

**POSITION STATEMENT****Hepatology**

# ESPGHAN recommendations on treatment of chronic hepatitis C virus infection in adolescents and children including those living in resource-limited settings

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**Abstract**

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide, with more than three million viraemic adolescents and children. Treatment of adults with HCV infection and HCV-related liver disease has advanced considerably thanks to development and improvements in therapy. Direct-acting antiviral regimens are safe and effective. Three regimens with pangenotypic activity (glecaprevir/pibrentasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir) and three regimens with genotype-specific activity (sofosbuvir/ribavirin, sofosbuvir/ledipasvir and elbasvir/grazoprevir) have been approved with age-specific limitation for treatment of children with chronic hepatitis C by the European Medicines Agency and the United States Food and Drug Administration. The World Health Organization has set the ambitious target to eliminate hepatitis C as a major public health threat by 2030 and based its actions against HCV on the large use of direct acting antivirals. These updated European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommendations on treatment of hepatitis C describe the optimal therapeutic management of adolescents and children with HCV infection including specific indications for those living in resource-limited settings.

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**KEYWORDS**

efficacy, position paper, safety, virological response

**1 | OBJECTIVES**

The objectives of this update of the 2018 European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) position paper on treatment of hepatitis C<sup>1</sup> is to describe the current optimal therapeutic management of adolescents and children with chronic hepatitis C virus (HCV) infection and to assist pediatricians and patients in the clinical decision-making of treating this population. The present position paper includes specific information on the therapeutic management of adolescents and children living in resource-limited settings.

**2 | BACKGROUND**

The estimated prevalence of HCV infection in children aged 0–18 years in 2018, based on studies from 104 countries, was 0.13% of the global population, corresponding to 3.26 million people (95% confidence intervals [CI] 2.7–3.9 million).<sup>2</sup> The prevalence of the infection was estimated to be 0.3% in high-income countries and 0.6% in low-income countries, with only 23 countries accounting for 80% of this global burden. Pakistan, China, India and Nigeria alone accounted for more than 50% of HCV infected children worldwide. Epidemiologic data from high-income countries are sparse, but the incidence of new cases has been increasing in adolescents in the United States and Europe, paralleling the increased use of opioid drugs and increasing rates of HCV infection in women of childbearing age.<sup>3</sup> The true prevalence of HCV in adolescents and children is likely underestimated.<sup>4</sup>

The natural history of HCV infection acquired in childhood is highly variable: in the short term, hepatic injury is usually mild<sup>5,6</sup> although extensive fibrosis, cirrhosis, hepatocellular carcinoma and extrahepatic manifestations have been reported.<sup>5,7,8</sup> A recent study from United Kingdom described a cohort of 1049 people who were infected with HCV in childhood, of whom 53% were infected through injection drug use in adolescence and 24% were infected through receipt of contaminated blood products.<sup>9</sup> In this cohort, one-third of patients developed liver disease with a median of 33 years after infection. Interestingly, patients with perinatal exposure to HCV developed cirrhosis at an earlier age compared to patients who acquired HCV in their childhood through drug abuse, blood transfusion, or with an unknown route of infection (36 years vs. 48, 46, and 52 years, respectively;  $p < .0001$ ). The incidence of HCC was 5%. Four percent of patients required a liver transplant and all-cause mortality was 3%.<sup>9</sup>

**What is Known**

- Direct-acting antiviral drug regimens are highly effective and safe for treatment of adults, adolescents and children with chronic hepatitis C.
- Two combination regimens with pangenotypic activity (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) and two with genotype-specific activity (sofosbuvir/ledipasvir and sofosbuvir plus ribavirin) have been approved by both the European Medicines Agency and the United States Food and Drug Administration for use in adolescents and children aged 3 years and older with chronic hepatitis C.

**What is New**

- We recommend treatment using direct-acting antiviral regimens for all adolescents and children 3 years of age and above with chronic hepatitis C, regardless of stage of disease.
- Pangenotypic and genotype-specific direct-acting antiviral regimens are equally recommended for treatment.
- Pangenotypic, ribavirin-free and regimens with the shortest treatment duration are preferable when available.
- Sofosbuvir plus daclatasvir may be considered for adolescents and children with chronic hepatitis C in resource-limited settings, as it is highly effective and widely available as low-cost generic formulations.

Since 2017 high rates of HCV viral clearance with the various pangenotypic direct acting antiviral (DAA) regimens have been demonstrated in adolescents and children.<sup>10</sup> This has led to approvals by key regulatory agencies, the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA). This update of the 2018 ESPGHAN Position paper on treatment of HCV infection in adolescents and children<sup>1</sup> is intended to describe the current optimal therapeutic management of adolescents and children with chronic HCV infection. Additionally, one of the goals of the present position paper is to provide physicians and clinical decision makers with guidance on updated treatment of HCV-infected adolescents and children. This update focuses on treatment.

### 3 | METHODS

This project started in February 2021, when a working group consisting of selected ESPGHAN and non-ESPGHAN members (GI, RPGP, MMJ, MHES, BF, ES, SW, and EN,) who have long-term clinical and research expertise in viral hepatitis was formed by the Hepatology Committee to prepare a position paper to be reviewed and approved by all the Hepatology committee members, representing the European pediatric hepatology community. The recommendations included in the present position paper were based on evidence from existing publications and presentations at international meetings reviewed in a systematic revision, and meta-analysis of existing papers on the topic published in 2021 and recently updated.<sup>11,12</sup> In the absence of such evidence, the experts' personal experiences and opinions have been considered. Citations were chosen on the basis of their relevance to the text. Furthermore, all the members of the working group were asked to search the literature relevant to the topic to possibly uncover further studies that may have been missed by the former search.

#### 3.1 | Consensus and voting

The first draft of the position paper was sent to working group members for review and comments. Then, the members of the working group anonymously voted on each statement, using the nominal voting technique. The consensus was formally achieved through nominal group technique, a structured quantitative method.

Consensus was reached for all recommendations. The final draft of the paper was sent to all the working group and Hepatology committee members for approval in January 2023.

#### 3.2 | Available drugs

The HCV drug combinations are described in this paragraph and listed in Table 1. The evidence on efficacy, pharmacokinetic and safety profiles are presented below. The panel recognizes the heterogeneity of healthcare systems and availability of the different regimens in different countries. One of the aims of the present position paper is to assist national and international regulatory agencies in hastening and facilitating the availability of the drugs for the specific target population of adolescents and children.

### 4 | REGIMENS WITH PANGENOTYPIC ACTIVITY

#### 4.1 | Glecaprevir/pibrentasvir

The fixed-dose combination of glecaprevir (a potent NS3/4 A protease inhibitor)/pibrentasvir (an NS5A inhibitor) is approved by the US FDA and EMA for the treatment of adolescents and children (3–17 years) with all genotypes chronic HCV infection. Treatment duration is 8 weeks for all children except for those who are interferon-experienced with cirrhosis who should receive 12 weeks of treatment and for those with HCV

**TABLE 1** Direct-active antiviral regimens for treatment of chronic hepatitis C virus infection in children (age > 3 years) and adolescents and formulations available.

Activity	Product	Formulations	Approval
Regimens with pangenotypic activity	Glecaprevir/pibrentasvir (FDC)	Film-coated tablets (FDC) 100/40 mg Oral pellets in sachet 50/20 mg	EMA and US FDA > 3 years of age
	Sofosbuvir/velpatasvir (FDC)	Film-coated tablets (FDC) 400/100 mg and 200/50 mg Oral pellets in sachet 200/50 mg and 150/37.5 mg	EMA and US FDA > 3 years of age
	Sofosbuvir/velpatasvir/voxilaprevir (FDC)	Tablet (FDC) 400/100/100 mg	EMA > 12 years of age
	Sofosbuvir + daclatasvir	Daclatasvir Film-coated tablets 60 mg	Not approved for use in children by the EMA and US FDA
Regimens with genotype-specific activity	Sofosbuvir/ledipasvir (FDC)	Film-coated tablets (FDC) 400/90 mg and 200/45 mg Oral pellets in sachet 200/45 mg and 150/33.75 mg	EMA and US FDA > 3 years of age
	Elbasvir/grazoprevir	Film-coated tablets (FDC) 50/100 mg	EMA and US FDA > 12 years of age

Abbreviations: EMA, European Medicines Agency; FDC, fixed-dose combination; US FDA, United States Food and Drug Administration in children.

genotype 3 infection who are interferon-experienced (with or without cirrhosis) who should receive 16 weeks of treatment.

