# Hepatitis C in children and adolescents : mode of acquisition, natural history and treatment

Xavier Stephenne, Etienne M. Sokal

Pediatric Hepatology, Cliniques St Luc, Université Catholique de Louvain, Bruxelles, Belgium.

## Abstract

**Hepatitis C is nowadays mainly acquired in childhood through vertical transmission, while transfusion or surgery related contamination is no more significant. The risk of maternal transmission is related to presence and amount of maternal HCV RNA at the time of delivery. Infection rate is higher in children form HIV positive mothers, and higher if they are themselves co-infected with HIV. Breast milk feeding is not a risk factor, and there is so far no argument to propose cesarean delivery to HCV positive mothers. Treatment with interferon alone is poorly efficient, although pediatric studies remain scarce. Combination treatment using Ribavirin plus interferon, or Ribavirin + pegylated interferon yield a higher success in eradicating viral infection in adults. These treatments can be considered for children in selected cases.** (Acta gastroenterol. belg., **2002**, 65, **95-98**).

## Epidemiology

Hepatitis C virus (HCV) infection is relatively infrequent in childhood, even in endemic areas, due to the lower exposure of children to efficient routes of transmission such as transfusions, drug abuse and other percutaneous routes (1). For this reason some aspects of infection and associated liver disease, such as the natural history and the efficacy of therapy, are largely undefined. In fact most attention in recent years has been devoted to the epidemiological aspects of infection, with particular respect to vertical transmission, which has become the main route of hepatitis C acquisition in children. Post-transfusion or post-surgery contamination has been nearly abolished since the systematic screening of blood products from 1990 (2,3).

Large series of mother infant pairs have been now analysed to establish the rate and predictors of transmission. Resti *et al*. (4) found that the transmission rate from 403 infected mothers without HIV co-infection to their offspring was 3%, including 5% of viremic and none of HCV RNA negative mothers. Other studies reported rates of maternal to infant transmission ranging from 3 to 12% (5-7). Transmission occurs exclusively in infants born to HCV RNA positive mothers. Hence, no risk of transmission is foreseen if the mother is tested negative for HCV RNA

### *Maternal Viral load*

Maternal virus load is thought to influence the rate of vertical transmission. While serum transaminases in the mother tend to decrease during pregnancy, HCV RNA levels were shown to increase late in pregnancy and return to baseline levels one year after delivery in women with chronic hepatitis C (8).

Several studies have linked the rate of transmission to the level of viral load, with an infection rate of 27% in mothers with a viral load > 2.5 $10^6$ RNA copies/ml. (9, 10). In these mothers, presence of anti NS4 antibodies may possibly protect against transmission.

### *HIV co-infection*

High viral load may be one of the factors influencing the higher rate of transmission in children born to HIV mothers. The higher rate of transmission from mothers who are HCV and HIV co-infected is confirmed by several studies (7,11,12). The rate of infection is on average three times higher (40%) in HIV coinfected children as compared to babies infected with HCV alone (7.5%). The significance of HIV and HCV co-transmission remains unexplained (6,11,12).

### *Breast feeding*

The risk of transmission is unrelated to breast feeding, nor to duration of breast feeding. The safety of breast feeding from asymptomatic mothers with HCV infection has been reported in various other studies, showing no increased rate of infection amongst breast fed infants as compared to artificially fed infants (4,5, 13).

The authors, however, describe putative transmission by breast (13) milk in three children delivered by cesarean section who become viremic at 3 months of age, when their mothers developed symptomatic hepatitis. They suggest to avoid breast feeding by symptomatic mothers with high viral charge (13). HIV coinfected women, with high viral load, should probably not breast feed their baby (5).

### *Mode of Delivery*

There is no evidence to promote cesarean section in HCV RNA positive mothers. Studies have not shown a difference in contamination rate between vaginal deliv-

Corresponding author : Etienne M. Sokal, Pediatric Hepatology, Cliniques St Luc, Université Catholique de Louvain, Bruxelles, Belgium, 10 av Hippocrate, B-1200 Bruxelles. E-mail : Sokal@pedi.ucl.ac.be.

ery or cesarean delivery (4,5). However, in these same studies, cesarean delivery was shown to decrease the risk of transmission in the subgroup of mothers with high viral load (10), and in HIV co-infected mothers (5). It would be erroneous to use these data to extend the indication of cesarean section to all HCV RNA positive women.

