


HCV in Children

Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of Children With HCV Infection

RECOMMENDED	RATING 
All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age.	I, A
Testing with an HCV-RNA assay can be considered in the first year of life, but the optimal timing of such testing is unknown.	IIa, C
Testing with an HCV-RNA assay can be considered as early as 2 months of age.	IIa, B
Repetitive HCV RNA testing prior to 18 months of age is not recommended.	III, A
Children who are anti-HCV positive after 18 months of age should be tested with an HCV-RNA assay after age 3 to confirm chronic hepatitis C infection.	I, A
The siblings of children with vertically-acquired chronic HCV should be tested for HCV infection, if born from the same mother.	I, C


Although the prevalence of chronic hepatitis C is lower in children than adults, an estimated 3.5 to 5 million children worldwide have chronic HCV infection ([Indolphi, 2019](#)); ([Gower, 2014](#)). Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are HCV antibody positive ([Alter, 1999](#)).

As birth to a woman with chronic hepatitis C is a known risk for infection, children born to these women should be evaluated and tested for HCV. The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although rates are higher among women with inadequately controlled HIV coinfection, and women with higher HCV-RNA levels, or viral loads ($>6 \log_{10}$ IU/mL) ([Benova, 2014](#)); ([Delotte, 2014](#)); ([Cottrell, 2013](#)); ([Shebl, 2009](#)). Identifying, following, and treating exposed children is recommended. The preferred assay for evaluation of HCV infection early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months ([Aniszewska, 2012](#)); ([England, 2005](#)). About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 4 years of age ([Indolphi, 2019](#)); ([Garrazino, 2014](#)); ([Farmand, 2012](#)); ([Yeung, 2007](#)); ([EPHCVN, 2005](#)); ([Mast, 2005](#)).

There is considerable debate about the utility of HCV-RNA testing within the first year of life. Proponents argue that use of a highly sensitive RNA assay early in life can increase the rate of infected infants detected, and that a negative result strongly suggests the infant is not infected while a positive result helps identify HCV cases earlier. Proponents also want to seize opportunity to test in a patient group that is often lost to follow up. Opponents argue that early testing does not change the need for definitive testing at or after 18 months; HCV RNA is more expensive than an antibody-based test; and there is no intervention or treatment that will occur prior to age 3—because of lack of approved drugs for this age group and to allow for possible spontaneous clearance. One large single center study demonstrated that HCV-RNA testing done in exposed infants aged 2 months to 6 months led to reliable positive and negative results that correlated with ultimate testing at 18 months ([Honegger, 2018](#)). There is no value in repeated HCV-RNA testing prior to 18 months of age, but anti-

HCV testing should take place at or after 18 months of age.


Transmission and Prevention

Recommendations for Counseling Parents Regarding Transmission and Prevention in Children with HCV Infection	
RECOMMENDED	RATING 
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, children with HCV infection do not pose a risk to other children and can participate in school, sports, and athletic activities, and engage in all other regular childhood activities without restrictions.	I, B
Parents should be informed that universal precautions should be followed at school and in the home of children with HCV infection. Educate families and children about the risk and routes of HCV transmission, and the techniques for avoiding blood exposure, such as avoiding the sharing of toothbrushes, razors, and nail clippers, and the use of gloves and dilute bleach to clean up blood.	I, B

HCV-infected children often face discrimination and stigmatization in school and child-care settings that is driven by public misunderstanding regarding hepatitis C transmission. HCV is not transmitted by casual contact in the absence of blood exposure. Families should not be forced to disclose a child's HCV infection status, and children should not be restricted from any routine childhood activity.

The risk of sexual transmission of hepatitis C is considered very low/rare. Sexual transmission occurs but is generally inefficient except among HIV-infected men who have unprotected sex with men (see [HCV Testing and Linkage to Care](#)) ([Tieu, 2018](#)); ([Vaux, 2015](#)); ([Schmidt, 2014](#)). Adolescents with HIV infection and those with multiple sexual partners or sexually transmitted infections (STIs) should be encouraged to use barrier precautions to prevent sexual transmission of HCV and other STIs. Other adolescents with HCV infection should be counseled that the risk of sexual transmission is low but barrier precautions are recommended for other reasons (see [Testing and Linkage to Care: Table 2 - Measures to Prevent Transmission of HCV](#)).