A Phase II-III, nonrandomized, open-label, multicentre, multi-cohort study evaluated the pharmacokinetics, safety and the efficacy of glecaprevir/pibrentasvir. Glecaprevir and pibrentasvir were used as an all-oral, fixed-dose combination for children with chronic HCV genotype 1, 2, 3, 4, 5, and 6 infection aged between 3 and 17 years. The standard duration of treatment was 8 weeks for all children but for those who were cirrhotic who were planned to receive 12 weeks of treatment and for those with HCV genotype 3 infection who were interferon-experienced (with or without cirrhosis) who were planned to receive 16 weeks of treatment.

#### 4.1.1 | Adolescents

Forty-seven (26 female; 55%) adolescents, with HCV infection were treated with the adult dosing (glecaprevir 300 mg, pibrentasvir 120 mg daily, orally with food) provided as three fixed-dose combination tablets (100/40 mg).<sup>13</sup> Exposures of glecaprevir and pibrentasvir were characterized with data from all the enrolled 47 adolescents. The adult dosing resulted in comparable plasma exposures in adolescents than those found in HCV-infected adults without cirrhosis. The median age was 14 years (range 12–17), the mean weight was 58 kg (kg, range 32–109). Forty-six percent of the children enrolled had baseline HCV RNA levels greater than or equal to 1,000,000 IU per mL. HCV genotype 1, 2, 3, and 4 were present in 37 (79%), 3 (6%), 4 (9%) and 3 (6%), respectively. No patient had cirrhosis. The sustained virological response 12 weeks after the end of treatment (SVR12) rate among all subjects was 100% overall (95% CI 92.4–100%, intention to treat analysis). The treatment was well tolerated. The three most reported adverse events were nasopharyngitis (26% of patients), upper respiratory tract infection (19%), and headache (17%). No serious or grade 3–4 adverse event was reported, and no patient discontinued treatment because of an adverse event.

#### 4.1.2 | Children 3–11 years of age

Eighty-one children aged 3–11 years (55% female), with HCV infection were treated with glecaprevir/pibrentasvir dosed by weight within different age cohorts (9–< 12 years, 6–< 9 years and 3–<6 years).<sup>14</sup> Glecaprevir/pibrentasvir was provided as film-coated granules. Eighty of 81 children underwent intensive pharmacokinetic evaluations of the concentrations of glecaprevir and pibrentasvir to confirm the appropriateness of the dosage selected. Overall, the median age

was 7 years (range 3–11), the median weight was 25 kg (range 13–44). Forty-one (51%) children had baseline HCV RNA levels greater than or equal to 1,000,000 IU per mL. HCV genotype 1, 2, 3, or 4 were in 58 (72%), 2 (3%), 18 (23%) and 2 (3%), respectively. None of the patients had cirrhosis. Seventy-eight participants received therapy for 8 weeks. One genotype 3-infected participant received therapy for 12 weeks and one genotype 3, interferon-experienced participant received therapy for 16 weeks, in accordance with the local adult prescribing label duration. One participant who was coinfecting with HIV received 8 weeks of treatment. The SVR12 rate among all subjects was 96% overall (77/80; 95% CI 90–99%, intention to treat analysis). One 9-year-old treatment-naive participant with HCV genotype 3b infection who was treated for 8 weeks relapsed by post-treatment Week 4. There were two premature discontinuations; one 3-year-old child refused to swallow the granule formulation on Day 1 without subsequent doses. Another 11-year-old participant discontinued treatment by Day 4 due to a drug-related rash. The treatment was well tolerated. The most reported adverse events were headache (14%), vomiting (14%) and diarrhoea (10%). No treatment-emergent serious adverse events were reported. No grade 3–4 lab abnormalities were reported.

## 4.2 | Sofosbuvir/velpatasvir

The fixed-dose combination of sofosbuvir (an NS5B inhibitor) and velpatasvir (an NS5A inhibitor) has been approved by US FDA for the treatment of adolescents and children (3–17 years) with any of the six HCV genotypes without cirrhosis (liver disease) or with mild cirrhosis.<sup>15</sup> Treatment duration is 12 weeks for all patients.

A Phase II-III, open-label, multicentre, multi-cohort study evaluated the safety and the efficacy of sofosbuvir/velpatasvir. Sofosbuvir and velpatasvir were used as an all-oral, pangenotypic, fixed-dose combination to children with chronic HCV infection aged between 3 and 17 years. The standard duration of treatment was 12 weeks for all children.

#### 4.2.1 | Adolescents

One hundred and two adolescents (52 female; 51%), with HCV infection were treated with the adult dosing (sofosbuvir 400 mg, velpatasvir 100 mg daily, orally with or without food) provided as one fixed-dose combination 400/100-mg tablet or 2 × 200/50-mg tablets. Separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir, GS-331007 and velpatasvir were taken in 17 patients. The adult dosing

resulted in comparable plasma exposures in adolescents to than those found in Phase II and Phase III clinical trials in adults with chronic hepatitis C. The majority of subjects (91; 89%) had been infected through vertical transmission. The median age was 15 years (range 12–17), the mean body mass index was 22.7 kg/m<sup>2</sup> (range 12.9–48.9). Fifty-eight percent ( $n = 59$ ) of the children enrolled had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1, 2, 3, 4, and 6 were in 77 (75%), 5 (5%), 12 (12%), 2 (2%) and 6 (6%). No patient was known to have cirrhosis. The SVR12 rate among all subjects was 95% overall (97/102, intention to treat analysis; 93% in subjects with genotype 1 HCV infection, 100% genotype 2, 3, 4, and 6). One 17-year-old girl had a virological failure after having discontinued treatment at Week 4 for pregnancy and subsequently relapsed. The remaining 4 cases did not achieve SVR for non-virological reasons. The treatment was well tolerated. The most reported adverse events were headache (29% of patients), nausea (17%), vomiting (9%), and fatigue (22%). Two serious and 2 grade 3–4 adverse event were reported that were considered unrelated to treatment and resolved without treatment interruption. Five grade 3–4 lab abnormalities were reported. Baseline NS5A and NS5B polymerase inhibitor RAS were found in 16b (16%) and 5 (5%) of the patients. All patients with baseline RAS achieved SVR12.

#### 4.2.2 | Children 6–11 years of age

seventy-three children aged 6–11 years (38; 52% female), with HCV infection were treated with half of the dose used in adults (sofosbuvir 200 mg and velpatasvir 50 mg daily, orally without regard for food) provided as 1 tablet (200/50 mg) or four packets of granules (50/12.5 mg).<sup>13</sup> Separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir, GS-331007 and velpatasvir were taken in 20 patients to confirm the appropriateness of the dosage selected. The majority of subjects (69; 95%) had been infected through vertical transmission. The median age was 8 years (range 6–11), the mean body mass index was 17.5 kg/m<sup>2</sup> (range 12.8–30.9) and the median weight was 30 kg (range 18–78). Thirty-five (48%) children had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1, 2, 3, and 4 were in 56 (77%), 2 (3%), 11 (15%) and 4 (5%). No patient was known to have cirrhosis. The SVR12 rate among all subjects was 93% overall (68/73; intention to treat analysis; 93% in subjects with genotype 1 and 3 HCV infection, 100% genotype 2 and 4). Of the five subjects who did not achieve SVR12, one girl aged 10 years with HCV genotype 1a

infection had a nonresponse after 8 weeks of treatment and discontinued sofosbuvir/velpatasvir. The remaining 4 cases did not achieve SVR for non-virological reasons (early treatment discontinuation and/or loss to follow-up). The treatment was well tolerated. The most commonly reported adverse events were vomiting (16%), headache and cough (15% each) and fatigue (12%). Two patient discontinued treatment because of an adverse event. A girl aged 6 years had a grade 3 serious adverse event of treatment related auditory hallucinations and 8-year-old girl who was not able to take the oral medication. No grade 3–4 lab abnormalities were reported. Baseline NS5A polymerase inhibitor RAS were found in 10% of the patients. No NS5B RAS was found at baseline. All patients with baseline RAS achieved SVR12.

