

Hepatitis C in 2020: A North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper

*Daniel H. Leung, †James E. Squires, ‡Ravi Jhaveri, §Nanda Kerkar, ||Chuan-Hao Lin, ¶Parvathi Mohan, #Karen F. Murray, **Regino P. Gonzalez-Peralta, ††Eve A. Roberts, and ‡‡Shikha S. Sundaram



Download Clinical Guidelines

ABSTRACT

In 1989, a collaboration between the Centers for Disease Control (CDC) and a California biotechnology company identified the hepatitis C virus (HCV, formerly known as non-A, non-B hepatitis virus) as the causative agent in the epidemic of silent posttransfusion hepatitis resulting in cirrhosis. We now know that, the HCV genome is a 9.6 kb positive, single-stranded RNA. A single open reading frame encodes a 3011 amino acid residue polyprotein that undergoes proteolysis to yield 10 individual gene products, consisting of 3 structural proteins (core and envelope glycoproteins E1 and E2) and 7 nonstructural (NS) proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B), which participate in posttranslational proteolytic processing and replication of HCV genetic material. Less than 25 years later, a new class of

medications, known as direct-acting antivirals (DAAs) which target these proteins, were introduced to treat HCV infection. These highly effective antiviral agents are now approved for use in children as young as 3 years of age and have demonstrated sustained virologic responses exceeding 90% in most genotypes. Although tremendous scientific progress has been made, the incidence of acute HCV infections has increased by 4-fold since 2005, compounded in the last decade by a surge in opioid and intravenous drug use. Unfortunately, awareness of this deadly hepatotropic virus among members of the lay public remains limited. Patient education, advocacy, and counseling must, therefore, complement the availability of curative treatments against HCV infection if this virus is to be eradicated.

Key Words: hepatitis C, direct-acting antivirals, treatment, diagnosis, prevention

Received December 24, 2019; accepted April 7, 2020.

From the *Division of Pediatric Gastroenterology, Hepatology, Nutrition, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, the †UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, the ‡Ann & Robert H. Lurie Children's Hospital of Chicago, the §Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY, the ||Children's Hospital of Los Angeles, Los Angeles, CA, the ¶Children's National Hospital, Washington, DC, the #Cleveland Clinic Children's Hospital, Cleveland, OH, the **AdventHealth for Children, AdventHealth Transplant Institute, Orlando, FL, the ††University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada, and the ‡‡Children's Hospital of Colorado, Digestive Health Institute, University of Colorado School of Medicine, Aurora, CO.

Address correspondence and reprint requests to Shikha S. Sundaram, MD, MSCI, Children's Hospital Colorado, University of Colorado School of Medicine, 13123 E 16th Ave, Aurora, CO 80045 (e-mail: shikha.sundaram@childrenscolorado.org).

This article has been developed as a Journal CME and MOC Part II Activity by NASPGHAN. Visit <https://learnonline.naspghan.org/> to view instructions, documentation, and the complete necessary steps to receive CME and MOC credits for reading this article.

Disclosures: D.H.L., grant/research support: Gilead, Abbvie, CF Foundation; Advisory Panel: Gilead, Merck. R.J., grant support: Gilead, Abbvie, Merck; Advisory Board: MedImmune, Saol Therapeutics, Hologic, Seqirus. R.G.-P., grant support: Gilead, Abbvie, Merck, Alexion, Axcella; Advisory Panel: Alexion, GMP-orphan, Gilead. K Murray; Consulting: Gilead, and Albireo. C.H.L., Gilead, Research grant support and Advisory panel. N.K., Advisory Panel: HighTide. S.S., Intercept Scientific Advisory Board. P.M., grant support: Gilead.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpjn.org).

Copyright © 2020 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0000000000002814

An infographic for this article is available at: <http://links.lww.com/MPG/B869>.

(JPGN 2020;71: 407–417)

EPIDEMIOLOGY

The global disease burden of HCV infection in the pediatric population is estimated to be approximately 5 million children and adolescents (1). Prevalence rates are rising, ranging from 0.05% to 0.36% in the United States and Europe to 1.8% to 5.8% in certain developing countries, including Mexico (2,3). These reports likely underestimate the true prevalence, given that current ascertainment practices enable identification of only 4.9% of expected pediatric cases of HCV infection (4). Six distinct HCV genotypes have been identified with significant global variation. In adults, genotypes 1 and 2 constitute most infections in Western countries. Genotype 3 is widely distributed in South and East Asia but is also prominent in European countries and the United States; genotype 4 in North Africa and the Middle-East; genotype 5 in South Africa, and genotype 6 in Asia (5,6). Whenever reported, affected children appear to demonstrate regional distribution patterns similar to those described in adults.

Historically considered a transfusion-related disease in children, modern blood-bank screening practices have nearly eliminated the risk of transfusion-transmitted HCV infection (7,8). Currently, mother-to-child transmission (MTCT) during the perinatal period is regarded as the most common mode of infection in children (9). Furthermore, it appears that the transmission occurs variably during the course of pregnancy and delivery, with 31% of transmissions occurring in utero and 50% to 79% during the peripartum period (10,11). The pattern of virologic, clinical, and serological events in children with perinatally acquired HCV

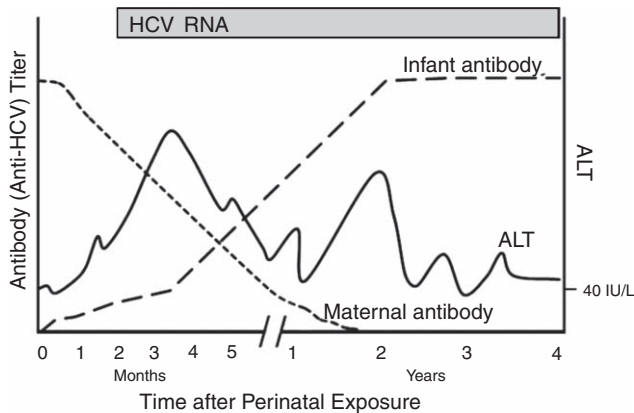


FIGURE 1. Pattern of virologic, clinical, and serological events in children with perinatal hepatitis C virus infection. Following perinatal acquisition (time 0), serum alanine aminotransferase (ALT) levels increase, indicating the onset of clinical hepatitis. A chronic undulant pattern often emerges reflecting ongoing infection. Maternal circulating antibody to HCV begins to decline in the first weeks of life, with complete resolution by 18 to 24 months of age. Divergently, the appearance of anti-HCV produced by the infant occurs shortly after infection; however, it is indistinguishable from maternal antibody. Polymerase chain reaction can detect HCV within several weeks of exposure and will persist barring spontaneous viral clearance. HCV = hepatitis C virus.

infection is shown in Figure 1. Although the rate of MTCT of HCV has remained stable at 5% to 6%, the incidence of HCV infection among women of child-bearing age is increasing (12,13). This raises concern about a growing cohort of pregnant women exposing their infants to HCV (14). Outside of the perinatal period, intravenous drug use (IVDU) is a significant and increasingly common cause of HCV infection in adolescents and young adults, with a reported 364% increase in IVDU among this age group over the last decade (12,15,16). This increase may represent an epidemiological shift in acquisition routes in this population (17).

HCV infection has also been associated with other high-risk activities, such as intranasal cocaine use and tattooing (18) in unregulated settings. In urban areas of Mexico, tattoos and/or piercings accounted for 22% of HCV infection (19). While engaging in high-risk sexual practices, multiple partners (especially if positive for human immunodeficiency virus [HIV]), and/or sexual activity with trauma (20,21) is associated with an increased risk of infection, transmission is rare among heterosexual couples in monogamous relationships (22,23). The risk of HCV transmission is also higher in patients on long-term dialysis, especially in developing countries. In addition, although HCV transmission rates were historically higher in solid organ transplantation recipients (24), the recent availability of DAAs has decreased infections in solid-organ transplant recipients (25). In a clinical trial, recipients of heart and lung transplants from hepatic C viremic donors (median viral load: 890,000 IU/ml) received preemptive therapy with sofosbuvir-velpatasvir within a few hours after transplantation, with undetectable HCV viral loads 6 months posttransplant (25).

