



EVALUATION OF DRUG USE IN HEPATITIS AND ASSOCIATED ADVERSE DRUG REACTIONS IN PEDIATRIC PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY.

Rahul Soni,^{1*} Shilpi Biswas², Ayush Jain³, Sanjeev Kumar Verma⁴, Ajay Kumar Patwa⁵,
Suyog Sindhu⁶, Narendra Kumar⁷

^{1*}MD PHARMACOLOGY, Junior Resident KGMU, Lucknow, UP, India,
dr.rahulsonipharmakgm@gmail.com

²MD PHARMACOLOGY, Junior Resident KGMU, Lucknow, UP, India,
drshilpibiswas.kgm@gmail.com

³MD, DNB PHARMACOLOGY, Assistant Professor, KGMU, Lucknow, UP, India,
ayushucms@gmail.com

⁴MD Padiatric, Professor, KGMU, Lucknow, UP, India, sanjeevkumar@kgmcindia.edu

⁵MD, DM MEDICINE, Professor, KGMU, Lucknow, UP, India, drajaymd12345@gmail.com

⁶MD PHARMACOLOGY, Associate Professor, KGMU, Lucknow, UP, India,
suyog@kgmcindia.edu

⁷MD PHARMACOLOGY, Professor, KGMU, Lucknow, UP, India, narenkgmu@gmail.com

***Corresponding author:** Dr. Rahul Soni
***Email:**dr.rahulsonipharmakgm@gmail.com

Abstract:

Background: Hepatitis in children is managed with antivirals, immunomodulators, and supportive therapies, all of which may cause adverse drug reactions (ADRs). Data on pediatric ADRs remain limited in India.

Objective: To evaluate the frequency, severity, onset, and causality of ADRs in pediatric hepatitis patients receiving direct-acting antivirals (DAAs), interferon, and supportive treatments at KGMU, Lucknow.

Methods: A prospective observational study was conducted from March 2024 to March 2025 in Pediatrics and Medicine OPD/IPD at KGMU. Sixty-two children (ages 1–18 years) diagnosed with hepatitis A, B, C, or autoimmune hepatitis were monitored for ADRs. Reactions were assessed using the WHO-UMC causality scale and Hartwig's severity scale.

Results: ADRs were reported in 14 patients (22.6% incidence). The most common ADRs included diarrhea (35.7%), fever (21.4%), abdominal pain (14.3%), fatigue (14.3%), itching (7.1%), and weight gain with hyperglycemia (7.1%). Most ADRs were mild (Level 1), while diarrhea was rated moderate (Level 2). Causality assessment showed 92.9% as *possible* and 7.1% as *probable*. Interferon-based regimens were associated with earlier onset of ADRs compared to DAAs.

Conclusion: ADRs were observed in about 25% of pediatric hepatitis patients, mainly as gastrointestinal symptoms. Most were mild, but some required management. DAAs showed a better safety profile than interferon-based treatments, emphasizing the need for routine monitoring and stronger pharmacovigilance in pediatric hepatology.

Keywords: Pediatric hepatitis, adverse drug reactions, DAAs, interferon, pharmacovigilance

Introduction

Hepatitis is a major cause of morbidity and mortality worldwide, with both infectious and non-infectious etiologies contributing to liver inflammation and damage. Among the viral hepatitis, types A, B, C, D, and E differ in transmission routes, disease severity, and chronicity. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are of particular concern, affecting more than 354 million people globally and accounting for the majority of cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths (WHO, 2022).

In pediatric populations, hepatitis has diverse etiologies including viral infections (HAV, HBV, HCV, HEV), autoimmune hepatitis (AIH), metabolic conditions such as Wilson's disease. Acute viral hepatitis, especially HAV and HEV, contributes substantially to pediatric acute liver failure in India, whereas chronic HBV and HCV infections drive long-term disease progression.

