**Expectations of Treatment of Hepatitis C in Children**

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## ABSTRACT

**Background:** HCV infection in children differs from infection in adult through transmission paths, spontaneous viral clearance rate, and fibrosis progression duration of chronic infection. It is estimated that the rate of children with chronic hepatitis C will develop cirrhosis is less than 2%, however there are reports of children requiring liver transplantation.

**Objective:** Was to present a general overview of the current treatments for HCV infection in children.

**Material and method:** Databases such as PubMed, MEDLINE and Scopus were used as information sources to identify and analyzed the current information about the treatment for HCV infection in children.

**Results:** In children the most commonly used drugs are pegylated alpha interferon in combination with ribavirin, both drugs are given in combination therapy in children over 3 years of age with detectable HCV RNA levels. The side effects reported are similar like to adults, including leukopenia, anemia, weight loss (determined by anorexia, nausea, and abdominal pain), changes in behavior, depression, suicidal ideation, thyroid disorders, and transient slowing of the growth rate. Recently, it has been approved that the other drugs with direct antiviral activity (DAAs), the protease inhibitors NS3/4, Boceprevir and Telaprevir were introduced into clinical practice in adults, only Boceprevir was tested and not approved for use in children, (Clinical Trials gob No P07614), adverse effects were reported in 37.5% of participants and included nausea, fatigue, malaise, increased systolic pressure, increased liver enzymes.

**Keywords:** Children, hepatitis C, peginterferon, ribavirin, treatment

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## INTRODUCTION

The hepatitis C virus (HCV) was identified in 1989 (1), and to date is one of the most important cause of chronic liver disease worldwide (2), which affects 2% of the adult population with some regional variations. The number of children affected is estimated at between 23,000 and 46,000 in the United States of America and 6,600 children in Canada (3, 4). From 1998 to 2009, 133 liver transplants were performed due to secondary liver failure as consequence of chronic hepatitis C virus infection and have been reported only two cases of hepatocellular carcinoma; however the existence of more cases cannot be ignored (5).

In the adults, HCV infection aggravates in an acute phase which is asymptomatic, and a large proportion progresses to chronic, cirrhosis and hepatocellular carcinoma (6,7) leading to 600,000 deaths every year (8). Only a small proportion of the population with chronic hepatitis C is observed in children (9, 10). There are reports of hepatocellular carcinoma in teenagers which are associated with chronic hepatitis of HCV infection. Unfortunately the extent of information about the evolution and treatment is reduced when compared against publications in adults (11).

HCV infection in children differs from infection in adult through transmission paths, spontaneous viral clearance rate (12, 13), and fibrosis progression duration of chronic infection. There are reports of deaths of children due to liver failure in the past nine years because of acquisition of infection and hepatocellular carcinoma cases are reported in 25 to 27 years after infection (14). It is estimated that the rate of children with chronic hepatitis C will develop cirrhosis is less than 2% (15, 16), however there are reports of children requiring liver transplantation (17). The scope of this review is to present a general overview of the current treatments for HCV infection in children.

## Virology

Hepatitis C virus (HCV) is an enveloped virus from 50 to 80 nm in diameter formed by a positive sense single stranded RNA of which seven are known genotypes and subtypes 100 (18) which belongs to the family Flaviviridae and genus *Hepacivirus* (19). The viral RNA functions as mRNA and its translation produces a polyprotein precursor of 3010 amino acids and from this functional, structural and nonstructural proteins by cellular and viral proteases will be generated. Untranslated 5 'and 3' ends contain important regions for viral replication, region nearby 5' end contains information coding for the structural proteins in the regions C, E1, E2 and NS1. The remainder of the genome codes for the nonstructural proteins is encoded by the regions NS2, NS3, NS4 and NS5 (20). The virus must interact with hepatocyte membrane receptors, then endocytosed and released into cytoplasm, there, the RNA is translated directly and peptidases present in the endoplasmic reticulum of the host cell cleave the 5'-end, causing proteins C, E1, E2 and NS1 nonstructural proteins to be released, which are cleaved by the action of viral proteases (21, 22), this cycle allows a wide range of targets. The virus replicates predominantly in the liver, but has tropism for other cells such as T and B lymphocytes, their half-life in blood is 2.7 h, a daily high production of viral particles (23, 24) and the error rate during viral replication is $10^{-3}$ to $10^{-5}$ added to the absence of the error correction by the NS5B polymerase in the same patient allows to identify different quasi species (25), in addition a high rate of polymerase error, a short replicative cycle, the small size genome are factors contributing to the generation of these quasi species, which differ in their biological properties: virulence, cell tropism and ability to evade the immune system (26). The virus can be inactivated at 60° C for 30 minutes or at 100° C for two minutes (27).

