

# HEPATITIS B

## Treatment Options for Children with Hepatitis B

*Updated 2007*

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When given the news that their child has chronic hepatitis B, the first question many parents ask is what treatment is available to eradicate the virus and prevent or slow liver disease?

Normally, chronic hepatitis B is a mild disease in children and teens. Often, young people experience an immune tolerant stage during the first two to three decades of infection, during which there is little damage to their livers. As a result, the incidence of liver inflammation, scarring, cirrhosis and liver cancer is low in children and adolescents.

However, in some children, the virus rapidly replicates and causes extensive liver damage when the child's immune system attacks infected liver cells. It is these children who may need immediate medical intervention from the small arsenal of drugs currently available to halt this liver disease.



The goals of treatment in children and adults have been to:

- strengthen the immune system so that it can effectively attack the infection
- prevent the virus from replicating
- halt any liver damage
- spur the immune system to create the hepatitis B e antibody (HBeAb)
- produce the surface antibody (HBsAb), which signifies complete recovery from the infection.

In addition to slowing liver disease in children, medical researchers have a long-term goal in mind: eradicating the disease in the pediatric population today will prevent cirrhosis and liver cancer in the adults of tomorrow.

Despite a natural tendency to utilize whatever medical tools are available to fight this disease, to date, the treatments available for hepatitis B infection in children have had limited success.

There are only a handful of pediatric clinical trials taking place to test drugs that so far have been used only in adults. Few studies have followed large numbers of children with chronic hepatitis B infections and fewer yet have tracked children a decade or more after treatment.

When to treat hepatitis B in children is an area of debate within the medical research and treatment communities. However, in 2007, the American Association for the Study of Liver Diseases (AASLD) published their Chronic Hepatitis B Practice Guidelines to provide flexible, data-supported treatment recommendations to physicians and other healthcare providers.

### **What Treatments Are Available For Children Today**

When reading this section, please keep in mind that most of the following information deals with loss of e antigen, not surface antigen. Loss of surface antigen and development of surface antibody signals complete recovery from infection.

Loss of e antigen is important but is not a cure.

The development of hepatitis B surface antibody is the ultimate goal of treatment, but that does not occur very often with today's treatment options.

As of June 2007, standard interferon and lamivudine are the only drugs approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis B in children. The AASLD guidelines indicate that it is appropriate to treat children with either interferon or lamivudine when alanine aminotransferase (ALT) levels have been greater than two times normal for longer than six months.

#### Standard Interferon

Interferons are naturally occurring proteins that spur the immune system to fight viral infections and tumors. Synthetic or "conventional" interferon has been the most studied drug for treatment of chronic hepatitis B infection in children and adults. It has been used to treat adults since 1991, and it was the first FDA-approved treatment for children infected with the hepatitis B virus (HBV).

It is administered for six to twelve months in three weekly injections, which parents generally learn to administer at home on their child.

Historically, interferon has been used in children who were experiencing noticeable liver damage, including elevated liver enzymes, or ALTs. These enzymes are released when liver cells are damaged. Doctors often wait until a child's ALT levels are greater than twice the normal limit for longer than 6 months before trying treatment.

But this type of interferon has proven to be a lackluster performer. Interferon generally has been found to produce the loss of hepatitis B e antigen (HBeAg) in approximately 33 percent of treated children. It is even less effective among children who have normal ALT levels; interferon produces HBeAg clearance in only 10 percent of those cases.

Various studies published between 1997 and 2004 have shown that 80 to 90 percent of patients who achieved HBeAg clearance with treatment sustained that response for four to eight years, resulting in a decreased risk of hepatic decompensation later in life. *Hepatic decompensation* means the liver becomes less able to compensate for injury or damage; so, with e antigen clearance, hepatic decompensation is less likely to occur.

Doctors have found that interferon works best in helping children clear HBeAg and reduce the amount of HBV DNA circulating in their bloodstream only if children have elevated ALT levels. Interferon has proven ineffective in children with normal or only slightly elevated liver enzymes.

Elevated ALT levels appear to indicate that the immune system has noticed the virus and gone on the attack. The interferon is effective only if the immune system is already engaged in war against the virus.

But interferon doesn't work in everyone, and it can cause some serious side effects, including fever, flu-like symptoms, growth impairment during the treatment phase, and anxiety and depression.

According to the 2007 AASLD guidelines, if a child fails to respond to standard interferon treatment, he or she can be retreated with lamivudine if ALT levels continue to be elevated to greater than two times normal.

### Lamivudine (Epivir)

In 2000, the FDA approved lamivudine, sold under the brand name Epivir, for children infected with hepatitis B. This drug is a nucleoside analog (artificial genetic material that prevents viral replication) that was originally developed to treat patients infected with HIV.

Administered as a pill or oral solution, lamivudine works by inhibiting the HBV polymerase, the viral enzyme that helps the virus replicate. When the number of viruses in the liver is reduced, liver damage and inflammation also decline.

While lamivudine rarely offers a permanent or complete cure, it appears to safeguard the liver while a patient is taking it. The 2007 AASLD guidelines state that an optimal daily dose for children is 3 mg per kilogram of body weight for one year.

After the first year of treatment, laboratory testing for HBeAg seroconversion should be done, to confirm loss of HBeAg and appearance of HBeAb. Seroconversion occurs when people develop e antibodies to the e antigen, seroconverting from antibody-negative to antibody-positive. The same holds true for surface antigen/antibody.

If lab work shows that HBeAg seroconversion has occurred, lamivudine treatment should continue for six more months.

If HBeAg seroconversion hasn't occurred after one year of lamivudine treatment, the AASLD guidelines suggest therapy can continue for a second year.

