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# Pediatric hepatitis C infection: to treat or not to treat...what's the best for the child?

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**Abstract. – *Objectives:*** **Pediatric hepatitis C mainly occurs through mother to child transmission, to date. Children usually present a mild disease, but they are not spared from its long-term complications. Thus this infection cannot be underestimated in children and intervention is necessary. Current treatment is based on the administration of pegylated-interferon associated with ribavirin, but few studies evaluated the efficacy and safety of this therapeutic protocol. Moreover, there is still no clarity on who, when and how to treat pediatric patients. This article, based on the information in literature, provides an overview of the main aspects of the disease, with particular attention to treatment.**

***Methodology and Results:*** **We describe the different treatment options available. About the association peginterferon plus ribavirin, we analyze thirteen non-randomized studies and one trial, found in recent literature. These studies are not directly compared because of differences in age, type of infection (vertical or not), viral genotypes and duration of treatment, between groups enrolled. The overall sustained viral response rate ranges from 28.6% to 81.8%. The rate of treatment success is higher in children infected with genotypes 2 and 3 than with other genotypes. The therapy does not induce severe adverse effects and children present better tolerance to antiviral than adults.**

***Conclusions:*** **The pharmacological efficacy of peginterferon and ribavirin seems to be proven by data collected in studies cited, but there are different opinions about who, when and how to treat children infected. Thus, further research is needed to define the best management of vertical acquired hepatitis C.**

*Key Words:*

HCV, Mother-to-child, PEG-IFN, Early treatment, Efficacy.

## Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family. It was cloned first in 1989 and identified as the causative agent of non-A, non-B hepatitis. It was classified in six major genotypes and numerous subtypes; this variability allows the virus to escape host immune surveillance. HCV infects individuals of any age and most of the complications become clinically apparent after a long time, often years. The infection mainly occurs through transfusion of infected blood or through mother to child transmission. Although this liver disease has a significant importance especially in adults, it is a morbid form that cannot be underestimated in children. Even though complications resulting from HCV hepatitis typically do not occur during pediatric age, an early intervention in childhood would prevent, or at least postpone, the unfortunate outcome of the disease.

### Epidemiology

HCV infection is a worldwide health problem with a global prevalence of approximately 2% and large regional variations[1]. Development of chronic hepatitis and late sequelae (liver cirrhosis and hepatocellular carcinoma) are the most significant consequences of this form of hepatitis.

Several viruses can cause liver disease, but since hepatitis B virus vaccine campaign started in industrialized countries, HCV has become the most significant cause of chronic liver disease of infectious etiology in children[2].

The highest prevalence of HCV infection is among the 30- to 49-year-old age group[3], but this value is not significant in the pediatric population, considering that the major route of HCV transmission is via mother-to-infant transmission.

In fact it's important to know that the majority of children infected with HCV before 1992 acquired infection through transfusion of blood or blood products. After 1992, following the improvements in detection of HCV, transfusion-associated hepatitis C has become extremely rare in countries where adequate facilities for screening blood are available. Therefore, at present most

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chronic hepatitis C in children is related to a vertical transmission[4]. This demonstrates that the epidemiological scenario has radically changed in the pediatric population over the last two decades.

It was observed that prevalence of HCV infection in children varies widely by country, ranging from 0% in Japan and 0.4% in Italy to up to 14.5% in Cameroon[5-7]. More indicative data were collected in an important study conducted in USA, showing that the seroprevalence of HCV antibodies in children ranges between 0.2%, in children aged 6-11 years, and 0.4%, in children aged 12-19 years[3].

So, although the infection rate is low, it may potentially result in 50,000 new cases per year[4], making it a public health problem of great dimensions.

### Mother to Child Transmission

The various factors that play a role in vertical transmission are listed in Table I.

Currently, vertical transmission is the most common route of HCV transmission in pediatric population, even though acquiring the infection through blood transfusion or invasive surgical procedures is still possible.

