REVIEW ARTICLE

Management of Hepatitis C in Children – A New Paradigm

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Introduction: With the advent of direct-acting antivirals (DAAs), the past decade has seen a paradigm shift in the management of hepatitis C (HCV) infection in children. In this review, we summarize the various treatment options for pediatric HCV infection, highlighting the recent changes in the management.

Methods: A literature search was performed using the PubMed database with the relevant keywords. Filters included were human, ages 0-18 years, and the English language.

Results: Initial phase of HCV treatment using conventional or pegylated interferon and ribavirin combination regimens yielded poor outcomes in children, especially in genotypes 1 and 4, with an overall sustained virologic response of 58%. Also, treatment with interferon and ribavirin combination was associated with significant side effects in up to 52% of those treated. Presently, various combinations of direct-acting antivirals (DAAs) have been approved in children above three years of age with documented evidence of high efficacy (SVR12 of 92% to 100%) and excellent safety, and the current standard of care.

Conclusion: With various DAA regimens now being approved for children above three years of age, the treatment of active HCV infection (HCV-RNA positive) in children has become simple. Besides the effectiveness of DAA therapy, public awareness about HCV transmission, better screening, and making the DAAs available at a subsidized price in the public sectors are necessary to eliminate HCV infection in India.

Keywords: *Direct-acting antivirals, Interferon, Outcome, Ribavirin*.

Hepatitis C virus (HCV) is a primarily hepatotropic single-stranded RNA virus belonging to the Flaviviridae family. HCV is classified into seven genotypes based on sequence variations. In India, genotype 3 is the most predominant genotype, accounting for more than 80% of the cases [1]. HCV is mainly transmitted through the parenteral route, sexual contact, and vertical transmission from mother to baby. Of all infections, 75%-85% develop chronic HCV (persistence of HCV for more than 6 months) [2]. However, the natural history of chronic HCV is relatively benign in children. It has been documented that HCV takes ten years to develop chronic hepatitis, 21 years for cirrhosis, and 29 years for hepatocellular carcinoma (HCC) [3]. Although morbidity in children is uncommon, a significant proportion of the infected children grow into adulthood with the risk of severe liver disease, including cirrhosis and hepatocellular carcinoma. A substantial shift in the treatment paradigm from interferon plus ribavirin-based therapy to all oral, safe and highly effective direct-acting antivirals (DAAs) in the current era has revolutionized the treatment of hepatitis C. Major milestones have been achieved from its initial report as a non-A, non-B virus in 1975 to the present achievement of effective virological cure. This review collates the literature on HCV treatment in children and the breakthroughs in HCV management.

HCV Prevalence - INDIAN SCENARIO

There is a scarcity of data on the prevalence of HCV infection in Indian children. A hospital-based study from North India [4] documented HCV as the cause in 5% (3/60) of Indian children presenting with cirrhosis. Schmelzer, et al. [5], in a modeling study, showed the global estimate for HCV viremic prevalence in children between 0–18 years of age was 0.13%, corresponding to over 3 million children with HCV in 2018. The same study showed a 0.04% (0.03-0.08) HCV prevalence in Indian children; however, the results were by extrapolation using regression analysis based on biological and epidemiological plausibility rather than by real epidemiological studies. Nevertheless, for various reasons, these reports likely underestimate the true prevalence. Most children with HCV infection are asymptomatic and, thus, are unaware of their status. Also, a recent change in epidemiological patterns has been reported, with an increased surge in the adolescent age group because of intravenous drug abuse and the opioid epidemic. A high HCV disease burden in young adults is a primary driver of an increased infection rate in pregnant women and as a consequence, more children are born to HCV-infected mothers (vertical transmission). In an adult

study, Puri, et al. [6] estimated that the prevalence of HCV infection in India is between 0.5% and 1.5%. Similar results were documented by Goel, et al. [7] in a systematic review with a prevalence of 0.49% in the low-risk adult population. The only community-based study from India, Chowdhury, et al. [1] have shown the prevalence of HCV among children (<10 years) is 0.31%, and 0.83% among adolescents (10-19 years) [1]. Multi-transfused children are at a higher risk of having HCV infection (13-65%) [8]. Though HCV screening has become mandatory since 2002, the serological tests used for screening cannot pick up cases in the window period. In developed countries, with the use of NAT-based (nucleic acid technology) screening in blood banks, the risk of transfusion-transmitted infection has been reduced significantly. In India, individual donation (ID) NAT testing is not yet compulsory and as a result of which HCV is still rampant among multi-transfused children [9].

