

## Hepatitis C in the pediatric population: Transmission, natural history, treatment and liver transplantation

Saira Khaderi, Ross Shepherd, John A Goss, Daniel H Leung

Saira Khaderi, John A Goss, Division of Abdominal Transplantation, Micheal E DeBaakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030, United States

Ross Shepherd, Daniel H Leung, Division of Pediatric Gastroenterology, Hepatology, Nutrition, Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, United States

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**Correspondence to:** Saira Khaderi, MD, MPH, Assistant Professor of Surgery, Division of Abdominal Transplantation, Micheal E DeBaakey Department of Surgery, Baylor College of Medicine, 6620 Main Street, Suite 1450, Houston, TX 77030, United States. [khaderi@bcm.edu](mailto:khaderi@bcm.edu)

Telephone: +1-832-3551400 Fax: +1-713-6102479

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### Abstract

The number of children affected by the hepatitis C virus (HCV) in the United States is estimated to be between 23000 to 46000. The projected medical cost for children with HCV in the United States is upwards of 200 million over the next decade. The implementation of routine screening of blood supply has virtually eliminated transmission *via* transfusion and vertical transmission is now the most common mode of infection in children. Infections acquired during infancy are more likely to spontaneously resolve and fibrosis of the liver tends to increase with age suggesting slow progressive histologic injury. Anti-viral treatment may be warranted in children with persistently elevated liver enzymes or with significant fibrosis on liver biopsy. Current standard of care includes weekly pegylated interferon and ribavirin twice daily. Predictors of high sustained viral response include genotype 2 and 3 and low viral load in children with genotype 1 (< 600000 IU/mL). Triple therapy is

associated with a significantly higher rate of sustained virologic response (> 90%). Only 34 pediatric patients were transplanted with hepatitis C between January 2008 and April 2013. The majority of pediatric patients were born prior to universal screening of blood products and, as of June 2013, there are only two pediatric patients awaiting liver transplantation for end-stage liver disease secondary to hepatitis C. Pediatric survival rates post-transplant are excellent but graft survival is noticeably reduced compared to adults (73.73% for pediatric patients at one year compared to 87.69% in adult patients). New safe potent, and all-oral effective antiviral therapies for recurrent HCV should help increase graft survival.

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**Key words:** Hepatitis C; Liver transplantation; Pediatric; Infection; Fibrosis; Liver disease

**Core tip:** The number of children affected by the hepatitis C virus (HCV) in the United States is between 23000 to 46000. Current standard of care treatment includes weekly pegylated interferon and ribavirin twice daily. New enrollment into phase 1 and 2 trials with triple therapy are currently on hold due to the upcoming availability of all oral, interferon-free, direct acting antivirals. Triple therapy is associated with a rate of sustained virologic response (> 90%). Only 34 children were transplanted with HCV between January 2008 and April 2013. Pediatric survival rates post-transplant are excellent but graft survivals are reduced compared to adults. New antiviral therapies for recurrent HCV should help increase graft survival.

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## INTRODUCTION

Children represent a small but important portion of those infected with the hepatitis C virus (HCV) and our understanding of the disease is limited in the pediatric population. HCV differs in children with regards to transmission, rates of clearance, natural history and treatment. This review aims to summarize our understanding of the major issues related to HCV in children, including pediatric liver transplantation.

## EPIDEMIOLOGY

The prevalence of hepatitis C antibody (anti-HCV Ab) in North America is estimated to be about 1% to 1.5%<sup>[1]</sup> and children represent an even smaller percentage. Recent data from the National Health and Nutrition Examinations Survey III (NHANES III) report that 0.17% of 6- to 11-year-olds and 0.39% of 12- to 19-year-olds are anti-HCV positive. Although the proportion of children who are anti-HCV positive who are also HCV RNA positive is unclear, the number of children affected by chronic HCV infection in the United States is estimated to be between 23000 and 46000<sup>[2]</sup>.

The prevalence of HCV is higher in children who received blood products prior to 1992 when routine screening of blood supply was instituted and a second-generation ELISA test was introduced. Most of these affected individuals had conditions such as hemophilia, malignancy or congenital heart disease and the risk of chronic HCV is related to the amount of blood products received<sup>[3-5]</sup>.

Hepatitis C has projected medical costs of a staggering \$10.7 billion for adults in the United States in the years 2010-2019<sup>[6]</sup> and \$199-336 million for children over the next decade<sup>[2]</sup>. Its impact on morbidity includes a 26-fold increased risk of liver-related death when acquired during childhood<sup>[7]</sup>.

