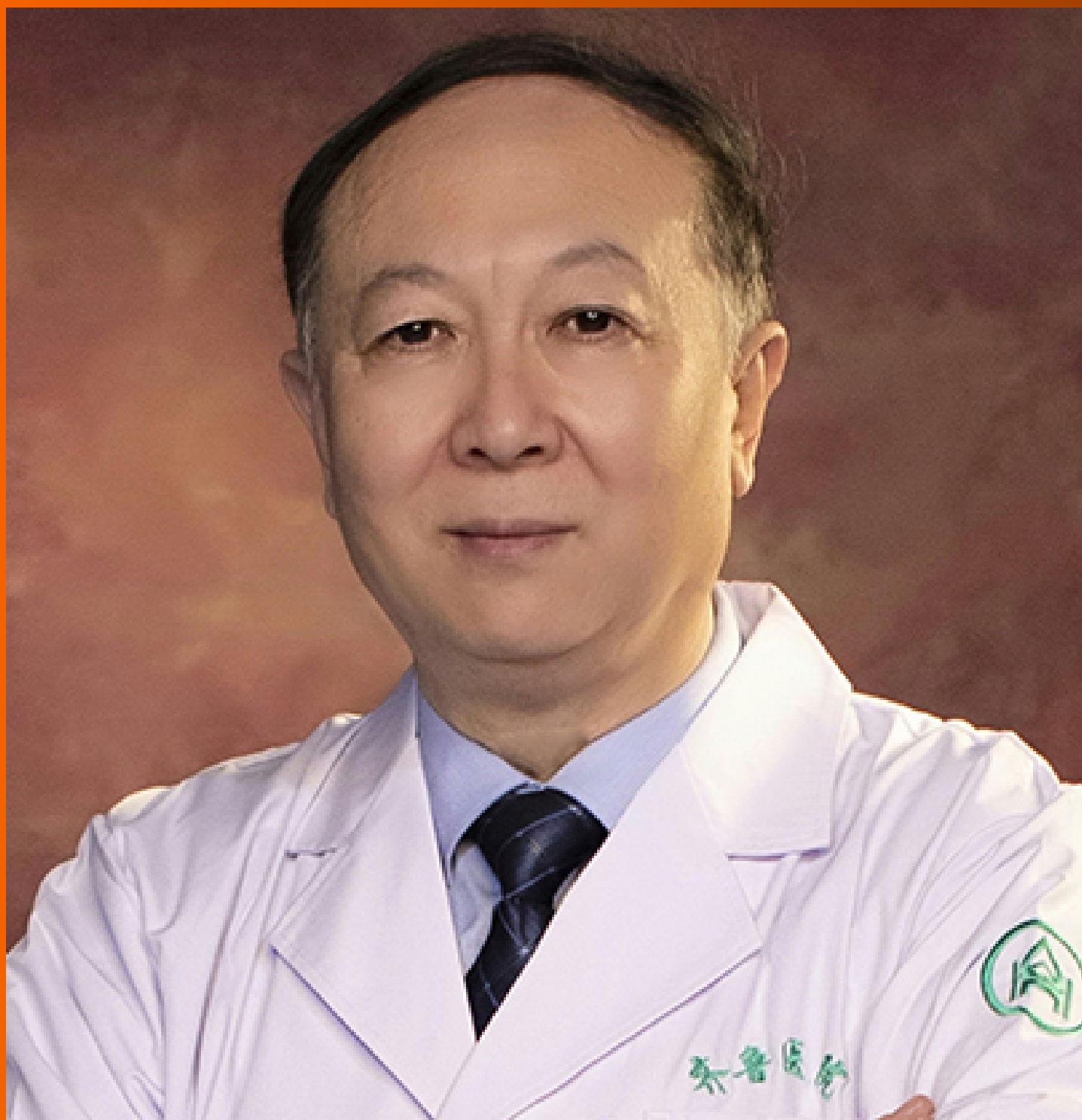


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Cascade of care for children and adolescents with chronic hepatitis C