#### 4.2.3 | Children 3–5 years of age

Forty-one children treatment-naïve and non-cirrhotic (24; 59% female), with HCV infection were treated with weight-based doses of sofosbuvir/velpatasvir fixed-dose combination granules (200/50 mg if their weight was <17 kg or 150/37.5 mg if their weight was ≥17 kg) once-daily.<sup>13</sup> Each packet of granules contained 50 mg of sofosbuvir and 12.5 mg of velpatasvir. Patients weighing <17 kg received three packets per dose, and patients weighing ≥17 kg received four packets per dose. The majority of subjects (40; 98%) had been infected through vertical transmission. The median age was 4 years (range 3–5), the mean body mass index was 17 kg/m<sup>2</sup> (range 13.9–22) and the mean weight was 19 kg (range 13–35). Forty-nine percent of the children enrolled had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1, 2, 3, or 4 were in 32 (78%), 6 (15%), 2 (5%) and 1(2%). The SVR12 rate among all subjects was 83% (34/41; 88% in subjects with genotype 1 HCV infection, 50% genotype 2, 100% genotype 3 and 4). None of the 34 subjects who completed the treatment had virologic failure. Of the remaining seven subjects who did not achieve SVR12, five discontinued treatment on Day 1, one on Day 7 and one on Day 20 for nonvirological reasons. The treatment was well tolerated. The most commonly reported adverse events were vomiting (27% of patients), cough, pyrexia and rhinorrhoea (15% each). No serious or grade 3–4 adverse event was reported. One patient experienced a grade 3–4 laboratory abnormality. Baseline NS5A and NS5B polymerase inhibitor RASs were found in 6/33 (18%) and 1/30 (3%) of the patients. All patients with baseline RASs achieved SVR12.

The results of the registration study have been confirmed in a recent real-world study using the same drug doses and treatment durations in adolescents.<sup>16</sup>

### 4.3 | Sofosbuvir/velpatasvir/voxilaprevir

The fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir (an NS3/4 inhibitor) has been approved by EMA for the treatment of adolescents (12–17 years), weighing at least 30 kg. Treatment duration is 8 weeks for all patients but for those who have cirrhosis or who have received treatment with other DAA who should be treated for 12 weeks. The recommended daily dose of sofosbuvir/velpatasvir/voxilaprevir is 400/100/100 mg once a day. This combination should not be used as a first line treatment but for DAA-experienced patients.

#### 4.3.1 | Adolescents

Twenty-one adolescents (14 female; 67%), with HCV infection were treated with the adult dosing (sofosbuvir/velpatasvir/voxilaprevir is 400/100/100 mg once a day, orally with food) provided as one fixed-dose combination 400/100/100 mg tablet. Separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir, GS-331007, velpatasvir, and voxilaprevir were taken in 14 patients. The adult dosing resulted in comparable plasma exposures in adolescents than those found in Phase II and Phase III clinical trials in adults with chronic hepatitis C. The majority of subjects (16; 76%) had been infected through vertical transmission. The median age was 14 years (range 12–16). Fifty-two percent ( $n = 11$ ) of the children enrolled had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1, 2, 3, and 4 were in 6 (29%), 4 (19%), 9 (43%) and 2 (10%). No patient was known to have cirrhosis. The SVR12 rate among all subjects was 100% (95% CI 84%–100%). The treatment was well tolerated. The most reported adverse events were abdominal pain and headache (each 24% of patients) and nausea (19% of patients). One grade 3–4 lab abnormality was reported (hyperkalaemia).<sup>17</sup>

### 4.4 | Sofosbuvir + daclatasvir

The combination of sofosbuvir plus daclatasvir is not approved for use in children by the EMA and the US FDA but it is recommended by the World Health Organization as a pangenotypic DAA regimen for adolescents and children (3–17 years) with chronic hepatitis C. Treatment duration is 12 weeks for all patients except for those who are treatment-experienced or with compensated cirrhosis who should receive 24 weeks of treatment.<sup>18</sup> In 2017, for the first time, the preliminary results of an Egyptian study on the

use of sofosbuvir 400 mg and daclatasvir 60 mg once daily were presented.<sup>19</sup> Thirteen adolescents aged between 15 and 17 years with HCV genotype four infection received 12 weeks of treatment. Ribavirin was used for the four patients with cirrhosis and SVR12 was 100%. No serious adverse event was reported while mild adverse events were noted in the form of mild headache, dizziness, itching, and ribavirin-induced hemoglobin reduction ( $<1$  g/dL). The adult dosing resulted in comparable plasma exposures in adolescents than those found in Phase II and Phase III clinical trials in adults with chronic HCV infection. Following this study, others confirmed the efficacy and the safety of this combination for adolescents and children.<sup>11,20,21</sup> A pilot study explored the efficacy of a shortened 8 weeks duration of sofosbuvir and daclatasvir in a cohort of 10 consecutive adolescents. All patients (10/10 [100%, CI: 72.25–100%]) achieved SVR12 with good tolerability and no serious adverse events.<sup>22</sup> Based on a recently published modeling study,<sup>23</sup> a population pharmacokinetic analysis was performed to predict daclatasvir exposure in children treated with available adult formulations showing that 30 mg once daily was predicted to achieve effective and safe exposures in children 14– $<35$  kg, perhaps down to 10 kg.<sup>24</sup> These preliminary data support the hypothesis that low-cost available adult daclatasvir formulations together with approved pediatric doses of sofosbuvir could expand global access to HCV treatment for children.

## 5 | REGIMENS WITH GENOTYPE-SPECIFIC ACTIVITY

### 5.1 | Sofosbuvir/ledipasvir

The fixed-dose combination of sofosbuvir (a potent NS5B polymerase inhibitor) and ledipasvir (an NS5A inhibitor) is approved by the US FDA and EMA for treatment of adolescents and children (3–17 years of age) with chronic HCV genotypes 1, 4, 5, or 6 infection. Treatment duration is 12 weeks for all except for interferon-experienced patients with compensated cirrhosis and HCV genotype 1 infection who should receive 24 weeks of treatment. The EMA extrapolating from adult data recently endorsed the use of sofosbuvir/ledipasvir for only 8 weeks in chronic hepatitis C infected children with genotype 1, treatment-naïve, non-cirrhotic, with pretreatment HCV viremia  $< 6$  million IU/mL.

A Phase II-III, open-label, multicentre, multi-cohort study evaluated the safety and the efficacy of sofosbuvir/ledipasvir for children with chronic HCV genotype 1, 3, 4, 5, and 6 infection aged between 3 and 17 years. The standard duration of treatment was 12 weeks for all children.

### 5.1.1 | Adolescents (12–17 years of age)

One hundred adolescents (63 female), with HCV genotype 1 infection were treated with adult dose (sofosbuvir 400 mg/ledipasvir 90 mg daily, orally without regard for food) provided as one fixed-dose combination tablet.<sup>25</sup> The first 10 adolescents underwent separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir and ledipasvir. The adult dosing resulted in comparable plasma exposures in adolescents to those found in Phase II and Phase III clinical trials in adults with chronic hepatitis C. The majority of subjects (84) had been infected through vertical transmission. The median age was 15 years (range 12–17), the mean body mass index was 21 kg/m<sup>2</sup> (range 13–37). Fifty-five children enrolled had baseline HCV ribonucleic acid (RNA) levels greater than or equal to 800,000 IU per mL. One patient was known to have cirrhosis, and 42 patients did not have cirrhosis; in the remaining 57 patients the stage of fibrosis/cirrhosis was unknown. The sustained virological response 12 weeks after the end of treatment (SVR12) rate among all subjects was 98% overall (98/100; 95% CI 93–100%, intention to treat analysis). Of the 100 patients who initiated treatment, 99 completed treatment. One patient discontinued treatment and was lost to follow-up. One patient completed treatment but did not attend the post-treatment follow up visits after having achieved end of treatment response. No patient had virologic non response, breakthrough or relapse. The efficacy was similar among treatment-naïve (78/80, SVR12 98%; 95% CI 91–100%) and interferon-experienced patients (20/20, SVR12 100%; 95% CI 83–99%). The only patient with cirrhosis was treatment-naïve, received 12 weeks of therapy, and achieved SVR12. The treatment was well tolerated. The three most reported adverse events were headache (27% of patients), diarrhoea (14%), and fatigue (13%). No serious or grade 3–4 adverse event was reported and no patient discontinued treatment because of an adverse event. Baseline NS5A and NS5B polymerase inhibitor resistance associated substitutions (RAS) were found in 5% each of the patients. All patients with baseline RAS were treatment naïve and all achieved SVR12.

