

Caring Ambassadors Hepatitis C Program Newsletter
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IN THE NEWS	1 – 4
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	4 – 10
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	10 – 15
HIV/HCV COINFECTION	15 – 19
COMPLEMENTARY & ALTERNATIVE THERAPY	19 – 19
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	19 – 26

IN THE NEWS

Life Story: Hepatitis C advocate was 49

http://www.appeal-democrat.com/news/hepatitis_66550_article.html/sherri_yuba.html

Sherri Ziegler was a strong advocate for education about Hepatitis C and services for those affected by the virus. She helped start the California Hepatitis Alliance, founded the Nor-Cal Hepatitis C Network, was a founding member the National Hepatitis C Advocacy Council and a member of the National Viral Hepatitis Roundtable and the California Hepatitis C Task Force. She often appeared before legislators in Sacramento and Washington, D.C. All because she couldn't find any information about the virus when she was diagnosed.

“She went in search for information ... searching out and finding what was out there,” said her sister, Jeanee Marler of Paradise. “The more she found out, the more depressing (it was) because nothing was out there.” Sherri Rae Ziegler, 49, of Yuba City, died June 26 at the University of California, San Francisco Medical Center due to a brain aneurysm, according to her family. Born in Sacramento, the longtime Yuba City resident was a graduate of Yuba City High School. Sherri never knew exactly how she contracted Hep C, her sister noted. [truncated]

Natalie Cole says she has hepatitis C

<http://ap.google.com/article/ALeqM5jAdavpEOtnwONtpOSAv4qaFTQvXAD91USTHO1>

Grammy-winning singer Natalie Cole has been diagnosed with hepatitis C, her publicist said in a statement Wednesday. Hepatitis C is a liver disease spread through contact with infected blood. The statement said the disease was revealed during a routine examination and was likely caused by her drug use years ago.

“I’ve been so fortunate to have learned so much from my past experiences,” said Cole. “I am embraced by the love and support of my family and friends; I am committed to my belief in myself and in my abiding faith to meet this challenge with a heartfelt optimism and determination. This is how I intend to deal with this current challenge in my life.” [truncated]

Improved culture system for hepatitis C virus infection

<http://www.sciencedaily.com/releases/2008/07/080715204843.htm>

A University of California, San Diego School of Medicine researcher has developed the first tissue culture of normal, human liver cells that can model infection with the Hepatitis C virus (HCV) and provide a realistic environment to evaluate possible treatments. The novel cell line will allow

pharmaceutical companies to effectively test new drug candidates or possible vaccines for the HCV infection, which afflicts about 170 million people worldwide. Currently, there is no animal model that is effective for testing such therapies.

“This is the first efficient and consistent model system for HCV to be developed,” said Buck, adding that it will now enable researchers not only to conduct mechanistic experiments in culture, such as blocking the virus pathways, but also to more effectively screen possible therapies for HCV. “There is a need for new treatments, and for development of a possible vaccine for HCV. Now we have a model system to support work by investigators in this area.” [truncated]

Hepatitis bout ignited Nebraska woman's activism against medical contamination

http://blog.mlive.com/grpress/2008/07/hepatitis_bout_ignited_nebrask.html

Evelyn McKnight beat the breast cancer that could have killed her, but her doctor's unsanitary practice infected her and 98 other patients with another life-threatening disease: hepatitis C. As a result, McKnight, an audiologist in Fremont, Neb., last year founded a nonprofit organization Hepatitis Outbreaks National Organization for Reform (HONORreform) to lobby for state and federal laws protecting patients from substandard care. [truncated]

County hepatitis C numbers lead to increased screening

High-risk people encouraged to visit county clinic

<http://www.summitdaily.com/apps/pbcs.dll/article?AID=/20080720/NEWS/848161573/1078&ParentProfile=1055&template=printart>

SUMMIT COUNTY, CO — Local health officials are concerned that increasing numbers of hepatitis-C cases are going undetected as exposure climbs. The Summit County Community Care Clinic has confirmed two positive tests for the disease since January and has records of 30 county residents who have been exposed, said Carolyn Lyle, a certified physician's assistant at the clinic. The actual number of people infected is likely much higher, she said.

Deborah Miliner, also a PA-C with the clinic, said many can carry the disease for 20 or 30 years without symptoms. “That’s the bummer: They might not have any symptoms ever, except that (their) liver is slowly dying,” she said. [truncated]

Many locals may be hepatitis C positive

<http://herald-zeitung.com/story.lasso?tool=print&ewcd=e208057e0903bd14&-session=HeraldZeitung:4A5F27BE11a101913FPwo407C0B8>

Doctors say between 10,000 and 20,000 people with Hepatitis C live in the collective New Braunfels, Kyle, Wimberley and Lockhart area — and many are wholly unaware they've contracted the blood-borne disease. “With most of the patients we're treating now, (the diagnosis) was picked up incidentally,” said Dr. Juan Guerrero, hepatologist with San Antonio's UT Health Science Center. A liver transplant isn't always needed, he said, but “by the time symptoms present themselves it's usually too late” to go another route. [truncated]

Genelabs, Taiwan company collaborate on hepatitis C research

<http://www.bizjournals.com/sanjose/stories/2008/07/21/daily48.html>

Genelabs Technologies Inc. said Wednesday it will collaborate with two entities to research and develop compounds that target the hepatitis C virus. Redwood City-based Genelabs said the agreement includes the National Health Research Institutes, a nonprofit foundation established by

the government of the Republic of China, and Genovate Biotechnology Co. Ltd., a biopharmaceutical company in Taiwan. Financial details were not disclosed.

In June Genelabs said Gilead Sciences Inc. ended a deal between the two companies to study a possible hepatitis C treatment. Genelabs said at the time it would get back all rights to the compounds developed in the deal with Foster City's Gilead. [truncated]

2 dates identified in Vegas hepatitis C outbreak

http://www.ktvn.com/Global/story.asp?S=8728308&nav=menu549_2

The Southern Nevada Health District is identifying the two dates in 2007 when officials believe hepatitis C was transmitted between patients at the Endoscopy Center of Southern Nevada. In a report prepared for the district board on Thursday, officials say genetic testing traced the virus to patients treated on July 25, 2007, and on Sept. 21, 2007.

On Wednesday, officials said a ninth case of hepatitis C was linked to the Las Vegas clinic and a sister facility, the Desert Shadow Endoscopy Center. In the biggest public health notification in U.S. history, the district last February advised some 50,000 clinic patients to get blood tests for hepatitis B, C and HIV, the virus that causes AIDS. Authorities say patients were exposed to the virus when clinic staff reused syringes and medicine vials. [truncated]

Researchers disprove long-standing belief about HIV treatment

<http://www.news-medical.net/?id=40269>

Researchers at Wake Forest University Baptist Medical Center have disproved a long-standing clinical belief that the hepatitis C virus slows or stunts the immune system's ability to restore itself after HIV patients are treated with a combination of drugs known as the "cocktail."

Hepatitis C (HCV) infection is more serious in HIV-infected people, leading to rapid liver damage, according to the Centers for Disease Control. Intravenous drug use is a main method of contraction for both HIV and HCV and 50 to 90 percent of HIV-infected drug users are also infected with HCV.

The Wake Forest Baptist study looked at whether having HCV coinfection impairs immune restoration in patients receiving highly active anti-retroviral therapy (HAART) to suppress their HIV infection. The results appear in the July issue of *Aids Research and Human Retroviruses*.

The research focused on levels of CD4 cells, the specific type of immune cell that is attacked by the HIV virus, and their ability to rebuild after HIV is suppressed. "We've been observing that in some patients that are co-infected with hepatitis C, we were treating their HIV with HAART but didn't always get very good restoration of CD4," said Marina Nunez, M.D., lead researcher and an assistant professor of infectious diseases. "Some studies suggested it was because of the hepatitis C. This study says it's not the presence of active hepatitis C replication."

Thus, said Nunez, genetic factors involved in the immune system regulation, confounding factors associated with HCV acquisition, or other unknown factors might explain the blunted immune restoration observed in some coinfecting patients. "Research efforts should pursue the role of those other factors in the immune restoration," she said. [truncated]

Idenix Pharmaceuticals advances HCV discovery program to clinic

Initiates IDX184 phase I clinical study and advances HCV protease inhibitor and non-nucleoside polymerase inhibitor clinical candidates into IND-enabling preclinical studies.

<http://www.earthtimes.org/articles/show/idenix-pharmaceuticals-advances-hcv-discovery-program-to-clinic,484062.shtml>

Idenix Pharmaceuticals, Inc., a biopharmaceutical company engaged in the discovery and development of drugs for the treatment of human viral and other infectious diseases, today announced that it has initiated a first-in-man study of IDX184 under a United States investigational new drug (IND) application. IDX184 is a once-daily, oral nucleotide prodrug polymerase inhibitor for the treatment of chronic hepatitis C. Today, Idenix also announced that it has selected a lead clinical candidate (IDX375) from its HCV non-nucleoside polymerase inhibitor discovery program and has advanced IDX375 into IND-enabling pharmacokinetic and toxicology studies. Idenix has also advanced two protease inhibitor drug candidates (IDX136 and IDX316) into IND-enabling pharmacokinetic and toxicology studies. [truncated]

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Lichen planus and other cutaneous manifestations in chronic hepatitis C: pre- and post-interferon-based treatment prevalence vary in a cohort of patients from low hepatitis C virus endemic area. Maticic M, et al. J Eur Acad Dermatol Venereol. 2008 Jul;22(7):779-88.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18452521&dopt=Abstract

BACKGROUND: Several controversies exist regarding the relationship between hepatitis C virus (HCV) infection and some cutaneous manifestations, lichen planus (LP) in particular.

OBJECTIVES: To determine the prevalence of LP and other cutaneous manifestations in a cohort of patients infected with HCV from low HCV endemic area of Slovenia, to correlate findings with chosen biological variables and to assess the role of interferon (IFN)-based treatment of HCV infection in cutaneous manifestations. **METHOD** A total of 171 consecutive HCV-seropositive patients and 171 HCV-seronegative age- and gender-matched controls were studied prospectively. Prevalence of cutaneous manifestations, comparison between study patients and controls and correlation of skin findings with demographic, biochemical, virological and liver histologic findings as well as IFN-based therapy were assessed. **RESULTS:** Overall presence of LP in HCV-seropositives was 2.3%; although LP was not found in controls, the difference was not statistically significant ($P = 0.123$). Significantly higher than in controls was the prevalence of pruritus (31.0%, $P < 0.001$), dry skin (16.4%, $P < 0.001$) and hair loss (9.9%, $P < 0.001$). In IFN-based treatment naïves, skin findings were more frequent compared with controls, but not significantly, with no correlation to chosen biological variables. Current IFN-based treatment was significantly connected to pruritus ($P < 0.001$) and dry skin ($P < 0.001$). Compared with treatment naïves, in post-treated patients pruritus (odds ratio, 19.13; 95% confidence interval, 6.85-53.42; $P < 0.001$), dry skin (odds ratio, 4.21; 95% confidence interval, 1.44-12.31; $P < 0.001$) and hair loss ($P < 0.001$) were significantly more common. **CONCLUSIONS:** LP was not significantly related to HCV infection. Prevalence of pruritus, dry skin and hair loss was significantly higher in post-compared with pre-treated patients. The role of IFN in post-treatment persistence of skin manifestations needs to be assessed.

Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. Pergam SA, et al. Am J Obstet Gynecol. 2008 Jul;199(1):38.e1-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18486089&dopt=Abstract

OBJECTIVE: The objective of the study was to determine the effect of hepatitis C virus (HCV) on selected maternal and infant birth outcomes. **STUDY DESIGN:** This population-based cohort study using Washington state birth records from 2003 to 2005 compared a cohort of pregnant women identified as HCV positive from birth certificate data (n = 506) to randomly selected HCV-negative mothers (n = 2022) and drug-using HCV-negative mothers (n = 1439). **RESULTS:** Infants of HCV-positive mothers were more likely to be low birthweight (odds ratio [OR], 2.17; 95% confidence interval [CI] 1.24, 3.80), to be small for gestational age (OR, 1.46; 95% CI, 1.00, 2.13), to need assisted ventilation (OR, 2.37; 95% CI, 1.46, 3.85), and to require neonatal intensive car unit (NICU) admission (OR, 2.91; 95% CI, 1.86, 4.55). HCV-positive mothers with excess weight gain also had a greater risk of gestational diabetes (OR, 2.51; 95% CI, 1.04, 6.03). Compared with the drug-using cohort, NICU admission and the need for assisted ventilation remained associated with HCV. **CONCLUSION:** HCV-positive pregnant women appear to be at risk for adverse neonatal and maternal outcomes.

Associations between hepatitis C viremia and low serum triglyceride and cholesterol levels: A community-based study. Dai Cy, et al. J Hepatol. 2008 Jul;49(1):9-16.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18486265&dopt=Abstract

BACKGROUND/AIMS: To evaluate the association of virologic status with serum cholesterol and triglyceride levels in individuals with hepatitis C virus (HCV) infection. **METHOD:** We conducted a large scale community-based study enrolling 11,239 residents in an area endemic for hepatitis B virus (HBV) and HCV infection in southern Taiwan. Overall, 703 (6.3%), 1,536 (13.7%), 84 (0.7%) and 9,084 (80.8%) subjects were sero-positive for anti-HCV antibody (anti-HCV), hepatitis B surface antigen (HBsAg), and both anti-HCV and HBsAg, and negative for anti-HCV and HBsAg, respectively. **RESULTS:** By multivariate logistic analyses, the independent factors significantly associated with elevated serum cholesterol level were older age, female, negative for diabetes, anti-HCV or HBsAg and elevated triglyceride levels. The independent factors significantly associated with elevated serum triglyceride level were male, positive for diabetes, negative for anti-HCV or HBsAg, higher body mass index (BMI) and elevated cholesterol levels. Of 642 anti-HCV-positive subjects that have HCV RNA tested by standardized automated qualitative PCR assay, 478 (74.5%) were positive for HCV RNA. By multivariate logistic analyses, the independent factors associated with elevated serum cholesterol level were female, elevated serum triglyceride levels, negative for diabetes or HCV RNA. The independent factors associated with elevated serum triglyceride levels were elevated serum cholesterol levels, positive for diabetes, higher BMI and negative for HCV RNA. Diabetes, lower cholesterol and triglyceride levels were independent factors associated with positive HCV RNA. **CONCLUSIONS:** Based on the result of this large scale community study, HCV viremia appears to be associated with lower serum cholesterol and triglyceride levels which implies that HCV itself might play a significant role on serum lipid profile of patients with chronic HCV infection.

Antiviral effects and safety of telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in hepatitis C patients. Lawitz E, et al. J Hepatol. 2008 Aug;49(2):163-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18486984&dopt=Abstract

BACKGROUND/AIMS: This study assessed the safety and antiviral effects of telaprevir (VX-950)

in combination with peginterferon alfa-2a and ribavirin. **METHOD:** Twelve treatment-naïve patients with chronic genotype 1 hepatitis C virus infection received telaprevir (750mg q8h), peginterferon alfa-2a (180µg/week), and ribavirin (1000 or 1200mg/day) for 28 days. Patients could then start off-study treatment with peginterferon alfa-2a and ribavirin for up to 44 weeks, at the discretion of the investigator and patient. **RESULTS:** The combination of telaprevir, peginterferon alfa-2a, and ribavirin was well tolerated, with no serious adverse events or treatment discontinuations. Rash or pruritus occurred in 5 of the 12 patients; all cases resolved either during or after the end of telaprevir treatment. All 12 patients had undetectable HCV RNA levels by day 28 (rapid viral response, RVR). Eight patients completed 44 weeks of off-study peginterferon alfa-2a and ribavirin treatment. Eight patients achieved a sustained viral response (SVR), including one patient who received only 22 weeks of treatment. **CONCLUSIONS:** The combination of telaprevir, peginterferon alfa-2a, and ribavirin was generally well tolerated. Events of pruritus and rash resolved during or after end of telaprevir dosing. All 12 patients achieved an RVR.

Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Chen CL, et al. *Gastroenterology*. 2008 Jul;135(1):111-21.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18505690&dopt=Abstract

BACKGROUND & AIMS: This study investigated whether obesity, diabetes, and other metabolic factors are independently associated with hepatocellular carcinoma (HCC), stratified by hepatitis B virus (HBV) and hepatitis C virus (HCV) serostatus, and explored the possible joint influence of obesity/diabetes and HBV/HCV infections on the risk of HCC. **METHOD:** A total of 23,820 residents in Taiwan were recruited and followed up for 14 years. All analyses were stratified by hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV) at enrollment, and 218 subjects positive for both seromarkers were excluded. Incident HCC cases were identified via linkage to the national cancer registry. Multivariate-adjusted relative risk (RR(a)) and 95% confidence interval (95% CI) were estimated using Cox proportional hazards models. **RESULTS:** Extreme obesity (body mass index ≥ 30 kg/m²) was independently associated with a 4-fold risk of HCC (RR(a), 4.13; 95% CI, 1.38-12.4) among anti-HCV-seropositive subjects and a 2-fold risk (RR(a), 2.36; 95% CI, 0.91-6.17) in persons without HBV and HCV infections, after controlling for other metabolic components, but not in HBsAg-seropositive subjects (RR(a), 1.36; 95% CI, 0.64-2.89). Diabetes was associated with HCC in all 3 groups, with the highest risk in those with HCV infection (RR(a), 3.52; 95% CI, 1.29-9.24) and lowest in HBV carriers (RR(a), 2.27; 95% CI, 1.10-4.66). We found more than 100-fold increased risk in HBV or HCV carriers with both obesity and diabetes, indicating synergistic effects of metabolic factors and hepatitis. **CONCLUSIONS:** The finding that both obesity and diabetes are predictors of HCC risk, possibly differently depending on HBV and HCV infection status, may shed some light in preventing HCC.

Erythropoiesis-stimulating agent use for anemia induced by interferon-ribavirin treatment in patients with hepatitis C virus infection is not associated with increased rates of cardiovascular disease, thrombosis, malignancy, or death. Costiniuk CT, Camacho F, and Cooper CL. *Clin Infect Dis*. 2008 Jul 15;47(2):198-202.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18532889&dopt=Abstract

BACKGROUND: Anemia is a complication of therapy for hepatitis C virus (HCV) infection, necessitating dose reductions or therapy abandonment. Administration of an erythropoiesis-stimulating agent (ESA) is a common strategy to manage this complication. Clinical data in other

patient populations demonstrate increased rates of cardiovascular events, thrombosis, malignancy, and death among ESA recipients. Event rates in the context of HCV treatment are unknown.

METHOD: All recipients of interferon-ribavirin-based HCV therapy at the Ottawa Hospital Viral Hepatitis Clinic from October 2003 through October 2006 were identified. Predictors of ESA use were assessed by regression analysis. Adverse events during and after treatment were evaluated.

RESULTS: A total of 174 courses of HCV therapy were initiated. Predictors of ESA use included older age, lower weight, lower baseline hemoglobin level, and infection with HCV genotype 1 or 4. Targeted hemoglobin levels of >110 g/L were achieved in 88% of ESA recipients. Although not statistically significant, sustained virological responses were obtained in more recipients of ESA (54%) than nonrecipients (45%). In the period after HCV treatment, no myocardial infarctions, deep vein thromboses, or pulmonary embolisms occurred; the frequency of stroke and cancer events were low; and rates of adverse events appeared to be similar between groups. **CONCLUSIONS:** ESA use is not associated with increased risk of cardiovascular events, malignancy, thrombosis, or death in HCV-infected patients during receipt of HCV therapy or in the period after completion. Given the inherent differences in patient populations, practitioners should exercise caution when extrapolating the results of studies of other diseases to HCV infection. Our efficacy and safety analysis suggests against the withholding of ESAs in the management of anemia induced by HCV treatment.

Efficacy of low-dose intermittent interferon-alpha monotherapy in patients infected with hepatitis C virus genotype 1b who were predicted or failed to respond to pegylated interferon plus ribavirin combination therapy. Akuta N, et al. J Med Virol. 2008 Aug;80(8):1363-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18551610&dopt=Abstract

The efficacy of interferon (IFN) monotherapy for non-responders to pegylated interferon (PEG-IFN) plus ribavirin (RBV) combination therapy is still unclear. To evaluate the impact of IFN monotherapy on biochemical response, 200 consecutive patients infected with HCV genotype 1b, who received low-dose intermittent IFN-alpha monotherapy, were investigated. A median IFN dose per day of 3 million units was administered during a median period of 74 weeks. As a whole, the ALT normalization rates were 50.5, 65.9, 58.4, and 61.7% at 4, 12, 24, and 48 weeks, respectively. In 40 patients, who had abnormal AFP levels at the start of treatment, 52.5% achieved normalization of AFP within 48 weeks. Multivariate analysis identified indocyanine green retention rate at 15 min as the parameter that influenced significantly and independently ALT normalization. ALT normalization rates of patients who were predicted to be poor responders to PEG-IFN plus RBV combination therapy (but not substitutions of amino acid 70 and/or 91 in the HCV core region, female sex, and lower levels of low-density lipoprotein cholesterol) were similar to others. Furthermore, the ALT normalization rates in non-responders to combination therapy were 29.2, 60.9, 60.0, and 40.0% at 4, 12, 24, and 48 weeks, respectively. The results suggest that low-dose intermittent IFN monotherapy is an efficacious therapeutic regimen for patients unsuitable for PEG-IFN plus RBV, including non-responders, because it can lead to ALT normalization and thus a reduced risk of hepatocarcinogenesis.

