Hepatitis B in children: some need therapy

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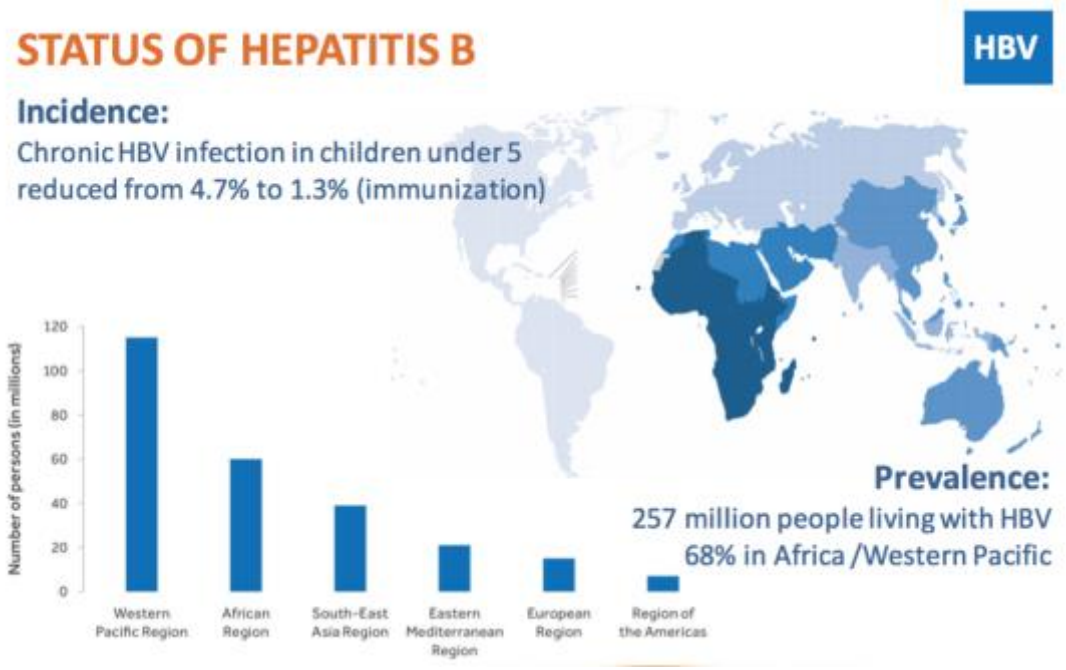
Can you tell us what is the burden of HBV in infants?

More than 360 million individuals worldwide have hepatitis B virus (HBV) infection, including numerous children (1-3), which makes this disease a major clinical issue for pediatricians. Although the incidence of HBV infection has declined since the 1990s with implementation of large vaccination programs and blood donor screening, a significant number of children are still infected every year. These patients have the potential to develop chronic infection and require immediate attention. Between the pre-vaccine era (ranging from the 1980s to the early 2000s) and 2015, the percentage of children younger than 5 years who became chronically HBV infected fell from 4.7% to 1.3% (4). Nonetheless, the prevalence remained at 3% in the WHO African Region member states. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%. This has substantially reduced HBV transmission in the first five years of life, but coverage with the initial birth dose vaccination is still low, at 39%. Other prevention interventions are available, but insufficiently implemented.



WHO, Global Hepatitis Report, 2017

What are the risk factors for HBV infection in children?