### 5.1.2 | Children 6–11 years of age

Ninety-two children aged 6–11 years (41% female), with HCV infection were treated with half of the dose used in adults (sofosbuvir 200 mg/ledipasvir 45 mg daily, orally without regard for food) provided as two fixed-dose combination tablets of 100/22.5 mg.<sup>26</sup> The first 12 children underwent separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir, GS-331007 and ledipasvir to confirm the

appropriateness of the dosage selected. Most subjects (89; 97%) had been infected through vertical transmission. The median age was 9 years (range 6–11), the mean body mass index was 17 kg/m<sup>2</sup> (range 13–31) and the median weight was 30 kg (range 17–76). Fifty-four (59%) children had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1, 3, or 4 were present in 88 (95%), 2 (2%) and 2 (2%) of them. Two patients (2%) were known to have cirrhosis, and 35 (38%) patients did not have cirrhosis; in the remaining 55 (60%) patients the stage of fibrosis/cirrhosis was unknown. Eighty-nine children received 12 weeks of treatment, children infected with HCV genotype 3 were treated for 24 weeks with ribavirin and 1 cirrhotic and interferon-experienced patient received 24 weeks of treatment. The overall SVR12 rate among all subjects was 99% (91/92; 95% CI 94–100%, intention to treat analysis). The single case who did not achieve SVR12 was an 8-year-old treatment-naïve female with genotype 1a infection and cirrhosis who received ledipasvir–sofosbuvir for 12 weeks and experienced virologic relapse 4 weeks after treatment. The high overall SVR12 rate precluded meaningful interpretation of subgroup analyses. The treatment was well tolerated. The most reported adverse events were headache (18% of patients), pyrexia (17%) abdominal pain (15%), fatigue (15%), vomiting (15%), and cough (15%). No patient discontinued treatment because of an adverse event. One patient had three serious adverse events of moderate intensity (abdominal pain, gastroenteritis, and tooth abscess), all of which were considered by the investigator as unrelated to study treatment. Most laboratory abnormalities were mild in severity; 4 patients (4%) had grade 3–4 lab abnormalities (asymptomatic amylase elevation, neutropenia, decrease in hemoglobin level). Baseline NS5A and NS5B polymerase inhibitor RASs were found in 14% and 3% of the patients. All patients with baseline RAS achieved SVR12.

### 5.1.3 | Children 3–5 years of age

Thirty-four children aged 3–5 years (24; 71% female), with HCV infection were treated with weight-based doses of sofosbuvir/ledipasvir fixed-dose combination granules (150 mg/33.75 mg if their weight was <17 kg or 200 mg/45 mg if their weight was ≥17 kg) once-daily.<sup>27</sup> Each packet of granules contained 50 mg of sofosbuvir and 11.25 mg of ledipasvir. Patients weighing <17 kg received three packets per dose, and patients weighing ≥17 kg received four packets per dose. The granules were administered with or without food. If taken with food, the granules were to be sprinkled on a spoonful of nonacidic soft food, such as pudding or ice cream, and then swallowed without

chewing. If taken without food, the granules were to be taken first and then washed down with liquid, not mixed into the liquid. The first 14 children underwent separate intensive pharmacokinetic evaluations of the concentrations of sofosbuvir and ledipasvir to confirm the appropriateness of the medication dosages selected. All the subjects had been infected through vertical transmission. The median age was 5 years (range 3–5), the mean body mass index was 16 kg/m<sup>2</sup> (range 13–25) and the median weight was 19 kg (range 11–34). Nineteen (56%) children had baseline HCV RNA levels greater than or equal to 800,000 IU per mL and HCV genotype 1 and 4 were present in 33 (97%) and 1 (3%). No patient was known to have cirrhosis, and 14 (41%) patients did not have cirrhosis; in the remaining 20 (59%) patients the stage of fibrosis/cirrhosis was unknown. All children received 12 weeks of treatment. The overall SVR12 rate among all subjects was 97% (33/34; 95% CI 85–100%, intention to treat analysis). The only patient who did not achieve SVR12 was 3 years old who discontinued treatment after 5 days due to “abnormal drug taste.” The high overall SVR12 rate precluded meaningful interpretation of subgroup analyses. The treatment was well tolerated. The most reported adverse events were vomiting (24% of patients), cough (21%), and pyrexia (21%). No serious or grade 3–4 adverse event was reported. No patient experienced a laboratory abnormality. Baseline NS5A and NS5B polymerase inhibitor RASs were found in 4/33 (12%) and 2/33 (6%) of the patients. All patients with baseline RAS achieved SVR12.

The results of the registration studies<sup>25–27</sup> have been recently confirmed in a number of real-world studies using the same drug doses and treatment durations<sup>11,12</sup> including adolescents with hematological malignancies.<sup>22</sup>

#### 5.1.4 | Treatment for 8 weeks

The treatment duration of sofosbuvir/ledipasvir explored in the phase II–III registration trial for adolescent was 12 weeks. The efficacy of 8 weeks of treatment for adults with chronic infection has been explored in the ION 3 study.<sup>28</sup> ION-3 was a randomized, open-label trial in treatment-naïve non-cirrhotic subjects with genotype 1 chronic hepatitis C. Subjects were randomized in a 1:1:1 ratio to one of the following three treatment groups and stratified by HCV genotype (1a vs. 1b): sofosbuvir/ledipasvir for 8 weeks; sofosbuvir/ledipasvir for 12 weeks; or sofosbuvir/ledipasvir with ribavirin for 8 weeks. The treatment difference between the 8-week treatment of sofosbuvir/ledipasvir and 12-week treatment of sofosbuvir/ledipasvir was –2.3% (97.5% CI –7.2% to 2.5%). Among subjects with a baseline HCV RNA less than 6 million IU/mL, the SVR12 was 97% (119/123) with 8-week treatment of

sofosbuvir/ledipasvir and 96% (126/131) with 12-week treatment of sofosbuvir/ledipasvir. Ribavirin was not shown to increase the SVR12 observed with sofosbuvir/ledipasvir. Three different studies reported the efficacy and the safety of sofosbuvir/ledipasvir used for 8 weeks of treatment in adolescents with chronic HCV infection. Eight weeks of treatment resulted in comparable efficacy and safety independently of HCV genotype.<sup>29–31</sup>

## 5.2 | Sofosbuvir and ribavirin

The combination of sofosbuvir and ribavirin is approved by US FDA and EMA for treatment of adolescents and children (3–17 years of age) with chronic HCV genotypes 2 or 3 infection. The recommended treatment duration is 12 weeks for genotype 2 and 24 weeks for genotype 3. This treatment combination had a pivotal role for treatment of HCV genotypes 2 or 3 infection when no alternative regimens were available.<sup>32</sup> Ribavirin has been associated with haemolytic anaemia and is teratogenic. Sofosbuvir and ribavirin is no more recommended for treatment of adults and will not be included among the preferred treatment regimens for children. Despite that, it is opinion of this panel that if no alternatives are available and deferral of treatment is not an option, this combination can be used. A Phase II-III, open-label, multicentre, multi-cohort, single-arm study evaluated the safety and the efficacy of sofosbuvir and ribavirin given to children aged between 3 and 17 years for 12 weeks for genotype 2 infection and for 24 weeks for genotype 3 infection. The results of the trial are reported as Supplemental Digital Content.<sup>33,34</sup>

## 5.3 | Elbasvir/grazoprevir

The fixed-dose combination of elbasvir (an NS5A inhibitor)/grazoprevir (an NS3/4 inhibitor) has been approved by the US FDA and EMA for the treatment of adolescents (12–17 years) or children weighing at least 30 kg. Treatment duration is 12 weeks for all patients but for those with genotype 1a infection, treatment-naïve or experienced (interferon) with baseline NS5A polymorphisms and those who are treatment-experienced (interferon) with genotype 4 infection who should be treated for 16 weeks with ribavirin. The recommended daily dose of elbasvir/grazoprevir is 50/100 mg in a single tablet taken orally once daily with or without food once a day. To determine duration of therapy, all patients with HCV genotype 1A should be tested for HCV NS5 polymorphisms before initiating treatment.

