

# Pangenotypic Glecaprevir/Pibrentasvir Therapy for Chronic Hepatitis C in Children

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**Background:** The elimination of hepatitis C virus (HCV) infection as a public health threat is impossible to achieve without micro-elimination in children. Our study aimed to analyze the use of glecaprevir/pibrentasvir (GLE/PIB), one of the pangenotypic options recommended in children, which provides the shortest possible therapy duration.

**Methods:** All consecutive children treated with an 8-week GLE/PIB regimen for chronic HCV infection between 2022 and 2024, whose data were collected retrospectively, were included in the analysis.

**Results:** The study population consisted of 42 patients with a median age of 10.5 years, mostly girls (61.9%), divided into age ranges of 3–5 years, 6–11 years and 12–18 years, comprising 6, 16 and 20 patients, respectively. Obesity was diagnosed only in the oldest group in as many as 25% of the children. Other comorbidities were present in 2 patients—kidney disease and bronchial asthma. All children were treatment-naïve, and almost half of them (47.6%) were infected with genotype 1b. The advancement of liver

disease by noninvasive elastography was assessed in 36 children, with half of them showing no fibrosis. Antiviral therapy was completed in all patients as planned, and the cure rate in the per-protocol population was 100% (39/39). Three girls were considered lost to follow-up. Adverse events were rare and mild, occurring only in the oldest group.

**Conclusions:** Eight-week GLE/PIB therapy in children is well tolerated and highly effective in all age ranges regardless of gender. Its use in routine clinical practice will bring the ambitious goal of eliminating HCV worldwide a step closer.

**Key Words:** children, pangenotypic therapy, pediatric, glecaprevir/pibrentasvir

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P.M., Z.-M.D. and F.R. designed the study; M.J., K.Z., P.-Ś.M., M.A. and M.-S.E. collected the data; D.K. conducted the statistical analysis and prepared tables; P.M., Z.-M.D., D.K. and F.R. were responsible for data interpretation; P.M., Z.-M.D., D.K. and F.R. conducted the literature search; P.M., Z.-M.D., D.K. and F.R. prepared the manuscript; all authors revised and approved the final version of the manuscript.

This study was retrospective, non-interventional, and based on data collected in the national EpiTer-2 database. Therefore, it does not require the approval of the Ethics Committee. Due to the retrospective nature of the presented study, written consent by participants was not necessary. The patients' data were protected according to the European Union General Data Protection Regulation. Parents gave their consent to start antiviral treatment for their children under the age of 18 in accordance with the requirements of the National Health Fund's drug reimbursement program; for adolescents 16–18 years old, their consent for treatment in drug program was also obtained.

Due to the retrospective nature of the study, a waiver of consent was in effect. Data supporting the reported results can be provided upon request from the corresponding author.

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According to current estimates of the World Health Organization (WHO), about 50 million people worldwide are chronically infected with the hepatitis C virus (HCV), with about 1 million new infections reported annually.<sup>1</sup> Based on available data, it is estimated that of all those infected, between 3.5 and 5 million are children.<sup>2,3</sup> Although the prevalence of HCV infection in this age group is lower than in adults, and the associated morbidity and mortality are uncommon, the elimination of chronic hepatitis C as a public health threat, as targeted by the WHO, is impossible to achieve without micro-elimination in the pediatric population. In this instance, micro-elimination is understood as the elimination of HCV infection in one of the discrete populations, which is less costly and less complex than pursuing full-scale initiatives.

Among adolescents, the predominant route of HCV infection is intravenous drug use, and the ongoing opioid epidemic in recent years is increasing the prevalence of chronic hepatitis C in this age group.<sup>4</sup> The epidemic of opioid drug use is also responsible for the increasing proportion of HCV-infected women of childbearing age observed in recent years.<sup>5</sup> Since vertical transmission remains the main route of infection in the youngest child population, with a risk of about 5%, this translates into a growing possibility of infection in infants.<sup>5</sup> To reduce this risk, it is recommended to test women of reproductive age for HCV infection to enable treatment before conception, as data on the safety of direct-acting antiviral drugs (DAA) in pregnancy are insufficient.<sup>5–8</sup>

About 50–75% of newborns infected with HCV perinatally do not eliminate the virus spontaneously in the first years of life; therefore, if the presence of anti-HCV antibodies is detected after the 18th month of life, it is advisable to test for HCV ribonucleic acid (RNA).<sup>2</sup> This creates the possibility of starting DAA therapy in a child after the age of 3.<sup>9–12</sup> This limits the risk of developing chronic liver disease, which may be accompanied by developmental disorders in the child.<sup>13</sup> Therefore, if chronic HCV infection is confirmed, antiviral therapy should be considered not only to prevent the progression of liver disease but also to improve quality of life and social functioning.<sup>14,15</sup> Although pangenotypic DAA therapies have been used in HCV-infected adults for several years, their European registration in children has occurred recently.

