Hepatitis C Virus Infection in Children and Adolescents

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Introduction

Hepatitis C virus (HCV) infection remains a major public health burden, with an estimated worldwide prevalence of 2.5% of the population (177.5 million infected adults); this ranges from 1.3% in the Americas to 2.9% in Africa.[1] In the United States alone, an estimated 3 million to 4 million persons are chronically infected with HCV, and approximately half are unaware of their infectious status and do not receive appropriate care. The current Centers for Disease Control recommendations for HCV screening and advances in HCV treatment are anticipated to diminish the clinical burden of the disease; however, medication cost and access to care remain significant barriers.[2] In order to provide a more structured approach to the dynamic landscape of HCV, adult-centric guidelines have been established.[3] These provide health care professionals with timely guidance as new therapies become available and are integrated into treatment regimens.

In children and adolescents as in adults, HCV infection is suspected to be grossly underestimated. HCV infection across the pediatric age spectrum differs from infection acquired later in life in a variety of ways, including modes of transmission, rates of spontaneous clearance or progression of fibrosis, the potential duration of chronic infection when acquired at birth, and significantly, available treatment options.[4] While several reviews have recently been published regarding aspects of HCV infection in adults,[3,5,6] our goal is to present a practical overview of the epidemiology, diagnosis, clinical features, natural history, and management of HCV infection in children and adolescents.

Epidemiology

The prevalence of HCV infection in children and adolescents has been reported to vary from 0.05%-0.36% in the United States and Europe to 1.8%-5.8% in certain developing countries.[7] However, these reports likely underestimate the true prevalence since current ascertainment practices enable only a small fraction of children expected to be infected with HCV to be identified.[8,9]

Six distinct HCV genotypes have been identified. In adults, HCV genotype 1, subtypes 1a, and 1b as well as genotype 2, subtypes 2a, 2b, and 2c represent the most common variants in Western countries. HCV genotype 3 is widely distributed in South and East Asia, with subtype 3a common among intravenous drug users from Europe; genotype 4 in North Africa and the Middle East; genotype 5 in South Africa; and genotype 6 in Asia.[10] While all six genotypes have been identified in children, robust epidemiological reports on the disease burden in children and adolescents are lacking. When reported, it appears affected children often demonstrate similar regional distribution patterns that are described in adults. For example, genotypes 1-3 dominate the HCV burden of both children and adults in the United States.[11-13]

Historically, HCV was considered to be a transfusion-related disease in children and adolescents; however, with the advent of blood-bank screening practices, no new pediatric cases of transfusion-transmitted acute HCV infection have been detected in the United States since 1994.[14] Consequently, mother to infant transmission during the perinatal period has emerged as the most common mode of acquisition of infection in children, accounting for approximately 60% of cases. Mechanisms leading to perinatal HCV transmission are currently not well understood. Likely risk factors include perinatal practices (fetal scalp monitoring and caesarean-section delivery), extended exposure to maternal blood, high levels of HCV viremia during pregnancy, and co-infection with human immunodeficiency virus (HIV).[15-19] Although some studies have challenged several of these assumptions,[20,21] a recent meta-analysis concluded that maternal HIV co-infection is the most important determinant of the risk of perinatal transmission.[15]

While the rate of perinatal transmission of HCV has remained stable at 5%-6%, from 2006 to 2012 the incidence of HCV infection among women of childbearing age increased 13% annually in nonurban counties and 5% annually in urban counties in the United States.[22] This raises concern about an increasing number of pregnant women exposing their infants to HCV at birth. In parallel, we have noted a greater than 4-fold increase in the number of HCV-infected infants referred to our centers.

Unfortunately, even when maternal HCV infection is identified, most of the at-risk children born to these women remain untested at 18 months of age,[23] underscoring an important challenge. Currently, universal screening for HCV is not performed routinely in pregnant women and is reserved for those who are known to engage in "at-risk" activities; this is highly likely to miss a significant number of infected children.[24,25] However, studies have shown that large-scale antenatal screening programs can be feasible, effective, and affordable.[26]

Outside of the perinatal period, additional routes of acquisition of HCV infection in children result from engagement in high-risk practices, such as intravenous drug abuse (IVDA), and intrafamilial transmission.