Monitoring and Medical Management

Recommendations for Monitoring and Medical Management of Children With HCV Infection	
RECOMMENDED	RATING 
Routine liver biochemistries at initial diagnosis and at least annually thereafter are recommended to assess for disease progression.	I, C
Appropriate vaccinations are recommended for children with HCV infection who are not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C

Recommendations for Monitoring and Medical Management of Children With HCV Infection

Disease severity assessment via routine laboratory testing and physical examination, as well as use of evolving noninvasive modalities (ie, elastography, imaging, or serum fibrosis markers) is recommended for all children with chronic HCV.	I, B
Children with cirrhosis should undergo hepatocellular carcinoma (HCC) surveillance and endoscopic surveillance for varices per standard recommendations.	I, B
Hepatotoxic drugs should be used with caution in children with chronic hepatitis C after assessment of potential risks versus benefits of treatment. Use of corticosteroids, cytotoxic chemotherapy, and/or therapeutic doses of acetaminophen are not contraindicated in children with chronic hepatitis C.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic hepatitis C.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for adolescents with chronic HCV infection and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with chronic HCV infection.	I, C

Liver disease due to chronic HCV infection generally progresses slowly in children, and cirrhosis and liver cancer occur infrequently. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never develop advanced liver disease.

The initial assessment of children with chronic HCV infection includes exclusion of other causes of liver disease, assessment of disease severity, and detection of extrahepatic manifestations of HCV infection. Testing for concomitant HBV (HBsAg, anti-HBc, and anti-HBs), HIV (anti-HIV), and immunity to HAV (anti-HAV IgG) are recommended due to shared risk factors and the need to vaccinate nonimmune children who may not have received routine childhood HAV and HBV vaccines.

Disease staging in children can be accomplished via physical examination and the assessment of routine laboratory parameters including albumin, serum hepatic aminotransferase levels, total bilirubin, international normalized ratio (INR), and platelet count every 6 to 12 months. Serum fibrosis markers also hold promise to stratify disease severity but require further validation ([Nielsen, 2019](#)); ([Pokorska-Spiewak, 2017](#)); ([Mack, 2012](#)). Of note, serum aminotransferase levels are not consistently reflective of disease severity in children. In one study nearly 33% of children had normal aminotransferase levels despite substantial necroinflammation on biopsy ([Casiraghi, 2004](#)).

For children in whom advanced liver disease is a concern, liver imaging to evaluate for splenomegaly or venous collaterals is recommended initially, using liver ultrasound instead of CT or MRI due to its widespread availability and lack of ionizing radiation. Although liver biopsy is considered the gold standard regarding the grade of inflammation and stage of fibrosis, sampling artifact is problematic and most patients and practitioners prefer noninvasive alternatives, such as liver elastography, to determine the presence/absence of cirrhosis, particularly in children. Ultrasound-based liver elastography in children requires the use of specialized probes and cutoff values for advanced fibrosis/cirrhosis that differ from those used in adults, but this approach appears promising for monitoring children with chronic HCV infection ([Behairy, 2016](#)); ([Geng, 2016](#)); ([Lee, 2013](#)).

Due to the slow rate of fibrosis progression among children, there are few, if any, established bona fide risk factors for disease progression. Development of advanced liver disease in children is infrequent until more than 30 years of infection ([Jhaveri, 2011](#)); ([Goodman, 2008](#)); ([Minola, 2002](#)). However, as in adults, children with comorbid disease—such as


obesity with nonalcoholic fatty liver disease and congenital heart disease with elevated right heart pressures—and those receiving hepatotoxic drugs should be monitored carefully for disease progression.

Hepatocellular carcinoma (HCC) is rarely encountered among children and has been reported almost exclusively in those with cirrhosis. There are reports that children with chronic HCV infection and a history of childhood leukemia may be at increased risk of developing HCC, but evidence is limited ([González-Peralta, 2009](#)). In children with cirrhosis, liver ultrasound with or without serum alpha-fetoprotein (AFP) testing every 6 months is recommended for HCC surveillance per AASLD guidelines ([Bruix, 2011](#)). A baseline endoscopy is advisable to detect esophageal varices in children with cirrhosis and every 3 years thereafter in the absence of viral clearance. After successful antiviral therapy, the risk for cirrhosis complications decreases substantially.

In children with advanced fibrosis from chronic HCV infection, medications that are known to accelerate hepatic fibrosis (eg, methotrexate) should be avoided, if possible. Similarly, abstinence from alcohol use is strongly advised to minimize disease progression. Although corticosteroids and other immunosuppressants may enhance HCV replication, they are not contraindicated in children with HCV infection and should be prescribed for appropriate indications based on overall risks vs benefits. Of note, icteric flares of HCV—as reported in children and adults with chronic HBV—have not been reported in children receiving organ transplants or cytotoxic chemotherapy. Although underlying liver disease is a risk factor for development of sinusoidal obstruction syndrome following bone marrow transplantation, the presence of HCV infection should not delay this therapy.

