

Hepatitis C: 11th International Symposium on Viral Hepatitis and Liver Disease

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Transmission of HCV in Medical Settings: Molecular Contact Tracing and Risk Factors

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Since introduction of blood donor screening and viral inactivation of plasma-derived products transfusion-related transmission of the hepatitis C virus (HCV), has been virtually eliminated. However, nosocomial and iatrogenic HCV infections still occur in a variety of medical settings.

Nosocomial infection of patients with HCV on haemodialysis due to end-stage renal failure remains an important problem. Transmission of HCV due to health-care related procedures other than haemodialysis have only occasionally been reported and were mostly associated with improper infection control precautions, including unsafe phlebotomy practices, contamination of multi-dose medication vials, or inadequate cleaning and disinfection of medical equipment.

The occupational risk for health-care workers (HCW) to acquire HCV by needlestick and other percutaneous injuries is well recognised. The rate of transmission has been calculated to be approximately 2 %.

During recent years, health care authorities as well as patients are increasingly concerned about another possible route of nosocomial HCV infection, i.e. transmission of the virus from an infected HCW to patients during exposure-prone procedures. Several transmissions have been identified. In 14 instances of proven transmission look back studies have been carried out to determine the number of patients infected and to calculate the overall risk of infection. Due to the high rate of chronic hepatitis C infection the identity of different HCV isolates can clearly demonstrated by sequence comparison using core or NS5 gene. When serum of the patient is available shortly after the potential event of transmission sequencing of HVRI of the E2 gene is very meaningful to reliably discriminate isolates belonging to the same subtype.

Among more than 11,000 former patients analysed in look back studies, only 22 cases of HCV infections were detected that could be undoubtedly linked to HCV-positive surgeons or anaesthesiology staff members by molecular and epidemiological analyses, resulting in an overall provider-to-patient transmission rate of less than 0,2 %. In most of these cases the transmitting event could not be attributed to certain surgical procedures. The results of comprehensive retrospective investigations of large numbers of patients who have been previously treated by HCV infected HCW indicate that the risk of such a provider to-patient transmission of HCV, however, appears to be low. Despite this apparently low risk, a controversial discussion on the management and guidance of HCW infected with HCV has lately emerged in the medical community.

The Natural History of HCV Infection Defined by Asymptomatic Blood Donors and Their Recipients

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Since 1990, we have enrolled 745 anti-HCV+ blood donors. Of these, 186 were RIBA indeterminate and 112 RIBA negative; 450 were RIBA+ and now followed for up to 12 years. Despite being volunteer donors, 41% subsequently admitted to time-limited IVDU; 24% were transfused and 4% had both IV risks. Cocaine snorting was independently associated with HCV infection. None of 150 long-term sexual partners of HCV-infected donors were anti-HCV+ unless they also had a parenteral exposure. Among RIBA+ (truly exposed) donors, 15% were persistently HCV RNA negative and presumed recovered. No HCV RNA+ donor had spontaneous loss of virus during follow-up. 90% were HCV genotype 1. In chronic hepatitis C, variations in viral load rarely exceeded one log. Among HCV RNA+ subjects, 24% had persistently normal ALT and 43% had elevations that never exceeded 2X ULN. On initial liver biopsy, 51% had mild (HAI<8) chronic hepatitis (CH), 44% moderate CH (HAI 8-12) and only 5%, severe CH (HAI 13-18); 10% had stage 3 fibrosis and only 1.5% had cirrhosis. 5-year follow-up biopsies showed improved or stable histology in 75% while 25% showed = 2 point increase in inflammation or = + increase in fibrosis. None progressed to bridging, but one with prior bridging progressed to cirrhosis. The incidence of cirrhosis after an estimated interval of 20-25 years from a deemed exposure was under 3% in this donor population.

Based on this study, related studies of transfusion recipients, rates of spontaneous recovery in early infection that approach 25% and sustained treatment responses near 50%, we estimate that severe outcomes will occur in less than 30% of those who sustain an acute HCV infection. Although this estimation provides reasonable hope for the individual patient, it does not diminish the enormous global impact of HCV infection engendered by the sheer magnitude of the infected population.

