Review Article

Treatment of Hepatitis C Virus Infection in Children Less than 12 Years of Age in Developing Countries

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Abstract

The treatment of hepatitis c virus (HCV) infection in children is difficult as few options are available. The standard therapy is combination pegylated interferon (PEG–IFN) α-2a or 2b and ribavirin, and the duration of therapy depends on HCV genotype. New oral drug therapies available for adults have still not been approved for treatment in children. Here, we review the causes of HCV infection in children, the therapeutic options for children, and the side effects of these treatments. The problems faced by physicians managing HCV infection in children less than 12 years of age in a developing country are also discussed.

Introduction

The global prevalence of antibody to hepatitis C virus (anti-HCV) is 1.6% (1.3–2.1%), corresponding to 115 (92–149) million previous and current infections. Of these, 104 (87–124) million were adults (age 15 years and older), with an anti-HCV rate of 2.0% (1.7–2.3%). The worldwide viremic (ribonucleic acid [RNA] positive) HCV infection rate was estimated to be 1.1%, corresponding to 80 (64–103) million infections. Regarding genotype, the most frequent was genotype 1 (46%), followed by genotype 3 (22%), genotype 2 (13%), and genotype 4 (13%).[1]

A recent systematic review found that between 1990 and 2005, the global prevalence of anti-HCV increased from 2.3% to 2.8%.[2] It is estimated that approximately 210 million individuals, *i.e*. approximately 3% of the world population, are chronically infected with HCV.[3,4,5] In the Nile Delta villages of Egypt, HCV infection increases with age from 2.7% at age 20 to more than 30% at age 45 and above.[6] The prevalence of HCV infection is less than 2.5% in the general population in Asian countries.[7] In Pakistan, the pediatric population has a positive anti-HCV frequency less than 2%.[8] In some areas of southern Pakistan, the frequency of HCV infection is as high as 30% (periurban and urban Sindh),[9] with 3a being the predominant genotype.[10]

There is little data available regarding the prevalence and treatment of HCV infection in the pediatric population, especially in children less than 12 years of age.[11,12,13] HCV infection is manifested differently in children than adults, where children are often asymptomatic, may spontaneously clear the virus, and have normal alanine aminotransferase (ALT) levels.[10] The diagnosis and testing of HCV in children is the same as that for adults, according to the American Association for the Study of Liver Diseases (AASLD).[14] If early diagnosis is required, the baby of an HCV-infected mother should have an HCV RNA done at one to two months of age, otherwise HCV antibody should be tested after 18 months of age.[14]

Regardless of the mode of transmission of HCV in the pediatric population, starting intervention early is better[15] than waiting untilthe infected childapproaches the adult age group at 16 or 18 years old. Early treatment is necessary because during childhood the HCV virus increases in intensity, causing damage to the liver and the general well-being of the child, culminating in cirrhosis and liver failure in adulthood.[2] Since more than 70% of individuals acutely infected with HCV develop a chronic infection (chronic HCV) and over time develop liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), early intervention is key for successful treatment of HCV. Antiviral therapy improves liver histology and decreases the incidence of HCC.[14] The mode of treatment in children is perplexing, as the current standard treatment is long-acting interferon, *i.e.* weekly subcutaneous pegylated interferon-α2a, (PEG-IFN-2a) Pegasys or α2b (PEG-2b) PegIntron in combination with ribavirin (RBV).[16]

This review discusses the global standard treatment regimen for HCV in children, and alterations, if any, in the treatment of children from poor socio-economic areas. Also addressed are the problems faced by pediatricians in the management of HCV infection, especially in developing countries, the affordability of treatment, and the development of child-friendly medication.

Causes of HCV infection in children

Although hepatitis C infection in children can be caused by vertical transmission,[14,17] the overall rate of transmission is

Keywords: Hepatitis C; Chronic; Child; Therapeutics; Developing countries.

Abbreviations: AAP, American Academy of Pediatrics; AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ART, antiretroviral therapy; DAAs, direct antiviral agents; EGD, esophagogastroduodenoscopy; EIA, enzyme immunoassay; EPI, Expanded Program of Immunization; FDA, Food and Drug Administration; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDUs, injectable drug users; LFT, liver function test; NCHS, National Center of Health Statistics; PCR, polymerase chain reaction; PEG–IFN, pegylatedinterferon; PT, prothrombintime; RBV, ribavirin; RCT, randomized controlled trial; SOF, sofosbuvir; SVR, sustained virologicalresponse; TMA, transcription-mediated amplification; WHO, World Health Organization.