*Current source of pediatric hepatitis C*

Independently of its low efficiency, vertical transmission has become the main route for pediatric HCV infection after the introduction of blood screening. Bortolotti *et al*. (2) investigated the routes of transmission in 106 consecutive, anti-HCV positive Italian children without underlying diseases and found that 93% of those born after 1990 had an anti-HCV positive mother, while 54% of older children had been transfused ; 45% of infected mothers had a history of covert percutaneous exposure, while one third reported drug abuse. The authors suggest that, following the adoption of general preventive measures, maternal drug abuse is likely to remain the most important source of infection for children in the Western world (2).

The American Academy of Pediatric recommends screening infants born to HCV-infected mothers and persons with risk factors for HCV such as injection drug use, transfusions received before 1992 or hemodyalisis. In addition, HCV screening should be performed in any child coming from international adoption.

The pathogeny of transmission from mother to infant remains unknown. HCV-RNA was detected in the amniotic fluid in only one of 16 HCV RNA positive mothers during the 4$^{th}$ month of pregnancy, and the child was not contaminated. Free viral particles issued from extrahepatic replication of the virus may migrate through the fetal membranes. However, maternal blood contamination during the amniotic punction is a possibility, and this procedure may increase the risk of fœtal contamination, particularly in case of anterior placenta (14).

*Liver transplantation*

One peculiar epidemiological aspect of HCV infection is its role in the development of chronic hepatitis after liver transplantation. Davison *et al*. studied the prevalence of HCV infection in 80 children with a median follow-up of 4.4 years after liver transplantation and found that only three children transplanted prior to donor screening were infected, but only one was associated with chronic hepatitis (15). A similar prevalence (4%) has been reported by McDiarmid *et al*. (16) in 321 children surviving more than one year. However the authors showed that all infected patients had histological features of chronic hepatitis with cirrhosis in one case ; all but one patient were treated with interferon and 23% died for liver failure. In Brussels, the incidence of post transplant hepatitis C was 13% before 1990, and none thereafter (overall incidence < 2.5%), confirming the efficiency of donor screening (3). Unfortunately, cases of chronic hepatitis and end stage cirrhosis were observed amongst HCV infected children.

*Natural history*

Chronic hepatitis C is most often a mild disease in children, but the expected disease duration is to be related to the long life span. Hepatitis C has a poor propensity for spontaneous remission over the years and thus can proceed to a more severe liver disease in adulthood (7,17,18).

Spontaneous recovery and viral clearance was however observed on the long term after cardiac surgery in German children. At a mean interval of 19.8 years after the first operation, 37 (55 percent) of 67 patients who were positive for anti-HCV had detectable HCV RNA in their blood while 30 other patients (45%) had cleared the virus (HCV RNA negative) (19). Among children with positive HCV RNA on follow up, no severe HCV related liver diseases was found.

Spontaneous viral clearance is also observed after perinatal transmission, in up to a quarter of the children after two years (7).

*Treatment*

Attempts have been made to treat children with hepatitis C with interferon. Recombinant interferon alpha 2a was used to treat 21 children (2 with thalassemia major) for 6 months at a dose of 3MU/m$^2$ thrice weekly (20). The response rate at this time, including normalisation of alanine aminotransferase and clearance of HCV RNA, was obtained in 19% of cases. Further management of patients was not homogeneous because the authors either protracted treatment or retreated some patients, thus introducing several biases which prevent an accurate evaluation of sustained response and of predictors of response.

Vegnente *et al*. (21) treated 25 otherwise healthy children with recombinant alpha 2b interferon at the dose of 5MU/m$^2$ for 12 months and obtained a complete response in only 12% at the end of treatment and of 8% at the end of a further 12 months follow-up. The data of these papers contrast with the results of previous pilot studies which provided greater response rates : a selection bias linked to the small sample size and the improvement of techniques for the detection of HCV RNA could explain the differences. Sawada *et al*. (22) investigated 24 children with chronic hepatitis C, most with haemato-oncologic diseases, treated with human lymphoblastoid interferon

At the dose of 0.1 MU/kg body weight daily for 2 weeks and then thrice weekly for 24 weeks. The response rate was 50% at 6 months and 42% at 18 months. Patients with primary malignant disease responded less well to interferon. The effects of IFN treatment of children with chronic hepatitis C has been reviewed by Al-Tawil (23).

A high proportion of children, as well as adults with hepatitis C do not benefit of interferon therapy. For this reason combination therapy with interferon associated with ribavirin administered orally have been experimented in adult patients. Using interferon and ribavirin, administered at the dose of 1000-1200 mg per day, for 24 or 48 weeks, the rate of sustained response, defined as an undetectable serum HCV RNA 24 weeks after treatment was completed, was 31 and 30% respectively, versus 13% in patients who received interferon alone for 48 weeks (24). These encouraging results are confirmed by the effect of combination therapy in patients who relapsed after a course of interferon. A sustained response was obtained in 48% of patients versus 8% of patients retreated with interferon alone (25).