Prospects for Vaccination Against the Hepatitis C Virus

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With an estimated 170 million carriers of the hepatitis C virus (HCV) world-wide and a large incidence of new infections, there is an urgent need for a prophylactic vaccine to prevent one of the leading causes of chronic liver disease. A member of the Flaviviridae family within its own Hepacivirus genus, HCV comprises a highly heterogeneous group of positive-stranded RNA viruses subdivided into 6 basic genotypes with more than 100 subtypes. This heterogeneity, along with the high propensity to cause chronic, persistent infection as well as question marks about the presence of natural immunity has led historically, to uncertainty over the prospects for effective vaccination. However, many recent developments allow a much more optimistic view. Firstly, the development of natural immunity following acute, resolving infection has now been demonstrated in humans and in the experimental chimpanzee model against both homologous and heterologous viral strains. Secondly, immune correlates of protection are beginning to be defined at the level of early and broad CD4+ and CD8+ T cell responses to the virus. Thirdly, vaccination of chimpanzees has been shown to protect against the development of persistent infection following experimental challenge with homologous and heterologous strains that are endemic in the USA and elsewhere.

Initial attempts to develop a vaccine have centered around the production of recombinant envelope glycoproteins gpE1 and gpE2 in mammalian cells and combining these with oil/water micro-emulsified adjuvants. In the chimpanzee model, which represents the only active immunisation and challenge model available, 3 immunisations with this vaccine led to the generation of sterilising immunity against challenge with homologous virus. This sterilising immunity correlated directly with the titer of anti-gpE1/gpE2 titers at the time of challenge. Recent studies conducted using challenge with a heterologous subtype 1a virus have shown that while sterilising immunity was not generated, the majority of animals did not progress to chronicity, unlike the situation with control, unvaccinated animals (1/10 vs 7/9 ; P = 0.005). Protection against the development of chronic infection following heterologous challenge *did not* correlate with anti-gpE1/gpE2 titers at the time of challenge, suggesting the involvement of HCV-specific T cell responses. As a result of this finding, new polypeptide and DNA vaccines designed to prime broad CD4+ and CD8+ T cell responses to the virus are being tested in the chimpanzee model. One highly immunogenic formulation comprises a yeast-derived, fusion polyprotein containing non-structural proteins 3, 4 & 5 linked with the nucleocapsid protein, formulated with

Peginterferon Alfa-2A (40KD) (Pegasis®) and Ribavirin in Patients with 'Difficulty-to-Treat' Chronic Hepatitis C

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Background:

HCV genotypes 1 and 4, high pre-treatment HCV RNA levels and cirrhosis have been considered predictors of poor response to antiviral therapy in chronic hepatitis C (CHC).

Objective:

To assess the efficacy of PEGASYS in combination with ribavirin in patients with 'difficult-to-treat' HCV in two large phase III studies.

Methods:

Adults with CHC received either IFN α -2b 3 MIU tiw for 48 weeks or PEGASYS 180 μ g qw for either 24 or 48 weeks in combination with ribavirin (RBV) either 800 or 1000/1200 mg daily. Sustained viral response (SVR) was assessed at the end of follow-up.

Results:

In patients with HCV genotype 1 (n=569) the highest SVR rate was seen among patients treated with

PEGASYS 180 µg qw in combination with RBV 1000/1200 mg daily for 48 weeks (52% and 46% in study 1 and 2, respectively). The same treatment regimen in 368 patients with genotype 1 and high HCV titres (>2x10⁶ copies/ml) resulted in an overall SVR rate of 44%. Patients with HCV genotype 4 receiving this regimen (n=24) achieved a SVR rate of 79%.

Among patients with cirrhosis treated with PEGASYS in combination with RBV 1000/1200mg for 48 weeks (n=171) the SVR rate was 49%. Patients with cirrhosis infected with genotypes 2/3 who were treated with less intensive regimens (treatment duration of 24 weeks and/or RBV dose of 800mg) achieved SVR rates of 70-75%.

Conclusions:

In patients with HCV genotypes 1 or 4, PEGASYS 180 µg qw in combination with 1000/1200 mg RBV for 48 weeks achieved the best responses. Overall response in cirrhotic patients was satisfactory with approximately half of the patients responding. Among cirrhotic patients with genotypes 2/3, 70-75% of the patients responded to a less intensive treatment regimen (PEGASYS 180 µg qw in combination with 800 mg RBV for 24 weeks).

Estimated Global Prevalence of Hepatitis C Virus Infection

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Background:

Robust estimates of the prevalence of hepatitis C virus infection are needed to support models of the global disease burden associated with HCV infection and to assist the development of appropriate prevention policies.