THE RECENT SURGE

IVDA is a significant and increasingly common route of HCV infection in adolescents and young adults. Mirroring the IVDA epidemic, there has been a significant increase in reported HCV infections over the last decade, with a recent study demonstrating a 364% increase in HCV infection among people 12 to 29 years of age living in the Appalachian region of the United States.[22,27,28] These findings show that a new wave of young individuals will require HCV-specific treatment or risk the development of progressive liver disease and its complications. Furthermore, these data suggest a potential surge in the rate of mother to infant HCV transmission with resultant increased disease burden among children.

HCV infection has been associated with other high-risk activities, including receiving tattoos in an unregulated setting, intranasal cocaine use, and engaging in sexual practices that involve multiple partners and/or sexual activity with trauma.

HORIZONTAL TRANSMISSION

Intrafamilial transmission of HCV is a complex phenomenon with routes of transmission not established and the risk of infection uncertain.[29] In the developing world, studies suggest that some HCV infections in children could not be fully accounted for by exposure to blood transfusions or unsafe injections, suggesting other modes of transmission.[30,31] Follow-up studies have demonstrated that the robust intrafamilial component seen in HCV occurrences within families could, in part,

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be explained by specific genetic predisposition to persistent HCV infection.[32] Future work will need to detect the exact routes of transmission in order to identify and implement preventative strategies.

Diagnosis

Blood tests available for the identification of HCV are the antibody assays for HCV (anti-HCV) and the nucleic acid tests intended for detection and quantification of HCV RNA. In older children, the recommended testing sequence parallels adult guidelines and begins with an investigation for the presence of anti-HCV. Current immunoassays for anti-HCV are at least 97% sensitive and 99% specific[4,33,34]; importantly however, both false positive (patients with autoimmune disease, mononucleosis, pregnancy) and false negatives (patients with hypogammaglobulinemia or immunosuppressed patients) can occur.[33] If the anti-HCV is positive, HCV RNA quantification and genotype should be performed to confirm the infection. Knowledge of the HCV genotype is an important factor as it can determine both the specific antiviral regimen and the length of therapy.[33]

Challenges associated with HCV testing on a global scale include access to health care, inadequate laboratory capabilities, and a lack of data to guide country-specific hepatitis testing and are significant barriers to the identification of affected children. Recent World Health Organization testing guidelines look to strengthen and expand current testing practices to address who and how to test for HCV infection when such obstacles exist.[35]

UNIQUE ASPECTS OF HCV DIAGNOSIS IN NEWBORNS/ INFANTS

In general, testing for HCV infection should occur in all children suspected to be "at risk" (Table 1). However, unique to children is the sequence of testing recommended for infants born to mothers with HCV infection and who are in danger of becoming infected (perinatal transmission of HCV). Mothers infected with HCV will have circulating anti-HCV immunoglobulin G, which crosses the placenta and can be measured in the serum of their infants. Maternal antibody can persist in the child for over a year, consequently testing for anti-HCV in infants is not informative during this period. The American

TABLE 1. CHILDREN AND ADOLESCENTS FOR WHOM SCREENING FOR HCV INFECTION SHOULD BE CONSIDERED

- Children born to HCV-infected mothers (after 18 months of age).
- Children and adolescents with intrafamilial exposure.
- Children and adolescents emigrating from a region with a high prevalence of HCV infection.
- Children and adolescents with signs or symptoms of hepatitis.
- Adolescents incarcerated in a correctional institution.
- Adolescents who received tattooing and body piercing in unregulated settings.
- Adolescents who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.
- Children and adolescents with conditions associated with a high prevalence of HCV infection, including
  ○ HIV infection
  ○ Unexplained abnormal aminotransferase levels
  ○ Adolescents who were recipients of transfusions or organ transplants before July 1992.
- Adolescents after a needle stick injury or mucosal exposure to HCV-positive blood.

