Chronic Hepatitis C management in Children

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Background

3.5 to 5 million children are estimated to have chronic hepatitis C virus (HCV) infection all over world while prevalence in pediatric population is 0.15% (0.6% in high income and 0.3% in low income countries).[1,2] In Indian studies HCV prevalence among all age groups is 1-1.9%.[3] In a recent population based study, in 5-18 years age group HCV seroprevalence was 0.7% while RNA positivity was 0.4%.[4] Main route of HCV acquisition in children is from mother to child vertical transmission. In children as compared to adults, HCV infection leading to cirrhosis (1-4%) is uncommon and hepatocellular carcinoma is rare.[5] Weather to treat HCV in childhood has been a point of debate due to lower HCV related complication in childhood and higher side effects due to interferon based treatment regimens. With the approval of safer and more efficacious direct acting antivirals (DAAs) in pediatric population, now treatment is recommended by ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition)[5] and AASLD-IDSA (American Association for the Study of Liver Diseases-Infectious Diseases Society of America)[6] in all HCV infected children above ≥ 3years age.

Investigations and diagnosis of chronic HCV infection in children

All infants born to HCV positive mothers should undergo antibody based test (anti HCV antibody) at 18 months age, as maternal antibodies can be found before this age in serum of the child. If antibody test is positive then HCV RNA should be performed at 3 years age, as 25-50% children may spontaneously clear the prenatally acquired HCV infection by this time.[1] To allay the parental anxiety or if loss to follow up is a concern, RNA based test can be performed as early as 2 months age.[6]

In other children suspected of HCV infection should undergo serology, if positive then RNA estimation.

HCV genotyping is not recommended in adults anymore due to approval of pangenotypic DAAs. Although in pediatric patients genotyping should be performed as pangenotypic DAAs are yet not approved for all age groups.

Routine liver function test should be performed at diagnosis and then yearly in asymptomatic children. Before starting treatment, it is not mandatory to perform tests for assessment of liver fibrosis like liver biopsy or fibroscan except in patients where advanced liver disease is suspected.[5]

Children with cirrhosis should undergo hepatocellular carcinoma (HCC) [ultrasound with or without serum alpha-fetoprotein (AFP) every 6 months] and endoscopic surveillance for variceal status (at screening and then every 3 yearly thereafter).[6]

Tests for active hepatitis B infection (HBsAg, anti-HBc, and anti-HBs) should be done before starting HCV DAA therapy due to risk of reactivation during or after treatment.[6]

Indication of HCV treatment in children

Treatment for HCV infection is not recommended in < 3 years age. All treatment naïve and experienced children (≥ 3-18 years) should be considered for treatment irrespective of liver disease status. In children with significant fibrosis or cirrhosis or extrahepatic manifestations treatment should be considered without delay. Similarly in patients planned for solid organ/hematopoietic stem cell transplant and on immunosuppressant treatment, there should be urgency to start anti HCV treatment.

After recent FDA approval of DAAs in ≥ 3 years age, therapy can be offered to all children above 3 years age. In case of unavailability of DAAs, risks and benefits of interferon based therapy or to wait till DDAs become available should be compared and discussed with parents before instituting treatment. In general PEG interferon and ribavarin based treatment can be deferred till DAAs become available.

Treatment of Chronic HCV infection

Goal of treatment

Goal is to cure HCV infection to prevent progression of HCV related liver disease. End point of therapy is undetectable HCV RNA in blood at 12 weeks [sustained virological response (SVR 12)] after end of DAAs treatment and at 24 weeks (SVR 24) after end of PEG IFN and ribavarin treatment.[5]

Following drugs are approved in children for HCV treatment (Table 1 and 2)

Ledipasvir and Sofosbuvir

This combination is now recommended from ≥ 3-18 years for genotypes 1, 4, 5 and 6 in patients without cirrhosis or with compensated cirrhosis.[5,6]

Sofosbuvir and ribavarin

Recently this combination is also approved by FDA for use in children ≥ 3 years for genotype 2 and 3.[6] Presently this is the only DAA combination approved in ≥ 3-11 years age for genotype 2 and 3. Clinical trials are underway evaluating weight-based dosing of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir and that may lead to FDA approval of these drugs soon in children aged 3 - 11 years.[6,7,8]

Glecapravir and Pibrentasvir

This is first pangenotypic combination approved by FDA in age group ≥12 years or ≥45kg.

As per AASLD HCV guidance panels if there is no compelling evidence to start immediate antiviral treatment in 3-11 years age then to wait till pangenotypic regimens are approved.[6]

PEG interferon (IFN) and ribavarin

ESPGHAN guidelines 2018 recommended that PEG IFN based therapy can be deferred till DAAs are available in that age cohort (3-11 years). With approval of DAAs across all age cohorts now there is no role of PEG IFN based therapy anymore unless DAAs are not available and treatment is strongly needed.

Other considerations for children with HCV infection

Hepatotoxic drugs should be used with caution in children with chronic hepatitis C after assessment of potential risks versus benefits of treatment. Use of corticosteroids, cytotoxic chemotherapy, and/or therapeutic doses of acetaminophen are not contraindicated in children with chronic hepatitis C. Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic hepatitis C.

Adolescents with chronic HCV infection and their families should be guided regarding potential risks of alcohol for progression of liver disease.

Conclusion:

All children with chronic HCV infection ≥ 3 years age should be considered for treatment even if liver functions are normal. With approval of DAAs, treatment is now highly effective and safe in children. Long term safety data are still not available. Availability of age/weight appropriate dose combinations of DAAs and high cost are the issues that need attention in developing countries like India.

Table 1: Drugs approved for children in HCV infection

Drug	Genotype	Dose
Ledipasvir and Sofosbuvir (Oral)	1,4,5,6	<17kg : 33.75mg/150mg 17 to <35 kg: 45mg/200mg >35kg : 90mg/400mg
Sofosbuvir and Ribavarin (Oral)	2,3	Sofosbuvir <17kg : 150mg 17 to <35 kg: 200mg >35kg : 400mg Ribavarin < 47kg : 15mg/kg 47-49kg : 600mg 50-65kg : 800mg 66-80 kg: 1000mg >80kg : 1200mg
Glecaprevir and Pibrentasvir (Oral)	Pangenotypic	300mg/120mg OD (≥12 years or ≥45 kg)
Interferon α-2b (subcutaneous)	Pangenotypic	6 X 10^6 IU/m^2 3 times a week (3-18 years)
Pegylated Interferon α-2a	Pangenotypic	100mg/ m^2 per week (5-18 years)
Pegylated Interferon α-2b	Pangenotypic	1.5mg/kg per week (3-18 years)

Table 2: Direct acting antivirals (DAAs) approved in children

Age	Drugs	Genotype	Duration
3-18years	Ledipasvir and Sofosbuvir	1,4,5,6 1	12 weeks* 24 weeks (treatment exposed# without or with compensated cirrhosis)
	Sofosbuvir and ribavarin	2	12 weeks*
		3	24 weeks*
12-18 years	Glecaprevir and Pibrentasvir	Pangenotypic 1,2,4,5,6 3	8 weeks* 12 weeks (treatment exposed§ without or with compensated cirrhosis) 16 weeks(treatment exposed§, without or with compensated cirrhosis)

* normal liver or compensated cirrhosis
# Interferon and/or protease inhibitor experienced
§ Interferon and/or Sofosbuvir experienced

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