Methods:

We derived estimates of HCV antibody prevalence (representing active or resolved infection) for the general populations in all 14 World Health Organization (WHO) subregions. Systematic literature searches were conducted in Medline using terms including Hepatitis C, Seroepidemiologic Studies, Incidence, and Prevalence, supplemented by articles and government publications identified from review articles, reference lists, and other sources. Over 2000 abstracts were examined to identify articles containing HCV antibody or RNA prevalence data among suitable study populations (e.g., community-based samples and antenatal women). Estimates were based on data abstracted from > 300 sources. Country-specific studies were reviewed to obtain representative estimates, placing greater weight on community surveys and studies that performed supplemental testing. Countries lacking data were associated with other countries on the basis of epidemiologic similarities. Regional estimates were calculated as population-weighted averages of country-specific estimates.

Results:

Preliminary estimates of global HCV infection prevalence are in the range of 2-2.5%, representing ~120-180 million persons with evidence of HCV infection. Regional HCV prevalences were typically 20-50% higher among males than females. The highest overall prevalences were estimated for the Eastern Mediterranean D region (7%), which includes Egypt, and for the Africa D region (4%). The greatest numbers of infected individuals reside in the Western Pacific B region (~38 million persons), which includes China, and in the Eastern Mediterranean D region (~25 million persons).

Conclusions:

These results generally validate previous WHO estimates that were based on more limited data. HCV affects substantial proportions of the population in all regions of the world, highlighting the need for comprehensive approaches aimed at reducing transmission and the long-term sequelae of chronic infection.

Longitudinal Study of Newly Acquired Hepatitis C Infection Among Injecting Drug Users

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Background:

The natural history of early hepatitis C virus (HCV) infection remains unclear. The objective of this study was to examine rates and predictors of HCV-RNA clearance in a longitudinal cohort of injecting drug users (IDUs) attending a primary care health facility.

Methods:

A cohort of IDUs attending the Kirkeaton Road Centre, Sydney with newly acquired HCV infection over the period 1992-2002 was established. Newly acquired HCV infection was defined by anti-HCV antibody seroconversion within a two-year time frame. Seroconversion date was estimated as the midpoint between last negative antibody and first positive antibody result. Stored frozen sera collected in the context of ongoing clinical care were retrieved, from date of last negative HCV antibody onwards. A total of 355 samples were available from 99 newly acquired HCV cases, and were retrospectively tested for the presence of HCV -RNA using qualitative and quantitative methods. HCV-RNA clearance was defined as two or more consecutive negative HCV RNA results. Demographic (age, gender, indigenous status), clinical (ALT, HIV status) and risk behaviour (type of drug, frequency, sharing) variables were available on a standardised clinic database.

Results:

Fifty-six cases had two or more HCV-RNA results after estimated seroconversion. Twenty-five cases (46%) cleared HCV-RNA, with Kaplan Meier estimated probability of clearance 16% at 6 months, 27% at 12 months, 40% at 18 months, and 44% at two years. Within a sub-group with detectable HCV -RNA at seroconversion (n=45), 14 cases (31 %) cleared HCV infection, and estimated clearance was 7% at 6 months, 14% at 12 months, 24% at 18 months, and 30% at two years. Female gender was associated with ALT normalisation, however, no demographic, clinical or risk behaviour variables predicted HCV-RNA clearance.

Conclusions:

An estimated 30-40% of people with newly acquired HCV infection undergo viral clearance, with clearance continuing for at least 2 years.

Hepatitis C Virus Hepatitis (HCV)-Infected Sex Partners as a Source for Infection Among Persons with Acute Hepatitis C

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Background:

Case-control studies of acute hepatitis C conducted in the US found sex with an infected partner or with multiple partners during the 6 months prior to illness significantly associated with acute disease. However, the role of sexual activity in the transmission of HCV is controversial.

Objective:

To determine the relatedness of viral strains between persons with acute hepatitis C and their HCV-positive sex partners.

Methods:

Acute, symptomatic cases of hepatitis C were identified in six Sentinel Counties during 1991 to 2001. Patients were extensively interviewed for risk factors for infection in the 6 weeks to 6 months prior to onset of illness. Serum samples on sexual partners were obtained and for HCV -positive concordant couples, the genetic relatedness was determined by sequencing the 5'UTR and the quasispecies from the hypervariable region (HVRI).