The sofosbuvir/velpatasvir (SOF/VEL) combination was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for children 6 years old and older with chronic HCV infection in 2020, and in 2021, the agencies expanded its use to children 3 years of age and older.<sup>16</sup> The second pangenotypic regimen, glecaprevir/pibrentasvir (GLE/PIB), was approved by the FDA and EMA for adolescents 12–17 years old with chronic hepatitis C in 2019, and registration for children 3–11 years of age followed in 2021.<sup>17</sup> For this reason, the efficacy and safety of GLE/PIB therapy in clinical practice have been assessed so far in only 2 studies involving a total of 86 children with diverse demographic characteristics.<sup>17,18</sup>

To fill this gap, our study aimed to analyze the use of the pangenotypic option of GLE/PIB in the pediatric population with an assessment of safety and effectiveness by age and gender.

## MATERIALS AND METHODS

### Data Collection

Data were collected retrospectively through the online nationwide database Epiter-2-ped, a Polish project managed and supported by the Polish Society of Epidemiology and Physicians of Infectious Diseases. Parameters collected included demographic and clinical characteristics such as gender, age, body mass index (BMI), HCV genotype (GT), comorbidities, comedications, hepatitis B virus and human immunodeficiency virus coinfection, treatment characteristics and safety. Baseline laboratory variables, such as HCV RNA, albumin, bilirubin, platelets, creatinine, hemoglobin, international normalized ratio and alanine aminotransferase (ALT) activity, were also analyzed. The BMI-for-age percentile was calculated using WHO centile charts for children 0–5 years of age. For children older than 5 years old, OLA (girl) and OLAF (boy) centile charts were used to calculate BMI-for-age percentile. The charts were adjusted for gender.<sup>19–21</sup>

### Study Population

Forty-two pediatric patients, diagnosed and treated for hepatitis C from 2022 to 2024, were included in the study. Patients were divided into 3 groups based on the age at the time of treatment initiation: Group 1, 3–5, Group 2, 6–11 and Group 3, 12–18 years old.

### Assessment of Liver Disease Severity

The degree of hepatic fibrosis was assessed through non-invasive means using transient elastography. The METAVIR scale was applied to define the degree of fibrosis as F0–F4 based on the values in kilopascals, and European Association for the Study of the Liver (EASL) recommendations were used for conversion.

### HCV Treatment

Treatment was based on GLE/PIB administered for 8 weeks, and the formulation of the treatment was determined by the physician, based on product characteristics and the Polish Group of Experts for HCV recommendations.<sup>6</sup> Adolescents 12 years of age and older and children weighing at least 45 kg received treatment in tablet form at the dose of 3 tablets (300/120 mg) once daily. Children 3–12 years old and weighing 13–45 kg received a granular form at a dose based on body weight (150/60 mg for body weight  $\geq 12$  kg and  $< 20$  kg; 200/80 mg for body weight  $\geq 20$  kg and  $< 30$  kg; 250/100 mg for body weight  $\geq 30$  kg and  $< 45$  kg). Sustained virological response (SVR), defined as an undetectable HCV RNA at least 12 weeks after the end of treatment (EOT), was considered the effectiveness endpoint. Patients who 12 weeks after EOT had detectable viral load were considered virologically unresponsive.

Patients who were lost to follow-up (LTFU) were considered non-virologic failures.

### Treatment Safety

Safety data, including course of therapy, adverse events (AEs), severe AEs and deaths, were collected during treatment and 12 weeks after EOT.

### Ethics

The patients were not exposed to experimental interventions, and therapy was carried out within the framework of routine clinical practice, using approved drugs according to label and national and international guidelines.<sup>6</sup> Personal data protection principles were in effect; therefore, informed consent was not required. Due to the observational, non-interventional nature of the study with the use of marketed drugs, according to the local law in force at the time of the study (Pharmaceutical Law of 6 September 2001, Article 37), the approval of an ethics committee was not required. Parents gave their consent to start antiviral treatment for their children under the age of 18 in accordance with the requirements of the National Health Fund's drug reimbursement program; for adolescents 16–18 years old, their consent for treatment in the drug program was also obtained.

### Statistical Analysis

Continuous data with a Gaussian distribution were presented as mean and standard deviations, while data with a non-normal distribution were presented as median and interquartile ranges. Categorical data were expressed by number and percentage. All patients who initiated the treatment were included in the intent-to-treat analysis. Per-protocol analysis included only those who completed 12 weeks of post-treatment follow-up with an HCV RNA evaluation.