## Epidemiology

In 2014, the World Health Organization (WHO) published the "Guidelines for the screening, care and treatment of persons with hepatitis C infection" where the number of infected persons in different regions of the world was described (Table 1) (28).

Worldwide studies of incidence and prevalence in children are limited and the clinical manifestations are rare and the diagnosis is usually performed during the realization of screening tests in those have identified risk factors or to diagnose HCV infection in a close relative. The incidence and prevalence are relatively low ranging from 0-0.4 to 14.5% (29). In the United States the seroprevalence is 0.2% for those under 12 years of age, and 0.4 for those between 12-19 years old.

## Routes of transmission

Globally it is considered that the most common forms of transmission in order of frequency are: intravenous drug use, blood transfusion, multiple sexual partners, tattoos, piercings and finally the perinatal. Although in some developing countries such as Mexico the most common cause of acquisition of C virus remains transfusion of blood and blood products (30, 31).

The main route of transmission in children is vertical transmission (32).there is no evidence of decreased transmission of infection by avoiding breast feeding (33), transmission rates reported for breast fed are 3.7% against 3.9% of formula-fed (34), is associated with the existence of free fatty acids produced by lipases destroy the lipid envelope of virus (35, 36). It is considered that the risk is greater in the presence of cracks and bleeding from the nipple of the mother. The infection rate among children of mothers with HCV infection is 2 to 18% (37) and is associated with viral load, HIV co-infection, premature rupture of membranes, exposure to

maternal blood during childbirth (38), with a spontaneous resolution rate is variable to 75 at the age of 15 months (39, 40). Spontaneous clearance occurs between 25 and 52 months old, initially documented transient elevation in liver function tests followed by normalization coincides with a decrease in viral load, suggesting that children infected through vertical transmission potent inflammatory response that involves may suggest specific cellular immunity to viral clearance (41-43). It is essential to signal elevation of transaminase after 3-4 years of age is associated with lack of viral clearance.

Horizontal transmission and domestic violence is of little relevance, and has been associated with inadvertent contact with contaminated blood through utensils personal use.

**Immunopathology**

Many factors influence the interaction between HCV and the infected host, and determine the presence of infection and liver disease is highly variable between viral factors are viral replication, viral protein expression, viral genotype, immunity of viral peptides and liver damage. Host factors include competition of the innate immune response, local and systemic cytokine production, humoral immune response and cell (44, 45).

The presence of lymphocytes in the liver parenchyma has been interpreted as evidence of immunologically mediated damage. Viral clearance is associated with development and persistence of viral specific cytotoxic T lymphocyte responses and helper T cells. Also, there is growing evidence that HCV may interfere with the innate and acquired immune activation at multiple levels (46, 47).

**Clinical manifestations**

The diagnosis of chronic hepatitis C in children is usually performed in screening programs, in subjects at risk for having a history of parenteral exposure, or after the discovery of an affected family. The clinical manifestations are rare, were more frequently reported in adolescents as fatigue, anorexia, weight loss, nausea, abdominal discomfort, hepatomegaly (48-50). The histopathological findings in children with chronic hepatitis C are significant liver fibrosis with percentages of 10% (51), which is more intense with increasing age, the degree of hepatic inflammation is related with the duration of less intense infection than in adult patients, has been reported cirrhosis at a rate of 4% (52). The diagnosis of chronic HCV infection should be based on the demonstration of HCV RNA positive at least 3 years after the exposure of risk.