Academy of Pediatrics' recommendations are to delay measurement of anti-HCV antibody until after 18 months of age.[4] HCV RNA testing can reliably indicate perinatal transmission; however, infants should be at least 2 months old for this test to be reliable.[4,36] Retesting at 12 months should occur to confirm chronic HCV infection and to rule out the possibility of spontaneous seroconversion, defined as the absence of detectable HCV RNA on two occasions >6 months apart,[37,38] which occurs in 25%-40% of infants infected via perinatal transmission.[4,39] In the absence of evidence suggesting active liver disease, delaying testing until 15-18 months of age is likely to produce the clearest results in cases of suspected perinatal transmission.

Clinical Features

Although rare, clinically apparent acute HCV infection has been reported in children and adolescents in both isolated cases and in the setting of widespread outbreaks.[40,41] Few studies describe the features of acute HCV infection in children, although in adults, nonspecific symptoms of fatigue, jaundice, dyspepsia, and abdominal pain are often reported.[42-44] At-risk children presenting with these symptoms should be considered for testing. While perhaps more common in endemic areas, HCV-induced fulminant hepatic failure is infrequent, with only a single case reported in the first 348 children enrolled into the Pediatric Acute Liver Failure Study Group database.[41]

More commonly, children and adolescents develop chronic hepatitis C infection, defined as the persistence

of HCV RNA for at least 6 months.[45,46] The typical pattern of virologic, clinical, and serological events in children with perinatal infection is demonstrated in Fig. 1. Children with chronic hepatitis C infection are most often asymptomatic, although mild nonspecific symptoms can occur. In one study of children who acquired the infection in the perinatal period, approximately 10% were found to have hepatomegaly over the first 4 years of life; however, the same study confirmed the low overall prevalence of HCV-related clinical signs and symptoms during the first 15 years of life.[47] The majority of HCV-infected children will have intermittent or persistent liver enzyme elevations. Importantly, aminotransferase levels do not correlate with histological severity.[46] Accordingly, a liver biopsy is not necessary for most pediatric patients with HCV. The exceptions to this recommendation are patients in whom a concomitant or alternative diagnosis is being considered, if the biopsy may influence their treatment, or in patients with comorbid conditions where hepatotoxic medications should be avoided. Prior studies that have included liver biopsies have shown that for the majority of infected children, inflammation is mild with severe inflammation in only 3%; moderate fibrosis and cirrhosis are found in only 4% and 2%, respectively.[48]

Extrahepatic manifestations of chronic hepatitis C infection occur in 40%-74% of adults during their lifetime.[7] Similar manifestations, while described, are less prevalent in children with HCV infection. For example, membranoproliferative glomerulonephritis, the most common renal disease associated with HCV infection in adults,[49] has been reported in only three children.[50-52] Thyroid dysfunction and thyroid autoimmune disease is rare, but thyroid-specific antibodies, subclinical hypothyroidism, and autoimmune thyroiditis have been described in children.[53-55] Development of nonorgan-specific autoantibodies, such as antinuclear antibodies, is well recognized,[53,54,56-58] although their clinical significance is debated.[54,59] Finally, some manifestations, such as the cutaneous features of vasculitis and porphyria cutanea tarda described in adults, have not been reported in children.[42,60]

Natural History of HCV Infection in Children and Adolescents

In children and adolescents, acute hepatitis due to HCV is not common and fulminant infection is rare.
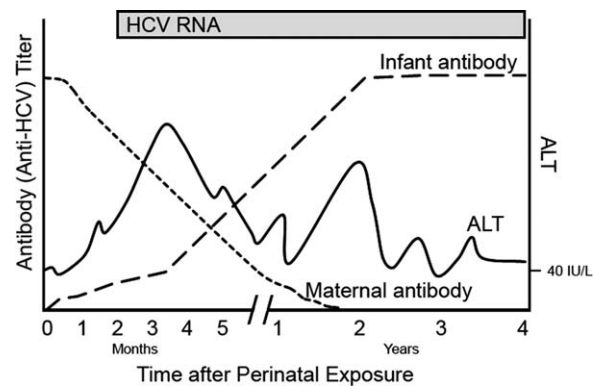
FIG. 1. The pattern of virologic, clinical, and serological events in children following perinatal HCV infection. Following viral acquisition (time 0), there is an increase in the serum ALT level, indicating the onset of clinical hepatitis. The ALT level follows a chronic undulant pattern, reflecting ongoing infection. Maternal antibody to HCV can be detected in the serum of the newborn; however, the level begins to decline in the first weeks of life, with complete disappearance by 18-24 months of age. Anti-HCV produced by the infant appears shortly after infection; however, it is indistinguishable from maternal antibody. Polymerase chain reaction can indicate HCV infection within several weeks of exposure and will persist unless spontaneous viral clearance occurs. Abbreviations: ALT, alanine aminotransferase; RNA, ribonucleic acid.