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low.[18] The mechanism and natural history of this mother-to-child transmission of HCV infection is not clear.[19] The risk of an infant contracting an HCV infection from the mother is 2–8%, and a recent study from Asia found that the vertical transmission rate was only 1.4%.[18] Hence, very few babies born to mothers with HCV infection were infected. In the Asia study, the HCV load in these mothers ranged from 584 to 170,00,000 copies/mL. The newborns were evaluated at 3 and 18 months, and their HCV profile included HCV RNA if the baby was positive for HCV antibody after 18 months.

One cause of HCV infection in children of an older age is the use of unsterile syringes. This is an important mode of transmission as there are many health personnel who are not fully qualified and unaware of the hazards of using infected syringes repeatedly. Also, use of the same toothbrush and comb in the family may cause transmission of HCV, especially if all family members are using the same comb and there is at least one carrier of HCV infection present in the family.[20]

Some cases of HCV infection secondary to blood products have been reported. This is seen frequently in thalassemic children, who, despite vigilance of the thalassemia center, receive transfusions of infected blood products.[21] Children with hemophilia may also be at risk to infection via similar mechanisms.

There are other risk factors in children for acquiring HCV. Drug and substance abuse are on the rise, especially in school children, and this may lead to other infections such as human immunodeficiency virus (HIV) infections. Body-piercing, especially of the ear lobes and nose, is commonly done in Asia and the developed world, and body-piercing and tattooing are frequent, especially in teenagers.[22,23] Child abuse is increasing, and sexual abuse in young children[24] which may cause hepatitis B or C and HIV infections, in children. Worldwide, HCV infection is present in 50% of injectable drug users (IDUs), and in South East Asia, HCV infection in IDUs is 34–93%.[25] Overall, more than 45% of the Pakistani population is under 18 years of age. Therefore, it follows that a significant proportion of children may be IDUs. Further research is needed on this important issue, especially in the pediatric population from the developing countries.

Investigating HCV infection in children

The process of investigating children with HCV infection is the same as that for adults.[14] Serological testing includes detection of specific anti-HCV by enzyme immunoassay (EIA), with a specificity of 90%. This test does not reflect disease severity or assessment per se. The other test is a molecular assay, real-time polymerase chain reaction (PCR) and transcription-mediated amplification (TMA), with sensitivities of 10–50 IU/mL. In addition, several commercial tests are available for determining genotype.

HCV infection in children is generally mild. However, if left untreated, liver biopsy may demonstrate cirrhotic changes.[26] Prior to initiating treatment in children, tests used to confirm HCV diagnosis include: liver function test (LFT), prothrombintime (PT), activated partial thromboplastin time (APTT), hepatitis B virus (HBV), HIV, autoimmune, ultrasound, esophagogastroduodenoscopy (EGD), if indicated, radiology, and elastography (Fig. 1).

A mother who is HCV RNA PCR positive with sufficient viremia may transmit the infection to the baby. Other causes of HCV infection in the child have already been highlighted. Before initiating HCV treatment in a child, it is advisable to screen the child also for hepatitis B surface antigen (HBsAg), HIV, and LFTs, and to perform HCV genotyping. Genotype (1, 2, 3, or 4) will determine the duration of treatment and morbidity. Genotype 1 and 4 require a therapy of one year and have a poor sustained virological response.[11,14,16] It is important to know the HBsAg status of the child as coinfection with any other hepatotropic virus increases the morbidity of the disease. Autoimmune profile is also done in children and adults prior to starting treatment as, again, a coinfection may persist, and this profile is performed by some centers as a matter of routine.[14]

Treatment of HCV infection in children

As a general rule, it is better to identify and treat any other infection present in a child, such as pneumonia, common flu, etc., before considering treatment for HCV infection. Despite recommended immunization of the Expanded Program of Immunization (EPI) by government institutions throughout developing countries, children are still not being immunized against various communicable diseases and may be suffering from or prone to any of a number of infections due to insufficient immunity. For example, hepatitis B vaccine, though easily available and free of cost in all government institutions, is often not given to children by their parents. Therefore, a child diagnosed with HCV must be investigated for other hepatotropic viruses, such as HBV, before starting HCV treatment.

