Treatment of Chronic Hepatitis C Virus Infection in Children

This guide has been produced by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Hepatology Committee to assist paediatricians and patients in the clinical decision-making of treating children with chronic hepatitis C virus (HCV) infection.

Causes of childhood HCV

Vertical transmission from mother to the child is the primary cause

In high-income countries, horizontal transmission through injection drug use is an emerging and concerning cause

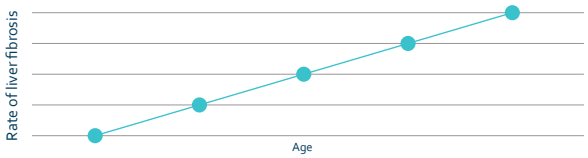
In low-income countries, horizontal transmission via medical treatment and through traditional practices such as scarification and circumcision could account for higher prevalence

Natural history of HCV infection

Following vertical transmission of HCV, approximately 20% of children clear the infection without any treatment and usually in the first 4 years of life, whereas the remaining 80% develop chronic infection that persists into adulthood.

Chronic HCV infection is usually associated with no symptoms during childhood and most children present with a near normal liver, even after a long period of infection, and little or no pain (compared to adults)

Liver fibrosis may slowly increase with the patient's age, duration of the infection and/or the severity of histological necroinflammation



The risk of cirrhosis is 1% to 4% while bridging fibrosis and severe inflammation have been described in approximately 15% of cases

Liver cancer is rare

Malignancy, haematological diseases with iron overload and viral coinfections (HIV and hepatitis B), alcohol consumption and obesity all accelerate the development of severe liver disease

Treatment of chronic HCV infection

All children with chronic HCV infection should be considered for treatment

Liver biopsy is not routinely advised but it should be evaluated on a case-by-case basis

Immediate treatment should be considered in children with significant fibrosis and cirrhosis, extrahepatic manifestations or co-morbidities which increase the risk of rapid on-set of liver disease (e.g. solid organ or hematopoietic stem cell transplant recipients or other patients undergoing immunosuppressive treatments)

Early treatment of adolescents is advised, before the age at which risk of horizontal infection increases through sexual transmission or injecting drug use

Approved drugs

Drugs approved by the European Medicines Agency and the FDA (USA) for treatment of children with chronic hepatitis C virus infection:

	Drug	Age (yr)	Genotype	Dosage	Administration
IFN	Interferon α-2b	3–18	1–6	6 x 10^6 IU/m^2 3 times a week	Subcutaneous
	Pegylated interferon α-2a	5–18	1–6	100µg/m^2 per week	Subcutaneous
	Pegylated interferon α-2b	3–18	1–6	1.5 µg/kg per week	Subcutaneous
RBV	Ribavirin	1–18	1–6	15 mg/kg per day in 2 divided doses	Oral
Direct-Acting Antivirals (DAAs)	Sofosbuvir	12–17	2, 3	400 mg/day	Oral
		3-11*	2, 3	200 mg/day if ≥17 kg 150 mg/day <17 kg	Oral
	Ledipasvir/sofosbuvir	12–17	1, 4–6	90/400 mg/day	Oral
		3-11*	1, 4-6	45/200 mg/day if ≥17 kg 33.75/150 mg/day <17 kg	Oral
	Glecaprevir/pibrentasvir	12-17	all	300/120 mg/day	Oral

When compared with the IFN and RBV based drugs, DAAs demonstrate superiority in terms of efficacy and safety profile. It has been demonstrated that adolescents treated with ledipasvir/sofosbuvir self-reported improvement of quality of life both during and at the end of their treatment. The cost of DAAs have been an obstacle to broader use of the treatment. The use of lower (compared to adults), and therefore cheaper, doses of DAAs in children could provide benefits in terms of potential cost savings.

*approved by FDA September 2019; approval by EMA still pending at time of publication.