## RESULTS

### Baseline Characteristics of the Population

The analyzed population consisted of 42 Caucasian patients with a median age of 10.5 years, predominantly girls (61.9%) with the largest group of 12–18 years (Table 1).

Comorbidities were present in 2 patients—kidney disease and bronchial asthma. Based on the information gathered from patients and their caregivers, none of the children were drug addicted.

Genotype was investigated in over 95% of children, and nearly half of them were infected with GT1b (47.62%) (Table 2). Liver fibrosis was evaluated in 26 children, with none diagnosed with advanced fibrosis or cirrhosis. ALT activity was slightly elevated in the entire group, whereas other laboratory parameters assessed (creatinine, bilirubin, albumin, hemoglobin, platelets and international normalized ratio) remained in the normal range.

### Treatment Characteristics, its Effectiveness and Safety

All children were treatment-naïve. SVR12 was achieved by all patients (100%) in per-protocol analysis. Three children were considered LTFU; these were all girls, one 6–11 years of age and 2 from the oldest group. Despite several attempts to contact the LTFU patients and their parents by mobile phone, it was not possible to reach and bring them in for the SVR assessment.

Children in all age groups completed therapy as planned, with no cases of discontinuation. Any AE was reported by 8 children, all of which were mild and nonspecific, such as headache and fatigue (Table 3).

**TABLE 1.** Demographic and Clinical Characteristics of HCV-Infected Pediatric Patients Treated With Glecaprevir/Pibrentasvir for 8 Weeks According to Age

Parameters	All n = 42	3–5 yrs n = 6	6–11 yrs n = 16	12–18 yrs n = 20
Age, median (IQR) (yrs), (min–max)	10.5 (6–14), (3–18)	3.5 (3–4)	8 (6–9.5)	14.5 (13.5–17)
Gender, n (%) (female/male)	26/16 (61.9/38.1)	3/3 (50/50)	10/6 (62.5/37.5)	13/7 (65/35)
BMI, median (IQR)	17.21 (15.28–21.51)	15.22 (14.14–16.62)	15.54 (14.25–17.04)	21.48 (19.2–26.16)
BMI-for-age percentile, n (%)				
5–85 (reference)	31 (73.81)	5 (83.33)	14 (87.5)	12 (60)
85–95 (overweight)	5 (11.9)	1 (16.67)	2 (12.5)	2 (10)
>95 (obesity)	5 (11.9)	0	0	5 (25)
Any comorbidity, n (%)	2 (4.76)	1 (16.67)	0	1 (5)
Renal diseases	1 (2.38)	0	0	1 (5)
Bronchial asthma	1 (2.38)	1 (16.67)	0	0
Drug addiction, n (%)	0	0	0	0
Concomitant medications, n (%)	1 (2.38)	1 (16.67)	0	0

IQR, interquartile range; yrs, years.

**TABLE 2.** Characteristics of HCV Infection and Liver Fibrosis in Children Treated With Glecaprevir/Pibrentasvir for 8 Weeks, According to Age Groups

Parameters	All n = 42	3–5 yrs n = 6	6–11 yrs n = 16	12–18 yrs n = 20
HCV RNA, median (IQR) ( $\times 10^5$ IU/l)	4.99 (2.2–17)	2.59 (1.35–20.3)	7.54 (1.59–37.6)	4.83 (3.32–14.1)
HCV genotypes, n (%)				
1	1 (2.38)	0	0	1 (5)
1a	7 (16.67)	1 (16.67)	5 (31.25)	1 (5)
1b	20 (47.62)	3 (50)	6 (37.5)	11 (55)
2	0	0	0	0
3	7 (16.67)	0	2 (12.5)	5 (25)
4	5 (11.9)	1 (16.67)	3 (18.75)	1 (5)
Unknown	2 (4.76)	1 (16.67)	0 (0)	1 (5)
Fibrosis/stiffness, n (%)				
F0	18 (42.86)	0	8 (50)	10 (50)
F1	6 (14.29)	1 (16.67)	0	5 (25)
F2	2 (4.76)	1 (16.67)	1 (6.25)	0
F3	0	0	0	0
F4	0	0	0	0
No data	16 (38.09)	4 (66.66)	7 (43.75)	5 (25)

IQR, interquartile range; yrs, years.

