



Caring Ambassadors Hepatitis C Program Newsletter  
www.HepCChallenge.org  
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## IN THE NEWS

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### Hepatitis C battle intensifying

<http://www.lvrj.com/news/27986474.html>

“Liver specialists in Nevada are seeing an increase in patients since health officials in February announced an outbreak of hepatitis C cases linked to an endoscopy clinic. Dr. Robert Gish, a California physician who has had a part-time practice in Nevada for the past two decades, said his patient load has doubled since the outbreak was made public. Some of his new patients underwent procedures at the 700 Shadow Lane facility and have tested positive for hepatitis C. Other patients are just learning they have the disease and are seeking treatment, Gish said.

Dr. Donald Hillebrand, another liver specialist from California with a part-time Nevada practice, said his patient load "has picked up substantially." Hillebrand was hired by Southwest Medical Associates in April to help with an anticipated growth in liver patients as a result of the outbreak, linked to the Endoscopy Center of Southern Nevada, 700 Shadow Lane. Hillebrand said he is seeing two general types of liver patients in Southern Nevada. One group is composed of those with end-stage liver disease; the other consists of general hepatology patients, those with hepatitis C or B or who just need a liver doctor.” [truncated]

### It's not visible to the naked eye, but Natalie Cole has just begun the fight of her life.

<http://www.etonline.com/news/2008/09/65285/>

“The Grammy winning singer is battling hepatitis C, and tonight on ET she's sharing her story for the very first time with her good friend and ours, Paula Abdul. "In 1980-1982, I was doing heroin," reveals Natalie, tracing the possible cause of contracting the disease. "The first day that "This Will Be" came out on the radio I was on my way to get heroin."

While she overcame her drug problems long ago, she's paying the price today. "This is a virus that was dormant in my body for 25 years," she explains. "I had no symptoms, was feeling great, working out like a crazy person -- and this just keeled me over, like a feather."” [truncated]

### Altor BioScience licenses T-cell receptors targeting HIV and hepatitis C from Massachusetts General Hospital

[http://www.earthtimes.org/articles/show/altor-bioscience-licenses-t-cell-receptors\\_534977.shtml](http://www.earthtimes.org/articles/show/altor-bioscience-licenses-t-cell-receptors_534977.shtml)

“Altor BioScience Corporation today announced that it has entered into an agreement with Massachusetts General Hospital (MGH) for exclusive, worldwide rights to develop and commercialize T-cell receptors (TCRs) specific for cells infected by HIV and Hepatitis C Virus (HCV). The license has resulted from the success of Altor’s collaboration established in 2004 with Howard Hughes Medical Institute and the Partners AIDS Research Center at MGH. Altor has already successfully improved and converted the licensed TCRs into targeted therapeutic reagents using its Soluble T-cell Antigen Receptor (STAR™) technology.

Hing Wong, Ph.D., President & CEO of Altor, commented, “The receptors we have licensed were discovered and characterized by Dr. Bruce Walker, one of the foremost authorities on viral antigen expression and T-cell immune responses in HIV and HCV patients. We are excited to have the opportunity to add these targeting molecules to our STAR™ program and look forward to taking an anti-HIV and anti-HCV drug candidate into the clinic.” Dr. Wong added, “The specific targeting to HIV-infected cells makes it possible for the first time to eliminate latent viral reservoirs, which cannot be achieved with currently available treatments.”” [truncated]

### **Hepatitis C patients may have abnormal blood sugar**

<http://in.reuters.com/article/health/idINHAR07676120080910>

“Nearly two thirds of patients with chronic hepatitis C infection may have abnormal blood sugar levels, according to a report in the American Journal of Gastroenterology. Blood sugar, or "glucose," abnormalities "are common and easily underestimated among patients with chronic hepatitis C infection," Dr. Ming-Lung Yu from Kaohsiung Medical University, Taiwan told Reuters Health. Careful evaluation for undetected glucose abnormalities is "essential" in caring for chronic hepatitis C patients.

