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REVIEW

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Hepatitis C virus infection in children and adolescents: a management update

Fahmida Begum[1*], Md.Wahiduzzaman Mazumder[1], Khan Lamia Nahid[1], Tahmina Jesmin[2] and Nadira Musabbir[1]

Abstract

Hepatitis C virus infection is an emerging problem for children and adolescents. Chronic HCV infection affects approximately 3.5–5 million children worldwide. Unaddressed HCV infection in children progresses to decompensated liver disease and hepatocellular carcinoma during adulthood. Early detection of HCV and the administration of appropriate antiviral therapy are required for the prevention of long-term morbidity associated with chronic HCV infection. The perinatal route is the most common source of childhood HCV infection. Anti-HCV positivity at or after 18 months of age necessitates an HCV-RNA assay after age 3 to recognize chronic HCV infection. Both anti-HCV and HCV-RNA positivity are the indications for antiviral therapy. At present, various combinations of oral, direct-acting antivirals (DAAs) have been approved for children above 3 years of age. Their efficacy is high. Apart from the effectiveness of DAA therapy, steps should be taken to screen pregnant women to prevent the transmission of viral infection from mother to child. To increase awareness about the mode of HCV spread, NAT-based tests in blood banks for better screening and making the DAAs available at a subsidized rate in the public sector are necessary to eradicate HCV infection.

Keywords Children, Adolescents, Direct-acting antiviral, Genotype, Hepatitis C infection

Introduction

Hepatitis C virus (HCV) infection has emerged as an important cause of hepatitis in children and adolescents, but the exact number is underestimated. Chronic progression with minimal symptoms made the HCV infection unrecognized in its early course. Pediatric HCV infection differs from infection acquired later in life in a variety of ways. Pediatric disease differs in terms of modes of transmission, rates of spontaneous clearance or progression of fibrosis, the potential duration of chronic infection when acquired at birth, and, surprisingly, treatment options [1]. The early detection of disease is critical because direct-acting antiviral (DAA) therapy effectively eliminates the virus, reducing the future burden of chronic liver disease (CLD), hepatocellular carcinoma (HCC), and the risk of future perinatal transmission [2]. The purpose of this review is to highlight the epidemiology, natural history, and diagnosis and put more focus on the management of HCV infection in children, as there have been recent advancements in the treatment of this infection.

Epidemiology

Globally, the HCV burden in pediatric populations is estimated to be around 3.5–5 million [3]. The prevalence in high-income countries is about 0.3% and in low-income countries is about 0.4% [3]. Among all viremic HCV infections, Pakistan, China, India, and Nigeria accounted for more than half, with Bangladesh ranking seventh [3]. The exact incidence of HCV in children and adolescents in Bangladesh is not known. Among the Rohingya refugees in Cox's Bazaar, Bangladesh, the prevalence rate is

*Correspondence:
Fahmida Begum
fahmidalily@gmail.com
[1] Department of Paediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
[2] Paediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

about 1% [4]. Existing facilities enable us to diagnose only a fraction of cases [5].

HCV has six genotypes. Among adults, some genotypes are distributed globally, and some are regional in distribution. HCV genotypes 1–3 are found worldwide; among them, HCV genotype 1, subtypes 1a and 1b, as well as genotype 2, and subtypes 2a, 2b, and 2c are the most common types in North America. Genotype 3 is concentrated in Southeast Asia, genotype 4 in the Middle East, genotype 5 in South Africa, and genotype 6 in Asia [6]. Children lack robust epidemiological data, but reported cases in affected children follow similar regional distribution patterns as in adults [7, 8].

Mode of transmission

The most common mode of acquisition of infection in the pediatric population is mother-to-infant transmission during the perinatal period, which is about 5% and accounts for approximately 60% of all pediatric HCV cases. Transmission rates are higher in women with poorly controlled HIV coinfection and in women with HCV RNA levels greater than 6 log10 IU/mL [9]. HCV spreads through intravenous drug sharing, blood and blood product transfusions, needle prick injuries, and poorly sterilized medical equipment. Although historically HCV was considered a transfusion-related disease in children and adolescents, the rate has declined in high-resource countries with the implementation of nucleic acid testing (NAT) along with Ab screening for HCV in blood-bank screening practices. Inclusion of NAT overcomes the failure of serological assays (anti-HCV) during the window period [10].