Studies reported in the *New England Journal of Medicine* in 2002 showed that 23 percent of children treated with lamivudine responded and lost HBeAg after one year of treatment compared to an HBeAg seroconversion rate of only 13 percent in untreated children.

Additional data from *Hepatology* in 2006 showed HBeAg seroconversion rates increased to 34 percent after children completed a second year of treatment.

Of those who do experience HBeAg seroconversion with lamivudine treatment, relapses are expected to occur within one year of treatment completion in up to 30 percent of patients.

Another study published in 2003 in *Clinical Infectious Diseases* demonstrated an HBeAg seroconversion rate of 50 percent in children after completing one year of treatment.

All of these seroconversions also exhibited normalization of ALT levels. Of the 50 percent who did not demonstrate HBeAg seroconversion after completing one year of lamivudine treatment, 63 percent exhibited normalization of ALT levels.

Three factors have been identified as predictors for successful HBeAg clearance with lamivudine treatment:

- higher ALT levels
- low serum HBV DNA load prior to initiation of therapy
- older age at the initiation of therapy

Besides the convenience of a once-a-day tablet or a liquid oral solution, lamivudine has fewer and less severe side effects than interferon. The most common side effects observed in the above studies were fatigue, headache, nausea and abdominal pain.

But, lamivudine has some notable drawbacks:

- ALT levels and the volume of viruses (HBV DNA) in the bloodstream appear to decline only while lamivudine is taken. When patients stop taking lamivudine, their ALT levels and HBV DNA often climb again. Basically, lamivudine works but often the gains are lost once treatment ends.
- Some patients who lost HBeAg and produced HBeAb while treated with lamivudine relapsed when treatment ended and the HBeAg returned. The relapse rates vary, depending on length of treatment and a patient's genotype of the virus.
- While lamivudine is effective against most hepatitis B viruses, use of the drug is also associated with lamivudine-resistant YMDD virus mutations in the hepatitis B virus. The AASLD guidelines indicate the risk of mutation development increases the longer one uses lamivudine, ranging from 19 percent after one year of treatment to 49 percent after two years of treatment, to 64 percent after three years of treatment. Resistant YMDD mutations are difficult to treat and they can result in replication of the mutated virus and acute exacerbations of liver disease.

Dr. Philip Rosenthal, Professor of Pediatrics and Surgery, Medical Director of the Pediatric Liver Transplant Program, and Director of Pediatric Hepatology at UCSF, agreed with the AASLD findings and added, "In adults, if YMDD (mutation) occurs, adefovir is added to the treatment regimen. In children, adefovir is not approved, so this (development of YMDD in a child) is a problem."

Consequently, he suggests that "once a child has had one year of lamivudine, it is time to consider stopping the drug before development of YMDD mutants."

Although not yet FDA approved for pediatric treatment, adefovir dipivoxil, a nucleotide drug, is sometimes used to treat the resistant YMDD variant commonly caused by longer periods of lamivudine treatment. Kidney damage has been associated with high doses of adefovir, so low doses are given and kidney functions are frequently tested throughout the treatment period.

Most physicians discontinue lamivudine once the YMDD mutation emerges as the dominant virus. There is some concern that after discontinuation of treatment, some patients experience ALT “flares” as the virus rebounds, no longer restrained by lamivudine’s antiviral action.

Although AASLD guidelines discourage use of combination therapies, studies combining lamivudine with interferon are ongoing to determine if this therapy can keep the viruses from replicating while simultaneously bolstering the immune response to the infection.

### Use of Combination Treatments

Given the mild to moderate success of lamivudine and interferon when taken alone, researchers have tried a combination of the two against hepatitis B. They hoped the double-whammy of boosting the immune system with interferon combined with the antiviral action of lamivudine would deliver a fatal, one-two punch to the virus.

The AASLD guidelines do not recommend use of interferon and lamivudine in combination. Data from five large adult studies occurring between 2000-2005 confirmed interferon and lamivudine combined were more effective than using lamivudine alone, but not more effective than using interferon alone.

In 2007, Dr. Kathy Schwarz, Director of the Pediatric Liver Center at Johns Hopkins University, stated that “combination treatments should not be given to children outside of clinical trials (because) there are no FDA-approved combination treatments.” However, she adds “My opinion is that these treatments are certainly worthy of clinical trials.”

Many researchers continue to experiment with the lamivudine and interferon combination treatment. One of the first groups of researchers to try the combination in HBV infected children was a group of Turkish doctors who reported their findings in the Pediatric Infectious Disease Journal in 2001.

They tried two durations of combination treatment: six months of treatment in 30 children and 12 months of treatment in 27 children. They administered fairly high doses of both interferon (10 MU/m<sup>2</sup> of body surface) and lamivudine (4 mg/kg of body surface, with a maximum 100 mg dose).

In the group treated for six months, 33 percent cleared HBeAg at the end of the treatment period. Six months after treatment ended, an additional 4 percent of patients had cleared the HBeAg.

In the group treated for 12 months, 59 percent cleared HBeAg at the end of treatment. Six months after treatment ended, the HBeAg had returned in only 3 percent of the patients.

About 96 percent of both groups had undetectable levels of HBV DNA six months after therapy ended, and everyone maintained normal ALT levels six months after treatment.

Twenty percent of the entire group treated for six months, and 37 percent of the group treated for 12 months achieved complete clearance of the virus—they cleared not only the HBeAg, but also the HBsAg and produced the HBsAb.

While the combination of interferon and lamivudine appears more effective in producing a sustained HBeAg seroconversion, its success rate is not outstanding and researchers are looking for more effective types of interferon and antiviral agents with which to vanquish the virus, including those that vanquish all viruses, including the YMDD mutants.