Mother-to-child HCV transmission usually occurs in women with HCV viraemia[8]. In fact vertical infection from mothers negative for HCV RNA is an extremely rare event. However, it is still unclear whether high levels of concentration of viral RNA are associated with an increased risk of transmission.

The risk level is higher in HIV/HCV co-infected mothers than in HIV-negative mothers[9]. It has been demonstrated that the rate of vertical transmission grow from 3.5% in HIV-negative mothers up to 19.4% in HIV-positive ones[10]. There are different hypotheses that would explain this phenomenon. Some Authors sustain that in women coinfected with HCV and HIV, there is a rise up of HCV viral load, as a result of HIV-mediated immunosuppression[11]. Other Authors demonstrated that HIV infection facilitates HCV entry and replication in blood cells, favoring child infection[12]. Anyway, it was reported that in HCV/HIV-co-infected women, transmission occurred with lower mean HCV viraemia than in non HCV/HIV co-infected women[13].

History of maternal intravenous drug use is an important predicting factor of perinatal infection associated to peripheral maternal blood mononuclear cell infection by HCV[14]. This evidence results to be one of the main risk factor for transmission. Even though the mechanism has not been yet clarified, it has been well demonstrated that lymphocytes may act as an HCV reservoir, playing a key role in the relapse of HCV disease after liver transplantation or after the discontinuation of therapy[12].

It's a curious fact that females are twice as likely to be infected than males, Therefore, child gender may be important for the possibility of transmission[15].

Prolonged rupture of membrane and delivery complications increase the risk of transmission, as well as obstetric procedures and intrapartum exposure to maternal blood infected[16].

The perinatal transmission is not influenced by the mode of delivery. In fact, there are similar infection rates between infants delivered by cae-

**Table I.** Factors impacting perinatal transmission of Hepatitis C Virus.

| Risk factors | Factors predicting the risk | Factors not associated with the risk |
|---|---|---|
| Maternal detection of HCV RNA by PCR | Human immunodeficiency virus coinfection | Mode of delivery |
| Peripheral blood mononuclear cell infection by HCV | History of intravenous drug use | Previous delivering of a child infected perinatally with HCV |
| Female gender | Maternal disease activity; alanine transaminase concentrations | Breast-feeding |
| Prolonged rupture of membrane and delivery complications | HCV infection of the father-sexual partner of the mother | Genotype |
| Obstetric procedures and intrapartum exposure to HCV-infected maternal blood | | Mother-child human leukocyte antigen concordance |

HCV = hepatitis C virus; RNA = ribonucleic acid; PCR = polymerase chian reaction. The table is adapted from Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. J Med Virol 2009; 81: 836-843.

sarean section or vaginally. Furthermore, although HCV RNA may be detected in breast milk and colostrum, breast feeding does not appear to increase the rate of HCV transmission, unless the mother is also HIV positive. Current recommendations are that women with HCV without HIV co-infection can be advised to breast feed[9].

### Diagnosis

Whereas there are no therapeutic interventions to prevent vertical transmission, there would be no indications to screen mothers for HCV. In fact it is important to investigate the presence of risk factors that influence the transmission rate and to test the presence of HCV RNA on maternal blood, because transmission occurs mostly in mothers presenting viraemia.

The diagnosis of perinatal infection is confused by passive transfer of maternal antibodies up to 13 months and occasionally 18 months, and this affects the significance of testing on newborn blood the presence of HCV antibodies[17].

However, our present knowledge indicates that all children born to anti-HCV positive women need to be tested. Anti-HCV testing at 12 and 18 months of age is highly effective for detecting the infection, considering that repeated blood sampling could be invasive for infants. Alternatively, to obtain an earlier diagnosis, PCR tests for HCV-RNA are useful. It is recommended that the first PCR test has to be performed at around 2 months of age and testing has to be repeated at around 6 months of age. Two positive results are highly suggestive of an infection. Although two negative PCR results strongly suggest that the infant is not infected, this needs confirmation by an antibody test performed at, or after, age 1 year[18].