Pioglitazone in chronic hepatitis C not responding to pegylated interferon-alpha and ribavirin. Overkbeck K, et al. J Hepatol. 2008 Aug;49(2):295-298.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18555553&dopt=Abstract

BACKGROUND/AIMS: Insulin resistance reduces the response to interferon alfa-based therapy of chronic hepatitis C patients. It has been speculated that improvement of insulin sensitivity might increase the chances of responding to treatment of such individuals. **METHOD:** We started a multicenter clinical trial of retreatment of chronic hepatitis C patients, who had failed to respond to the pegylated interferon alfa/ribavirin combination, with a triple therapy consisting in these same antivirals plus an insulin-sensitizer (pioglitazone) (The INSPIRED-HCV study). **RESULTS:** None of the first five patients fulfilling the inclusion criteria and included in the trial achieved a satisfactory virological response after 12 weeks of retreatment, despite the fact that in at least three of them the insulin resistance score improved. As a result, the study was terminated. **CONCLUSIONS:** Different schedules are warranted to improve insulin sensitivity prior to attempting retreatment of chronic hepatitis C patients with insulin resistance.

Antiviral therapy for recurrent hepatitis C after liver transplantation: sustained virologic response is related to genotype 2/3 and response at week 12. Raziorrouh B, et al. Eur J Gastroenterol Hepatol. 2008 Aug;20(8):778-83.

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve>

[&list_uids=18617783&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18617783&dopt=Abstract)

OBJECTIVES: Recurrent hepatitis C virus (HCV) infection after liver transplantation (LT) is a major cause of transplant failure in HCV-positive patients. We retrospectively assessed the efficacy and safety of antiviral therapy and determined the factors influencing sustained virologic response (SVR) in LT recipients. **METHOD:** Between 1998 and 2007, we treated 36 LT recipients for hepatitis C cirrhosis and subsequent HCV recurrence (27 genotype 1 and 9 genotypes 2/3) with pegylated interferon alpha-2a (180 mug/week), pegylated interferon alpha-2b (1.5 mug/kg per week), or standard interferon alpha-2b (3 MIU 3X/week) plus ribavirin (600-1200 mg/day) for 48 weeks. **RESULTS:** SVR was achieved in seven of 27 (26%) of genotype 1 patients versus nine of nine (100%) genotype 2/3 patients (P=0.0001). Early virologic response at week 12 was associated with permanent viral clearance. Side effects included cytopenia and acute hearing loss, but rate of therapy withdrawal and dose reduction was low. **CONCLUSION:** Combination therapy in patients with HCV reinfection after LT yields an excellent SVR rate in genotype 2/3 patients, but remains unsatisfactory in genotype 1 patients. Virologic response at week 12 (early virologic response) can determine whether therapy should be continued or not.

Suitable treatment period in patients with virological response during combination therapy of peginterferon and ribavirin for chronic hepatitis C. Arase Y, et al. Intern Med. 2008;47(14):1301-7. [Epub 2008 Jul 15]

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve>

[&list_uids=18628577&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18628577&dopt=Abstract)

OBJECTIVE: The aim of this study was to determine the suitable treatment period in patients who achieve virological response during combination therapy of peginterferon and ribavirin for chronic hepatitis C virus infection. **METHOD:** Inclusion criteria were HCV-genotype 1b, serum HCV RNA level of > or =100 KIU/ml before treatment, and negativity of serum HCV RNA during treatment. The 366 patients were enrolled in this retrospective cohort study. Patients were classified into four groups according to difference of response: rapid-virological response (RVR) at week 4 after the initiation of treatment (n=37), early-virological response (EVR) at week 5-12 (n=161), late-virological response (LVR) at week 13-24 (n=131), and superlate-virological response (SLVR) at week 25-48 (n=37). A non-relapse in patients with undetectable HCV RNA during therapy was defined as clearance of HCV RNA 6 month after the cessation of therapy. **RESULTS:** Of the 366

patients, 241 had non-relapse and the non-relapse rate in each group was 89% (33/37) in RVR, 79% (127/161) in EVR, 54% (71/131) in LVR, and 27% (10/37) in SLVR. In RVR, 26 of 27 patients with continuance of negative HCV RNA of > or =30 weeks during treatment had non-relapse. In EVR, patients with period of negative HCV RNA of > or =40 weeks had non-relapse rate of 90% (71/79). In LVR and SLVR, all nine patients with continuance of negative HCV RNA of > or =60 weeks had non-relapse. **CONCLUSION:** A suitable treatment period of combination therapy for chronic hepatitis C should be determined based on the time of attainment of negative HCV RNA.

The Response to Pegylated Interferon Alpha 2a in Haemodialysis Patients with Hepatitis C Virus Infection. Akhan SC, Kalender B, and Ruzgar M. *Infection*. 2008 Jul 15. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18629437&dopt=Abstract

The aim of this retrospective study was to focus the efficacy of pegylated interferon (PEG-IFN) alpha 2a in chronic hemodialysis patients with hepatitis C and to compare the therapy responses with other chronic hepatitis C patients. Of the anti-HCV positive patients who were admitted to the Infectious Diseases and Clinical Microbiology policlinic from January 2004 to December 2006, 99 were candidates for interferon therapy. Of those, 12 patients were on HD. We began 47 patients on PEG-IFN alpha 2a (180 lg/week) subcutaneously plus ribavirin (1,000-1,200 mg/day) (Group 1), and 12 patients on HD, PEG-IFN alpha 2a, without ribavirin at a dose of 135 lg weekly for 48 weeks (Group 2). In this study of PEG IFN alpha 2a with or without ribavirin, the predictability of a sustained viral response (SVR) was based on the early virologic response (EVR) defined at week 12 as an at least 2-log decline from baseline of the HCV RNA level. About 77% (39/47) of patients achieved an EVR in Group 1 and 58% (7/12) in Group 2 ($p = 0.004$). A total of 34 (72.34%) patients in Group 1 and 6 patients (50%) in Group 2 had negative HCV RNA at the end of the treatment ($p = 0.213$). We evaluated SVR after 6 months finishing the therapy; 29 (61.7%) patients in Group 1 and 6 patients (50%) in Group 2 had negative HCV RNA ($p = 0.109$). PEG-IFN alpha 2a (135 lg weekly) for 48 weeks is efficacious and well tolerated in HD patients with HCV, as well as other chronic HCV patients. However, due to more side effects of IFN specially on platelet counts as compared non-renal HCV patients a closer follow-up, in HD patients is suggested.

Liver transplant for hepatitis C virus: effect of using older donor grafts on short- and medium-term survival. Doyle MB, et al. *Arch Surg*. 2008 Jul;143(7):679-85.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18645111&dopt=Abstract

HYPOTHESIS: Older donor grafts will provide suitable results of liver transplant, even in recipients with hepatitis C virus (HCV). Although HCV remains the leading indication for liver transplant in adults in the United States, it is associated with HCV recurrence, increased graft loss, and reduced survival. In addition, recent studies suggest that the use of older donors in recipients with HCV is associated with significantly worsened short- and long-term survival. **DESIGN:** Prospective database analysis. **SETTING:** Washington University School of Medicine. **PATIENTS:** Between January 1, 1997, and June 30, 2006, a total of 579 liver transplants were performed. Ninety pediatric transplants were excluded. Of the remaining 489 adult patients (84.5%), 187 (38.2%) had HCV and 302 (61.8%) had other indications. **MAIN OUTCOME MEASURES:** Patient and graft survival, recurrence of HCV, and need for and results of retransplant. **RESULTS:** At 1, 3, and 5 years, overall patient survival was 88.1%, 78.3%, and 69.2%, respectively, and graft survival was 85.6%, 75.6%, and 65.6%, respectively, in patients with HCV. There was no significant

difference in patient or graft survival between patients with and those without HCV. Recurrent HCV with clinically significant disease was 20% at 1 year and 62% at 10 years. Seventy-two patients received transplants from donors 60 years or older (24 of 187 [12.8%] with HCV and 48 of 302 [15.9%] without HCV). No difference was demonstrated in short- or medium-term patient or graft survival in recipients of grafts from older donors. **CONCLUSION:** The increasing use of marginal donors, including carefully selected older donors, does not seem to adversely affect short- or medium-term results and may be a source of additional organs for expanding liver transplant waiting lists.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Fibrosis progression rates between chronic hepatitis B and C patients with elevated alanine aminotransferase levels. Fujiwara A, et al. J Gastroenterol. 2008;43(6):484-91.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18600393&dopt=Abstract

BACKGROUND: We evaluated the annual rate of fibrosis progression in chronic hepatitis B and C patients with elevated alanine aminotransferase (ALT) levels. **METHOD:** Forty-nine chronic hepatitis B patients and 21 chronic hepatitis C patients, each of whom had undergone two or more liver biopsies at an interval of more than 1 year, were enrolled in this retrospective clinical research protocol. The annual rate of fibrosis progression was calculated by dividing the change in fibrosis stage between the first and second liver biopsies by the interval in years between them. **RESULTS:** The median interval in chronic hepatitis B and C was 3.4 (first and third quartiles, 1.8-4.7) and 3.2 (2.1-6.5) years, respectively. Overall, the mean fibrosis progression rate was 0.21 +/- 0.31 (mean +/- SD) fibrosis units (FU) per year in 49 patients with chronic hepatitis B, and 0.13 +/- 0.18 FU/year in 21 patients with chronic hepatitis C. The ALT level was an independent variable correlating with fibrosis progression. In patients whose median ALT level was 70 IU/l or more, the mean fibrosis progression rate was 0.28 +/- 0.32 FU/year in 36 patients with chronic hepatitis B, and 0.22 +/- 0.23 FU/year in eight patients with chronic hepatitis C. **CONCLUSION:** This paired-biopsy study of untreated chronic hepatitis B or C demonstrated that fibrosis progression occurred largely in patients with continuously elevated ALT levels even over a relatively short period, and that liver fibrosis might progress by one stage within an average of 4-5 years of follow-up in patients with elevated ALT of 70 IU/l or more.