## TRANSMISSION

The implementation of routine screening of the blood supply has virtually eliminated transmission *via* transfusion, and vertical transmission is now the most common mode of infection in children. There are approximately 8000 new cases of hepatitis C per year in the United States from vertical transmission<sup>[2]</sup>. The estimated risk of transmitting HCV from mom to child is 4.3% in a mother with detectable HCV RNA<sup>[8]</sup>. A maternal HCV load of 600000 IU/mL or higher increases the risk of mother-to-infant transmission<sup>[9]</sup>. A combination of HCV and HIV infection increases the risk of vertical transmission two to three fold<sup>[9]</sup>. Fortunately, the rate of HCV transmission seen in pregnant HIV/HCV coinfecting women normalizes to that of mono-infected mothers when maternal

HIV activity is controlled with highly active antiretroviral therapy (HAART)<sup>[10]</sup>.

There are inconsistent reports on the role that mode of delivery may play in the risk of vertical transmission. Delivery by cesarean section is not routinely recommended as it provides no added benefit in reducing the risk of perinatal transmission<sup>[8,11]</sup>. However, prolonged rupture of membranes, placement of fetal scalp monitors, exposure to contaminated maternal blood and fetal anoxia at the time of delivery all have been associated with increased risk of perinatal HCV infection<sup>[11,12]</sup>. The precise timing and process by which the virus is transmitted from mother to infant are unknown but recent data suggest transmission is more likely to occur *in utero* than during the perinatal period<sup>[13]</sup>.

## NATURAL HISTORY

Infections acquired during infancy are more likely to spontaneously resolve than those acquired as an adult. In a large, multi-center, prospective study in Europe, 266 children with vertical HCV infection were followed for a median of 4.2 years<sup>[14]</sup>. Approximately twenty percent cleared the infection while 80% remained chronically infected. Children who remained HCV RNA PCR positive during and after one year of age had a lower likelihood of clearance.

Higher rates of spontaneous resolution have been found in infants with the Rs12979860 CC genotype for the IL28B polymorphism<sup>[15]</sup>. Infants, in particular, may have defense mechanisms that explain the inefficiency of HCV perinatal transmission. The placenta has been shown to play an immunoprotective role against HCV transmission in the neonate, and infants with human leukocyte antigen DR13 are also less likely to develop chronic HCV from vertical transmission.

As in adults with chronic HCV, fibrosis of the liver in pediatric patients tends to increase with age suggesting slow progressive histologic injury<sup>[16-18]</sup>. Although uncommon, progression to cirrhosis in childhood has been reported. A large multi-center Italian study analyzed 504 consecutive anti-HCV antibody positive patients over a 15 year period<sup>[19]</sup>. Nearly 95% were HCV RNA positive and the majority (56%) acquired HCV vertically. Although 8% demonstrated spontaneous clearance, 1.8% developed cirrhosis in a 2-9 year period. Risk factors for developing cirrhosis included genotype 1a and steatosis.

## SCREENING

Screening for hepatitis C should be considered in those children with risk factors for HCV. The largest group is comprised of children born to HCV-infected mothers or mothers with a history of intravenous drug abuse. Other groups include children with HIV infection, children who are victims of a sexual assault, children with a history of multiple sexual partners, and adolescents with a history of intravenous drug use.

**Table 1** Selected pegylated interferon/ribavirin treatment trials in children with chronic hepatitis C infection *n* (%)

Ref.	<i>n</i>	Treatment	Sustained virological response		
			All types	HCV type 1	HCV type 2/3/6
Wirth <i>et al</i> <sup>[26]</sup>	41	IFN-2b-ribavirin	25 (61)	18 (53)	7 (100)
González-Peralta <i>et al</i> <sup>[25]</sup>	118	IFN-2b-ribavirin	54 (46)	33 (36)	21 (84)
Wirth <i>et al</i> <sup>[27]</sup>	62	PEG-IFN-2b-ribavirin	36 (59)	22 (48)	13 (100)
Wirth <i>et al</i> <sup>[28]</sup>	107	PEG-IFN-2b-ribavirin	70 (65)	38 (53)	28 (93)
Schwarz <i>et al</i> <sup>[29]</sup>	55	PEG-IFN-2a-ribavirin	29 (53)	21 (47)	8 (80)
Schwarz <i>et al</i> <sup>[29]</sup>	59	PEG-IFN-2a	12 (21)	8 (17)	4 (36)

Modified from reference [20]. PEG-IFN: Pegylated interferon; HCV: Hepatitis C virus.