Preventive measures such as vaccination against hepatitis A, B, and E, combined with advances in antiviral therapy, have improved outcomes. Direct-acting antivirals (DAAs) have transformed HCV management with cure rates exceeding 90% and a favorable safety profile compared to interferon-based therapy. However, DAAs are not devoid of adverse events, with reports of gastrointestinal disturbances, fatigue, and rare hepatotoxicity. Interferon therapy, although once the mainstay, is associated with systemic adverse effects such as flu-like symptoms, cytopenia, neuropsychiatric disorders, and impaired growth in children.

Adverse drug reactions (ADRs) in children warrant special attention due to differences in pharmacokinetics, pharmacodynamics, and immature hepatic enzyme systems compared with adults. Pediatric patients are more vulnerable to drug toxicity, and ADRs can exacerbate underlying hepatic dysfunction, complicating treatment regimens and compliance. Recent pharmacovigilance data highlight that ADRs in pediatric hepatitis are underreported and poorly characterized in India.

Materials and Methods

Study Design and Setting

A prospective observational study was conducted in the Department of Pharmacology & Therapeutics in collaboration with the Departments of Pediatrics and Medicine at King George's Medical University (KGMU), Lucknow, India. The study was carried out over a period of one year (March 2024 – March 2025).

Study Population

The study population included pediatric patients aged 1–18 years who were clinically diagnosed with hepatitis and attending the outpatient (OPD) or inpatient (IPD) departments of Pediatrics and Medicine at KGMU.

Inclusion Criteria

Children (1–18 years) with a confirmed diagnosis of hepatitis (viral hepatitis A, B, C, E, or autoimmune hepatitis), Patients receiving treatment with direct-acting antivirals (DAAs), interferon-based regimens, or supportive therapies (e.g., corticosteroids, azathioprine, hepatoprotectives), Patients whose parents/guardians provided informed consent.

Exclusion Criteria

Patients with incomplete medical records, Children with co-morbid conditions unrelated to hepatitis that could confound ADR evaluation, Patients lost to follow-up before assessment of ADRs.

Sample Size

Total 302 patients were screened, 62 pediatric patients were enrolled in the study.

The study protocol was reviewed and approved by the Institutional Ethics Committee of KGMU, Lucknow (IEC) via letter no. **PGTSC IIA/P14 of KGMU** written informed consent was obtained from parents or legal guardians prior to enrollment, and assent was obtained from older children, wherever applicable.

Data Collection

For each patient, demographic details (age, sex, residence), clinical profile (type of hepatitis, comorbidities), and drug history were recorded. Prescribed medications were noted, and patients were followed prospectively for the occurrence of adverse drug reactions (ADRs).

Assessment of ADRs

Causality: Evaluated using the WHO–UMC causality assessment scale (certain, probable, possible, unlikely). **Severity:** Graded according to Hartwig severity assessment scale (mild, moderate, severe). **Time of Onset:** The duration between initiation of the suspected drug and appearance of the ADR was documented. **System Organ Classification (SOC):** ADRs were categorized according to WHO Adverse Reaction Terminology.

Statistical Analysis

Collected data were entered into Microsoft Excel and analyzed using SPSS version XX (please insert version from your thesis). Descriptive statistics were used to calculate frequencies, percentages, and means ($\pm$ SEM). Categorical data were expressed as proportions, while continuous variables were summarized using mean $\pm$ standard deviation.

Results

1. Demographic Profile

A prospective evaluation was conducted on 62 pediatric hepatitis patients who attended the outpatient (OPD) and inpatient (IPD) services of the Department of Pediatrics and General Medicine, King George Medical University (KGMU), Lucknow, between March 2024 and March 2025.

