Hepatitis B and C in Children: Current Treatment and Future Strategies

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Acquisition during childhood is responsible for a large proportion of chronic hepatitis B virus (HBV) infections. Although children represent a minority of the chronic hepatitis C virus (HCV) infections in comparison to adults, there are thousands of children with this serious infection throughout the world. Management and treatment of these chronic infections in children continue to be challenging because there are limited data and studies addressing these diseases in pediatric populations. It is important that practitioners do not extrapolate data from adults to children; the epidemiology, natural history, progression of disease, and response to treatment are different in children.

At this time, in the United States the Federal Drug Administration (FDA) has approved only a few medications for the treatment of chronic viral hepatitis in children. This article describes the medications currently approved for children and future directions being considered.

Hepatitis B

Epidemiology

The transmission of HBV infection in children differs by population and region of the world. In highly endemic regions of Asia and Africa, vertical
transmission is the predominant mode of acquisition, contributing up to 40% to 50% of all new cases [1]. In the United States and other developed countries, immigration and adoption of children from endemic regions are the most common sources of childhood cases of HBV infection. Horizontal, or child-to-child, transmission continues in the United States in children who live in households with HBV-infected individuals or in communities of immigrants who have a high prevalence of infection.

Natural history

The likelihood of chronic HBV infection in children is inversely proportional to the child’s age at acquisition. Chronic infection develops in 90% of vertically infected infants but decreases to 25% to 50% in children infected between the ages 1 and 5 years, and to 6% to 10% in older children [2].

Infection in infants often leads to an immune-tolerant phase, with high HBV DNA levels and hepatitis B early antigen (HBeAg) in serum for years, usually into late childhood or adolescence. Alanine aminotransferase (ALT) levels are usually normal during this phase, with minimal liver disease [3]. Spontaneous seroconversion rates in these children are low, occurring in fewer than 2% per year of children younger than 3 years and in 4% to 5% of children older than 3 years [4]. These rates are in contrast to the higher seroconversion rates in children infected after the perinatal period. Longitudinal studies of children who have predominantly horizontally acquired, HBeAg-positive infection in Italy and Spain showed a 70% to 80% seroconversion of HBeAg to anti-HBe over a period of 1 to 20 years [5,6].

Histologic findings of the liver in children who have chronic hepatitis B usually include mild inflammation with mild fibrosis but may be more severe. In a recent study of 76 children who had chronic HBeAg-positive HBV infection and elevated ALT (aged 1 to 19 years; mean age, 9.8 years), at least half had moderate to severe fibrosis, and 35% had either bridging fibrosis with lobular distortion or cirrhosis [7].

Of great concern to pediatricians is the increased risk of hepatocellular carcinoma (HCC) from decades of chronic infection and inflammation. HCC is rare in children except for those who have chronic HBV infection or metabolic diseases. Before HBV vaccination programs were instituted in Taiwan, where HBV is endemic, the annual incidence rate of HCC in children younger than 15 years was 15 to 35 times greater than in children in the United States [8,9].

Treatment

There is no treatment of proven efficacy for children who have acute HBV infection, and care should be only supportive. The majority of acute infections acquired after the newborn period resolve without intervention.
Each child who has chronic HBV infection must be managed individually, taking age, age at acquisition, and level of immune reactivity into consideration. General principles of management are outlined in Box 1. There are several goals of pharmacologic treatment for chronic HBV infection in childhood: cessation or decrease in viral replication, normalization of aminotransferase levels and liver histology, and prevention of cirrhosis and HCC.

To ensure the highest likelihood of treatment success, children over the age of 2 years should have documented chronic infection (hepatitis B surface antigen [HBsAg] for at least 6 months), evidence of immune activity for at least 3 to 6 months as manifested by an ALT elevated twice the upper limit of normal or higher, and active HBV replication, such as positive HBeAg or HBV DNA of at least 4 log (measured by quantitative polymerase chain reaction [PCR] assays) detected in serum (Fig. 1). Monitoring for some period of time before treatment is important, because high ALT levels and low levels of HBV DNA may indicate imminent seroconversion that would not require treatment. HBeAg-negative (high viral DNA) infection (precore mutant) is uncommon in children, because it probably represents a late stage of chronic infection. For this reason, there are no published data regarding the treatment of HBeAg-negative HBV infection in children. Liver biopsy is not mandatory before treatment but is recommended to

