Hepatitis B in childhood: An update for the paediatrician

Latifa TF Yeung MSc MD FRCPC, Eve A Roberts MD FRCPC
Division of Gastroenterology and Nutrition, Department of Paediatrics, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario

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Hepatitis B virus (HBV) infection may lead to acute or chronic hepatitis, cirrhosis and hepatocellular carcinoma. The incidence rate of paediatric hepatitis B is 0.2/100,000 to 1.8/100,000 in Canada. Hepatitis B virus infection is acquired largely through mother-to-infant (vertical) or community-based (horizontal) transmission in early childhood, whereas older children are susceptible to HBV infection through exposure to contaminated blood during intravenous drug use or through sexual transmission. Immigrants from endemic areas and some Native Canadian populations are also at a higher risk for HBV infection. Infection with HBV may manifest in three forms: acute self-limited hepatitis, chronic hepatitis or massive hepatic necrosis causing acute liver failure. The identification of HBV infection and the characterization of the disease relies on serological and virological tests. The course of chronic hepatitis B may be classified into three phases: an immunotolerant phase, an active phase and an inactive phase. Current treatment options include interferon-alpha and lamivudine for individuals with elevated serum alanine aminotransferase levels and markers of persistent viral replication. Children with chronic hepatitis B require regular monitoring and age-appropriate lifestyle counselling. Paediatricians are well-positioned to promote vaccination and encourage testing of those who are at risk for hepatitis B. With effective universal vaccination against hepatitis B, this infection could be essentially eliminated in Canada.

Key Words: *Diagnosis; Hepatitis B virus; Natural history; Review; Treatment; Vaccination*

L'hépatite B dans l'enfance : Une mise à jour pour le pédiatre

RÉSUMÉ : L'infection au virus de l'hépatite B (VHB) peut provoquer une hépatite aiguë ou chronique, une cirrhose et un carcinome hépatocellulaire. Le taux d'incidence de l'hépatite B pédiatrique est de 0,2 à 1,8 cas pour 100 000 habitants au Canada. L'infection au VHB s'acquiert largement par transmission de la mère à l'enfant (verticale) ou communautaire (horizontale) dans la première enfance, tandis que les enfants plus vieux y sont susceptibles par une exposition à du sang contaminé pendant des relations sexuelles ou l'utilisation de drogues intraveineuses. Les immigrants de régions endémiques et certaines populations autochtones canadiennes présentent également un risque plus élevé d'infection au VHB. Celle-ci se manifeste sous trois formes : une hépatite aiguë résolutive, une hépatite chronique ou une nécrose hépatique massive causant une insuffisance hépatique aiguë. Le dépistage de l'infection au VHB et la caractérisation de la maladie se fondent sur des examens sérologiques et virologiques. L'évolution de l'hépatite B chronique se classe en trois phases : la phase immunotolérante, la phase active et la phase inactive. Les possibilités courantes de traitement incluent l'interféron-alpha et le lamivudine pour les personnes présentant un taux élevé de sérum alanine aminotransférase et des marqueurs de réplication virale persistante. Les enfants atteints d'une hépatite B chronique ont besoin d'une surveillance régulière et de conseils sur le mode de vie adaptés à leur âge. Les pédiatres sont bien placés pour faire la promotion de la vaccination et favoriser le dépistage des enfants à risque d'hépatite B. Grâce à une vaccination universelle efficace contre l'hépatite B, cette infection pourrait être à peu près éradiquée au Canada.

Hepatitis B virus (HBV) infection may lead to acute or chronic hepatitis, cirrhosis and hepatocellular carcinoma. It is estimated that two billion people worldwide are infected with HBV and that more than 350 million people have chronic hepatitis B infection. Complications from HBV infection result in one million deaths each year. In 1998, Health Canada reported that the incidence rate of hepatitis B in childhood was 0.2 to 1.8/100,000. Despite the introduction of safe and effective vaccines against hepatitis B in 1982, the overall incidence of hepatitis B worldwide is twice that of acquired immune deficiency syndrome (http://cythera.ic.gc.ca/dsol/ndis/index_e.html).

