

# HEPATITIS C IN CHILDREN

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## Introduction

*Hepatitis C virus (HCV)* infection of the liver can occur during childhood and creates many problems and concerns for both the infected children and their families. The purpose of this chapter is to discuss:

- ways that children contract hepatitis C
- the type of liver damage that can occur
- the types of treatment available
- special questions related to hepatitis C in mothers and/or in children such as breastfeeding and school entry

Although there are many challenges for children with hepatitis C infection, families should know that there are a number of pediatric liver disease specialists (pediatric *gastroenterologists*) who are working on solutions to these problems. There are also several sources of information about HCV for families. These are listed in the *Resource Directory*.

## Hepatitis C Testing

As with any other area of knowledge in medicine, there is a special vocabulary doctors use in discussing hepatitis C infection. One easy way to screen individuals for hepatitis C is with a blood *antibody* test, usually referred to as *anti-HCV*. A positive antibody test usually indicates that the individual has been infected with the hepatitis C virus and that the person's *immune system* has attempted to get rid of the infection. (See *Chapter 6, Laboratory Tests and Procedures* for more information about hepatitis C antibody testing.) Unfortunately, hepatitis C antibodies are not usually very effective and many people who are anti-HCV positive are still infected with the virus. This is known as viral "persistence."

HCV belongs to a group of viruses called *RNA viruses* (the virus made out of a type of chemical called *ribonucleic acid*). To check for the presence of the hepatitis C virus itself (not the antibody) in the blood, an *HCV RNA* test is used. This test is known by several different names including an HCV molecular test, *HCV PCR*, *HCV TMA*, and *HCV viral load*. (See *Chapter 6, Laboratory Tests and Procedures* for more information about hepatitis C virus testing.)

## Hepatitis C Testing in Newborns

Mothers with hepatitis C are usually anti-HCV positive and frequently pass this antibody to their offspring. However, most anti-HCV positive newborns are not actually infected with the hepatitis C virus. The hepatitis C antibodies showing up in the newborn's blood are most often the mother's antibodies that were passed to the baby before birth.

**Most babies born to mothers with hepatitis C do not have hepatitis C.**

A baby born to a mother with hepatitis C will probably have antibodies to the virus for the first 12 to 18 months of life. That is, the baby will have a positive hepatitis C antibody test (also known as anti-HCV).

But this does not necessarily mean the baby has the hepatitis C virus.

Newborns lose the antibodies from their mothers over time. Most maternal (from the mother) antibodies are no longer detectable in the baby by around 18 months of age. In the case of hepatitis C antibodies, if anti-HCV is still present at 18 months of age, then it is much more likely that the infant is actually infected with the hepatitis C virus. An HCV molecular test is often performed to confirm the presence of HCV in the blood if the anti-HCV test remains positive at 18 months.

## Routes of Transmissions and Prevalence of HCV in Children

It is believed that between 68,000 to 100,000 children in the U.S. have *chronic hepatitis C*.<sup>1,2</sup> However, certain information on hepatitis C virus infection in children is lacking.<sup>3,4</sup>

The ways in which children become infected with HCV have changed over the past several years. Before 1990, HCV infection in children was mostly due to transfusion of blood or products derived from blood (for example, anti-hemophilic factor, factor IX, or intravenous *immune globulin*). Screening of blood and its products for the presence of HCV in the last 10 years has drastically decreased this type of transmission. Since 1990 infections in children are primarily caused by transmission from mothers who have chronic hepatitis C.<sup>5</sup>

### Mother-to-Child Transmission of HCV

Overall, the risk of HCV transmission from an infected mother to her newborn infant is only about 5%. However, more than one out of every 100 women of childbearing age may be infected with HCV. Therefore, mother-to-child transmission may contribute to a substantial number of cases of new HCV infections in children worldwide.<sup>2</sup>