A second study in Turkey that compared children treated with only interferon against a group treated with the combination of interferon and lamivudine found that, while the combination therapy had a more beneficial effect than interferon alone in normalizing ALT and clearing HBV DNA, the response rate at six months after the therapy ended was not statistically significant between the two groups.

*A Management of Hepatitis B 2006* report by Dr. Jean Molleston cited several small pediatric combination interferon/lamivudine studies that were originally published between 2002 and 2006.

These studies demonstrated a 55 percent HBeAg seroconversion rate and loss of detectable HBV DNA compared to a 33 percent HBeAg seroconversion rate with interferon alone, and a 34 percent HBeAg seroconversion rate with lamivudine alone.

The report states that combination treatment resulted in a 22 percent HBeAg seroconversion rate among a group of Asian children who had normal ALT levels compared to a 10 percent HBeAg seroconversion rate with interferon used in children with normal ALTs, and a 19 percent HBeAg seroconversion rate with three years of lamivudine treatment used in subjects with normal ALTs.

## **Other Drugs That Have Been Approved to Treat Adults**

Between 2002 and 2006, another interferon drug, a nucleotide drug, and two nucleoside analog drugs were approved by the FDA to treat chronic hepatitis B in adults. In the U.S., any new drug must first gain approval for use in adults before drug makers can plan pediatric clinical trials.

Any combination usage of the drug, such as combining an interferon drug with a nucleoside analog drug must also win approval from the FDA. Many of these newly-approved adult drugs are being studied for use in children.

### Pegylated Interferon

Pegylated interferon was approved for treatment for adults in 2005. In June 2006, Dr. Rosenthal reported at the B Informed Patient Conference that pediatric trials for this drug had not yet been planned in the US. Many doctors and parents are anxiously waiting to see how effective this new formulation of interferon will be in boosting a child's immune system that is trying to clear the virus.



While conventional interferon is administered in three weekly injections—traumatic for parents and children alike—pegylated interferon requires only one weekly injection.

Pegylated interferon is formulated so it remains in the body longer, and ideally the immune-boosting interferons remain at a more consistent level in the bloodstream over the course of a week.

What is interesting from a pediatric perspective is that this interferon formula has proven effective in adults who have the HBeAg, high HBV DNA levels and normal ALT levels. These three characteristics are common in children who are in the immune tolerant stage of the infection.

In a study reported at the AASLD meeting in 2002, two groups of adults with HBeAg, high HBV DNA levels and normal ALTs were given either pegylated interferon or conventional interferon.

At the end of 48 weeks, 25 percent of those given pegylated interferon had lost HBeAg and dramatically reduced their HBV DNA, compared to 12 percent who had been given conventional interferon.

When only the loss of HBeAg is examined in this group of 194 adults, 44 percent of those receiving pegylated interferon lost HBeAg, compared to 17 percent treated with regular interferon.

### Adefovir (Hepsera)

In 2002, the FDA approved the first nucleotide analog drug, adefovir dipivoxil, marketed as Hepsera, for treatment of hepatitis B in adults. Clinical trials for use of this drug in children were in process in 2007.

Adefovir is a daily pill that works similarly to lamivudine. Both are antiviral medications that work by preventing viruses from reproducing.

But adefovir has an important advantage: it appears to be quite effective against all hepatitis B viruses, even the lamivudine-resistant YMDD mutation. Compared with lamivudine, resistance rates for adefovir are significantly lower. While lamivudine resistance rates are 64 percent after 5 years of treatment, adefovir's resistance rate is 11 percent after 3 years of treatment, and 29 percent after 5 years of treatment, according to data published in 2005 in *Hepatology*.

Adefovir also offers another benefit—it appears effective against the hepatitis B viruses that are able to replicate without secreting HBeAg. This other type of viral mutation is found most frequently in Asians and often emerges in adults when the immune tolerant stage ends and their immune systems try to clear the virus.

The immune system has a hard time identifying and zeroing in on this type of hepatitis B infection, which is called HBeAg-negative hepatitis.

In a study reported in the February 2003 issue of the *New England Journal of Medicine*, two-thirds of a group of 185 patients with HBeAg-negative hepatitis were given adefovir. The one-third not given adefovir was treated as the control group.

At week 48, 64 percent of patients showed improvements, compared to 33 percent of the untreated control group. HBV DNA levels dramatically declined in the group treated with adefovir, while those in the control group remained unchanged.

ALT levels had normalized at week 48 in 72 percent of patients receiving adefovir, compared with 29 percent of those without treatment.

Among patients who went on to complete 4 to 5 years of treatment in the study, ALT levels were maintained in 70 percent, and HBV DNA was undetectable in 65 to 67 percent of the cases.

The researchers concluded that patients with HBeAg-negative chronic hepatitis B infection showed significant histologic, virologic, and biochemical improvement, with few signs of an adefovir-resistant mutation emerging.

Several studies presented at the 2002 AASLD conference found adefovir was also effective in targeting the virus's genetic material, the cccDNA, which is believed to play a critical role in the rugged persistence of the virus.

The only potential problem that researchers are aware of at this time is that adefovir can cause kidney problems when administered at high doses. This potential renal toxicity makes the process of establishing safe dose levels in children critically important.

Dr. Rosenthal explains that the good news is "most children in need of therapy do not have significant renal issues." He does not foresee any significant examples of this side effect.

However, like lamivudine, when adefovir is no longer administered in adults, ALT levels and HBV DNA levels tend to rebound.

Adefovir also appeared to work best in patients who had elevated liver enzymes.