Yu and colleagues compared the prevalence and characteristics of glucose abnormalities among 522 chronic hepatitis C patients and a comparison group of 447 without hepatitis C infection ("controls"), based on the results of an oral glucose tolerance test. After excluding the subjects who were known to have diabetes, just over one third of the hepatitis C patients (34.2 percent) had normal results on the oral glucose tolerance test, the authors report, whereas 42.8 percent had impaired glucose tolerance and 23.0 percent had undiagnosed diabetes. In contrast, 64.7 percent of the controls had normal levels of glucose, 32.4 percent had impaired glucose tolerance, and 2.9 percent had diabetes.” [truncated]

### **Woman with hep C files suit against HMO**

<http://www.kvbc.com/Global/story.asp?S=8987289&nav=15MV>

“A woman who says she contracted Hepatitis C during a procedure at the Endoscopy Center of Southern Nevada has filed a law suit against her health insurance company - not the clinic. 71-year-old Alynne Griffiths says her HMO, PacifiCare of Nevada, forced her to go to the doctors involved in the Hepatitis crisis. Griffiths filed the lawsuit in an attempt to make her insurance offer a broader doctor referral system. The Southern Nevada Health District has linked eight acute cases of Hepatitis to the Shadow Lane facility and at least 77 chronic cases.”

### **Evidence to support belief in transmission of hepatitis C by sharing drug sniffing equipment**

<http://www.aidsmap.com/en/news/CD24D656-6727-41F9-87A2-CF084595E9D0.asp>

“Hepatitis C can be detected in the nasal passage, and in straws which are inserted in the nose, report researchers in the October 1st edition of Clinical Infectious Diseases. Their findings support the hypothesis that hepatitis C can be transmitted by sharing straws or banknotes which are used to snort drugs. The theory of hepatitis C transmission through this route is that frequent or long-term sniffing or snorting of drugs such as cocaine can cause damage and bleeding in the nasal passage. Straws or banknotes that are inserted in the nose could come into contact with hepatitis C infected blood or mucus, which may then be transmitted to someone else sharing the same straw.” [truncated]

### **New York City dialysis center exposes nearly 700 patients to hepatitis C**

<http://www.foxnews.com/story/0,2933,423882,00.html>

“A New York City dialysis center was shut down by the state Health department after one patient tested positive for hepatitis C. Now, nearly 700 patients of the Life Care Dialysis Center in Manhattan are being urged to get tested for both hepatitis B and C strains, as well as HIV, webstv.com reports. In a press release, the Health Department said they uncovered poor conditions, including “blood on the treatment chairs and dialysis machines, lack of proper hand hygiene, and inadequate disinfection of equipment.”...

Officials say anyone treated at the center between Jan. 23, 2004 and the present should contact their physicians and get tested, the news station reported.” [truncated]

### **Hepatitis C sufferers miss out on treatment**

<http://www.theage.com.au/national/hepatitis-c-sufferers-miss-out-on-treatment-20080923-4mld.html>

“Hepatitis Australia has called for urgent action to assist people with hepatitis C after new figures revealed more than 98% of the 200,000 Australians living with the virus did not receive any treatment last year. Despite an available cure for many cases, the number of people with severe liver disease as a result of untreated hepatitis C has risen from 35,900 to 47,600 in the past five years. Helen Tyrrell, head of Hepatitis Australia, said she was alarmed by new figures from the National Centre in HIV Epidemiology and Clinical Research that showed only 3539 people, or 2% of Australians with hepatitis C, accessed treatment last year.” [truncated]

### **SciClone reports encouraging results from Phase IIa hepatitis trial**

[http://www.pharmaceutical-business-review.com/article\\_news.asp?guid=4701FB13-5207-47A6-B2DA-4D9770DD04D5](http://www.pharmaceutical-business-review.com/article_news.asp?guid=4701FB13-5207-47A6-B2DA-4D9770DD04D5)

“SciClone Pharmaceuticals, a biopharmaceutical company, has announced encouraging results from its proof-of-concept Phase II clinical trial using its proprietary, immunomodulatory compound SCV-07 as a sole agent administered to patients chronically infected with the hepatitis C virus. The trial was designed to evaluate the effect of SCV-07 on hepatitis C viral load, as well as on other measures of immune response. SCV-07 demonstrated activity in some treated patients in the higher dosage groups, and the decrease in viral load in these patients was accompanied by an increase in an immunological biomarker which is usually correlated with response against hepatitis C virus (HCV). Additionally, SCV-07 was shown to be generally safe and well-tolerated with no dose limiting toxicities or serious adverse events reported.” [truncated]

### **22 die from side effects of hepatitis C drugs: health survey**

<http://mdn.mainichi.jp/mdnnews/news/20080926p2a00m0na014000c.html>

“Over 220 reports of lung-tissue diseases among patients using interferon drugs to treat hepatitis C were received between April 2004 and May this year, with 22 cases ending in death, a government survey has found. A survey by the Ministry of Health, Labor and Welfare found a total of 223 cases of the side effect of interstitial pneumonitis during the period. Based on the results, the ministry ordered Chugai Pharmaceutical Co., the producer of the drug Pegasys, which was named in many of the reports, to alter package leaflets to prohibit the use of the drug by patients who had suffered interstitial pneumonitis in the past.” [truncated]