CLINICAL SIGNS AND SYMPTOMS

Significant morbidity from HCV infection is uncommon in children (26,27). Adults with acute hepatitis C infection may be asymptomatic or present with typical icteric hepatitis indistinguishable from acute hepatitis A or B. In children and adolescents, acute

hepatitis C is rare (28,29), with only a single case of HCV-induced acute liver failure reported out of 986 children enrolled into the Pediatric Acute Liver Failure Study Group database (30).

Typically, children and adolescents develop chronic HCV infection, defined as the persistence of detectable serum HCV RNA for ≥ 6 months (31,32). Children with chronic hepatitis C are most often asymptomatic, although mild, nonspecific symptoms, such as fatigue and abdominal pain associated with chronic infection and hepatomegaly may be found on physical examination (33). Biochemically, the majority of HCV-infected children have intermittent or persistent mild aminotransferase elevations (Fig. 1), which do not correlate with histological severity (32). Histologically, hepatocellular inflammation is mild, but severe inflammation is described in 3%, moderate fibrosis in 4%, and bridging fibrosis or cirrhosis in 2% to 12% (34–36) of infected individuals. Extrahepatic manifestations of chronic hepatitis C, including membranoproliferative glomerulonephritis, thyroid dysfunction with or without thyroid autoimmune disease, and the development of nonorgan specific antibodies, are exceedingly rare (37–42).

NATURAL HISTORY OF HEPATITIS C VIRUS INFECTION IN CHILDREN AND ADOLESCENTS

Progression of chronic hepatitis C in children and adolescents may follow several different routes. Spontaneous resolution of viremia (viral clearance) (43,44) is estimated to occur in approximately 20% of acutely infected adults (45–47) and in 25% to 40% of children with MTCT, usually by age 2 (48), especially in children with higher serum ALT levels (29,44,49–53). Over age 2 years, 6% to 12% of children may still spontaneously clear the virus before adulthood (29,35,48,54–56). Spontaneous viral clearance is considered a permanent state, essentially a “cure” of the HCV infection, with rare (<1%) relapses reported (57).

Both host and viral factors have been associated with spontaneous viral clearance, including infection with genotype 3 HCV and presence of the interleukin 28B rs12979860 single-nucleotide polymorphism (44,49,58,59). Several genetic factors in the mother or child, including HLA class I/II, killer-cell immunoglobulin-like receptor (KIR), and KIR-ligand-binding polymorphisms, have also recently been linked to MTCT, as well as the development of chronicity and clearance of HCV in the child (60). Significant differences in circulating natural killer (NK) cells (CD56+CD3), along with other lymphocyte phenotypes in children with chronic HCV infection, compared with healthy controls, underscores the potential importance of immune differences in HCV-infected children (61).

Potential for Progression

In children with chronic hepatitis C who ultimately do not clear the virus, progression of liver disease is typically insidious (62–66) and advanced liver disease is uncommon before adulthood (67–72). One study that included up to 35 years of follow-up established that HCV infection acquired early in life is mild and progresses slowly in the absence of other risk factors (68). In a separate study from Japan spanning 30 years in children primarily infected via MTCT, no patient developed cirrhosis or hepatocellular carcinoma (35). A study from the United Kingdom, however, disputed the benign nature of chronic hepatitis C acquired in childhood, with over 30% of patients developing cirrhosis at a median duration of 33 years (17). Children with comorbid conditions, such as obesity, HIV or HBV co-infections, cancer, and anemia, are at risk for more severe disease (48,73,74). In addition, high-risk behaviors including alcohol and intravenous drug use, and adverse social conditions, such as homelessness or incarceration, are associated with worse outcomes (53,75–78).

TABLE 1. Laboratory and radiologic monitoring for children and adolescents with chronic hepatitis C virus infection

	Pretreatment	During treatment	Posttreatment
Laboratory test	Frequency	Frequency	Frequency
AST, ALT, GGT, Total and direct (or conjugated) bilirubin	Annual Repeat if clinically indicated	Every 4 weeks until completed	At 12 weeks to monitor SVR12 If cirrhotic, every 6 months
Complete blood count	Annual	Every 4 weeks	Only if clinically indicated
Prothrombin time, INR	Annual Repeat if clinically indicated	Only if clinically indicated	Only if clinically indicated
HCV RNA quantitative PCR	Annual	Every 4 weeks	At 12 weeks and 12 months post-treatment
Urine HCG (females of childbearing age)	Prior to treatment	Every 4 weeks if sexually active	N/A
Alpha-fetoprotein	Noncirrhotic, as needed If cirrhotic, every 6 months	N/A	N/A if SVR 12 achieved and non-cirrhotic If cirrhotic, every 6 months
Liver ultrasound	Noncirrhotic, as needed If cirrhotic, every 6 months	N/A	If cirrhotic, every 6 months until becomes non-cirrhotic

N/A = not applicable; SVR12 = sustained virologic response at 12 weeks posttreatment.

Complications from chronic HCV-related liver disease in children and adolescents, such as portal hypertension, ascites, variceal bleeding, and hepatocellular carcinoma (HCC), although uncommon, have been reported (62,79–82). Decompensated cirrhosis in children as young as 4 years old has also been described (34,67,82,83). Additionally, the risk for developing HCC may be increased with concurrent diabetes, obesity, or steatosis, but additional data are needed (74). The reported effects of chronic HCV infection on health-related quality of life and cognitive function, demonstrating higher caregiver stress, strain on the family system, and poorer health status, require confirmation in larger pediatric cohorts (84,85).

SCREENING, DIAGNOSIS, AND MONITORING IN CHILDREN

Children suspected of having an HCV exposure, including those born to HCV-positive mothers, should be screened for infection. Currently, the American Academy of Pediatrics recommends anti-HCV antibody screening of children with maternal HCV risk factors at 18 months of age, when detection of passively acquired transplacental immunoglobulin G should have waned (Fig. 1) (86). Waiting until 18 months of age or older is, however, frequently unpalatable for parents and physicians concerned about reliable follow-up. Therefore, after the infant is 2 months of age, the AASLD-IDS A *HCV Guidance Panel* (87) suggests consideration of examining serum HCV RNA by polymerase chain reaction (PCR). The optimal timing of PCR testing is unknown (87). Any child found to be positive for anti-HCV antibody should have confirmatory HCV quantitative PCR testing. Siblings of children with MTCT should be tested for HCV infection if born to the same infected mother (87).

Once confirmed HCV RNA PCR-positive, and hence HCV-infected, further evaluation and monitoring should be initiated. Infected children who are not receiving antiviral therapy should be evaluated annually for clinical and biochemical evidence of liver disease progression. Recommended laboratory investigations include serum aminotransferases, bilirubin, albumin, HCV RNA level, complete blood count, prothrombin time/INR (if cirrhosis is present), and urinalysis. Annual abdominal ultrasound and semi-annual alpha-fetoprotein (AFP) measurements may be reserved for children with a family history of early cirrhosis, HCC, or evidence of rapid disease progression. Although HCC in children is estimated to be exceedingly rare, it has been reported with age-adjusted

incidence rates of 0.24 to 0.65/1,000,000 (88). Liver biopsy may be indicated in rare instances where the results may influence medical decision-making but is increasingly deferred and often unnecessary in the era of DAA therapy. Table 1 highlights suggestions for laboratory and radiologic monitoring of HCV-infected patients (before, during, and after) treatment.

PREVENTION OF HEPATITIS C VIRUS INFECTION IN CHILDREN

Optimal prevention strategies to mitigate HCV infection in children are poorly understood. Advancements in this area may be best operationalized at a public health level. In 2016, the World Health Organization (WHO) outlined strategies to eliminate viral hepatitis as a public health threat by 2030, with a 65% reduction in mortality and a 90% reduction in chronic hepatitis C (89). Unfortunately, the concurrent ‘opioid crisis’ in North America demonstrably changed the character of chronic hepatitis C in the United States, with attendant increases in the incidence of HCV infection (90–92). This rapidly evolving epidemic, along with existing deficits across the care continuum (93), poses significant barriers to HCV elimination, both in the United States and worldwide.