### Entecavir

In April 2005, the FDA approved entecavir, a nucleotide analog, for adult treatment. After adefovir, this may be the next drug approved for treatment of children with hepatitis B. As of April 2007, several centers in the United States were in the early stages of recruitment for initial pediatric trials for entecavir.

Entecavir is currently considered the most powerful antiviral for chronic hepatitis B. Compared to lamivudine, entecavir has demonstrated superior effectiveness in reducing HBV DNA levels in patients with and without HBeAg, according to a Phase II study report published in *Gastroenterology* in 2005.

The 24-week randomized, double-blind study was conducted in 169 patients in China, Malaysia, the Philippines, Belgium, Canada and the United States.

In a phase III trial, reported in *Gastroenterology* in 2006, entecavir reduced HBV DNA more effectively than lamivudine in both HBeAg positive and HBeAg negative patients.

In adult patients treated with entecavir at 0.5 mg/day, 83.7 percent had an HBV DNA level below the lower limit of detection, compared with 57.5 percent treated with 100 mg/day of lamivudine.

However, few patients achieved HBeAg loss and/or seroconversion by week 22. More patients treated with entecavir achieved normal ALT levels than with lamivudine.

Entecavir is associated with the lowest rate of drug resistance. It suppresses both the lamivudine-resistant and the adefovir-resistant viruses.

Entecavir was well tolerated by adults and most adverse events were mild to moderate and temporary.

It is important to note that this drug can cause extreme damage to the liver and lactic acidosis, a build-up of acid in the blood.

### Telbivudine (LdT)

In October 2006, telbivudine (Tyzekda), a nucleoside analog, was approved for treatment of hepatitis B in adults. Telbivudine is another antiviral compound that inhibits HBV replication by interfering with its DNA polymerase.

In clinical trials, telbivudine exhibited antiviral qualities that suppressed the hepatitis B virus and decreased liver inflammation at rates comparable to lamivudine.

Telbivudine is effective against lamivudine-resistant mutations and is associated with lower rates of drug resistance compared with lamivudine; however, compared to adefovir and entecavir, its resistance rates are higher, and like lamivudine, the resistance rates increase with duration of treatment.

Most of the drug's reported side effects were mild to moderate, with the most common side effects being fatigue, abdominal pain, cough and an elevated creatinine phosphokinase (CPK), which is an enzyme in muscle tissue that enters the blood stream when muscle tissue is broken down.

The telbivudine phase IIb study includes a design to evaluate the safety and effectiveness of a combination of telbivudine and lamivudine.

### **When Should a Child Be Treated?**

Because of the scant medical treatments available, doctors have usually treated only the children who had clear signs of liver disease—those whose liver enzyme levels were at least double what is considered normal in children.

Also, it was primarily children with elevated ALT levels who responded to interferon or lamivudine treatment, thus reinforcing the belief that only those with elevated ALT levels should receive treatment.

The AASLD guidelines suggest that treatment is not indicated in HBeAg positive patients who have normal ALT levels.

Guidelines recommend lab testing for HBeAg, HBV DNA, and ALT levels at 3-6 month intervals and initiation of treatment only if ALT levels rise to greater than two times the upper limit of normal for 6 months, or if the individual is over the age of 40.

According to authors Chu and Liaw in the *Journal of Viral Hepatitis*, 90 percent of infected children will spontaneously clear the HBeAg and produce HBeAb between the ages of 15 and 35. But meanwhile, the virus can damage their livers—and cause scarring and set the stage for liver problems later in life—even when liver enzyme levels are normal.

A researcher in England had some surprising successes treating children with chronic hepatitis B who were asymptomatic and had no obvious sign of active liver damage.

Dr. Giordina Mieli-Vergani, Alex Mowat Professor of Paediatric Hepatology at the Institute of Liver Studies, Kings College Hospital in London, treated 23 children who had normal ALT levels with lamivudine and interferon and found that after one year:

- five patients (22 percent) cleared the HBeAg and developed HBeAb
- of these five, four cleared the virus and the infection completely and developed surface antibodies

Dr. Mieli-Vergani began researching in the mid-1990s whether asymptomatic children could be treated. In a study published in *Hepatology* in 1996, she and other researchers described an innovative approach that set the groundwork for her later work with asymptomatic children.

The researchers “primed” or administered prednisolone (a steroid similar to prednisone) followed by interferon-alpha treatment in 34 children. They administered only interferon in another 30 children, and had a control or untreated group of 31 infected children.

Nearly all of the children, even those with normal ALT or AST levels, had received liver biopsies that showed some liver inflammation before treatment began.

After treatment, researchers found that of the 20 children with normal liver enzymes, 5 of the 11 children (with normal ALT/AST levels) who had been pretreated with steroids seroconverted and produced HBeAb.

Only one of the nine who received interferon but was not pre-treated with steroids seroconverted.

Of 50 children with slightly elevated or normal liver enzymes, 16 of them seroconverted compared to two out of 31 children in the untreated group.

For the first time, researchers noticed that even children with normal or only slightly elevated liver enzymes could benefit from treatment.

Next, Dr. Mieli-Vergani tried a new approach with 23 children (8 boys and 15 girls, 16 of Asian descent, avg. age 10) who had been infected with HBV during the first year of life. Liver biopsies were performed on all the children and showed only mild inflammation in most patients and minimal fibrosis (scarring) in a few patients.

Except for two children, these children all had normal or only slightly elevated liver enzymes and all tested positive for:

- surface antigen (HBsAg)
- e antigen (HBeAg)
- and HBV DNA

First, the group was pretreated for eight weeks with just lamivudine, then Dr. Mieli-Vergani added conventional interferon for 44 weeks of combination treatment.