**Box 1. Management of chronic hepatitis B in children [10]**

1. Prove chronic infection in at least two HBsAg-positive samples taken 6 months apart or positive anti-HBc, not IgM.
2. Measure ALT every 6 months in children older than 2 years.
3. Measure HBeAg and anti-HBe yearly in patients who have normal ALT to detect spontaneous seroconversion.
4. Perform liver biopsy and consider treatment for children older than 2 years who have ALT levels higher than 1.5 to 2 times the upper limit of normal for more than 3 months and no evidence of seroconversion.
5. Perform regular physical examinations for evidence of chronic liver disease.
6. Immunize all household contacts.
7. Immunize all hepatitis B patients with hepatitis A vaccine.
8. Check serum alpha-fetoprotein yearly and perform liver ultrasound yearly.*

* No data support optimal age to begin liver ultrasound surveillance or optimal interval between ultrasounds.

document chronic hepatitis secondary to HBV infection and to determine the severity of inflammation and fibrosis.

Age is an important consideration, because treatment regimens are approved only for children older than 2 years. The two medications approved in the United States are interferon-alfa (IFN-\(\alpha\)) and lamivudine. IFN-\(\alpha\) is the only medication approved in Europe for children who have chronic HBV infection.

Interferon-alfa

IFN-\(\alpha\) has been used for the treatment of hepatitis B in children for at least 10 years. The reported success rates have varied greatly. Published data from Western countries have shown response rates (loss of HBV DNA or HBeAg) in 20% to 58% of treated subjects, in comparison with 8% to 17% of untreated controls [11–14].

The largest multinational, randomized, controlled trial of IFN-\(\alpha\) was performed in 144 children who had chronic HBsAg-, HBeAg-positive disease with an elevated ALT greater than twice the upper limit of normal. Treated patients received IFN-\(\alpha\), 6 megaunits (MU)/m\(^2\) of body surface area (maximum 10 MU), three times per week, for 24 weeks. Serum HBeAg and HBV DNA became negative in 26% of treated children, in comparison with 11% of untreated controls.
addition, 10% of treated children lost HBsAg, in comparison with 1% of controls [14]. This study showed no statistical difference in response rate between Asian children (22%) and non-Asian children (26%), as had been previously described.

Variables that have been associated with a higher likelihood of response to IFN-α are listed in Box 2. A recent study indicated that IFN treatment might be more effective in eliciting HBeAg and HBsAg loss in children younger than 5 years of age [15]. Studies indicate that high-dose IFN-α (10 MU/m²) and

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**Box 2. Variables associated with virologic response to IFN-α [14,15,18,19] or lamivudine [20,21] in children who have chronic hepatitis B**

**Interferon**

*Factors associated with higher likelihood of response*
- ALT two times the upper limit of normal or higher
- Female gender
- Low level of HBV DNA
- Younger age, with abnormal ALT
- Active inflammation on liver biopsy*

*Factors not associated with likelihood of response*
- Ethnicity
- Body surface area

**Lamivudine**

*Factors associated with higher likelihood of response*
- Elevated baseline ALT
- High baseline Histologic Activity Index score

*Factors not associated with likelihood of response*
- Baseline HBV DNA level
- Race/ethnicity
- Age
- Gender
- Previous interferon therapy
- Baseline weight
- Baseline body mass index

* Shown to be associated with higher response in adults and presumed to be similar in children.
prednisone priming of standard doses of IFN-α have not improved response rates, and these measures are not routinely recommended [16,17].

Side effects of IFN-α in children include the flulike symptoms of fever, myalgia, headache, arthralgia, and anorexia. Neutropenia may occur in up to 39% of children during treatment, sometimes requiring dose adjustments. Discontinuation of the medication for side effects is rare [22]. Children have weight loss, as do adults, but may also have decreased growth velocity during treatment. These side effects are reversible, resolving at least 6 months after treatment is complete [23]. Mood disturbances may be significant, and younger children may have personality changes, irritability, and temper tantrums [14,22].

Contraindications to IFN-α in children are similar to those in adults and include decompensated cirrhosis, underlying autoimmune disorder, organ transplantation, or serious neuropsychiatric disease. IFN-α is currently recommended for children aged 2 years and older who have consistently abnormal ALT values, at 6 MU/m² (maximum 10 MU) three times per week for 24 weeks. HBeAg seroconversion may occur during or up to 12 months after the completion of therapy. ALT flares during treatment do not mandate cessation of therapy if there are no signs of decompensation; these flares often herald impending seroconversion. There is a small but reproducible rate of HBsAg seroconversion after successful IFN-α therapy that is rarely seen in untreated children.