Recommendations for treatment

ESPGHAN recommendations for children >12 years of age:

HCV genotype	Treatment	Treatment goals
All	Fixed-dose combination of glecaprevir/pibrentasvir 300/120 mg. Once daily for 8 weeks (12 weeks for patients with compensated cirrhosis; 16 weeks for treatment-experienced patients with genotype 3 infection)[1]	1. To cure HCV infection and prevent the possible progression of HCV-related liver disease and its complications. 2. Undetectable HCV RNA in blood samples 12 weeks after the end of treatment
	Alternative options	
1, 4	Fixed-dose combination of ledipasvir/sofosbuvir 90/400 mg. Single tablet once daily for 12 weeks (24 weeks for treatment-experienced children with genotype 1 + compensated cirrhosis)	
2	Sofosbuvir 400mg once daily + weight-based RBV (15mg/kg in 2 divided doses) for 12 weeks	
3	Sofosbuvir 400mg once daily + weight-based RBV (15mg/kg in 2 divided doses) for 24 weeks	

ESPGHAN recommendations for children <12 years of age:

- PEG IFN + RBV treatment no longer recommended
- In most cases treatment could be postponed until DAAs are approved for use in children between 3 and 11 years of age
- Once the EMA approve the extension of indication to children aged between 3-11, ESPGHAN's recommendations will also include:

Genotype	Treatment
Genotype 1, 4, 5, 6[2,3]	ledipasvir/sofosbuvir ≥ 35 kg: 90/400 mg 17 - <35 kg: 45/200 mg <17 kg: 33.75/150 mg Once daily for 12 weeks (24 weeks for treatment-experienced children with genotype 1 + compensated cirrhosis)
Genotype 2, 3[4]	sofosbuvir ≥ 35 kg: sofosbuvir 400 mg 17 - <35 kg: 200 mg <17 kg: 150 mg + weight-based RBV (15mg/kg in 2 divided doses) Once daily for 12 weeks for children with genotype 2 infection and for 24 weeks for those with genotype 3 infection.
Referral to a centre of excellence (where available)	

References

1. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Adolescents With Chronic Hepatitis C Virus: Part 1 of the DORA Study. Jonas MM, Squires RH, Rhee SM, Lin CW, Bessho K, Feiterna-Sperling C, Hierro L, Kelly D, Ling SC, Strokova T, Del Valle-Segarra A, Lovell S, Liu W, Ng TI, Porcalla A, Gonzalez YS, Burroughs M, Sokal E. Hepatology. 2019 Jun 29. doi: 10.1002/hep.30840. [Epub ahead of print]
2. Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. Schwarz KB, Rosenthal P, Murray KF, Honegger JR, Hardikar W, Hague R, Mittal N, Massetto B, Brainard DM, Hsueh CH, Shao J, Parhy B, Narkewicz MR, Rao GS, Whitworth S, Bansal S, Balistreri WF. Hepatology. 2019 Jun 20. doi: 10.1002/hep.30830. [Epub ahead of print] PMID: 31220349
3. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. Murray KF, Balistreri WF, Bansal S, Whitworth S, Evans HM, Gonzalez-Peralta RP, Wen J, Massetto B, Kersey K, Shao J, Garrison KL, Parhy B, Brainard DM, Arnon R, Gillis LA, Jonas MM, Lin CH, Narkewicz MR, Schwarz K, Rosenthal P. Hepatology. 2018 Dec;68(6):2158-2166. doi: 10.1002/hep.30123. Epub 2018 Nov 17.
4. Sofosbuvir and Ribavirin Therapy for Children Aged 3 to <12 Years With Hepatitis C Virus Genotype 2 or 3 Infection. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, Lin CH, Kelly DA, Nightingale S, Balistreri WF, Bansal S, Jonas MM, Massetto B, Brainard DM, Hsueh CH, Shao J, Parhy B, Davison S, Feiterna-Sperling C, Gillis LA, Indolfi G, Sokal EM, Murray KF, Wirth S. Hepatology. 2019 Jun 20. doi: 10.1002/hep.30821. [Epub ahead of print]

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