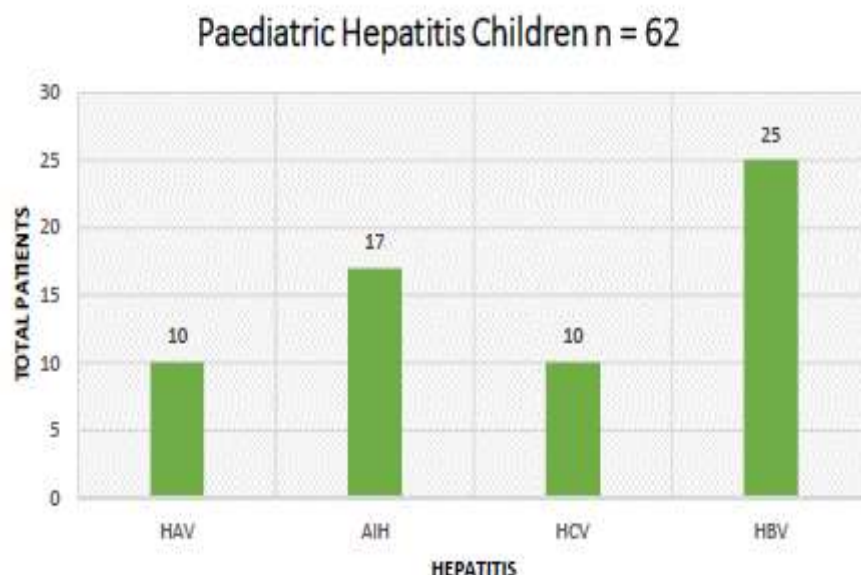
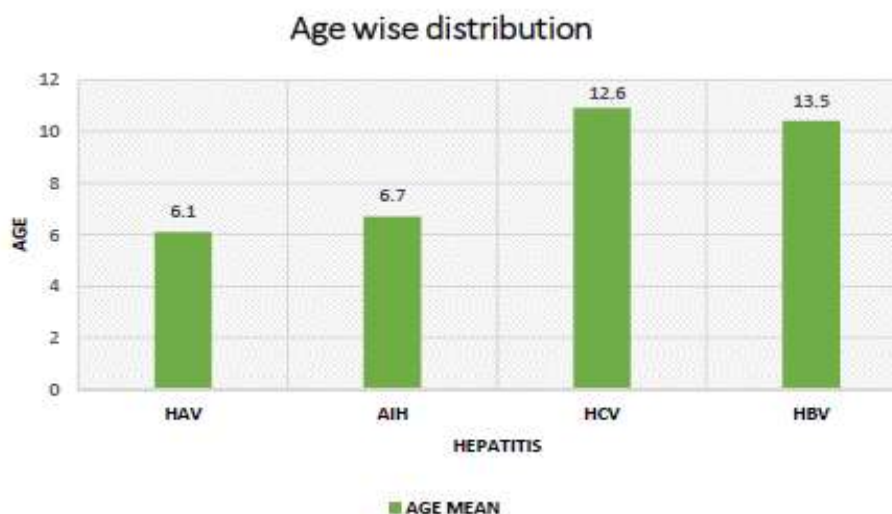


Figure 1: Sample size distribution amongst four groups comprising HAV(hepatitis A virus), AIH(Autoimmune hepatitis), HCV(Hepatitis C virus),and HBV(Hepatitis B virus)

2. Age wise Distribution



3. Common etiologies for Hepatitis in children

Hepatitis A virus (HAV) infection was primarily associated with contaminated food or water and poor hygiene. Autoimmune hepatitis (AIH) was linked to genetic predisposition and immune dysregulation. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infections were mainly attributed to vertical transmission, with HBV additionally related to household exposure and HCV associated with unsafe injections.

4. Clinical characteristics

Table 1 presents the clinical characteristics of pediatric patients diagnosed with HAV, AIH, HCV, and HBV. The parameters analyzed include hematological markers (hemoglobin [Hb] and total leukocyte count [TLC]), liver function markers (serum bilirubin, SGOT, SGPT, serum protein, and serum albumin), kidney function markers (serum urea and serum creatinine), and a coagulation marker (PT/INR). For each disease category, the mean laboratory values are reported, along with standard deviation (SD), minimum, and maximum values, providing insight into the variability and range of measurements.