**Diagnosis**

The importance of establishing the diagnosis is that the clinical manifestations are subtle, but the liver damage is cumulative and increases with time period. Concerning with laboratory studies, it is recommended to test for HCV using RNA PCR at 2 and 6 months of age, and serology for the antibodies against hepatitis C virus to 18 months old.

**Natural history of the disease**

Symptomatic chronic infection in children is not frequent, as the infection was discovered during routine laboratory tests or during the deliberate search of children of mothers with chronic hepatitis C. Of the patients exposed and infected with the 10% clearance of virus at 12 months after exposure and between 20 to 30% at 24 months, after this period it is less probable for spontaneous clearance (3.5%).

In relation to liver function tests, 90 % of children have elevated transaminases subsequently tend to normalize although the infection persists. Unlike adult evolution is moderate, severe liver damage and cirrhosis only occur in 2% of chronic patients infected with HCV (53), which is attributed to the lack of exposure to alcohol, drugs and concomitant infections that may influence prognosis. There is evidence that the infection progresses to chronicity in 50-60% of children exposed (54, 55).

**Histopathology**

Due to the nature of the HCV, a RNA virus with a life cycle confined to the cytoplasm (56), is little probable with integration of their genetic material into the host genome, the manner in which chronic HCV infection contributes to the development of hepatocellular carcinoma is by an indirect route through chronic liver inflammation, progressive liver fibrosis, selection and persistence of clones of neoplastic cells, a process that can last from 20-40 years (57). In about 10% of biopsies data are mild condition, the rest constitutes moderate condition being less frequent necrosis and inflammation. Approximately 4 to 6% of children with chronic hepatitis C have histological evidence of advanced fibrosis or cirrhosis. The histological pattern tends to worsen with age and duration of infection.

**Treatment**

The goal of treatment is to achieve sustained viral clearance in early stages that may alter the natural history of the disease, normalization of liver function tests, reversal of histological lesions and symptoms when present (58).

The most commonly used drugs are pegylated alpha interferon in combination with ribavirin (59-61), the response rate achieved in adults with drugs approved by FDA in 2008 and EMEA in 2009 (62). The first of these drugs is an alpha interferon attached to a polyethylene glycol molecule with two different molecular weights of 40kDa (2a) and 12 kDa (2b) to increase half-life, increase the bioavailability and reduce the number of subcutaneous applications, has no direct antiviral activity act through the via JAK-STAT signaling (63), increase the immune response to HCV by the phagocytic activity of macrophages, stimulation of lymphocyte cytotoxicity activity against cells infected HCV and biochemical changes that cause a non-selective antiviral state in cells exposed to the same species(64). The second is a guanosine analogue that prevents viral RNA synthesis by inhibiting HCV polymerase (65). The duration of treatment is 48 weeks if patients are infected with genotype 1 and 24 weeks in all other cases (66).

Both drugs are given in combination therapy in children over 3 years of age (67), with detectable HCV RNA levels greater than 50 IU/mL with liver biopsy with fibrosis, moderate inflammation and necrosis. Similar side effects are reported to adults, including leukopenia, anemia, weight loss (determined by anorexia, nausea, and abdominal pain), changes in behavior, depression, suicidal ideation, thyroid disorders, and transient slowing of the growth rate (68). Adverse effects determine that about 10-14% of adult patients discontinue their treatment and 4% of pediatric patients (69). In children treated with pegylated interferon α2a + ribavirin in the PEDS-C trial was evident that the changes in body weight, height, BMI and body composition, some of the effects were reversible except the index weight for age that was not recovered in two years tracking the following initial period, although extended to six years monitoring has shown the recovery rate and the absence of effects on height was long term, (70, 71).