Prevention of Mother-to-Child Transmission

In the United States, 1% to 2.5% of pregnant women are infected with HCV (94). Prevention of MTCT requires the ability to intervene in a timely and effective manner in mothers at-risk for exposing their infants to HCV. Current recommendations limit testing for HCV in pregnancy only to mothers who, by medical history, may be at higher-than-average risk for hepatitis C. This strategy has been recognized as ineffective (95–98), given the social stigma surrounding HCV infection and lack of accurate history provision. Pregnancy is a unique time during which women may have more immediate access to medical resources. This could facilitate identification of those who have chronic hepatitis C, prevention strategy deployment, establishment of long-term care, and treatment plans for both the mother and infant (99). The lack of data on cost-effectiveness of this approach, however, has been an impediment to substantial clinical changes (94). This may, however, change given the new availability and safety of DAAs and rising prevalence of chronic hepatitis C in women of child-bearing age (100). With recent AASLD/IDS A recommendations to test all

pregnant women for HCV infection (98,101), healthcare providers will be able to more effectively identify and prevent MTCT of HCV.

Suspected risk factors for MTCT include perinatal practices (fetal scalp monitoring), prolonged exposure to maternal blood, high levels of HCV viremia during pregnancy, and coinfection with HIV (9,102–107). Recent studies, however, suggest that highly effective antiretroviral therapy for HIV co-infection eliminates the increased risk of perinatal HCV transmission found in HIV-HCV coinfecting women (108–110). The Society for Maternal-Fetal Medicine does not recommend opting for cesarean section solely for the indication of HCV infection but it recommends avoiding internal fetal monitoring and episiotomy, and prolonged rupture of membranes by initiating active labor management when indicated. Furthermore, if invasive prenatal testing is required, amniocentesis is preferable over chorionic villus sampling (94). Recommendations on breast-feeding conclude that obstetric care providers should not discourage breast-feeding based on a positive HCV infection status unless the mother is co-infected with HIV (9,102–105).

Prevention of Horizontal Transmission

Implementation of strategies to reach unique groups infected with HCV, who are often difficult to identify, counsel, test, and treat, are critical in the prevention of HCV transmission. People who inject drugs, men who have sex with men (MSM), individuals co-infected with HIV, and those residing in correctional facilities or institutions, have a much higher prevalence of HCV infection compared with the general population (101,111). An HCV seroprevalence of 10% to 70% is reported in the United States and Europe among people who inject drugs. It is critically important to include adolescents in prevention efforts as newer data underscore the increasing prevalence of HCV in this population. Testing and identifying individuals with HCV infection is a vital first step. Equally important, however, is the linkage to care and access to new antiviral therapies, which will ultimately reduce the incidence and prevalence of HCV infection (112). Unfortunately, current policies at the global, federal, regional, and local levels limit identification of high-risk individuals, including children and adolescents, and directing them towards the treatment they needed (113).

Harm reduction is an important aspect of this strategy. The strong association of chronic hepatitis C with illicit drug use (mainly not only intravenous but also intranasal) demands a strong public health effort to decrease exposure to contaminated equipment. Providing clean needles through “safe injection sites” to those addicted to illicit drugs may be an efficient and cost-effective intervention (114) that deserves further study. These facilities can also serve as a contact point for HCV-infected individuals to access both education about hepatitis C and medical care.

Prevention strategies enacted for adults who inject drugs are also applicable to adolescents, including annual or more frequent HCV testing (combined reflex PCR testing with HCV antibody positivity or point-of-care PCR testing), substance use disorder treatment programs, and counseling. Implementation of electronic medical record-based screening programs for HIV and HCV in urgent care settings, as reported in a study in Appalachia, may be highly effective and practical (115). Attention to the social needs of at-risk adolescents, such as homelessness and preventing incarceration, represent important strategies at a social or public health level (77,78). Moreover, there is much ignorance leading to stigmatization related to the risks and modes of transmission of HCV. Dispelling this ignorance and misinformation through proper counselling is an important step in the overall scheme of preventing HCV infection.

Although transmission via blood products has decreased significantly in developed countries, immigration from endemic areas and nosocomial exposure are potential sources of HCV exposure. Global health programs collecting data on resettled refugees may allow for identification, prevention, counselling, and implementation of HCV treatment (116). Although ordinary activities of daily living in a household are not associated with HCV transmission, sharing sharp objects, such as razors, tweezers, and toothbrushes/floss should be avoided (48). Blood spills should be dealt with while wearing protective gloves, cleaning the contaminated area with bleach, and encouraging others to follow universal precautions. The risk of contracting HCV infection through sports is unquantified but likely negligible if equipment is decontaminated and universal precautions are observed for first aid.

TREATMENT IN CHILDREN

New classes of direct-acting antiviral (DAA) therapies that target several HCV protein products, as depicted in Figure 2, are highly effective in children. A few DAA regimens with high efficacy and excellent tolerance are now approved for children 3 years of age and older. Consequently, once the diagnosis of chronic hepatitis C is established and HCV genotype is identified, DAA therapy should be initiated regardless of serum aminotransferase levels (117). Similarly, hepatic histology is no longer necessary for decision-making regarding treatment with DAAs for chronic HCV infection. For children younger than the approved age for DAA use, treatment is often deferred in expectation of increased DAA availability in the future. Recently published expert opinion suggests that the antiquated regimen of PEG-IFN/RBV should not be utilized (118).

Approved Direct-acting Antivirals for Hepatitis C Virus Infection in Children

The advent of oral DAAs for the treatment of chronic HCV infection has significantly changed the HCV-treatment landscape. In the United States, limited efficacy and significant medication side effects have relegated interferon-alpha and ribavirin to historical interest. Although multiple DAA treatment options have been approved for adults chronically infected with HCV, only 3 options currently (February 2020) exist for children at the time of press, with 2 regimens approved for children as young as 3 years of age. After safety and high efficacy were proven in adults, rapid and competitive enrollment of pediatric patients with HCV infection in multi-national clinical trials studying the pharmacokinetics (PK), safety, and efficacy of DAAs have resulted in expedited Food and Drug Administration (FDA) approval of these combination therapies for use in children. In April 2017, the FDA first approved the combination of sofosbuvir (SOF, 400 mg) with ledipasvir (LDV, 90 mg) (Harvoni) once daily for 12 weeks for the treatment of genotypes 1, 4, 5, or 6 in children 12 years of age and older, or 35 kg in weight. In September 2019, this approval was further extended down to age 3 years of age (SOF, 150–200 mg ith LDV, 33.75–45 mg). For genotypes 2 and 3, 12 weeks of SOF (400 mg daily, Sovaldi) with ribavirin (RBV, 15 mg/kg in 2 divided doses) was similarly first approved for the treatment of children 12 years of age and older, or 35 kg in weight, and was approved for children 3 to 11 years (SOF, 150–200 mg) in August 2019. Sustained virologic response (SVR), defined as the attainment and persistence of undetectable HCV RNA, was reported following treatment initiation. In clinical trials using the regimens above, SVR 12 weeks posttherapy (SVR12) was 97%, with an adverse event profile comparable with placebo; fatigue and headache were most commonly reported. In April 2019, the FDA approved the DAA