MANAGEMENT OF HCV IN CHILDREN

The current era of DAA therapy has made a paradigm shift in the management of HCV infection in children, with recently published guidelines suggesting that the regimen of pegylated-interferon (PEG-IFN) and ribavirin (RBV) should not be utilized [10]. A review of historical antiviral therapeutic strategies, including PEG-IFN plus ribavirin, is warranted to appreciate the degree of superiority of DAA therapy over previous older HCV regimens.

Initial Phase of HCV Treatment

The initial phase of HCV treatment was based on interferon (IFN) monotherapy starting from the early 1990s before advanced treatment in the form of long-acting pegylated interferon plus ribavirin was approved in the late 2000s. The achievement and persistence of undetec-table HCV-RNA off treatment, defined as the sustained virologic response (SVR) at 6 month of stopping therapy is a satisfactory endpoint for a virological cure. Jacobson, et al. [11] reviewed 19 trials using IFN-alpha monotherapy for children with HCV infection, documenting an overall SVR of 36%. Most of the adverse events were mild and did not result in any treatment discontinuation. As none of the studies systematically recorded these adverse events, only a qualitative description of these events is available. The common adverse effects reported were influenza-like symptoms, fever, weight loss (reportedly regained after the treatment), neutropenia, alopecia, allergic reactions, pruritus, thrombocytopenia, and febrile convulsions [11].

Druyts, et al. [12], in a metanalysis of eight randomized control trials (RCTs) evaluating the efficacy of PEG-IFN (alfa-2a or alfa-2b) and ribavirin combination therapy in children, reported an SVR of 58%, with a higher SVR for genotypes 2 and 3 (87% and 89%) than for genotypes 1 and 4 (61% and 52%). The most common side effects seen were leukopenia (52%), neutropenia (32%), injection site erythema (27%), alopecia (13%), anemia (11%), pruritus (10%) and thrombocytopenia (5%) leading to a discontinuation rate of 4% [12]. Therapy has also been shown to negatively affect body weight, linear growth, and body composition, putting children at risk for developmental blunting [13]. Neuropsychiatric disturbances such as mood alteration, irritability, agitation, and aggressive behavior were reported in up to 30% of children [13]. Ribavirin is also a known teratogenic agent (category X) in women of childbearing age.

Further complicating the use of this combination regimen was the prolonged duration of treatment (with a total of 48 weeks for genotypes 1 or 4 and 24 weeks for genotypes 2 or 3), child-unfriendly formulation (subcutaneous injection), the need for intensive monitoring, and the known serious side effects profile. Ultimately, the treatment with PEG-IFN and ribavirin regimens, with their well-proven drawbacks, left pediatric gastroenterologists searching for alternatives. This often resulted in the deferral of treatment in expectation of improved therapeutic options in the near future.

Present Status of HCV Treatment

The origin of the newer agents for HCV treatment in the form of DAAs is based on the advanced understanding of HCV virology. HCV genome encodes for a 3011 amino acid residue polyprotein which undergoes proteolysis to yield ten individual proteins. Among them are three structural proteins (two envelope glycoproteins E1 and E2 and core protein) and seven non-structural (NS) proteins, which are p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (RNA polymerase activity), which participate in post-translational proteolytic processing and replication of HCV genetic material. These drugs target specific non-structural proteins of the virus and disrupt viral replication and infection.

