Neonatal Hepatitis C

Introduction

Hepatitis C virus (HCV) is an RNA virus which was first described in 1989, and for which a diagnostic antibody test became available in 1990. This virus accounted for the majority of infections previously referred to as non-A non-B hepatitis. HCV has 6 major genotypes with subtypes a and b. It displays a high mutation rate which allows it to evade immune detection and destruction, to render antibody tests unreliable, allow reinfection, lead to variable responses to treatment, and finally to make it difficult to produce an effective vaccine. Although anti-HCV antibody is detectable using commercial 3rd generation immunoassays in the majority of HCV RNA positive patients, there is a group of such patients (~10%) who are antibody negative.

HCV has been shown to spread readily by exposure to infected blood. For our community, this occurs most commonly in the context of injecting drug users. By contrast, intrafamilial horizontal spread is low, the main route being sexual contact. However, a significant route remains vertical (mother to baby) perinatal transmission. In HIV-negative HCV RNA-positive women, the risk is between 5 and 10% (see Table), and at present there are no proven methods to reduce this risk. In HIV co-infected women, transmission of HCV is about 3 times greater.

Incidence

In the general population, the incidence usually ranges from 0.5 to 1.8%, depending on the population studied. However, in some areas (Italy, Japan, Africa) certain communities were identified with incidences in the 10-30% range.

At KGV, about 1.0% of screened antenatal clinic women were found to be HCV antibody positive. The majority of these had a history of injecting drug use. The incidence in injecting drugs users was found to be almost 90% antibody positive, of whom about 70% were RNA positive (HCV PCR positive).

Risk Factors

1. **Parenteral - High Risk**
   - transfusion of contaminated blood products
   - especially renal dialysis patients, haemophiliacs, and organ transplant recipients
   - repeated use or sharing of contaminated needles
   - body piercing
   - tattooing
   - acupuncture
   - sharing razors and other sharp instruments

2. **Occupational - Low Risk**
   - needle stick injuries - reported risk of 0% to 5%

3. **Vertical transmission - Low Risk**
   - Viraemia: Transmission only occurs from mothers who have circulating HCV RNA. No instances of transmission have been reported from PCR-negative mothers.
   - Severity: Multiple studies have documented a relationship between markers of the severity of
maternal infection and subsequent infection of the infant. The viral load is the most reported marker\(^3\), 6, 21. Other markers include elevated transaminases and anti-HCV IgM antibody.

- **Mode of delivery:** Controversy exists as to whether delivery by elective caesarean section affords protection, as it does in the case of HIV infection. A number of observational studies found no difference between outcomes according to mode of delivery, but most of the caesarean sections occurred in labour, presumably following rupture of membranes (see Table). However, one study reported increased risk with time of membrane rupture\(^3\), and another has found no cases of transmission where mothers had a caesarean section prior to rupture of membranes\(^11\). Further evidence supporting a protective effect of elective caesarean section comes from a study of HBV positive women in which maternal placental alkaline phosphatase and HBsAg were measured in cord blood following elective caesarean (n=16), NVD (n=56), instrumental vaginal delivery (n=12), and emergency caesarean section (n=13)\(^1\). Both measures of maternal blood microtransfusion were significantly reduced in the elective caesarean group, suggesting that it may provide protection for all kinds of viral vertical transmission. A randomised trial is needed to prove or disprove this promising method.

- **HIV Co-infection:** Women with HIV co-infection have more severe HCV disease, and are more likely to transmit HCV to their offspring\(^4\), 11, 24, 25.

4. **Spread between family members - Low Risk** 1, 18
   - Sexual intercourse
   - Other exposure to body fluids

5. **Breast feeding - Low to Zero Risk**
   - Numerous observational studies concerning risk factors for vertical transmission of HCV from HIV-negative HCV-positive mothers have not found any association between breast feeding and subsequent acquisition of HCV infection\(^3\), 6, 7, 8, 10, 11, 13, 16, 20, 22, 24. The data is difficult to interpret, since some institutions may have encouraged breast-feeding, while others discouraged it, so it occurred in a non-random fashion. Studies with data which allows one to relate neonatal outcome to method of feeding in HIV-negative HCV PCR positive mothers, either individually or combined, show that breast feeding is not a significant risk factor for transmission (see Table). In some studies, HCV RNA was not detected in samples of expressed breast milk\(^6\), 26, 27, while in others where HCV RNA was detected, it was generally only detected in mothers with a high serum viral loads, and usually at a much lower level\(^12\), 22, 23, 28. As mothers with high serum viral loads are more likely to directly transfer virus at birth, the significance of these findings regarding breast-milk is uncertain. In summary, so weak is the evidence at present that breast milk itself can cause infection with HCV, that a policy of encouraging breast feeding should be pursued because of its other numerous benefits, except perhaps for the occasional mother with markedly advanced disease. Mothers with HIV co-infection should not breast-feed.

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**Consequences**

1. **Acute infection:** There is still a great deal to be learned about the natural history of perinatal HCV infection. Recent studies have revealed that clearance of HCV and recovery from infection occurs much more commonly than at first thought. For example, Ceci *et al*\(^15\), 30 detected HCV RNA in 8 out of 60 (13%) infants of HCV RNA positive mothers at 6-12 months of age, but only 2 of these remained HCV RNA positive after 24 month follow-up. Other studies have reported recovery from infection, although not as impressive.

