully, particularly in patients with cirrhosis and leucopenia and thrombocytopenia due to hypersplenism. There is sometimes some hair loss towards the end of therapy, although not to the extent of baldness. Induction of autoimmunity has been recorded. Most frequent is the development of autoimmune thyroditis, but a type of autoimmune hepatitis has also been described, and theoretically any autoimmune disease can be reactivated. Interferon can cause psychological depression and can aggravate preexisting heard disease.

There are contra-indications to therapy with interferon. Patients with evidence of hepatic failure (elevated bilirubin, prolonged prothrombin time, ascites, encephalopathy) should not be treated. These individuals get life-threatening infections. Because interferon can cause depression, a pre-existing depressive illness is a contra-indication. The presence of autoimmune disease is a relative contra-indication, because interferon is an immune stimulant, and there is a risk that the autoimmune disease could be activated or reactivated. Preexisting cardiac disease is also a contra-indication.

Hepatocellular Carcinoma. Hepatitis B carriers have about 100 times the risk of developing hepatocellular carcinoma (HCC) than non-carriers. The risk is lower in women, and is probably also lower in North American Caucasians (compared to South East Asians).

Hepatocellular carcinoma usually carries a dismal prognosis. Tumors which cause symptoms are rarely resectable and are usually only slightly sensitive to chemotherapy. Newer therapies, such as chemoembolization, ethanol injection, etc., have not been shown to enhance survival or prolong life. With early detection programs, smaller lesions can be found, and resection is more often feasible. Large scale screening programs to detect early lesion have been described, and indeed it has been stated that all hepatitis B carriers should be screened with yearly alphafetoprotein levels. However, there is no evidence that screening for HCC reduces

mortality from the disease, nor that screening and early treatment prolongs life beyond that expected from the natural history of small hepatocellular carcinomas. Coexisting cirrhosis limits resectability. Recurrence after resection is common, and death from progression of the underlying liver disease also occurs.

Ultrasonography has also been used to screen for hepatocellular carcinoma. At present there is even less information about the efficacy of such screening than for alphafetoprotein. Thus screening with ultrasonography is not recommended. Indeed, in the only North American study in which this has been looked at, alphafetoprotein was better at detecting small HCC's than ultrasonography.

Summary. Hepatitis B is no longer the simple disease it once was. The availability of vaccination and therapy means that each patient and his or her contacts have to be carefully evaluated to determine whether either is appropriate. Neither vaccination nor therapy is inexpensive, and therapy certainly is not simple. For all these reasons, evaluating these patients is more difficult than before. However, the clinical problem is only increasing as the numbers of carriers being detected increases, and the effect of this disease on healthcare costs and lost productivity is substantial.