Direct-acting Antivirals- A Boon for HCV Cure

DAAs are categorized into four classes based on their mechanism of action and therapeutic target. The four classes are non-structural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors (**Fig.1)**. Monotherapy with DAA should be avoided. Regimens should contain a combination of two different classes of

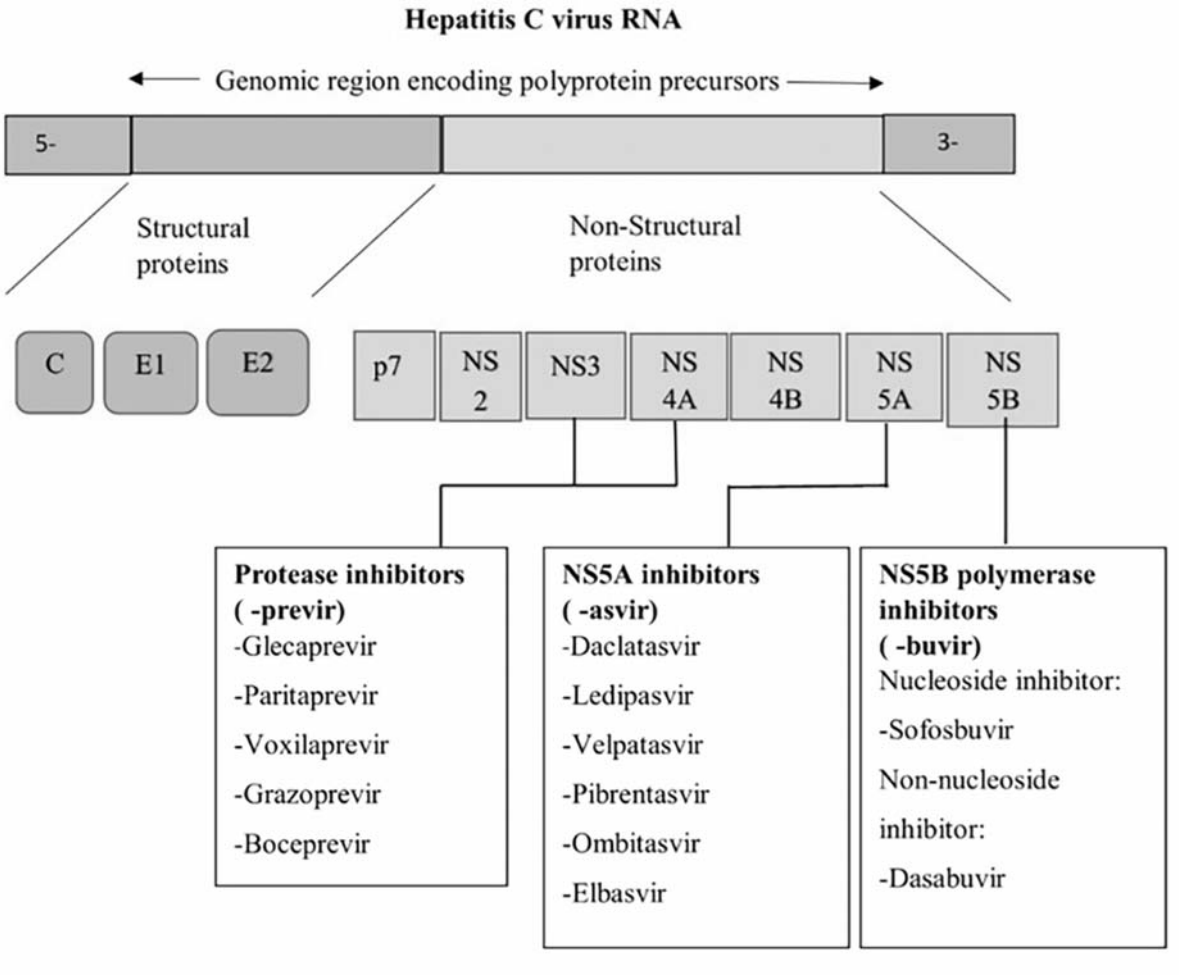

Fig. 1 HCV genome with its encoded proteins as targets for direct-acting antiviral agents.

DAAs, as drugs from the same class share cross-resistance. Various combinations of DAA-regimens (with a high genetic barrier to resistance) have been approved for children with HCV infection, showing high effectiveness and excellent safety with an adverse event profile comparable with placebo (**Table I**).