A Phase IIb, open-label, multicentre, multi-cohort study evaluated the safety and the efficacy of elbasvir/grazoprevir. Elbasvir and grazoprevir were used as an



all-oral, fixed-dose combination to children with chronic HCV genotype 1 or 4 infection aged between three and 17 years. The standard duration of treatment was 12 weeks for all children.

### 5.3.1 | Adolescents

Twenty-two adolescents (11 female; 50%), with HCV infection were treated with the adult dosing (elbasvir 50 mg, grazoprevir 100 mg daily, orally without regard for food) provided as one fixed-dose combination 50/100-mg tablet. Dosing was initiated in a mini cohort of seven participants. The adult dosing resulted in comparable plasma exposures in adolescents than those found in clinical trials in adults. The mean age was 14.1 years (standard deviation 1.9). HCV genotype 1a, 1b and 4b were in 16 (73%), 5 (22%), and 1 (64.5%). No patient had evidence of Child-Pugh class B/C cirrhosis and/or decompensated liver disease. The SVR12 rate among all subjects was 100% overall. The treatment was well tolerated. The most reported adverse events were headache (13% of patients), nausea (9.5%) and fatigue (4.5%). One serious adverse event was reported (fractured fingertip) that was considered unrelated to treatment.

Although this combination is not approved for children 3–11 years of age, all the children in this age cohort completed the trial and achieved SVR12.<sup>35</sup>

## 6 | GOAL AND ENDPOINT OF HCV THERAPY

The goal of therapy in children is to cure HCV infection, to prevent progression of HCV-related liver disease and its complications including the impact of this chronic infection on the quality of life of children, adolescents and their families. Furthermore, successful treatment prevents onward transmission of HCV, ensures equity in access to treatment and removes the stigma associated with HCV-infection in adolescents and children. The endpoint of therapy with DAA in children is undetectable HCV RNA in blood by a sensitive assay with a lower limit of detection of 15 IU/mL 12 weeks after the end of treatment (SVR12). Long-term follow-up studies in adults and children have shown that an SVR12 corresponds to the cure of HCV infection in the majority of cases.<sup>36,37</sup>

### 6.1 | RECOMMENDATION

1. *The goal of therapy in children with hepatitis C is to cure the infection and thereby prevent the progression of HCV-related liver disease and its complications (8,9,9,9,9,9,9).*

## 7 | PRETHERAPEUTIC ASSESSMENT

Testing for hepatitis B virus infection (HBs antigen, anti-HBc antibodies and anti-HBs antibodies) is indicated before treatment for all adolescents and children with chronic hepatitis C. Various studies have described hepatitis B reactivation after a successful clearance of hepatitis C using DAA therapy in patients with HCV/hepatitis B virus coinfection. In line with adult guidelines,<sup>38,39</sup> patients with detectable hepatitis B-viraemia should be assessed for whether they fulfill the standard criteria for hepatitis B virus treatment. Patients who are HBs antigen-positive should either receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post-anti-HCV therapy and be monitored monthly if hepatitis B virus treatment is stopped or warrant careful monitoring for reactivation.

Cirrhosis is uncommon in adolescents and children with chronic infection and unless it is associated with hepatic decompensation it has no bearing on the treatment strategy. Noninvasive tests for assessment of liver fibrosis are not fully validated in children. The decision of performing a liver biopsy should be evaluated on a case-by-case basis. Diagnosing advanced liver disease (bridging fibrosis and cirrhosis) is critical as it could impact the post-treatment prognosis raising the indication for surveillance for hepatocellular carcinoma.<sup>1</sup>

### 7.1 | HCV RNA quantification, genotyping, and assessment of baseline resistance-associated substitutions

HCV RNA quantification with a reliable and sensitive assay, must be available before initiating therapy. In the majority of cases, pan-genotypic HCV drug regimens can be used to treat without identifying HCV genotype and subtype. This approach simplifies therapy, especially in low- and lower-middle-income countries. Genotyping should be ascertained in patients from countries where less treatment-susceptible HCV subtypes are known to be prevalent. If a patient is cirrhotic, has received previous treatment, or is infected with HCV genotype 3, the duration may vary for the currently available drug regimens. Assessment of baseline resistance-associated substitutions is needed before starting treatment for genotype 1a-infected patients being considered for elbasvir/grazoprevir.

### 7.2 | Assessment of drug-drug interactions before starting therapy

A comprehensive listing of drug-drug interactions is available at [www.hep-druginteractions.org](http://www.hep-druginteractions.org) and additional information on individual DAA could be found in

the summary of product characteristics. Before starting treatment with a DAA, the drug history of the patients should be taken including over-the-counter drugs, herbal and vitamin preparations and, for adolescents, any illicit drugs.

## 8 | CONTRAINDICATIONS TO THERAPY

Treatment regimens comprising an HCV protease inhibitor (*-previr*), are contraindicated in patients with decompensated cirrhosis. Drug-drug interactions should be carefully evaluated before treatment. Some cytochrome P450/P-gp-inducing agents (such as phenytoin, phenobarbital and carbamazepine) can significantly reduce the concentrations of HCV DAA and contraindicate treatment.

## 9 | INDICATIONS FOR TREATMENT: WHO SHOULD BE TREATED?

Endorsing previous recommendations, all treatment-naïve and treatment-experienced adolescents and children with chronic HCV infection should be considered for treatment. The new paradigm that we propose, given the high efficacy and the excellent safety profile of the DAA, is that treatment is indicated in all children and adolescents to clear the infection and prevent the possible development of liver disease.

Treatment is urgent in the few patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), patients with extrahepatic manifestations, patients with HCV recurrence after liver transplantation and patients with comorbidities who are at risk of a rapid progression of liver disease. Treatment should be prioritized in adolescents at risk of horizontal transmission of the infection. Liver biopsy for obtaining liver tissue for histopathologic examination is not routinely indicated in children with chronic HCV infection but should be considered on a case-by-case basis.

HCV treatment may improve the quality of life in adults with chronic HCV infection and remove the stigma of being HCV-positive. Three studies have also examined the impact of DAA treatment on the quality of life of adolescents and children and their caregivers before, during, and after treatment.<sup>40–42</sup> Overall, in all three studies, there was an improvement in health-related quality of life scores after achieving SVR12. Data is available from one cost-effectiveness mathematical modeling study to assess the cost effectiveness of treating a hypothetical cohort of 30 000 adolescents with chronic HCV compared with deferring treatment until adulthood from a societal perspective. Results suggest that treatment is cost-effective compared with

deferred treatment especially if treatment is initiated with the currently available pan-genotypic regimens.<sup>43</sup>

Few HCV-infected children aged 3–5 years have been included in studies on the use of DAA. In the sofosbuvir/velpatasvir trial, SVR12 was 83% (34/41 children). This is one of the lowest efficacy rates ever reported in pediatric studies on the use of DAA for children. In the sofosbuvir/velpatasvir trial as well as in the other studies exploring the efficacy and safety of DAA regimens in young children, non-adherence and early treatment discontinuations due to non-virological reasons were the main causes for treatment failure. Difficulty in taking the oral medication by young children seems to be a major limitation to the treatment efficacy. The ability of children to swallow the medications is seen as a requirement for initiating therapy, so treatment may be deferred in the youngest children given the typical absence of any urgency and the impact of noncompliance with treatment administration on the efficacy.