### **Kidney disease risk increased for patients with HIV and hepatitis C**

<http://www.aidsmap.com/en/news/8E85364E-349F-4555-B3B1-19C80466E6A3.asp>

“People who are both HIV and hepatitis C infected are at significantly higher risk of kidney disease compared to those with HIV only, say US researchers in a study published in the September 12th edition of AIDS. Chronic kidney disease and its most serious form, end-stage renal disease, is more common in HIV infected individuals. Now researchers at the Mount Sinai School of Medicine have attempted to find out what effect HIV/hepatitis C coinfection had on the risk of developing chronic kidney disease. They reviewed the data from any study which looked at chronic kidney disease and HIV infection but also recorded hepatitis C infection status. A total of 24 studies were included in their analysis.” [truncated]

### **ZymoGenetics “Sleeper” for Hepatitis C Aims to Wipe Out Side Effects of Anti-Viral Therapy**

<http://www.xconomy.com/seattle/2008/09/30/zymogenetics-sleeper-for-hepatitis-c-aims-to-wipe-out-side-effects-of-anti-viral-therapy/>

“Lots of people on Wall Street are hyped up about new treatments for hepatitis C from Vertex pharmaceuticals and Schering-Plough. But a little-known drug in development from Seattle-based ZymoGenetics could steal a bit of thunder, and possibly ride the wave of enthusiasm those companies are creating among doctors and patients ... Instead of developing another protease inhibitor to be taken in

addition to the standard of care, ZymoGenetics has developed an alternative that has the viral killing power of interferon alpha, without causing the side effects. It calls its version of the standard of care “pegylated interferon lambda,” or IL-29.” [truncated]

### **StemCells, Inc. Receives NIH Grant to pursue cell-based therapeutic for hepatitis C**

<http://www.earthtimes.org/articles/show/stemcells-inc-receives-nih-grant,564246.shtml>

“StemCells, Inc. announced today that it has been awarded a \$305,000 grant from the National Institute of Diabetes and Digestive and Kidney Diseases to research and develop a potential cell-based therapeutic for liver disease arising from infection by the hepatitis C virus (HCV). Hepatitis C is a global health challenge, with approximately 170 million people affected worldwide and an estimated three million new infections each year. The virus targets liver cells and is a leading cause of end-stage liver disease.

The grant will fund work over the next year to investigate whether the Company’s proprietary human liver engrafting cells (hLEC) can be made resistant to infection by the hepatitis C virus. The studies will be done in collaboration with Jeffrey Glenn, M.D., Ph.D, Associate Professor of Gastroenterology and Hepatology at Stanford University School of Medicine. Dr. Glenn is a recognized and widely published expert in hepatitis C, and his research has focused on designing novel antiviral strategies.” [truncated]

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## **CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

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### **Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: A pilot study.** Enjoji M, Kotoh K, Kato M, et al. *Int J Mol Med.* 2008

Oct;22(4):521-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18813860&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18813860&dopt=Abstract)

Fatty liver is one of the local morphological manifestations of metabolic syndrome and is frequently associated with insulin resistance. Insulin resistance is also common in patients with chronic hepatitis C. Hyperinsulinemia is an independent risk factor for hypertension and cardiovascular mortality. **The aim of this study** was to evaluate the therapeutic efficacy of angiotensin II receptor blockers (ARBs), telmisartan and olmesartan, for patients with non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C (CH-C). We analyzed the incidence of obesity, insulin resistance, and other disorders in patients with NAFLD (Group A), CH-C (Group B), or other liver diseases (Group C). **We evaluated** whether the ARBs, telmisartan and olmesartan, improved insulin resistance and liver injury by measuring the homeostasis model assessment ratio of insulin resistance (HOMA-IR) and serum alanine aminotransferase (ALT). The incidence of obesity (BMI  $\geq$  25 kg/m<sup>2</sup>) was significantly higher in Group A than in Groups B and C. The incidence of insulin resistance (HOMA-IR  $\geq$  2.5) in Groups A and B was significantly higher than in Group C. Regular doses of telmisartan and olmesartan significantly improved HOMA-IR and ALT levels not only in NAFLD patients but also in patients with CH-C. The effects tended to be more notable with telmisartan. **In conclusion**, telmisartan and olmesartan improved insulin sensitivity and may possibly be used as liver protecting agents in CH-C as well as NAFLD patients.