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Abstract

Chronic hepatitis C virus (HCV) infection presents a significant global public health burden. In 2015, over 400000 deaths worldwide were attributed to HCV infection. This led the World Health Organization (WHO) in 2016 to set the ambitious goal of eliminating HCV by 2030. Adult-centered guidelines have been established in order to provide direction for healthcare professionals, allowing integration of the newest screening policies and therapeutic strategies into their practices. However, for children and adolescents, HCV is a significant, unrecognized public health problem. HCV infection rates in the United States in women of childbearing age and those who are pregnant have increased in parallel with the rising opioid epidemic. An estimated 29000 women with HCV infection gave birth each year from 2011 to 2014 in the United States, with approximately 1700 of their infants being infected with HCV. Newer HCV-specific therapeutics, namely direct acting antivirals (DAA), has brought a new and highly successful approach to treatment of hepatitis C. Recent studies have confirmed similar levels of effectiveness and safety of DAA therapies in the pediatric population. Thus, an enhanced cascade of care, which should include the population under 18 years of age, can help achieve the WHO goal by focusing on elimination in the youngest populations. This review will present an overview of the natural history, clinical features, and management of HCV in children and adolescents.

Key Words: Hepatitis C virus; Hepatitis C education; Hepatitis C elimination

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Core Tip: In 2020, the landmark series of accomplishments which started with the discovery of the hepatitis C virus (HCV) and led to the development of pharmaceutical

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agents capable of curing HCV infection was underscored by the awarding of the Nobel Prize in Medicine. These innovative cures are now being applied to the pediatric population. Furthermore, programs such as The Kentucky Hepatitis Academic Mentorship Program have been developed to train general pediatricians on HCV epidemiology, diagnosis, management, treatment and prevention. Thus this cascade of care will hopefully help achieve the World Health Organization goal of eliminating HCV by 2030.

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INTRODUCTION

The arc of discovery—from identification of the hepatitis C virus (HCV) as the causative agent of what was termed “Non-, Non-B Hepatitis” in 1989 to the development of pharmaceutical agent capable of efficiently curing HCV infection was remarkably short. In October 2020, this landmark series of accomplishments was underscored by the awarding of the Nobel Prize in Medicine to Drs. Alter, Houghton, and Rice. The Nobel committee recognized that their work transformed molecular virology/immunology and revolutionized the management of infected patients worldwide^[1,2].

HCV infection presents a significant global public health burden. It is currently estimated that over 70 million individuals are chronically infected with HCV and that many are unaware of their infectious status^[3]. In 2015, over 400000 deaths worldwide were attributed to HCV infection. This led the World Health Organization (WHO) in 2016 to set the ambitious goal of eliminating HCV by 2030. Despite the advances in HCV therapeutics, significant cost and access to care are the major barriers to the achievement of this goal^[4].

Adult-centered guidelines have been established in order to provide direction for healthcare professionals, allowing integration of the newest screening policies and therapeutic strategies into their practices. For children and adolescents, HCV is a significant, unrecognized public health problem. Perinatal transmission accounts for the majority of recognized HCV infections in the pediatric population. HCV infection rates in the United States in women of childbearing age and those who are pregnant have increased in parallel with the rising opioid epidemic. An estimated 29000 women with HCV infection gave birth each year from 2011 to 2014 in the United States, with approximately 1700 of their infants being infected with HCV^[5].

Newer HCV-specific therapeutics, namely direct acting antivirals (DAA), have brought a new and highly successful approach to treatment of hepatitis C. Recent studies have confirmed similar levels of effectiveness and safety of DAA therapies in the pediatric population. Thus, an enhanced cascade of care, which should include the population under 18 years of age, can help achieve the WHO goal by focusing on elimination in the youngest populations.

This review will present an overview of the natural history, clinical features, and management of HCV in children and adolescents.

EPIDEMIOLOGY OF HEPATITIS C

All 6 HCV genotypes have been diagnosed in the pediatric population; based on limited reporting, the genotypic distribution appears to mimic what is seen in the adult population, with genotype 1 predominating^[6].

HCV infection is most often asymptomatic in the pediatric population; therefore, it is difficult to estimate the true global prevalence. Schmelzer *et al*^[7] combined past modelling and epidemiological work in 104 countries and territories to estimate the prevalence in children in 2018. They reported the global estimated viremic prevalence in the population under 18 years of age to be 0.13%, corresponding to 3.26 million children with HCV in 2018, with wide variability. The prevalence increased with age in all countries and territories. The strongest predictor of HCV prevalence in children

aged 0-4 years was the HCV prevalence in women of childbearing age. The proportion of HCV infections in adults who inject drugs was significantly associated with HCV prevalence in children aged 15-19 years^[8]. In view of the wide heterogeneity, reliable country- or territory-specific and age-specific HCV prevalence estimates will be required in order to allow countries and territories to improve national HCV elimination and treatment strategies.