Results:

Of 263 cases of acute hepatitis C interviewed, 13% reported sexual exposure as their only risk factor; 9% had an anti-HCV-positive sex partner and 4% multiple sex partners. Serum samples from 7 of 24 HCV positive couples were available for analysis; 5 had concordant genotypes and the nucleotide identity of the quasispecies sequences for each partner-pair was 97.8%-99.3%. For the two unrelated partner-pairs, the nucleotide identity of the quasispecies sequences was 81.8% and 91.0%. Of 5 related couples, 4 acute cases were female and one was a man whose sex partner was a man. Of the other 2 couples, one case reported three sex partners in the 6 months prior to illness onset, but only one partner had a sample available for analysis.

Conclusions:

The close relationship found between viral strains of most HCV-positive sexual partners and cases of acute hepatitis C who denied other risk factors provides further support for sexual activity as a mode of HCV transmission in the US.

Natural Immunity and Vaccine Induced Immunity in HCV Infection

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In contrast to HIV infections, HCV infections can resolve naturally or following antiviral treatment. It is now established that cellular immune responses involving the contribution of long lasting, functional CD4 + T lymphocytes and that of fully mature IFN- γ producing CD8 + T cells play a key role in the control or eradication of the virus. Independent of the infection outcome, during acute phase of infection, CD8 + T cells which have a memory phenotype (CD28 negative, CD 27positive) seem altered in their lytic capacity and ability to produce IFN-gamma. Early recovery of such activities together with the detection of a vigorous and

maintained CD4+ mediated response is associated with resolution of infection. While mechanisms responsible for such recovery are yet unknown, studies are beginning to address the role potentially played by dendritic cells (DC), key actors in the development of innate as well as adaptive immunity, in HCV chronicity or its resolution. Their allostimulatory capacity and capacity to produce IFN-alpha seem altered during chronic infection and under antiviral treatment and HCV RNA has been found in monocyte and circulating DC subpopulations. Thus, although immune correlates of protection require to be further elucidated, candidate vaccines are in the making. Various murin and non human primate models have been used to evaluate vaccines based on naked DNA, viral vectors and adjuvanted recombinant antigens. HCV vaccine induced immunity can be enhanced by manipulation of the choice of regions flanking the immunogen, its glycosylation status and the combined used of vaccine vehicles. Encouraging data indicate that Th 1- oriented responses and/ or high anti-envelope antibody titers can be generated by various vaccine formulations, including in primates and that non-sterile immunity can be achieve in the chimpanzee model.

The Epidemiology of Newly-Diagnosed Chronic Liver Disease in the United States

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Background:

Chronic liver disease (CLD) is the tenth leading cause of death in the United States, but the epidemiology has not been well described. We report preliminary findings of prospective population-based sentinel surveillance for CLD among patients newly-diagnosed in referral practices.

Methods:

We conducted active surveillance for adult cases of newly-diagnosed CLD in gastroenterology practices in New Haven County CT, Multnomah County OR, and Alameda County Kaiser Permanente Health Plan, Oakland, CA (total population under surveillance 1.48 million). CLD was defined as abnormal liver tests of at least six month's duration, or pathologic, clinical, or radiographic evidence of CLD. Consenting patients were interviewed, a blood specimen obtained, and the medical record reviewed.

Results:

We identified 922 patients with newly-diagnosed CLD in 2000 (incidence 62.4/100,000 population), including 566 hepatitis C patients (incidence 38.3/100,000). Overall CLD incidence was higher among men (75.5/100,000) than women (49.9/100,000). Among the 373 (40.5%) patients interviewed to date, the median age was 47 years (range 19-86; 217 (58.2%) were male. Etiologies included hepatitis C, either alone (160; 42.9%) or with heavy alcohol use (83; 22.3%), heavy alcohol use alone (28; 7.5%), nonalcoholic fatty liver disease (50; 13.4%), and hepatitis B (14; 3.8%). Other identified etiologies each accounted for < 3% of cases. Data were insufficient to determine etiology for 28 (7.5%) patients. At least one recognized source of infection was reported by 206 (84.8%) hepatitis C patients, including injection drug use (65.0%), blood transfusion before 1992 (22.2%), household or sexual contact with an infected person (22.6%) or an occupationally-related needle stick injury (7.0%).

Conclusions:

Extrapolating from this population-based study, an estimated 130,000 patients were newly-diagnosed with CLD in U.S. specialists' offices in 2000, including an estimated 80,000 patients with newly-identified hepatitis C. Additional sites and a non-referred patient base will extend the generalizability of these results.

HCV Prevalence and Risk Behaviours Among Young IDU at Sentinel NSP in Australia, 1995-2001

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Objective:

To examine changes in prevalence of hepatitis C virus (HCV) antibody and related risk behaviours among injecting drug users (IDU) aged less than 25 years at sentinel Needle and Syringe Programs (NSP) from 1995 to 2001.