TRANSMISSION AND HIGH RISK POPULATIONS

In early childhood, HBV is acquired largely through mother-to-infant (vertical) or community-based (horizontal) transmission. Proposed modes of horizontal transmission include contact with open wounds; sharing of bath towels, food, dental cleaning materials; unsterilized

Correspondence: Dr EA Roberts, Division of Gastroenterology and Nutrition, The Hospital for Sick Children, Room 8267, Black Family Foundation Wing, 555 University Avenue, Toronto, Ontario M5G 1X8. Telephone 416-813-7733, fax 416-813-4972, e-mail eve.roberts@sickkids.ca

TABLE 1: Clinical interpretation of classic profiles of hepatitis B virus (HBV) serology and virology

Clinical interpretation	HBsAg	Anti-HBc	Anti-HBs	HBeAg	Anti-HBe	HBV DNA
Chronic infection	+ for longer than 6 months					
'Window period' of resolved HBV infection (HBsAg lost but anti-HBs yet to develop)	–	+* (IgM)	–			
Highly infectious (high viral replication)	+			+	–	+
HBsAg-carrier at low risk of transmitting HBV (inactive replication)	+			–	±	–
Possible mutant				–	±	+
Possible escape mutant (eg, taking lamivudine)				±	±	Increased
Immune following vaccination	–	–	+			

**Current or previous infection (highly specific for acute infection in older children and adults) forms approximately eight weeks after infection. + Positive; – Negative; ± May be positive or negative; Anti-HBc Antibody to hepatitis B core antigen; Anti-HBe Antibody to hepatitis B e antigen; Anti-HBs Antibody to hepatitis B surface antigen; HBeAg Hepatitis B e antigen; HBsAg Hepatitis B surface antigen; IgM immunoglobulin M*

multiple intramuscular injections; and biting of fingernails in conjunction with scratching the backs of carriers (1-4). Older nonimmunized children are susceptible to HBV infection through exposure to contaminated blood, intravenous drug use or sexual transmission (5). Immigrants from certain endemic areas (China, Southeast Asia, Eastern Europe, the Central Asian republics, most of the Middle East, Africa, the Amazon Basin, some Caribbean islands, and the Pacific Islands) and some Native Canadian populations are also at higher risk for HBV infection. Other high risk paediatric groups include residents of institutions for the developmentally disabled, patients receiving blood products (eg, hemophiliacs), hemodialysis patients and household contacts of HBV carriers (6). The risk of infection is greatly diminished by timely immunization.

DISEASE PRESENTATION

Infection with HBV may manifest in three forms: acute self-limited hepatitis, chronic hepatitis or massive hepatic necrosis resulting in acute liver failure. Chronic infection is distinguished from acute infection by the persistence of hepatitis B surface antigen (HBsAg) beyond six months after acute infection. Children infected early in life are most likely to develop chronic infection whereas older individuals who acquire HBV from drug use or sexual activity tend to develop acute infection. Acute infection usually resolves spontaneously (7). The likelihood of progressing from acute to chronic hepatitis is inversely correlated with age. Massive hepatic necrosis resulting in hepatic failure accounts for approximately 1% of HBV infections.

On clinical grounds alone, it is difficult to distinguish hepatitis B from other forms of liver disease. Acute or chronic infection may be asymptomatic or present with jaundice and elevated aminotransferase levels. Arthralgias, arthritis, macular rashes or glomerulonephritis may occur. In many cases, a history of recent exposure to risk factors (such as recent intravenous drug use) suggests acute infection, whereas a history of having lived since childhood in an endemic region favours chronic infection. When entertaining the diagnosis of HBV infection, testing for hepatitis A virus and hepatitis C virus should also be considered.

DIAGNOSIS

The identification of HBV infection and the characterization of the disease rely on serology and virology. Although not all inclusive, Table 1 provides the clinical interpretation of typical patterns of HBV serology and virology. The duration of detectable HBsAg beyond six months indicates chronic infection. The antibody to this viral surface antigen (anti-HBs) develops during convalescence from acute hepatitis B, conferring immunity to future infection. A 'window period' may exist during which HBsAg is lost and anti-HBs has yet to develop. During this time, the antibody to hepatitis B core antigen (anti-HBc) may be detectable (see below). Anti-HBs also develops following hepatitis B vaccination.

A second antigen, hepatitis B e antigen (HBeAg) is released into the blood during periods of high viral replication, indicating a highly infectious state. If seroconversion occurs, HBeAg is lost and anti-HBe develops. An anti-HBe-positive state may develop after an acute infection or in the late phases of chronic infection. The presence of anti-HBe identifies HBsAg carriers who are at low risk for transmitting HBV. Rarely, seroconversion may result from the development of a 'precore mutant' (whereby a mutation occurs at nucleotide 1896 in the precore region of the HBV DNA genome). This mutation of uncertain virulence occurs during the course of infection and renders the virus incapable of producing HBeAg (8).