Ledipasvir-sofosbuvir: The first pediatric study assessing the IFN-free treatment with DAAs was a phase 2, multicentric, open-label study which evaluated the efficacy and safety of ledipasvir plus sofosbuvir in 100 children between the age of 12 to 17 years with chronic HCV genotype 1 infection [14]. Overall, 98% of patients reached SVR12 (at 12 weeks after stopping therapy), and no patient had a virologic failure. Two children who did not achieve SVR12 were lost to follow up either during or after treatment [14]. The approval of ledipasvir plus sofosbuvir in the pediatric population aged 3 through 11 years was supported by two clinical trials, which demonstrated high SVR12 rates of 99% and 97%, comparable to those seen in adults [15,16]. Across the three studies, there were no serious adverse events with the most common side effects reported being headache (18% to 27%), fever (17% to 21%), vomiting (24%), abdominal pain (15%), diarrhea (14%), and fatigue (13%) [14,17,18]. Ledipasvir plus sofosbuvir was approved by the Food and Drug Administration (FDA) in 2017, initially for children 12 to 17 years of age, with an extension to those over three years of age in 2019. Ledipasvir plus sofosbuvir is currently recommended for children aged ≥3 years with genotypes 1, 4, 5, or 6 [10].

Sofosbuvir-Velpatasvir: Jonas, et al. [19], in an open-label study, evaluated the efficacy of sofosbuvir plus velpatasvir for 12 weeks in children more than six years of age without cirrhosis or with compensated cirrhosis having genotypes 1, 2, 3, 4 or 6 HCV infection. Most of the study participants (147/173; 85%) were treatment-naive, and the rest (26/173; 15%) were treatment-experienced. Overall, SVR12 was ≥92%, with no treatment-related

Table I Studies on the Efficacy and Safety of DAA Regimens in the Treatment of HCV Infection in Children

DAA regimen	*Author, year, age group, number of study participants*	*Genotype*	*SVR12(%)*	*Common adverse events*
Ledipasvir and sofosbuvir combination	Balisteri, et al. [14], 2017; 12-17 y, *n*=100	1	98	Headache (18 -27%), fever (17-21%), vomiting (24%). No serious adverse events.
	Murray, et al. [17], 2018; 6-11 y, *n*=90	1	98	No reported drug discontinuation due to serious adverse events
	El Khayat, et al. [15], 2018; 12-17 y, *n*=144	1,4-6	99	
	Schwarz, et al. [16], 2019; 3-6 y, *n*=34	1 or 4	97	
Sofosbuvir and velpatasvir combination	Sokal, et al. [18], 2020; 3-17 y, *n*=216	1-4,6	92	Headache (20%), fatigue (17%), vomiting (15%), cough (12%), nausea (10%)
	Jonas, et al. [19], 2019; 6-17 y, *n*=173	1-4,6	>92	A severe adverse effect reported was auditory hallucination (0.5%)
Glecaprevir and pibrentasvir	Jonas et al. [20], 2020; 12-17 y, *n*=47	1-4	100	Nasopharyngitis (26%), upper respiratory tract infection (19%), headache (14-17%) etc.
	Jonas, et al. [21], 2021; 3-12 y, *n*=81	1-4,6	98	

DAA – direct-acting antivirals; SVR 12 – sustained virologic response 12.

severe adverse events or discontinuation [19]. Sofosbuvir plus velpatasvir use in pediatric patients aged 3-17 years has been assessed by the phase-2 registration trial (*n*=216), demonstrating high efficacy (SVR12 in 92% cases, virological failure in <1%) [16]. Overall tolerability of the drug was good, with the common side effects reported in the study were headache (20%), fatigue (17%), vomiting (15%), cough (12%), nausea (10%), etc. and serious adverse effects in the form of auditory hallucinations in one patient (0.5%) and treatment discontinuation due to side effects in 1.3% [18]. Based on reports of experience in adults, coadministration with amiodarone is not recommended due to the risk for symptomatic bradycardia. Sofosbuvir plus velpatasvir was approved by FDA in 2020 as a pan-genotypic regimen initially for children above six years of age, followed by an extension to three years and more in 2021 [10].