Methods:

Annually repeated cross-sectional surveys of one-week duration were carried out since 1995. All clients at participating NSP sites were asked to complete a questionnaire and provide a finger-prick blood sample. Analysis was restricted to IDU aged less than 25 years.

Results:

Survey response was 42% (n=323), 50% (n=515), 57% (n=719), 48% (n=950), 47% (n=815), 36% (n=847) and 43% (n=688) from 1995 to 2001, respectively.

Reported reuse of someone else's syringe in the month before survey decreased significantly from 1995 (33%) to 2001 (19%, trend $p < 0.001$). However, after an initial decrease from 1995 (36%) to 1997 (22%), HCV prevalence increased significantly from 1998 (24%) to 2001 (41%, trend $p < 0.001$).

Risk factors independently associated with HCV prevalence included being female (OR 1.6, 95% CI 1.2-2.1), longer duration of drug injection (OR 2.4, 95% CI 1.7-3.4), heroin injection (OR 2.1, 95% CI 1.4-3.1) or injection of more than one type of drug (OR 2.0, 95% CI 1.1-3.6) compared to amphetamine, daily or more frequent injection (OR 1.4, 95% CI 1.1-1.9), re-use of someone else's syringe (OR 1.6, 95% CI 1.2-2.2), outdoor injection in the previous month (OR 1.4, 95% CI 1.0-1.9), and imprisonment in the year before survey (OR 2.1, 95% CI 1.5-2.9). Over the study period HIV prevalence remained less than 1%.

Conclusions:

Despite continuing low HIV prevalence and an apparent decline in syringe sharing, HCV prevalence among young IDU has increased in recent years. Other HCV risk behaviours such as frequent injection and imprisonment may explain this trend and indicate the need to re-evaluate current harm-reduction strategies.

Viral Molecular Mimicry by HCV E2 and Hepatitis C Virus-Associated Autoimmunity

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Introduction:

Chronic HCV has been associated with autoimmune diseases including Sjogren's syndrome (SS). About 14% of SS patients are anti-HCV positive and over 50% of chronic HCV patients have some sicca symptoms and or lymphocytic infiltrates in their salivary glands. Antibodies to HCV have been found in saliva

and evidence of viral replication by the presence of negative strand HCV RNA in salivary glands suggests a role for HCV in the development of sialadenitis. Finally, transgenic mice expressing the HCV envelope glycoproteins have been shown to have salivary gland pathology similar to SS.

We found that the envelope protein E2 shares sequence identity with and inhibits PKR and its substrate, the translation initiation factor, eIF2. Here we report that patients who have HCV-associated SS have antibodies that react with both E2 and PKR and all patients who had high levels of anti-PKR antibodies also have SS. We tested 45 HCV-positive serum samples from patients without sicca symptoms for the presence of E2 and PKR antibodies. Nearly all of the patients we tested had E2 antibodies, but only two had slightly elevated anti-PKR levels. To test whether PKR autoantibodies resulted from liver disease, and because sicca symptoms are correlated with primary biliary cirrhosis (PBC), we tested serum from two patients with PBC and neither had elevated levels of anti-PKR or anti-E2 antibodies. We immunodepleted patient serum with purified E2-GST fusion protein and those samples that previously had reacted with PKR lost reactivity after the immunodepletion, demonstrating that the antibodies are cross reactive. Cellular immune responses are currently being investigated.

Conclusion:

Taken together, these data suggest that the HCV E2 protein can induce autoimmune cross-reactivity with the host protein PKR through molecular mimicry and that PKR may be an antigen target associated with SS.

HCV Prevalence in Pregnant Woman in Central Sydney

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Objective:

To determine the virological and epidemiological characteristics of HCV infection in pregnant women in Central Sydney.

Methods:

All antenatal patients attending King George V Hospital were screened at 16 weeks gestation for anti HCV between January 2001 and November 2002. Positive patients were invited to answer a risk factor questionnaire and provide a second blood sample at 36 weeks for repeat testing for HCV RNA by RT-PCR, and if positive, for genotype (by sequence in both UTR and NS5 region) and viral load by real time PCR.