## MONITORING

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recently reviewed available data to assist providers in the diagnosis, management and prevention of HCV infection in children and adolescents<sup>[20]</sup>. Newly diagnosed pediatric patients should undergo a thorough physical exam and laboratory evaluation to determine risk factors for infection and to detect the presence of associated sequelae of liver disease. Annual alpha-fetoprotein or liver ultrasound is also recommended in the setting of elevated transaminases during non-treatment monitoring. Liver biopsy is not always necessary but should be considered if the results will influence clinical decision making (for example, patients being considered for antiviral treatment or to exclude comorbid disease such as autoimmune hepatitis). HCV-infected patients with significant fibrosis or cirrhosis should be monitored annually with alpha-fetoprotein and abdominal ultrasound<sup>[21]</sup>.

## CLINICAL SIGNS AND SYMPTOMS

The clinical course of acute and chronic HCV in children is generally benign. Symptoms are often non-specific and mild. Progression to decompensated liver disease may occur but is rare in children. Growth is generally unaffected in young children with chronic HCV<sup>[22]</sup> and biochemical markers of liver dysfunction will fluctuate. Transaminases may be normal or minimally elevated in chronic HCV and in some cases may remain elevated despite anti-HCV seronegativity<sup>[23,24]</sup>.

## TREATMENT

Determining candidacy for treatment of chronic HCV in a child or adolescent is often controversial. Annual follow-up until adulthood when superior medications will likely be available may be a good option for children and adolescents who have no indicators of progressive disease. Anti-viral treatment, however, may be warranted in children with persistently elevated liver enzymes or those with significant fibrosis on liver biopsy.

The current standard of care includes pegylated interferon once weekly in combination with ribavirin twice daily. Several smaller single-center and large multicenter

pediatric studies have proven the superiority of achieving sustained virologic response (SVR), defined as being HCV RNA negative 6 mo after completion of treatment, with combination therapy compared to interferon alone<sup>[25-29]</sup> (Table 1). Predictors of high rates of SVR include genotypes 2 and 3 (> 80% SVR) and low viral load in children with genotype 1 (< 60000 IU/mL)<sup>[25,29]</sup>. It is important to note that biochemical and virologic response is accompanied by histologic improvement in patients with SVR in these trials and interferon was well tolerated in children.

As in adults, adverse events related to interferon such as fever, headache, and flu-like symptoms are common during the first weeks of treatment, though appear to be short-lived and less intense in children. Persistent symptoms may include anorexia, weight loss and psychiatric complications such as depression and anxiety. Hematologic abnormalities are also frequent with this combination, including ribavirin-induced anemia, thrombocytopenia, and neutropenia which may require dose adjustment. Growth colony stimulating factor, blood transfusions, or erythropoietin for treating neutropenia and anemia are rarely recommended in children. Decreases in body weight, growth, BMI related to interferon have been shown to be reversible with cessation of therapy<sup>[30]</sup>.

Two protease inhibitors, boceprevir and telaprevir, were licensed separately in the United States in 2011 for use in combination with pegylated interferon and ribavirin in adults with chronic HCV genotype 1. This triple therapy is associated with a significantly higher rate of sustained virologic response (> 90%) compared with dual therapy alone. Currently, phase 1 and 2 trials are ongoing in children. However, the FDA has halted pediatric studies using Boceprevir and the sponsor for telaprevir has discontinued pediatric enrollment due to the availability of interferon-free options which should be available to children through clinical trials soon.

Led by the recent approval of sofosbuvir, several compounds, including daclatasvir, asunaprevir, and ledipasvir are awaiting expedited FDA approval after initial studies in the adult population with tremendous efficacy and tolerability - including HCV non-responders and relapsers to previous therapy<sup>[31]</sup>. Advantages of these combinations include a high resistance profile, decreased toxicity, and increased sustained viral response in the absence of interferon. Phase 2 trials with sofosbuvir and ribavirin

**Table 2** Orthotopic liver transplants performed from January 1, 2008 through April 30, 2013 for pediatric patients (age 0-17) with a diagnosis of hepatitis C

	2008	2009	2010	2011	2012	2013	Total
Initial OLT	8	3	6	4	7	4	32
Retransplant	0	1	0	0	1	0	2
Total	8	4	6	4	8	4	34

Based on Organ Procurement and Transplantation Network data. OLT: Orthotopic liver transplant.

in children with genotypes 2 and 3 began in 2014. HCV-infected children may soon realize the benefits from the tremendous research in anti-HCV therapy in the last 5 years<sup>[32-34]</sup>.