This timing for PCR test is due to its low sensitivity, when executed at birth. In fact, in a study on 547 children, born to HCV infected mothers, it resulted that sensitivity of PCR test is low at birth (22%), but increases to 85% by 6 months; specificity is constant over age at 98%; the positive predictive value of PCR testing rises from 33% at birth to 78% at 9 months of age, while negative predictive value ranges from 96% to 99%[19].

A possible approach to diagnosis is defined in Table II.

Infants born to anti-HCV positive mothers are considered infected when HCV RNA is detected in peripheral blood by PCR in at least two serum samples during the first year of life and/or when anti-HCV positivity persists beyond 18-24 months of life[20].

Resolution is determined by the disappearance of HCV RNA, even though it is fundamental to consider that the disappearance of HCV RNA may be due either to previous transient viraemia phenomenon or to a real infection resolution.

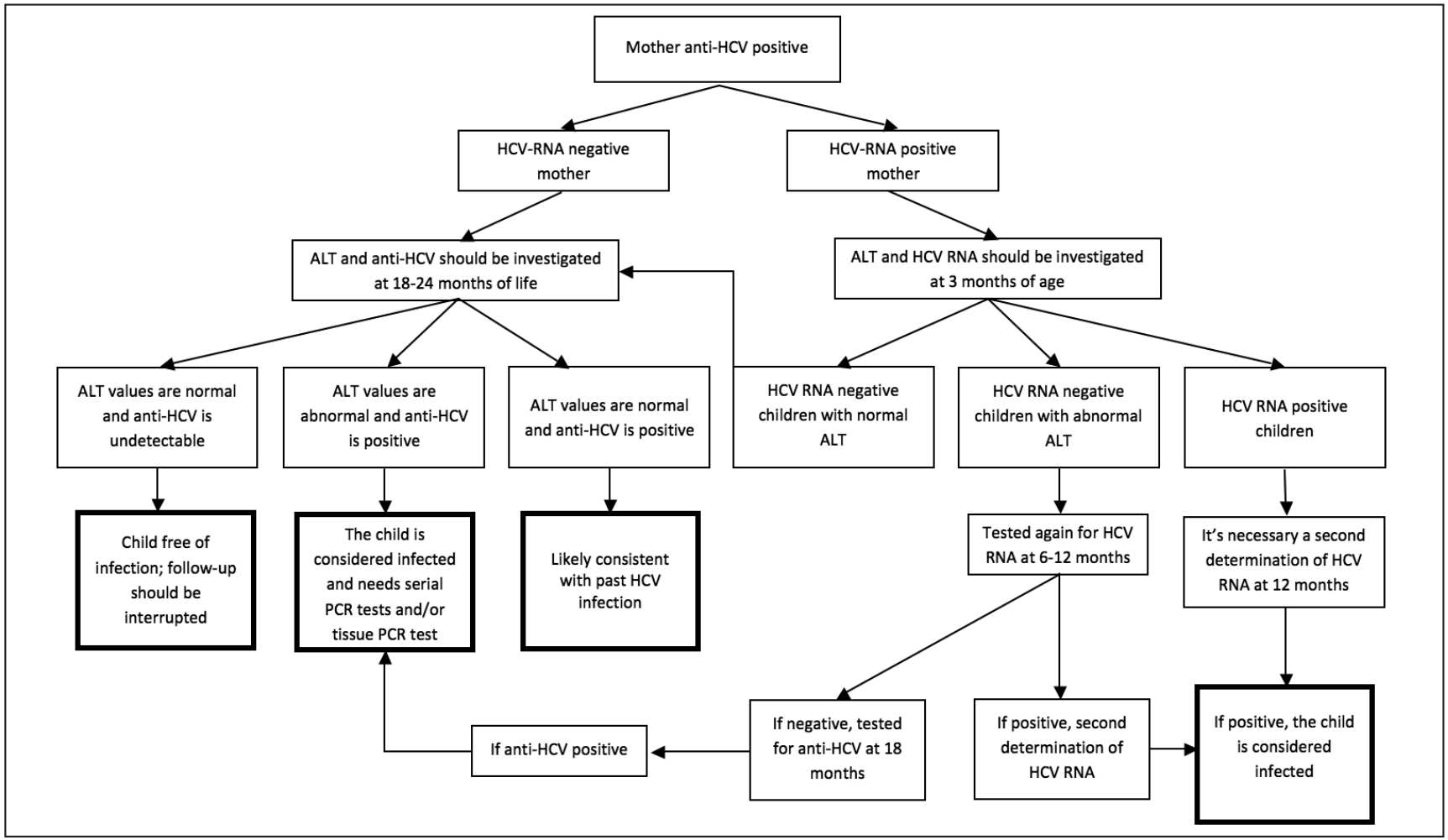
### Natural History

Before facing this section, it's of primary importance to know that studies conducted to date on pediatric hepatitis C course generally include both vertical and horizontal infections, patients of any age and often associated with other diseases.

It has been showed that not all infected children will develop chronic infection. In fact clearance of viraemia occurs spontaneously in 19-24% of perinatally infected children in the first 2-3 years of life and the remaining 70-80% develop chronic hepatitis C, as demonstrated in a study on 70 children born to HCV infected woman, enrolled consecutively in five European centers between 1990 and 1999[21,22]. Children and adolescents who experienced the infection, without virus clearance, usually present a mild disease with normal or only mildly abnormal serum alanine aminotransferase levels[23]; children who have vertically acquired the infection are asymptomatic too. Moreover, pediatric patients have less inflammation, fibrosis, and steatosis than adults[24], but significant fibrosis and even cirrhosis may develop during childhood and the risk of progressing to end-stage liver disease later in life remains[25]. In fact, several case reports link chronic HCV infection with the development of hepatocellular carcinoma in adolescents and young adults infected during childhood[26].