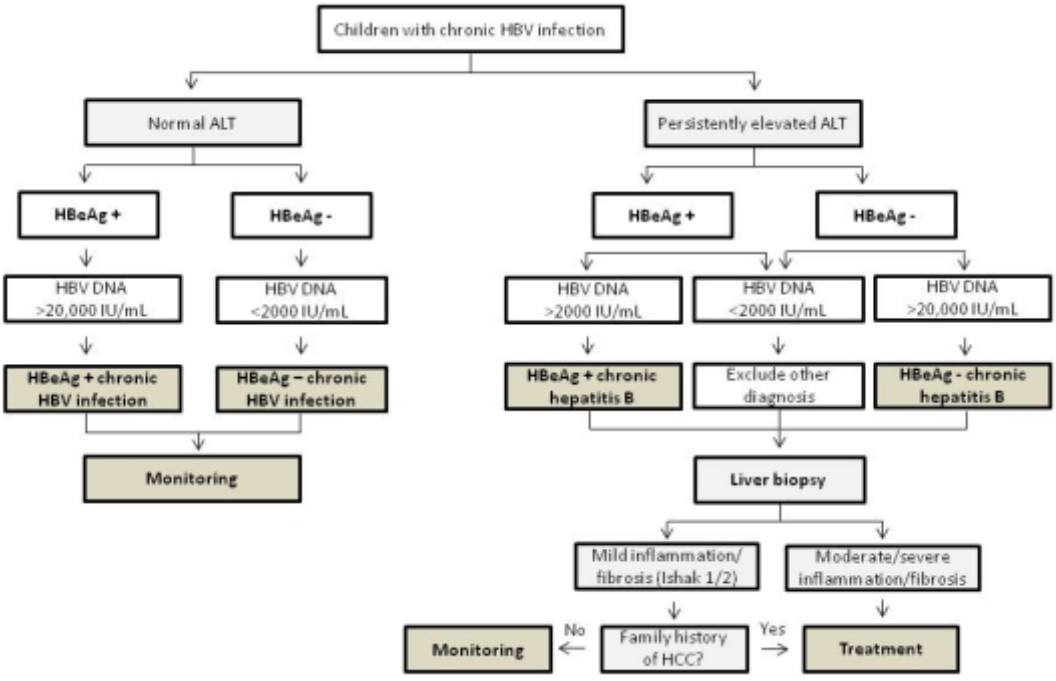
The risk factors for HBV infection depend on the endemicity of the infection in a given country. Chronic HBV in areas where the infection is endemic is related with perinatal transmission. The high disease rates in pregnant women are the most important cause of chronic infection in children (6-7). Factors associated with a high likelihood of transmission from mother to child are a high maternal viral load or HBsAg levels, HBV genotype C, and hyper-responsiveness to HBV vaccine (4-7). In non-endemic countries, perinatal infection also occurs, but it is less common and mainly seen in children of HBV-infected mothers who did not received appropriate HBV immunoprophylaxis (7-8). Most children with chronic HBV infection in non-endemic countries are immigrants, have immigrant parents, or were exposed through household contacts with HBV infection (9). Breastfeeding does not contribute significantly to HBV transmission from infected mothers to infants if the mothers receive immunoprophylaxis (10).

Acute HBV infection is rare in the pediatric age. Adolescents from high-risk groups, such as intravenous or intranasal drug users or men who have sex with men can develop acute disease, as can those living in communities with a high percentage of individuals from endemic areas.

Are the treatment algorithms the same as for the adult populations?

The goal of HBV therapy is to improve long-term survival and quality of life by reducing the risk of progressive liver disease, cirrhosis, and hepatocellular carcinoma (11). This goal is achieved by induction of sustained hepatitis B surface antigen (HBsAg) loss, although this occurs in a minority of treated patients. Hence, long-term HBV DNA suppression is the main endpoint of all current treatment strategies. Because of the low rates of HBsAg loss, the decision to treat is based on ALT concentrations, HBV DNA levels, and the degree of liver fibrosis. The efficacy and safety of antiviral agents approved for HBV therapy of children should also be considered (2,11). The drugs approved and recommended for children aged 2 years and older with chronic HBV infection and evidence of active viral replication and disease activity are entecavir, and tenofovir. A trial with tenofovir alafenamide fumarate (TAF) is currently ongoing in children aged 2 to 11 years. Lamivudine, adefovir, and telbivudine are not recommended, and pegylated interferon is not approved for children.

A treatment logarithm is proposed in the following Figure:



What are the challenges ahead?

The decision to treat patients with HBeAg-positive chronic infection, previously known as immune-tolerant patients, is still controversial. The latest European HBV guidelines do not recommend therapy in patients with HBeAg-positive chronic infection, defined by a persistently normal ALT concentration and high HBV DNA levels (11). Only HBeAg-positive patients, those with HBeAg-negative chronic HBV infection, and those with a family history of hepatocellular carcinoma or cirrhosis and extrahepatic manifestations can be treated. The decision to initiate treatment is primarily based on ALT concentration, and the upper limit of normal (ULN) for ALT in children has not been clearly established. For this reason, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines recommend that patients be considered for antiviral therapy if ALT levels exceed either 1.5 to 2.0 times the laboratory ULN or 60 IU/L (2). It would be important to clarify the most appropriate ALT level for this purpose.

Not all drugs approved for treatment of chronic HBV in children are available in all countries, possibly because of a lack of consensus regarding either the benefits to be sought or the endpoints to be considered when treating children. Whereas HBsAg loss, along with the development of hepatitis B surface antibody (HBsAb), is considered the ultimate treatment goal, this is rarely achieved with current treatment modalities.

Recent research has deepened our understanding of the HBV replicative cycle, and has led to identification of drugs that target parts of the cycle. Some of these are in phase-2 testing in adults. However, there is still a long way to go before these drugs are evaluated in children.

Finally, in some low-income and middle-income countries, where the number of infected individuals remains high, the cost of the vaccine is still an unresolved issue.

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