To remain well, untreated children with chronic hepatitis C are encouraged to maintain a healthy body weight due to the known deleterious effects of insulin resistance on fibrosis progression with HCV infection ([Petta, 2011](#)); ([Cua, 2008](#)); ([Moucari, 2008](#)). Other commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, nonsteroidal anti-inflammatory drugs and aspirin should be avoided, if possible, in children with cirrhosis and esophageal varices due to concerns of gastrointestinal bleeding and nephrotoxicity. Acetaminophen is a safe and effective analgesic for children with chronic HCV infection when dosed per package insert recommendations.

Whom and When to Treat Among Children and Adolescents With HCV Infection

Recommendations for Whom and When to Treat Among Children and Adolescents With HCV Infection	
RECOMMENDED	RATING 
Direct-acting antiviral (DAA) treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged ≥ 3 years as they will benefit from antiviral therapy, regardless of disease severity.	I, B
The presence of extrahepatic manifestations—such as cryoglobulinemia, rashes, and glomerulonephritis—as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

HCV-related, advanced liver disease is uncommon during childhood. However, liver disease progresses over time with increasing fibrosis severity ([Indolfi, 2019](#)); ([Mizouchi, 2018](#)); ([Bortolotti, 2008](#)); ([EPHCVN, 2005](#)); ([Resti, 2003](#)). Although uncommon, cirrhosis occurs occasionally in children and adolescents (aged < 18 years) with HCV infection. Children have a long life expectancy during which HCV complications may develop. Children and adolescents with HCV infection may also transmit the virus to others.

The high success rates with DAA regimens in adults with chronic HCV infection are increasingly being replicated in the pediatric population. Interferon and ribavirin exert general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Additionally, interferon-based regimens have limited success in children and adolescents with genotype 1 or 4. Promising early and emerging clinical trial data evaluating DAA regimens in children and adolescents usher in the opportunity to expand use of these safe, well-tolerated, efficacious HCV therapies in the pediatric population. Treatment of children as young as 12 years is predicted to be very cost-effective with currently approved DAA regimens as well as those in clinical trials ([Nguyen, 2019b](#)). Another cost-utility analysis compared DAA treatment at age 6 vs delaying treatment until age 18. The researchers reported the incremental cost-utility ratio for early vs delayed DAA therapy was <\$12,000/QALY gained. They concluded that treatment during early childhood is cost-effective and delaying therapy until early adulthood may result in increased lifetime risk of complications of late-stage liver disease ([Greenway, 2019](#)). Approval of additional DAA regimens for children aged 3 through 11 is anticipated in the near future.

HCV Antiviral Therapy for Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for treatment-naive adolescents aged ≥12 years or weighing ≥45 kg with any genotype, without cirrhosis or with compensated cirrhosis ^a	8 weeks	I, B
Combination ledipasvir/sofosbuvir (weight-based dosing; see table 1) for treatment-naive or interferon-experienced children aged ≥3 years with genotype 1, 4, 5, or 6, without cirrhosis or with compensated cirrhosis ^a	12 weeks	I, B

^a Child-Pugh A

Recommended regimens listed by evidence level and alphabetically for:

DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING
Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, <u>without cirrhosis</u>	8 weeks	I, C

Recommended regimens listed by evidence level and alphabetically for:

DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis^a

Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, <u>with compensated cirrhosis^a</u>	12 weeks	I, C
Genotype 3: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis or with compensated cirrhosis ^a	16 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to NS3/4A protease inhibitors but <u>no NS5A inhibitor exposure</u> , without cirrhosis or with compensated cirrhosis ^a	12 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an NS5A inhibitor but <u>no NS3/4A protease inhibitor exposure</u> , without cirrhosis or with compensated cirrhosis ^a	16 weeks	I, C
Genotype 1: Combination ledipasvir/sofosbuvir (weight-based dosing; see table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, <u>without cirrhosis</u>	12 weeks	I, C
Genotype 1: Combination ledipasvir/sofosbuvir (weight-based dosing; see table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, <u>with compensated cirrhosis^a</u>	24 weeks	I, C
Genotype 4, 5, or 6: Combination ledipasvir/sofosbuvir (weight-based dosing; see table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis or with compensated cirrhosis ^a	12 weeks	I, C

^a Child-Pugh A

Table 1. Weight-Based Dosing of Ledipasvir/Sofosbuvir for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Ledipasvir/Sofosbuvir
<17 kg	33.75 mg/150 mg
17 to <35 kg	45 mg/200 mg
≥35 kg	90 mg/400 mg per day

Table 2. Weight-Based Dosing of Sofosbuvir in Combination With Ribavirin for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Sofosbuvir
<17 kg	150 mg
17 to <35 kg	200 mg
≥35 kg	400 mg