**Lamivudine**

Lamivudine is an oral nucleoside analogue that is approved in the United States for treatment of childhood HBV infection. In 2002, a multicenter randomized, double-blind, placebo-controlled, 52-week trial was conducted [20]. All children enrolled had been HBsAg positive for at least 6 months, were positive for HBeAg and anti-HBe negative, had detectable HBV DNA in serum, had ALT levels greater than 1.3 times the upper limit of normal but lower than 500 IU/L, and had evidence of inflammation on liver biopsy. Children received lamivudine, 3 mg/kg (100 mg maximum), or placebo daily. Clearance of HBeAg and HBV DNA at 52 weeks occurred in 23% of treated children, in comparison with 13% of controls [20]. In children whose baseline ALT was at least twice normal, the response rate increased to 35%.

Nonresponders treated with open-label lamivudine showed a cumulative 3-year virologic response (loss of HBeAg and undetectable HBV DNA) of 35%. HBsAg loss occurred in 3% of patients. HBeAg seroconversion from the first year of study was durable in 88% of patients at 36 months [24]. Factors associated with a greater likelihood of virologic response to lamivudine in children are shown in Box 2.

The necessary duration of treatment with lamivudine seems to be at least 1 year, and the medication should be continued for at least 6 months after HBeAg seroconversion. In adults, treatment for longer than 1 year has been associated with an increased risk of resistance [25,26]. Lamivudine resistance by development of the YMDD mutant was evident in 19% of children treated for 1 year; and
only one of these patients subsequently lost HBeAg [20]. Continued treatment with lamivudine once resistance is noticed is controversial. It has been recommended that lamivudine be continued while HBV DNA remains suppressed but discontinued in the child who has virologic breakthrough and no serious underlying liver disease.

Lamivudine is safe for children who have hepatitis B, and it is well tolerated in liquid or tablet form. Serious side effects were not reported after 3 years of continuous treatment [24]. In comparison with treatment with IFN-α, decreased height velocity and weight loss were not observed.

Interferon and lamivudine

Combination therapy with IFN-α and lamivudine has been reported in two studies of Turkish children [27,28]. These studies compared combination and monotherapy, as well as response rates using different schedules of combination therapy. Neither study documented improved virologic response with combination therapy as compared with that achieved with IFN-α monotherapy.

Treatment of hepatitis B virus with coinfections

At this time, there are no data regarding the best treatment of children who have coinfections such as hepatitis C virus or HIV, because these coinfections are rare in pediatric patients. Treatment of children coinfect ed with hepatitis D virus with IFN-α had some short-term effects on hepatitis D virus RNA but did not seem to induce significant long-term virologic response or histologic change in several trials in Europe [29,30].

Future treatment directions

Two additional nucleotide/nucleoside analogues and peginterferon alfa-2a have been approved by the FDA for the treatment of chronic HBV infection in adults. These medications seem to induce less viral resistance than lamivudine. Other medications are being used off-label or are in various stages of development at this time (Table 1) [31–33].

Table 1

<table>
<thead>
<tr>
<th>Treatments for chronic hepatitis B infection: present and future</th>
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<tbody>
<tr>
<td>FDA approved</td>
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<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Interferon-α&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lamivudine&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Adefovir dipivoxil</td>
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<tr>
<td>Entecavir</td>
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<td>Peginterferon alfa-2a</td>
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<sup>a</sup> Approved for use in children older than 2 years.

<sup>b</sup> Refs. [31–33].
Adefovir dipivoxil is an oral nucleotide analogue that inhibits both HBV reverse transcriptase and DNA polymerase activity. It has been shown to be effective in suppressing wild-type HBV and its lamivudine-resistant mutants [34,35]. Adefovir dipivoxil, taken for 48 weeks, results in improvement in histology, HBeAg loss (12%), normalization of ALT, and reduction of HBV DNA in adults [34]. In comparison with lamivudine, adefovir dipivoxil seems to induce significantly less viral resistance, with a frequency of approximately 3% at 3 years, with no cross-resistance between the two medications [36]. A multicenter, randomized, placebo-controlled trial of adefovir dipivoxil is currently being conducted in children 2 to 17 years of age who have chronic HBV infection.