The true prevalence of pediatric HCV infection in the United States is also unknown due to a lack of uniform screening strategies. In 2020, the United States Preventive Services Task Force (USPSTF) issued revised recommendations that encourages clinicians to screen all adults aged 18 to 79 years for HCV infection^[9]. Previously, they had expressed a concern that HCV screening might be associated with negative psychological and social consequences. However, treatment with DAA therapy has been associated with improved quality of life in addition to high rates of curing HCV^[10]. Thus, as screening tests for HCV are highly accurate, they now conclude that the combination of screening with DAA therapy indicates improved long-term outcomes.

The USPSTF recommendations specifically suggest HCV screening for all pregnant women during each pregnancy. This is important since the rate of HCV infection in pregnant women has continued to increase, with an associated increase in the number of infants exposed to HCV.

The risk of perinatal transmission is confined to HCV infected women who have detectable HCV RNA. The risk of transmission is increased with higher levels of HCV viremia, as well as co-infection with HIV^[11-14]. The mode of delivery (vaginal *vs* cesarean-section) does not typically affect risk of transmission^[13]. However, if the mother is co-infected with HIV, then there may be a protective affect by undergoing a cesarean-section for delivery^[11]. HCV RNA may be detected in breast milk and colostrum; however, breast feeding does not appear to increase the rate of HCV transmission (with the exception of HIV co-infected mothers)^[15].

While prenatal care settings are potential venues for expanding HCV testing, implementation is sporadic. Epstein *et al*^[8] characterized the HCV diagnostic cascade for women attending an obstetric clinic serving individuals with substance use disorders. They reported successfully screening for HCV among pregnant women with opioid use. In retrospective cohort study of infants exposed to HCV who were enrolled in the Tennessee Medicaid program, testing was conducted in only 23% of infants and less frequently among African American infants^[16]. These two observations indicate that infant HCV screening is currently imperfect, emphasizing the need for programmatic changes to improve both mother and infant follow-up to bridge gaps in the cascade to cure. Because current testing recommendations may not properly address the barriers to HCV testing among high-risk infants, contributing to missed HCV infections, new policies (such as universal pediatric testing) may address the gaps^[6,17,18].

Screening in adolescents may also be improved. Epstein *et al*^[19] reported that only 30% of adolescents with identified opioid, amphetamine, or cocaine use were tested for HCV; 7% were found to be positive. Barritt *et al*^[20] reported that in the United States from 2006-2012, the hospitalization rates of children with HCV increased by 37%; the majority of these patients were adolescents. This further reflects that our attempts at identifying and treating HCV in early childhood and adolescents are inadequate.

NATURAL HISTORY

Children with chronic HCV infection are typically asymptomatic^[6,17]. An estimated 20%-40% will undergo spontaneous clearance within the first 5 years of life^[21,22]. A combination of perinatal transmission and genotype 1a is associated with decreased rates of clearance, persistent viremia, and higher likelihood of development of end-stage liver disease in children who are treatment naïve^[23]. Albeit uncommon, progression to cirrhosis has been described and hepatocellular carcinoma (HCC) secondary to HCV and cirrhosis in a child has also been reported^[24].

Younossi *et al*^[25] reported that HCV infection in adolescents was associated with poor social functioning and health-related quality of life (HRQoL). Children chronically infected with HCV had a significant reduction in a wide range of intelligence and memory testing. Vocabulary, reading comprehension, abstract visual reasoning, and short-term memory were all statistically inferior in HCV infected children compared to healthy controls^[26]. Treatment of HCV led to improved quality of life, using multiple validated patient reported outcome instruments^[25]. Therefore,

while the liver disease in HCV infected children is often absent or mild, treatment may lead to improved HRQoL in addition to prevention of cirrhosis and end-stage liver disease.

CLINICAL FEATURES AND OUTCOMES

Jaundice, fatigue, dyspepsia, and abdominal pain are the most common signs and symptoms reported in adults^[27]. Unfortunately, there is less robust prospective data regarding clinical symptoms in children and adolescents. When reported, minimal nonspecific and brief symptoms are found in approximately 15% of children. These symptoms can be in the form of fatigue, anorexia, nausea, vomiting, and abdominal colic^[28].