**TABLE 3.** Treatment Characteristics and Safety of Antiviral Therapy in HCV-Infected Pediatric Patients Treated With Glecaprevir/Pibrentasvir for 8 Weeks According to Age Groups

Parameter	All n = 42	3–5 yrs n = 6	6–11 yrs n = 16	12–18 yrs n = 20
Treatment course, n (%)				
According to schedule	42 (100)	6 (100)	16 (100)	20 (100)
Therapy discontinuation	0	0	0	0
Patients with at least one AE, n (%)				
Any AE	4 (9.52)	0	0	4 (20)
Nausea	1 (2.38)	0	0	1 (5)
Fatigue	1 (2.38)	0	0	1 (5)
Pruritus	1 (2.38)	0	0	1 (5)
Headache	1 (2.38)	0	0	1 (5)

Yrs, years.

## DISCUSSION

The pediatric population gained the opportunity to be treated with DAA regimens much later than adults; hence, experience and knowledge of treatment effects are much more modest. However, there is no doubt that the implementation of the WHO's strategy to eliminate HCV infection is not possible without considering children. In a survey conducted in 2021 among 137 pediatric hepatologists from 38 countries, 60% of respondents

reported a strong preference for treating children 3 to <6 years, 81% for treating those 6 to <12 years and 95% for 12 to <18 years of age, respectively.<sup>22</sup> The main service delivery barriers in the pediatric HCV-infected population, identified by the respondents, even those from high-income countries, were the unavailability of pediatric DAA formulations (58%), followed by the lack of national policies and treatment guidelines (43%), the lack of treatment awareness among patients and parents (42%) and the

lack of DAA registration in pediatric populations (39%). The most preferred DAA treatment regimens in children, according to respondents, were the genotype-specific combination of sofosbuvir/ledipasvir and pangenotypic options: SOF/VEL and GLE/PIB.<sup>22</sup>

In our analysis, we focused on the GLE/PIB 8-week regimen in children 3–18 years old. The approval of this option in the pediatric population by EMA and FDA was based on the results of the DORA clinical trial. The first part of the study included children 12 to <18 years treated with the adult preparation, and the second part included children 3 to <12 years old receiving the pediatric formulation.<sup>9,10</sup>

In Poland, the pediatric form has been available in routine clinical practice since 2022, and is recommended for children over 3 years of age by WHO, international and national guidelines.<sup>6,15,23</sup> In this paper, we present the results of an 8-week GLE/PIB treatment in 42 HCV-infected children 3 to 18 years old, divided into 3 groups according to age at therapy initiation. Regardless of age, the treatment was highly effective, with a cure achieved by all patients in per-protocol analysis.

This is comparable to the efficacy documented in both parts of the DORA study. In the 6–9 age group, as well as the 12–18 age group, all children responded to treatment. In the other age ranges, 3 of 53 children were found to be nonresponders, with only 1 child experiencing virological failure, while 2 discontinued treatment at an early stage. Thus, the overall efficacy in the group of 127 patients, excluding the 2 children who discontinued treatment, was 99% (124/125). Worth noting is that the size of the children's population participating in the DORA multicenter clinical trial underway on several continents was only 3 times larger than the population from real-world practice evaluated in our study. It makes our analysis a significant contribution to the knowledge of hepatitis C therapy with the GLE/PIB regimen in the pediatric population. The scarcity of studies evaluating this therapeutic option in children is further underlined by the fact that a meta-analysis of 49 clinical and observational studies evaluating DAA therapies in a pediatric population of 2484 patients, for GLE/PIB, did not include other than both parts of the DORA trial.<sup>23</sup>

To the best of our knowledge, the current study is 1 of 3 real-world experience (RWE) reports of GLE/PIB therapy in the pediatric population. The material published so far covers a relatively small group of children, very diverse in terms of age and ethnicity, including a small group of children constituting a pilot study of the currently presented results.<sup>17,18,24</sup> A prospective Japanese study carried out in 2019 involved 13 pediatric centers treating 25 children 12–17 years old, mainly (96%) for 8 weeks.<sup>18</sup> Virological response was achieved in 24 children; 1 nonresponder was treatment-naïve infected with GT2a. Interestingly, this patient received GLE/PIB retherapy for 12 weeks with sustained viral eradication.

The RWE population of Italian children treated with the GLE/PIB between 2020 and 2023 was larger, with 61 patients, and included a wider age range of 3–18 years.<sup>17</sup> All children participating in this multicenter prospective study were treated with a weight-based dose (up to 300/120 mg) of GLE/PIB once daily for 8 weeks. SVR12 was achieved by 60/61 patients (98.4%). One patient died because of an oncological illness while on treatment. The most recent published RWE analysis is a retrospective single-center study also from Italy. However, only 1 child was of Italian origin, while the others were of Moldovan, Albanian, Romanian or Pakistani origin.<sup>25</sup> A case series of 6 patients 3 to 12 years old treated with the 8-week regimen between 2023 and 2024 documented a 100% SVR, confirming our findings on the effectiveness of the GLE/PIB regimen.