Entecavir, an oral guanosine nucleoside analogue, inhibits HBV polymerase in three different steps. Phase III trials in adults have shown HBV DNA suppression and histologic improvement in nucleoside-naive HBeAg-positive or HBeAg-negative patients, as well as in patients who did not respond to lamivudine. The FDA recently approved entecavir for the treatment of chronic HBV infection in adults. There are no data available regarding its use in children.

Peginterferon alfa-2a was recently approved by the FDA for the treatment of HBeAg-positive and HBeAg-negative adults. Several multicenter studies have documented greater frequency of virologic and histologic responses 24 weeks after a 48-week course of either peginterferon monotherapy or of combination therapy with lamivudine than with lamivudine alone. The addition of lamivudine had no benefit over peginterferon monotherapy [37,38]. These studies again showed a measurable rate of HBsAg loss (7%) with peginterferon therapy. There are no data available regarding the use of peginterferon for chronic HBV infection in children.

Genotype evaluation

To date, eight genotypes (A–H) and two subtypes of HBV (Aa/Ae) and (Ba/Bj) have been identified. Specific genotypes have been clearly linked with the propensity to HBeAg seroconversion, reduced HBeAg expression, and response to antiviral therapy [39]. Analyses from Asia have shown that genotype B has a higher rate of spontaneous HBe seroconversion than genotype C [40] and a greater likelihood of response to IFN-α [41,42]. No difference was seen between genotypes B and C in response to lamivudine or adefovir dipivoxil treatment [43,44]. Studies from Europe have shown that genotype A responds better than genotype D to IFN-α [45]. This increasing knowledge of HBV genotype differences may soon be used to tailor treatment decisions.

Summary

Currently, there are two approved treatments for chronic HBV infection in children, IFN and lamivudine. The seroconversion rates after 1 year of treatment are similar. Each has advantages and disadvantages. IFN-α, in addition to in-
ducing HBeAg seroconversion, has a higher likelihood of inducing loss of HBsAg or HBsAg seroconversion, and the duration of treatment is finite (6 months). This medication requires subcutaneous administration, however, and it has common side effects and growth effects. Lamivudine is associated with similar HBeAg seroconversion rates but does not frequently induce HBsAg loss and has a high rate of resistance if taken for an extended period of time. There is no defined optimal treatment duration, and some children may require this medication for several years. Oral forms are available in both tablet and liquid forms, and the side-effect profile is much more tolerable for patients and their families than that of IFN-α.

Optimal treatment for each patient should be individualized, depending on comorbid conditions, clinical and histologic status, ability to take medications, contraindications, and familial concerns. The goal of treatment should be durable HBeAg seroconversion and cessation of active viral replication to prevent the long-term consequences of inflammation and fibrosis, which include cirrhosis and hepatocellular carcinoma.

**Hepatitis C**

*Epidemiology*

Data from the Centers for Disease Control and Prevention have shown that the seroprevalence of antibody to HCV in the United States is 0.2% for children 6 to 11 years of age and 0.4% for those aged 12 to 19 years [46]. Before 1992, the mode of acquisition in children was predominantly transfusion of blood or blood products. After the implementation of universal testing of blood products, vertical transmission has become the leading source of infection for children [47]. Vertical transmission of HCV occurs in 4% to 5% of infants born to viremic mothers but is significantly higher (20%) when mothers are coinfected with untreated HIV [48].

*Natural history and prognosis*

In infants who acquire HCV infection perinatally, there is a high incidence of viremia and abnormal aminotransferase levels during the first 12 months of life. Of 70 prospectively followed infants in five European centers from 1990 to 1999, 93% had abnormal ALT levels during the first 12 months, and only 19% cleared HCV RNA and developed normal ALT by 30 months of age [49]. In another study of 200 HCV-infected children in Europe (45% infected perinatally), only 6% of children followed for 1 to 17.5 years (mean, 6.2 years) achieved spontaneous sustained virologic clearance and normalization of ALT [50].

Chronic HCV infection is asymptomatic and benign during the first 2 decades in most cases. Severe liver disease and decompensated cirrhosis are rare during childhood but have been reported [49–51]. Liver biopsies of children who have
chronic HCV infection usually demonstrate mild inflammation and necrosis, but fibrosis may be significant and usually worsens with age and duration of disease [52–54]. Cirrhosis is reported in a small percentage of these liver biopsies [52,54].

