# CURRENT MANAGEMENT: VIRAL HEPATITIS

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Chronic hepatitis B and C virus (HBV and HCV) infections present an important health problem causing significant morbidity and mortality worldwide. The younger the patient is at time of infection with HBV, the higher the risk to develop chronic infection and cirrhosis. There is limited knowledge about the natural history of chronic HCV infection in children. Treating children remains a challenge and tailored treatment modalities are required for the pediatric population. Treatment is aimed at reducing hepatic inflammation, decreasing long-term sequelae such as hepatocellular carcinoma and increasing the survival rate.

HEPATITIS B virus (HBV) infection is a global public health problem, with approximately one third of the world's population having serologic evidence of past or present HBV infection. Currently, about 350 million people are chronically infected and HBV accounts for over half a million deaths annually [1-2]. Spontaneous viral clearance, prolonged latency and progressive damage to the liver are the variable courses of the disease. The younger the patient is at time of infection with HBV, the higher the risk to develop chronic infection and cirrhosis [3]. Compared to adults, with a 10% risk to acquire HBV after exposure, the risk value increases remarkably to 25-30% in children below 5 years and can be 90% in untreated newborns of hepatitis Be antigen (HBeAg) positive mothers.

Outcome of acute HBV infection ranges from asymptomatic subclinical infection (70%) and symptomatic acute hepatitis (30%) to fulminant hepatic failure (0.1-0.5%) [4]. Hepatitis B surface antigen (HBsAg) positive children show slow spontaneous clearance of HBsAg (0.6% per year) and low rates of surface antibody development. A proportion of children infected with HBV progress to chronicity, defined as persistence of infection for more than six months [5]. The spectrum of chronic HBV infection ranges from the asymptomatic carrier state to chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma (HCC) (*Table* 1). The risk to develop HCC increases substantially with confirmed HBV infection at early age than compared to acquisition at a later stage [6]. Overall, chronic hepatitis progresses to end stage liver disease in 15-40% of patients [7]. Patients with chronic

**Table 1: Classification of patients with chronic HBV infection.**

| Characteristic | Chronic Hepatitis B* | Inactive HBsAg carrier |
|---|---|---|
| HBsAg | Positive for >6 months | Positive for >6 months |
| Alanine aminotransferase | Intermittently or persistently raised (>2 times upper limit of normal) | Normal |
| Serum HBV DNA level | $>10^5$ copies/ml ** | $<10^5$ copies/ml |
| Liver biopsy (histological activity index) | > OR = 4# | < 4 |

* No clinical or histological evidence of cirrhosis; this group is further subdivided into HBeAg positive chronic hepatitis B (HBeAg positive and anti-HBe negative) and HBeAg negative chronic hepatitis B (HBeAg negative and anti-HBe positive) forms.

** HBV DNA levels measured using a quantitative method (for example, quantitative polymerase chain reaction assay) or testing positive with a method other than polymerase chain reaction (for example, hybridisation assay) with sensitivity in the range of 105 copies/ml.

# Necro-inflammatory score [8].

hepatitis B have viral replication, high HBV DNA concentrations, and biochemical evidence of hepatitis. Chronic Hepatitis B is either HBeAg positive or HBeAg negative. The HBeAg negative patients may lack detectable HBeAg despite a high rate of viral replication and high HBV DNA levels; this paradox arises from a mutation (pre-core mutation), which permits viral replication but prevents production of HBeAg. HBeAg negative chronic Hepatitis B has a poorer prognosis and treatment response than does HBeAg positive chronic hepatitis.

### *Indications to treat*

In acute Hepatitis B, among previously healthy children who present with clinically apparent disease, recovery occurs in approximately 99%. Patients in inactive carrier stage do not need treatment, since their liver disease progresses very slowly. The risk of developing HCC in these patients, though higher than in people without infection, is much lower than in HBeAg positive patients. Their alanine aminotransferase levels should be determined every 6-12 months [9], and every two years they should be screened for HCC with ultrasonography and $\alpha$-fetoprotein levels [8]. Raised alanine aminotransferase in such patients may indicate HBeAg negative chronic hepatitis B and should prompt assessment for HBV replication (HBV DNA testing) and for other unrelated causes of liver injury (other hepatotropic viruses, drugs etc).

Only those patients who have chronic Hepatitis B (active HBV replication with a high viral load and ongoing necro-inflammation) qualify for treatment. Patients with chronic HBV infection (HBsAg positive for >6 months), alanine aminotransferase persistently exceeding twofold higher than normal, HBV DNA $>10^5$ copies/mL, and histological activity index >4 are the most suitable candidates for treatment. It is advisable to wait till transaminase has been raised for one to three months, in order to allow time for the spontaneous viral clearance that occurs in a sizeable proportion of such patients [8-10]. In patients with ongoing viral replication and normal transaminase concentrations, response rate is quite poor; in such patients alanine aminotransferase should be measured every three months, and they should be treated if raised concentrations persist [11].