### **Chronic viral hepatitis is a significant contributor to the immunosenescent phenotype of parenteral drug addiction.** Reece AS. *Addict Biol.* 2008 Sep 22; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18811680&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18811680&dopt=Abstract)

Intravenous drug addiction is known to be associated with an inordinate morbidity and mortality. As our previous report had identified an immune phenotype consistent with accelerated ageing, we

wished to investigate how much of this change may have been related to chronic viral hepatitis. A total of 12 409 clinical pathology results from the period 1995-2007 were reviewed. To control for the differences in age, only patients less than 48 years of age were considered. A total of 636 substance use disorder (SUD) and 6103 non-SUD (N-SUD) patients were studied. They had comparable ages (mean +/- SD 31.32 +/- 6.90 versus 31.57 +/- 9.23, P-value not significant), but the SUD group had more males (74.37% versus 53.20%, P < 0.001). For most of the changes examined splitting the two SUD groups into hepatitis C positive (HCV+) and hepatitis C negative (HCV-) demonstrated that the majority of the described changes were most marked in the HCV+ group. The globulins were higher in the HCV+ group and the albumin was lower and fell more markedly with age than in N-SUD or HCV- (all P < 0.001). The globulin/albumin ratio was significantly higher in HCV+ than HCV- or N-SUD (both P < 0.0001) and rose more with age. These changes were paralleled by the ESR, elevations in the CRP and lymphocyte count. Transaminases were elevated in SUD and HCV+ groups compared with N-SUD (all P < 0.02). At multivariate analysis ESR, lymphocyte count, dual hepatitis B and C seropositivity, AST and HCVAb were significant predictors of the serum globulin level and accounted for 21% of the variance. These data extend our earlier report and show that much of the immunosenescent phenotype of SUD, encompassing the known immunosuppression and the observed immunostimulation, is statistically related to chronic viral hepatitis. Important theoretical and practical management (vaccination) implications ensue.

**Thiazolidines: a new class of drugs for the treatment of chronic hepatitis B and C.** Rossignol JF, Keefe EB *Future Microbiol.* 2008 Oct;3:539-545

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18811238&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18811238&dopt=Abstract)

Nitazoxanide, the first thiazolidine, was originally developed for the treatment of *Cryptosporidium parvum*. The antiviral activity of nitazoxanide was discovered by serendipity in patients with AIDS who were treated for cryptosporidial diarrhea and had HBV or HCV co-infection. In preliminary open-label studies of patients with chronic hepatitis B, nitazoxanide suppressed serum HBV DNA and led to loss or seroconversion of hepatitis B e antigen in the majority of patients, as well as hepatitis B surface antigen in approximately a quarter of patients. In Phase II studies of patients with chronic hepatitis C genotype 4, nitazoxanide combined with peginterferon alfa-2a, with or without ribavirin, increased the sustained virologic response rate to 79-80 versus 50% with peginterferon plus ribavirin standard of care. Randomized, controlled studies of naive and nonresponder patients with chronic hepatitis C genotype 1 and patients with chronic hepatitis B are underway, and new second generation thiazolidines are being developed.

**Liver steatosis: investigation of opposed-phase T1-weighted liver MR signal intensity loss and visceral fat measurement as biomarkers.** Bahl M, Qayyum A, Westphalen AC, et al.

*Radiology.* 2008 Oct;249(1):160-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18796674&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18796674&dopt=Abstract)

**PURPOSE:** To investigate if opposed-phase T1-weighted and fat-suppressed T2-weighted liver signal intensity (SI) loss and visceral fat measurement at magnetic resonance (MR) imaging and body mass index (BMI) are correlated with grade of liver steatosis in patients with nonalcoholic fatty liver disease (NAFLD) or hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-related liver disease. **MATERIALS AND METHODS:** Committee on Human Research approval and patient consent were obtained for this HIPAA-compliant study. Fifty-two patients (15 men, 37

women) with NAFLD (n = 29) or HCV and HIV-related liver disease (n = 23) underwent prospective contemporaneous MR imaging and liver biopsy. Liver SI loss was measured on opposed-phase T1-weighted and fat-suppressed T2-weighted MR images. Visceral fat area was measured at three levels on water-suppressed T1-weighted MR images (n = 44). Spearman rank correlation coefficients and recursive partitioning were used to examine correlations. **RESULTS:** Histopathologic liver steatosis correlated well with liver SI loss on opposed-phase T1-weighted MR images ( $\rho = 0.78$ ), fat-suppressed T2-weighted MR images ( $\rho = 0.75$ ), and average visceral fat area ( $\rho = 0.77$ ) (all  $P < .01$ ) but poorly with BMI ( $\rho = 0.53$ ,  $P < .01$ ). Liver SI losses on opposed-phase T1-weighted MR imaging of less than 3%, at least 3% but less than 35%, at least 35% but less than 49%, and at least 49% corresponded to histopathologic steatosis grades of 0 (n = 16 of 17), 1 (n = 11 of 16), 2 (n = 7 of 13), and 3 (n = 5 of 6), respectively. A visceral fat area of greater than or equal to 73.8 cm<sup>2</sup> was associated with the presence of histopathologic steatosis in 41 of 44 patients. **CONCLUSION:** Liver SI loss on opposed-phase T1-weighted MR images and visceral fat area may be used as biomarkers for the presence of liver steatosis and appear to be superior to BMI.