Finally, anti-HBc develops approximately eight weeks following infection. Its presence may indicate current or previous infection. One anti-HBc assay detects both immunoglobulin (Ig) G and IgM antibodies, while a second assay only detects IgM antibody. In older children and adults, IgM anti-HBc is highly specific for the diagnosis of acute infection because it exists early during the infection and during the window period. Serum HBV DNA titre, measured by hybridization assay, correlates with the level of viral replication.

NATURAL HISTORY

The course of chronic hepatitis B may be classified into three phases: an immunotolerant phase, an active phase and an inactive phase (Table 2) (9). The immunotolerant phase is characterized by high viral replication (positive HBeAg) with high titres of virus in serum (positive HBV DNA), yet minimal hepatic inflammation. For individuals infected during early childhood, this phase may last as long as three decades. The subsequent active phase is marked by liver damage because hepatocytes supporting HBV replication are cleared by the host immune system. Low viral replication and episodic flares of hepatitis, demonstrated by intermittent elevations of aminotransferase levels, are noted. Seroconversion to anti-HBe positivity may occur during this phase. Clearance of HBeAg in HBsAg carriers is more likely to occur in children who are older, symptomatic with elevated aminotransferase levels and born to HBsAg-negative mothers (10). This second phase may also last up to two decades, but usually lasts one to two years. Lastly, the inactive carrier state has absent or minimal viral replication with detectable anti-HBe and minimal hepatic inflammation. The rate of disease progression is slow, but may be accompanied by cirrhosis. The degree of cirrhosis is related to the overall severity of inflammation during the second active phase. Cirrhosis may regress over decades in the absence of active viral infection.

TREATMENT

Generally, children with elevated aminotransferase levels and markers of persistent viral replication (HBeAg- and HBV DNA-positive) should be considered for treatment (if the serum alanine aminotransferase [ALT] level is two to three times the upper limit of normal for more than four months without becoming anti-HBc-positive). Treatment response is commonly defined as seroconversion of HBeAg to anti-HBe with loss of HBV DNA because such outcomes are associated with a decreased incidence of cirrhosis and hepatocellular carcinoma. Adult studies have established interferon-alpha and lamivudine as treatment options for patients with hepatitis B (11-14). The role of corticosteroid therapy as a priming agent to enhance therapeutic efficacy remains to be clarified, but appears to be unnecessary and possibly dangerous (15). Thus far, in children with chronic hepatitis B, results of studies that use priming with steroids do not differ significantly from those without steroids (16-18). Long term follow-up results of adults with chronic hepatitis B who were treated in a randomized controlled trial suggest that interferon-alpha is more effective than placebo in preventing the development of hepatocellular carcinoma and prolonging survival (19).

Decisions to treat should be made in consultation with a hepatologist. Ongoing monitoring for treatment compliance, adverse reactions and treatment response may be coordinated between the local physician and consulting hepatologist.

TABLE 2: Phases of chronic hepatitis B

Phase	HBV DNA titre	HBeAg/ anti-HBe status	Hepatic inflammation
1 – immunotolerant	High	HBeAg-positive	Minimal
2 – active	Low	Seroconversion from HBeAg- to anti-HBe-positive	Significant
3 – inactive	None or minimal	Anti-HBe-positive	None (but subsequent cirrhosis is possible)

Chance of reverting from phase 3 to phase 2: approximately 10% to 15% during lifetime. Anti-HBe Antibody to hepatitis B e antigen; HBV Hepatitis B virus; HBeAg Hepatitis B e antigen

Interferon-alpha

Treatment with recombinant interferon-alpha is currently the only licensed antiviral treatment for chronic hepatitis B. In children, a randomized controlled trial of interferon-alpha compared with no treatment found that interferon-alpha promoted loss of viral replication markers (HBeAg and HBV DNA). Serum HBeAg and HBV DNA became negative in 26% of treated children and 11% of control subjects. Virological response was associated with the normalization of aminotransferase levels and improvement in liver histology (20). The indications for treatment included detectable serum HBsAg for at least six months, HBV DNA and HBeAg measured on at least two occasions at least one month apart, ALT at least 1.5 times the upper limit of normal (measured on four occasions at least one month apart) and histological evidence of chronic hepatitis. Normal white blood cell count; hemoglobin, hematocrit, albumin and creatinine levels; and a negative pregnancy test were also required. Patients with psychiatric illness (especially depression or impulsive destructive behaviours), hepatic decompensation (marked by ascites, variceal hemorrhage or encephalopathy), epilepsy or serious central nervous system disease, other additional liver disease, hepatitis C, hepatitis D, or human immunodeficiency virus (HIV) were excluded. Because the safety of interferon-alpha during pregnancy is not well-established (21), contraceptive measures are recommended during treatment.