At the end of the 52 weeks of treatment, of the 23 children:

- 22 percent (5 patients) seroconverted and developed HBeAb.
- 17 percent (four of the five who developed the e antibodies) also completely cleared the virus, developed the surface antibody and have remained negative for HBV DNA long-term.

- 82 percent (19) of those treated had no HBV DNA at the end of treatment. (HBV DNA eventually rebounded in all but five children after treatment with lamivudine stopped.)

Among the five who responded to the combination treatment, four were of Asian descent. All five had started treatment with normal liver enzymes and four had HBV DNA of less than 1,000 pg/ml when treatment began.

There was no control arm, or untreated group of children in this trial.

Does this study suggest asymptomatic children with normal liver enzymes and the HBeAg should be treated? Dr. Mieli-Vergani is careful in her response, “We need more studies in these children before saying how they should be treated,” she said. But she points out that children do tolerate interferon better than adults, and it is important to hasten the HBeAg seroconversion and produce antibodies in children as soon as possible to lessen the chance of liver damage.

In 2006, Mieli-Vergani’s research focused on using lamivudine in combination with interferon to treat immunotolerant children who have been perinatally infected with HBV. In a pilot study reported in *The Journal of Pediatrics*, 23 eligible subjects recruited from a chronic HBV infection database of 202 were accepted into the study. Eligible subjects were accepted according to the following criteria:

- infection had to have been acquired perinatally
- ages had to be between 2-16 years old
- HBsAg and HBeAg had to be positive for at least one year
- HBV DNA had to be positive twice during the previous year
- normal or nearly normal ALT levels

These patients were initially given lamivudine 3mg/kg daily (not to exceed 100mg/day) for eight weeks in an effort to lower HBV DNA. After eight weeks, interferon was added to the lamivudine treatment for an additional 44 weeks. Interferon was given daily for the first 5 doses and then 3 times weekly every other day for 44 weeks.

At the end of the 52-week study, HBV DNA was positive in 22 percent of subjects, 22 percent seroconverted to HBeAb, and 17 percent cleared HBsAg and seroconverted to HBsAb.

These results challenge current trends to exclude children with normal ALT levels from treatment by suggesting treatment rates in this population are similar to those with elevated ALT levels that are more likely to be accepted for treatment.

Mieli-Vergani's future research will examine treatment results in similar populations using pegylated interferon (which is not currently approved for use in children in the US) in combination with lamivudine.

In 2007, Mieli-Vergani clarified her belief that "the subjects for whom it is important to get rid of the virus are those unlikely to clear it spontaneously and who have the highest risk of developing later complications."

### **The Challenge of Treatment in Children's Immune Tolerant Stage**

When the hepatitis B virus is transmitted perinatally or during the first 12 months of life, the child's immune system is not sophisticated enough to recognize the virus as a danger. The immune system thinks the virus is just a normal part of the body and doesn't try to create antibodies against it.

During this "immune tolerant" stage, the virus rapidly replicates in the liver and moves into the blood, producing high HBV DNA serum levels, but little actual damage occurs.

The challenge of treating a child in the immune tolerant stage is to convince the child's immune system to activate against this virus, which it thinks is just a normal part of the body.

In Dr. Anna Lok's "Clinical Manifestations and Natural History of Hepatitis B Virus Infection," in *UpToDate*, she writes about children infected perinatally and why they may not respond well to interferon treatment.

In the initial phase of the disease, there are high levels of viral replication (hepatitis B e antigen is present and there are high levels of HBV DNA in serum) but not much active liver disease—the child is asymptomatic, has normal ALTs and little change on the liver biopsy.

According to Dr. Lok, during the second and third decades of life, there is a transition from immune tolerant to immune clearance. During this time, many patients begin to lose the e antigen and show abrupt increases (exacerbations) in ALT levels.

Elevated ALT levels are believed to be caused by a sudden increase in immune-mediated lysis (breaking down or disintegration) of infected liver cells (hepatocytes) preceded by an increase in HBV DNA in serum and a shift of hepatitis B core antigen from nuclear to cytoplasmic (the cytoplasm is the contents of a cell other than the nucleus) sites within the structure of the liver cell.

This may suggest that immune clearance is triggered by an increase in the number of viruses replicating in the body, or a change in cellular make-up of the virus's antigens. It's unknown how these changes occur.

However, not all exacerbations lead successfully to e antigen seroconversion and clearance of HBV DNA from serum—this is called abortive immune clearance.

These patients may have recurring exacerbations with intermittent disappearance of serum HBV DNA with or without a temporary loss of the e antigen. These repeated episodes of hepatitis might increase the risk of developing cirrhosis and liver cancer (hepatocellular carcinoma).

Abrupt elevations in serum ALTs appear to happen more frequently in men than women, although no one knows why. This may account in part for the higher incidence of HBV-related cirrhosis and liver cancer in men.

In a few patients, abrupt ALT elevations can lead to hepatic decompensation or, rarely, to death from hepatic failure.

Dr. Lok suggests those with severe exacerbations should be referred to specialized centers for liver transplantation or treatment with antivirals such as lamivudine. She feels interferon treatment isn't indicated for these cases because it can cause additional exacerbations or flares of the disease.

In those who are infected as children (but not perinatally), the disease tends to start out differently. It begins with a phase of viral replication and active liver disease and later, a phase of nonreplication and remission of liver disease. As adults, this group tends to have a lower percentage of people who test positive for e antigens.

A person with chronic hepatitis B may be e antigen negative, e antibody positive, have undetectable HBV DNA in serum and even lose the hepatitis B surface antigen and still develop cirrhosis or even liver cancer, although this doesn't happen very often.