Glecaprevir-Pibrentasvir: Jonas, et al. [20] in part 1 of the DORA study among 47 adolescents with chronic HCV infection (genotype 1, 2, 3, 4, or 6) reported a high efficacy (SVR12 100%) with just eight weeks of treatment duration and no serious adverse events or treatment-related discontinuation. Part 2 of the DORA study supported the approval of glecaprevir plus pibrentasvir in the pediatric population aged 3 to 11 years, achieving high SVR12 rates of 96% (77/80) with no serious adverse events [21]. One child (1.2%) discontinued the drug due to a non-serious erythematous rash [20]. Both the studies (DORA part 1 and DORA part 2) reported only mild to moderate side effects commonly as nasopharyngitis (26%), upper respiratory tract infection (20%), headache (14% to 17%), vomiting (14%), fatigue (11%), fever (11%), diarrhea (10%) etc. [20,21]. An added advantage of this combination is its availability in the granule form (packaged as sachets) rather than as tablets aiding easier administration, especially in younger children without the need to score the tablets. However, it is not yet available in the Indian market, unlike ledipasvir-sofosbuvir and sofosbuvir-velpatasvir combinations. Glecaprevir plus pibrentasvir was approved by FDA in 2019 as a pan-genotypic regimen initially for children above 12 years of age, followed by an extension to three years or more in 2021 [10].

Sofosbuvir-Daclatasvir: Abdel Ghaffar, et al. [22], in an open-label, prospective study evaluating the efficacy and safety of sofosbuvir-daclatasvir in 40 children (above eight years of age or >17kg) with genotype 4 HCV infection showed high efficacy with SVR12 of 97.5% and no treatment-related serious adverse events or drug discontinuation. The most commonly reported side effects were cough (8%), fever (5%), and fatigue (5%). Similar results were reported by El-Shabrawi, et al. [23] in a study of 10 children with HCV infection (pan-genotypic), documenting an SVR12 of 100% and no serious adverse

events. The data to support the use of this combination in younger children (above three years of age) was based on modelled pharmacokinetic data in adolescents [24]. Based on this evidence, WHO has recommended using sofosbuvir plus daclatasvir in children above three years of age regardless of the genotype [25]. However, due to lack of well-powered studies and no direct study in children less than 8 years of age, the combination is not yet approved by the FDA and is not currently recommended by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in the treatment of pediatric HCV infection [10].

Indolfi, et al. [26], in a systematic review and metanalysis of 39 pediatric studies (1796 subjects) using various combinations of DAA regimens in children and adolescents, showed a pooled proportion among those receiving all doses of treatment and reaching SVR12 of 100%. Reported side effects were mild, the most common being headache (19.9%) and fatigue (13.9%), while serious adverse events were uncommon, highlighting the efficacy and safety of the various DAA regimens [26].

Implications of DAAs for HCV in Children

Although no direct studies are comparing DAAs with the older regimens (PEG-IFN and ribavirin), reported evidence suggests a high efficacy (92% to 100% vs 58%), mild or no serious side effects (discontinuation rate due to adverse effects <1.5% vs 4%) and very low risk of relapses (<1% vs 7%) for DAA based regimens over Peg-IFN plus ribavirin [10,12,27], no need to do a liver biopsy to document significant fibrosis in genotype 1. On the