2. **Long term consequences:** Little has been reported regarding the long-term outcome of children following mother-to-infant transmission of HCV\(^1\). 31. More is known regarding infected adults, where about 50% will go on to hepatic damage, with fibrosis and ultimately cirrhosis. This usually becomes increasingly evident after about 10 or more years. A small proportion will develop hepatic carcinoma.

3. **Quality of life:** Paediatric HCV infection is usually asymptomatic for many years. Some studies attempting to measure QOL using physical and psychosocial measures of well-being suggest that
infected children perform worse than uninfected children\textsuperscript{31}. There is also the problem of possible discrimination similar to that suffered by HIV positive patients. However, this needs to be weighed against the value of knowing the diagnosis so that potentially curative treatment can be undertaken.

### Diagnosis

1. **Anti-HCV Antibodies:** Anti-HCV antibodies passively derived from the mother decay after birth, with about 75\% still positive at 6 months, 40\% positive at 9 months, 15\% at 12 months, and 4\% at 15 months. All uninfected infants should be antibody negative by 18 months\textsuperscript{11}.

2. **PCR for HCV RNA:** The PCR test is highly specific (97\%, CI 96-99) at all ages, but sensitivity is age specific. During the first month it was only 22\% (CI 7-46), but thereafter was 97\% (CI 85-100)\textsuperscript{11}.

3. **LFTs:** Measurement of the ALT is not very useful in babies, as they may be elevated transiently or not at all in infected infants, and not until 9 or more months.

4. **Follow-up investigation of infants born to HCV carrier mothers**
   - Since the majority of HCV carrier mothers (at least in our institution) are or were injecting drug users, the sooner follow-up is arranged in the post natal period, the better the chance of seeing the baby again. As infected babies can be reliably diagnosed using PCR after 2 months of age\textsuperscript{11}, we suggest it be done at this time. The large proportion of babies carry maternally-derived anti-HCV antibodies beyond 12 months, but are largely gone by 18 months. We therefore recommend the measurement of anti-HCV antibodies at around 18 months. Those infants identified as carriers should then be referred to an appropriate clinic for further evaluation and consideration for future treatment. For this institution, the current arrangement is the Infectious Diseases Clinic at the Children’s Hospital at Westmead (contact Dr Cheryl Jones).

### Interventions

1. **Prevention - General Issues**
   - **Universal precautions** for health-care workers.
   - **Needle exchange** for injecting drug users.
   - **Vaccines:** Much research on vaccines is underway, but a useful product is probably a long way off.

2. **Prevention - Vertical transmission**
   - **Mode of delivery:** As mentioned above, recent studies suggested that there may be an advantage in delivery by caesarean section if done prior to rupture of membranes, although other studies have not consistently shown a benefit of caesarean section over vaginal delivery.

3. **Treatment:**
   - **Interferon alpha (INF) monotherapy:** Meta-analysis of six RTCs of adults with acute HCV infection, concluded that treatment achieved end-of-treatment and sustained viral clearance in 42\% (CI 30-56) and 32\% (CI 21-46) respectively\textsuperscript{32}. Only 4\% (CI 0-13\%, p<0.0001) of controls achieved sustained viral clearance. The situation was not as good for patients with chronic infection, where a meta-analysis of 54 trials concluded that INF could achieve sustained viral clearance in 17\%, versus 3\% in controls\textsuperscript{33}. Less information is available in children, but a number of small trials suggest sustained viral clearance in 33-56\%, with INF being better tolerated than adults. However, it is not known at present what the ideal time for treatment is following perinatal infection, especially considering the apparently high rate of spontaneous recovery that has been recently reported\textsuperscript{30}.
   - **INF-ribavirin combination therapy:** The addition of ribavirin appears to significantly improve
viral clearance. Studies of HCV infected children with haemophilia showed sustained viral clearances of 45%\(^{34}\) and 72%\(^{35}\), or in remission from malignancy showed sustained viral clearances of 50%\(^{36}\) and 64%\(^{37}\). One trial compared combination therapy versus INF monotherapy in paediatric patients and found viral clearances of 50% versus 30% respectively\(^{38}\). Two recent multicentre, randomized controlled trials in adults with chronic HCV infection showed significant superiority of combination over mono therapy\(^{39,40}\). Newer research involving pegylated INF (INF conjugated to a polyethyleneglycol derivative), which has similar efficacy but extended half life, appears to further boost response to around 60%\(^{41}\).

### Key Points

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<th>Infants born to anti-HCV positive but HCV RNA negative mothers are not at risk of developing HCV infection.</th>
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<td>Between 5 and 10% of infants born to anti-HCV positive, HCV RNA positive mothers will themselves develop HCV infection.</td>
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<td>Diagnosis should involve measurement of HCV RNA at about 2-3 months of age, and/or anti-HCV Ab at 18 months.</td>
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<td>All mothers with asymptomatic HCV infection should be allowed to breast feed</td>
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<td>Interferon alpha plus ribavirin achieves sustained viral clearance in up to 50% of patients with HCV infection</td>
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### References


Last Review: October 2002