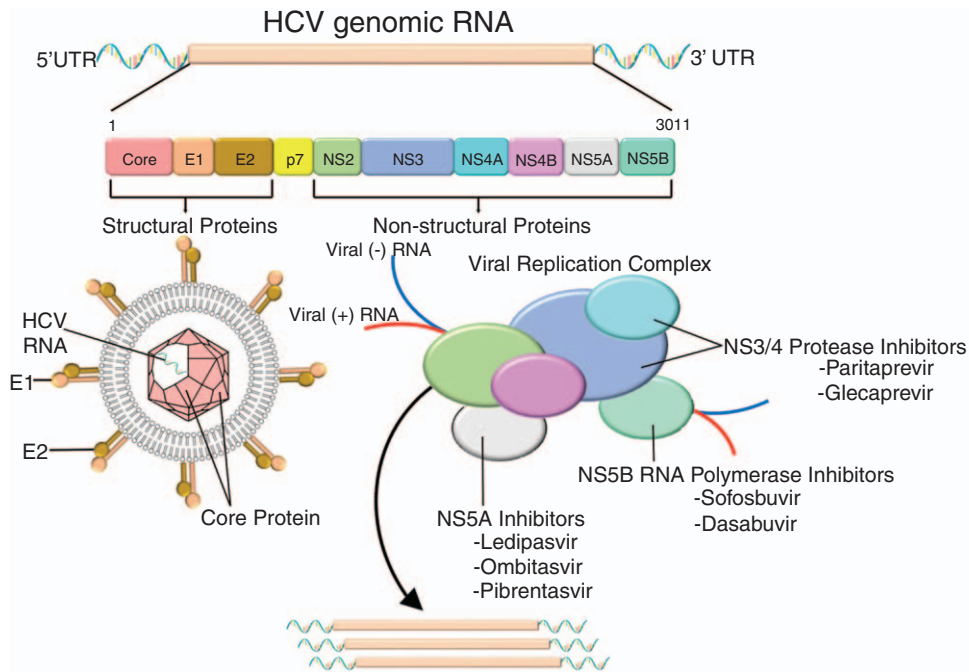


FIGURE 2. The hepatitis C virus genome is a 9.6 kb positive, single-stranded RNA. A single open reading frame encodes a 3011 amino acid residue polyprotein that undergoes proteolysis to yield 10 individual gene products, consisting of 3 structural proteins (core and envelope glycoproteins E1 and E2) and 7 nonstructural (NS) proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) which participate in posttranslational proteolytic processing and replication of HCV genetic material. New classes of direct-acting antiviral (DAA) therapies target several HCV protein products including NS3/4A which is a protease/helicase required for HCV polyprotein cleavage and RNA secondary structure and unwinding, the NS5A multifunctional protein with key roles in modulating viral replication, and the NS5B RNA-dependent RNA polymerase. HCV = hepatitis C virus.

combination of glecaprevir (GLE) and pibrentasvir (PIB) (Mavyret) to treat all 6 genotypes of HCV in children ages 12 to 17 in as short as 8 weeks (DORA Study, Part 1, ClinicalTrials.gov Identifier: NCT03067129). Notably, the ease and efficacy of GLE/PIB for genotypes 2 and 3 have resulted in adult recommendations advocating its use over the older SOF/RBV regimen. The rapid timeline for attaining FDA approval for GLE/PIB in children is remarkable, given that FDA approval in adults was just 20 months prior (August 2017). Historically, approval of therapies for treating HCV infection in children have lagged 5 to 8 years behind approvals for treatment in adults, but high SVR12 rates following short treatment durations across all genotypes in children, with minimal adverse events, have provided compelling data in a condensed period of time.

In Canada, the only DAA therapies approved for use in children (as of December 2019) are the combination of sofosbuvir and ledipasvir for children with HCV genotype 1 and the combination of glecaprevir and pibrentasvir for children with any genotype, but both are only approved for youth ages 12 to 17 years (119). In Mexico, available DAA therapies include daclatasvir, asunaprevir, simeprevir, sofosbuvir, and combination therapies with grazoprevir/elbasavir, ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r/DSV), sofosbuvir/ledipasvir and grazoprevir/elbasavir, though many are not available for children under the age of 12 years (120).

Direct-acting Antivirals Studied in Children With Chronic Hepatitis C

Recent DAAs studied in children with chronic hepatitis C to evaluate safety, efficacy, and pharmacokinetics have yielded

outstanding patient outcomes and are summarized in Table 2. Dosing and efficacy in adolescents 12 years and older mirror that of adults, whereas younger children receive weight-based dosing with nested PK studies.

Ongoing Hepatitis C Virus Clinical Trials

Part 2 of the phase 2/3 DORA study using a pediatric formulation of GLE/PIB for 8, 12, or 16 weeks depending on HCV genotype, cirrhosis status, and prior treatment experience in participants 3 to 11 years of age recently completed enrollment (ClinicalTrials.gov Identifier: NCT03067129) and allowed subjects with HIV co-infection to enter the study. Clinical trials in children are also now allowing other comorbidities, such as compensated cirrhosis and renal disease, highlighting the safety and tolerability of DAAs. The GS-7977/GS-5816 study, a phase 2, open-label, multicenter, multicohort study investigating the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination in pediatric participants ages 3 to 17 years with HCV (ClinicalTrials.gov Identifier: NCT03022981) also completed enrollment in May 2019. Notably, SOF/VEL was FDA-approved for pan-genotypic HCV (1–6) in adults less than 3 years earlier (June 2016).

Another promising fixed-dose combination therapy for children currently in study is elbasvir (EBR) and grazoprevir (GZR), which has been highly effective and safe in HCV-infected adults, even those on hemodialysis. This fixed-dose combination of EBR and GZR was approved for treatment of adults (March 2016) with genotypes 1 and 4, and has been available to children since 2018 through an ongoing phase IIb clinical study (MK-5172) designed to assess the PK, safety, and efficacy of the combination of EBR/GZR

in children 3 to 17 years (ClinicalTrials.gov Identifier: NCT03379506). Other actively enrolling pediatric trials include daclatasvir with sofosbuvir, and sofosbuvir with velpatasvir and voxilaprevir, for all HCV genotypes.

From a research standpoint, the safety and high efficacy profiles of DAAs have both altered the duration and the design of HCV clinical trials, evolving from primarily placebo-controlled to exclusively open-label studies, without a significant need for a natural-history arm. Treatment has not been extensively studied and is unlikely to be recommended for children younger than 3 years of age because of high rates of spontaneous resolution. Effective treatment with DAA regimens, however, has been reported in children as young as 6 months (121). The promise of a once-daily, patient tailored (ie, HIV co-infection, renal insufficiency, with or without cirrhosis), single pill treatment with a >95% cure and minimal side effects for children has now been delivered.

Treatment of Hepatitis C Virus Infection in Pregnancy

Currently, universal treatment for HCV infection during pregnancy is not recommended because of the lack of substantive safety and efficacy data (98). Older regimens with ribavirin are contraindicated in pregnancy because of their association with embryocidal and/or teratogenic effects in all animal species studied (94). Given the efficacy and short treatment course of DAAs, however, further study of these medications in pregnancy is urgently needed (116). Emerging data suggests that DAA treatment during pregnancy is likely to be safe and effective. A recent phase 1 study of ledipasvir/sofosbuvir (LDV/SOF, ClinicalTrials.gov: NCT02683005) in pregnant women reported that 8 participants had a rapid response to therapy and achieved sustained virologic response at 12 weeks posttreatment (SVR12). Seven of the 8 mothers delivered at term with all infants having undetectable HCV RNA, with all adverse events related to LDV/SOF rated as \leq grade 2 (122). The AASLD and IDSA jointly recommend that antiviral therapy should be provided to women of child-bearing age and HCV infection before considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring (87).

ADDITIONAL CHALLENGES AND IMPORTANT CONSIDERATIONS IN CHILDREN

Co-infection With Human Immunodeficiency Virus

Limited evidence is currently available regarding the timing, efficacy, and safety of treatment in children and adolescents co-infected with HIV and HCV. HIV is historically described to have a negative effect on the natural progression of HCV infection. Co-infected HCV/HIV patients, including pediatric populations, have higher rates of viral persistence, increased viral load, and a more rapid progression to end-stage liver disease (123). Many clinicians postulate that this increased rate supports early and aggressive therapy for HIV/HCV co-infected children. Currently available data support the use of DAAs to treat HCV infection in HIV-co-infected adults, with similar SVR rates between mono- and co-infected individuals (124). Although there are currently no published data on outcomes of DAA-treated HIV-co-infected children and adolescents, we anticipate emerging data from the above trials soon. Until then, limited experience in the clinical management of this group and the lack of evidence to guide policy remain barriers to optimizing treatment for HIV-co-infected children.

Social Stigma, Parental Anxiety, Confidentiality, and Disclosure

Although HCV was discovered nearly 30 years ago, HCV infection remains a stigmatizing condition. Destigmatizing the origin of disease by public health education campaigns is likely to increase trust in health care personnel and enhance HCV-screening programs. In children, screening often requires parental consent, and therefore, identifying HCV infection in the seemingly well pediatric population rests on adult awareness and education. In a recent study, participants acknowledged shame, fears of potential stigmatization, and extreme caution around disclosing HCV infection (125). Stigma in the health care setting relates to moral assumptions linking HCV infection and IVDU, breaches of confidentiality, and inappropriate fears regarding contagion (125). In pediatric cohorts, where most have MTCT, childhood HCV infection is associated with increased caregiver stress and strain on the family system (2). Demystifying HCV infection by providing timely, accurate and reliable information about viral transmission, natural history, and potential treatment options is critically important to reassure patients and families.

