HCV in Children

Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of HCV-Infected Children	
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 a test is unknown.	IIa, C
Repetitive testing by HCV RNA 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 HCV is lower in children than adults, an estimated 5 million children worldwide have active HCV infection (Gower, 2014). Data from the National Health and Nutrition Examination Survey (NHANES) collected between 2003 and 2010 indicates 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 chronically infected with HCV (Denniston, 2014).

As birth to an HCV-infected mother is a known risk for infection, such offspring 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 IU/mL) (Benova, 2014); (Delotte, 2014); (Cottrell, 2013). Identifying, following, and treating exposed children is recommended. The basis for evaluation early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months. About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 3 years of age (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. 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. On balance, optional early HCV-RNA testing may facilitate more infants getting tested and retained in care if they are positive. The optimal timing of HCV-RNA testing is still unknown, but 2 to 6 months after birth is reasonable. 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 HCV-Infected Children

RECOMMENDED	RATING
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, HCV-infected children 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 inadequate public understanding of hepatitis C. 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 generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (see HCV Testing and Linkage to Care) (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 HCV-Infected Children	
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 HCV-infected children 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.	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 HCV after assessment of potential risk versus benefit of treatment. Use of corticosteroids, cytotoxic chemotherapy, or therapeutic doses of acetaminophen are not contraindicated in children with chronic HCV.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for children with HCV and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with HCV infection.	I, C

In children, liver disease due to chronic HCV infection generally progresses slowly, and cirrhosis and liver cancer are infrequently encountered. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never have 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. 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 all nonimmune children that may not have received routine childhood vaccines against HAV and HBV.

Disease staging in children can be accomplished via physical examination and the assessment of routine laboratory parameters including albumin, serum 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 (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 children with cirrhosis. There are reports that children with chronic HCV 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 antiviral therapy. After successful antiviral therapy, the risk for cirrhosis complications is substantially less.

In children with advanced fibrosis from chronic HCV, 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 and should be prescribed for appropriate indications based on overall risk vs benefit. 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. Other commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, NSAIDs 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.

Treatment

Recommendations for Whom and When to Treat Among HCV-Infected Children

RECOMMENDED	RATING
If direct-acting antiviral (DAA) regimens are available for a child's age group, treatment is recommended for all HCV-infected children older than 3 years as they will benefit from antiviral therapy, independent of disease severity.	I, B
Treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available.	II, C
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

Recommended regimens listed by evidence level and alphabetically for:

Adolescents ≥12 Years Old or Weighing ≥35 kg, Without Cirrhosis or With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naive without cirrhosis or with compensated cirrhosis[a], or treatment-experienced[b] without cirrhosis	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced[b] with compensated cirrhosis[a]	24 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 2 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 3 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	24 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, B

[a] Child-Pugh A
[b] Patients who have failed an interferon-based regimen, with or without ribavirin
[c] See ribavirin dosing table for recommended weight-based dosages.

Table. Dosing for Ribavirin in Combination Therapy With Sofosbuvir for Adolescents ≥12 Years Old or Weighing ≥35 kg

Body Weight (kg)	Daily Ribavirin Dosage (in 2 divided doses)
<47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
>80	1200 mg/day

Advanced liver disease due to HCV infection is uncommon during the childhood years. However, liver disease progresses over time with increasing fibrosis severity. Although uncommon, cirrhosis is occasionally seen in infected children and adolescents younger than 18. Children have a long life expectancy during which HCV complications may develop. Infected children and adolescents may also transmit HCV to others.

DAA regimens have a very high success rate in adults with chronic HCV infection. In addition, interferon-based regimens have limited success in children with genotype 1 or 4 infection. Interferon and ribavirin have general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Several clinical trials are underway, early data have been published, and DAA regimens are now available for adolescents 12 years and older. It is anticipated that additional safe and effective DAA regimens will be available for children aged 3 through 11 in the near future.

In a phase 2, multicenter open-label study of 100 adolescents with chronic genotype 1 infection treated for 12 weeks with the adult formulation of ledipasvir-sofosbuvir, sustained virologic response (SVR) was documented in 98% of participants (Balistreri, 2017). The two patients who did not achieve SVR12 were lost to follow-up during or after treatment. Most of the patients were treatment naive (80%). 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.

The combination of sofosbuvir and ribavirin at doses approved for adults was tested in adolescents with chronic genotype 2 (12 weeks of treatment) or genotype 3 (24 weeks of treatment) infection (Wirth, 2017). Of the 52 adolescents, 75% had genotype 3 infection, and 83% were treatment naive. Cirrhosis status was negative in 40% and unknown in 60% of the participants. SVR12 rates were 100% (13/13) and 97% (38/39) in genotype 2 and 3 infections, respectively. This regimen was safe and well tolerated, and pharmacokinetic properties of sofosbuvir were equivalent to those observed in adults.

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Related References

Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin C-H, Kersey K, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology (Baltimore, Md.). 2017;66(2):371 - 378.

Behairy B-S, Sira MM, Zalata KR, Salama el-SE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter?. World Journal of Gastroenterology. 2016;22(16):4238 - 4249.

Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2014;59(6):765 - 773.

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022.

Casiraghi MAntonietta, De Paschale M, Romanò L, Biffi R, Assi A, Binelli G, et al.. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. Hepatology (Baltimore, Md.). 2004;39(1):90 - 96.

Cottrell EBarth, Chou R, Wasson N, Rahman B, Guise J-M. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2013;158(2):109 - 113.

Delotte J, Barjoan EMariné, Berrébi A, Laffont C, Benos P, Pradier C, et al.. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2014;27(7):664 - 670.

Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160(5):293-300.

European Paediatric Hepatitis C Virus Network: A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. The Journal of Infectious Diseases. 2005;192(11):1872 - 1879.

Geng X-X, Huang R-G, Lin J-M, Jiang N, Yang X-X. Transient elastography in clinical detection of liver cirrhosis: A systematic review and meta-analysis. Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association. 2016;22(4):294 - 303.

Gonzalez-Peralta RP, Langham MR, Andres JM, Mohan P, Colombani PM, Alford MK, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. Journal of Pediatric Gastroenterology and Nutrition. 2009;48(5):630 - 635.

Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. Hepatology (Baltimore, Md.). 2008;47(3):836 - 843.

Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology. 2014;61(1 Suppl):S45 - 57.

Jhaveri R. Diagnosis and management of hepatitis C virus-infected children. The Pediatric Infectious Disease Journal. 2011;30(11):983 - 985.

Lee CK, Perez-Atayde AR, Mitchell PD, Raza R, Afdhal NH, Jonas MM. Serum biomarkers and transient elastography as predictors of advanced liver fibrosis in a United States cohort: the Boston children's hospital experience. The Journal of Pediatrics. 2013;163(4):1058 - 1064.e2.

Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. Journal of Pediatric Gastroenterology and Nutrition. 2012;54(6):838 - 855.

Mast EE, Hwang L-Y, Seto DSY, Nolte FS, Nainan OV, Wurtzel H, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. The Journal of Infectious Diseases. 2005;192(11):1880 - 1889.

Minola E, Prati D, Suter F, Maggiolo F, Caprioli F, Sonzogni A, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood. 2002;99(12):4588 - 4591.

Schmidt AJ, Falcato L, Zahno B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection?. BMC Public Health. 2014;14(1):3.

Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Lin C-H, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology (Baltimore, Md.). 2017;.