Clinical Characteristics	Mean	Std.	Min.	25%	50%	75%	Max.
Hb	9.625	1.82	7.8	8.4	9.4	10.63	11.9
TLC	11125	3701.69	8100	8325	10200	13000	16000
S. Bilirubin	2.41	3.59	0.33	0.59	0.76	2.58	7.79
SGOT	44.73	34.15	18.5	27.76	32.76	49.73	94.9
SGPT	48.52	24.55	27.8	34.12	41.39	55.78	83.5
S. Protein	7.00	0.83	6.33	6.52	6.74	7.22	8.2
S. Albumin	4.15	0.44	3.64	3.90	4.15	4.4	4.67
S. Urea	20.46	6.50	11.3	18.95	21.98	23.49	26.6
S. Creatinine	0.67	0.21	0.42	0.54	0.69	0.82	0.89
PT/INR	4.10	6.20	0.99	1.005	1.01	4.11	13.4

Table 1: Summary of the clinical characteristics across the four disease groups by calculating statistical measures

5. Laboratory markers of infection

Illustrates the number of positive cases for various biochemical markers in patients with HAV, HCV, and HBV. In the HAV group, six patients tested positive for IgM anti-HAV, while four were positive for IgG anti-HAV. Among HCV patients, ten cases were positive for HCV core antigen (HCVcAg).

In the HBV group, HBsAg showed the highest positivity with 14 cases, followed by six patients' positive for IgM anti-HB and five positive for IgG anti-HB.

6. First Line Drug Combination

Hepatitis	First Line Drug Combination	Percentage
HAV	CAP AQUISOL, CAP. EVION, VITAMIN D	3(30%)
	NO TREATMENT	7(70%)
AIH	PLASMAPHERESIS	1(5.8)
	PREDNISOLONE 40 MG/DAY + ADEK SUPPLEMENTS	2(11.7)
	ADEK SUPPLEMENTS	14(82.3)
HCV	RIBAVIR, SOFOSBUVIR <3 years: not recommended 3-8: 15 mg/kg/day, 8-12:15 mg/kg/day, 200 mg once daily >12 years: 1000–1200 mg/day, 200 mg once daily	8(80)
	LEDIPASVIR, SOFOSBUVIR <3 years: not recommended 3-8: not recommended 8-12:45 mg, 200 mg once daily >12 years: 90 mg, 200 mg once daily	2(20)
HBV	TAB LAMIVUDIN 100 MG	13(17.14)
	INTERFERON ALFA-2A (PEGYLATED IFN):180 µg SC /week	1(1.43)
	TENOFOVIR DISOPROXIL FUMARATE 300 MG/DAY	11(11.43)

Mean: 6.48

Standard Deviation: 3.81

Table 2: Hepatitis patients receiving drug combinations with statistical measures, including the mean and standard deviation of patients

7. Evaluation of ADR

S.No	CLASSIFIED CATEGORY	ABBRIEVIATION
	Drug for treatment	
1.	CAP AQUISOL CAP EVION, VITAMIN D	A
2.	NO TREATMENT	B
3.	PLASMAPHERESIS	C
4.	PREDNISOLONE 40 MG/DAY + ADEK SUPPLEMENTS	D
5.	ADEK SUPPLEMENTS	E
6.	RIBAVIR, SOFOSBUVIR	F
7.	LEDIPASVIR, SOFOSBUVIR	G
8.	TAB LAMIVUDIN 100 MG	H
9.	INTERFERON ALFA-2A (PEGYLATED IFN):180 µg SC /week	I
10.	TENOFOVIR DISOPROXIL FUMARATE 300 MG/DAY	J

Table 3: Categorization of each drug category for evaluation of ADR in viral type