According to Dr. Lok, the ability of the virus to cause complications despite clearance of the surface antigen probably results from its integration into the genome, or genetic material, of liver cells.

Factors that indicate a poorer prognosis include:

- a prolonged replication phase
- older age

- hypoalbuminemia (the liver produces albumin—a protein in blood—and when the liver isn't working well, less albumin is produced)
- thrombocytopenia (low platelet counts)
- splenomegaly (enlarged spleen)
- hyperbilirubinemia (high bilirubin or jaundice)
- general decompensated liver disease

### **cccDNA – Future Target for Treatment**

In *Viral Hepatitis*, Dr. Elizabeth Fagan identifies the cccDNA as a critical part of the hepatitis B virus. HBV cccDNA (covalently closed circular DNA) is a form of the viral genome that gets into the nucleus of liver cells and sets up shop. (The life cycle of the hepatitis B virus goes through various stages or forms, much like insects do in their maturation process.)

Essentially, this cccDNA form of the virus acts like a factory, churning out copies of the hepatitis B virus that are then released into the blood of the infected person in a slightly altered version. It's this second form of the virus that is measured in the serum when a blood test is evaluated to detect HBV DNA.

The available arsenal of drugs can sometimes make the blood level of HBV DNA in a patient undetectable, creating the impression that the body has successfully defeated the virus, or reduced it to small, inconsequential levels. But, the cccDNA residing in the liver is still holding firm, ensconced in the nucleus of the liver cells. It's very resistant to treatment. The only way to find out what is happening to the cccDNA is to sample the liver through a liver biopsy.

To find a true cure for hepatitis B, it's imperative to develop a treatment that will kill the cccDNA in a patient's liver cells and clear the HBV DNA from the blood. Because the harm done to the liver of a hepatitis B patient is done not by the virus itself, but by the body's immune system trying to kill the virus by killing the cells in which it's hiding, a way must be found to eliminate the cccDNA without killing the host (the liver cells) in which it lives. When that is accomplished, the viral factory will close and the patient will truly be cured of hepatitis B.

As of 2007, work with cccDNA focuses on measuring cccDNA and understanding how cccDNA measurements relate to measurements of HBV DNA, HBeAg, and HBsAg.

In the future, treatment goals will focus on elimination of cccDNA from liver cells. Real-time PCR (a testing technique that is more sensitive to polymerase chain reaction

assays compared to gel-based assays which were previously used) has become the gold standard for distinguishing cccDNA from the other forms of HBV DNA present in a liver biopsy specimen.

In 2007, Bourne et al. reported in the *Journal of Viral Hepatitis* that they found and measured cccDNA in liver cells and compared that value to measured amounts of HBV DNA found in liver cells. The study made comparisons between levels of cccDNA in liver cells and levels of HBV DNA in the blood.

For the study, liver cell and blood HBV DNA, liver cell cccDNA, and blood HBeAg and ALT levels were monitored during a 52-week study of eight adult patients who were treated with either lamivudine, lamivudine and standard interferon, or a placebo.

Most patients experienced a decrease in HBV DNA in their liver cells, including those who were using the placebo.

HBeAg seroconversion was associated with reduced levels of cccDNA in the liver cells. HBeAg seroconversion was also associated with a change in the ratio of cccDNA in the liver cells compared to the total HBV DNA in the liver cells. This is a desired result in that it indicates the nonreplicating viruses had become the predominant form of HBV DNA after HBeAg seroconversion.

The study also found that decreases in blood HBV DNA levels were always associated with decreases in HBV DNA in the liver cells, but decreases in HBV DNA in the liver cells were not always associated with immediate reduction in blood HBV DNA levels.

In two-thirds of the placebo recipients, increased ALT levels in the blood were associated with decreasing HBV DNA levels in the liver cells. HBV DNA levels in the blood did not decrease, presumably because the natural cellular response necessary to decrease the circulating virus had not yet occurred.

Future research will try to clarify the relationship between cccDNA and total HBV DNA levels in liver cells and the way the levels affect the overall liver health of the patient.

In the future, drugs will be able to eliminate or reduce HBV cccDNA, which will eliminate the virus's ability to replicate.

Measurement of HBV DNA and cccDNA in liver cells has become an important piece of the puzzle in current drug studies. Among currently approved drug therapies, entecavir has demonstrated an ability to reduce cccDNA levels.

## **Identifying and Treating Hepatitis B-Related Liver Cancer**

Eighty percent of all primary liver cancers are caused by chronic hepatitis B in people who have been infected since birth or early childhood.

Sustaining positive HBeAg past the age of 40 is associated with a higher risk for developing cirrhosis and liver cancer. Other factors that increase risk for liver cancer include male gender, family history of liver cancer, and cirrhosis, although 30 to 50 percent of liver cancer cases do not show evidence of cirrhosis.

Scientists at the Asian Liver Center at Stanford University state that 25 percent of chronic HBV carriers will die from either liver cancer or cirrhosis.

Although rare, liver cancer can occur in children.

There is no evidence that antiviral therapy decreases the risk of liver cancer, but it can decrease or even prevent cirrhosis, which in turn decreases the risk of liver cancer. The challenge is to determine when antivirals should be given to prevent cirrhosis.

Some individuals have developed liver cancer and tumors even after clearing HBV surface antigen.

Researchers have discovered that patients can develop liver cancer without active liver disease. It's imperative to detect liver cancer early enough so that it can be removed or treated to improve long-term survival, even if the risk of recurrence remains.

In "Screening for Hepatocellular Carcinoma in Alaska Natives Infected with Chronic Hepatitis B: A 16-year Population-Based Study," published in the journal *Hepatology*, Dr. Brian McMahon followed 1,400 people with chronic hepatitis B in Alaska up to 16 years between 1982 to 1998.

