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

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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

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

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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
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 DAAAS has decreased infections in solid-organ transplant recipients (25). In a clinical trial, recipients of liver transplantation (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).
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-IDSA 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 DAAs (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/IDSA recommendations to test all

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

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

N/A = not applicable; SVR12 = sustained virologic response at 12 weeks posttreatment.
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 coinfected 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 throughout the community 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 tolerability 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 DAAAs 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/15 kg/12 weeks for the treatment of genotypes 1–6) and expanded to age 2 years (SOF, 150–200 mg/20 kg/12 weeks for the treatment of genotypes 1–6). For genotypes 2 and 3, 12 weeks of SOF (400 mg/120 kg) + 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...
A 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/elbasvir, ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r/DSV), sofosbuvir/ledipasvir and grazoprevir/elbasvir, 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 DAAAs 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 Ib 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: NCT03379056). 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 DAA s 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 DAAs, 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 ≤ 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 (HIPPA) 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.hepatitis.c.uw.edu/page/treatment), although the actual cost paid for the medications may be significantly lower. Cost-effectiveness studies in children are limited, but a 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 subside 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 SVR 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

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

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)

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REFERENCES