Finally, other equally important implications characterize chronic course of hepatitis C in children. In fact, although the evolution of the disease does not produce evident signs of illness in pediatric age, it's not possible to ignore the psychological implications of the infection and the difficulties of the family in managing the sick child. HCV infection, in its early stages, does not lead to global impairment in quality of life, or in cognitive, behavioral, emotional disfunctioning in children, but it is associated with higher caregiver stress and strain on the family system, and it may be associated with some cognitive changes in children[27].

**Table II.** Screening and follow-up of infants born to anti-HCV positive mothers.




ALT = alanine aminotransferase; HCV = hepatitis C virus; RNA = ribonucleic acid; PCR = polymerase chian reaction. The flowchart is adapted from Resti M, Bortolotti F, Vajro P, Maggiore G; Committee of Hepatology of the Italian Society of Pediatric Gastroenterology and Hepatology Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. Dig Liver Dis 2003; 35: 453-457.

### Treatment

The main aim of therapy is to achieve a sustained viral response (SVR), defined as undetectable serum HCV RNA 24 weeks after treatment cessation.

From the pharmacological point of view three types of approaches have demonstrated effectiveness over the years: first, administration of interferon (IFN) alone, subsequently of IFN with ribavirin and finally the newest protocol, based on the administration of pegylated-interferon (PEG-IFN) with ribavirin. As in the evaluation of natural history, we don't have targeted studies concerning therapy options focused on mother to child acquired infections.

IFN is part of a group of naturally occurring proteins that have antiviral, antiproliferative and immunomodulatory activity. Even though the exact mechanism of action is not well known, this compound is taken up by cells. This reaction leads to a cascade mechanism that inhibits the viral attachment, replication and assembly. In this way the administration of interferon induces a form of resistance against viral infection. This molecule has been the only basis of hepatitis C therapy for a long time.

The efficacy of IFN monotherapy has been evaluated in various randomized and non-randomized studies, often performed in small populations. In an analysis of published trials of interferon monotherapy in children with chronic hepatitis C, an average SVR was observed in 36% of children, with a range from 0% up to 73%[28].