Clinical features

Although clinically apparent acute HCV infection in children and adolescents is rare, some cases have been reported [11]. Apart from mild, nonspecific symptoms, children with chronic HCV are most often asymptomatic. According to one study, approximately 10% of infants with perinatally acquired HCV infection had hepatomegaly during their first 4 years of life [12]. In the majority of HCV-infected children, there are only intermittent or persistent elevations of liver enzymes. Unlike adults, children less frequently develop extrahepatic manifestations [13].

Natural history

Acute hepatitis due to HCV is uncommon, and fulminant hepatic failure is rare [11]. The progression of chronic hepatitis C in children and adolescents may follow several different routes. Approximately 20% of acutely infected adults can clear the virus spontaneously [12]. About 25–40% of children with perinatal transmission may achieve spontaneous viral clearance, usually by age 2, which is also described as a resolution of neonatal HCV infection. Also, another 6–12% of them may clear the virus before adulthood [1]. Spontaneous clearance of the virus can occur later in life at a lower rate [13–15]. It occurs more frequently in children with higher alanine aminotransferase levels in the first 2 years of life. These children were reported to achieve biochemical remission of hepatitis as well [16]. Spontaneous clearance of the virus is considered the "state of cure" of the HCV infection, with rare (< 1%) relapses reported [17]. In comparison with adults, HCV-related liver disease generally shows slow progression in children and adolescents, in the absence of comorbidities, such as obesity with nonalcoholic fatty liver disease and congenital heart disease with elevated right heart pressure. Advanced liver disease is not common before adulthood, but disease progression is unpredictable [16, 18].

When to screen?

Universal screening for HCV is recommended for any individual aged 18 years or older [19]. For pediatric cases, screening should be done in the following conditions [20]:

- Children born to HCV-infected mothers
- Children and adolescents with intrafamilial exposure
- Children on long-term hemodialysis and on repeated blood or blood product transfusion
- Children and adolescents with signs or symptoms of hepatitis
- Adolescents incarcerated in a correctional institution
- Children and adolescents with conditions associated with a high prevalence of HCV infection, including the following:

  HIV infection
  Unexplained abnormal aminotransferase levels

- Children and adolescents emigrating from a region with a high prevalence rate of HCV infection
- Adolescents who have injected illicit drugs
- Adolescents after a needle stick injury or mucosal exposure to HCV-positive blood

As approximately 60% of all pediatric HCV cases are due to mother-to-infant transmission during the perinatal period, AASLD-IDSA recommends in all pregnant women to test for HCV in each pregnancy to reduce future disease burden [20].

When to screen for a perinatal case?

Screening for HCV should be done for all children born to women with acute or chronic hepatitis C, and the recommended test is an antibody-based test at or after 18 months of age. As per the recommendation of the HCV guidance panel, a positive HCV antibody test at or after 18 months of age necessitates HCV-RNA testing at age ≥ 3 years to determine chronic infection versus spontaneous clearance, the reason why treatment is postponed for 3 years. Moreover, DAA regimens are not recommended for children younger than 3 years of age. Virtually, no child develops HCV-related advanced liver disease [20].

Maternal antibody may persist in the infant's serum for up to 18 months; for this reason, earlier antibody testing is not recommended [21]. HCV-RNA testing can be considered in the first year of life, beginning at 2 months of age, if there is concern about loss to follow-up. Positive HCV RNA during the first year of life reliably correlates to anti-HCV positivity at 18 months. There is no recommendation to repeat HCV-RNA test prior to 18 months of age. Siblings of children with an HCV-infected mother should be tested for HCV infection [21].