In the United States, the Health Insurance Portability and Accountability Act (HIPAA) establishes confidentiality as the standard. Medical privacy is the practice of maintaining security and confidentiality of patient records. Disclosure involves sharing of protected information. Education and information about useful resources is critical. Disclosing HCV infection to day-care and school personnel, sports coaches, authorities, peers, and casual dates can be a contentious and anxiety-provoking proposition. Although national and international regulations may differ with regards to this issue, there is generally no legal requirement to disclose HCV infection in the United States. The Centers for Diseases Control and Prevention and many patient advocate groups suggest revealing this sensitive information to sexual partners whenever appropriate (www.hcvadvocate.org; www.cdc.gov/hepatitis/hcv). This decision should be individualized and reached only after thoroughly considering all the advantages and risks of transmitting this sensitive information. In Canada, however, HCV is considered a notifiable disease and must be reported (<https://diseases.canada.ca/notifiable/diseases-list>). Further information can be obtained from the HCV Advocate website (<http://hcvadvocate.org>).

Cost-effectiveness of Direct-acting Antiviral Therapy in Children

The economic cost of HCV-related illness on the healthcare system has been well documented. Pre-DAA cost estimates ranged from \$4.3 to 8.4 billion (US dollars), with lifetime costs for individuals estimated at \$64,490 (126). Cost analyses by age demonstrated that younger individuals (<18 years old) with infection would be expected to accrue an estimated lifetime cost of \$116,540 (126). The availability of highly effective DAA therapy has made the global elimination of HCV a realistic goal, one that has been endorsed by the WHO (89). The high cost of DAA regimens, however, have led individual states, Medicaid programs, and insurance companies to control drug costs by placing restrictions on access to DAAs that focus on fibrosis severity (either by liver biopsy, Fibroscan, or Fibrotest), sobriety, or type of prescriber (www.stateofhepc.org). Within the United States, 18 of the 50 (36%) states have been assessed as having a grade of C or D (scale A–F) based on Medicaid patient access to DAAs according to the National Viral Hepatitis Roundtable and the Center for Health Law and Policy Innovation at the Harvard Law School.

Despite the high initial cost of DAA therapy, studies in various populations (cirrhosis, HIV co-infection, renal disease, etc) now demonstrate that HCV treatment is cost-effective (127–130). After initial list prices upwards of \$150,000 for a regimen that included sofosbuvir and simeprevir individually, currently approved pan-genotypic fixed-dose combination regimens now have an average list price ranging from \$26,000 (glecaprevir/pibrentasvir) to \$75,000 (sofosbuvir/velpatasvir) per treatment course (www.hepatitisc.uw.edu/page/treatment), although the actual cost paid for the medications may be significantly lower. Cost-effectiveness studies in children are limited, but 1 study recently evaluated the following combinations: sofosbuvir/ledipasvir (FDA approved in >3 years old), sofosbuvir/velpatasvir (clinical trial in process), and glecaprevir/pibrentasvir (FDA approved in >12 years old and clinical trial in process) (131). The current FDA-approved regimens, as well as those in clinical trials, were all deemed cost-effective for children treated as young as age 12, and highly cost-effective compared to waiting until 18 years or later to treat. Whenever considering the costs of therapy compared with the preventable costs of untreated infected and the improved quality of life, the values generated by each regimen (incremental cost-effectiveness ratios [ICER]) were well below the accepted \$50,000 threshold, considered high value: \$26,802 for sofosbuvir/ledipasvir, \$20,604 for sofosbuvir/velpatasvir, and \$10,088 for glecaprevir/pibrentasvir (131).

Treatment Access

Historically, DAA access has been restricted to adults with more advanced liver disease. In recent years, these restrictions are slowly changing. In some states, children as young as 12 years have gained access to DAAs, previously only available through participation in clinical trials. This access, however, is not universal and securing DAAs for children who meet the FDA labeling criteria remains challenging for many providers. Many public and commercial insurance carriers prioritize therapy for those with

advanced liver disease, uncommonly seen in children and adolescents. The medication authorization process is cumbersome, usually requiring completion of adult-oriented questionnaires and time-consuming peer-to-peer discussions with insurance company physicians who lack pediatric and/or viral hepatitis expertise. Securing treatment in specialized centers with access to specialty pharmacists can facilitate this process and reduce the burden on patients, families, and health care providers. When available, the involvement of a specialty pharmacist is highly encouraged.

Additional barriers to treatment access include unreliable follow-up of HCV-exposed infants and newly infected adolescents, a lack of awareness that children can suffer poor outcomes from HCV infection including cirrhosis and HCC, and the limited numbers of providers comfortable treating HCV-infected children (132). The false notion that children are too healthy to treat, or reluctance of insurance companies to subsidize DAA therapy in a child with high-risk socioeconomic risk factors at risk for potential re-infection, require education of medical professionals in conjunction with advocacy.

Treatment Adherence

A growing body of literature highlights the impact of non-adherence to DAA regimens. In adults, LDV/SOF adherence (taking >80% of prescribed doses) has been shown to significantly affect SVR12 attainment, with 97.1% of adherent patients achieving SVR12 compared with only 82.5% of nonadherent patients ($P < 0.0001$) (133). Numerous factors affect adherence to these drug regimens, including patient-specific challenges, navigating complex healthcare systems, and medication factors (134). In children, unique challenges include a reliance on caregivers, inappropriate expectations of self-care without regard for varying stages of developmental and independence, and ability to tolerate medications. Review of those patients who did not achieve SVR12 from the large clinical trials highlighted in Table 2, suggests that while the majority were “lost to follow up,” the second most common cause

TABLE 2. Direct-acting antivirals studied in children with chronic hepatitis C

Study, year	DAAs	Age (y/o)	HCV GT	Sample size	SVR12	Most Common AE	SAE
Balistreri et al, 2016 (136)	Ledipasvir/sofosbuvir (90 mg/400 mg)	12–17	1 (a and b)	100	98%	Headache (27%), diarrhea (14%), fatigue (13%)	None
Wirth et al, 2017 (137)	Sofosbuvir (400 mg) and ribavirin (weight-based)	12–17	2 and 3	52	98%	Nausea (27%), headache (23%)	None
Murray et al, 2018 (138)	Ledipasvir/sofosbuvir (45 mg/200 mg) and ribavirin (weight-based)	6–11	1, 3, and 4	92	99%	Headache (18%), pyrexia (17%)	One case (tooth abscess), not related to study treatment
Leung et al, 2018 (139)	Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin	12–17	1 and 4	38	100%	Headache (21%), fatigue (18%), nasopharyngitis (13%)	None
Rosenthal et al, 2019 (140)	Sofosbuvir and ribavirin (weight based)	3–11	2 and 3	54	98%	6–11 y: Vomiting (32%), headache (29%) 3–5 yr: Vomiting (46%), diarrhea (39%)	RBV overdose
Schwarz et al, 2019 (141)	Ledipasvir/sofosbuvir (weight-based)	3–5	1 and 4	34	97%	Vomiting (24%), cough (21%), pyrexia (21%)	None
Jonas et al, 2019 (142)	Glecaprevir/pibrentasvir (300 mg/120 mg)	12–17	1, 2, 3, or 4	47	100%	Nasopharyngitis (26%) URI (19%)	None

AE = adverse event; DAAs = direct-acting antivirals; SAE = serious adverse event; SVR12 = percentage of patients with a sustained virologic response 12 weeks posttreatment; URI = upper respiratory tract infection.

was inability to tolerate the medicines because of “bad taste.” It is likely that concentrated efforts to support DAA adherence in children will be needed in order to optimize outcomes.

CONCLUSIONS

We recommend that children and adolescents less than 18 years of age be included in age-stratified national data collection and global reporting on seroprevalence of HCV, both in high-risk groups and the general population, rather than simply extending or extrapolating from adult data. Identification of hard-to-reach or high-risk populations, particularly adolescents who inject drugs, MSM, or belonging to other at-risk groups with poor access to health care should be a priority. Counseling of primary care givers, school officials, staff of institutions, and correctional facilities to avoid stigmatization, increase awareness, and facilitate appropriate medical care is essential. Interventions aimed at preventing horizontal transmission at all levels will serve to prevent recurrent HCV infection. Further research to eliminate MTCT, possibly through an effective vaccine and safe treatment of pregnant women with DAAs, should also be a priority. Lastly, we must strongly advocate for easier access to FDA-approved DAA combination therapies for all children infected with HCV.