In order to increase the rate of response, ribavirin has been associated with the IFN in the HCV infection therapy.

Ribavirin is a synthetic guanosine analogue with activity against several RNA and DNA viruses, including Flaviviridae. It seems to act by interfering with the synthesis of guanosine triphosphate, inhibiting the viral capping of mRNA and inhibiting viral RNA polymerase.

In a randomized control trial a SVR of 59% was observed by this addition[29].

However, these therapeutic protocols are no longer used as standard therapies, since the PEG-IFN was produced. So, in adults the approved treatment is based on combination of this new compound and ribavirin. PEG-IFN is synthesized by covalently linking a polyethylene glycol moiety to the IFN. This addition confers an extended serum half-life, compared with the normal IFN, allowing once-weekly dosing. This new pharmacologic property is very important, considering that resolves the problems due to the IFN administration. In fact, the thrice-weekly dosing of the IFN were not well tolerated by children.

Two kind of PEG-IFN are available: the PEG-IFN $\alpha$2b and $\alpha$2a. The first one was approved by the US Food and Drug Administration for children aged 3 years and older and the second drug will be approved soon. There is no SVR rate difference between the two formulations in adults[30].

Concerning the efficacy of this drug associated to ribavirin, various international studies have been conducted in pediatric patients group. We found 13 non-randomized studies (characteristics of non-randomized studies are summarized in Table III) and 1 randomized control trial published in literature, all including children both with vertical and parenteral acquired infection. There is no study that specifically evaluates only children with vertical acquired infection to date.

In terms of treatment response, a range of SVR values from 28,6%[31] to 81,8%[32] was obtained from non-randomized studies (Table IV and Figure 1). This spread is probably due to different virus genotypes infecting children enrolled. In fact it's necessary to know that the genotype 1, in particular, and 4 are associated with lower response rates to all therapies than are genotype 2 or 3. Thus, the different proportion of genotypes in the groups is the main confounding factor in results interpretation. In those studies that report the subgroups, distinguished by genotypes, it's possible to observe higher rate of SVR related to genotypes 2 and 3[32-37].

Sokal et al[33], in their study, compared the group including genotypes 2 and 3 with the group including genotypes 1 and other genotypes, both receiving treatment with PEG-IFN. Early virologic response at week 12 was observed in 83% of the first group patients and in 57% of second and SVR was maintained in 89% of patients in first group and in 57% of second one.

In the only randomized controlled trial of PEG-IFN and ribavirin compared with PEG-IFN and placebo, the efficacy of this association has been demonstrated by the higher SVR rate obtained in children treated with PEG-IFN plus ribavirin than the control group (53% vs 21%). Moreover, the higher SVR rate was related both to a higher end-of-treatment response (no detectable HCV RNA in plasma at the end of therapy) and to a lower relapse rate after stopping therapy than children treated with PEG-IFN and placebo[38].