Results:

Two percent (N130) of the 6804 mothers with 90% screened were anti-HCV positive and 90 participated in the study. Patients were aged 18-45, 76% had injected drugs, 48% were tattooed, 37% had body piercing, and 10% a history of blood transfusion. 11% denied all risk factors. 76% of the total antenatal patient cohort, but 85% of the anti-HCV positive were born in Australia and New Zealand. Very few of these admitted injecting drugs are currently. Nine of the patients lacking an identified risk factor for infection were born abroad. Fifty-one of 74 (69%) anti-HCV positive patients so far tested were viraemic. Neither maternal age nor country of origin was significantly associated with viraemic status. Of 31 patients so far genotyped in NS5 region, all are 1b like but UTR results are more varied. The HCV viral load was 10 in 5 of 51. 28(31%) of 90 anti-HCV positive women were unaware of their status before being screened as antenatal patients.

Conclusions:

The prevalence of anti-HCV in pregnant women in Central Sydney (2%) is close to that of HBsAg (3%). A history of known risk factors would fall to reveal one third of HCV infections. Ten percent have a high viral

load.

Prospective Community-Based Cohort Investigating Perinatal HCV Transmission in the Egyptian Delta

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Introduction:

Previously reported estimates of vertical HCV transmission have been varied. The high HCV prevalence in the Egyptian Nile Delta presents a unique opportunity for efficient, prospective community-based investigation of mother-to-infant HCV transmission, which would not be possible in most other parts of the world. Reported herein are the results of an ongoing community-based study in 3 rural villages. Pregnant women and their offspring are undergoing periodic evaluation of serum specimens for antibodies to HCV (anti-HCV) and HCV-RNA (by RT-PCR).

To date, 1855 women have enrolled in the study: 285 (15.4%) were anti-HCV positive and 161 (56.5%) were also HCV-RNA positive at their initial prenatal visits. 193 initial samples were collected from the offspring of anti-HCV positive mothers. Although 74.6% of these infants were initially anti-HCV positive, revealing a high prevalence of passively-acquired maternal antibodies, only 5 (4.4%; 95% CI 1.6, 10.5) of the 113 infants born of HCV-RNA positive mothers were also RT-PCR positive at their first visit. The geometric mean of HCV viral titers of transmitting mothers was significantly higher than those of 12 randomly selected HCV-RNA positive pregnant controls (9.15×10^5 IU/mL vs. 3.36×10^5 IU/mL, $p=0.004$). These results show low rates of HCV mother-to-infant transmission in our cohort. Updated results as well as community-acquired HCV incidence in both mothers and children will be presented.

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High Frequency of New Diagnoses of Hepatitis C Virus Infection in an Antenatal Population

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Introduction:

National Centre in H.I.V Epidemiology and Clinical Research, Darlinghurst, N.S.W. Australia Guidelines for screening blood borne viruses during pregnancy recommend testing for hepatitis C (HCV) be limited to women assessed as having "high risk" factors for HCV infection. However, it can be argued that selective screening practices of "high risk" women may potentially exclude infected women. This study aimed to investigate the proportion of women newly diagnosed with HCV and risk factors related to HCV acquisition in a cohort of healthy pregnant women.

Methodology:

Women attending their first antenatal assessment during June to October 2002 were asked to complete a written questionnaire and consent to medical record review of HCV results. Women were actively recruited once a week by a dedicated research nurse and on other days by antenatal clinic staff. The association

between HCV risk factors and HCV infection was evaluated by Chi squared analysis.

Results:

During the study period 34% of attending antenatal clients (315/928) enrolled into the study. Active recruitment achieved a 72% uptake rate. Of the 315 women enrolled nine women were aware of their positive HCV status and subsequently excluded from study analysis. Newly diagnosed women accounted for 2.29% (n=7) of the study population of which, 57% (n=4) tested positive for HCV RNA. A history of injecting drug use was reported by 2.6% (n=8) of the cohort of whom 50% (n=4) were found to be anti-HCV antibody positive. Identified risk factors for the three remaining cases include termination of pregnancy and receiving blood products after 1990, tattooing or Italian origin of birth. As expected, IVDU was found to be the strongest associated risk factor for HCV acquisition (p=0.001) with termination of pregnancy (p=0.09) and having a tattoo (p= 0.075) reporting a trend of significance.

Conclusions:

Within this cohort 2.29% of women were newly diagnosed. Close to half of the women reported risk factors not considered “high risk” for HCV acquisition.

Modeling Immune Effects on Viral Dynamics and Outcome of Primary Hepatitis C Infection in chimpanzees

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We analyzed the dynamics of HCV RNA and alanine aminotransferase (ALT) with respect to the innate (interferon-alpha) (IFN- α) and induced (interferon- gamma) (IFN- γ) immune responses during primary infection in 10 naïve chimpanzees inoculated with H77 clonal RNA (n=3) or monoclonal virus (n=7). Four of the animals cleared the infection, 6 developed persistent infections.