Regardless of the wealth or stability of health economies, few countries, including the United States, are currently on target to achieve elimination of HCV as a public health problem by 2030 (135). Programmatic restrictions are preventing many children from being effectively treated, further contributing to the pool of HCV-infected adolescents of child-bearing age. Lack of access to DAAs earlier in childhood, a key barrier to treatment and cure, must be overcome. Given that the overwhelming majority of children are infected with HCV via MTCT, we recommend treatment be considered and offered to all children with chronic HCV as early as 3 years of age with currently approved and anticipated DAA combination therapies. To address the needs of HCV-infected children, pediatric providers will not only require a strong working knowledge of available DAAs for their patients, but also unrelenting advocacy for greater access to these highly efficacious and cost-effective treatments. Much work is needed to achieve political engagement, removal of stigma, voluntary licensing agreements for generic manufacturers, and alignment of frequent screening with access/feasibility of treatment if we are to eradicate HCV infection in children.

Recommended Resources for Pediatric Gastrointestinal and Liver Providers

1. HCVguidelines.org (living online reference of HCV therapies in children)
2. <https://www.niaid.nih.gov/clinical-trials/hepatitis-c-clinical-research-studies> (NIH website of ongoing trials in Hep C)

The NASPGHAN practice guidelines and position papers are evidence-based decision-making tools for managing health conditions. They are authorized by the NASPGHAN Executive Council, peer reviewed, and periodically updated. They are not to be construed as standards of care and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. All decisions regarding the care of a patient should be made by the health care team, patient, and family in consideration of all aspects of the individual patient’s specific medical circumstances. Although NASPGHAN makes every effort to present accurate and reliable information, these guidelines are provided “as is” without any

warranty of accuracy, reliability, or otherwise, either express or implied. NASPGHAN does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither NASPGHAN nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, nor consequential damages, incurred in connection with the guidelines or reliance on the information presented.

REFERENCES

1. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014;61(1 Suppl):S45–57.
2. El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. *World J Gastroenterol* 2013;19:7880–8.
3. Escobedo-Melendez G, Fierro NA, Roman S, et al. Prevalence of hepatitis A, B and C serological markers in children from western Mexico. *Ann Hepatol* 2012;11:194–201.
4. Delgado-Borrego A, Smith L, Jonas MM, et al. Expected and actual case ascertainment and treatment rates for children infected with hepatitis C in Florida and the United States: epidemiologic evidence from statewide and nationwide surveys. *J Pediatr* 2012; 161:915–21.
5. Kuiken C, Simmonds P. Nomenclature and numbering of the hepatitis C virus. *Methods Mol Biol* 2009;510:33–53.
6. Shahnazarian V, Ramai D, Reddy M, et al. Hepatitis C virus genotype 3: clinical features, current and emerging viral inhibitors, future challenges. *Ann Gastroenterol* 2018;31:541–51.
7. Centres of Disease Control and Prevention. Viral hepatitis statistics and surveillance. 2013.
8. Luban NL, Colvin CA, Mohan P, et al. The epidemiology of transfusion-associated hepatitis C in a children’s hospital. *Transfusion* 2007;47:615–20.
9. Benova L, Mohamoud YA, Calvert C, et al. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014;59:765–73.
10. Mok J, Pembrey L, Tovo PA, et al., European Paediatric Hepatitis CVN. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child Fetal Neonatal Ed* 2005;90:F156–60.
11. Pott HJ, Theodoro M, de Almeida Vespoli J, et al. Mother-to-child transmission of hepatitis C virus. *Eur J Obstet Gynecol Reprod Biol* 2018;224:125–30.
12. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban people who inject drugs in the United States, 2006–2012. *Clin Infect Dis* 2014;59:1411–9.
13. Chappell CA, Hillier SL, Crowe D, et al. Hepatitis C Virus Screening Among Children Exposed During Pregnancy. *Pediatrics* 2018;141:e20173273.
14. Ly KN, Jiles RB, Teshale EH, et al. Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014. *Ann Intern Med* 2017;166:775–82.
15. Centers for Disease Control and Prevention. Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. *MMWR Morb Mortal Wkly Rep* 2011;60:537–41.
16. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged <=30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *MMWR Morb Mortal Wkly Rep* 2015;64:453–8.
17. Modin L, Arshad A, Wilkes B, et al. Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol* 2019;70:371–8.
18. Jafari S, Copes R, Baharlou S, et al. Tattooing and the risk of transmission of hepatitis C: a systematic review and meta-analysis. *Int J Infect Dis* 2010;14:e928–40.
19. Romero-Figueroa S, Ceballos-Salgado E, Santillan-Arreygue L, et al. Risk factors associated with hepatitis C virus infection in an urban population of the State of Mexico. *Arch Virol* 2012;157:329–32.
20. Carney K, Dhalla S, Aytaman A, et al. Association of tattooing and hepatitis C virus infection: a multicenter case-control study. *Hepatol* 2013;57:2117–23.

21. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology* 2010;52:1497–505.
22. Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV partners study. *Hepatology* 2013;57:881–9.
23. Kwong AJ, Wall A, Melcher M, et al. Liver transplantation for hepatitis C virus (HCV) non-viremic recipients with HCV viremic donors. *Am J Transplant* 2018;19:1380–7.
24. Periera BJ, Wright TL, Schmid CH, et al. The impact of pretransplantation hepatitis C infection on the outcome of renal transplantation. *Transplantation* 1995;60:799–805.
25. Woolley AE, Singh SK, Goldberg HJ, et al., DONATE HCV Trial Team. Heart and lung transplants from HCV-infected donors to uninfected recipients. *N Engl J Med* 2019;380:1606–17.
26. Jonas MM, Baron MJ, Bresee JS, et al. Clinical and virologic features of hepatitis C virus infection associated with intravenous immunoglobulin. *Pediatrics* 1996;98 (2 Pt 1):211–5.
27. Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006;148:652–8.
28. Bunchorntavakul C, Jones LM, Kikuchi M, et al. Distinct features in natural history and outcomes of acute hepatitis C. *J Clin Gastroenterol* 2015;49:e31–40.
29. Yeung LT, To T, King SM, et al. Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepat* 2007;14:797–805.
30. Narkewicz MR, Horslen S, Hardison RM, et al. A Learning Collaborative Approach Increases Specificity of Diagnosis of Acute Liver Failure in Pediatric Patients. *Clin Gastroenterol Hepatol* 2018;16:1801.e1–10 e3.
31. Davison SM, Mieli-Vergani G, Sira J, et al. Perinatal hepatitis C virus infection: diagnosis and management. *Arch Dis Child* 2006;91:781–5.
32. Mohan N, Gonzalez-Peralta RP, Fujisawa T, et al. Chronic hepatitis C virus infection in children. *J Pediatr Gastroenterol Nutr* 2010;50:123–31.
33. European Paediatric Hepatitis CVN. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis* 2005;41:45–51.
34. Goodman ZD, Makhlof HR, Liu L, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* 2008;47:836–43.
35. Mizuochi T, Takano T, Yanagi T, et al. Epidemiologic features of 348 children with hepatitis C virus infection over a 30-year period: a nationwide survey in Japan. *J Gastroenterol* 2018;53:419–26.
36. Turkova A, Volynets GV, Crichton S, et al. Advanced liver disease in Russian children and adolescents with chronic hepatitis C. *J Viral Hepat* 2019;26:881–92.
37. Bogdanos DP, Mieli-Vergani G, Vergani D. Non-organ-specific autoantibodies in hepatitis C virus infection: do they matter? *Clin Infect Dis* 2005;40:508–10.
38. Bortolotti F, Vajro P, Balli F, et al. Non-organ specific autoantibodies in children with chronic hepatitis C. *J Hepatol* 1996;25:614–20.
39. Gehring S, Kullmer U, Koepplmann S, et al. Prevalence of autoantibodies and the risk of autoimmune thyroid disease in children with chronic hepatitis C virus infection treated with interferon-alpha. *World J Gastroenterol* 2006;12:5787–92.
40. Gregorio GV, Pensati P, Iorio R, et al. Autoantibody prevalence in children with liver disease due to chronic hepatitis C virus (HCV) infection. *Clin Exp Immunol* 1998;112:471–6.
41. Indolfi G, Bartolini E, Olivito B, et al. Autoimmunity and extrahepatic manifestations in treatment-naive children with chronic hepatitis C virus infection. *Clin Dev Immunol* 2012;2012:785627.
42. Muratori P, Muratori L, Verucchi G, et al. Non-organ-specific autoantibodies in children with chronic hepatitis C: clinical significance and impact on interferon treatment. *Clin Infect Dis* 2003;37:1320–6.
43. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. *Lancet* 2008;372:321–32.
44. Resti M, Bortolotti F, Vajro P, et al., Committee of Hepatology of the Italian Society of Pediatric Gastroenterology and Hepatology. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. *Dig Liver Dis* 2003;35:453–7.
45. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000;284:450–6.
46. Villano SA, Vlahov D, Nelson KE, et al. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999;29:908–14.
47. Wang CC, Krantz E, Klarquist J, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. *J Infect Dis* 2007;196:1474–82.
48. Mack CL, Gonzalez-Peralta RP, Gupta N, et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr* 2012;54:838–55.
49. Garazzino S, Calitri C, Versace A, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. *Eur J Pediatr* 2014;173:1025–31.
50. Tovo PA, Calitri C, Scolfaro C, et al. Vertically acquired hepatitis C virus infection: correlates of transmission and disease progression. *World J Gastroenterol* 2016;22:1382–92.
51. Arafa N, El Housseiny M, Rekaewicz C, et al. Changing pattern of hepatitis C virus spread in rural areas of Egypt. *J Hepatol* 2005;43:418–24.
52. Farmand S, Wirth S, Löffler H, et al. Spontaneous clearance of hepatitis C virus in vertically infected children. *Eur J Pediatr* 2012;171:253–8.
53. Serra MA, Escudero A, Rodriguez F, et al. Effect of hepatitis C virus infection and abstinence from alcohol on survival in patients with alcoholic cirrhosis. *J Clin Gastroenterol* 2003;36:170–4.
54. Indolfi G, Mangone G, Bartolini E, et al. Hepatitis C viraemia after apparent spontaneous clearance in a vertically infected child. *Lancet* 2016;387:1967–8.
55. Iorio R, Giannattasio A, Sepe A, et al. Chronic hepatitis C in childhood: an 18-year experience. *Clin Infect Dis* 2005;41:1431–7.
56. Sheiko MA, Golden-Mason L, Giugliano S, et al. CD4+ and CD8+ T cell activation in children with hepatitis C. *J Pediatr* 2016;170:142.e1–8.e1.
57. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011;52:889–900.
58. Indolfi G, Mangone G, Bartolini E, et al. Comparative analysis of rs12979860 SNP of the IFNL3 gene in children with hepatitis C and ethnic matched controls using 1000 Genomes Project data. *PLoS One* 2014;9:e85899.
59. Indolfi G, Mangone G, Calvo PL, et al. Interleukin 28B rs12979860 single-nucleotide polymorphism predicts spontaneous clearance of hepatitis C virus in children. *J Pediatr Gastroenterol Nutr* 2014;58:666–8.
60. Ruiz-Extremera A, Pavon-Castillero EJ, Florido M, et al. Influence of HLA class I, HLA class II and KIRs on vertical transmission and chronicity of hepatitis C virus in children. *PLoS One* 2017;12:e0172527.
61. Nafady A, Nafady-Hego H, Abdelwahab NM, et al. Peripheral lymphocytes analyses in children with chronic hepatitis C virus infection. *Eur J Clin Invest* 2018;48:e13004.
62. Bortolotti F, Verucchi G, Camma C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008;134:1900–7.
63. El-Guindi MA. Hepatitis C viral infection in children: updated review. *Pediatr Gastroenterol Hepatol Nutr* 2016;19:83–95.
64. Jonas MM. Children with hepatitis C. *Hepatology* 2002;36(5 Suppl 1):S173–8.
65. Lee CK, Jonas MM. Hepatitis C: issues in children. *Gastroenterol Clin North Am* 2015;44:901–9.
66. Zein NN. Hepatitis C in children: recent advances. *Curr Opin Pediatr* 2007;19:570–4.
67. Birnbaum AH, Shneider BL, Moy L. Hepatitis C in children. *N Engl J Med* 2000;342:290–1.
68. Casiraghi MA, De Paschale M, Romano L, et al. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. *Hepatology* 2004;39:90–6.
69. Guido M, Bortolotti F, Leandro G, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *Am J Gastroenterol* 2003;98:660–3.
70. Matsuoka S, Tatara K, Hayabuchi Y, et al. Serologic, virologic, and histologic characteristics of chronic phase hepatitis C virus disease in children infected by transfusion. *Pediatrics* 1994;94 (6 Pt 1):919–22.