Extrahepatic manifestations of HCV infection are well documented in the adult population. These include glomerulonephritis, polyarteritis nodosa and cryoglobulinemia. Other non-specific extrahepatic symptoms reported in adult studies include fatigue, renal impairment, lymphadenopathy, fever, and thyroid dysfunction^[29-31]. Although there appears to be a low incidence of extrahepatic manifestations in children, careful monitoring is still recommended. Indolfi *et al*^[32] noted that subclinical thyroiditis (not autoimmune thyroid disease) has been reported in children with HCV. Other extrahepatic manifestations such as myopathy and opsoclonus-myoclonus syndrome have also been reported.

It is rare for HCV-associated liver disease to advance to the point of requiring liver transplant in children or adolescents. Based on retrospective analysis of the United Network of Organ Sharing, Gupta *et al*^[33] found that children transplanted for HCV had a one-year survival of 97% and a three-year survival of 89% in the post-pediatric end-stage liver disease era. These findings are consistent with best practice liver transplant outcomes in children.

DIAGNOSIS AND SCREENING CHILDREN AND ADOLESCENTS

In children older than 18 mo of age, diagnostic criteria are the same as those established for adults. An enzyme immunoassay is used to detect antibody (anti-HCV); however, the presence of anti-HCV alone is unable to distinguish if the patient has an active or resolved infection. Thus, in children with detectable anti-HCV antibodies, the next step is to verify viral infection by detecting HCV RNA. This is accomplished *via* polymerase chain reaction (PCR) testing. The diagnosis of chronic HCV infection is made based on presence of detectable HCV RNA for more than 6 mo^[34,35].

The diagnosis of perinatal transmission in infants under 18 mo of age is confounded by the passive transfer of maternal antibodies, which can last for one year or more postnatally. Thus, anti-HCV testing is of limited value during the infantile period. Diagnosis in this age group can be reliably established by HCV RNA positivity on two or more occasions after two months of age^[36-38]. Criteria for spontaneous clearance requires two negative HCV RNA tests spread at least 6 mo apart, followed by negative anti-HCV testing after 18 mo of age^[39,40].

For the population < 18 years of age, the screening guidelines are unclear. Assoumou *et al*^[41] completed a cost-effective analysis which revealed improved quality of life years (QALY) gained if universal screening for HCV was expanded to include adolescents (15 years and older). However, as the diagnosis of infants is more difficult to interpret, studies on the cost effectiveness of screening younger patients are needed. Recent efforts in the United States have focused on infants born to HCV infected mothers^[42,43].

Jhaveri *et al*^[44] endorsed a national strategy for HCV screening that integrates follow-up of infants with HCV exposure by using a model similar to HIV mother-to-child transmission prevention programs. This, and related calls to action to primary care providers, will lead to enhanced recognition and screening for children with HCV exposure, similar to the efforts to combat the HIV epidemic^[45].

TREATMENT

The arrival of DAA therapies has led to a paradigm shift in the treatment and

eradication of HCV in all populations^[3,4]. The spate of DAAs available have been shown to be as safe and effective in children and adolescents as in the adult populations. Pegylated-interferon (PEG-IFN) and ribavirin (RBV), the initial recommended combination for treatment of HCV in children and adolescents, are no longer recommended^[46]. DAA therapies are specific and more effective at achieving sustained virologic response (SVR) in the pediatric population with few side effects. DAA therapies can also achieve SVR in no more than 12 wk of treatment, as compared to the RBV and PEG-IFN combination which required 48 wk of treatment, close monitoring, and significant side effect profiles including pancytopenia. Furthermore, regimens of PEG-IFN have sustained efficacy of only just above 50%, whereas DAA regimens have been shown to be persistently more effective (SVR > 95%) in children^[3,4,17,46,47].

DAAs target three HCV proteins: (1) The nonstructural protein 3/4A (NS3/4A) protease inhibitors (PIs) which work by inhibiting HCV polypeptide processing; (2) NS5A inhibitors, which inhibit viral replication and assembly; and (3) NS5B polymerase inhibitors that block HCV RNA replication^[48,49]. By combining two or more of these classes of drugs with different mechanisms attacking the Hepatitis C virus, DAAs are able to achieve high SVR rates.