## 9.1 | RECOMMENDATIONS

1. *We recommend treatment using DAA regimens for all treatment-naïve and treatment-experienced children ( $\geq 3$  years of age) with chronic hepatitis C (8,9,9,9,9,9,9,9).*
2. *We recommend that swallowability assessment is done before starting treatment and treatment should be postponed for children who are unable to swallow the locally available drug formulation (7,7,8,8,8,8,9,9).*

## 10 | WHICH DRUGS?

Pangenotypic DAA-based regimens (including sofosbuvir/velpatasvir, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir) are the recommended options in HCV-infected adults. Both pangenotypic and genotype specific DAA-based regimens are easy to use, efficacious and safe in adolescents and children.<sup>32</sup> The panel recognizes that the major difficulty for treatment of adolescents and children is in the availability of the drugs and of the age-appropriate formulations and therefore, the utilization of any of the combinations is recommended. Given the impact of duration of treatment on the possible compliance of the patient and the safety profile of ribavirin-based regimens when more than one alternative is available, the regimen with the shortest duration, and ribavirin-free should be chosen. To simplify the treatment and avoid the need of genotypes and/or baseline resistance-associated substitutions assessment, pangenotypic regimens are preferable when available. Sofosbuvir/velpatasvir/voxilaprevir is generally considered a second line-treatment for patients who have failed a previous regimen.

## 10.1 | RECOMMENDATION

1. *Pangenotypic and genotype-specific DAA-based regimens are equally recommended for treatment of adolescents and children (7,7,8,9,9,9,9,9).*
2. *Pangenotypic, ribavirin-free and regimens with the shortest treatment duration are preferable when alternatives are available (7,8,8,9,9,9,9,9).*

## 11 | Treatment of chronic HCV infection in adolescents and children without cirrhosis or with compensated cirrhosis

The majority of the adolescents and children with chronic hepatitis C included in the phase 2–3 studies on the use of DAA were non-cirrhotic or diagnosed with compensated cirrhosis. The few real-life studies confirm the high efficacy and the optimal safety profile of DAA in adolescents and children without cirrhosis or with compensated cirrhosis.

### 11.1 | RECOMMENDATION

*We recommend the following fixed dose combination regimens for adolescents and children without cirrhosis or with compensated cirrhosis:*

1. *Glecaprevir/pibrentasvir administered once daily with food.*
2. *Sofosbuvir/velpatasvir administered once daily.*
3. *Sofosbuvir/ledipasvir administered once daily.*

*(8,8,9,9,9,9,9,9).*

Treatment duration according to the presence or absence of cirrhosis, regimen, genotype and treatment history is described in Table 2. Table 3 summarizes the treatment dosages and formulations.

## 12 | Treatment of chronic HCV infection in adolescents and children in resource-limited settings

In countries with the highest burden of HCV in children, generic medicines are available for use in the adult population but the high costs of producing pediatric formulations can be a barrier to scale-up for the younger age groups particularly in the absence of informative epidemiological data. In these settings, a less expensive and more widely available pangenotypic combination of sofosbuvir plus daclatasvir with

or without ribavirin can be used for adolescents and children. The combination of sofosbuvir plus daclatasvir is not approved by US FDA and EMA for use in adolescents and children. The two drugs are produced by two independent originator companies that are no longer collaborating.

Recently, in June 2022, the World Health Organization updated the recommendations on treatment to include adolescents and children down to 3 years.<sup>12</sup> The World Health Organization recognized that sofosbuvir plus daclatasvir is the most appropriate pangenotypic option to optimize access for adolescents and children in low- and lower-middle-income countries and aligned the existing recommended pangenotypic DAA regimens (sofosbuvir plus daclatasvir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) for adults, to those for adolescents and children. This alignment is expected to simplify procurement, promote access to treatment among children in low- and lower-middle-income countries and contribute to global efforts to eliminate the disease.<sup>32,44,45</sup>

Safety and efficacy of sofosbuvir plus daclatasvir in adolescents and children have been reported in multiple observational studies. A recent modeling PK study supported the use of the adult dose of sofosbuvir plus daclatasvir (400 mg/60 mg) in children at least down to 25 kg, and a half dose (200 mg/30 mg) for those weighing 14–25 kg, potentially down even to 10 kg.<sup>23,24</sup>

### 12.1 | RECOMMENDATIONS

*In alignment with the World Health Organization, we recommend the following treatments for adolescents and children without cirrhosis or with compensated cirrhosis in resource-limited settings:*

1. *The fixed-dose combination of glecaprevir/pibrentasvir administered once daily with food.*
2. *The fixed-dose combination of sofosbuvir/velpatasvir administered once daily.*
3. *The combination of sofosbuvir plus daclatasvir administered once daily.*

*(6,8,8,9,9,9,9,9).*

## 13 | Treatment of chronic HCV infection in adolescents and children with decompensated cirrhosis

Across the different studies on the use of DAA for adolescents and children with chronic HCV infection, few patients have been included with compensated

**TABLE 2** Treatment duration in patients without cirrhosis or with compensated cirrhosis according to the regimen and genotype.

Activity	Product	Genotype	Cirrhosis status	Treatment	Weeks
Regimens with pangenotypic activity	Glecaprevir/pibrentasvir	All genotypes	No cirrhosis and compensated cirrhosis	Naïve	8
		1, 2, 4–6	No cirrhosis	Experienced	8
	Sofosbuvir/velpatasvir	3	Compensated cirrhosis	Experienced	12
		All genotypes	No cirrhosis and compensated cirrhosis	Experienced	16
Regimens with genotype-specific activity	Sofosbuvir/velpatasvir/voxilaprevir	All genotypes	No cirrhosis and compensated cirrhosis	Naïve and experienced	12
		All genotypes	No cirrhosis	Naïve	8
	Sofosbuvir + daclatasvir <sup>b</sup>	1, 4, 5, 6	Compensated cirrhosis	Naïve and experienced	12
			No cirrhosis and compensated cirrhosis	Experienced	12
Sofosbuvir/ledipasvir	1, 4	No cirrhosis	Naïve and experienced	12 or 8 <sup>a</sup>	
		Compensated cirrhosis	Experienced	24 or 12 with ribavirin	
Elbasvir/grazoprevir	1, 4	No cirrhosis and compensated cirrhosis	Naïve and experienced	12 or 16 <sup>c</sup>	
		No cirrhosis and compensated cirrhosis	Naïve and experienced	12 or 16 <sup>c</sup>	

<sup>a</sup>Sofosbuvir/ledipasvir for 8 weeks may be considered in previously untreated genotype 1-infected patients with HCV viremia levels < 600 000 IU/mL.

<sup>b</sup>Not approved by European Medicines Agency and United States Food and Drug Administration.

<sup>c</sup>Genotype 1a infection, treatment-naïve or experienced (interferon) with baseline NS5A polymorphisms and genotype four infection, treatment-experienced (interferon) should be treated with elbasvir/grazoprevir for 16 weeks with ribavirin.

**TABLE 3** Dosage of the different regimens according to body weight.

Product	Doses by weight/age
Glecaprevir/pibrentasvir	≥45 kg or 12–17 years: 300/120 mg once a day
	30–< 45 kg: 250/100 mg once a day
	20–< 30 kg: 200/80 mg once a day
	12–< 20 kg: 150/60 mg once a day
Sofosbuvir/velpatasvir	≥30 kg: 400/100 mg once a day
	17–<30 kg: 200/50 mg once a day
	<17 kg: 150/37.5 mg once a day
Sofosbuvir/velpatasvir/voxilaprevir	≥30 kg (12 years): 400/100/100 mg once a day
Sofosbuvir + daclatasvir	>26 kg 400/60 mg once a day
	14–25 kg 200/30 mg once a day
Sofosbuvir/ledipasvir	≥35 kg: 400/90 mg once a day
	17–<35 kg: 200/45 mg once a day
	<17 kg: 150/33.75 mg once a day
Elbasvir/grazoprevir	≥30 kg or 12–17 years: 50/100 mg once a day

cirrhosis and none with decompensated cirrhosis. Development of cirrhosis is described in 2–5% of adolescents and children with the infection.<sup>7</sup> In the unlikely event of decompensated cirrhosis patients younger than 18 years of age should be treated in experienced pediatric liver centers. In the absence of pediatric evidence treatment should follow the adult guidelines.<sup>38,39</sup>

DAA-based pangenotypic regimens are the most suitable options for patients with decompensated (Child-Pugh B or C) cirrhosis. Protease inhibitor-containing regimens are contraindicated because of higher risk of toxicity. Thus, the fixed-dose combination of sofosbuvir/velpatasvir with weight-based ribavirin is the treatment of choice for adult patients with decompensated (Child-Pugh B or C) cirrhosis. Close monitoring of patients with decompensated cirrhosis during therapy is required.