8. The time of onset of ADR

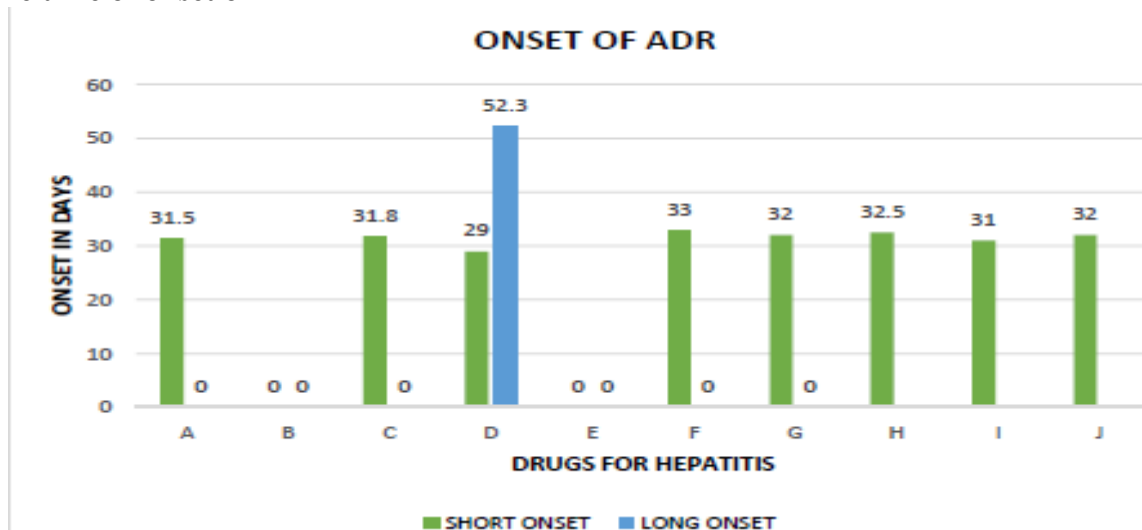


Figure : Time of Onset of ADR

9. Description of ADRs seen in patients

Hepatitis	Number of cases	Drug	ADR	No. of Patients affected by ADR	Action taken	Severity of ADR (Hartwig's Scale Level)	Causality Assessment (WHO-UMC)
HAV	10	A: CAP AQUISOL CAP EVION, VITAMIN D	Diarrhea	1	ORS, Probiotic	Level 2	Possible
			Abdominal discomfort	1	No action taken	Level 1	Possible
		B: NO TREATMENT		0			
AIH	10	C: PLASMAPHERESIS	Itching	1	Levocetirizine	Level 1	Probable
		D: PREDNISOLONE 40 MG/DAY + ADEK SUPPLEMENTS	Weight gain: long-term Blood sugar: short onset	2	-	Level 2	Possible
		E: ADEK SUPPLEMENTS	NO ADR	0	Nil	Nil	Nil
HCV	17	F: RIBAVIR, SOFOSBUVIR	Diarrhea	1	ORS, Probiotic	Level 2	Possible
			Fever, Abdominal Pain	2	Paracetamol, Dicyclomine	Level 1	Possible
		G: LEDIPASVIR, SOFOSBUVIR	Diarrhea	1	ORS, Probiotic	Level 2	Possible
HBV	25	H: TAB LAMIVUDIN 100 MG	Fatigue	2	Nil	Level 1	Possible
		I: INTERFERON ALFA-2A	fever	1	Paracetamol	Level 1	Possible
		J: TENOFOVIR DISOPROXIL FUMARATE 300 MG/DAY)	Diarrhea	2	ORS, Probiotic	Level 2	Possible

TOTAL NUMBER OF CASES	62			14			
-----------------------	----	--	--	----	--	--	--

Table 4: Description of ADRs seen in patients of Hepatitis and the drug combination associated, along with severity and causality assessment