**Table III.** Non-randomized studies characteristics.

| Author/ Year | N. | Characteristics | Age | PEG-IFN | RBV | Weeks | Lost | G1 and others | G2/ G3 |
|---|---|---|---|---|---|---|---|---|---|
| Sokal EM/2010 | 65 | Naive | 13-17 | 100 μg/m$^2$ | 15 mg/kg/day | -24 for G1 and others<br>-48 for G2/G3 | 10 | 47 | 18 |
| Al Ali J/2010 | 12 | NR | 14-17 | 1.5 mg/kg | 15 mg/kg/day | -48 | 1 | 12* | 0 |
| Wirth S/2010 | 107 | Naive | 3-17 | 60 μg/m$^2$ | 15 mg/kg/day | -48 for G1, G4 and G3 with viral load ≥ 600.000 IU/ml | | | |
| | | | | | | -24 for G2 and G3G3 with viral load < 600.000 IU/ml | 1 | 77 | 30 |
| Tajiri H/2009 | 37 | 16 previously treated with IFN | < 30 | 1.5 mg/kg | 15 mg/kg/day | -48 for G1, -24 for G2/G3 | 4 | 22 | 15 |
| Ghaffar TY/2009 | 7 | 6 naïve | 8-16 | 1.5 μg /Kg | 15 mg/kg/day | -52 | 0 | 6* | 0 |
| Jara P/2008 | 30 | 75% naïve | 3-16 | 1.0 μg /Kg | 15 mg/kg/day | -48 for G1, -24 for G2/G3 | 3 | 27 | 3 |
| Kowala-Piaskowska A/2007 | 23 | NR | 6-18 | 1.5 μg /Kg | 15 mg/kg/day | -12 | 0 | 22 | 1 |
| Baker RD/2007 | 10 | 7 naïve | 11-18 | 1.5 μg /Kg | 800 mg/day | -48 for G1, -24 for G2/G3 | 1 | 9 | 1 |
| Pawlowska M/2006 | 13 | 4 previously treated with IFN and 9 with IFN plus ribavirin | 13,9 (mean age) | 1.5 μg /Kg | 15 mg/kg/day | -12 | 1 | 13 | 0 |
| Zhang HF/2005 | 54 | inductive treatment with IFN for a week | 11,3 (mean age) | 104 μg/m$^2$ | 15-20 mg/kg/day | -52 | 0 | 38 | NR |
| Wirth S/2005 | 62 | NR | 2-17 | 1.5 μg /Kg | 15 mg/kg/day | -48 | 1 | 48 | 13 |
| Służewski W/2005 | 10 | NR | NR | NR | NR | NR | 0 | 10** | 0 |
| Kowala-Piaskowska A/2005 | 20 | NR | NR | NR | NR | -48 | | 20** | 0 |

*In the studies of Al Ali J and Ghaffar TY there were only genotype 4 patients; **In Sluzwski W and Kowala-Piaskowska studies there were only genotype 1 patients.

**Table IV.** Efficacy parameters evaluated in non-randomized studies.

| Author/Year | EVR (%) | SVR (%) | G1 and others SVR (%) | G2/G3 SVR (%) |
|---|---|---|---|---|
| Sokal EM/2010 | 42 (64.6) | 43 (66.1) | 27 (57) | 16 (89) |
| Al Ali J/2010 | NR | 9 (75) | 9 (75)* | |
| Wirth S/2010 | NR | 70 (65) | 42 (54.5) | 28 (93) |
| Tajiri H/2009 | 10 (30.3) | 27 (81.8) | 16 (80) | 11 (84.6) |
| Ghaffar TY/2009 | NR | 2 (28.6) | 2 (28.6)* | |
| Jara P/2008 | 19 (72) | 15 (50) | 12 (44.4) | 3 (100) |
| Kowala-Piaskowska A/2007 | 15 (65.3) | NR | NR | NR |
| Baker RD/2007 | NR | 3 (33.3) | 2 (22.2) | 1 (100) |
| Pawlowska M/2006 | 6 (50) | NR | NR | NR |
| Zhang HF/2005 | 42 (87.5) | NR | NR | NR |
| Wirth S/2005 | NR | 35 (57.3) | 23 (47.9) | 13 (100) |
| Służewski W/2005** | | ETR 8 (80) | | |
| Kowala-Piaskowska A/2005** | | ETR 17 (85) | | |

*In the studies of Al Ali J and Ghaffar TY there were only genotype 4 patients; **In these studies only ETR was reported; EVR is defined as undetectable HCV RNA in serum or >2 log10 decrease in HCV RNA compared with baseline values; SVR is defined as a negative HCV RNA at least 24 weeks after cessation of therapy; ETR is defined as negative HCV RNA at the end of treatment.

The role of genotype has been also confirmed in this study: 47% of SVR was achieved in children infected by genotype 1 virus and 80% of SVR in those infected by the other genotypes[38]. These results are similar to those obtained in previous non-randomized studies and give further support to the choice of using this therapy in pediatric hepatitis C.