Chronic hepatitis C infection in children and adolescents can follow several different paths of progression with a variety of outcomes. One important outcome is the attainment of a spontaneous resolution of viremia (viral clearance).[37,38] Viral clearance is estimated to occur in approximately 20% of adults, while children have a slightly greater chance of viral clearance.[61-63] In children with perinatal transmission, 25%-40% may spontaneously undergo viral clearance, usually by age 2; this has been described as a resolution of neonatal HCV infection.[4] Another 6%-12% of those with chronic hepatitis C infection may clear the virus before adulthood.[4,39,64-66] Spontaneous viral clearance, which is associated with biochemical remission of hepatitis, has been reported to occur more frequently in children with higher alanine aminotransferase levels in the first 2 years of life.[30,38,66-70] Both host and viral factors have been associated with the attainment of spontaneous viral clearance; these include infection with genotype 3 and the interleukin 28B rs12979860 single-nucleotide polymorphism.[38,67,71,72] Spontaneous viral clearance has historically been considered a permanent state and an essential "cure" of the HCV infection in the child; however, a recent case report described recurrence of viremia following seroconversion and suggests that a more

TABLE 2. CHARACTERISTICS OF DIRECT-ACTING ANTIVIRAL AGENTS FOR HEPATITIS C VIRUS

	Protease Inhibitors	Polymerase Inhibitors	NS5A Inhibitors
Viral enzyme target	NS3/4A	NS5B	NS5A
Mechanism(s) of action	Inhibit the NS3/4A enzyme involved in posttranslational processing and replication of HCV.	2 classes: Nucleot(s)ide analogues target the catalytic site of NS5B and result in chain termination Nonnucleoside inhibitors allosteric inhibitors of NS5B	Unknown. Thought to be related to viral replication and virion assembly
Drug	Simeprevir, Paritaprevir, Grazoprevir	Sofosbuvir, Dasabuvir	Ledipasvir, Daclatasvir, Ombitasvir, Elbasvir, Velpatasvir

nuanced approach to the care of these children may be warranted.[64]

In children with chronic hepatitis C infection who fail to clear the virus, liver disease is typically minor, with little evidence of progression. This pattern has been validated in multiple studies.[4,42,46,73-76] One study included up to 35 years of follow-up and established that HCV infection acquired in early life typically shows a slow progression and mild course and outcome in the absence of other risk factors, such as obesity.[77]

POTENTIAL FOR PROGRESSION

Hepatocellular damage with the development of fibrosis related to HCV infection in children can occur and tends to increase with age; however, advanced liver disease is uncommon before adulthood.[77-82] Nevertheless, disease progression can be hastened in the presence of certain risk factors. In adults, more rapid disease progression has been shown to be affected by viral load, serum aminotransferase levels, gender, ethnicity, obesity, toxins, and other environmental factors. Comorbidities, including hemolytic anemia, malignancy, immunosuppression, HIV, and hepatitis B virus (HBV) co-infection and certain genetic factors, like single-nucleotide polymorphisms, may also promote progression.[83] Similarly, children with comorbid conditions, such as obesity, HIV, and HBV co-infections, cancer, and anemia, are at risk for more severe disease.[4,84] In addition, high-risk behaviors are associated with poor outcomes of disease, including alcohol use, IVDA, homelessness, and incarceration.[70,85-88]