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The risk of mother-to-child transmission of HCV also depends on a number of additional maternal, socioeconomic, and geographic factors. The risk of mother-to-child transmission (also called vertical transmission) of HCV depends on the HCV viral load of the mother, and whether she also has HIV. In a recent study among mothers with hepatitis C, the rate of transmission among hepatitis C infected mothers who also had HIV (*human immunodeficiency virus*) was 25.0%<sup>6</sup> compared to 3.8% in mothers who did not have HIV. A high HCV viral load in the mother has also been found to increase the risk of HCV transmission.<sup>7</sup> However, elective Cesarean section is not recommended for women with chronic HCV infection alone.<sup>8</sup>

## Natural History of Hepatitis C in Children

Evidence suggests that hepatitis C disease is relatively mild and usually does not cause symptoms in infected children. The rate of liver damage can vary depending on whether the child was infected by the mother or by a blood transfusion. Generally, transfusion-related infection in children with blood disorders such as hemophilia, thalassemia, or leukemia may differ according to the underlying disease. When infection is acquired from the mother, most children only show a signs of mild liver disease for the first one to two decades of life.

There are also many cases of *spontaneous clearance* where an HCV RNA positive infant becomes negative for the virus.<sup>6</sup> The spontaneous clearance of HCV appears to be more common in children than among adults, especially those past the age of 40.

Severe liver disease leading to *cirrhosis*, *liver cancer*, and/or *liver failure* requiring liver transplantation can occur during childhood but is very rare. Children infected with HCV probably do have some risk of developing these serious liver diseases in adulthood, but the exact risks are not known at the present time.

## Liver Biopsy in Children

Microscopic characteristics of liver tissue obtained by a biopsy indicate the extent of damage to the liver by the hepatitis C virus as well as the body's immune response to the virus. Changes in the liver cells are typically mild in children. These changes may include swelling (*inflammation*), and death of cells (*necrosis*).

Sometimes permanent replacement of liver cells with scars made of fibrous tissue (*fibrosis*) may be seen. This fibrosis may progress with age and duration of infection. Permanent replacement of the liver cells with fibrous tissue may, in the long run, harm the many functions of the liver, which include the production of proteins related to blood clotting and to processing of medications.<sup>9-12</sup>

## Hepatitis C Treatment in Children

There are several factors to consider when discussing treatment of children with chronic HCV infection, including the wide variation of the course of the disease in children as well as lack of definitive information on the safety and effectiveness of drugs in children. Although the issue of who is best treated has not been completely resolved, based on available data, the combination of *interferon* plus *ribavirin* is recommended by the American Association for the Study of Liver Disease for children with HCV who are considered appropriate candidates. The combination of interferon plus ribavirin has been approved by the U.S. Food and Drug Administration (FDA) for use in children 3 to 18 years of age.

### Interferon Monotherapy

Alfa-interferon is FDA approved for use in children. How this drug acts is not definitely known, but it stimulates the body's immune response to the hepatitis C virus. Several studies in children have shown that the response rates are better and the side effects are less severe in children compared to adults.<sup>13</sup> The overall sustained viral response (SVR) with standard interferon in children is 36% compared to 10% to 15% in adults. For *genotype 1*, the SVR in children is reported to be 27% compared to 8% to 10% for adults when treated with standard interferon.<sup>13</sup>

Pegylated interferon is a long-acting form of interferon, which only has to be given once per week compared to standard interferon, which has to be given at least 3 times per week. Since treatment with pegylated interferon produces higher SVR's in both adults and children, standard interferon has largely been abandoned as a treatment for HCV in children. Interferon has many side effects including flu-like symptoms, appetite loss, depression, fever, and depression of both white cell and red blood cell counts, all of which are fairly common. More rarely, interferon can cause thyroid disease, *autoimmune* disease, and/or visual problems.