In the study, 30,000 alpha fetoprotein tests (a test that can detect cancer and tumors) were performed and those at risk for liver cancer were notified.

The risk group had blood drawn and sent to labs, using 15 pg/ml as a ceiling. If levels were above the cut-off and the participants were not pregnant, they underwent liver function tests and sometimes a computed tomography imaging (CT or CAT) scan.

Dr. McMahon discovered 32 carcinomas (malignant cancers); one-third of the cancers were in children under the age of 19. All of these pediatric patients were asymptomatic.

Most of the 32 patients did not have cirrhosis and 23 of the 32 cancerous tumors were small enough to be removed. Fifty percent had recurrence of cancer within five years of the surgery.

There was no control group because it would have been unethical, but there was significant long-term survival compared to historical controls.

The benefit of screening was greatest in children and younger patients—significant numbers of tumors were removable in children, and it is more cost-effective to do this versus fighting full-blown liver cancer many years later.

Dr. McMahon noted he felt it was more effective but much more expensive to use both an alpha fetoprotein and an ultrasound to detect liver cancer early in the disease stage. He suggested limiting that combination to those with cirrhosis, men over 45, and those with a family history of liver cancer.

In 2007, Dr. McMahon's research, published in *The Journal of Infectious Diseases*, focused on identifying cases of liver cancer by hepatitis B genotype among Alaska Native people.

Currently, there are eight strains or genotypes of hepatitis B virus that have been identified throughout the world. These genotypes are referred to as types A-H. Dr. McMahon's research attempted to determine which genotypes, if any, were more likely to cause liver cancer.

The 2007 study compared HBV genotypes among Alaska Native people who had liver cancer to HBV genotypes among Alaska Native people who did not have liver cancer.

A registry identified 47 patients who were diagnosed with liver cancer and chronic HBV infection between 1969 and 2003. For the study, these patients consented to testing for HBV genotype.

Previous studies conducted between 2000 and 2005 recognized an association between HBV genotype C and liver cancer in Asian populations. The 2007 study among Alaska Native people confirmed an association between HBV genotype C and liver cancer, but found that HBV genotype F was most significantly associated with the development of a liver cancer called hepatocellular carcinoma, or HCC, in this population. In fact, 32 of the 47 patients studied had genotype F.

The study also found a significant difference between ages at the time of liver cancer diagnosis. Persons with genotype F and liver cancer were diagnosed with liver cancer at

a median age of 22.5 years compared to a median age of 60 years at the time of liver cancer diagnosis for all the other genotypes. In this study, genotype B was not found in any of the patients with liver cancer.

Future studies will examine the qualities of genotype F in hopes of gaining an understanding of the role it plays in causing liver cancer.

### **Treatments on the Horizon**

Better treatment is needed to combat hepatitis B at any age and during any stage of infection.

There is no treatment available that is consistently effective in curing this infection, and currently no medication produces durable results in lowering HBV DNA and ALT levels in the majority of those treated.

Therapy with only interferon or lamivudine is effective in only a minority of patients. Interferon therapy requires thrice weekly injections and carries with it serious side effects.

Bottom line: current therapies are inadequate for 60 to 90 percent of patients with chronic hepatitis B. The good news is that four additional drug treatments for adults were added to the arsenal of treatment options between 2002 and 2007.

### Nucleoside Analogues

In 2006, eight additional nucleoside analog drugs were undergoing clinical trials in adults. Of these, emtricitabine and clevudine are in phase III trials.

### Emtricitabine (Coviracil)

Emtricitabine, marketed as Coviracil, is a drug that has been approved for HIV treatment. It is currently in Phase III trials as a treatment for hepatitis B.

Emtricitabine is an antiviral agent that has proven effective against the hepatitis B virus; however, a study published in *Archives in Internal Medicine* showed 13 percent of patients developed the same type of drug resistance seen in patients treated with lamivudine. This drug will not likely be used alone, but may fill a niche in combination treatments.

According to a study of 98 patients treated with emtricitabine presented to the AASLD in 2002 by Dr. Robert Gish, after 48 weeks of treatment:

- 55 percent of patients treated had undetectable HBV DNA levels
- 50 percent lost HBeAg
- 23 percent seroconverted and produced HBeAb
- 6 percent developed signs of viral resistance

After two years of treatment, of the 98 patients originally enrolled in the study:

- 76 percent had normal ALT levels
- 41 percent had undetectable levels of virus
- 51 percent had lost HBeAg
- 29 percent had seroconverted to HBeAb

After two years, the incidence of resistance was 19 percent for patients receiving 200 mg for the full two years. Preliminary data from the post-treatment period show that eight patients experienced a return of hepatitis B with resurgence of HBV DNA.

Interestingly, among patients who had undetectable serum viral DNA at least at one point during the two-year treatment period, 68 percent lost HBeAg and 43 percent seroconverted to HBeAb.

Among patients with detectable HBV DNA levels, only 12 percent had lost HBeAg and 3 percent seroconverted to HBeAb at two years.

Results from this two-year study show:

- a sustained virologic response with 41 percent of the patients
- a favorable response with 51 percent of the patients with HBeAg loss and 29 percent seroconversion to HBeAb
- the drug was well tolerated
- viral resistance appeared in 19 percent of patients who received the 200 mg dose

In February 2006, Emtricitabine was in Phase III studies for use in adults with HBV.

### Clevudine

In 2006, clevudine was in phase III trials for adult use. This drug has shown ability to sustain antiviral response.

This drug appears to have limited side effects, and there have been no identified cases of antiviral resistance.

