

Hepatitis B in Children - Selection of Patients for Treatment

Steven R. Martin MD, FRCP(C)



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Treatment of children with chronic HBV infection is founded on the principle of reducing long-term morbidity associated with the disease and reducing the probability of subsequent horizontal and vertical transmission throughout the lifetime of the infected child.

Natural history studies show that the risk of development of chronic HBV infection is inversely proportional to the age of acquisition:

*85-90% of vertically infected newborns;

*25-30% of children infected at < 5 years develop chronic HBV infection

This compares to <10% of adults.

Perinatal infection, occurs more frequently when the mother is HBeAg(+) and is particularly associated with a prolonged immune tolerance phase and is characterized by normal aminotransferases, high levels of circulating HBV-DNA and the presence of HBeAg in serum. HBeAg seroconversion is marked by a period of variable duration during which flares of liver inflammation are followed by normalization of aminotransferases, low levels of HBV DNA and the development of anti-HBe antibodies. The concern that a prolonged clearance phase increases the risk of severe hepatitis, cirrhosis and subsequent hepatocellular carcinoma (HCC) has stimulated the search for suitable treatments. However, a drive towards universal treatment for all children with chronic HBV infection must be tempered by a closer analysis of the natural history of chronic HBV infection in children. Spontaneous HBeAg clearance rates are greatly affected by the mode of transmission, viral load, liver inflammatory activity, ALT levels, sex, host immunocompetence, genotype and possibly the region in which the child is raised. Similarly, geographical variations in the development of cirrhosis and HCC may be affected by many of the same factors, requiring care in generalizing observations to local practice.

Treatment of HBV infection in children has to date been limited to interferon or lamivudine. The immediate goal each therapy is to induce HBeAg seroconversion and not the more desirable goal of eradication of hepatitis B virus. Clinical trials using either agent have shown a modest improvement of about 15% over spontaneous seroconversion rates usually during relatively short periods of follow-up (usually < 2 years). Natural history studies show that with longer follow-up periods (3-4 years) the difference between treatment-induced and spontaneous seroconversion is negligible. It remains unclear whether an acceleration in seroconversion of three years confers any real long-term benefit to the infected child. No data is available to show that the development of either cirrhosis or HCC is reduced by these therapies. Indeed, of reports of HCC in the more recent era (where HCV detection has been possible) most pediatric cases of HCC are described in HBeAg(-) children with short durations of chronic HBV infection and relatively short (6 m-6 yrs) HBeAg clearance phases.

HCC may even develop in the absence of cirrhosis suggesting that viral DNA integration into the host genome could be factor in HCC development.

The selection of children for whom treatment will be most beneficial will require the answers to a number of questions:

1. What is the long-term effect of current treatment on the development of cirrhosis and HCC in HBV-infected children compared with untreated controls?
2. How do genotype, pre-core and core promoter mutations and genetic polymorphisms affect

the natural history of HBV infection and the response to treatment.

3. What role does persistence of low levels of HBVDNA and/or fluctuations of ALT for years after HBeAg seroconversion have in the development of cirrhosis and HCC?

4. What is the role of environmental co-factors in the natural history and in the development of HBV-related complications in children?

5. What are the long-term side-effects of currently used therapies?

Until such answers are known, patients most at risk of developing severe hepatitis or cirrhosis may be selected for treatment while acknowledging the limitations of current therapies. In this group might be included immunosuppressed patients and those with more than 6 months duration of ALT elevation ($> 2 \times N$) and a biopsy showing inflammatory activity. All treated patients should be followed annually with aminotransferases, HBV DNA levels and HBV serology.

Editor's Note:

In his presentation, Dr. Martin commented: "What's the Rush?" since most children with HBV do not progress on to serious disease he believes that physicians should carefully monitor children for disease progression and consider treatment if the disease progresses.

Additional key points by Dr. Martin:

- ◆ Treatment of HBV in children with interferon may be preferable to lamivudine since interferon does not produce drug resistance and the relapse rate of interferon is lower than lamivudine.
- ◆ A liver biopsy should be performed when considering treatment because the degree of severity is important for deciding which treatment medication to use – interferon or lamivudine.
- ◆ We do not really know if liver enzymes predict prognosis of disease severity in children with HBV.

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