## Initial evaluation

Patients with chronic HBV infection should undergo a detailed evaluation to assess baseline liver function and the need for further treatment and follow up as shown in box 1.

## Treatment goals

The initial goals are to suppress HBV replication and induce remission of the liver disease. The ultimate goals are to eliminate HBV, prevent progression to cirrhosis and HCC and improve survival.

**Box 1: Initial evaluation of a patient with chronic HBV infection.**

- History and physical examination
  - I. Symptoms and signs of portal hypertension (abdominal wall collaterals, splenomegaly, hypersplenism, ascites)
  - II. Liver failure (jaundice, haematemesis, ascites, encephalopathy, etc)
- Laboratory tests: Liver function tests (amino-transferases, serum albumin, prothrombin time, serum alkaline phosphatase); complete blood counts, renal function tests
- Screen for oesophageal varices (upper gastrointestinal endoscopy)
- Screen for HCC (ultrasonography and $\alpha$-fetoprotein levels)
- Tests for viral replication status (HBeAg, anti-HBe, HBV DNA {HBVDNA})
- Screen for co-infection with other parenterally transmitted viruses (anti-hepatitis C virus antibodies, HIV serology)
- Liver biopsy

## Treatment end points

Response to treatment is expressed as a combination of the specific aspects of response studied (biochemical or alanine aminotransferase levels, virological or viral DNA levels, or histological activity), and the time of assessment in relation to treatment.

## Treatment options

Interferon alfa (IFN-$\alpha$) and lamivudine (Lam) are

**Box 2: Treatment end points.**

| | |
|---|---|
| **Treatment responses** | |
| Biochemical response | Return of alanine aminotransferase to within normal range |
| Virological response | Decline in HBV DNA to < 10 copies/ml |
| Serological response | HBeAg loss and appearance of anti-HBe |
| Histological response | Decrease in necro-inflammatory score by 2 points |
| **Time frame for assessment of response** | |
| On-treatment response | Response assessed while receiving treatment |
| End of treatment response | Response assessed at the end of treatment duration |
| Sustained response | Response after a period off drugs (6 months or 12 months) |

currently the only FDA-approved treatment modalities for children with chronic HBV infection. Of these, IFN-$\alpha$ has both antiviral and immunomodulatory activity, while Lam is primarily antiviral. While treatment with standard IFN-$\alpha$ requires daily subcutaneous injections and shows immediate peaks followed by zero-levels, pegylated interferon (peg-IFN) has a constant serum concentration level and seems to provide better viral clearance than IFN-$\alpha$ [12]. Pediatric data on treatment with peg-IFN in hepatitis B however is limited and further trials are eagerly awaited.

## Interferon

IFN-$\alpha$, a host cytokine produced in response to any viral invasion, has immunomodulatory, antiviral, and anti-fibrotic properties. It was first used in the 1980s and was the first drug to be found useful in the treatment of chronic hepatitis B.

**Dosage:** 6 MU/ $m^2$ (million units per meter square body surface area) given subcutaneously thrice weekly.

**Duration of treatment:** in cases of HBeAg positive cases it should be given for 16- 24 weeks. In case with HBeAg negativity it should be given for at least 12 months. Longer duration of treatment may increase the rate of sustained response.

**Side effects:** An influenza-like illness (fever, chills, headache, malaise, myalgias) occurs in 25-30% of patients but rarely needs discontinuation of treatment. More serious adverse events (myelosuppression (leucocytes <1000/$\mu$L and platelets <60,000/$\mu$L), emotional lability and depression, development of autoantibodies and thyroid dysfunction may lead to discontinuation of interferon; thus, pretreatment screening for low leucocyte and platelets counts, autoantibodies, and thyroid function is mandatory. The frequency of subcutaneous injections, side effects and the high cost have prompted search for other treatment options.

## Lamivudine

Lam, a synthetic nucleoside (cytosine) analogue available since 1998, undergoes intracellular phosphorylation to its active metabolite lamivudine triphosphate and inhibits viral reverse transcriptase, causing premature chain termination during viral DNA synthesis.

**Dosage:** 3 mg/kg/day (max up to 100 mg/day).

**Duration of treatment:** It should at least be given for one year.

**Side effects:** Reduce dose with renal impairment; if on hemodialysis, administer afterwards; common adverse effects include headache, tiredness, dizziness, and nausea; may elevate liver enzyme levels; may cause lactic acidosis; severe acute exacerbations of Hepatitis B may occur in patients who discontinue Antihepatitis B therapy.