HCV RNA kinetics in all animals exhibited a bi-phasic increase (rapid replication with mean $t_2 = 0.5$ days that slows to $t_2 = 7.5$ days), with a transient decline between the phases. This early blocking of virion production correlates in both groups with an increase in the intrahepatic level of 2'5' oligoadenylate synthetase 1 (2OAS 1) mRNA, indicative of an IFN- α response. A plateau of RNA during which ALT levels stay close to baseline is followed in all animals by a rapid decline in HCV titer correlating with an ALT flare after a mean of 8.9 weeks and an increase in intrahepatic IFN gamma mRNA levels. This decline can be explained by increased death of infected cells, presumably due to cytotoxic T cell activity, together with viral elimination from infected cells through noncytolytic mechanisms.

Similar patterns of kinetics, viral titers and immune response markers were observed in all animals regardless of infection outcome. However, factors found to be predictive of spontaneous HCV clearance were timing (not intensity) of ALT flare (p<0.01), timing (not intensity) of IFN-gamma response, and viral decrease slope during the ALT flare and IFN gamma response (p<0.05).

These data indicate that regardless of outcome all chimpanzees generate immune responses to HCV that at least partially control virus replication during the early and late acute phase. However, a more rapid onset of the induced response seems to determine clearance of the virus. The induction of this response may be controlled by mechanisms or events occurring earlier during infection that have yet to be identified.

The 24-HR Interferon-Induced Decline in HCV Genotype 1 Load is a Good Predictor of Response to PEG IFN 2a/Ribavirin Therapy

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Background:

The 24h response to a single IFN dose (24hVR) identifies unresponsiveness to standard IFN/ribavirin therapy (decrease in viral load of <0.8 log predicted nonresponse with 100% specificity; Jessner, *Lancet* 2001). Early virologic response (EVR) after 12 weeks has a high predictive value for sustained response to 48 weeks of 4OkD-PEG-IFNalpha2a/ribavirin therapy (Ferenci, AASLD2001).

Aim:

To investigate the value of 24hVR prospectively.

Methods:

In an ongoing prospective trial comparing amantadine and placebo in addition to 180 µg 4OKDPEG-IFNalpha2a (Roche, Basel, CH)/week+ 1-1 .2g ribavirin/d in chronic hepatitis C (genotype 1) patients are stratified according to the 24hVR at randomization (stratum A: >1 .5 log decrease in viral load within 24 hrs; stratum B: 0.8-1.49; stratum C: <0.8). All patients had a liver biopsy and none had received an antiviral therapy before signing an informed consent. Currently all planned 220 patients were recruited, and 131, 101, and 39 completed 12, 24, and 48 weeks of treatment, respectively. In these patients the 24hVR was compared with the 12 week EVR, the 24 week and end of treatment response (each defined as HCV-RNA neg)

Analysis was done without breaking the randomization code. The 24hVR was calculated from the decrease in viral load within 24 hours after a single dose of 9 MU IFNalpha2a (Roferon®, Roche, Basel, CH) 2 weeks prior to randomization. Viral load was determined by the Cobas Amplicor Monitor HCV Test®, v2.0 (Roche Diagnostic Systems, USA).

Results:

The table below summarizes the data.

stratum	Week 12	24	48*
A	27/29(93.1%)	23/24(95.8%)	9/10
B	35/49(71.4%)	37/44(84.1%)	20/20
C	17/52(32.7%)	24/43(55.8%)	7/9
p (A/B; A/C;B/C)	0.04;0.00001;0.0002	0.24;0.0016;0.008	

* only HCV RNA neg pts. at week 24

Conclusion:

The 24hVR is a good predictor of the response to PEGASYS/ribavirin therapy. Patients with predicted poor response to standard-IFN/ribavirin therapy may still achieve a virologic response on PEGASYS/ribavirin therapy.

Therapy Induced Decline of Hepatitis C Virus RNA Levels in Partly Immune Mediated

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Background:

Interferon (IFN) exerts both direct and indirect effects during antiviral therapy of chronic hepatitis C virus (HCV) infections. The indirect antiviral effects have been attributed to the host immune system, although no direct evidence has been obtained.

Aims:

A kinetic analysis of HCV RNA levels and HCV-specific T cell responses during antiviral therapy.