### Non-Nucleoside Antivirals (sometimes called HAPs)

A new class of compounds, non-nucleoside antivirals, which are sometimes called HAPs (for heteroaryldihydropyrimidines), has been found to inhibit HBV replication in a way that is distinctly different from existing antiviral medications.

Unlike lamivudine or adefovir, non-nucleoside antivirals do not inhibit the HBV polymerase. Investigators aren't clear exactly how non-nucleoside antivirals work to stop viral replication, but because they don't impact the viral polymerase, non-nucleoside antivirals may stop the virus without allowing "mutated" viruses to survive.

In a study reported in the Feb. 7, 2003, issue of *Science*, researchers found that non-nucleoside antivirals work by inhibiting formation of the nucleocapsids, the nucleic acid core of the virus that is needed for viral replication.

In 2006, five drugs of this class were in early stages of study. One of these, BAM-205, has been approved for use in Russia since 2001. This drug has demonstrated a reduction in viral load and ALT levels. This drug is in phase II/III clinical trials in the US.

Another nucleoside antiviral, (Bay 41-4109), has shown particular promise as a potent therapeutic agent in mice.

### Non-Interferon Immune Enhancers

These types of drugs are similar to interferon in the way they stimulate or enhance the immune system, but these drugs specifically assist T cells to find and fight tumors and viruses.

Two immune enhancer drugs under study include HE2000 and Zadaxin.

HE2000 was in phase II trials in Singapore in 2006, and has been shown to trigger specific cells in the immune system to fight hepatitis B and HIV.

Zadaxin is a hormone that stimulates T-cells to mature. In combination with standard interferon, this drug resulted in a long-term sustained response rate indicated by normal ALT levels and negative HBV DNA in difficult-to-treat patients.

Zadaxin was in phase II clinical trials in 2006.

### Therapeutic Vaccination

For several years, researchers have been investigating whether it is possible to use a vaccine with surface antibodies to spur a patient's immune system into action against the hepatitis B virus.

In 2005, Akbar and Onji, two researchers in Japan, summarized research findings in the use of therapeutic vaccination for people with chronic hepatitis B.

Akbar and Onji report in the *Hepatitis B Annual* that several vaccine therapy clinical trials have occurred over the last decade. They also point out that while Western therapies have focused on use of antiviral therapies, it is becoming apparent that antivirals will not be able to completely cure hepatitis B in chronic cases.

Because of the limitations of antivirals, they believe it is worthwhile to approach treatment from a different angle. To do this, they examined the differences between acute infection and chronic infection and found the main difference is that chronic patients have an impaired immune response to HBV-related antigens.

The problem is not an impaired immune system in general; the problem exists in mounting an immune response to the hepatitis B virus in specific. Therefore, an ability to induce a normal immune response without causing harm to hepatocytes could be a valuable therapy.

Three types of vaccines have been studied: peptide vaccine, DNA vaccine, and antigen-based vaccine:

- The peptide vaccine injects modified HBV-related proteins to enhance the immune system's cytotoxic T cells' (CTL) ability to identify and destroy liver cells that are infected with HBV.
- The DNA vaccine injects encoded HBsAg to cause the body's natural immune system to produce HBsAb.
- The antigen-based vaccine injects HBsAg to restore the immune system's ability to recognize the HBV as a foreign object so that a natural immune response can occur.

In 2003, researchers investigated whether vaccinating children who were in the immune tolerant phase of HBV infection—with normal liver enzymes and high levels of HBV DNA—with an antigen-based vaccine would cause an immune response.

Twenty-three children were vaccinated with three standard injections of the GenHevac B vaccine. Twenty-eight children in a control group received no medication or vaccine.

They were evaluated at six months after the first injection and at the end of the 12th month.

Unfortunately, the vaccine had little or no effect on HBV DNA levels or ALT levels. It was also ineffective in causing any HBeAg to HBeAb seroconversion.

Research in adults has produced similar results, though this continues to be an area of research interest.

Akbar and Onji explain that peptide-based vaccines and DNA vaccines have shown effectiveness in a few studies, but their use is still in early stages. There are also concerns about ethical use and long-term side effects of DNA vaccine. These types of therapies show little promise.

However, in 2005, drug researchers presented data from a U.S. Phase II study of a DNA-based immune-boosting vaccine. At week 26 of treatment, results demonstrated loss of HBeAg in 29 percent of vaccine recipients and seroconversion in 14 percent of vaccine recipients.

When compared to a control group of lamivudine recipients, there were no cases of seroconversion at 26 weeks, and only 9 percent demonstrated HBeAg loss.

Akbar and Onji suggest future therapeutic vaccine research should continue to focus on animal study to induce an immune response either with the HBsAg, hepatitis B core antigen, other HBV antigens, or any of these in combination.

One promising next-generation vaccine that has been trialed in humans is HBsAg-pulsed DCs. Here, HBsAg is injected, and dendritic cells (DCs) present at the injection site recognize and internalize the HBsAg. Then, the DCs communicate with T and B lymphocytes present in the immune system. As a result, B lymphocytes learn to recognize HBsAg and secrete HBsAb.

When the HBsAg is pulsed, the HBsAg is paired with DCs in the laboratory and then injected back into the body to concentrate the effect of the vaccine.

In 2004, human studies demonstrated an increase of HBsAb in all participants with no adverse side effects. Future research will consider differences among races and individuals.

Akbar and Onji also recommend development of HBsAg-based vaccination protocols and better systematic study of the vaccines.

They blame the current disorganization of vaccination study on a lack of funding and technical support for trials, but advocate that vaccine therapy is a less costly option when compared to interferon treatment or treatment for drug resistant mutations.

Because of cost, many individuals in the world have been told that no treatment options exist for them.

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