The experience with Lam in children is limited. One controlled trial involved 286 children, ages 2 to 17 years, with ALT >1.3 times normal. They were randomized in a 2:1 ratio to Lam (doses mentioned above) or placebo for 52 weeks. In this trial, HBeAg conversion developed in a higher proportion of treated than the placebo (23% vs 13%). As in adults, the seroconversion rate was higher among children with ALT >2 times the normal (34% vs 16%). In this trial 18% of children developed Lam resistant mutants. Increasing duration of treatment leads to increased proportion of patients developing a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) motif in the catalytic domain of viral DNA polymerase, which confers Lam resistance (14% at one year to 69% at five years), which affects the disease course adversely. Higher pretreatment alanine aminotransferase levels predict a higher response rate; HBV DNA levels do not influence response to Lam. Lam treatment in HBeAg negative chronic hepatitis B is associated with less durable responses and a higher rate of emergence of YMDD mutants (60% at four years) [13]. Therefore in spite of effective oral therapy, less costs and better tolerance, Lam must be used cautiously in children and treatment indications should be followed carefully due to the emergence of resistant strains.

## Adefovir

Adefovir dipivoxil, a nucleotide analogue of deoxyadenosine monophosphate, inhibits viral reverse transcriptase activity in both wild-type and YMDD mutant HBV [14]. Thus; it is the drug of choice for patients treated with Lam who have developed YMDD mutation. It has also been used in patients with HBeAg positive chronic hepatitis B [15] and HBeAg negative chronic hepatitis B [16], with efficacy rates at one year similar to those with Lam, albeit with no drug resistant mutations. Adefovir may thus be a useful alternative to Lam though further data is needed and pediatric trials are ongoing. Recently, adefovir resistant mutants of HBV have been described and their clinical importance must be evaluated.

## Drugs in the near future

Drugs that are of interest in the future apart from Lam and adefovir dipivoxil, include antiviral agents like emitricitabine, entecavir, clevudine, $\beta$-L-thymidine and telbivudine. Other than that the time regimen and recommendations on combination treatment shall be decisive on the outcome and avoidance of mutant viruses.

## Treatment of Hepatitis C

A hundred million people are believed to be infected with chronic HCV infection worldwide and the number of children affected is difficult to estimate since they often

have an asymptomatic presentation. It is the most common cause of post – transfusion and community acquired non-A, non-B hepatitis and cryptogenic cirrhosis worldwide [17]. Although the natural history of HCV infection in children is not well characterized, almost 50-80% will progress to chronic hepatitis among vertically infected and blood transfusion acquired Hepatitis C cases. Children have been reported to have a lower viral load, lower ALT values and milder histological derangement as compared to adults with chronic HCV infection. There is limited knowledge however about the natural history of HCV infection in children and thus, there have been apprehensions about the management and choice of drugs in this young age group. Just recently published data of current studies has now been able to give an insight towards which direction we are moving and long-term study results are awaited.

A dilemma is when to label a child as a case of chronic Hepatitis C since the natural history and immunological response is very variable. While treatment goals are to eradicate Hepatitis C virus (HCV) by complete loss of HCV RNA from liver and serum, to decrease progression of liver disease as well as reduce frequency of HCC and improve survival, selecting the ideal time of initiating therapy poses a challenge. Generally, patients with evidence of ongoing infection (HCV RNA positive), elevated transaminases more than twice the normal value and evidence of histological liver disease should be started on therapy, as studies suggest that significant liver disease may occur and timely initiation of treatment might be beneficial in the longer run [18]. Direct correlation between HCV seropositivity and extent of liver disease is not always present and serum AST/ALT levels may in fact be normal in spite of histological evidence of inflammation [19]. The definitions used to assess Hepatitis C treatment and responses are listed in Box 3.

**Box 3: Definitions used to assess hepatitis C therapy.**

| | |
|---|---|
| Virological response: | Absence of detectable HCV RNA in the serum by an assay with a sensitivity of atleast 100 copies (50 IU) per mL |
| Sustained virological response: | Virological response at the end of treatment and 6 months afterwards |
| Early virological response: | Lack of detectable HCV RNA or a greater than 2 log unit drop in HCV RNA level during first 12 weeks of therapy. |
| Relapse after therapy: | Virological response at the end of treatment followed by subsequent detectability of HCV RNA in the 24 weeks after the end of treatment. |
| Late virological relapse: | Appearance of detectable HCV RNA more than 6 months after treatment in a patient with a 6-month post treatment SVR |
| Non-response: | Continued presence of detectable HCV RNA at the end of treatment |

## Goals of treatment

The aims of specific therapy in chronic Hepatitis C are

- Improvement in liver pathology
- decrease in the risk of carcinogenesis and also
- a reduction of infectivity

The goal of therapy is the clearance of viraemia and concomitant ALT normalization persisting after therapy withdrawl. The availability of markers of HCV replication (e.g., HCV RNA) is essential for monitoring response to therapy.