How long to administer these drugs is still subject of debate. Even though 24 weeks of PEG-IFN plus ribavirin are effective for genotypes 2 and 3 in adults[39], the duration of therapy recommended for all children is 48 weeks for all genotypes. The evaluation of a shorter duration of treatment is still ongoing and some pediatric studies[33] have already shown excellent re-

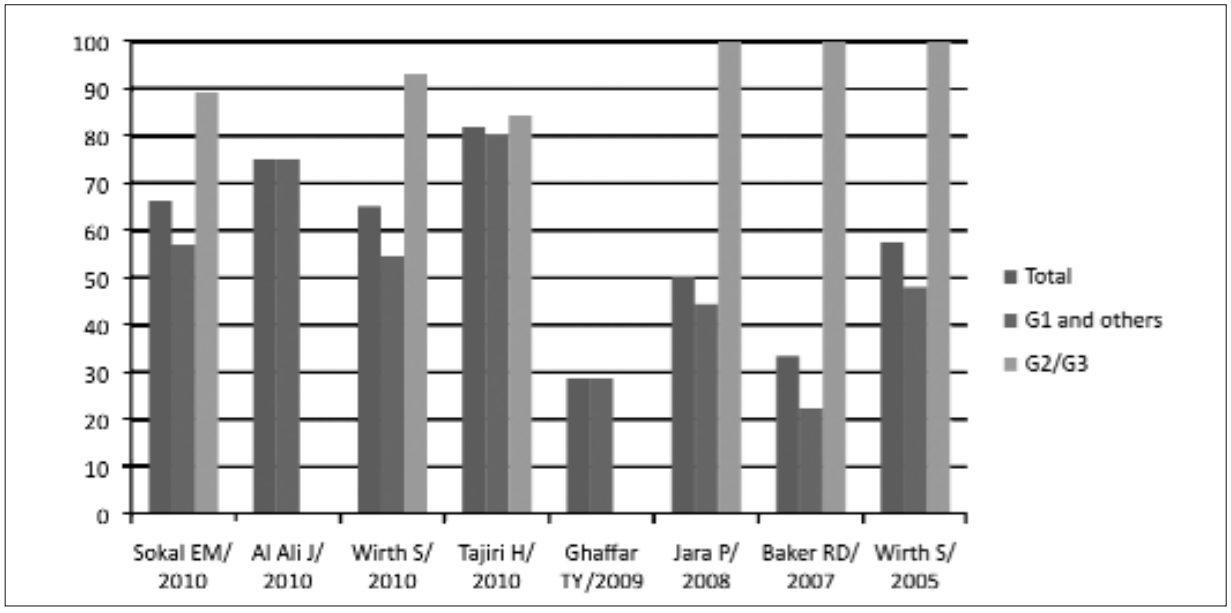



**Figure 1.** SVR total and by genotype of PEG-IFN/ribavirin therapy in non-randomized studies. We included in this graphic only the studies that reported the SVR rates. All patients in the Al Ali J and Ghaffar studies were genotype 4.

sults with 24 weeks of treatment for genotypes 2 and 3.

Furthermore, when treatment with PEG-IFN and ribavirin is started, possible side effects have to be considered. Flu-like and gastrointestinal symptoms arise quite often, similarly to side effects following administration of IFN. As we could see in all studies mentioned[33-38], these symptoms occurred in most children treated. Moreover, therapy leads to significant decline in total white blood cell count, absolute neutrophil count and hemoglobin, which generally return to baseline at the end of treatment[38]. These adverse events are important, but they do not involve the treatment discontinuation. In any case when they occur the dose of PEG-INF and/or ribavirin should be reduced.

It's important to know that a better compensatory bone marrow function was observed in children aged 3-11 years, demonstrating a better tolerance of youngest children to these drugs[34].

Body height and weight loss are common during the treatment phase. However, a weight gain after the end of therapy is generally observed along with an improved growth velocity, even though these children remain slightly below the median for their population[34].