Prognostic factors for successful response to treatment are identified with infections of genotypes 2 and 3, less than 12 years of age and viral load of less than two million copies, sustained virologic response (SVR) rate is about 50% for children infected with Genotype 1 and 4 (72, 73), and increased to 90% in those with genotypes 2 and 3 (74). Recently, it has been approved that the other drugs with direct antiviral activity (DAAs), the protease inhibitors NS3/4, Boceprevir and Telaprevir were introduced into clinical practice in 2011, when they were added to the conventional double therapy, increased the rate of SVR from 25- 30% (75), the addition of Sofosbuvir increases the response rate to 90%. The results have been encouraging in adults, but for children no new drugs have been approved yet.

These new drugs block viral proteins in a selective and directed way. Because of the combinations of these drugs, among which may be included or not interferon-α, recent clinical trials obtain a sustained viral response rate above 90% in most patients (76). (Table 2).

From the new drugs DAAs only Boceprevir was tested and not approved for use in children, (Clinical Trials gob No P07614), adverse effects were reported in 37.5% of participants and included nausea, fatigue, malaise, increased systolic pressure, increased liver enzymes. The rest of the DAAs have not yet been tested in pediatric Population and the high cost to be a barrier to use it universally since the prevalence of infection in children with chronic hepatitis C is low, long-term effects occurs rarely in children. Further investigation is needed on the safety and efficacy of new drugs in children, still there is a long way to go in the treatment of chronic hepatitis C in children.

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Table 1: Estimated number of infected peopl in the world by hepatitis C virus

| Region | Estimated number of infected people |
|---|---|
| Asia Pacific | > 2.4 million people |
| Central Asia | > 2.9 million people |
| East Asia | > 50 million people |
| South Asia | > 50 million people |
| Southeast Asia | > 11 million people |
| Australasia | > 0.6 million people |
| Central Europe | > 2.9 million people |
| Eastern Europe | > 6.2 million people |
| Western Europe | > 10 million people |
| North America | > 4.4 million |
| Caribbean | > 0.7 million people |
| America Central | > 3.4 million people |
| South America | > 0.9 million people |
| Tropical South America | > 2.3 million people |
| Andean Latin America | > 1 million people |
| Oceanía | > 0.2 million people |
| Central Africa Sub-Saharan | > 1.9 million people |
| East Sub-Saharan Africa | > 6.1 million people |
| West Africa Saharan | > 1.4 million people |
| Southern Africa Sub-Saharan | > 8.4 million people |

Table 2. Classification of drugs for treatment of hepatitis C virus infection

| Drug Type | Drugs | Mechanism | Genotypes / genetic barrier (72) | Adverse effects |
|---|---|---|---|---|
| Inhibitors of hepatitis C virus protease (NS3 / NS4) [30, 69] | Boceprevir<br>Telaprevir<br>Simeprevir (TMC 435)<br>Asunaprevir (BMS-650032)<br>Faldaprevir (BI 201335)<br>Danoprevir (RG-7227)<br>Vaniprevir (MK 7009) | Inhibitor of NS3 / 4A serine protease which performs the proteolytic cleavages of the HCV encoding NS4A, NS4B, NS5A, NS5B | Genotype 1 / Low genetic barrier | anemia, dysgeusia, and neutropenia, rash |
| HCV NS5A inhibitor | Daclatasvir (BMS-790052)<br>Ledispavir (GS-5885)<br>ABT 267<br>MK8742<br>ACH-3102<br>PPI-668 | Inhibit the action of RNA-binding phosphoprotein that is involved in RNA replication | Pangenotype / intermediate genetic barrier | Headache, asthenia, diarrhea, nausea, abdominal pain |
| NS5B polymerase inhibitors | | | | |
| Nucleotide analogues | Sofosbuvir (PSI-7851)<br>Mericitabine (RG7128)<br>Valopicitabine (NM283) | Selectively inhibits the NS5B polymerase | Pangenotype / High genetic barrier | Nausea, fatigue, headache, insomnia, anemia |
| Non- Nucleotide Analogues | ABT 333<br>ABT 072<br>BMS 791325<br>Deleobuvir | Selectively inhibits the NS5B polymerase | Genotype 1 / Low genetic barrier | |