Further evaluation of the HCV-confirmed children

To assess for disease severity Routine hepatic laboratory testing and physical examination should be done to assess disease severity. However, serum aminotransferase levels do not consistently correlate with HCV liver disease severity [22]. A liver biopsy is still the gold standard for determining liver inflammation and fibrosis. But due to potential adverse events (e.g., bleeding), most clinicians prefer noninvasive alternatives such as transient elastography, imaging, or serum fibrosis markers to determine the presence or absence of cirrhosis, particularly in the pediatric population [23]. Cirrhotic children should be monitored 6 monthly with liver ultrasonography and serum alpha-fetoprotein levels for the development of hepatocellular carcinoma. Cirrhotic patients should be monitored continuously, as successful treatment of HCV does not diminish the risk of hepatocellular carcinoma [24].

Testing for co-infection Concomitant HBV (HBsAg, anti-HBc, and anti-HBs), HIV (anti-HIV), and immunity to HAV (anti-HAV IgM and IgG), anti-HEV testing are recommended, and vaccination should be done in non-immune children against HAV and HBV vaccines. Children who are HBsAg positive and also fulfill the standard criteria for HBV treatment should receive treatment, as DAA treatment can reactivate HBV [25].

When to start therapy? Children with anti-HCV and RNA positivity are candidates for antiviral therapy. Newer DAAs are more expensive, but the introduction of newer DAAs has made a paradigm shift and ushers in a new era in the management of chronic HCV infection [26, 27].

Regardless of disease severity, DAA is recommended for all children and adolescent ≥ 3 years with HCV infection as they will be benefitted from the therapy [28]. The presence of extrahepatic manifestations also get benefit from early initiation of DAA therapy by reducing morbidity and mortality [22]. These patients should be further tested to determine the genotype [29]. For duration of DAA treatment, genotype determination is necessary, especially if there is advanced liver disease or if previous treatment has failed [15].

Direct-acting antivirals

There are four classes of DAA based on their mechanism of action and therapeutic target. The four classes are nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. DAA should not be given as a monotherapy. Because of sharing cross-resistance from same class DAA, each regimen should contain a combination of two different classes of DAAs. Earlier various combinations of DAA regimens (with a high genetic barrier to resistance) are used for children aged 3 to < 18 years with genotype 1, 4, 5, or 6 infection and for children aged 6 to < 18 years with any genotype. But now pangenotypic DAA regimens have been approved for children at or more than 3 years of age showing high effectiveness and excellent safety with an adverse event profile comparable with placebo [20]. Interferon, which was previously used, was not well tolerated and had major side effects. Various combinations of DAA therapy are discussed in Tables 1, 2, and 3 [20].

Drug therapy for children and adolescents, without cirrhosis or with compensated cirrhosis (Child–Pugh A) [20]

Treatment of patients with decompensated CLD (Child-Pugh B and C) is not recommended to date [20].

Table 1 Weight-based dosing of LED/SOF for children aged ≥ 3 years

Body weight (kg)	LED/SOF (once daily)
< 17	33.75 mg/150 mg
17–< 35	45 mg/200 mg
> 35	90 mg/400 mg per day

Table 2 Weight-based dosing of SOF/VEL for children aged ≥ 3 years

Body weight (kg)	SOF/VEL (once daily)
< 17 kg	150 mg/37.5 mg
17–< 30 kg	200 mg/50mg
> 30 kg	400 mg/100 mg per day

Table 3 Weight-based dosing of G/P for children aged ≥ 3 years

Body weight (kg)	G/P (once daily)
< 20 kg	150 mg/60 mg
≥ 20–< 30 kg	200 mg/80mg
≥ 30–< 45 kg	250 mg/100 mg per day
≥ 45 kg or 12 years of age and older	300 mg/120 mg per day

Infected children younger than 3 years of age virtually never develop advanced liver disease [20].

Treatment-naive or interferon-experienced children [20]

Combination of ledipasvir/sofosbuvir (LED/SOF) (weight-based dosing) for children aged ≥ 3 years with genotypes 1, 4, 5, or 6 for 12 weeks (Table 1).