A set of reference sequences for the hepatitis C genotypes 4d, 4f, and 4k covering the full open reading frame. Kuntzen T, et al. J Med Virol. 2008 Aug;80(8):1370-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18551618&dopt=Abstract

Infection with genotype 4 of the Hepatitis C virus is common in Africa and the Mediterranean area, but has also been found at increasing frequencies in injection drug users in Europe and North America. Full length viral sequences to characterize viral diversity and structure have recently become available mostly for subtype 4a, and studies in Egypt and Saudi Arabia, where high proportions of subtype 4a infected patients exist, have begun to establish optimized treatment regimens. However knowledge about other subtype variants of genotype 4 present in less developed African states is lacking. In this study the full coding region from so far poorly characterized variants of HCV genotype 4 was amplified and sequenced using a long range PCR technique. Sequences were analyzed with respect to phylogenetic relationship, possible recombination and prominent sequence characteristics compared to other known HCV strains. We present for the first time two

full-length sequences from the HCV genotype 4k, in addition to five strains from HCV genotypes 4d and 4f. Reference sequences for accurate HCV genotyping are required for optimized treatment, and a better knowledge of the global viral sequence diversity is needed to guide vaccines or new drugs effective in the world wide epidemic.

Histologic abnormalities are common in protocol liver allograft biopsies from patients with normal liver function tests. Abraham SC, et al. Am J Surg Pathol. 2008 Jul;32(7):965-73.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18460980&dopt=Abstract

The utility of protocol liver allograft biopsies remains controversial, particularly in patients with normal liver function tests (LFTs). However, histologic evaluation of these biopsies provides an opportunity to examine the types and severity of liver diseases that can occur in livers with normal clinical and biochemical function. We studied 165 protocol allograft biopsies taken from 100 liver transplant patients at the time of normal LFTs and normal clinical function at 3 to 8 months (n=36), 1 year (n=52), 2 to 3 years (n=54), and 4 to 5 years (n=23). Biopsies were classified as normal, minimal changes (eg, nonaggressive portal or lobular mononuclear inflammation, steatosis <10%), fatty liver disease, recurrent primary liver disease, and transplant-related disease (portal-based rejection or central venulitis, an inflammatory pattern that encompasses perivenular hepatocyte dropout, mononuclear inflammation, pigment-laden macrophages, and variable zone 3 fibrosis). Among these 100 patients, a total of 394 protocol biopsies were performed, and 165 (42%) were taken at the time of normal LFTs and normal clinical function. One hundred twenty-one (73%) were normal or showed minimal/nonspecific changes. Forty-four (27%) showed histologic abnormalities that included fatty liver disease (n=19, nonalcoholic in 18 cases; 13 with mild steatosis, 6 with moderate steatosis, 7 with grade 1/3 steatohepatic activity, and 2 with stage 1/4 steatohepatic fibrosis), recurrent primary biliary cirrhosis (n=9; all stage 1/4), recurrent hepatitis C infection (n=6; grade 0/4 in 1, grade 1/4 in 5, stage 0/4 in 4, stage 1/4 in 1, and stage 2/4 in 1), recurrent sarcoidosis (n=1), Ito cell hyperplasia (n=4; marked in 2 and mild in 2), central venulitis (n=10; 5 with mild zone 3 fibrosis or central vein obliteration and 1 with central-portal bridging fibrosis), and mild acute portal rejection (n=2). We judged the histologic changes to be of clinical significance in 19 (11.5%) cases. These results indicate that even at the time of normal clinical and laboratory function, a significant fraction of protocol allograft biopsies harbor histologic (27%) and clinically significant (11.5%) abnormalities. These most commonly include fatty liver disease, low-grade/low-stage recurrent hepatitis C and primary biliary cirrhosis, and central venulitis (including some cases with subsequent fibrosis progression). The data support performance of protocol biopsies to assess allograft status, and provide insight into the types and severity of liver diseases that can smolder in transplanted (and by extension, probably also in native) livers with apparent normal function.

Kinetics of hepatitis C viral RNA and HCV-antigen during dialysis sessions: evidence for differential viral load reduction on dialysis. Kaiser T, et al. J Med Virol. 2008 Jul;80(7):1195-201.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18461613&dopt=Abstract

Hepatitis C infection is a common problem in dialysis units. The prevalence ranges from 3% to more than 50%. Several reports have described a variable reduction of HCV-RNA during hemodialysis treatment sessions. But so far nothing is known about the HCV antigenemia or the kinetics of the reduction of HCV-RNA and HCV antigenemia during these sessions. HCV-RNA was monitored using the VERSANT HCV bDNA assay 3.0 (Bayer Healthcare Diagnostics,

Leverkusen, Germany) or the HCV-Monitor TaqMan (Roche Diagnostics). HCV antigenemia was tested by using Ortho-trac-C assay (Ortho Clinical Diagnostics, Neckargemünd, Germany). Kinetics of HCV-RNA were available in 15 dialysis sessions measured by bDNA assay and in 5 dialysis sessions measured by rt-PCR. Quantitative HCV-antigenemia was available in fourteen dialysis sessions. Not only HCV-RNA but as expected also the HCV-antigenemia fell during the dialysis session. However, while the average reduction of HCV-antigen appears steady and linear, the level of HCV-RNA seems to be stable during the first 3 hr of dialysis, and decreases rapidly during the last 2 hr. The results seem to be independent of the HCV-RNA detection method. The different kinetics of HCV RNA and HCV antigen load suggest that there are different mechanisms responsible for the reduction of the HCV antigen and HCV-RNA, respectively. Reduction of viral load during dialysis session indicates a potential benefit of dialysis in case of HCV associated antiviral therapy.

Hepatitis C virus infection in mouse hepatoma cells co-expressing human CD81 and Sip-L.

Yeh CT, et al. *Biochem Biophys Res Commun*. 2008 Jul 18;372(1):157-61.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18474223&dopt=Abstract

Although human CD81 has been shown to be essential for hepatitis C virus (HCV) infection, non-hepatic cells or transgenic animals expressing human CD81 alone did not support HCV replication. Co-expression of other cofactors was thus necessary for HCV replication. Previously, a hepatic factor named Sip-L was found to support HCV replication in an otherwise non-permissive cell line. To understand the species specificity of hepatic factors required for HCV replication, mouse hepatoma cells co-expressing human CD81 and Sip-L (Hepa1-6-CD81-Sip-L cells) were subjected for HCV infection assay. It was discovered that Hepa1-6-CD81-Sip-L cells were permissive for HCV infection and replication. An animal model was thus established by subcutaneous injection of the permissive cells into nude mice to generate tumors. Viral passages could be achieved in these animals. The antiviral effects of interferon and sodium stibogluconate administered as a single agent or in combination were demonstrated in this animal model.

Efficient trans-encapsidation of hepatitis C virus RNAs into infectious virus-like particles.

Steinmann E, et al. *J Virol*. 2008 Jul;82(14):7034-46.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18480457&dopt=Abstract

Recently, complete replication of hepatitis C virus (HCV) in tissue culture was established using the JFH1 isolate. To analyze determinants of HCV genome packaging and virion assembly, we developed a system that supports particle production based on trans-packaging of subgenomic viral RNAs. Using JFH1 helper viruses, we show that subgenomic JFH1 replicons lacking the entire core to NS2 coding region are efficiently encapsidated into infectious virus-like particles. Similarly, chimeric helper viruses with heterologous structural proteins trans-package subgenomic JFH1 replicons. Like authentic cell culture-produced HCV (HCVcc) particles, these trans-complemented HCV particles (HCV(TCP)) penetrate target cells in a CD81 receptor-dependent fashion. Since HCV(TCP) production was limited by competition between the helper and subgenomic RNA and to avoid contamination of HCV(TCP) stocks with helper viruses, we created HCV packaging cells. These cells encapsidate various HCV replicons with high efficiency, reaching infectivity titers up to 10⁶ tissue culture infectious doses 50 per milliliter. The produced particles display a buoyant density comparable to HCVcc particles and can be propagated in the packaging cell line but support only a single-round infection in naïve cells. Together, this work demonstrates that subgenomic HCV

replicons are assembly competent, thus excluding cis-acting RNA elements in the core-to-NS2 genomic region essential for RNA packaging. The experimental system described here should be helpful to decipher the mechanisms of HCV assembly and to identify RNA elements and viral proteins involved in particle formation. Similar to other vector systems of plus-strand RNA viruses, HCV(TCP) may prove valuable for gene delivery or vaccination approaches.

Cryofibrinogen in patients with hepatitis C virus infection. Delluc A, et al. Am J Med. 2008 Jul;121(7):624-31.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18589059&dopt=Abstract

BACKGROUND: Mixed cryoglobulin is usually associated with hepatitis C virus (HCV) infection and might cause systemic vasculitis. The presence and impact of cryofibrinogen, another cryoprotein, in the serum of HCV-infected patients have not yet been evaluated. The objective was to study the prevalence and the clinical and therapeutic impacts of cryofibrinogen in HCV-infected patients. **METHOD:** A total of 143 consecutive HCV-infected (RNA+) patients (including 57 patients with HCV-related vasculitis) were screened for cryofibrinogen and cryoglobulin (positive if >0.05 g/L). The main characteristics and outcome were evaluated according to the cryofibrinogen/cryoglobulin status at baseline. **RESULTS:** At baseline, 53 of 143 patients (37%) were cryofibrinogen positive, most of whom (47/53 [89%]) were also cryoglobulin positive. Only 37 of 90 cryofibrinogen-negative patients (41%) were cryoglobulin positive ($P<.001$). In patients with HCV-related vasculitis, 28 of 57 (49%) were cryofibrinogen positive compared with 25 of 86 patients (29%) without vasculitis ($P=.03$). There was a higher rate of renal involvement in cryofibrinogen-negative/cryoglobulin-positive patients than in cryofibrinogen-positive/cryoglobulin-positive patients (10/25 [40%] vs 3/27 [11%], respectively; $P=.02$). After a mean follow-up of 32.6 months, among patients who were cryofibrinogen positive at baseline, 12 of 26 (46%) of those who received an HCV treatment were cryofibrinogen negative at the end of follow-up compared with 4 of 16 (25%) of those who did not receive antiviral drugs. Most patients who became cryofibrinogen negative also became cryoglobulin negative (93%). **CONCLUSION:** Cryoproteins, including cryoglobulin and cryofibrinogen, are frequently found in the serum of HCV-infected patients. In such patients, a positive cryofibrinogen status is closely related to the presence of cryoglobulin at baseline and after antiviral therapy.

Persistence of hepatitis C virus in peripheral blood mononuclear cells of sustained viral responders to pegylated interferon and ribavirin therapy. Gallegos-Orozco JF, et al. Dig Dis Sci. 2008 Jul 2.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18594984&dopt=Abstract

The aim of this paper was to assess the persistence of hepatitis C virus (HCV) among patients successfully treated with peginterferon and ribavirin. The persistence of viral RNA was evaluated in the serum and peripheral blood mononuclear cells (PBMCs) of 25 chronic hepatitis C patients with sustained viral response to peginterferon and ribavirin treatment up to 56 months after the completion of therapy. Viral RNA was detected in the peripheral blood mononuclear cell cultures of five patients (20%), but none had detectable serum HCV RNA. At present, the clinical relevance of this finding is unclear. It is possible that viral persistence and, specifically, the presence of HCV RNA in PBMCs may lead to HCV reactivation under special circumstances, such as immunosuppression.