Interferon-alpha is administered by subcutaneous injection. The initial dose is 3 MU/m^2 body surface area three times per week for one week, then the dose may be increased to 6 MU/m^2 body surface area (maximum dose 10 MU/dose) for subsequent weeks for a minimum of 16 weeks and a maximum of 24 weeks total duration of treatment, depending on virological response to therapy. Treatment is completed at 16 or 20 weeks if serum HBeAg is undetectable on two separate occasions measured one month apart.

Children tend to tolerate interferon-alpha treatment

with only mild to moderate adverse effects. The most common complaint of flu-like illness self-resolves after treatment. In contrast to adults, children reported more alopecia and subtle behavioural changes such as irritability, sleep disturbance and depression. All the side effects were transient (20), and the patients' health-related quality of life returned to normal following interferon-alpha treatment (22).

Successful treatment with interferon-alpha may enhance the clearance of HBV infection (as indicated by seroconversion of HBsAg to anti-HBs). Loss of HBsAg occurred in 19% to 34% of adults who had a sustained response to interferon-alpha, whereas HBsAg was lost in 0% to 20% of untreated control subjects who spontaneously lost HBeAg (23-25). Paediatric data suggest similar trends; of the patients who had a sustained response to interferon-alpha, 25% to 39% lost HBsAg, whereas 0% to 12% of untreated children who spontaneously lost HBeAg also lost HBsAg (20,26,27).

Lamivudine

Lamivudine is an oral nucleoside analogue that inhibits viral DNA replication that was initially used in the treatment of HIV. Adult studies show that one year of lamivudine treatment has response rates (measured as HBeAg seroconversion to anti-HBe-positive) of 17% to 33%, comparable with that of interferon-alpha (14,28). In contrast to interferon-alpha, which only results in a histological benefit in patients who lose HBeAg, the majority of patients treated with lamivudine have histological benefit (14). In adults, the indications for treatment with lamivudine are similar to those for interferon-alpha. In children, lamivudine is a particularly attractive alternative to interferon-alpha because of its oral formulation and minimal side effects. The paediatric dose of lamivudine has been established (3 mg/kg/day if the child is two to 12 years of age, 100 mg once daily if the child is 13 to 17 years of age) (29). Currently, lamivudine is being investigated for use in children; studies leading to licensing are nearly complete.

A phase 3 trial of lamivudine in paediatric hepatitis B is underway. Enthusiasm for lamivudine treatment is somewhat attenuated by concerns regarding the possible emergence of viral mutants. Although lamivudine results in a rapid decline in HBV DNA, the viral load returns to baseline levels after the cessation of treatment, unless HBeAg seroconversion to anti-HBe occurs in association with HBV DNA clearance (13). Future paediatric data must characterize whether the restoration of DNA levels on lamivudine withdrawal is associated with markers of disease progression such as abnormal aminotransferase levels or more severe histological changes. The durable benefits of lamivudine therapy remain to be defined. Also, long term paediatric data are needed to monitor the development of the viral 'tyrosine, methionine, aspartate, aspartate (YMDD) mutants' that have been noted in adult trials of lamivudine (14,28).

MONITORING

Patients who are chronically infected with hepatitis B but not eligible for treatment require regular follow-up. Changes in ALT and HBV serology may reveal spontaneous seroconversion (loss of HBeAg and gain of anti-HBe) or suitability for treatment (persistent elevation of ALT and HBeAg). Although no evidence has directly proved that screening for hepatocellular carcinoma reduces mortality, many hepatologists screen for hepatocellular carinoma with serum alpha-fetoprotein and/or annual ultrasound.

Children infected with HBV require age-appropriate lifestyle counselling. They should be taught body substance precautions; personal items, such as toothbrushes and razors, should not be shared with others. Teenagers should be encouraged to minimize alcohol intake and use barrier protection during sexual activities. Blood donation must be avoided.