## Combination treatment Interferon with Ribavirin

Just this year in 2005 the U.S. Food and Drug Administration has approved treatment of chronic HCV infection in children (3-17 years) with a combination of IFN $\alpha$2b and ribavirin [18]. Ribavirin is a synthetic combination of nucleoside analogues, which interferes with DNA and RNA synthesis. It results in biochemical improvement (normalisation of ALT levels), but does not produce a virological response as monotherapy. However, a combination of ribavirin with IFN results in a higher sustained response as compared to IFN monotherapy in adults [20,21]. Although large, randomised controlled trials of combination therapy in children are lacking, some studies have suggested that sustained response is higher with this combination in children also [22-25]. Suoglu, *et al.* treated 22 pediatric patients with either IFN $\alpha$ monotherapy (10 patients) at 3 million IU/m$^2$ thrice weekly or peg-IFN (same dose) with ribavirin 15 mg/kg/day in two divided doses (12 patients) [31]. Two patients in each group stopped treatment due to side effects and sustained response was observed in 3/10 (30%) and 6/12 (50%) of the patients in monotherapy and combination therapy group, respectively. Woynasowski, *et al.* have also reported similar results from their study of 35 pediatric patients with sustained response of 18-36% in monotherapy group and 70% in combination therapy group [22]. Another study (uncontrolled) of 12 children has reported a 50% sustained response at 6 month [24]. Bunn, *et al.* used $\alpha$ 2b (3 MU/m$^2$ s.a. thrice weekly) combined with varying doses of ribavirin (either 8, 12 or 15 mg/kg body weight daily) in 61 children between 5-11 year of age. The dose-dependent anemia from ribavirin was less severe in children than in adults and the pharmacokinetics of the drugs were similar. The overall SVR was 38% (31%

in genotype 1) and ribavirin dose of 15 mg/kg was associated with highest virological response and similar toxicity compared to lower dose [21]. The results of these preliminary studies suggest that the combined virostatic therapy with IFN and ribavirin is a promising and safe treatment approach for children.

## Pegylated interferon

Peg-IFN is currently standard treatment for adults in combination with oral ribavirin. While there is limited data on treatment with peg-IFN in children with HCV, results of an ongoing study with peg-IFN $\alpha$2a in combination with ribavirin are eagerly awaited.

IFN-$\alpha$ may be modified into covalent attachment of a polyethylene glycol moiety to enhance its circulating half-life and remove its immunogenicity. This leads to sustained blood levels, improves its tolerance and compliance to therapy. Peg-IFN is given once a week subcutaneously. Two peg-IFNs are now undergoing trials viz, Peg-IFN $\alpha$2a and Peg-IFN $\alpha$2b. These two have different half-lives and metabolism and elimination rates differ. Initial trials demonstrated that monotherapy with Peg IFN (both Peg-IFN $\alpha$2a and Peg-IFN $\alpha$2b) improved sustained response rates compared to standard interferons. Even in patients with liver cirrhosis, good sustained virologic response was achieved. A meta analysis reported that ranges of SVR rates were higher with Peg-IFN than standard IFN-monotherapy in adult naive patients (10-39% vs 3-19%).

## Predicting response to antiviral drugs

Factors associated with sustained virological response are enumerated in box 4 and a suggested monitoring flow chart is given in box 5.

In spite of being able to see some direction in where we are heading in the treatment of chronic hepatitis in children, the fact remains that children react differently to chronic hepatitis viruses than adults and their treatment must be tailored accordingly. Treating children remains a challenge and preventive measures remain on the priority list.

**Box 4: Factors associated with a sustained virological response.**

| | |
|---|---|
| ***Baseline*** | |
| *Viral* | • Non - 1 genotype<br>• Lower HCV RNA level |
| ***Disease related*** | |
| | • Absence of bridging fibrosis or cirrhosis<br>• Higher ALT quotient (ratio of ALT to upper limit of normal range) |
| ***Host factors*** | • Lower bodyweight<br>• Lower surface area<br>• Younger age |
| ***On treatment*** | |
| *Viral* | • Early virological response |
| *Adherence* | • >80% of intended treatment for >80% of intended duration. |

**Box 5: *Monitoring during therapy.***

I. Viral genotype determination prior to treatment.

II. Patients with genotype 2 or 3 to be treated for 24 weeks; 12-weeks assessment of EVR not required.

III. Patients with genotype 1 to have quantitative HCV RNA level determined at start of treatment and 12-weeks later, using the same assay.

IV. EVR at 12 weeks, complete full 48-week treatment.

V. No EVR at 12 week, discontinue treatment.

VI. EVR at 12 week but still HCV RNA positive, retest by qualitative PCR at 24 week. Stop therapy if HCV positive.

VII. SVR to be determined 6 months after completing treatment

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