The above-cited studies also confirm the favorable safety profile shown in our analysis. No serious side effects were reported in both parts of the DORA study, and although the percentages of any side effects were 87% and 71%, respectively, they were mild and transient, being the reason for treatment discontinuation in only one case of the previously described rash. Among them, the most common AEs with frequency exceeding 10% were vomiting, headache, diarrhea, nasopharyngitis, upper respiratory tract infection, fatigue, oropharyngeal pain and pyrexia.<sup>9,10</sup>

A much lower percentage of AEs was reported in the RWE studies conducted in Japan and Italy, with prevalence of 24% and 13%, respectively.<sup>17,18</sup> The most common AEs in the prospective Italian study were headache, weakness, abdominal pain and diarrhea. In the Japanese pediatric population, clinical side effects occurred in only a few children and consisted of skin pruritus, rash, abdominal pain, nausea and zoster. Apart from the death of a child with oncological disease, which was unrelated to antiviral therapy, no serious AE was reported.<sup>17,18</sup> In our study, there were also no serious AEs, and transient symptoms of mild intensity, not affecting the treatment course, were reported only in the oldest age group in 4 adolescents, mainly girls (10%).

Our study observed the highest infection activity in the context of HCV viral load and ALT activity in the 6–11 age group. Such differences in viral load in different age groups were not observed in the DORA study, and other RWE studies did not evaluate this issue, so it is difficult to comment on this phenomenon. Therefore, this area requires further research conducted on a much larger pediatric population.

There is also no reference in the available reports to the BMI of treated children in the context of overweight or obesity in the available analyses of GLE/PIB, either clinical trials or RWE. In our study, the combined percentage of overweight and obese children was about 24%, with the highest numbers in adolescents. This phenomenon appears to be related not to HCV infection, but to the alarming trend of increasing rates of overweight and obesity in the pediatric population.<sup>26</sup>

Another finding is the observation of relatively highest values of liver fibrosis in the youngest children. This calls into question the value of assessing fibrosis by elastography in this population. Liver biopsy to obtain liver tissue for histopathological examination is not routinely indicated in children with chronic HCV infection, but should be considered on an individual basis. FibroScan ultrasound elastography enables noninvasive and painless examination of the liver and is increasingly used to assess liver fibrosis in children and adolescents. Its use has been described in pediatric populations with mixed liver diseases and also in more homogeneous populations, for example, biliary atresia. The technique undergoes constant improvement, and recently, a sensitivity and specificity of 81% and 91%, respectively, have been reported for liver fibrosis in children.<sup>27</sup> To eliminate difficulties related to atypical anatomical conditions in the pediatric group, a special S probe (S1, S2) was developed. In the population of the youngest children, especially those under 5 years of age, obtaining reliable measurements may be difficult. It has been shown that sedation and food intake may affect liver stiffness results. In addition, caution is advised when interpreting data if liver stiffness values in children seem unusually high—this may be the result of anatomical difficulties in performing the test (narrow intercostal spaces and inability to properly position the young patient).<sup>28</sup>

It should be noted that in the latest WHO guidelines, apart from the GLE/PIB regimen, which is the subject of this analysis, other pangenotypic options recommended for children are SOF/VEL and the combination of SOF with daclatasvir.<sup>15</sup> The

SOF+daclatasvir regimen is broadly used in low- and middle-income countries because it is widely available as inexpensive generic formulations and its high effectiveness has been documented in real-world analyses from countries with high HCV prevalence rates.<sup>23,29</sup>

Our study has limitations that we are aware of. These are primarily due to the retrospective nature of our analysis, which results in potential biases, possible gaps in the data collected, and underestimation of AEs. Data on drug dependence history were collected based on the declarations of children and their caregivers. We did not collect the data on the route of HCV infection. The size of the population we analyzed is small in absolute numbers, which can be read as a limitation of the analysis. However, comparing our study to available reports, the size of our population is a strength. The multicenter nature of our study should also be considered a strength, as well as the inclusion of all age groups of children for whom the GLE/PIB regimen is registered.

## CONCLUSIONS

Eight-week GLE/PIB therapy in children is highly effective, very safe and well tolerated. Its use in routine clinical practice will contribute to achieving the goals of the WHO HCV elimination strategy. Successful HCV eradication in the pediatric population will help reduce the infectious pool and bring us closer to achieving the ambitious goal of worldwide HCV elimination.

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