Over the past few years, several phase 2 clinical trials have been completed revealing the safety and efficacy of DAA therapy in children as young as 3 years of age (Table 1)^[50-77]. For example, the first pediatric trial showed the safety and efficacy of Harvoni, the combination of Ledipasvir (90 mg) and sofosbuvir (400 mg), for treatment of HCV genotype 1 over a 12 wk period in children ages 12-17 years^[50]. Subsequent clinical trials have been completed which show the efficacy and safety of newer combinations of DAA therapy for a wider range of HCV genotypes and pediatric age groups. For example, Jonas *et al*^[74] reported the utility of the pangenotypic combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in children ages 12-17 years. They found 100% SVR at 12 wk post therapy (SVR12) in as few as 8 wk of treatment. The safety profile was also consistent with that in adults. Wirth *et al*^[75], reported that the fixed-dose combination of elbasvir/grazoprevir in children ages 3-17 years for HCV genotypes 1 and 4 was safe and efficacious in all study participants. Furthermore, SVR12 was achieved by all 57 participants. Sokal *et al*^[76] also recently completed a study on the safety and tolerability of sofosbuvir/velpatasvir in pediatric patients aged 3-17 years with chronic HCV infection through 24-wk post-treatment. They found a 92% SVR12 rate regardless of HCV genotype, prior treatment experience, or presence of compensated cirrhosis.

Rosenthal *et al*^[72] revealed that sofosbuvir plus ribavirin (RBV) was well-tolerated and highly effective in children aged 3 to < 12 years with chronic HCV genotype 2 or 3 infection. However, over one-third of the participants experienced gastrointestinal symptoms (vomiting, diarrhea), common side effects to RBV treatment. This combination is an option for young children until we have more published evidence for RBV-free DAA regimens. The hope is that in 2021, we will have approval by the United States Food and Drug Administration (FDA) for the use of a wide variety of DAA combination therapies.

Higher risk groups, such as children who are survivors of cancer, have also had high success rates with DAA therapy. El-Shabrawi *et al*^[66] prospectively followed 20 childhood cancer survivors ages 8-17 years with HCV genotype 4 in Egypt. They all received Sofosbuvir plus Daclatasvir over a 12 wk period. They achieved 100% SVR12 in their study group without any treatment related adverse events. Furthermore, no relapses were detected during treatment and throughout the follow up period (36 wk) for either the original malignant disease or the HCV infection.

Studies are also assessing the efficacy of smaller doses and shorter duration^[60,67,77]. For example, Behairy *et al*^[77] reported the effect of a shortened 8-wk regimen of ledipasvir/sofosbuvir at smaller dosing of 45 mg and 200 mg respectively. They found that this regimen is safe and effective with 100% SVR12 in treatment-naïve children aged 4-10 years with chronic HCV infection genotype 4.

WHERE DO WE STAND?

The American Association for the Study of Liver Diseases (AASLD) published updated guidelines for the evaluation and management of HCV infection to reflect the DAA era^[78]. The AASLD supports the use of ribavirin-free DAA regimens as early as possible (all children >3 years of age) to avoid future complications. A policy paper from the North American Society of Pediatric Gastroenterology Hepatology and

Table 1 Completed studies of direct acting antivirals regimens in children and adolescents