### 13.1 | RECOMMENDATIONS

1. *We recommend that adolescents and children with decompensated cirrhosis are treated in experienced pediatric liver centers (9,9,9,9,9,9,9).*
2. *In the absence of pediatric evidence, treatment should follow the adult guidelines (5,9,9,9,9,9,9).*

## 14 | RETREATMENT OF DAA FAILURES

Failure to achieve SVR12 in adolescents and children is rare. Retreatment should be guided by the knowledge of the drugs administered in previous treatment course and/or should be based on RAS testing. Studies in adults demonstrated that in patients previously exposed to an NS5A inhibitor, glecaprevir/pibrentasvir does not achieve optimal SVR rates while sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is effective in adults exposed to protease and/or NS5A inhibitors. The triple combinations of sofosbuvir/velpatasvir/voxilaprevir and of sofosbuvir plus glecaprevir/pibrentasvir with the addition of weight-based ribavirin and with the extended treatment duration of 16 to 24 weeks have been used for retreatment of difficult-to-cure adults, such as those with complex NS5A RAS patterns and/or those with advanced liver disease. The opinion of the panel is that the combination of sofosbuvir/velpatasvir/voxilaprevir should not be used as a first line treatment but should be reserved as the second line for the few children who fail a DAA combination.

## 15 | TREATMENT OF SPECIAL GROUPS

Little data are available on children with comorbidities.<sup>22</sup> Treatment with DAA in adults with co-infections (hepatitis B virus, human immunodeficiency virus), renal impairment, non-hepatic solid organ transplant recipients, before and after liver transplantation, active drug users, patients with haemoglobinopathies and coagulation disorders and non-sustained virological responders to DAA demonstrated high efficacy. Adults with decompensated cirrhosis without hepatocellular carcinoma awaiting liver are treated as soon as possible to complete a full treatment course before transplantation.

## 16 | MONITORING OF TREATMENT WITH DAA IN CHILDREN WITH CHRONIC HEPATITIS C

DAA regimens are well tolerated in adults, adolescents and children. The adverse events reported both in registration and real world studies were mild and mostly unrelated to treatment.<sup>11</sup> Overall, based on the adult suggestions, a reasonable approach seems to evaluate adolescents and children clinically and with laboratory tests at baseline. Nowadays, clinical side effects related to treatment can be periodically assessed through telehealth technologies. Treatment efficacy could be evaluated by measuring HCV RNA levels

### Goal and endpoint of HCV therapy

The goal of therapy in children with hepatitis C is to cure the infection and thereby prevent the progression of HCV-related liver disease and its complications

### Indications for treatment: who should be treated?

- We recommend treatment using DAA regimens for all treatment-naïve and treatment-experienced children ( $\geq 3$  years of age) with chronic hepatitis C
- We recommend that swallowability assessment is done before starting treatment and treatment should be postponed for children who are unable to swallow the locally available drug formulation

### Which drugs?

- pangenotypic and genotype-specific DAA-based regimens are equally recommended for treatment of adolescents and children
- pangenotypic, ribavirin-free and regimens with the shortest treatment duration are preferable when alternatives are available

### Treatment of chronic HCV infection in adolescents and children without cirrhosis or with compensated cirrhosis

We recommend the following fixed dose combination regimens for adolescents and children without cirrhosis or with compensated cirrhosis:

- glecaprevir/pibrentasvir administered once daily with food
- sofosbuvir/velpatasvir administered once daily
- sofosbuvir/ledipasvir administered once daily

### Treatment of chronic HCV infection in adolescents and children in resource-limited settings

In alignment with the WHO, we recommend the following treatments for adolescents and children without cirrhosis or with compensated cirrhosis in resource-limited settings:

- the fixed-dose combination of glecaprevir/pibrentasvir administered once daily with food
- the fixed-dose combination of sofosbuvir/velpatasvir administered once daily
- the combination of sofosbuvir plus daclatasvir administered once daily

### Treatment of chronic HCV infection in adolescents and children with decompensated cirrhosis

- We recommend that adolescents and children with decompensated cirrhosis are treated in experienced paediatric liver centres
- in the absence of paediatric evidence, treatment should follow the adult guidelines

**FIGURE 1** Summary of the recommendations.

with a highly sensitive assay (with a lower limit of detection  $\leq 15$  IU/mL) 12 weeks after the end of therapy. It is crucial to counsel families about the importance of adherence with the treatment prescription and plan additional visits when risk factors for non-adherence are identified or suspected.

It should be noted that for sofosbuvir-based regimens renal functions should be checked before and during treatment. When renal functions, as measured by calculated glomerular filtration rate is low ( $<30$  mL/min/1.73 m<sup>2</sup>), the use of sofosbuvir is generally not recommended. When normal calculated glomerular filtration rate is reduced but higher than 30 mL/min/1.73 m<sup>2</sup> renal function should be checked monthly. As the use of ribavirin can be associated with anaemia, hemoglobin levels should be assessed at weeks two and four of therapy and at 4–8-week intervals thereafter. Adequate counseling and an effective form of contraception are needed during treatment and for a period of 6 months after the treatment has concluded for women of child-bearing potential and/or their male partners. Potential drug-drug interactions should be monitored in the few adolescents taking other necessary medication particularly those with human immunodeficiency virus co-infection.

The availability of the age-appropriate formulations is still a major global concern. Recent evidence suggests that tablet manipulation (halving and crushing) does not impact the safety and effectiveness of HCV DAA.<sup>46</sup>

## 17 | CONCLUSIONS

With the advent of DAA and prospective of increasing numbers of cured HCV patients, the World Health Organization global health sector strategy on viral hepatitis 2016–2021 defined targets and actions for countries to achieve the goal of eliminating hepatitis C as a major public health threat by 2030.<sup>47</sup> Achieving the elimination goals, however, requires a mass scale-up of testing and treatment in both adults and children particularly in the settings with the highest burden of disease, which are mostly the low-income ones Figure 1.

The present position paper advocates treatment of adolescents and children with chronic HCV infection and is directed to healthcare systems to recognize the importance of treating this special group of patients and including them in national strategies to achieve the 2030 elimination goal.

## ESPGHAN DISCLAIMER

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment are at the discretion of physicians.

## CONFLICTS OF INTEREST STATEMENT

Giuseppe Indolfi: consultancy Mirum, Albireo, Kedrion Pharma. Regino P. Gonzalez-Peralta: grants Gilead, Merck, Abbvie. The remaining authors declare no conflict of interest.