In children, early treatment for HCV infection is recommended, and it has been shown that the sustained virological response (SVR) in children is better than adults.[11] This may be due to a shorter duration of infection in the younger age group. Younger children will benefit from early treatment, as psychosocial issues and periods of rapid growth at later ages, such as puberty, can be avoided. Serious psychiatric issues in children receiving treatment have been reported, but other studies have reported only mild to moderate mood changes[17] or no changes in neuropsychiatric behavior. The nutritional status of children need to be assessed prior to consideration of HCV treatment. Once the decision has been made to treat the child, the duration of HCV treatment in children, as in adults, depends on the genotype.

Previously, some centers used standard interferon alpha 2b in combination with RBV when treating children with HCV. This required injections three times a week and was distressing for the young child and parents. In addition, as most children with hepatitis come from a low socioeconomic community, afford ability was an issue. This protocol was used globally in the under developed world, especially for genotype 2 and 3 HCV infections, with an SVR of 85%. However, currently, it is no longer recommended in either adult or pediatric populations, regardless of the genotype.

The US Food and Drug Administration (FDA), European Medicine Agency, and the Polish group have approved the use of PEG-IFN-2a and 2b for the treatment of HCV.[27–29] Combination of RBV and PEG-IFN was shown to be superior to PEG-IFN and placebo for children and adolescents with chronic hepatitis C.[30]

For genotypes 1 and 4, combination PEG-IFN alpha-2b and RBV achieved SVR of 64% in naive patients.[31] For genotype 2, SVR was 89%.[11,17] In genotype 1 and patients with high viral load, an SVR of only 50% was achieved.[32] The recommended dosing regimen in children is 60 mg/m^2 or 1.5 μg/kg subcutaneously of PEG-IFN alpha-2b weekly plus 15 mg/kg RBV