Association of Peylated interferon and Ribavirin may increase further the sustained virological response beyond 50% reaching 54% in patients with the higher dosage schedule (Peginterferon alpha-2b 1.5 µg/kg per week plus ribavirin 10.6 mg/kg during 48 weeks) (26).

*Acute hepatitis C*

Patients with acute hepatitis C may benefit from interferon treatment, and this treatment may prevent chronicity : 43 of 44 patients with acute hepatitis C were treated with interferon during 24 weeks and reached a sustained biochemical and virological response 6 months later (27). These preliminary data deserve further studies, using pegylated Interferon and/or Ribavirin.

## Conclusions

Unfortunately, no prevention method is available for hepatitis C acquired vertically from HCV positive mothers, and this remains currently the first mode of acquisition in children. There is no evidence to propose systematic cesarean section to HCV RNA positive mothers. Cesarean section may however be useful to decrease transmission from highly viremic mothers, and those who are HIV-HCV co-infected. Amniotic punction should be avoided, since it may introduce the virus in the amniotic cavity. Breast feeding is authorized, unless in highly viremic - immunocompromised and HIV positive mothers.

Treatment is becoming more efficient, thanks to association of Ribavirin with Interferon and /or Pegylated interferon. Treatment studies in children are still pending, and treatment should be considered taking into account the possible spontaneous clearance, the slow diseases evolution, but also the long life span – and hence disease duration – in children.