## REFERENCES

- Indolfi G, Hierro L, Dezsofi A, et al. Treatment of chronic hepatitis C virus infection in children: A position paper by the hepatology committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):505-515.
- Schmelzer J, Dugan E, Blach S, et al. Global prevalence of hepatitis C virus in children in 2018: a modelling study. *Lancet Gastroenterol Hepatol.* 2020;5(4):374-392.
- Centers for Disease Control and Prevention (CDC). Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. *MMWR Morb Mortal Wkly Rep.* 2011;60(17):537-541.
- Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol.* 2019;4(6):477-487.
- Bortolotti F, Verucchi G, Cammà C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology.* 2008;134(7):1900-1907.
- Stinco M, Bartolini E, Veronese P, et al. Epidemiology and natural history of Childhood-Acquired chronic hepatitis C: A Single-Center Long-Term prospective study. *J Pediatr Gastroenterol Nutr.* 2022;75(2):e2-e7.
- Indolfi G, Guido M, Azzari C, Resti M. Histopathology of hepatitis C in children, a systematic review: implications for treatment. *Expert Rev Anti Infect Ther.* 2015;13(10):1225-1235.
- Indolfi G, Bartolini E, Olivito B, Azzari C, Resti M. Autoimmunity and extrahepatic manifestations in treatment-naïve children with chronic hepatitis C virus infection. *Clin Dev Immunol.* 2012;2012:1-4.
- Modin L, Arshad A, Wilkes B, et al. Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol.* 2019;70(3):371-378.
- Indolfi G, Serranti D, Resti M. Direct-acting antivirals for children and adolescents with chronic hepatitis C. *Lancet Child Adol Health.* 2018;2(4):298-304.
- Indolfi G, Giometto S, Serranti D, et al. Systematic review with meta-analysis: the efficacy and safety of direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection. *Aliment Pharmacol Ther.* 2020;52(7):1125-1133.
- Indolfi G, Easterbrook P, Giometto S, et al. Efficacy and safety of DAA in children and adolescents with chronic HCV infection: a systematic review and meta-analysis. *Liver Int.* 2024. Published online January 31, 2024. doi:10.1111/liv.15827
- Jonas MM, Squires RH, Rhee SM, et al. Pharmacokinetics, safety, and efficacy of Glecaprevir/Pibrentasvir in adolescents with chronic hepatitis C virus: part 1 of the DORA study. *Hepatology.* 2019;71(2):456-462.
- Jonas MM, Rhee S, Kelly DA, et al. Pharmacokinetics, safety, and efficacy of Glecaprevir/Pibrentasvir in children with chronic HCV: part 2 of the DORA study. *Hepatology.* 2021;74(1):19-27.
- Jonas M, Romero R, Sokal E, et al. Safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) in pediatric patients 6 to 18 years old with chronic hepatitis C (CHC) infection. *Gut.* 2020;69(suppl 2):A74.
- Pokorska-Śpiewak M, Talarek E, Aniszewska M, et al. Efficacy and safety of treatment with sofosbuvir/velpatasvir in patients aged 6 to 18 years with chronic hepatitis C—results of the PANDAA-PED study. *Liver Int.* 2023;43(9):1871-1878.
- Indolfi G, Kelly D, Nebbia G, et al. Sofosbuvir-velpatasvir-voxilaprevir in adolescents 12 to 17 years old with HCV infection. *Hepatology.* 2022;76(2):445-455.
- WHO Updated recommendations on treatment of adolescents and children with chronic HCV infection, and HCV simplified service delivery and diagnostics. *World Health Organization; Geneva: World Health Organization* 2023.
- El-Sayed M, Hassany M, Asem N. A pilot study for safety and efficacy of 12 weeks sofosbuvir plus daclatasvir with or without ribavirin in Egyptian adolescents with chronic hepatitis C virus infection. *J Hepatol.* 2017;66(S1):S178.
- Yakoot M, El-Shabrawi MH, AbdElgawad MM, et al. Dual Sofosbuvir/Daclatasvir therapy in adolescent patients with chronic hepatitis C infection. *J Pediatr Gastroenterol Nutr.* 2018;67(1):86-89.
- Abdel Ghaffar TY, El Naghi S, Abdel Gawad M, et al. Safety and efficacy of combined sofosbuvir/daclatasvir treatment of children and adolescents with chronic hepatitis C genotype 4. *J Viral Hepatitis.* 2019;26(2):263-270.
- El-Sayed MH, Ebeid FSE, Zekri AR, et al. Ledipasvir-sofosbuvir in adolescents with chronic hepatitis C and hematological malignancies undergoing chemotherapy. *J Pediatr Gastroenterol Nutr.* 2022;74(5):626-630.
- Al-Nahari MM, Abbassi MM, Ebeid FS, Hassany M, El-Sayed MH, Farid SF. Pharmacokinetics of daclatasvir in Egyptian adolescents with genotype-4 HCV infection. *Antivir Ther.* 2020;25(2):101-110.
- Cressey TR, Abbassi M, Lallemand M, et al. Effective and safe daclatasvir drug exposures predicted in children using adult formulations. *Pediatr Infect Dis J.* 2021;40(12):1081-1086.
- Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12–17 years old with hepatitis C virus genotype 1 infection. *Hepatology.* 2017;66(2):371-378.
- Murray KF, Balistreri WF, Bansal S, et al. Safety and efficacy of Ledipasvir-Sofosbuvir with or without ribavirin for chronic hepatitis C in children ages 6 - 11. *Hepatology.* 2018;68(6):2158-2166.
- Schwarz KB, Rosenthal P, Murray KF, et al. Ledipasvir-Sofosbuvir for 12 weeks in children 3 to <6 years old with chronic hepatitis C. *Hepatology.* 2019;71(2):422-430.
- Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888.
- El-Khayat H, Kamal EM, Yakoot M, et al. Effectiveness of 8-week sofosbuvir/ledipasvir in the adolescent chronic hepatitis C-infected patients. *Eur J Gastroenterol Hepatol.* 2019;31(8):1004-1009.
- El-Sayed MH, Hassany M, El-Sayed Ebeid FS, et al. Ledipasvir/sofosbuvir for 8 weeks cures genotype 4 chronic hepatitis C in non-cirrhotic children and adolescents. *J Hepatol.* 2019;70(1):e221.
- Serranti D, Dodi I, Nicastro E, et al. Shortened 8-Week course of Sofosbuvir/Ledipasvir therapy in adolescents with chronic hepatitis C infection. *J Pediatr Gastroenterol Nutr.* 2019;69(5):595-598.
- Indolfi G, Thorne C, El Sayed MH, Giaquinto C, Gonzalez-Peralta RP. The challenge of treating children with hepatitis C virus infection. *J Pediatr Gastroenterol Nutr.* 2017;64(6):851-854.

33. Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12–17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology*. 2017;66(4):1102-1110.
34. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin therapy for children aged 3 to <12 years with hepatitis C virus genotype 2 or 3 infection. *Hepatology*. 2019;71(1):31-43.
35. Gonzalez-Peralta RP, Wirth S, Squires RH, et al. Elbasvir/grazoprevir in children aged 3-18 years with chronic HCV genotype 1 or 4 infection: a pharmacokinetic modeling study. *Hepatology Communications*. 2023;7(3):e0031.
36. Sarrazin C, Isakov V, Svarovskaia ES, et al. Late relapse versus hepatitis C virus reinfection in patients with sustained virologic response after Sofosbuvir-Based therapies. *Clin Infect Dis*. 2017;64(1):44-52.
37. Wen JW, Leung S, Rosenthal DH, et al. term follow-up of safety and efficacy of sofosbuvir-based treatments for chronic HCV infection in pediatric patients. *J Pediatr Gastroenterol Nutr*. 2022;74:669-670.
38. Pawlotsky JM, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C: final update of the series(\*). *J Hepatol*. 2020;73(5):1170-1218.
39. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. 2024. <http://www.hcvguidelines.org>
40. Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol*. 2008;23(2):226-230.
41. Rodrigue JR, Balistreri W, Haber B, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr*. 2009;48(3):341-347.
42. Younossi ZM, Stepanova M, Balistreri W, et al. Health-related quality of life in adolescent patients with hepatitis C genotype 1 treated with sofosbuvir and ledipasvir. *J Pediatr Gastroenterol Nutr*. 2018;66(1):112-116.
43. Nguyen J, Barritt AS, Jhaveri R. Cost effectiveness of early treatment with direct-acting antiviral therapy in adolescent patients with hepatitis C virus infection. *J Pediatr*. 2019;207:90-96.
44. El-Sayed MH, Indolfi G. Hepatitis C virus treatment in children: a challenge for hepatitis C virus elimination. *Semin Liver Dis*. 2020;40(3):213-224.
45. Indolfi G, Fischler B, Gonzalez-Peralta RP, et al. Comparison of recommendations for treatment of chronic hepatitis C virus infection in children and adolescents: a position paper of the federation of international societies of pediatric gastroenterology, hepatology, and nutrition. *J Pediatr Gastroenterol Nutr*. 2020;70(5):711-717.
46. Whelchel K, Zuckerman AD, Koren DE, Derrick C, Bouchard J, Chastain CA. Crushing and splitting direct-acting antivirals for hepatitis C virus treatment: a case series and literature review. *Open Forum Infect Dis*. 2021;8(11):ofab525.
47. WHO. *Global health sector strategy on viral hepatitis 2016-2021*. World Health Organization; 2016.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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