### Pegylated Interferon Monotherapy

A small pilot study of *pegylated interferon-alfa 2a* in 14 children (2 to 8 years of age, all but one infected with genotype 1) showed an overall SVR of 43%.<sup>14</sup> The drug was generally well tolerated, but several children developed low white blood cell counts. It is clear that further studies in children with this drug should be done before it can be routinely prescribed. There are two forms of pegylated interferon, and neither of them are FDA-approved for children at the present time (April 2008).

### Interferon Plus Ribavirin

Ribavirin in combination with interferon is more effective for the treatment of HCV in adults compared to each drug when given alone. Interferon plus ribavirin is the FDA approved regimen for treatment of HCV in children aged 3 to 18 years. A recent study found the combination of interferon-alfa 2b in combination with ribavirin in 270 children was effective and safe. The overall SVR was 46%, and SVR for genotype 1 was 36%.<sup>15</sup>

## Pegylated Interferon Plus Ribavirin

Pegylated interferon plus ribavirin is the standard of care for adults with chronic HCV infection. To date, only three studies have published the results of pegylated interferon *combination therapy* in children, and all have been performed using pegylated interferon alfa-2b and ribavirin. The largest of these studies (61 children) lends support to the idea that the combination of pegylated interferon plus ribavirin in children will offer the good response rates seen in adults with chronic HCV.<sup>16</sup> “PEDS C” is a multi-center, randomized, controlled trial in 112 children evaluating the safety and effectiveness of 6 to 12 months of pegylated interferon with or without ribavirin.<sup>17</sup> The study should answer whether it is beneficial to add ribavirin to pegylated interferon for the treatment of HCV in children. Because ribavirin can cause birth defects when taken by pregnant females and since children with HCV infection appear to respond better to interferon-based *therapies* than adults do, this question is very important.

## To Treat or Not to Treat?

Given present knowledge about the disease, there is enough evidence to treat selected children with chronic HCV infection.

- Children in the 3 to 4 year age group should be considered for treatment before they enter school. The only FDA-approved therapy for this group is the combination of interferon given thrice weekly plus ribavirin (which fortunately is available as a syrup).
- Therapy for children in the 5 to 18 year age group should be individualized. Until the results of PEDS C are available, many authorities would reserve treatment for children with aggressive liver disease.
  - Children 5 to 12 years of age could be treated with the FDA-approved combination of interferon and ribavirin.
  - Off-label use of pegylated interferon could be considered for adolescents, but the treating physician must monitor patients very carefully for side effects such as low white blood cell counts.

There are certain conditions in childhood for which there is little information to guide therapy other than the experience in adults. These conditions include organ or bone marrow transplant, autoimmune diseases including HCV with autoimmune hepatitis, kidney failure, and/or significant disease in another organ system.

## Special Pediatric Issues

### Pregnancy and HCV Transmission

Pregnant women at risk for HCV infection should be screened for antibodies to HCV (anti-HCV), and HCV RNA testing should be performed if anti-HCV is positive.

Infants born to women with hepatitis C should be tested for anti-HCV at 18 months of age.<sup>18</sup> If the antibody test is positive, HCV RNA testing should be done. If the HCV RNA test is positive, the infant should be referred to a specialist in pediatric liver disease.

### Breastfeeding

Currently there is no evidence of mother-to-infant transmission of HCV infection from breastfeeding. According to guidelines from the Centers for Disease Control and Prevention and the American Academy of Pediatrics, maternal HCV infection is not a *contraindication* to breastfeeding. However, the mother should consider not breastfeeding the child if her nipples are cracked and bleeding.<sup>19</sup>

### Parenting Issues

Multiple important issues surround parenting with a child with HCV. Women may be particularly concerned about social stigma, sexual transmission, pregnancy, and childcare. These worries may affect their close relationships<sup>20</sup> as well as

their ability to take care of their child. Additionally, there might be concerns about the risk of HCV transmission in a household with a chronically infected individual such as a parent or sibling. The HCV infection risk to uninfected children living in the same household of people with chronic hepatitis C is believed to be very low.<sup>4</sup> Blood-to-blood contact should be avoided by not sharing personal hygiene items such as toothbrushes, razors, cuticle scissors, or any other item that may be contaminated with blood. Any blood from an infected person (even dried blood) should be cleaned with a 10% bleach solution (one part bleach to 9 parts water).

