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 women with HCV should be tested for HCV infection.. Testing is recommended using an HCV RNA test performed between 2 months and 6 months of age.* Those who test positive should be referred for follow-up and possible future treatment, while those who are negative can be reassured with no further follow-up required.	I, A
Repetitive HCV RNA testing prior to 18 months of age is not recommended.	III, A
The siblings of children with vertically-acquired chronic hepatitis C should be tested for HCV infection if born from the same mother.	I, C

*If testing between 2-6 months is missed, an HCV RNA test is recommended for perinatally exposed infants aged 7-17 months, and an HCV antibody test with reflex HCV RNA is recommended for perinatally exposed children ≥18 months who have not been previously tested.

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 person 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, (>6 $\log_{10}$ IU/mL) (Ades, 2023); (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 hepatitis C antibody (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 (Indolfi, 2019); (Garazzino, 2014); (Farmand, 2012); (Yeung, 2007); (EPHCVN, 2005); (Mast, 2005).

Due to many reports describing the majority of infants with perinatal exposure never receiving proper HCV testing (Lopata, 2020); (Kuncio, 2016), the US Centers for Disease Control and Prevention (CDC) issued new recommendations prioritizing early use of HCV RNA testing (Panagiotakopoulos, 2023). The preferred window is 2 months to 6 months of age to allow for ample opportunity to perform testing during already scheduled vaccine and well-child visits. This recommendation is supported by data from a large, single center study which 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 (Gowda, 2021). If an infant presents between 7 months and 17 months of age, a single HCV RNA test can be sent at that visit. For children who present aged 18 months or older, HCV antibody testing can be performed with follow-up HCV RNA if positive. 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. For those infants who test positive for HCV RNA, there is no intervention or treatment that will occur prior to age 3 years—because of lack of approved drugs for this age group and to allow for possible spontaneous clearance. However, families can be given anticipatory guidance about plans for future testing and possible treatment. For those infants who test negative, families can be reassured that the infant does not have HCV infection and there is no need for further follow-up.

Importantly, siblings of infants born to mothers with HCV infection should be tested for HCV if they have not been previously tested.

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

Children with HCV infection often face discrimination and stigmatization in school and childcare 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 extremely low/rare. Sexual transmission occurs but is generally inefficient except among men with HIV infection who have unprotected sex with men (see HCV Testing and Linkage to Care) (Vaux, 2019); (Tieu, 2018); (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 chronic HCV infection who are not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C
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 infection.	I, B
Children with cirrhosis should undergo hepatocellular carcinoma surveillance and endoscopic surveillance for varices per standard recommendations.	I, B
Hepatotoxic drugs should be used with caution in children with chronic HCV infection 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 HCV infection.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV infection.	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, children with HCV infection 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. Testing for concomitant hepatitis B virus infection (hepatitis B surface antigen, hepatitis B core total antibody, and hepatitis B surface antibodies), HIV infection (HIV antibodies), and immunity to hepatitis A virus (hepatitis A virus immunoglobulin G) are recommended due to shared risk factors and the need to vaccinate nonimmune children who may not have received routine childhood hepatitis A virus and hepatitis B virus vaccines.

Disease staging in children can be accomplished via physical examination and assessment of routine laboratory parameters including albumin, serum hepatic aminotransferase levels, total bilirubin, international normalized ratio (INR), and platelet count every 6 months 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 computed tomography or magnetic resonance imaging 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 or 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. Nonetheless, 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 in 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 metabolic dysfunction-associated 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 testing every 6 months is recommended for HCC surveillance per AASLD guidelines (Marrero, 2018). 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 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 versus benefits. Of note, icteric flares of HCV—as reported in children and adults with chronic hepatitis B infection—have not been reported in children receiving an organ transplant 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 (Kukla, 2015); (Petta, 2011); (Cua, 2008); (Moucari, 2008). 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 administered in dosages recommended in the package insert.