Complications from chronic HCV-related liver disease in children and adolescents, such as portal hypertension, ascites, variceal bleeding, and hepatocellular carcinoma, although uncommon, have been reported.[2,73,89-91] Decompensated cirrhosis in children as young as 4 years of age has been described.[48,78,91,92] HCV infection in children has also been suggested to negatively affect both health-

related quality of life and cognitive functioning; however, these findings would need to be confirmed in larger cohorts.[93,94]

Management

Given the rarity of **acute** HCV infection, there is a paucity of data determining when and how to initiate treatment in affected children. Therefore, this section will focus on the management of **chronic** HCV infection specific to children and adolescents.

The general goals of treatment in children mirror those of adults; mainly, to eradicate the virus, induce a remission of liver injury, prevent transmission, and ultimately avert and improve the outcomes relating to chronic inflammation and liver injury by decreasing or eliminating the development of fibrosis, cirrhosis, and hepatocellular carcinoma. The development of new antivirals (Table 2) has ushered in an era of well-tolerated medications with high efficacy. Recent cure rates attained with the use of direct-acting antivirals (DAA) in adults enables optimism. However, clinical trials in children are in their early stages (Table 3), and thus the pace of DAA approval for children and adolescents is lagging behind that set by adult studies and approvals.

CURRENT STATUS OF HCV TREATMENT IN CHILDREN AND ADOLESCENTS

The new era of DAA therapy has enabled dramatic changes in the medical management of adults with HCV. Ever-evolving treatment regimens are available that reliably achieve a >95% "real-world" cure rate for all HCV genotypes.[6] Efficacy has also been demonstrated in historically difficult to treat populations, such as patients with pretreatment cirrhosis, renal disease, patients previously exposed to antiviral therapy,

TABLE 3. REGISTERED CLINICAL TRIALS OF DAAS IN CHILDREN AND ADOLESCENTS WITH HEPATITIS C INFECTION

Clinicaltrials.gov	Drug	Phase	Status
NCT02249182	Ledipasvir/Sofosbuvir ± Ribavirin	2	Recruiting
NCT02175758	Sofosbuvir + Ribavirin	2	Recruiting
NCT02486406	Ombitasvir ± Dasabuvir and ± Ribavirin	3	Recruiting
	Paritaprevir ± Dasabuvir and ± Ribavirin		
	Ritonavir ± Dasabuvir and ± Ribavirin		
NCT01701063	Telaprevir + Peginterferon + Ribavirin	1,2	Terminated - has results
NCT02985281	Sofosbuvir + Ribavirin	2,3	Enrolling by invitation

prior null responders, those with HIV co-infection, and patients following liver transplantation.[95-99]

Despite these advances, DAAs are not yet licensed for pediatric use. Currently, the only Food and Drug Administration-approved options for children with chronic HCV infection are ribavirin (RBV) and pegylated-interferon (PEG-IFN). While sustained viral responses (SVRs) have improved over the last several decades from ~16% with IFN monotherapy to >50% with the combination of RBV and PEG-IFN, multiple studies have shown that SVR rates remain frustratingly low compared to adults with access to DAA regimens.[6,13,100-116] Consequently, in the absence of approved DAA therapies in the United States, the chance of attaining SVR in HCV-infected children and adolescents is little more than 50% (Table 4). Further complicating treatment decisions are the known side-effect profiles of IFN and RBV. Adverse events, such as anemia, neutropenia, leukopenia, and thrombocytopenia, have been reported in up to 52% of those treated, leading to a discontinuation rate of 4%.[103] Therapy has also been shown to negatively affect body weight, linear growth, and body composition, putting children at risk for developmental blunting.[117] However, recent follow-up studies have not observed any long-term effects on height-for-age z scores that could be attributed to HCV treatment.[118]

Neuropsychiatric disturbances, such as mood alteration, irritability, agitation, and aggressive behavior, have been reported in up to 30% of children[119]; depression, anxiety, and suicidal ideation have been reported as well.[13,110]

Several studies have suggested that certain factors may predict a more favorable response to PEG-IFN/RBV therapy, including host characteristics, such as the interleukin 28B polymorphisms, having genotype 2 or 3, and mode of transmission (iatrogenic versus vertical transmission).[114,119-122] Ultimately, the current standard of care in the treatment of HCV-infected children with IFN and RBV regimens with their well-documented toxicities, inconvenient modes of administration (subcutaneous IFN injections), longer durations of treatment, and poor overall efficacy often leaves pediatric hepatologists searching for alternatives. More often than not, this results in the deferring of treatment in expectation of increased availability of DAAs in children.