VACCINATION

The hepatitis B recombinant vaccine is 95% effective in preventing HBV infections from developing. In 1991, in response to recommendations from the World Health Organization, 116 countries incorporated hepatitis B vaccination into their immunization programs. Efforts are in progress to vaccinate children in countries that have not been able to afford the vaccine (http://www.who.int/inf-fs/en/fact204.html). Universal vaccination in Taiwan has been correlated with a declining incidence of childhood hepatocellular carcinoma (30).

Although vaccination policies differ among countries, the eventual goal of universal HBV mass vaccination is the same (31). Babies of HBsAg-positive women require hepatitis B immunoglobulin and HBV vaccine within 12 h of birth, with subsequent vaccine doses at one to two and six months of age. Accountability mechanisms should be in place to ensure that this schedule is followed, and testing for serologic response to the vaccine should be performed one month after the completion of the three-dose series to monitor the success of the prophylaxis. Currently, formulations of the hepatitis B vaccine (Engerix-B; SmithKline Beecham, Canada and Recombivax HB; MerckFrosst, Canada) are given on a first day of vaccination, then one month and six month schedule. Infants of low birth weight (less than or equal to 1500 g) should be immunized with the hepatitis B vaccine starting at one month of chronological age (32). Adolescents aged 11 to 15 years may receive a hepatitis B vaccine in a two-dose schedule: 10 mg (1.0 mL adult formulation) on the first day of vaccination and then four to six months later. The immunogenicity of this two-dose schedule has been found to be comparable with that of the usual three-dose schedule using 5 mg HbsAg (33). For patients who may also benefit from hepatitis A vaccination (34) (eg, children with hepatitis C), a combined hepatitis A and hepatitis B vaccine is available for those older than one year of age (Twinrix Junior; SmithKline Beecham, Can-

ada). Efforts are underway to develop a vaccine to combine diphtheria, polio, tetanus, pertussis, hemophilus B and hepatitis B to simplify vaccination protocols and ensure universal vaccination during infancy (35).

IDENTIFICATION OF THOSE AT RISK

Paediatricians have an excellent opportunity to promote the importance of vaccination and the testing of individuals who may be at risk for HBV infection. All family members from endemic regions should be tested for hepatitis B with serum HBsAg and anti-HBs. Vaccination should be provided to patients who are negative for surface antigen and antibody. Vaccinated individuals have detectable anti-HBs and are negative for HBsAg. Those with detectable HBsAg are infected and require further workup (determination of HBeAg status and aminotransferase level) to determine the extent of liver disease and eligibility for treatment.

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Internet addresses are current at the time of publication.

Hepatitis B in childhood – Quiz

Answer the following questions by circling the letter of the correct answer(s). Answers can be found on page 672.

1. Children and adolescents with hepatitis B are *least* likely to acquire their infection:
   (a) at birth from an infected mother.
   (b) from fecal-oral transmission.
   (c) from another child (horizontal transmission) in early childhood.
   (d) from sexual transmission.
2. Hepatitis B infection may present with:
   (a) jaundice.
   (b) elevated serum aminotransferase levels.
   (c) no symptoms.
   (d) all the above.
3. Match the serology with the most likely diagnosis of hepatitis B virus (HBV):
   (a) antibody to hepatitis B surface antigen (anti-HBs)-positive, hepatitis B surface antigen (HBsAg)-negative, antibody to hepatitis B core antigen (anti-HBc)-positive.
   (b) anti-HBs-positive, HBsAg-negative, anti-HBc-negative.
   (c) anti-HBs-negative, HBsAg-negative.
   (d) HBsAg-positive, hepatitis B e antigen (HBeAg)-positive, HBV DNA-positive.
   (I) infected and highly infectious.
   (II) vaccinated for hepatitis B.
   (III) never infected and never vaccinated – susceptible to infection.
   (IV) infected carrier (resolved infection).
4. Which of the following *is not* an indication for treatment of paediatric hepatitis B?:
   (a) histological evidence of chronic hepatitis.
   (b) elevated alanine aminotransferase level.
   (c) detectable HBV DNA and HBeAg.
   (d) persistent jaundice.
   (e) persistent HBsAg.
5. Which statement is false?:
   (a) Interferon-alpha has been shown to promote loss of viral replication markers, normalize aminotransferase levels, and improve liver histology in paediatric randomized controlled trials.
   (b) subcutaneous injections of interferon-alpha are administered three times a week for up to 24 weeks.
   (c) although oral lamivudine is well-tolerated in children, concerns about the development of tyrosine, methionine, aspartate, aspartate (YMDD) mutants remain.
   (d) low birth weight infants should not receive the hepatitis B vaccine until one year of age.