### LIVER TRANSPLANT

Hepatitis C is the most common indication for liver transplantation in US adults but is a rare indication in the pediatric population. Little is known about the natural course of HCV following orthotopic liver transplantation (OLT) in children. The largest study to date evaluating post-transplant outcomes in pediatric patients transplanted for hepatitis C was published by our group in 2006<sup>[35]</sup>. Sixty-seven children were transplanted for hepatitis C between January 1988 and June 2005 in the United States with a total of 83 grafts. Patient and allograft survivals after the initial transplant were 71.6% and 55%, respectively, at 5 years. Nearly 30% of the patients were listed for retransplantation (the overwhelming majority for HCV recurrence) and 19.3% were ultimately retransplanted. The median time between OLTs for those re-transplanted because of HCV was 290 d. Patient and allograft survival rates decreased to 55.0% and 33.8%, respectively, following retransplantation. At the time of publication, these outcomes were similar to that of adult patients. These data revealed that children can benefit from transplantation but also highlighted our limitations in HCV viral suppression during the post-transplant period and prevention of HCV reinfection.

Children who underwent liver transplant prior to the availability of HCV antibody screening of blood products and donors were at high risk for HCV infection and up to 10.2% developed *de novo* hepatitis C<sup>[36]</sup>. McDiarmid *et al*<sup>[36]</sup> evaluated 13 pediatric patients transplanted between 1984 and 1996 with *de novo* hepatitis C. Of these, twelve patients were treated with interferon-2 alpha monotherapy (standard of care at the time the paper was written) and 4 developed rapidly progressive liver failure while on interferon treatment requiring urgent retransplantation. Three of the patients ultimately developed aggressive recurrent HCV after the second OLT and subsequently died from HCV-induced liver failure. In a series published in 2011, Venturi *et al*<sup>[37]</sup> reported improved outcomes in a group of 10 pediatric patients with *de novo* hepatitis C following pediatric liver transplantation

**Table 3** 1, 3, and 5-year graft and patient survival rates for deceased donor liver transplants performed for patients with hepatitis C between January 1, 2002 through April 30, 2007

		1-yr (95%CI)	3-yr (95%CI)	5-yr (95%CI)
Pediatric	Graft	73.73% (56.73-90.73)	64.52% (46.72-82.31)	52.23% (34.45-70.01)
	Patient	87.69% (72.66-100.0)	83.70% (66.93-100.0)	79.05% (60.34-97.76)
Adult	Graft	83.29% (82.58-83.99)	71.58% (70.72-72.43)	64.36% (63.45-65.28)
	Patient	87.29% (86.65-87.93)	76.58% (75.76-77.40)	69.75% (68.85-70.66)

Based on Organ Procurement and Transplantation Network data.

(transplanted between 1985 and 2010). Five patients did not receive antiviral therapy post-OLT - two of which achieved spontaneous viral clearance. Of the 5 patients treated, all received the pegylated form of interferon with ribavirin. Eventually, four achieved SVR and the fifth patient was completing therapy at the time of manuscript publication. All patients were alive with a mean follow-up of 7.3 ± 5.5 years after the diagnosis of HCV. Overall the patients demonstrated a favorable long-term outcome and responded well to treatment.

Since the initiation of routine screening of the blood donor supply in the early 1990's, the number of pediatric patients with hepatitis C requiring liver transplantation has decreased. Per review of UNOS/OPTN Registry data, as of June 2013, there were only 2 pediatric patients awaiting a liver transplant for liver disease secondary to hepatitis C. Between January 2008 and April 2013, only 34 pediatric patients were transplanted with hepatitis C compared to 13754 adults (Table 2). The majority of the pediatric patients were born just prior to the beginning of universal screening of blood products or soon afterwards. Although 1, 3, and 5-year patient survival rates in the pediatric population are better than adult survival rates, the graft survival rates are noticeably reduced (Table 3). This could be due to HCV recurrence prior to the approved use of pegylated interferon or skewed by the small sample size. Overall improved pre and post-transplant care for children and approval of pegylated interferon likely played a role in improved pediatric survival rates.

Liver transplant for children with primary hepatitis C disease is rare and our understanding of the disease in this population is limited. The incidence of hepatitis C in children has decreased since the implementation of routine and effective screening and the number of children requiring liver transplantation for hepatitis C has significantly decreased. In the current era, the treatment goal for pediatric patients with hepatitis C is to prevent progression to end-stage liver disease. Although the current standard of care has remained unchanged for several



years, trials with new regimens are currently ongoing. These combinations are known to have a high resistance profile, decreased toxicity and high rates of cure. Liver transplantation is still the best option for children with end-stage liver disease from hepatitis C and recent data report excellent patient survival rates post-transplant. Although graft survival rates are not as high as in adults, new antiviral therapies to safely and effectively eradicate recurrent HCV following transplant should help increase graft survival rates like never seen before.

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