Ref.	Year	Participant age in years (n)	HCV genotype	Therapy (duration)	SVR12 (%)
Balistreri <i>et al</i> ^[50]	2016	12-17 (100)	1	Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	98
Wirth <i>et al</i> ^[51]	2017	12-17 (52)	2 or 3	Sofosbuvir 400 mg + ribavirin (variable)	98
Hashmi <i>et al</i> ^[52]	2017	5-18 (35)	1 or 3	Sofosbuvir 400 mg + ribavirin (variable)	97
El-Khayat <i>et al</i> ^[53]	2018	12-17 (144)	1, 4-6	Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	99
Murray <i>et al</i> ^[54]	2018	6-11 (90)	1	Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	98
El-Karakasy <i>et al</i> ^[55]	2018	12-18 (40)	4	Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	100
Leung <i>et al</i> ^[56]	2018	12-17 (38)	1 or 4	Ombitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin (variable)	100
Alkaaby <i>et al</i> ^[57]	2018	7-18 (22)		Ledipasvir + sofosbuvir +/- ribavirin (variable)	91
Tucci <i>et al</i> ^[58]	2018	0.5 (1)	4	Ledipasvir 22.5 mg + sofosbuvir 100 mg (12 wk)	100
El-Shabrawi <i>et al</i> ^[59]	2018	6-12 (20)	4	Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	95
El-Shabrawi <i>et al</i> ^[60]	2018	12-17 (10)	1-6	Sofosbuvir 400 mg + daclatasvir 60 mg (8 wk)	100
Yakoot <i>et al</i> ^[61]	2018	12-17 (30)	4	Sofosbuvir + daclatasvir (12 wk)	97
Quintero <i>et al</i> ^[62]	2019	6-18 (9)	1 or 4	Ledipasvir + sofosbuvir (variable)	100
Ghaffar <i>et al</i> ^[63]	2019	8-18 (40)	4	Sofosbuvir + daclatasvir (variable)	97.5
Fouad <i>et al</i> ^[64]	2019	11-17.5 (51)	4	Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	100
Ohya <i>et al</i> ^[65]	2019	10-13 (3)	1b	Ombitasvir + paritaprevir + ritonavir (12 wk) Or glecaprevir + pibrenastavir (8 wk)	100
El-Shabrawi <i>et al</i> ^[66]	2019	8-17 (20)	4	Sofosbuvir + Daclatasvir (12 wk)	100
Serranti <i>et al</i> ^[67]	2019	12-17 (14)	1	Ledipasvir 90 mg + sofosbuvir 400 mg (8 wk)	100
Marascio <i>et al</i> ^[68]	2019	13, 16 (2)	4	Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	100
Fouad <i>et al</i> ^[69]	2020	12-18 (46)	Not performed	Ledipasvir 180 mg + sofosbuvir 400 mg (12 wk)	98
Kamal <i>et al</i> ^[70]	2020	3-6 (22)	4	Ledipasvir 45 mg + sofosbuvir 200 mg (8 or 12 wk)	100
El-Araby <i>et al</i> ^[71]	2020	9-12 (100)	4	Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	100
Rosenthal <i>et al</i> ^[72]	2020	3-11 (54)	1 or 4	Sofosbuvir 400 mg + ribavirin (variable)	98
Schwarz <i>et al</i> ^[73]	2020	3-< 6 (34)	1 or 4	Ledipasvir + sofosbuvir (variable)	97
Jonas <i>et al</i> ^[74]	2020	12-17 (47)	1-4	Glecaprevir 300 mg + pibrentasvir 120 mg (8-16 wk)	100
Wirth <i>et al</i> ^[75]	2020	3-17 (57)	1 or 4	Elbasvir + grazoprevir (12 wk)	100
Sokal <i>et al</i> ^[76]	2020	3-17 (216)	1-4, 6	Sofosbuvir + velpatasvir (12 wk)	92
Behairy <i>et al</i> ^[77]	2020	4-10 (30)	4	Ledipasvir 45 mg + sofosbuvir 200 mg (8 wk)	100

Table adapted from Squires *et al*^[17]. HCV: Hepatitis C virus.

Nutrition (NASPGHAN), included pediatric guidelines for treating children with DAA therapy^[79]. They agreed with starting applicable DAA therapy as early as 3 years of age.

Outside of North America, guidelines are being updated to reflect the advent of DAA therapy. The European Association for the Study of the Liver (EASL) recently published a new guidance for management of HCV^[80]. They recommend treating HCV positive children (with or without cirrhosis) as young as 3 years of age with DAA regimens of either combined sofosbuvir and velpatasvir, or glecaprevir and pibrentasvir. Indolfi *et al*^[46] as part of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) also updated their position to

recommend initiation of DAA therapy for children as young as 3 years of age with HCV, regardless of the presence of fibrosis or active inflammation. We agree with AASLD, NASPGHAN, EASL, and ESPGHAN recommendations for an aggressive approach to treating children 3 years of age and older with a RBV-free DAA combination. Furthermore, we agree with these worldwide guidelines that if there is any signs or evidence of fibrosis, then patients should continue to be monitored even after completing DAA therapy and achieving SVR (please refer to monitoring below).

Anecdotally, one of the main hurdles is determining an age when a young child is capable of daily compliance with the medications for the recommended 8-12 wk period. The advent of DAA therapies in the form of granules/pellets is a promising strategy for younger children who cannot swallow whole tablets. For example, Schwarz *et al*^[73] allowed for the granules to be sprinkled on a spoonful of nonacidic soft food, such as pudding or ice cream. SVR12 was achieved in 97% of patients, with only one patient discontinuing the trial after 5 d due to "abnormal drug taste".