## References


1. LU S.N., CHEN H.C., TANG C.M., WU M.H., YU M.L., LU C.F., CHANG W.Y., CHEN C.J. Prevalence and manifestations of hepatitis C seropositivity in children in an endemic area. *Pediatr. Infect. Dis*., 1998, **17** : 142-145.
2. BORTOLOTTI F., RESTI M., GIACCHINO R,. CRIVELLARO C., ZANCAN L., AZZARI C., GUSSETTI N., TASSO L., FAGGION S. Changing epidemiology pattern of chronic hepatitis C virus infection in Italien children. *J. Pediatr.*, 1998, **133** : 378-381.
3. PASTORE M., WILLEMS M., CORNU CH., BUTS J.P., REDING R., DE VILLE DE GOYET J., RAHIER J., OTTE J.B., YAP S.H., SOKAL E.M. Role of Hepatitis C virus in chronic liver disease occuring after orthotopic liver transplantation in children. *Arch. Dis. Child*., 1995, **72** : 403-407.
4. RESTI M., AZZARI C., MANNELLI F., MORIONDO M., NOVEMBRE E., DE MARTINO M., VIERUCCI A. Mother to child transmission of hepatitis C virus : prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. *Br. Med. J*., 1998, **317** : 437-440.
5. EUROPEAN PAEDIATRIC HEPATITIS C VIRUS NETWORK. Effects of mode of delivery and infant feeding on the risk of mother-to- child transmission of hepatitis C virus. *Br. J. Obstet. Gynaecol*., 2001, **108** : 371-377.
6. GIBB D.M., GOODALL R.L., DUNN D.T., HEALY M., NEAVE P., CAFFERKEY M., BUTLER K. Mother-to-child transmission of hepatitis C virus : evidence for preventable peripartum transmission. *Lancet*, 2000, **356** : 904-907.
7. BERNARD O. Mother-to-infant transmission of hepatitis C. *Acta Gastroenterol. Belg*., 1998, **61** : 192-194.
8. WEJSTAL R, WIDELL A., NORKRANS G. HCV-RNA levels increase during pregnancy in women with chronic hepatitis C. *Scand. J. Infect. Dis*., 1998, **30** : 111-113.
9. OHTO H., TERAZAWA S., SASAKI N., SASAKI N., HINO K., ISHIWATA C., KAKO M., UJIIE N., ENDO C., MATSUI A. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N. Engl. J. Med*., 1994, **330** : 744-750.
10. OKAMOTO M., NAGATA I., MURAKAMI J., KAJI S., IITSUKA T., HOSHIKA T., MATSUDA R., TAZAWA Y., SHIRAKI K., HINO S. Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus : high virus load, vaginal delivery, and negative anti-NS4 antibody. *J. Infect. Dis*., 2000, **182** : 1511-1514.
11. MAZZA C., RAVAGGI A., RODELLA A., PADULA D., MUSE M., LOMINI M., PUOTI M., ROSSINI A., CARIANI E. Prospective study of mother-to-infant transmission of hepatitis C virus (HCV) infection. Study Group of Vertical Transmission. *J. Med. Virol*., 1998, **54** : 12-19.
12. PAPAEVANGELOU V., POLLACK H., ROCHFORD G., KOKKA R., HOU Z., CHERNOFF D., HANNA B., KRAZINSKI K., BORKOWSKY W. Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV) - infected infants of HIV- and HCV-coinfected women. *J. Infect. Dis*., 1998, **178** : 104-152.
13. KUMAR R.M., SHAHUL S. Role of breast-feeding in transmission of hepatitis C virus to infants of HIV-infected mothers. *J. Hepatol*., 1998, **29** : 191-197.
14. DELAMARE C., CARBONNE B., HEIM N., BERKANE N., PETIT J.C., UZAN S., GRANGE J.D. Detection of hepatitis C virus RNA (HCV RNA) in amniotic fluid : a prospective study. *J. Hepatol*., 1999, **31** : 416-420.
15. DAVISON S.M., SKIDMORE S.J., COLLINGHAM K.E., IRVING W.L., HUBSCHER S.G., KELLY D.E. Chronic hepatitis in children after liver transplantation : role of hepatitis C virus and hepatitis G virus infections. *J. Hepatol*., 1998, **28** : 764-770.
16. MC DIARMID S.V., CONRAD A., AMENT M.E., VARGAS J., MARTIN M.G., GOSS J.A., BUSUTTIL R.W. De novo hepatitis C in children after liver transplantation. *Transplantation*, 1998, **66** : 311-318.
17. EBELING F. Epidemiology of the hepatitis C virus. *Vox Sang*., 1998, **74** : 143-146.
18. THOMAS S.L., NEWEL M.L, PECKHAM C.S., ADES A.E., HALL A.J. A review of hepatitis C virus (HCV) vertical transmission : risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. *Int. J. Epidemiol*., 1998, **27** : 108-117.
19. VOGT M., LANG T., FROSNER G., KLINGLER C., SENDL A.F., ZELLER A., WIEBECKE B., LANGER B., MEISNER H., HESS J. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N. Engl. J. Med*., 1999, **341** : 866-870.
20. JONAS M.M., OTT M.J., NELSON S., BADIZADEGAN K., PEREZ-ATAYDE A. Interferon-alpha treatment of chronic hepatitis C virus infection in children. *Ped. Infect. Dis. J*., 1998, **17** : 241-246.
21. VEGNENTE A., IORIO R., PENSATI P. Treatment of pediatric hepatitis C : results and perspectives. *Acta Gastroenterol. Belg*., 1998, **61** : 235-236.
22. SAWADA A., TAJIRI H. KOZAIWA K., GUO W., TADA K., ETANI Y., OKADA S., SAKO M. Favorable response to lymphoblastoid interferon alpha in children with chronic hepatitis C. *J. Hepatol*., 1998, **28** : 184-188.

23. AL-TAWIL Y., NELSON C. Interferon treatment of children with chronic hepatitis C. *Hepatogastroenterology*, 1998, **345** : 541-548.
24. MC HUTCHISON J,G., GORDON S.C., SCHIFF E.R., SHIFFMAN M.L., LEE W.M., RUSTGL V.K., GOODMAN Z.D., LING M.H., CORT S., ALBRECHT J. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N. Engl. J. Med.*, 1998, **339** : 1485-1492.
25. DAVIS G.L., ESTEBAN-MUR R, RUSTGI V., HOEFS J., GORDON S.C., TREPO C, SHIFFMAN M.L., ZEUZEM S., CRAXI A., LING M.H., ALBRECHT J. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N. Engl. J. Med.*, 1998, **339** : 1493-1499.
26. MANNS M.P., MCHUTCHISON J.G., GORDON S.C., RUSTGI V.K., SHIFFMAN M., REINDOLLAR R., GOODMAN Z.D., KOURY K., LING M., ALBRECHT J.K. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomised trial. *Lancet*, 2001, **358** : 958-965.
27. JAECKEL E., CORNBERG M., WEDEMEYER H., SANTANTONIO T., MAYER J., ZANKEL M., PASTORE G., DIETRICH M., TRAUTWEIN C., MANNS M.P. Treatment of acute hepatitis C with interferon alfa-2b. *N. Engl. J. Med.*, 2001, **345** : 1452-1457.