10. WHO-UMC causality assessment scale

S. NO.	CAUSALTY	TOTAL	PERCENT
1	CERTAIN	0	0
2	PROBABLE	1	7.15%
3	POSSIBLE	13	92.85%
4	UNLIKELY	0	0
5	UNCLASSIFIED	0	0
6	UNCLASSIFIABLE	0	0

Table 5: WHO-UMC causality assessment scale

11. ADR Distribution across Hepatitis Types in Pediatric Patients

Hepatitis	System	ADR	No. of Patients Affected	% ADR in System
HAV	GIT	Diarrhoea	1	10%
HAV	GIT	Abdominal discomfort	1	10%
AIH	Skin	Itching	1	5.80%
AIH	Metabolic	Weight gain, Blood sugar	2	11.76%
AIH	None	NO ADR	0	0%
HCV	GIT	Diarrhoea	1	10%
HCV	GIT	Fever, Abdominal Pain	2	20%
HCV	GIT	Diarrhoea	1	10%
HBV	GIT	Diarrhoea	2	8%
HBV	General	Fatigue	2	8%
HBV	General	Fever	1	4%

Table 6: ADR Distribution Across Hepatitis Types in Pediatric Patients

Discussion

This prospective study assessed adverse drug reactions (ADRs) in pediatric hepatitis patients at KGMU, Lucknow. Among 62 children, ADRs were noted in 14 cases (22.6%), mostly mild to moderate in severity. Gastrointestinal (GI) disturbances—particularly diarrhea (35.7%) were the most common, aligning with known ADR profiles of antiviral therapies. Interferon-based regimens had a higher frequency and earlier onset of ADRs than direct-acting antivirals (DAAs), which were associated with fewer and milder side effects.

The ADR incidence observed is consistent with previously reported rates (15–30%) in pediatric populations. Fever (21.4%) and fatigue (14.3%) correspond with flu-like symptoms commonly seen with interferon treatment. In autoimmune hepatitis (AIH), corticosteroids and azathioprine were linked with a higher ADR rate (30%), including weight gain and hyperglycemia, reflecting the known metabolic risks of long-term steroid use, and azathioprine-induced cytopenias. No severe ADRs were reported, and most were classified as mild (64.3%) or moderate (35.7%). Causality assessments

showed 92.9% of ADRs as “possible” and 7.1% as “probable,” typical for pediatric cases where polypharmacy and comorbidities make attribution challenging.

DAAs were better tolerated than interferon-based therapies, with delayed and self-limiting ADRs, supporting global data that advocate for DAA use in pediatric HCV due to their superior safety and sustained virological response. Compared to historical data showing high ADR rates with interferon (50–60%), our lower rate may reflect improved screening and supportive care.

The study’s strengths include its prospective design, real-time ADR monitoring, use of standardized assessment tools (WHO-UMC, Hartwig), and inclusion of both viral and autoimmune hepatitis cases, enhancing relevance. However, limitations include the single-center setting, small sample size, lack of pharmacogenomic data, and short follow-up, which may limit generalizability and miss delayed effects.

Clinically, the study reinforces the need for routine ADR surveillance, especially in AIH patients on long-term immunosuppression. Public health efforts should aim to expand access to DAAs in India and incorporate pediatric ADR data into national pharmacovigilance system.

Conclusion

This study found that nearly one-fourth of pediatric hepatitis patients experienced adverse drug reactions (ADRs), primarily mild to moderate gastrointestinal disturbances. Interferon-based therapies showed a higher and earlier ADR incidence compared to direct-acting antivirals (DAAs), while corticosteroid use in autoimmune hepatitis was linked to metabolic side effects. No severe ADRs were observed, highlighting the effectiveness of timely monitoring and management.

The results support growing evidence favoring the safety and tolerability of DAAs in children and stress the importance of balancing efficacy with long-term safety, especially in autoimmune hepatitis. Clinically, routine ADR monitoring and metabolic surveillance in corticosteroid-treated children are essential, along with improving access to DAAs in resource-limited settings.