Table 3. Weight-Based Dosing of Ribavirin for Children Aged ≥3 Years

Body Weight	Daily Dose of Ribavirin (divided AM and PM)
<47 kg	15 mg/kg
47 to 49 kg	600 mg
50 to 65 kg	800 mg
66 to 80 kg	1000 mg
>80 kg	1200 mg

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) was approved for adolescents aged 12 through 17 years in April 2019. In the registration trial, 47 adolescents were treated with the adult-approved coformulated preparation; the duration of treatment was based on viral genotype, prior treatment, and cirrhosis status ([Jonas, 2019](#)). Genotypes 1 through 4 were represented in the trial. Two participants were HIV coinfecting, none had cirrhosis, and 11 had a prior treatment failure with peginterferon/ribavirin. SVR12 was 100%. The study drugs were well tolerated with no serious adverse events and no drug discontinuations.

Although there are no data from the adolescent population, EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 343 treatment-naïve adults with genotype 1, 2, 3, 4, 5, or 6 and compensated cirrhosis. Overall SVR12 rates were 99.7% (334/335) in the per-protocol population and 97.7% (335/343) in the intention-to-treat population ([Brown, 2019](#)). Similarly, FDA approval and HCV guidance panel HCV treatment recommendations for DAA-experienced adolescents are based on clinical trial data from adults ([Asselah, 2018b](#)); ([Puoti, 2018](#)); ([Wyles, 2018](#)); ([Zeuzem, 2018](#)); ([Forns, 2017](#)).

Given its pangenotypic activity, safety, and efficacy record in adult patients, glecaprevir/pibrentasvir is recommended as the first choice for adolescent HCV treatment. As in adults, coadministration of carbamazepine, efavirenz-containing regimens, and St. John's wort is not recommended since these compounds may decrease concentrations of glecaprevir and pibrentasvir.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) is approved for use in children 12 to 17 years

old. In a phase 2, multicenter, open-label study of 100 adolescents with genotype 1 treated for 12 weeks with the adult formulation of ledipasvir/sofosbuvir, SVR12 was documented in 98% of participants ([Balistreri, 2017](#)). The 2 patients who did not achieve SVR12 were lost to follow-up during or after treatment. Eighty percent of the patients were treatment naive. One patient had cirrhosis, 42 did not, and the cirrhosis status was unknown in the remaining 57. The regimen was safe and well tolerated in this population, and the adult dosage formulation resulted in pharmacokinetic characteristics similar to those observed in adults.

In August 2019, the FDA approved an expansion of pediatric indications for ledipasvir/sofosbuvir to include the 3- through 11-year-old age group for specific clinical scenarios. Dosing is weight based (see table 1). Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive children and adolescents aged ≥ 3 years with genotype 1, 4, 5, or 6, without cirrhosis or with compensated cirrhosis (Child-Pugh A). This regimen is also recommended for interferon-experienced (\pm ribavirin, with or without an HCV protease inhibitor) children and adolescents aged ≥ 3 years with genotype 1 or 4. A 12-week course is recommended for patients without cirrhosis; 24 weeks is recommended for those with compensated cirrhosis. Two clinical trials supporting the approval of ledipasvir/sofosbuvir in the pediatric population aged 3 through 11 years demonstrated high SVR12 rates comparable to those seen in adults ([Schwarz, 2019](#)); ([Murray, 2018](#)).

Sofosbuvir Plus Ribavirin

In September 2019, the FDA newly approved weight-based sofosbuvir plus ribavirin (see tables 2 and 3) for treatment-naive or interferon-experienced (\pm ribavirin) children aged ≥ 3 years with genotype 2 or 3, without cirrhosis or with compensated cirrhosis (Child-Pugh A). A 12-week course is recommended for patients with genotype 2; 24 weeks is recommended for those with genotype 3. The registration trial conducted in children aged 3 to < 11 years demonstrated an SVR12 of 98% ([Rosenthal, 2019](#)). The use of sofosbuvir plus ribavirin is further supported from clinical trials conducted among adolescents ([Wirth, 2017](#)) and adults with genotype 2 or 3 infection ([Sulkowski, 2014](#)); ([Zeuzem, 2014a](#)); ([Jacobson, 2013](#)); ([Lawitz, 2013](#)).

Currently, sofosbuvir plus ribavirin remains the only FDA-approved DAA for children 3 through 11 years with genotype 2 or 3 infection. However, recent clinical trials evaluating weight-based dosing of sofosbuvir/velpatasvir ([Jonas, 2019a](#)) and glecaprevir/pibrentasvir ([Jonas, 2019b](#)) are expected to lead to FDA approval for children aged 3 through 11 years. The HCV guidance panel recommends awaiting approval of a pangenotypic regimen unless there is a compelling need for immediate antiviral treatment of children aged 3 through 11 years with genotype 2 or 3 infection.

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