Since there are no all-oral DAA regimens that have been approved for children with chronic HCV infection, we conducted a phase 2, multicenter, open-label study to evaluate the efficacy and safety of ledipasvir–sofosbuvir in 100 adolescents with chronic HCV genotype 1 infection.[123] Each subject received a combination tablet of 90 mg ledipasvir and 400 mg

TABLE 4. TREATMENT TRIALS OF HCV IN CHILDREN AND ADOLESCENTS

Author, Year [ref]	Number Studied	Treatment Regimen	%SVR for Genotype 1/4	%SVR for Genotype 2/3
Wirth, 2002 [115]	41	IFN2b + ribavirin	53	100
Gonzalez-Peralta, 2005 [112]	118	IFN2b + ribavirin	36	84
Wirth, 2005 [116]	62	Peg-IFN2b + ribavirin	48	100
Jara, 2008 [107]	30	Peg-IFN2b + ribavirin	44	100
Sokal, 2010 [113]	65	Peg-IFN2a + ribavirin	57	89
Wirth, 2010 [110]	107	Peg-IFN2b + ribavirin	53	93
Schwarz, 2011 [14]	55	Peg-IFN2a + ribavirin	47	80
Wisniewska-Ligier, 2013 [111]	79	Peg-IFN2b + ribavirin	44	-
Suzuki, 2016 [114]	84	Peg-IFN2b + ribavirin	72	100

Note: Table adapted from ref 117.

sofosbuvir once daily for 12 weeks.[123] The primary efficacy endpoint was the percentage of patients with a sustained virologic response 12 weeks posttreatment (SVR12). A majority of subjects (80%) were HCV treatment naïve, and 84% of subjects were infected through perinatal transmission. Overall, 98% of patients reached SVR12, and no patient had virologic failure. The 2 subjects who did not achieve SVR12 were lost to follow-up either during or after treatment. No serious adverse events were reported; commonly reported events were headache, diarrhea, and fatigue. We also noted that the dose of ledipasvir−sofosbuvir currently used in adults was well tolerated in adolescents and had an appropriate pharmacokinetic profile.

MONITORING

As progression of HCV infection can occur in children and adolescents, it is appropriate to ensure consistent monitoring of these patients to ensure timely intervening measures can be taken. Sequential testing of serum aminotransferase concentrations and regular office visits to assess for evidence of disease progression or complications is suggested. In adults with chronic hepatitis C infection, recent advancements have enabled the validation of both circulating biomarker tests and vibration-controlled transient elastography in determining the stage of fibrosis,[3,124-128] progression and regression of fibrosis,[129-131] as well as their use in determining liver-related complications and overall survival.[132,133] Validation of these technologies in children and adolescents is emerging; however, the low incidence of progressive hepatitis C infection in the pediatric population will require large cohorts with extended follow-up to determine their efficacy. Ultimately, the most adept approach to fibrosis assessment in children and adolescents with chronic hepatitis C infection will likely combine biomarker assessment, physical exam findings, and vibration-controlled transient elastography. In patients who demonstrate a more severe clinical course with the development of fibrosis, even with the current SVR outcomes with IFN/RBV, treatment may be warranted in hopes of interrupting disease progression. Furthermore, in patients with cirrhosis, hepatocellular carcinoma can occur and regular ultrasound and alpha fetoprotein surveillance should be considered.[89]

In addition, a "liver-healthy lifestyle" should be discussed early in the course of HCV infection in children and adolescents, focusing on appropriate lifestyle choices, prevention of obesity, avoidance of alcohol,

and proper medication management. Because of the high rate of severe hepatitis in patients with chronic liver disease from HCV infection who become co-infected with hepatitis A or B virus, all patients should be immunized against hepatitis A and hepatitis B.