Patients:

Serum and peripheral blood mononuclear cells were collected on day 0, 1, 2, 3, 7, 14, 28, 56, and 84 (week 12) from therapy start, during antiviral therapy in 32 patients with chronic HCV infection.

Methods:

The HCV viral load was determined by a commercial assay. The T cell response to the HCV non-structural-3 protein was determined by an in vitro T cell proliferation assay.

Results:

In 13 (41%) patients proliferative T cell responses developed in the periphery within 12 weeks. Appearance of a T cell response correlated with a shorter time to reach a viral load of <600 genome copies/mL (30 ± 7 days among T cell responders versus $60 + 8$ days among T cell non-responders; $p < 0.05$), and to HCV RNA negativity at week 12. A kinetic analysis revealed a shorter half-time (T) of the viral load decline among those who mounted a T cell response within the first 12 weeks of therapy as compared to those who did not ($T = 3.2$ days vs. $T_{1/2} = 7.0$ days; $p < 0.05$).

Conclusions:

Therapy-induced decline of HCV RNA levels is not only due to direct antiviral effects, but also partly immune-mediated.

Ordinal Regression Model Correctly Predicts HCV Patients' Response to Pegylated Interferon / Ribavirin at Week 4

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Background:

Given the burden of combination interferon therapy, physicians are seeking early prediction of non-response. We used data from chronic hepatitis C patients under pegylated combination therapy to develop a SLS model to predict outcome at baseline and week 4.

Materials and Methods:

81 patients with chronic hepatitis C (61% male, mean age 48) of which 43 were naïve and 38 were non-responders (NR) to interferon or interferon /ribavirin were treated with pegylated interferon a 2b 1.5mg/kg/week, plus ribavirin 800-1200 mg/day. Naïve genotypes 1 and 4 and previously failed patients were treated for 48 weeks, genotypes 2, 3, and 5, for 24 weeks. Sustained responders (SR) had undetectable HCV RNA by VERSANT HCV qualitative assay (HCV TMA) at EOT and for FU 24 weeks. Eleven variables were entered into the SLS™ program that uses ordinal regression to map HCV responder classes to a score scale. They included: baseline and week 4 viral load (assessed by the VERSANT HCV 3.0 assay), sex, baseline and week 4 ALT, inflammatory score, fibrosis score, genotype, week 4 TMA, age, and treatment status. The model, which employs prospective prediction statistics, outputs 3 probabilities of response — SR, relapser, and NR which sum to 100%. It assigns a given outcome to the highest probability score.

Results:

The week 4 model correctly identified all 47 SRs, 11 relapsers, and 23 NRs, assigning a probability of > 99% of a given outcome to all patients. Using baseline data, the probability of correct prediction is 72% for SRs and 65% for NRs.

Conclusions:

SLS™ models may be useful to physicians looking to modify therapy on the basis of prediction outcomes. Larger independent data sets would be helpful in further cross validating the model.

The Rapidly Changing Epidemiology of HCV Genotypes: Consequences for the Individual Therapeutic Regimen

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The prevalence of HCV genotypes in a given population is subjected to dynamic changes due to emergence and spread of new genotypes. Besides the epidemiological importance of these changes, we were interested in the impact on the individual patient. The HCV genotype is known as one independent predictor for the success of antiviral therapy, and different genotypes require different therapy regimens. Therefore, 39 patients practicing intravenous drug use (IVDU) were examined longitudinally. IVDU is known to be one of the main risk factors for acquiring HCV infection, and patients with IVDU are on a high risk for multiple infections with HCV. All isolates were typed by nucleotide sequencing.

A change of the HCV genotype was observed in 7 patients (18.4%) within a range of 2 months to 7 years. Three of the patients had undergone antiviral therapy with pegylated interferon and ribavirin. However, no

response to viremia levels below the detection limit could be induced in any of them and a different HCV genotype than before was detected during therapy. A reinfection during therapy could be excluded because the patients had stopped IVDU as a precondition for therapy.

In two samples the genotypes 1a and 3a were detected in parallel. It has been shown that in kidney transplanted patients who became superinfected by a second HCV subtype, except from a short episode where both strains were detectable, usually one strain established predominance. Only this strain was detectable by PCR based typing methods.

Our data provide evidence that in multiply infected patient's one strain will establish predominance. However, the minor strain does not become eliminated. Obviously, under the pressure of antiviral therapy on the viremic strain the minor strain can reemerge and establish viremia. This should be taken into account when an antiviral therapy regimen is planned.