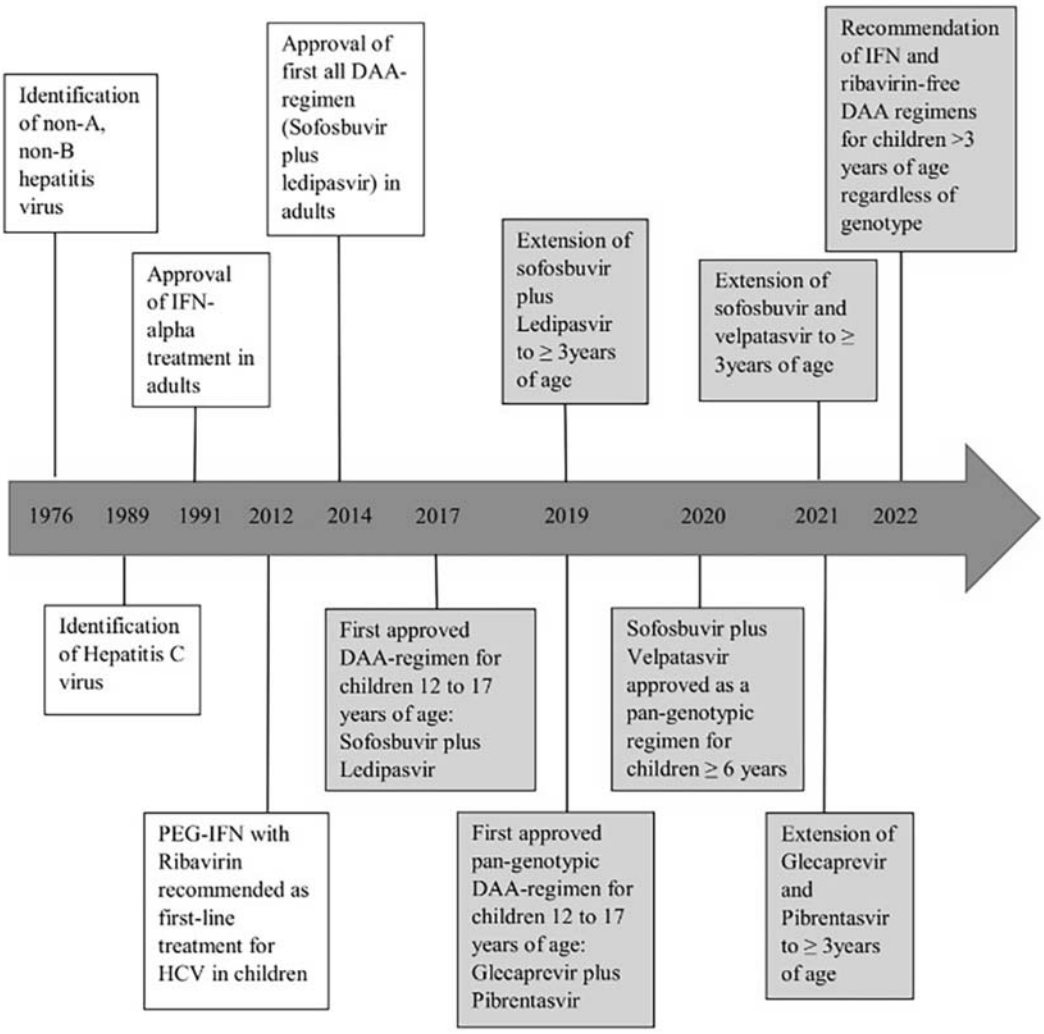

Fig. 2 Timeline of advancements in HCV discovery and treatment. Colored boxes signify milestones related to the approval of DAA therapy for children and adolescents.

basis of this well-documented evidence, updated recommendations paved the way for a completely IFN and ribavirin-free DAA-based treatment in children above three years of age irrespective of the genotype **(Fig. 2)** [10,25]. Also, therapy with DAAs is indicated for all children (>3 years) with active/current HCV infection (HCV-RNA positive) even if they are asymptomatic or have normal liver function tests; and liver biopsy is not necessary for starting treatment [10,28]. The rationale for this recommendation comes from well-documented evidence of the high efficacy and safety of DAA combination regimens in curing HCV infection thus preventing the risk of later development of complications like cirrhosis [10,28]. Additionally, curative DAA therapy during childhood or adolescence supports HCV treat-ment by preventing viral transmission, which is a major pillar in global/national preventive health strategies [10,28]. This has led to a significant shift from the historical approach of treatment deferment to a more aggressive strategy of initiating DAA therapy for all children (older than three years of age) with HCV infection, irrespective of liver function tests, genotype, or degree of liver injury [10,28].