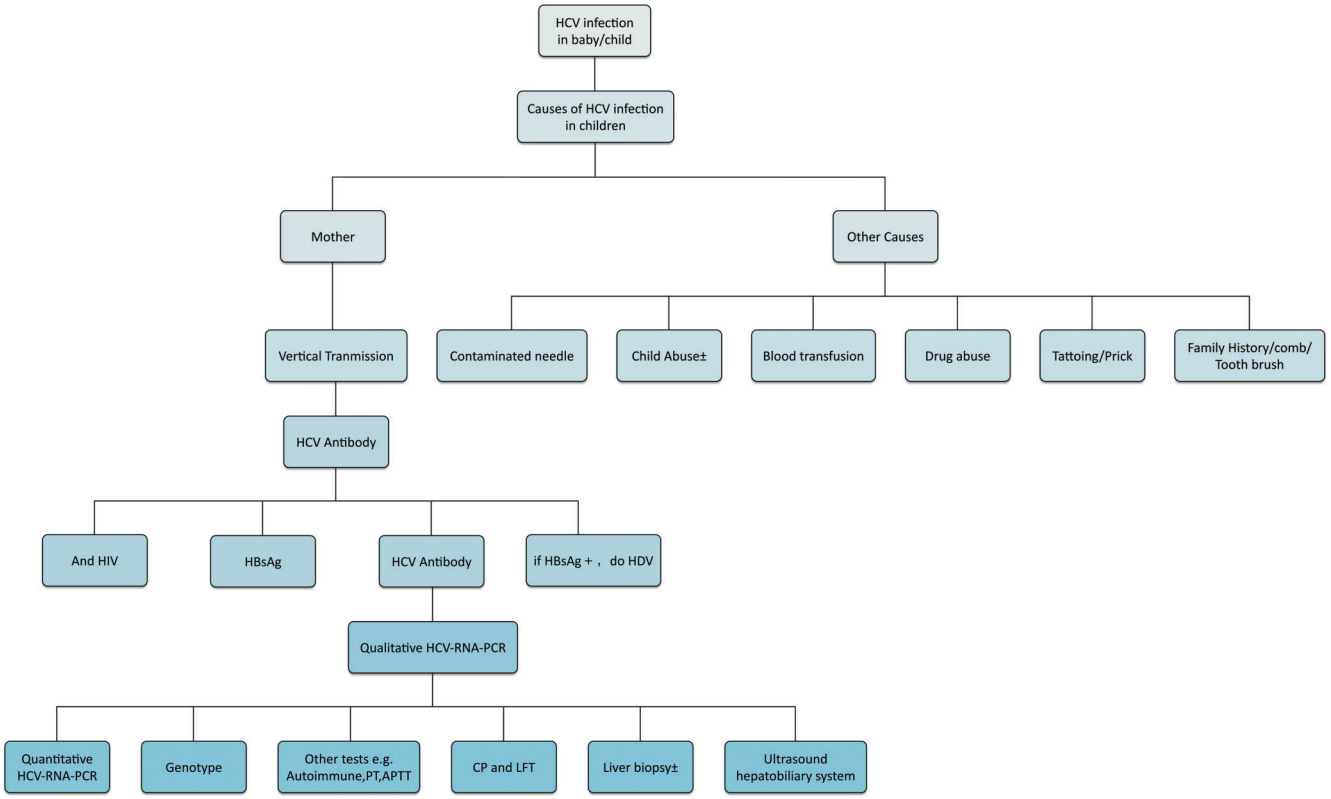

Fig. 1. Possible causes and recommended investigations in a child with hepatitis C virus (HCV) infection prior to starting treatment.

daily for 48 weeks for genotype 1 and 4 infections and 24 weeks for genotype 2 and 3.[14,33]

Medications not yet approved for children with HCV infection

The oral direct antiviral agents (DAAs) have an efficacy of 80–90%.[34,35] In adults, combination of PEG and RBV with two protease inhibitors of the non-structural (NS) 3/4 region of the virus, Boceprevir and Telaprevir,[36,37] have been used. The use of PEG-IFN, RBV, and DAA as a combination therapy results in SVR of nearly 80% in patients with genotype 1 infections. However, this therapy has not been used in children to date.

New DAAs (sofosbuvir (SOF), daclastavir, and asunaprevir) interact with important components of the virus, such as NS3/4, NS5, and polymerase.[38,39] Some of the new DAAs are oral agents that are used for a period of 12 weeks with negligible side effects and 80% to 90% virus eradication. More than 99% of patients who achieve SVR no longer test positive for HCV and are cleared permanently of the virus.[40]

SOF (Sovaldi) is an HCV NS5B nucleotide polymerase inhibitor. Patients infected with genotype 1–6 that were treated with SOF in combination with RBV with or without PEG-IFN for 12 or 24 weeks had a high SVR. In patients with HIV/HCV coinfection, cirrhotic patients,[41] and patients who received previous treatment, high efficacy rates were achieved with SOF for the treatment of hepatitis C.[42] The FDA has not approved SOF for the treatment of HCV in children.

Effective and well-tolerated antiretroviral therapy (ART) based regimens are currently under FDA review. The treatment is comprised of 150 mg dose ABT-450 (an HCV NS3/4A protease inhibitor), with 100 mg daily ritonavir (ABT-450/r), 25 mg daily ABT-267 (a nonnucleoside NS5A inhibitor, ombitasvir), and 250 mg twice daily ABT-333 (an NS5B RNA polymerase inhibitor, dasabuvir). This treatment is given with or without weight-based RBV. This regimen has been shown to interrupt the HCV replication process and optimize SVR rates in different patient populations.[43] There is hope that these oral medications for the treatment of HCV infection may be available to the much-needed pediatric population who are exposed to the physical and emotional trauma of injections. Results of such trials in children are eagerly awaited.

Trials are now being conducted on the safety and efficacy of sofosbuvir and RBV in adolescents and children with genotype 2 or 3 chronic HCV infection. This study is currently recruiting participants for the study.[44]

Problems faced in the management of HCV infection in children

Socioeconomic status

The challenge of treating HCV infection in children is due to their very poor socio-economic status. Often these children live in conditions where electricity is not always present, the person-to-area-square-foot is not sufficient, the bathroom is not made of concrete, and food is not always available (*i.e.* the child does not take three meals per day). These families are large, with siblings, uncles, aunts, and grandparents

Table 1. Practical points to be considered when treating a child with hepatitis C virus (HCV) infection

HCV Infected mother	Children born to HCV infected mothers: must treat mother and baby after breast feeding is completed (minimum time period of breast feeding is 6 months) and screen father and siblings of the child
Nutrition	Nutritional status of the child: anthropometric measurement must be maintained and followed throughout treatment and thereafter
Counseling	Counseling parents for nutrition and compliance of treatment and follow up
Written agenda	Written agenda of the treatment routine *i.e.* time, day, dose, side effects of PEG interferon injection, and ribavarin must be given to the parents in the local language
Adverse reaction	Parents be advised in writing when they should come in case of adverse reaction, such as high grade fever not subsiding by analgesics
Counseling	Counseling of child and parents repeatedly regarding injections and side effects
Consent	Written consent from parents before starting treatment
Liver biopsy	Liver biopsy if being considered, parents counseled and written consent taken
Activity of child	Encourage child to do regular activities, including physical activity if not febrile and minimal side effects
School	Child can go to school on a regular basis, provided afebrile
Schedule of Medication	Give child PEG interferon on weekend e.g. Friday evening for tolerance of side effects and recuperation over Saturday and Sunday before going back to school on Monday
Childs toiletries	Example tooth brush, comb, etc. not to be used by anyone else