Although many children have minimal liver disease for decades, the pressing concern for pediatricians is the risk of cirrhosis and HCC in adulthood. HCC is rare in the first 2 decades of HCV infection but has been reported [55].

Liver transplantation for complications of chronic HCV infection is rarely necessary during childhood. Given the significant morbidity and mortality with long-standing hepatitis C infection, treatment should be considered for childhood infection.

Treatment

Children found to have HCV antibody must be further evaluated for the presence of HCV RNA by a PCR-based assay to confirm infection. In addition, laboratory tests should be used to determine HCV genotype and to assess liver synthetic function and hematologic abnormalities suggestive of portal hypertension. A liver biopsy is suggested before treatment but perhaps could be deferred for children who have HCV genotypes 2 or 3, because the response rate of these genotypes to treatment is so high. Reasons to biopsy children with HCV genotypes 2 or 3 would include a physical examination or laboratory evaluation showing evidence of advanced liver disease, the presence of important comorbidities, or other confounding factors that could influence the severity of liver disease.

Because the natural history of chronic HCV infection in children is not fully characterized, treatment decisions may be difficult. Before therapy, consideration must be given to the specific circumstances of each child, such as age, viral genotype, degree of liver injury or decompensation, liver biopsy findings, and possible contraindications to or complications from treatment. Children are different from their adult counterparts in that their infections are usually of shorter duration, and children have fewer comorbid conditions such as HIV coinfection, chronic alcohol use, or autoimmune disorders that would complicate treatment with IFN. They may have a higher frequency of response and a lower frequency of relapse [56]. In addition, it seems that children are less likely than adults to discontinue treatment because of side effects or to exhibit nonadherence.

Treatment should be at least considered for most children who have HCV genotype 2 or 3 infection, because they have an excellent response to therapy. The more difficult decision is management of the child who has an HCV viral genotype other than 2 or 3. Therapy is probably indicated for the child who has significant liver injury or fibrosis on liver biopsy, because this finding may indicate a high likelihood of progressive disease. Children who have HCV genotype 1 infection and minimal inflammation and fibrosis may be followed clinically. Participation in clinical trials may be an option for some children.
Some children may eventually benefit from newer treatment options that may have better response rates for genotype 1 infections.

**Interferon-alfa**

Interferon monotherapy was studied in children before FDA approval. There were no multicenter trials, but IFN-α therapy did seem to have a higher sustained virologic response rate in children (36%) than in adults [56]. A significant difference in response by genotype was noted: 26% for genotype 1 compared with 70% for the other genotypes. Given the success rates of combination IFN-α and ribavirin therapy in adults, no large trials were conducted using monotherapy.

**Interferon-alfa and ribavirin**

Combination therapy with IFN-α and ribavirin is the only FDA-approved treatment regimen for children aged 3 to 17 years who have chronic HCV infection. There have been four reports of combination therapy in children (Table 2) [57–61]. The largest series to date was a multicenter study of 70 children aged 3 to 17 years given IFN-α-2b, 3 mU/m² of body surface area three times per week, and ribavirin, 15 mg/kg/day, for 48 weeks [57]. Of these children, 49% had a sustained virologic response (SVR), defined as absence of HCV RNA 24 weeks after the end of treatment. Factors associated with likelihood of SVR were age less than 12 years, genotypes 2 and 3, and fewer than 2 million copies/mL of HCV RNA in those children who had genotype 1 infection. Baseline ALT, ethnicity, gender, mode of acquisition, and duration of infection were not associated with SVR. Side effects of combination therapy were similar to those seen in adults, including fever, headache, fatigue, and influenza-like symptoms. Anemia occurred in 14%, and neutropenia developed in 27%. Adverse events led to dosage modifications in 20% and to discontinuation in 7% of the children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Sustained virologic response</th>
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<tr>
<td></td>
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<td>All genotypes % (n)</td>
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<tr>
<td>Lackner et al, 2000 [60]</td>
<td>IFN/ribavirin</td>
<td>50 (6/12)</td>
</tr>
<tr>
<td>Christensson et al, 2000 [61]</td>
<td>IFN/ribavirin</td>
<td>64 (7/11)</td>
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<tr>
<td>Wirth et al, 2002 [62]</td>
<td>IFN/ribavirin</td>
<td>61 (25/41)</td>
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<tr>
<td>Peralta et al, 2002 [57]</td>
<td>IFN/ribavirin</td>
<td>49 (34/70)</td>
</tr>
<tr>
<td>Wirth et al, 2005 [59]</td>
<td>Peginterferon/ribavirin</td>
<td>59 (36/61)</td>
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*Abbreviation:* IFN, interferon.
Similar results were reported from a study of 41 children. Again, baseline ALT and mode of acquisition were not associated with likelihood of response [62].