Response to interferon therapy affects risk factors for postoperative recurrence of hepatitis C virus-related hepatocellular carcinoma. Uenishi T, et al. J Surg Oncol. 2008 Jul 21.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18646001&dopt=Abstract

BACKGROUND: Interferon therapy might reduce recurrence after resection of hepatitis C virus-related hepatocellular carcinoma, especially among sustained virologic or biochemical responders.

METHOD: Of 209 patients who underwent curative resection for early-stage hepatitis C virus related hepatocellular carcinoma, 70 patients underwent interferon therapy. A sustained virologic or biochemical response was achieved in 40 patients (SVR/BR group). Thirty no responders and 139 patients who had not received interferon therapy were classified as the NR/non-IFN group. Risk factors for postoperative recurrence in each group were analyzed. **RESULTS:** The tumor-free survival rates in the SVR/BR group were significantly higher than those in the NR/non-IFN group. By multivariate analysis, the presence of multiple tumors was independently associated with recurrence after resection in both groups, while histologic evidence of cirrhosis was another independent risk factor for postoperative recurrence in the NR/non-IFN group.

CONCLUSIONS: Newly multicentric carcinogenesis after resection could be suppressed when active hepatitis is controlled by interferon therapy. Patients with single hepatitis C virus related hepatocellular carcinoma detected after successful interferon therapy are good candidates for surgical resection. Adjuvant interferon therapy might be indicated for patients who undergo curative resection for single hepatocellular carcinoma associated with hepatitis C.

The impact of combination therapy with peginterferon alfa-2a and ribavirin on the energy intake and body weight of adult hepatitis C patients. Hamer C. J Hum Nutr Diet. 2008 Jul 18.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18647213&dopt=Abstract

BACKGROUND: It is recognized that interferon therapy has an adverse effect on the appetite and nutritional status of children with hepatitis B and C. No similar studies have been undertaken in adults. The aim of the present study was to determine if and how combination therapy with peginterferon alfa-2a and ribavirin affects energy intake and body weight in adult hepatitis C patients. A secondary aim was to investigate whether any changes are related to the presence of perceived side effects of treatment. **METHOD:** The energy intake of 15 adult hepatitis C patients was measured using a 3-day food diary. A visual analogue scale (VAS) was used to investigate patients' perception of fatigue, appetite and nausea. These measurements and body weight were taken before the start of treatment and at weeks 1, 3, 11, 24 and 28 in order to assess changes at intervals throughout interferon therapy. **RESULTS:** Fourteen patients (93%) lost weight during therapy. The greatest rate of mean [95% confidence interval (CI)] weight loss occurred at week 1 [1.64% (0.95-2.33)]. Weight loss continued until week 24. The greatest decrease in mean (95% CI) energy intake occurred at week 1 [9.74% (0.78-18.70)]. Mean VAS scores for fatigue, loss of appetite and nausea increased at week 1 and remained above pretreatment levels throughout the study period. **CONCLUSION:** Adult hepatitis C patients treated with a combination of peginterferon alfa-2a and ribavirin are likely to experience decreased energy intake and weight loss during treatment. This may be related to the impact of side effects of treatment and may require dietetic intervention.

Hepatitis C virus-specific T-cell immune responses in seronegative injection drug users.

Zeremski M, et al. J Viral Hepat. 2008 Jul 17.

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve>

[&list_uids=18647233&dopt=Abstract](#)

T-cell responses to hepatitis C virus (HCV) antigens have been reported in high-risk HCV seronegative persons, suggesting that an effective cellular immune response might be able to clear infection without the development of antibodies. Such findings, however, could be explained by waning antibody or cross-reactivity to other antigens. To address these issues, we evaluated HCV-specific T-cell responses in 26 young (age 18-33 years) aviremic, seronegative injection drug users (IDUs) (median duration of injection, 6 years) by interferon-gamma enzyme-linked immunospot (ELISpot) assay using 429 overlapping HCV peptides pooled in 21 mixes. Seventeen aviremic, seropositive IDUs (spontaneous responders) and 15 healthy people were used as positive and negative controls, respectively. The percentage of patients with HCV-specific cellular immune responses was similar in seronegative and seropositive aviremic IDUs (46% vs 59%, $P = 0.4$), while these responses were not detected in any of the negative controls. Among the seronegative IDUs, six (23%) had intermediate to very strong responses to 10-20 peptide mixes and another six (23%) had moderately strong responses for two to six mixes. The 12 seronegative IDUs with HCV-specific T-cell responses had higher demographical and behavioural risk profiles than the 14 IDUs without T-cell responses (estimated risk of HCV infection, 0.47 vs 0.26, $P < 0.01$). **In conclusion**, HCV-specific T-cell responses are common among high-risk, seronegative IDUs. The responses are broad and are associated with risk factors for HCV exposure, suggesting that they reflect true exposure to HCV in seronegative persons.

HIV/HCV COINFECTION

Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Balagopal A, et al. Gastroenterology. 2008 Jul;135(1):226-33.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18457674&dopt=Abstract

BACKGROUND & AIMS: Human immunodeficiency virus (HIV)-1 infection has been associated with enhanced microbial translocation, and microbial translocation is a mechanism through which alcohol and some enteric conditions cause liver disease. We hypothesized that HIV promotes liver disease by enhancing microbial translocation. **METHOD:** We studied human cohorts in which hepatitis C virus (HCV) and HIV outcomes were carefully characterized. **RESULTS:** HIV-related CD4(+) lymphocyte depletion was strongly associated with microbial translocation as indicated by elevated levels of circulating lipopolysaccharide (LPS), LPS-binding protein, soluble CD14, and fucose-binding lectin (AAL) reactive to immunoglobulin G specific for the alpha-galactose epitope and suppressed levels of endotoxin core antibodies (EndoCAb IgM) in HIV-infected subjects compared with the same persons before they had HIV infection and compared with HIV-uninfected subjects. The same measures of microbial translocation were strongly associated with HCV-related liver disease progression (cirrhosis), eg, LPS, odds ratio, 19.0 ($P = .002$); AAL, odds ratio, 27.8 ($P < .0001$); in addition, levels of LPS were elevated prior to recognition of cirrhosis. **CONCLUSIONS:** Microbial translocation may be a fundamental mechanism through which HIV accelerates progression of chronic liver disease.

Management of chronic hepatitis C virus infection in HIV-infected patients. Pol S and Soriano V. Clin Infect Dis. 2008 Jul 1;47(1):94-101.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18513148&dopt=Abstract

The management of chronic hepatitis C virus infection in patients coinfecting with the human immunodeficiency virus poses a significant challenge. Treatment is influenced by a number of viral and host characteristics, including hepatitis C virus genotype, baseline viremia, and adherence to medication regimen. Accelerated progression of liver disease, immunodeficiency, and hepatotoxicity of antiretroviral drugs are additional concerns in coinfecting patients. According to the results of 5 randomized clinical trials, 27%-55% of coinfecting patients who received therapy with pegylated interferon-alpha and ribavirin attained a sustained virologic response. These studies also confirm the importance of early virologic response as a predictor of treatment outcome and reveal the considerable proportion of patients who experience hematologic tolerability issues. Effective management strategies that encompass patient and viral factors are necessary to improve the long-term outlook for coinfecting patients.

Role of pegylated interferon-alpha-2a and ribavirin concentrations in sustained viral response in HCV/HIV-coinfecting patients. Lopez-Cortes L, et al. Clin Pharmacol Ther. 2008 Jul 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18596682&dopt=Abstract

The effect of simultaneous plasma concentrations of pegylated interferon-alpha-2a (pegIFN-alpha-2a) and ribavirin (Rbv) on viral response has not been addressed to date. Hepatitis C virus (HCV)/human immunodeficiency virus (HIV)-coinfecting patients received pegIFN-alpha-2a and Rbv under routine clinical care conditions. Plasma concentrations of the two drugs were measured using enzyme-linked immunosorbent assay and high-performance liquid chromatography after 2, 4, 8, and 12 weeks and at the end of the treatment period (24-48 weeks, according to HCV genotype and treatment duration). Large interindividual variability was observed in the plasma levels of both drugs. After multivariate analysis, only HCV genotype 3, low HCV-RNA levels, and pegIFN-alpha-2a exposure remained as independent factors associated with sustained viral response (SVR). The probability of attaining an SVR in HCV genotypes 1 and 4 was more than three to four times higher in patients with pegIFN-alpha-2a levels above the selected cutoff point. Early therapeutic drug monitoring of pegIFN-alpha-2a levels could be beneficial in improving current treatment outcomes.

Identification of novel markers for liver fibrosis in HIV/hepatitis C virus coinfecting individuals using genomics-based approach. Suzman DL, et al. AIDS. 2008 Jul 31;22(12):1433-1439.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18614866&dopt=Abstract

OBJECTIVE: The degree of liver fibrosis is a determinant for initiation of therapy for hepatitis C virus. Liver biopsy is invasive, risky and costly, but is required to assess fibrosis. This study intended to identify novel noninvasive markers to accurately assess fibrosis in HIV/hepatitis C virus coinfection. **METHOD:** Using 100 biopsies from 68 HIV/hepatitis C virus coinfecting patients, we developed a predictive model consisting of six serum markers along with age and antiretroviral therapy experience. DNA microarray analysis of peripheral blood mononuclear cells associated with a subset of 51 biopsies obtained from 28 patients was performed and incorporated into a second model. **RESULTS:** The eight-marker model yielded an area under the receiver operating characteristic curve of 0.904. Combined analysis of clinical and DNA microarray data in the 51-biopsy subset identified two genes (alanine amino peptidase-N and mitogen-activated protein kinase kinase-3) that predicted fibrosis with high significance. The four-marker model that included the two genes and two serum markers had an area under the receiver operating characteristic curve of 0.852,

which did not differ significantly from the eight-marker model on this subset (area under the receiver operating characteristic curve = 0.856, P = 0.96). **CONCLUSION:** Both models accurately predicted fibrosis with an accuracy of 87.9%, thereby sparing 83% of patients from obtaining a biopsy. DNA microarray analysis can be invaluable in identifying novel biomarkers of liver fibrosis.