living in the same space. Also, the recent urbanization of the family from village to the city makes it difficult for the family to cope.[9] These factors, together or alone, make it very challenging for a family of an HCV infected child to afford medications. Although some government hospitals provide these medications free of cost, the child will need to go to the hospital to receive the injections, as the cold chain for keeping the drugs at home cannot be maintained.[11] In our personal experience, the parents are sometimes so poor that they will not come to the center to get the investigation done or get the injectable medication (*i.e.* IFN) if funds/donations are not available for transportation. Hence, it is important for the physician to be vigilant in cases of non-affording patients and to make sure that the child gets the medication on time by way of government or local funds and donations. Patients from our region were treated free of cost, counselled repeatedly with hand-outs, and provided dietary supplements, when possible, in the form of 1 mL one calorie diet. Children were responsive to treatment, maintained bodyweight at the start of the treatment, and gained weight in the last 2 months of treatment. These findings are based solely on our observation, and we did not conduct a randomized controlled trial (RCT) to generate statistical significance. Such studies may perhaps be performed in the future.

Nutrition and anthropometric measurement

Prior to initiating treatment for HCV, the nutritional status of children needs to be assessed as the side effects of treatment may debilitate a child. Due to fever, anorexia, lethargy, and nausea, the child may not take a balanced diet and may lose weight. Use of a dietary supplement in addition to the regular diet can be added to help boost the child's energy requirement and maintain weight during treatment. In our experience, the addition of supplements helps the child, as children in under privileged areas are invariably below the 10 to 25 percentile on the National Centre of Health Statistics (NCHS) charts and are already borderline malnourished.[11]

The American Academy of Pediatrics (AAP) does not recommend restricting children with chronic HCV infection from school attendance or participation in routine activities, including sports.[45] We manage children at our local hospital in accordance with this an approach. However, we did try to inject children with PEG-IFN Friday evenings, so as to avoid the presence of possible acute side effects, such as fever, on Monday when the school week begins. The majority of parents followed the schedule given to them. Also, the treatment was generally started in summer vacation or winter so that the child and family had the opportunity to adjust to the treatment and associated side effects.

It is important that the child continues physical activity in school and at home. However, if febrile, then proper precautions need to be taken and the physical activity of the child has to be adjusted with appropriate support. The growth and weight of children requiring treatment for 24 months were less affected than those receiving the treatment for 12 months, such as in genotype 1 infection. Although the 12 month group did have a growth deficit, the catch-up growth was not disturbed.[17,30]

The quality of life in children receiving treatment with PEG-IFN and RBV is decreased during the early phase of the treatment. At around 12 weeks of treatment, the health of the child is poorer, with limited physical activity and frequent pain and fever. As the duration of treatment increases, the child develops tolerance to the drugs and the side effects are observed with less frequency.[17,27,30,32] As detailed in Table 1, there are some practical points that physicians need to consider when treating an affected child.

A key to effectively treat HCV infected children is proper counselling of the parents. The parents need to understand the significance of compliance (strict and timely schedule) with the medications, the side effects, and when to return to hospital in case of any adverse side effects. In our part of the world, myths persist promoting the restriction of all foods to a child when he or she is ill. Restricted diet consists of boiled vegetables and no protein (meat in any form, including chicken), butter, jam, ice cream, etc. The child then loses

weight. Hence, it is essential that these infected children receive a regular diet according to his age and requirement, supplements, and extra care so as to encourage him to take food. At the same time, counselling of the parents and other family members living in the home is an important part of the management.

The recommendation of the World Health Organization (WHO) guidelines for the management of HCV infection in children is to treat these children with an integrated health care system. This can be feasibly achieved by creating a close liaison involving primary care and maternal and child health service providers.[46]

Conclusions

To date, HCV infected children are treated with combination PEG-IFN and RBV. This requires monitoring of hematological parameters and strict follow-up on diet, height, and weight of the child. In children of poor socioeconomic status, extra counselling and support is required for both the child and parents.

Conflict of interest

None

Author contributions

Writing the manuscript (SA).

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