**Hepatitis C is not spread through sharing the same dishes, drinking glasses, silverware, or pots and pans. Hepatitis C is not spread through food.**

### HCV in Children With Blood Disorders

HCV infection has been demonstrated in 50% to 98% of children with hemophilia treated with factor concentrates prepared from pooled plasma. Furthermore, there is clear evidence that HCV infection is associated with liver disease in children with hemophilia.<sup>21-24</sup> There is evidence for similar trends in children with thalassemia.<sup>25-27</sup>

### Vaccines and HCV

There is currently no *vaccine* to prevent the transmission of HCV. However, children with chronic HCV should be vaccinated against the hepatitis A and *hepatitis B* viruses.<sup>28</sup>

### School Issues and Social Stigma

No studies have been performed to date examining the effects of having HCV infection on health-related quality of life or normal childhood development. However, the PEDS C study (currently underway) is examining these issues.

With regard to children's knowledge of hepatitis C, one study conducted in Australia found students' knowledge about HCV to be extremely poor.<sup>29</sup> In the authors' experience, there are significant schooling issues that stem from the infection and the effects of the treatment used. These include missed school days as well as risk of loss of privacy.

In addition to concerns about serious liver disease, children and their families often face the added burden of social stigma, especially when it comes to entry into day care or school. Fortunately, the American Academy of Pediatrics has provided guidelines to ease this burden stating there is no reason to exclude children with HCV from entry into day care and school.<sup>18</sup>

## Summary

Hepatitis C (HCV) is an important public health issue that includes both children and adults. An estimated 68,000 to 100,000 children in the U.S. have chronic hepatitis C. Since hepatitis C blood screening procedures have been put in place, children are primarily infected at the time of birth from mothers who have chronic hepatitis C.

Available evidence suggests that chronic hepatitis C is relatively mild and is usually *asymptomatic* in infected children. Rarely, however, severe disease leading to cirrhosis, liver cancer, and liver failure requiring liver transplantation may occur during childhood and adolescence.

Interferon with ribavirin is the FDA-approved regimen for treatment of HCV in children aged 3 to 18 years. It has been found effective and safe in children with chronic hepatitis C virus. Pegylated interferon may, in the future, offer response rates similar to that seen in adults with chronic HCV. However, pegylated interferon is not currently FDA-approved for use in children. Whether it will be necessary to add ribavirin to the treatment regime is not known at present.

There is presently no hepatitis C vaccine, but children with HCV should be immunized against the hepatitis A and hepatitis B viruses.