Cost-effective analyses for treating children with DAA therapy are limited. Nguyen *et al*^[81] found that early DAA treatment in adolescent patients with chronic HCV infection was cost-effective compared with deferred treatment, with approximately \$27000 per QALY gained after 30 years. Greenaway *et al*^[82] published data comparing treatment at age 6 years *vs* delaying treatment until age 18 years. In their model covering 20 years and treating 10000 children early, 330 cases of cirrhosis, 18 cases of hepatocellular carcinoma, and 48 liver-related deaths would be avoided. The incremental cost-effectiveness ratio of early treatment compared to delayed treatment was approximately \$12690 per QALY gained and considered cost-effective. Thus delaying treatment until age 18 years results in an increased lifetime risk of late stage liver complications that can otherwise be avoided. Early treatment is associated with saving money and lives, as well as improving quality of life.

IMPROVING THE CASCADE OF CARE

In addition to inadequate screening, a major barrier to treatment and elimination is access to care and treatment. However, several programs have been conceived in order to provide DAA therapy to more individuals, with a focus in the primary care setting. In Australia, DAA treatments are available through the national Pharmaceutical Benefits Scheme (PBS) as of 2016. The PBS is a publicly funded scheme which provides highly subsidized prescription drugs *via* Australia's universal healthcare system^[83]. Australia was also one of the first countries to allow DAA treatment to be initiated by general practitioners. Since the advent of these practices, they have seen marked improvements in the cascade of hepatitis C care among patients attending primary care clinics^[84].

In the United States, certain regions have much higher rates of HCV infection. For example, the Appalachian region leads the nation in reported new cases. Thus, new developmental strategies have been created focusing on these communities. The Kentucky Hepatitis Academic Mentorship Program (KHAMP) was created with the goal to build a hepatitis C elimination model which would then be easily modified and used to improve the health of rural and underserved communities throughout the Appalachian region. KHAMP has trained primary care providers on HCV epidemiology, diagnosis, management, treatment and prevention. General practitioners in this region are thus equipped with the skills needed to increase the number of individuals treated, ensuring that they will no longer be required to travel and consult with a specialist in order to prescribe DAA therapy^[17,85,86].

This blueprint is being applied to the rest of the United States, continuing the focus on the Appalachian region. For example, West Virginia has recently implemented the West Virginia Hepatitis Academic Mentoring Partnership which will use the same strategies as KHAMP to provide education for primary care providers on HCV^[86,87]. Virginia and Ohio are also participating to improve their education and access at the primary care level.

The advent of telemedicine has also had a positive impact towards treating HCV. Arora *et al*^[88] developed the Extension for Community Healthcare Outcomes (ECHO) model. In a prospective cohort study, the ECHO model through use of video-conferencing technology, trained primary care providers to care for underserved populations with HCV infection who live in New Mexico. Results showed that ECHO was an effective approach to treating HCV infection in underserved communities. Piao *et al*^[89] have implemented ECHO to California with improvements in SVR, advocating for such programs to be an essential part of HCV care moving forward.

In Australia, hepatitis C treatment (DAA therapy) using a decentralized, nurse-led telemedicine model of care has been highly effective at reaching a treating large numbers of prisoners, many of which are IV drug abusers^[90]. Canada has also implemented a telemedicine program in order to effectively increase the use of DAA therapy with a high success rate of SVR (approximately 95%)^[91]. As more programs are being initiated, the possibility of reaching the WHO goal of eradication by 2030 is still possible.

IMPACT OF TREATMENT ON PROGRESSION

Progression of HCV from an inflammatory hepatitis, to fibrosis, and eventually cirrhosis can occur starting in early childhood. In the past, most HCV-infected children would develop chronic HCV with a lifetime risk of liver disease. Modin *et al*^[92] quantified the development of long-term liver disease and the effect of treatment in patients infected with HCV in childhood. They reported that liver disease developed in 32% of patients, a median of 33 years after infection; patients with perinatal exposure developed cirrhosis at an earlier age than the rest of the risk groups. The incidence of HCC was 5%, liver transplant 4% and death occurred in 3%. Among those treated there was a higher mortality rate among patients that did not achieve an SVR, and treatment was more effective in patients without cirrhosis. Disease progression was less frequent than in patients with cirrhosis at the time of therapy. The authors make a strong case for early treatment, before development of cirrhosis.

MONITORING

Finding non-invasive methods to assess for progression to fibrosis is an important aspect of monitoring children with chronic HCV. Transient elastography (TE) *via* ultrasound (US) evaluation of the liver is gaining traction in the pediatric population^[93]. TE as a measurement of liver fibrosis has been validated in a variety of chronic liver diseases, including HCV^[94-97].