References:

1. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021. Geneva: WHO; 2022.
2. Pandey A, Nagral A, Malhotra V. Epidemiology and burden of hepatitis B in India. *J Clin Exp Hepatol*. 2020;10(5):491-501. doi:10.1016/j.jceh.2020.06.005
3. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2019 update. *Hepatol Int*. 2019;13(4):353-90. doi:10.1007/s12072-019-09918-3
4. Alexander J, Torres R, Joshi P. Pediatric hepatitis: an update on causes, clinical features and management. *Pediatr Clin North Am*. 2022;69(5):1001-18. doi:10.1016/j.pcl.2022.06.002
5. Patel A, Kalra N, Sharma R. Pediatric autoimmune hepatitis: current perspectives. *World J Hepatol*. 2019;11(8):677-89. doi:10.4254/wjh.v11.i8.677
6. World Health Organization. Global hepatitis report 2021. Geneva: WHO; 2021.
7. Roma MG, Sánchez Pozzi EJ, Crocenzi FA. Hepatitis in children: insights into viral and immune-mediated injury. *J Pediatr Gastroenterol Nutr*. 2023;76(1):19-27. doi:10.1097/MPG.0000000000003654
8. Indolfi G, Easterbrook P, Dusheiko G, Siberry G, Chang MH, Thorne C, et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol*. 2018;4(6):477-87. doi:10.1016/S2468-1253(18)30347-9
9. Dhiman RK, Grover GS, Premkumar M, Taneja S, Duseja A, Chawla YK. Treatment of chronic hepatitis C with direct acting antivirals: experience of 5000 patients from North India. *Indian J Gastroenterol*. 2019;38(6):517-25. doi:10.1007/s12664-019-00978-6
10. Hyppolito E, Galdino MR, Coelho H. Safety profile of direct-acting antivirals in real-world pediatric cohorts. *J Viral Hepat*. 2024;31(1):45-53. doi:10.1111/jvh.14012

11. Ustaoglu M, Demir NA, Kaya S. Adverse events associated with direct-acting antivirals for chronic HCV infection: a meta-analysis. *Expert Opin Drug Saf.* 2021;20(10):1187-96. doi:10.1080/14740338.2021.1942683
12. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet.* 2001;358(9286):958-65. doi:10.1016/S0140-6736(01)06102-5
13. Bootsma HP, Spijkerman IJ, de Bie P, Peeters PM. Interferon treatment in pediatric hepatitis: long-term outcomes and side effects. *J Hepatol.* 2013;59(4):872-9. doi:10.1016/j.jhep.2013.05.025
14. Ferri S, Muratori L, Lenzi M. Autoimmune hepatitis in children: clinical features and therapy. *Hepatol Res.* 2012;42(4):340-8. doi:10.1111/j.1872-034X.2011.00934.x
15. Johnson P, Beath SV, McKiernan P. Advances in immunosuppressive management of pediatric autoimmune hepatitis. *Front Pediatr.* 2024;12:1183457. doi:10.3389/fped.2024.1183457
16. Coleman M, Cuzzolin L, Kearns GL. Pharmacokinetics and pharmacodynamics in pediatric hepatology. *Clin Pharmacol Ther.* 2016;100(4):354-66. doi:10.1002/cpt.379
17. Smith L, Banerjee S, Yadav A. Drug metabolism and adverse drug reactions in pediatric liver diseases. *Pediatr Drugs.* 2024;26(2):115-28. doi:10.1007/s40272-023-00573-7
18. Yu Y, Xu H, Chen Y. Adverse drug reaction reporting in pediatric populations: challenges and recommendations. *Drug Saf.* 2020;43(4):341-52. doi:10.1007/s40264-019-00889-2
19. Liu J, Wang J, Zhang Q. Pharmacovigilance in pediatric hepatitis: a systematic review. *Eur J Clin Pharmacol.* 2023;79(6):913-25. doi:10.1007/s00228-023-03456-8