Serum alpha-fetoprotein predicts virologic response to Hepatitis C treatment in HIV coinfecting patients. Carrat F, et al. AIDS. 2008 Jul 31;22(12):1513-1515.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18614875&dopt=Abstract

We explored the link between serum alpha-fetoprotein levels and virologic response in 383 HIV-hepatitis C virus coinfecting patients. A low alpha-fetoprotein level (<5.0 ng/ml) was an independent predictor of sustained virologic response (odds ratio = 1.83; 95% confidence interval 1.05-3.20). Serum alpha-fetoprotein measurement should be integrated in the pretreatment assessment of prognostic factors of a virologic response.

Expansion of CD56- NK cells in chronic HCV/HIV-1 co-infection: reversion by antiviral treatment with pegylated IFNalpha and ribavirin. Gonzalez VD, et al. Clin Immunol. 2008 Jul;128(1):46-56. [Epub 2008 May 20]

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WCJ-4SJGWS5-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&_view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=2fe39e5675da69b6fe72e036b251ffe8

Co-infection with HCV and HIV-1 is a problem of increasing importance and the role of innate cellular immunity in this co-infection is incompletely understood. Here, we have observed sharply elevated numbers of CD56(-)CD16(+) perforin(low) NK cells in HCV/HIV-1 co-infected subjects on antiretroviral therapy. Interestingly, this expansion of unconventional CD56(-) NK cells rapidly reverted when HCV was suppressed by IFNalpha and ribavirin treatment, and was not seen in mono-infected control groups. In vitro experiments suggested that this effect of treatment was due to suppression of HCV viremia rather than a direct effect of IFNalpha on these cells. In contrast, the conventional CD56(+) NK cells were largely unchanged in subjects with high HCV loads, although they exhibited slightly decreased perforin expression. With delayed kinetics, the CD56(bright) immuno-regulatory NK cell subset temporarily increased to supranormal levels in response to HCV treatment. In contrast to the NK compartment, the CD1d-restricted NKT cells were severely reduced by the co-infection and not restored by treatment. Together, our data suggest that the high HCV loads in HCV/HIV-1 co-infection alter the NK cell compartment in a way not observed in HCV mono-infection.

Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. Fierer DS, et al. J Infect Dis. 2008 Jul 15. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18627270&dopt=Abstract

Outbreaks of acute hepatitis C virus (HCV) infection are occurring in HIV-infected men who have sex with men. We evaluated risk factors and liver histopathology in 11 consecutively enrolled men with newly acquired HCV infection that was diagnosed on the basis of antibody seroconversion, new elevations in alanine aminotransferase level, and wide fluctuations in HCV RNA level. Ten patients reported unprotected anal intercourse, and 7 reported "club-drug" use, including methamphetamine. Liver biopsy showed moderately advanced fibrosis (Scheuer stage 2) in 9 patients (82%). No cause of liver damage other than acute HCV infection was identified. The

specific pathways leading to periportal fibrosis in HIV-infected men with newly acquired HCV infection require investigation.

Response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C due to genotype 4. Martín-Carbonero L, et al. *J Viral Hepat.* 2008 Jul 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18637070&dopt=Abstract

Hepatitis C virus (HCV) genotypes 1 and 4 respond less well to pegylated interferon (pegIFN) plus ribavirin (RBV) therapy. For this reason most studies merge these two genotypes when assessing virological response. However, in most trials the HCV genotype 4 population is rather small, and conclusions are mainly derived from what occurs in HCV-1 patients. All HCV-4 patients coinfecting with HIV who received pegIFN plus RBV in two different multicentre studies, PRESCO and ROMANCE, conducted respectively in Spain and Italy, were retrospectively analyzed. Baseline plasma HCV-RNA, proportion of patients with HCV-RNA <10 IU / mL at week 4 (rapid virological response), and HCV-RNA declines >2 logs at week 12 (early virological response, EVR) were all assessed as predictors of sustained virological response (SVR). Overall, 75 patients (60 men) were evaluated. Median age was 40 years and median CD4 count 598 cells / mm³; 49% had plasma HIV-RNA <50 copies / mL; 71% had elevated liver enzymes and 31% had advanced liver fibrosis (Metavir F3-F4). Median serum HCV-RNA was 5.7 log IU / mL. Rapid virological response was attained by 10 (20%) patients and EVR by 26 (42%). Using intention-to-treat and on-treatment (OT) analyses, SVR was achieved by 21 / 75 (28%) and 21 / 62 (34%) of HCV-4 patients, respectively. In the multivariate analysis (OT), baseline HCV-RNA (OR 0.09 for every log increment; 95% CI: 0.01-0.7) and EVR (OR: 7.08; 95% CI: 1.8-27.2) were significantly and independently associated with SVR. This is the largest series of HIV-infected patients with chronic hepatitis C due to HCV-4 treated with pegIFN plus RBV examined so far and the results show that HCV-4 behaves similarly to HCV-1. Therefore, these patients should be considered as difficult to treat population. Baseline serum HCV-RNA and EVR are the best predictors of SVR in HCV-4 / HIV-coinfecting patients.

Therapeutical aspects and outcome of HIV/HCV coinfecting patients treated with pegylated interferon plus ribavirin in an Italian cohort. Righi E, et al. *Infection.* 2008 Jul 19. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18642111&dopt=Abstract

BACKGROUND: One-third of HIV-infected individuals suffer from chronic hepatitis C virus infection (HCV) in Europe. Recommendations from HCV-HIV International Panel advise current treatment with pegylated interferon plus ribavirin. We assessed the impact of interferon and ribavirin combination in 43 patients between 2002 and 2006. **PATIENTS AND METHOD:** All coinfecting patients treated for HCV during the 5-year period were included in retrospective data collection. CD4⁺ T-lymphocyte count, HAART discontinuation, reasons for treatment interruption and factors correlated to sustained virological response (SVR) were monitored. **RESULTS:** The mean age was 41 +/- 6.7 years; the risk factor for coinfection was intravenous drug abuse in 32/43 (74%). The baseline CD4⁺ T-lymphocytes cell count was > 500 in 51% (22/43). Genotype 3a represented 51% (22/43); 37% were on HAART at baseline (16/43) and half of patients showed high HCV RNA levels (> 800,000 IU/ml). High rates of treatment discontinuation were observed (27/43, 63%), caused by voluntary interruptions in 52% (14/27) and virological failure in 26% (7/27). The overall population had an SVR of 30%; genotypes 3a and 1 had SVR of 38% and 24%, respectively. The

SVR was significantly lower in three groups: high HCV RNA viral load (chi (2) = 6, p < 0.0025), CD4+ T-lymphocyte historical nadir <350 cells/mm³ (chi (2) = 3.26, p < 0.01) and genotype 1 with high viral load (chi (2) = 4.8, p < 0.005). **CONCLUSIONS:** Although factors such as HCV viral load rates and genotype 1 have been confirmed to threaten the response to therapy, we observed a significant response rate when patients had a history of CD4+ T-lymphocyte nadir >350 per mm³. The high dropout rates due to voluntary discontinuations complicated the patients' case management.

COMPLEMENTARY & ALTERNATIVE THERAPY

Two flavonoids extracts from Glycyrrhizae radix inhibit in vitro hepatitis C virus replication.

Sekine-Osajima Y, et al. Hepatol Res. 2008 Jul 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18647187&dopt=Abstract

AIM: Traditional herbal medicines have been used for several thousand years in China and other Asian countries. In this study we screened herbal drugs and their purified compounds, using the Feo replicon system, to determine their effects on in vitro HCV replication. **METHOD:** We screened herbal drugs and their purified extracts for the activities to suppress hepatitis C virus (HCV) replication using an HCV replicon system that expressed chimeric firefly luciferase reporter and neomycin phosphotransferase (Feo) genes. We tested extracts and 13 purified compounds from the following herbs: Glycyrrhizae radix; Rehmanniae radix; Paeoniae radix; Artemisiae capillari spica; and Rhei rhizoma. **RESULTS:** The HCV replication was significantly and dose-dependently suppressed by two purified compounds, isoliquiritigenin and glycy coumarin, which were from Glycyrrhizae radix. Dose-effect analyses showed that 50% effective concentrations were 6.2 +/- 1.0 microg/mL and 15.5 +/- 0.8 microg/mL for isoliquiritigenin and glycy coumarin, respectively. The MTS assay did not show any effect on cell growth and viability at these effective concentrations, indicating that the effects of the two compounds were specific to HCV replication. These two compounds did not affect the HCV IRES-dependent translation nor did they show synergistic action with interferon-alpha. **CONCLUSION:** Two purified herbal extracts, isoliquiritigenin and glycy coumarin, specifically suppressed in vitro HCV replication. Further elucidation of their mechanisms of action and evaluation of in vivo effects and safety might constitute a new anti-HCV therapeutics.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Validation of a strategy for HCV antibody testing with two enzyme immunoassays in a routine clinical laboratory.

Vermeersch P, Van Ranst M, and Lagrou K. J Clin Virol. 2008

Aug;42(4):394-8.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18448386&dopt=Abstract

BACKGROUND: Centers for Disease Control (CDC) guidelines require confirmation of hepatitis C virus (HCV) screening-test-positive sera with a low signal/cut-off (S/CO) ratio by recombinant immunoblot or PCR. The UK Health Protection Agency has suggested that a second enzyme immunoassay (EIA) could be used as an alternative for confirmation in non-immunocompromised patients. **OBJECTIVE:** To evaluate the UK HPA approach in 17,936 consecutive in-house sera submitted for HCV testing. **STUDY DESIGN:** AxSYM-positive sera (S/CO >= 1.0) were tested

with Monolisa Plus. AxSYM-positive sera of patients that were confirmed PCR-positive were considered HCV+. All other AxSYM-positive sera were confirmed with immunoblot according to CDC guidelines. **RESULTS:** 17,299 sera were negative with AxSYM. Of the 637 AxSYM-positive sera, 384 were from patients confirmed as PCR-positive. Of other 250 sera, 120 were negative with immunoblot, 103 were positive and 30 were indeterminate. All 30 immunoblot-indeterminate sera were PCR-negative. Two patients were Monolisa Plus+ and immunoblot- and PCR-. One patient was known as immunoblot-, while the other patient was diagnosed with non-A non-B hepatitis in 1980s. Nine sera from HCV-positive patients were Monolisa Plus-. Two PCR- sera were from immunocompetent patients who were PCR- for ≥ 8 years and six PCR- sera and one PCR+ serum were from immunocompromised patients. Sensitivity and specificity of confirmation with Monolisa Plus were 98.15% and 98.33% and the positive and negative predictive values were 99.58% and 92.91% in AxSYM-positive sera (excluding immunoblot-indeterminate/PCR-negative sera). If immunocompromised patients that were false-negative were excluded, sensitivity was 99.58%. **CONCLUSION:** Monolisa Plus can be used as an alternative to immunoblot for the confirmation of AxSYM-positive sera.