Pokorska-Śpiewak *et al*^[98] reported their prospective analysis on the prevalence of fibrosis in adolescents (12-17 years) with chronic HCV. Using TE, they found that over 10% of their patients had evidence of significant fibrosis (fibrosis score > 2), and that 9% had evidence of cirrhosis (Fibrosis score of 4). Other markers of liver fibrosis, such as the aspartate transaminase-to-platelet ratio index score, correlated positively with liver stiffness from TE. Otherwise, serial monitoring with in-clinic visits, as well as laboratory testing of aminotransferases and gamma-glutamyl transferase are recommended to occur at least twice yearly. Monitoring for signs of HCC with serum alpha-fetoprotein and US imaging is also warranted^[29,99,100].

Based on the previously completed studies on DAA therapy in pediatrics, our current practice involves obtaining HCV PCR at baseline (prior to initiation of DAA therapy), at 4 wk, at 12 wk, and at 24 wk post initiation of therapy^[50,54,70]. As long as there was no evidence of long-term damage (fibrosis, cirrhosis, *etc.*), then patients can have a repeat HCV PCR one year after completion of therapy to affirm SVR^[50,54,72-76,81]. No pediatric studies with the children completing the DAA therapy has revealed evidence of children being unresponsive to DAA therapies.

Children with evidence of liver fibrosis should continue to be closely monitored even after eradication of their underlying HCV. However, adult studies are emerging which reveal that fibrosis may be to-some-extent reversed by DAA treatment^[101-104]. One study revealed a 32% reduction in liver stiffness measurements after DAA completion among 392 adults with chronic HCV and fibrosis^[105]. However, for patients with evidence of high-grade fibrosis or cirrhosis, they are still at high risk of developing HCC even after achieving SVR^[106]. More histological data is needed to further support the hypothesis of improved liver scarring post DAA treatment. At this time, children with evidence of fibrosis must be closely followed given the continued risk of complications such as HCC and portal hypertension.

IMPACT OF DAA THERAPY ON LIVER TRANSPLANT

The number of patients requiring HCV-related liver transplant has decreased, increasing organ availability for other liver disorders, such as NASH. In addition,

given the safety and effectiveness of DAA therapy, the idea of placing HCV-infected livers into uninfected recipients is gaining traction. With the rising demand of liver transplant, treating recipients with an appropriate course of DAA therapy immediately after transplant appears safe and efficacious^[107,108]. In one small study, 8 veterans received HCV-infected livers and all 8 became viremic with HCV. However, after a 12 wk course of DAA treatment, all 8 patients achieved SVR12^[109]. Bohorquez *et al*^[110] increased this sample size and, after completing an appropriate DAA regimen, had 100% SVR12 in all 51 HCV-naïve patients who received HCV positive livers. Therefore, solid organ transplant from HCV infected recipients appears to be safe, is associated with excellent outcomes, and should be considered for recipients who would benefit from receiving an organ earlier than they would if they waited for an organ from an uninfected donor. Thus, reducing wait-list associated mortality. The same concept applies to other solid organ transplants. While no studies has been performed, based on the efficacy of DAA therapy in children, using HCV-infected donors should be an option.

CORONAVIRUS DISEASE AND HCV

The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted access and healthcare practices for many patients and providers, including the pediatric population. As children will now have access to DAA therapies and potential HCV cure, it is imperative that diagnosis and treatment of this population is not overlooked. A related issue is for patients with chronic liver disease to avoid COVID-19 exposure and infection, by educating patients/parents on the risk and the recommended precautions^[111]. This is especially true in rare cases of children with cirrhosis or end-stage liver disease secondary to HCV, as there appears to be a higher risk of a severe course of COVID-19^[112].

The advent of telemedicine is playing an important role in the care of children with HCV. This allows patients to undergo lab testing locally, for DAA prescriptions to be sent to their home, and allow providers to safely communicate, educate, and closely monitor their patients during treatment^[113]. Thus this pandemic should not be a hindrance to continuing the goal of eradication of HCV in the pediatric population.

CONCLUSION

The discovery of the HCV and the related advances in biomedical research-the establishment and implementation of diagnostic tests to ensure the safety of blood products, and antiviral drug development has, and will continue to have, a major impact on health care outcomes for patients of all ages...including the smallest victims. Enhanced screening and awareness efforts and continued education of healthcare providers will improve the outcomes of HCV infection in the pediatric population.

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