Liver transplantation for HCV-related liver disease is rare in children and adolescents, accounting for less than 1% of cases. When transplantation is required, outcomes are generally good. In an analysis of the United Network for Organ Sharing database assessing outcomes in children who received a liver transplant for complications related to HCV, 1-year and 3-year graft survival rates were reported to be 89.7% and 76.2%, respectively, and 1-year and 3-year patient survival rates were 97.5% and 89.4%, respectively. Retransplantation, mainly due to disease recurrence, was reported as 10%.[134]

Future Directions

Despite the success of DAA agents in adults and the preliminary data that suggest similar safety and efficacy will be demonstrated in children, there remain additional avenues of pursuit in the march toward eradication of HCV worldwide. In addition to expanding pharmaceutical options and determining optimal antiviral regimens, strategies aimed at improving diagnosis, identifying patients who would benefit from treatment, and eliminating perinatal transmission from mother to child are needed to optimize the overall management of HCV in children. Finally, and in parallel, is the continued march toward the development of a broadly directed HCV vaccine that would target both humoral and cellular immune responses and assist with worldwide viral eradication.

The majority of children and adolescents with HCV remain undiagnosed; therefore enhanced efforts focused on case identification are needed so that patients can be appropriately managed. While universal screening for adults of a certain age is recommended,[135] no such guidelines exist for children. One large study investigating the prevalence of HCV in urban children suggested that screening is not warranted.[136] However, this study was undertaken prior to the explosive IVDA epidemic and the dramatic increase in HCV infection among young persons.[22,27,28] Increased patient identification must be followed with a linkage to care that enables patients to receive evaluation and treatment by an experienced health care provider.[137]

Antenatal screening programs also represent an opportunity to possibly prevent the passage of viral infection from mother to child. Current antenatal screening programs for HCV are not standard of care, and cost effectiveness is debated.[26,138,139] However, strategies aimed at preventing perinatal transmission will be impactful. Recent data have demonstrated that reductions in perinatal transmission of HCV can be achieved in select populations. Mothers with HCV–HIV co-infection who were treated with combined anti-retroviral therapy at the time of delivery demonstrated a lower rate of HCV transmission to their newborns than what has historically been described.[140] Additional advances seen in the prevention of mother to child transmission of hepatitis B infection during pregnancy[141] suggests that future efficacy and safety data will be informative as it relates to newer anti-HCV therapies during pregnancy and the prevention of perinatal transmission of the HCV.

VACCINE UPDATE

Improved treatment regimens, greater disease awareness, improved access to care, and lower cost will undoubtedly decrease the global disease burden of HCV infection. However, no virus to date has been globally eradicated without the development of a prophylactic vaccine. A preventative vaccine is needed to stop HCV transmission to uninfected individuals and to those who are cured with DAA but remain at risk for re-exposure and persistence of infection.[5] Major obstacles to HCV vaccine development are the diversity of the virus, the ability of the virus to evade the immune response in infected individuals with high rates of mutation, and development of "quasispecies," which are distinct but closely related HCV variants that can be present in a single individual.[5,137,142] Additional immune-evading strategies that have been identified include antibody avoidance, cytotoxic T lymphocyte escape, and a failure to initiate an appropriate T cell response during the beginning of infection, among others.[143-148] Despite these challenges, several investigations have demonstrated success in preclinical animal studies showing induction of both humoral and cellular immunity against HCV.[149,150] Promising preliminary results have been demonstrated in trials conducted in humans based in part on these findings.[151] As a result, a phase II human clinical trial (https://clinical-trials.gov/ct2/show/NCT01296451) is underway. Ultimately, the path to a successful preventative

vaccine requires comprehensive evaluation of all aspects of protective immunity, innovative application of state-of-the-art vaccine technology, and properly designed clinical trials that can affirm definitive endpoints of safety and efficacy.

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