CURRENT RECOMMENDATIONS

Whom and When to Treat

All children diagnosed with active HCV infection (HCV-RNA positive) who are above three years of age should be treated with a DAA-approved regimen regardless of disease severity, alanine aminotransferase (ALT) levels, genotype, history of treatment experience, and whether the infection is acute or chronic [10]. A liver biopsy is not necessary to initiate treatment in children with HCV. Testing for HCV genotype should be considered for those in whom it may alter treatment recommendations based on the age and availability of pan-genotypic regimens. Screening for HBV infection (i.e., HBsAg, anti-HBc, and anti-HBs) is recommended before initiating HCV DAA therapy due to the risk for HBV reactivation during or after treatment.

Treatment Regimens

Simplified treatment regimens are recommended for treatment-naive or interferon (± ribavirin) experienced children without cirrhosis and with compensated cirrhosis. Approved genotype-based and pan-genotypic DAA regimens and the drug doses are summarized in **Table II**. Decompensated liver disease and recurrent HCV after liver transplantation is rare in children. DAA-experienced pediatric HCV patients are rarely encountered in clinical practice (**Table III**).

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 I**.

CONCLUSION

There is a paradigm shift in the management of HCV infection in children with the approval of highly effective and safe DAA therapy. Current guidelines recommend only DAA-based combination regimens for treating HCV infection in children above three years, regardless of liver function test values, duration of infection (acute or chronic), and the genotype. Besides the effectiveness of

Table II Recommended DAA Regimens for Treatment-naive or Interferon-experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommendation	*Duration of treatment*	*Dose (weight based)*
Combination of ledipasvir plus sofosbuvir for children aged ≥3 y with genotype 1, 4, 5, or 6	12 wk	Once daily dose of ledipasvir/sofosbuvir < 17 kg= 33.75 mg/150 mg 17 to <35 kg = 45 mg/200 mg ≥35 kg=90 mg/400 mg
Combination of sofosbuvir plus velpatasvir for children ≥3 y of age with any genotype	12 wk	Once daily dose of sofosbuvir/velpatasvir < 17 kg= 150 mg/37.5 mg 17-<30 kg= 200 mg/50 mg ≥30 kg=400 mg/100 mg
Combination of glecaprevir plus pibrentasvir for children aged ≥3 y with any genotype	8 wk	Once daily dose of glecaprevir/pibrentasvir < 20 kg= 150 mg/60 mg ≥20 kg to <30 kg= 200 mg/80 mg ≥30 kg to <45 kg= 250 mg/100 mg ≥45 kg or ≥12 y=300 mg/120 mg

A longer duration of therapy (16 wk) may be needed for genotype 3 interferon-experienced patients.
Source: Reproduced from reference 10, with permission.

Table III Recommended Treatment Regimens for DAA-experienced Children Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommendation	*Duration*
Genotype 1: Ledipasvir plus sofosbuvir for children aged ≥3 years with prior exposure to interferon (± ribavirin) plus an HCV protease inhibitor regimen	12 wk (without cirrhosis) 24 wk (with compensated cirrhosis)
Genotype 4, 5, or 6: Ledipasvir plus sofosbuvir for children aged ≥3 years without cirrhosis or with compensated cirrhosis, having prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen	12 wk
Genotype 1, 2, 4, 5, or 6: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg having prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors	8 wk (without cirrhosis) 12 wk (with compensated cirrhosis)
Genotype 3: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors	16 wk
Genotype 1: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 y or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to NS3/4A protease inhibitors but no NS5A inhibitor exposure	12 wk
Genotype 1: Glecaprevir (300 mg) plus pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg without cirrhosis or with compensated cirrhosis, having prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure	16 wk

Source: *Reproduced from referemce 10, with permission. DAA-direct-acting antivirals; HCV-hepatitis C virus.*

Box I Recommendations 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 interactions.

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.
- HBsAg-positive patients undergoing DAA therapy should be monitored for HBV DNA every 4 to 8 weeks during treatment and for three months 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)

- Regimens 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 recipients (*HCV negative recipients from HCVviremic donors*)

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

Source: *Reproduced from reference 10, with permission.*

DAA therapy, increasing awareness about the mode of HCV spread, better screening (use of ID-NAT-based tests in blood banks), and making the DAAs available at a subsidized rate in the public sectors are necessary to eliminate HCV infection from India without a preventive vaccine.

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