- Combination of sofosbuvir/velpatasvir (SOF/VEL) (weight-based dosing) for children aged ≥ 3 years with any genotype for 12 weeks (Table 2).
- Combination of glecaprevir/pibrentasvir (G/P) (weight-based dosing) for children aged ≥ 3 years any genotype for 8 weeks (Table 3).

DAA experienced

Genotypes 1, 2, 4, 5, or 6 Daily fixed-dose combination of G(300 mg)/P(120 mg) for adolescents aged ≥ 12 years or weighing ≥ 45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or SOF but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis for 8 weeks.

Genotypes 1, 2, 4, 5, or 6 Combination of G/P (weight-based dosing) with prior exposure to an interferon-based regimen (±ribavirin) and/or SOF but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis (Child-Pugh A) for 12 weeks (Table 3).

Genotype 3
Combination of G/P (weight-based dosing) with prior exposure to an interferon-based regimen (±ribavirin) and/or SOF but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis for 16 weeks (Table 3).

Genotypes 1–6
Combination of G/P (weight-based dosing) with prior exposure to NS3/4A or but no NS5A protease inhibitor exposure, without cirrhosis or compensated cirrhosis for 12 weeks (Table 3).

Genotypes 1–6
Combination of G/P (weight-based dosing) with prior exposure to an NS5A protease inhibitor or but no exposure to NS3/4A protease inhibitor, without cirrhosis or compensated cirrhosis for 16 weeks (Table 3).

Genotypes 1–6
Combination of SOF/VEL (weight-based dosing) with prior exposure to an interferon-based regimen (± ribavirin) and/or SOF but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis (Child-Pugh A) for 12 weeks (Table 2).

SVR12 cure rates

SVR12 rates in children were high (≥ 95%) across all age groups and for the key pangenotypic DAA regimens SOF/DCV, SOF/VEL, G/P, and SOF/LED. There are, however, a few exceptions in the case of SOF and VEL. SVR12 for SOF/VEL is higher in older children (93% (86–98)) than in younger children (83% (70–93) (16)). In younger children, the rates of SOF/VEL SVR12 were lower because of difficulties in taking the oral medication and due to virological failure. There were no study data for SOF/DCV in young children [29, 30].

DAA in children with other co-morbidities DAA can safely be given to children having other comorbidities like thalassemia and acute leukemia. Studies supported that DAA is highly efficacious in those patients as well as no drug-drug interaction [31, 32].

Effect of DAA on fibrosis and liver stiffness

In one study on 85 children in Egypt, Fahmy et al. found a non-progression or regression of liver fibrosis with DAA treatment for chronic HCV infection after assessing by noninvasive fibrosis measurements at 12 months after treatment in the majority of cases [33]. Another study on Egyptian children also supports such findings. In their study, they found a significant regression in liver stiffness after treatment with DAA [34].

Treatment in special situations

Recommendations for treatment of co-infection with HIV, co-infection with hepatitis B, decompensated cirrhosis, and allograft recipients from HCV viremic donors are given in Box-Table 4 [35].

On-treatment assessment

Children with HCV infection should be assessed within 3 months of initiating treatment with a complete blood count, an international normalized ratio (INR), hepatic function panel (i.e., albumin, total and direct bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and a calculated glomerular filtration rate (eGFR). Children may need earlier testing if any features of hepatic decompensation arise (i.e., jaundice, ascites, encephalopathy, or any liver-related new complaint [19].

Posttreatment assessment of cure

A virologic cure is the proximate goal of HCV therapy. A continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy is virologic cure [25]. To confirm virologic cure, assessment of qualitative HCV RNA and a hepatic function panel is recommended 12 weeks or later following completion of therapy. AASLD 2022 patients with elevated transaminase levels after achieving SVR according to standard guidelines should be evaluated for other causes of liver disease [20].

Follow-up after achieving virologic cure (SVR)

Noncirrhotic patients who achieve SVR do not require any liver-related follow-up. Ongoing monitoring for hepatocellular carcinoma is needed for patients with histologic evidence of fibrosis or cirrhosis [20].