Hepatitis C virus (HCV)-specific immune responses of long-term injection drug users frequently exposed to HCV. Mizukoshi E, et al. J Infect Dis. 2008 Jul 15;198(2):203-212.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18505381&dopt=Abstract

BACKGROUND: Injection drug users (IDUs) who successfully clear hepatitis C virus (HCV) have a reduced risk of developing chronic reinfection, despite their continuing exposure to the virus. To identify immunological correlates for this apparent protection, we studied HCV-specific immune responses in long-term IDUs (duration, >10 years). **METHOD:** HCV-specific T cell responses were assessed in proliferation, enzyme-linked immunospot (ELISPOT), interferon (IFN)-gamma secretion, and cytotoxicity assays, whereas HCV-specific antibodies were assessed in enzyme immunoassays (EIAs), chemiluminescent assays, and in vitro neutralization assays. **RESULTS:** HCV-specific T cell proliferation and IFN-gamma production were more common in nonviremic EIA-positive IDUs (16 [94%] of 17 IDUs) than in viremic EIA-positive IDUs (9 [45%] of 20 IDUs) ([Formula: see text]). They were also noted in 16 (62%) of 26 nonviremic EIA-negative IDUs. In contrast, 19 (90%) of 21 viremic IDUs displayed neutralizing antibodies (nAbs), compared with 9 (56%) of 16 nonviremic EIA-positive IDUs ([Formula: see text]) and 0 of 24 nonviremic EIA-negative IDUs. Nonviremic IDUs with nAbs were older ([Formula: see text]) than those without nAbs, but these groups did not differ in terms of either injection drug use duration or HCV-specific T cell responses. **CONCLUSION:** The reduced risk of HCV persistence in IDUs previously recovered from HCV infection correlated with T cell responses, and prolonged antigenic stimulation appears to be required to maintain humoral responses.

Factors influencing Hepatitis C virus sero-prevalence among blood donors in north west Pakistan. Khattak MN, et al. J Public Health Policy. 2008 Jul;29(2):207-25.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18523475&dopt=Abstract

Hepatitis C virus infection is a major health problem worldwide. The current study estimated seroprevalence of Hepatitis C virus (HCV) and evaluated associated factors among volunteer blood donors of the Northwest Frontier Province (NWFP), Pakistan. Of 1,131 volunteer blood donors enrolled, 46 (4.1%) were positive for anti-HCV antibodies. Multivariate logistic regression analysis revealed that positive donors were more likely to be 27-32 years old or >32 years old, have had 1-2

injections or >2 injections in the past year, or 1-5 intravenous (IV) drips or >5 I/V drips in the past 5 years. Positive donors had a family history of jaundice and were more likely to have been shaved (facial and armpit) by barbers. There was high prevalence of anti-HCV antibodies among blood donors of the NWFP. Public awareness programs should target the identified risk factors to prevent HCV transmission. We highlight the weakness of the health care system for blood donation, as it does not offer any record management for donors.

Impact of viral eradication on mortality related to hepatitis C: a modeling approach in

France. Deuffic-Burban S, et al. *J Hepatol.* 2008 Aug;49(2):175-83.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18538441&dopt=Abstract

BACKGROUND/AIMS: In France, two recent studies enabled modeling of the impact of viral eradication on HCV mortality. **METHOD:** The French HCV population was simulated from infection to death using a computer-based model. We took into account the impact of alcohol, present screening and antiviral therapy to predict 2006-2025 HCV mortality and to assess the impact of viral eradication. **RESULTS:** In 2006, the model estimated that among HCV-RNA+, 55% were F0-F1, 18% F2, 22% F3-F4 and 6% had liver complications. The mortality ratio was 11-fold higher in alcoholic patients 40-65 years old. Current therapy will save 14,400 (95% CI, 13,900-15,000) lives compared to absence of therapy. Sensitivity analyses did not change the main results. Contrary to guidelines, if patients F<2 were treated in the same proportions as those with F2, 700 (95% CI, 700-750) lives would be saved. If screening were to reach 75% in 2010, 4 years earlier than model expectation, 950 (95% CI, 900-1000) lives would be saved. If a new molecule improving eradication for genotype 1/4 by 40% were to become available in 2010, 1500 (95% CI, 1400-1600) lives would be saved. **CONCLUSIONS:** Current therapy is reducing HCV mortality. Therapeutic guidelines must take into account their impact on HCV mortality.

The influence of alcohol consumption and hepatitis B and C infections on the risk of liver cancer in Europe.

Ribes J, et al. *J Hepatol.* 2008 Aug;49(2):233-42.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18571275&dopt=Abstract

BACKGROUND/AIMS: To assess the variability of liver cancer (LC) risk associated with hepatitis B (HBV) and hepatitis C (HCV) viruses and alcohol intake in 2002 throughout Europe.

METHOD: Incidence data were obtained from population-based cancer registries whereas mortality, HBV, HCV and alcohol exposures were obtained from the WHO databases. Relative risk of LC and their posterior probabilities to be >1 were obtained and plotted in maps through a Bayesian random effects model. **RESULTS:** HBV prevalence >2% increased the risk of developing LC a 15% in men and 21% in women; HCV prevalence >2%, 54% in men and 33% in women and, pure alcohol intake >11l, 26% and 14%, respectively (all of them statistically significant). These risk factors played a similar role in the risk of dying from LC among men, whereas HBV and alcohol were not statistically significant among women. Significant high LC risk, after HBV/HCV and alcohol adjustment were observed for both sexes in: Hungary, Moldova, Romania, Croatia, Greece, Italy, Spain, France and Austria. **CONCLUSIONS:** South-North and East-West decreasing gradients for LC risk were observed in Europe. HBV, alcohol and, mainly, HCV are independent risk factors that could explain this geographical pattern.

Sustained virologic response to treatment in 100% of patients recently infected,

nosocomially, with HCV genotype 2. Sikuler E, et al. *J Clin Gastroenterol.* 2008 Jul;42(6):730-

733.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18574394&dopt=Abstract

OBJECTIVE: In 2003, a cluster of hepatitis C virus (HCV)-infected patients with a common history of a surgical procedure, performed during 2001 to 2003, was identified in a medical center. An epidemiologic investigation linked a physician, infected with HCV genotype 2, as the possible source of infection in 35 patients. The evaluation, therapy, and outcome of this unique cohort are presented. **DESIGN:** HCV-RNA was isolated from sera of all patients and the double-stranded phosphorylation homology domain region was sequenced. After a routine clinical investigation 33 patients were offered antiviral therapy. Two patients were not treatment candidates due to old age and comorbidity. **RESULTS:** Twenty-two (66%) were women. The mean age was 48.5+/-16.9 years. Alanine aminotransferase level was 117+/-135 IU/L. Thirty patients were treated with pegylated interferon alpha 2a, 1 with pegylated interferon alpha 2b, and 1 with standard interferon. All received ribavirin 800 mg daily. One patient refused to be treated and was lost for follow-up. Time from acquisition of disease to initiation of therapy was 14.8+/-4.9 month (5.5 to 26). Therapy duration was 24 weeks except for 1 patient who stopped therapy after 16 weeks. Sustained virologic response was achieved in all 32 treated patients. The sequence motif of the phosphorylation homology domain region, studied in all patients, predicted good response to interferon. **CONCLUSIONS:** Our excellent results can be explained by a constellation of favorable viral characteristics, a short-term disease and adherence to therapy.

External validation of the platelet count/spleen diameter ratio for the diagnosis of esophageal varices in hepatitis C virus-related cirrhosis. Agha A, et al. Dig Dis Sci. 2008 Jul 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18594972&dopt=Abstract

Background Screening for esophageal varices (EV) is an important part of the diagnostic workup of cirrhotic patients. **AIMS:** To independently validate the use of the platelet count/spleen diameter ratio for the non-invasive diagnosis of EV in patients with HCV-related cirrhosis and in a sub-group of patients with compensated disease. **METHOD:** A platelet count/spleen diameter ratio cut-off value of 909 was evaluated for the diagnosis of EV in the whole population (n = 311) and in patients with compensated disease alone (n = 114). Compensated disease was defined as the absence of ascites as detected by abdominal ultrasound in patients who are not on diuretics and absence of hepatic encephalopathy. **RESULTS:** In the whole cohort (EV prevalence 49.5%), the platelet count/spleen diameter ratio 909 cut-off value had 96.9% positive predictive value, 100% negative predictive value, and 98.4% efficiency for EV diagnosis. In compensated cirrhotics (EV prevalence 26.3%), the platelet count/spleen diameter ratio 909 cut-off showed an excellent negative predictive value (100%) and a positive predictive value of 93.8%. for the diagnosis of EV. **CONCLUSION:** In patients with HCV-related cirrhosis, the platelet count/spleen diameter may be proposed as a non-invasive tool for EV diagnosis, especially in financially deprived developing countries.

Epidemiological characteristics and medical follow-up of 61 patients with acute hepatitis C identified through the hepatitis C surveillance system in France. Brouard C, et al. Epidemiol Infect. 2008 Jul;136(7):988-96.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=17697444&dopt=Abstract

This study aimed to describe current epidemiological and clinical characteristics, medical follow-up

and outcome in the real practice of acute hepatitis C (AHC) patients. AHC cases were retrospectively identified through the French Hepatology Reference Centres Surveillance system and additional data were collected. Sixty-one patients with AHC were identified (sex ratio: M/F 1.7/1; mean age 39 years). Forty-four (72%) had documented seroconversion within a 6-month period. Main reported risk exposures were intravenous or nasal drug use (35%), invasive medical procedures (25%) and sexual contact with a HCV-positive partner (20%). Spontaneous clearance of HCV RNA was observed in seven out of 16 patients followed without therapy. This study confirms the major role of drug use in HCV transmission and highlights the role of invasive medical procedures and occupational exposure.