71. Minola E, Prati D, Suter F, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. *Blood* 2002;99:4588–91.
72. Stallings-Smith S, Krull KR, Brinkman TM, et al. Long-term follow-up for incident cirrhosis among pediatric cancer survivors with hepatitis C virus infection. *J Clin Virol* 2015;71:18–21.
73. Cesaro S, Bortolotti F, Petris MG, et al. An updated follow-up of chronic hepatitis C after three decades of observation in pediatric patients cured of malignancy. *Pediatr Blood Cancer* 2010;55:108–12.
74. Dyal HK, Aguilar M, Bhuket T, et al. Concurrent obesity, diabetes, and steatosis increase risk of advanced fibrosis among HCV patients: a systematic review. *Dig Dis Sci* 2015;60:2813–24.
75. Beech BM, Myers L, Beech DJ. Hepatitis B and C infections among homeless adolescents. *Fam Community Health* 2002;25:28–36.
76. Murray KF, Richardson LP, Morishima C, et al. Prevalence of hepatitis C virus infection and risk factors in an incarcerated juvenile population: a pilot study. *Pediatrics* 2003;111:153–7.
77. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009;200:1216–26.
78. Wise M, Finelli L, Sorvillo F. Prognostic factors associated with hepatitis C disease: a case-control study utilizing U.S. multiple-cause-of-death data. *Public Health Rep* 2010;125:414–22.
79. Hepatitis C: global ambition, national realities. *Lancet* 2016;387:1970.
80. Gonzalez-Peralta RP, Langham MR Jr, Andres JM, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2009;48:630–5.
81. Jara P, Resti M, Hierro L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;36:275–80.
82. Rumbo C, Fawaz RL, Emre SH, et al. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol Nutr* 2006;43:209–16.
83. Badizadegan K, Jonas MM, Ott MJ, et al. Histopathology of the liver in children with chronic hepatitis C viral infection. *Hepatology* 1998;28:1416–23.
84. Nydegger A, Srivastava A, Wake M, et al. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol* 2008;23:226–30.
85. Rodrigue JR, Balistreri W, Haber B, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr* 2009;48:341–7.
86. Committee on Infectious Diseases; American Academy of Pediatrics; David W, et al, editors. Red Book (2018). 1153 pp.
87. Panel A-IHG. Hepatitis C Guidance 2018 Update: AASLD-IDS recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2018;67:1477–92.
88. Khanna R, Verma SK. Pediatric hepatocellular carcinoma. *World J Gastroenterol* 2018;24:3980–99.
89. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016–2021. Geneva, Switzerland: World Health Organization; 2016. <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>. Accessed March 13, 2020.
90. Watts T, Stockman L, Martin J, et al. Increased risk for mother-to-infant transmission of hepatitis C virus among medicaid recipients - Wisconsin, 2011–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:1136–9.
91. Patrick SW, Bauer AM, Warren MD, et al. Virus infection among women giving birth - Tennessee and United States, 2009–2014. *MMWR Morb Mortal Wkly Rep* 2017;66:470–3.
92. Snodgrass SD, Poissant TM, Thomas AR. Notes from the field: underreporting of maternal hepatitis C virus infection status and the need for infant testing - Oregon, 2015. *MMWR Morb Mortal Wkly Rep* 2018;67:201–2.
93. Epstein RL, Sabharwal V, Wachman EM, et al. Perinatal transmission of hepatitis C virus: defining the cascade of care. *J Pediatr* 2018;203:34.e1–40.e1.
94. Society for Maternal-Fetal Medicine. Electronic address psoHughes BL, Page CM, et al. Hepatitis C in pregnancy: screening, treatment, and management. *Am J Obstet Gynecol* 2017;217:B2–12.
95. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2005;192:1153–61.
96. Urbanus AT, van Keep M, Matser AA, et al. Is adding HCV screening to the antenatal national screening program in Amsterdam, the Netherlands, cost-effective? *PLoS One* 2013;8:e70319.
97. Selvapatt N, Ward T, Bailey H, et al. Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. *J Hepatol* 2015;63:797–804.
98. Kanninen TT, Dieterich D, Ascitti S. HCV vertical transmission in pregnancy: new horizons in the era of DAAs. *Hepatology* 2015;62:1656–8.
99. Kushner T, Terrault NA. Hepatitis C in pregnancy: a unique opportunity to improve the hepatitis C cascade of care. *Hepatology Commun* 2019;3:20–8.
100. Aebi-Popp K, Duppenhaler A, Rauch A, et al. Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals (DAAs)? Short review and analysis of the situation in Switzerland. *J Virus Erad* 2016;2:52–4.
101. panel AIHG. Hepatitis C guidance 2018 update: AASLD-IDS recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2018;67:1477–92.
102. Dal Molin G, D'Agaro P, Ansaldo F, et al. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. *J Med Virol* 2002;67:137–42.
103. 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. *J Infect Dis* 2005;192:1872–9.
104. 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;192:1880–9.
105. Wen JW, Haber BA. Maternal-fetal transmission of hepatitis C infection: what is so special about babies? *J Pediatr Gastroenterol Nutr* 2014;58:278–82.
106. Garcia-Tejedor A, Maiques-Montesinos V, Diago-Almela VJ, et al. Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers. *Eur J Obstet Gynecol Reprod Biol* 2015;194:173–7.
107. Delotte J, Barjoan EM, Berrebi A, et al., ALHICE study group. Obstetric management does not influence vertical transmission of HCV infection: results of the ALHICE group study. *J Matern Fetal Neonatal Med* 2014;27:664–70.
108. Checa Cabot CA, Stoszek SK, Quarleri J, et al. Mother-to-child transmission of hepatitis C virus (HCV) among HIV/HCV-coinfected women. *J Pediatric Infect Dis Soc* 2013;2:126–35.
109. Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000;31:751–5.
110. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ* 1998;317:437–41.
111. Grebely J, Dore GJ, Morin S, et al. Elimination of HCV as a public health concern among people who inject drugs by 2030 - what will it take to get there? *J Int AIDS Soc* 2017;20:22146.
112. Martin NK, Hickman M, Hutchinson SJ, et al. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clin Infect Dis* 2013;57 Suppl 2:S39–45.
113. Indolfi G, Bailey H, Serranti D, et al. Treatment and monitoring of children with chronic hepatitis C in the Pre-DAA era: a European Survey of 38 Paediatric Specialists. *J Viral Hepatitis* 2019;26:961–8.
114. Platt L, Sweeney S, Ward Z, et al. Assessing the impact and cost-effectiveness of needle and syringe provision and opioid substitution therapy on hepatitis C transmission among people who inject drugs in the UK: an analysis of pooled data sets and economic modelling. Public Health Research. Southampton (UK). 2017.
115. Burrell CN, Sharon MJ, Davis SM, et al. Implementation of a Collaborative HIV and Hepatitis C Screening Program in Appalachian Urgent Care Settings. *West J Emerg Med* 2018;19:1057–64.

116. Carrico RM, Goss L, Wiemken TL, et al. Infection prevention and control and the refugee population: experiences from the University of Louisville Global Health Center. *Am J Infect Control* 2017;45:673–6.
117. Karnsakul W, Schwarz KB. Management of hepatitis C infection in children in the era of direct-acting antiviral agents. *J Viral Hepat* 2019;26:1034–9.
118. Indolfi G, Hierro L, Dezsofi A, et al. Treatment of chronic hepatitis C virus infection in children: a Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018;66:505–15.
119. Greenway E, Feld BM, Ling JJ, et al. C virus infection in mothers and children. *Canad Liver J* 2019;2:210–24.
120. Aiza-Haddad I, Ballesteros-Amozurrutia A, Borjas-Almaguer OD, et al. The Mexican consensus on the treatment of hepatitis C. *Rev Gastroenterol Mex* 2018;83:275–324.
121. Tucci F, Calbi V, Barzaghi F, et al. Successful treatment with ledipasvir/sofosbuvir in an infant with severe combined immunodeficiency caused by adenosine deaminase deficiency with HCV allowed gene therapy with Strimvelis. *Hepatology* 2018;68:2434–7.
122. Chappell C, Bunge K, Macio I, et al. A phase one study of Ledipasvir/Sofosbuvir in pregnant women with hepatitis c virus. *Conderence on Retroviruses and Opportunistic Infections Seattle, Washington Abstract Presentation*. 2019.
123. Indolfi G, Bartolini E, Serranti D, et al. Hepatitis C in children co-infected with human immunodeficiency virus. *J Pediatr Gastroenterol Nutr* 2015;61:393–9.
124. Sikavi C, Chen PH, Lee AD, et al. Hepatitis C and human immunodeficiency virus coinfection in the era of direct-acting antiviral agents: No longer a difficult-to-treat population. *Hepatology* 2018;67:847–57.
125. Northrop JM. A dirty little secret: stigma, shame and hepatitis C in the health setting. *Med Humanit* 2017;43:218–24.
126. Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013;57:2164–70.
127. Chhatwal J, Kanwal F, Roberts MS, et al. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med* 2015;162:397–406.
128. Linas BP, Barter DM, Morgan JR, et al. The cost-effectiveness of sofosbuvir-based regimens for treatment of hepatitis C virus genotype 2 or 3 infection. *Ann Intern Med* 2015;162:619–29.
129. Martin NK, Vickerman P, Dore GJ, et al. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. *J Hepatol* 2016;65:17–25.
130. Rein DB, Wittenborn JS, Smith BD, et al. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. *Clin Infect Dis* 2015;61:157–68.
131. Nguyen J, Barritt AS, Jhaveri R. Cost Effectiveness of Early Treatment with Direct-Acting Antiviral Therapy in Adolescent Patients with Hepatitis C Virus Infection. *J Pediatr* 2019;207:90–6.
132. Espinosa C, Jhaveri R, Barritt AS. Unique challenges of hepatitis C in infants, children, and adolescents. *Clin Ther* 2018;40:1299–307.
133. Younossi ZM, Stepanova M, Henry L, et al. Adherence to treatment of chronic hepatitis C: from interferon containing regimens to interferon and ribavirin free regimens. *Medicine (Baltimore)* 2016;95:e4151.
134. Slevin AR, Hart MJ, Van Horn C, et al. Hepatitis C virus direct-acting antiviral nonadherence: relationship to sustained virologic response and identification of at-risk patients. *J Am Pharm Assoc* 2019;59:51–6.
135. Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. *J Virus Erad* 2017;3:117–23.
136. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology* 2017;66:371–8.
137. Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2017;66:1102–10.
138. Murray KF, Balistreri WF, Bansal S, et al. Safety and efficacy of ledipasvir-sofosbuvir with or without ribavirin for chronic hepatitis C in children ages 6-11. *Hepatology* 2018;68:2158–66.
139. Leung DH, Wirth S, Yao BB, et al. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with or without ribavirin for adolescents with HCV genotype 1 or 4. *Hepatol Commun* 2018;2:1311–9.
140. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin therapy for children aged 3 to <12 years with hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2019;71:31–43.
141. Schwarz KB, Rosenthal P, Murray KF, et al. Ledipasvir-sofosbuvir for 12 weeks in children 3 to <6 years old with chronic hepatitis C. *Hepatology* 2019;71:422–30.
142. Jonas MM, Squires RH, Rhee SM, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in adolescents with chronic hepatitis C virus: part 1 of the DORA Study. *Hepatology* 2019;71:456–62.