Mild or moderate psychiatric disorders may also occur, but similarly to the previous problems, they do not generally cause changes in therapy. These symptoms could appear as mild anxiety, irritability, insomnia, agitation, restlessness, mood swings, behavioral changes, affect lability and depression. It's an extremely rare occurrence that these conditions necessitate treatment discontinuation or antidepressant therapy[33-38].

In a few cases hypothyroidism, hyperthyroidism and related TSH abnormalities may appear, but permanent endocrinological disorders are uncommon.

New onset juvenile diabetes mellitus is extremely rare.

### To Treat or Not to Treat?

While studies and research on antiviral therapy are advancing, there is still no clarity about what children should be treated with and how to perform the therapy. In fact, concerning chronic HCV hepatitis, there are many opinions both in support and against the administration of antiviral drugs during pediatric age.

Although the US Food and Drug has approved the administration of PEG-IFN for children aged 3 years or older, the hesitations on the use of this compound associated to ribavirin in children remain. The studies we cited seems to prove the pharmacological efficacy of this treatment protocol, but this is not the only aspect that needs to be considered, in order to choose whether to treat or not. Moreover, it is even more difficult to answer questions about who, when and how to treat in the specific case of vertically acquired HCV infection. Studies focused on this particular population have not yet been designed, though at present this is the major route of transmission. So, even considering results supporting the efficacy of PEG-INF plus ribavirin, it is difficult to establish precise treatment guidelines.

In fact, HCV hepatitis is a mild disease that is not expressed in its entirety during pediatric age, thus infected children are usually asymptomatic and some of them have the possibility of a spontaneous resolution[22,23]. Thereby, considerations about the natural history of disease make the choice of whether to treat or not rather very hard.

Risk to develop severe liver disease could be the ideal criterion for selecting individuals to treat.

In such an ideal approach, patients who expected to have a benign course would be spared treatment and thereby, avert potential medication-related adverse effects[40]. However, it's necessary to consider the long-term complications of the disease, which will occur with high probability in adulthood; the psychological component related to the long term course of hepatitis C should also be taken into account. In fact, deferring the therapy to adulthood could pose significant psychological implications, due to the possible social exclusion of the child; being considered "infected" would unable to develop social relationships in his environment[27]. Management, continuous monitoring and procedures used to evaluate the course of hepatitis may become sources of great stress for the child and his family.

Choices on pediatric therapy may be also influenced by the economic burden of managing these patients, which can become substantial in the future. An evaluation from this point of view has been made in 2006, where medical costs associated with diagnostic procedures and care of children with chronic HCV infection over the next 10 years were evaluated[41]. A charge from $168 up to $404 million was estimated in USA, that may be considered large enough to justify a therapeutic intervention in children affected.

Anyway, it needs to be highlighted that therapy generally gives better results in children as ev-

idenced by the studies already mentioned. In addition to the high rate of success, demonstrated by the SVR rate, children present an excellent tolerance to treatment with fewer side effects determined by drugs. In particular an optimal compensatory bone marrow function was observed in children aged 3-11 years[34], allowing them to have a good response to the decline in total white blood cell count and absolute neutrophil count, due to antiviral administration.

For these reasons, initiating therapy before adolescence or adulthood offers higher efficacy, better compliance, eradication before initiation of high risk behaviors (that may transmit infection to others), economic advantages, and improved quality of life with less long-term anxiety, fewer medical visits for observation, and less testing for disease progression[42].

Given that there seems to be an inverse relation between age of initiation of treatment and chances of success, a prospective for the future could be starting therapy early before three years of age. Mother-to-child transmitted hepatitis C, in fact, could be considered as a recent infection at the time of birth, since it occurred in utero or during delivery.

Studies conducted in adults show that intervention during the acute phase of the infection are more effective. Treatment started within 12 weeks from diagnosis causes , in fact, an higher rate of viral clearance, compared with no treatment[43].

A question still remains unsolved: should an early treatment be evaluated in HCV-vertical infected children?

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