## References

1. Alter, MJ. Epidemiology of hepatitis C. *Hepatology*. 1997; 26(3 Suppl 1): 62S-65S.
2. Alter, MJ, D Kruszon-Moran, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341(8):556-62.
3. Gonzalez-Peralta, RP. Hepatitis C virus infection in pediatric patients. *Clin Liver Dis*. 1997;1(3): 691-705, ix.
4. Jonas, M. M. Children with hepatitis C. *Hepatology*. 2002;36(5 Suppl 1):S173-8.
5. Bortolotti, F., M. Resti, et al. Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. *J Pediatr*. 1998;133(3): 378-81.
6. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;Dec 1;192(11):1880-9 Epub 2005 Oct 28.
7. Newell ML, Pembrey L. Mother-to-child transmission of hepatitis C virus infection. *Drugs Today (Barc)*. 2002;May;38(5):321-37.
8. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology*. 2002;Nov;36(5 Supl 1):S106-13.
9. Kage, M., T. Fujisawa, et al. Pathology of chronic hepatitis C in children. Child Liver Study Group of Japan. *Hepatology*. 1997;26(3): 771-5.
10. Badizadegan K, Jonas MM, et al. . Histopathology of the liver in children with chronic hepatitis C viral infection. *Hepatology*. 1998;28(5): 1416-23.
11. Guido, M., F. Bortolotti, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *Am J Gastroenterol*. 2003;98(3): 660-3.
12. Guido, M., M. Rugge, et al. Chronic hepatitis C in children: the pathological and clinical spectrum. *Gastroenterology*. 1998;115(6): 1525-9.
13. Jacobson KR, Murray K, Zellos A, et al. An analysis of published trials of interferon monotherapy in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr*. 2002;Jan;34(1):52-8.
14. Schwarz KB, Mohan P, Narkewicz MR, et al. Safety, efficacy and pharmacokinetics of peginterferon alpha2a (40 kd) in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr*. 2006;43(4):499-505.
15. Gonzales-Peralta, RP, Kelly DA, Haber B, et al. Interferon Alfa-2b in Combination with Ribavirin for the Treatment of Chronic Hepatitis C in Children: Efficacy, Safety, and Pharmacokinetics. *Hepatology*, 2005;42(5):1010-18.
16. Wirth S, Pieper-Boustani H, Lang T, et al. Peginterferon alfa-2b Plus Ribavirin Treatment in Children and Adolescents with Chronic Hepatitis C. *Hepatology*, May 2005;41(5);1013-18.
17. Maryland Medical Research Institute. PEDS-C: A Clinical Trial for Children with Hepatitis C. Available at: <http://www.peds.org/>. Accessed September 18, 2008.
18. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics* 1998;101(3 Pt 1): 481-5.
19. Mast EE. Mother-to-infant hepatitis C virus transmission and breastfeeding. *Adv Exp Med Biol* 2004;554: 211-6.
20. Teixeira MC, Ribeiro MF, Gayotto LC, et al. Worse quality of life in volunteer blood donors with hepatitis C. *Transfusion*. 2006;Feb;45(2):278-83.
21. Blanchette, V. S., E. Vorstman, et al. Hepatitis C infection in children with hemophilia A and B. *Blood*. 1991;78(2): 285-9.
22. Leslie, D E, Rann S, et al. Prevalence of hepatitis C antibodies in patients with clotting disorders in Victoria. Relationship with other blood borne viruses and liver disease. *Med J Aust*. 1992: 156(11): 789-92.
23. Kanesaki, T., S. Kinoshita, et al. Hepatitis C virus infection in children with hemophilia: characterization of antibody response to four different antigens and relationship of antibody response, viremia, and hepatic dysfunction. *J Pediatr* 1993;123(3): 381-7.
24. Wagner N, and Rotthauwe HW. Hepatitis C contributes to liver disease in children and adolescents with hemophilia. *Klin Padiatr*. 1994;206(1): 40-4.
25. Lai, M. E., S. De Virgilis, et al. Evaluation of antibodies to hepatitis C virus in a long-term prospective study of post transfusion hepatitis among thalassaemic children: comparison between first- and second-generation assay. *J Pediatr Gastroenterol Nutr* 1993;16(4): 458-64.
26. Lai, ME, Mazzoleni AP, et al. Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalassaemic children. *Lancet* 1994;343(8894): 388-90.
27. Ni YH, Chang MH, et al. Hepatitis C viral infection in thalassaemic children: clinical and molecular studies. *Pediatr Res* 1996 39(2): 323-8.
28. Arankvalle, VA, Chadha MS. Who should receive hepatitis A vaccine? *J Viral Hepat*. 2003: May;10(3):157-8.
29. Lindsay J, Smith Am, Rosenthal DA. Uncertain knowledge: a national survey of high school students' knowledge and beliefs about hepatitis C. *Aust N Z J Public Health*. 1999;Apr;23(2):135-9.