Monitoring of the patient

Patients should be monitored for liver biochemistry initially and thereafter annually. All the hepatotoxic drugs are to be used with caution after analyzing the risk-benefit ratio. Though there is a chance of enhancement of HCV infection with corticosteroids and cytotoxic drugs, they are not contraindicated but rather could be used with caution if there is an appropriate indication. Acetaminophen, if used, should shorten the duration [13]. Maintenance of a healthy body weight is important for children with chronic HCV, as insulin resistance has a bad effect on fibrosis progression with HCV infection [36].

Prevention

Although DAA treatment can effectively cure HCV, there is a risk of reinfection [37]. A prophylactic vaccine is the key to eradicating a virus globally. There are currently no HCV vaccines available. The diversity of the virus along with the ability to evade the immune response in infected individuals with high rates of mutation, and the development of "quasispecies," is major obstacles to the development of an HCV vaccine [38]. In 2016, WHO announced a strategy to eliminate viral hepatitis as a public health threat by 2030, with a 65% reduction in mortality and a 90% reduction in chronic hepatitis C [39]. Preventive measures are still the most effective way to reduce HCV infection.

Table 4 Recommendation for the management of hepatitis C in special situations

Co-infection with HIV

- All HIV-positive children with HCV co-infection should be started on antiretroviral therapy (ART) irrespective of CD4 cell count
- HCV treatment with DAA should be initiated in the presence of HCV viremia
- ART and DAA regimens should be selected with particular consideration for potential drug-drug interaction

Co-infection with HBV

- HCV treatment is indicated for children with HCV viremia
- Treatment of HCV with DAAs may cause reactivation of HBV. Children fulfilling the standard criteria for HBV treatment should receive antiviral treatment.
- HBs Ag-positive patients undergoing DAA therapy should be monitored for HBV DNA every 4 to 8 weeks during treatment and for 3-month post-treatment for those who do not meet treatment criteria for HBV
- Although HCV-positive children with occult HBV infection have a very low risk of HBV reactivation during DAA therapy, they require close monitoring. Monitoring should be done with ALT levels at baseline, at the end of treatment, and on follow-up, with HBV-DNA and HBsAg tested in whom ALT levels increase or fail to normalize during or post-treatment

Decompensated cirrhosis (rare in children)

- Regimen with extended duration (24 weeks) or the addition of low-dose ribavirin are used in these patients.
- Any protease inhibitor-containing (e.g. glecaprevir, grazoprevir, and voxilaprevir) or interferon-based regimens are contraindicated.

Allograft recipient (HCV negative recipient from HCV viremic donor)

- Informed consent and formulation of treatment and follow-up strategies
- Prophylactic (before HCV RNA results, immediately pre-transplant or day 0 post-transplant) or preemptive (day 0 to within one-week post-transplant in clinically possible) DAA therapy with a pan-genotypic regimen is recommended
- For recipients of liver grafts, early treatment within the first week is recommended after a liver transplant

Conclusion

Untreated HCV infection in children may progress to end-stage liver disease in adulthood. Early identification and appropriate antiviral therapy can arrest the progression of HCV and reduce the future disease burden. The approval of highly effective DAA therapy has brought a paradigm shift in the management of HCV in children. DAA can be given to children regardless of liver function test values, duration of infection (acute or chronic), and the genotype of HCV. Apart from effectiveness of DAA therapy, steps should be taken to screen pregnant women to prevent the transmission of viral infection from mother to child, to increase the awareness about the mode of HCV spread, and NAT-based tests in blood banks for better screening, and making the DAAs available at a subsidized rate in the public sectors, are necessary to eradicate HCV infection.

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Authors' contributions
Authors' contribution and participation were as follows: FB participated in search in the literatures, prepared the final manuscript and is the corresponding author. WM in choosing the issue of the study and prepared the final manuscript. KLN and NM participated in search in the literatures. TJ participated in choosing the issue of the study and was a major contributor in writing the manuscript. The authors read and approved the final manuscript.

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