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 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); (Mizuochi, 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-related complications may develop. Children and adolescents with HCV infection may also transmit the virus to others.

The high success rates with direct-acting antiviral (DAA) regimens in adults with chronic HCV infection have been replicated in the pediatric population. Clinical trial data evaluating DAA regimens in children and adolescents have allowed expanded 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 (Nguyen, 2019b). Another cost-utility analysis compared DAA treatment at age 6 versus delaying treatment until age 18. The researchers reported the incremental cost-utility ratio for early versus delayed DAA therapy was $12,690 per quality-adjusted life year gained. They concluded that treatment during early childhood is cost-effective and delaying therapy until early adulthood may result in an increased lifetime risk of complications of late-stage liver disease (Greenaway, 2020). US Food and Drug Administration (FDA) approved DAA regimens are available for children aged 3 to <18 years with any genotype of HCV.

HCV Antiviral Therapy for Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis

Recommended regimens listed by pangenotypic, evidence level, and alphabetically for:

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

RECOMMENDED	DURATION	RATING
Combination of glecaprevir/pibrentasvir (weight-based dosing;	8 weeks	I, B

Recommended regimens listed by pangenotypic, evidence level, and alphabetically for: **Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]**		
see Table 1) for children aged ≥3 years with any genotype[b]		
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children aged ≥3 years with any genotype	12 weeks	I, B
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 3) for children aged ≥3 years with genotype 1, 4, 5, or 6	12 weeks	I, B
[a] Child-Pugh A [b] A longer duration of therapy (ie, 16 weeks) may be needed for children or adolescents with genotype 3 infection and interferon experience.		

Table 1: Weight-Based Dosing of Glecaprevir/Pibrentasvir for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Glecaprevir/Pibrentasvir
<20 kg	150 mg/60 mg
≥20 kg to <30 kg	200 mg/80 mg
≥30 kg to <45 kg	250 mg/100 mg
45 kg and greater or 12 years of age and older	300 mg / 120 mg / day

Table 2: Weight-Based Dosing of Sofosbuvir/Velpatasvir Fixed-Dose Combination in Children Aged ≥3 Years

Body Weight	Once Daily Dose of Sofosbuvir/Velpatasvir
< 17 kg	150 mg/37.5 mg
17 - < 30 kg	200 mg/50 mg

Body Weight	Once Daily Dose of Sofosbuvir/Velpatasvir
≧ 30 kg	400 mg/100 mg

Glecaprevir/Pibrentasvir

Adolescents aged 12 years or older receive the adult tablet formulation of glecaprevir/pibrentasvir. Younger children receive a formulation of small film-coated granules that are mixed with nonacidic, non-liquid foods (eg, peanut butter or Nutella).

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, 2020). Genotypes 1 through 4 were represented in the trial. Two participants were HIV coinfected, none had cirrhosis, and 11 had a prior treatment failure with peginterferon/ribavirin. SVR12 rate 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-naive adults with genotype 1, 2, 3, 4, 5, or 6 infection 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, 2020). 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).

Part 2 of the DORA trial examined the pharmacokinetics, safety and efficacy of glecaprevir/pibrentasvir among children aged 3 to <12 years with HCV infection of any genotype who were treatment naive or interferon/ribavirin experienced. Although the trial was designed to include children with compensated cirrhosis, none of the participants had cirrhosis at enrollment. The majority (98%; 78/80) of the children who received glecaprevir/pibrentasvir were treatment naive; a single participant had HIV/HCV coinfection. The overall SVR12 rate with the optimal drug dosages/ratios was 96%. Of the 2 nonresponders, 1 child discontinued treatment after a single dose because of drug palatability and the other after 4 days due to a drug-related rash. No clinically significant laboratory abnormalities or liver-related toxicities were observed (Jonas, 2021). Glecaprevir/pibrentasvir was approved for use in children aged 3 to <12 years in 2021.