Prevalence of infection with hepatitis B and C viruses and co-infection with HIV in three jails: a case for viral hepatitis prevention in jails in the United States. Hennessey KA, et al. J Urban Health. 2008 Jul 12; [Epub ahead of print]

<http://www.springerlink.com/content/j43m23mq1518841j/>

Hepatitis B vaccination and targeted testing for hepatitis C virus (HCV) are recommended for jails with medical services available. This study estimates hepatitis B virus (HBV) and HCV infection prevalence among jail inmates, since most previous studies have been conducted among prison inmates. Prison and jail populations differ: jails hold a wide spectrum of persons for an average of 10-20 days, including persons awaiting arraignment, trial, conviction, or sentencing, while prisons typically hold convicted criminals for at least 1 year. A stratified random sample of sera obtained during routine syphilis testing of inmates entering jails in Chicago (March-April 2000), Detroit (March-August 1999), and San Francisco (June 1999-December 2000) was tested for serologic markers of HBV and HCV infection. All sera had been previously tested for antibody to HIV (anti-HIV). A total of 1,292 serum samples (12% of new inmates) was tested. Antibody to HCV (anti-HCV) prevalence was 13%. Antibody to hepatitis B core antigen (anti-HBc) prevalence was 19%, and hepatitis B surface antigen (HBsAg) prevalence was 0.9%; 12% had serologic evidence of hepatitis B vaccination. Hispanics had high rates of chronic HBV infection (3.6% HBsAg positive) along with Asians (4.7% HBsAg positive). Among HIV-infected persons, 38% were anti-HCV positive and 8.2% were HBsAg positive. Anti-HBc positivity was associated with anti-HCV positivity (aOR = 4.58), anti-HIV positivity (aOR = 2.94), syphilis infection (aOR = 2.10), and previous incarceration (aOR = 1.78). Anti-HCV-positivity was associated with anti-HBc positivity (aOR = 4.44), anti-HIV-positivity (aOR = 2.51), and previous incarceration (aOR = 2.90). Jail entrants had high levels of HCV and HBV infection and HIV co-infection; HBV prevalence was comparable to previous prison studies, and HCV prevalence was lower than prison studies. Hispanics had an unexpectedly high rate of chronic hepatitis B infection and had the lowest rate of hepatitis B vaccination. The finding that hepatitis B vaccination coverage among jail entrants is lower than the general population, despite this population's increased risk for infection, highlights the need to support vaccination in jail settings.

Evaluation of the new ARCHITECT anti-HCV screening test under routine laboratory conditions. Berger A, et al. J Clin Virol. 2008 Jul 15. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18635393&dopt=Abstract

BACKGROUND: An improved test version of the Abbott ARCHITECT anti-hepatitis C virus (HCV) test became available at the end of 2005. **STUDY DESIGN:** We compared the new test version with the Ortho Vitros anti-HCV test by evaluating 2034 serum samples in parallel on both systems under routine laboratory conditions. Discordant samples were tested in the Inno-LIA HCV

Score assay as well as in the RIBA HCV 3.0. **RESULTS:** Of the 2034 samples 140 (6.9%) yielded positive and 1856 (91.2%) negative results in both assays. We observed discordant results in 38 samples (1.9%). All discrepant samples showed a low S/CO ratio of 1.0-6.9 (mean 2.8) in the Ortho assay and of 1.3-3.0 (mean 1.96) in the ARCHITECT assay. As expected, most of them could not be confirmed by immunoblot testing. Comparison of the results of the two immunoblots (Inno-LIA and RIBA) revealed a great variability in test results. **CONCLUSIONS:** This study represents the first comparative evaluation of the modified version of the Abbott ARCHITECT anti-HCV assay in comparison with the Ortho Vitros anti-HCV test. Under routine laboratory testing, we observed good overall concordance between the two assays and no evidence that one assay shows more false-reactive or negative results than the other.

Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. Bruggmann P, et al. J Viral Hepat. 2008 Jul 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18637072&dopt=Abstract

Reluctance has been expressed about treating chronic hepatitis C in active intravenous (IV) drug users (IDUs), and this is found in both international guidelines and routine clinical practice. However, the medical literature provides no evidence for an unequivocal treatment deferral of this risk group. We retrospectively analyzed the direct effect of IV drug use on treatment outcome in 500 chronic hepatitis C patients enrolled in the Swiss Hepatitis C Cohort Study. Patients were eligible for the study if they had their serum hepatitis C virus (HCV) RNA tested 6 months after the end of treatment and at least one visit during the antiviral therapy, documenting the drug use status. Five hundred patients fulfilled the inclusion criteria (199 were IDU and 301 controls). A minimum exposure to 80% of the scheduled cumulative dose of antivirals was reached in 66.0% of IDU and 60.5% of controls (P = NS). The overall sustained virological response (SVR) rate was 63.6%. Active IDU reached a SVR of 69.3%, statistically not significantly different from controls (59.8%). A multivariate analysis for treatment success showed no significant negative influence of active IV drug use. **In conclusion**, our study shows no relevant direct influence of IV drugs on the efficacy of anti-HCV therapy among adherent patients.

Hepatocellular carcinoma in long-term sustained virological responders following antiviral combination therapy for chronic hepatitis C. Scherzer TM, et al. J Viral Hepat. 2008 Jul 10.

[Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18637075&dopt=Abstract

Antiviral treatment results in a sustained virologic response (SVR) in 50-75% of patients with chronic hepatitis C. Long-term follow up studies have observed ongoing SVR in the overwhelming majority of them. Thus chronic hepatitis C is considered 'cured' if an SVR is achieved. Consequently, it is expected that in sustained virologic responders long-term complications of hepatitis C virus (HCV) related chronic liver disease including hepatocellular carcinoma are eliminated or have a decreased incidence. We report on five patients (three from Austria, two from USA) who developed hepatocellular carcinoma during follow up (3-6 years) after achieving SVR. During follow up and at diagnosis all were HCV-RNA neg. None of the patients had other liver diseases. One patient presented with bilateral adrenal metastasis, the remaining four with large hepatic tumours. Three patients were noncirrhotic at the start of treatment at the time of tumour diagnosis. Successful antiviral treatment in HCV patients does not prevent development of hepatocellular carcinoma even

in non-cirrhotic livers. Long-term follow up of patients with SVR is mandatory and should include surveillance for hepatocellular carcinoma.

A continuous (13)C methacetin breath test for noninvasive assessment of intrahepatic inflammation and fibrosis in patients with chronic HCV infection and normal ALT.

Lalazar G, et al. J Viral Hepat. 2008 Jul 10. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18638013&dopt=Abstract

Up to 30% of patients with hepatitis C virus (HCV) infection and normal serum alanine aminotransferase (NALT) have significant liver disease. Currently, many of these patients undergo a liver biopsy to guide therapeutic decisions. The BreathID((R)) continuous online (13)C-methacetin breath test (MBT) reflects hepatic microsomal function and correlates with hepatic fibrosis. To assess its role in identifying intrahepatic inflammation and fibrosis in NALT patients, we tested 100 patients with untreated chronic HCV infection, and 100 age- and sex-matched healthy volunteers using (13)C MBT following ingestion of 75 mg methacetin. All HCV patients had undergone a liver biopsy within 12 months of performing the MBT. Patients with a necroinflammatory grade ≤ 4 or > 4 , based on Ishak (modified HAI) score, HAIa + HAIb + HAIc + HAId, were defined as having low or high inflammation, respectively. Patients with a histological activity fibrosis stage ≤ 2 or > 2 , were defined as having nonsignificant or significant fibrosis, respectively. A proprietary algorithm to differentiate intrahepatic inflammation within chronic HCV patients with NALT achieved an area under the curve (AUC) of 0.90. Setting a threshold on the point of best agreement (at 83%) results in 82% sensitivity and 84% specificity. With application of another proprietary algorithm to differentiate patients with nonsignificant or significant fibrosis, 67% of liver biopsies performed in the patient group could have been avoided. This algorithm achieved an AUC of 0.92, with a sensitivity of 91% and a specificity of 88%. There was no correlation between body mass index (BMI) and MBT scores for patients with the same histological score. The continuous BreathID((R)) (13)C MBT is an accurate tool for measuring the degree of inflammation and fibrosis in patients with chronic HCV infection and NALT. As such, it may prove to be a powerful, noninvasive alternative to liver biopsy in the management of this patient population.

Prevalence and genotype distribution of hepatitis C virus among apparently healthy individuals in Mongolia: a population-based nationwide study. Baatarkhuu O, et al. Liver Int. 2008 Jul 16. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18647237&dopt=Abstract

BACKGROUND & AIMS: Hepatitis C virus (HCV) is one of the major causes of liver cirrhosis and hepatocellular carcinoma (HCC) in Mongolia. However, there are no data concerning nationwide prevalence of HCV infection in Mongolia. We intended to investigate the population-based prevalence of HCV infection and genotype distribution among 1512 apparently healthy individuals in this country. **METHOD:** Between April 2003 and December 2005, sera from 1512 residents of Ulaanbaatar and 12 provinces were collected by two-stage cluster random sampling, and anti-HCV was tested. Anti-HCV-positive samples were tested for HCV RNA by reverse transcription polymerase chain reaction, and HCV genotype was determined. **RESULTS:** The mean age of the subjects was 46.2 \pm 17.8 years, and 812 (53.7%) were male. Overall, the prevalence of anti-HCV was 15.6% (236/1512) and HCV RNA was detected in 167 subjects (11.0%), with the most common genotype being 1b (165/167, 98.8%). When the HCV RNA-positive subjects were categorized by decade of age, the prevalence in each age group was as follows: 2.5% in subjects

</=10 years of age, 4.5% in teens, 10.1% in 20's, 12.5% in 30's, 24.2% in 40's, 29.0% in 50's and 32.6% in subjects >/=61 years of age. The seroprevalence of anti-HCV in a risk group, nurses, was not significantly different from the general population in each decade of age (P>0.05).

CONCLUSIONS: Approximately 11.0% of apparently healthy population had detectable HCV RNA in Mongolia, and the predominant genotype of HCV was 1b. Preventive and therapeutic strategies for chronic hepatitis C are urgently warranted in this HCV-endemic area.

Clinicopathological features of elderly patients with hepatitis C virus-related hepatocellular carcinoma. Miki D, et al. J Gastroenterol. 2008;43(7):550-7.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18648742&dopt=Abstract

BACKGROUND: It is well known that the incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) correlates with progression of liver fibrosis. However, there is little information on the impact of aging on hepatocarcinogenesis. The aim of this study was to elucidate the clinicopathological features of elderly patients with HCV-related HCC. **METHOD:** The study subjects were 693 consecutive patients newly diagnosed with HCC with anti-HCV. First, we divided them into a younger group (<70 years) and an elderly group (>/=70 years) and compared clinicopathological features between the two groups. Next, we selected pure HCV-related HCC patients by excluding the patients with other probable factors for hepatocarcinogenesis (anti-HBc, interferon therapy, and alcohol) and compared the two groups again. **RESULTS:** Higher platelet count, lower male/female ratio, lower rate of habitual alcohol consumption, and better Child-Pugh class were recognized in the elderly group than the younger group, statistically. In 133 cases of hepatic resection, fibrosis stage was lower in the elderly than the younger group. After selection of pure HCV-related HCC patients, in a stepwise multi variate analysis, male sex and platelet count <math><10 \times 10^4/\text{mm}^3</math> were significant variables associated with age <70. Regarding the latency period to HCC development, the patients who received a blood transfusion at an older age developed HCC sooner despite their lower grade of fibrosis. **CONCLUSIONS:** The elderly patients developed HCC more often, despite their lower grade of fibrosis, compared with the younger patients. In addition to fibrosis, aging could be a factor affecting HCV-related hepatocarcinogenesis.