Recommendations for treatment duration differ by viral genotype. Children who have genotype 2 or 3 infection should be treated for 24 weeks. Patients who have genotype 1 infection should be scheduled for 48 weeks of therapy, but treatment should be discontinued if there is not a 2-log drop in HCV RNA by 12 weeks (early virologic response) or undetectable HCV RNA at 24 weeks, because the absence of these responses predicts a low likelihood of SVR. All children who responded to therapy should have an HCV RNA checked 24 weeks after therapy is complete to confirm SVR.

All children should be monitored for IFN-α side effects such as neutropenia, depression, weight loss, and thyroiditis with regular monitoring of blood counts and thyroid-stimulating hormone. Although some degree of hemolytic anemia caused by ribavirin is virtually universal, dose reductions or the use of erythropoietin are occasionally necessary for more severe anemia.

*Future treatment directions*

**Peginterferon**

Peginterferon plus ribavirin is now standard therapy for chronic HCV infection in adults, because studies have shown significant improvement in SVR (50%–60%) when compared with thrice-weekly IFN-α plus ribavirin [58,63].

There are few reports of peginterferon use in children. One pilot study, done primarily to examine peginterferon alfa-2a pharmacokinetics and reported only in abstract form, demonstrated a SVR in 6 of 14 children (42%) [64].

A recent study evaluated combination therapy with peginterferon alfa-2b, 1.5 µg/kg once a week, and ribavirin, 15 mg/kg/day, in 62 children aged 2 to 17 years treated for 48 weeks [59]. The overall rate of SVR was 59%, and all 13 children who had genotype 2 or 3 infection lost HCV RNA. The SVR rate was 48% in children who had genotype 1 infection, which is similar to that reported with the standard treatment of thrice-weekly IFN-α and ribavirin [57,62]. The likelihood of SVR was independent of baseline ALT levels and mode of acquisition, whether transfusion-associated or perinatal. Side effects were similar to those previously reported.

A multicenter, randomized, controlled trial comparing peginterferon alfa-2a monotherapy with peginterferon alfa-2a plus ribavirin is now enrolling patients in the United States [65].

*Other treatments*

No new medications will be available in the next few years for chronic HCV infection. Drugs in development are shown in Table 3. Viramidine, a liver-targeted prodrug of ribavirin, seems promising, because its metabolites are targeted toward the liver instead of red blood cells, and hemolytic anemia is much less common. Levovirin is the L-isomer of ribavirin and causes less hemolysis but is not easily absorbed from the intestine in humans. Inosine monophosphate
dehydrogenase inhibitors, such as mycophenolate mofetil and VX-497, are currently being evaluated. It seems that VX-497, when combined with peginterferon and ribavirin, is able to increase the frequency of HCV RNA loss after 24 weeks [66]. SVR data are not yet available. Small-molecule inhibitors and viral enzyme inhibitors have been a major area of research. Recent pilot studies involving the NS3-serine protease inhibitor BILN-2061 have shown antiviral activity, with greater inhibition of genotype 1 [67,68].

The goal of treatment of chronic HCV infection in children is viral eradication to prevent the complications of long-standing inflammation and fibrosis: cirrhosis and HCC. Currently, IFN-α plus ribavirin is the only approved treatment for chronic HCV infection in children 3 years and older. During the next few years, more information will become available regarding the effectiveness and safety of peginterferon monotherapy versus peginterferon plus ribavirin in children and will indicate whether either treatment will become the standard of care in childhood HCV infection. It is also hoped that further development of hepatitis C regimens in adults will lead to more treatment options for children.

**Summary**

Chronic HBV and HCV infections are important disorders in children, although advanced liver disease caused by these infections may not be manifest until adulthood. Treatment of chronic HBV and HCV infection in children is challenging, given the shortage of long-term data and the limited number of approved medications. Chronically infected children should be referred to specialists who are knowledgeable about the natural history and treatment of these infections in this special population. Pediatric studies such as the peginterferon and ribavirin trial are crucial to test medications properly in children.

**References**


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