Given its pangenotypic activity, safety, and efficacy record in adults, glecaprevir/pibrentasvir is recommended as a first choice for pediatric and adolescent HCV treatment. As in adults, coadministration of carbamazepine, efavirenz-containing regimens, and St. John's wort is not recommended because these compounds may decrease concentrations of glecaprevir and pibrentasvir. For children and adolescents with compensated cirrhosis, longer durations of treatment (12 weeks to 16 weeks) may be necessary; consultation with a pediatric liver specialist is recommended.

Sofosbuvir/Velpatasvir

Adolescents aged 12 years or older receive the adult tablet formulation of glecaprevir/pibrentasvir. Younger children receive a formulation of small film-coated granules that are mixed with nonacidic, non-liquid foods (eg, peanut butter or Nutella).

Sofosbuvir/velpatasvir was approved by the FDA for children aged ≥6 years in March 2020 and for children aged 3 to <6 years in June 2021. The efficacy of sofosbuvir/velpatasvir once daily for 12 weeks was evaluated

in a phase 2, open-label trial among 216 pediatric participants aged 3 through 17 years with any genotype infection, without cirrhosis or with compensated cirrhosis (Jonas, 2024). Eighty-eight percent of participants (190/216) were treatment naive and 12% (26/216) were treatment experienced. Seventy-six percent of participants had genotype 1 infection; no participants had known cirrhosis. Overall SVR12 rate was ≥92% across genotypes: 97% in the 12-year-old through 17-year-old group; 93% in the 6-year-old through 11-year-old group; and 83% in the 3-year-old through 5-year-old group. Among the participants who did not respond to therapy, 7 were lost to follow-up; 3 had treatment discontinued at the investigator discretion; 2 discontinued treatment due to nonadherence; 1 had parents who withdrew consent for the study; and 2 participants were spitting up study drug.

Adverse events in children/adolescents treated with sofosbuvir/velpatasvir were minor and included headache (30%), fatigue (22%) and nausea (17%). Two participants had adverse events of suicidal ideation that was judged to be unrelated to study drugs but rather due to preexisting mental health conditions. There were no significant effects on growth and development of any study participant.

Given its pangenotypic activity, safety, and efficacy, sofosbuvir/velpatasvir is recommended as a first choice for HCV DAA treatment in children and adolescents. Due to reports from experience among adults, coadministration of sofosbuvir/velpatasvir with amiodarone is not recommended due to the risk for symptomatic bradycardia.

Children and Adolescents Who Do Not Respond to DAA Therapy

In the rare event that a child or adolescent does not respond to a first-line pangenotypic regimen, the combination of sofosbuvir/velpatasvir/voxilaprevir may be an option. This combination is currently FDA-approved adults only; there are only limited pharmacokinetic data from clinical trials in older children. Consultation with an expert in pediatric HCV management to determine the timing and dose of treatment is strongly suggested.

Other Regimens No Longer Used in the United States

Sofosbuvir/Daclatasvir

Sofosbuvir and daclatasvir are no longer used in the US but remain the main option for DAA therapy in most resource-limited settings round the world. The combination has proved highly effective, including for children and adolescents in population-wide HCV treatment programs in Egypt to advance goals of elimination of HCV.

Ledipasvir/Sofosbuvir

Ledipasvir/sofosbuvir was approved for use in children aged 3 through 17 years with genotype 1, 4, 5, or 6 infection and was commonly used until pangenotypic regimens became available for children. Because of its limited genotype activity, this regimen is no longer recommended for use. If this is the only option available, genotype testing prior to treatment is necessary to confirm activity.

Sofosbuvir Plus Ribavirin

In September 2019, the FDA approved weight-based sofosbuvir plus ribavirin for treatment-naive or interferon-experienced (± ribavirin) children aged ≥3 years with genotype 2 or 3 infection, without cirrhosis or with compensated cirrhosis (Child-Pugh A). This regimen is no longer favored because pangenotypic ribavirin-free

treatments are now available for children aged as young as 3 years. If this is the only option available, genotype testing prior to treatment is necessary to confirm activity.

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