**Peg-interferon alpha-2a versus peg-interferon alpha-2b in nonresponders with HCV active chronic hepatitis: A pilot study.** Scotto G, Fazio V, Fornabaio C, et al. J Interferon Cytokine Res. 2008 Sep 8; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18778199&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18778199&dopt=Abstract)

**BACKGROUND:** The efficacy and tolerability of Peg-Interferon alpha-2a (Peg-IFNalpha-2a) versus Peg-Interferon alpha-2b (Peg-IFNalpha-2b) were compared in a patient cohort with hepatitis C virus (HCV)-related active chronic hepatitis, unresponsive to previous antiviral treatment with standard IFN (6 MU three times/week) plus ribavirin (10.6mg/kg/day) for a period of at least 3 months. **PATIENTS AND METHODS:** A total of 143 patients were enrolled and randomized into two treatment groups (A-B). Group A (71 patients) received one vial of Peg-IFNalpha-2a weekly (180 mug) subcutaneously whereas Group B (72 patients) received 1.5 mug/kg of Peg-IFNalpha-2b weekly subcutaneously. Interferon was combined with ribavirin (15mg/kg/day) in both groups and all patients who demonstrated nondetectable HCV-RNA or a  $\geq 2$ (log) reduction in viral load at week 12, were treated for 48 weeks, with a 24-week follow up. **RESULTS:** Group A (10/71) and Group B (8/72) patients discontinued treatment due to severe side effects. At the end of therapy, HCV-RNA was undetectable in 17/71 (23.9%) Group A and in 19/72 (26.4%) of Group B patients. When terminating follow up, a sustained virological response was observed in 14/71 in Group A (19.7%) and 13/72 in Group B (18.0%). **CONCLUSIONS:** Within the limits of the relatively small sample size, Peg-IFNalpha-2a and Peg-IFNalpha-2b demonstrated nonstatistically significant differences in effectiveness in patients nonresponsive to previous antiviral treatment.

**The Tor Vergata weaning off immunosuppression protocol in stable HCV liver transplant patients: The updated follow up at 78 months.** Orlando G, Manzia T, Baiocchi L, et al. Transpl Immunol. 2008 Sep 4; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18773958&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18773958&dopt=Abstract)

**BACKGROUND:** We report the update of the Tor Vergata immunosuppression (IS) weaning protocol in stable hepatitis C virus (HCV) liver transplant (LT) recipients. **METHODS:** The weaning off IS was attempted in 34 patients who had received a LT 63.5 $\pm$ 20.1 months earlier, for HCV-related end stage liver disease. Patients were observed over a period of 6.5 years. During this

time, yearly protocol liver biopsies were performed. Primary endpoints were determined as the feasibility of weaning off IS and its impact on the long term disease progression. Secondary endpoints were defined as the impact on patient morbidity and quality of life. **RESULTS:** Of the 8 originally tolerant patients, 7 remain alive and in good condition, while 1 died of severe HCV recurrence 10years post-LT and 6years after complete removal of IS. Four out of 26 intolerant individuals died of HCV recurrence (2x), lung carcinoma (1x) and acute myocardial infarction (1x), after a mean follow up period from LT of 115 (range 100-124). The 10-year survival from LT was comparable (89% vs. 87.5%). Liver graft pathology showed no significant differences between the two groups in terms of staging, fibrosis progression rate, and grading. Quantitative HCV RNA assay showed a significant non-logarithmic difference between the two groups ( $p = 0.03$ ). The two groups were comparable in terms of liver function tests and lipid profile, whereas they differed with regards to glycaemia. While all tolerant individuals were euglycemic, 11 intolerant individuals developed new onset diabetes that required specific treatment ( $p = 0.03$ ). Finally, significantly more intolerant patients are suffering from either cardiovascular (14/22 vs. 0/7,  $p = 0.01$ ) or infectious diseases (13/22 vs. 0/7,  $p = 0.01$ ). **CONCLUSIONS:** After a 6.5-year follow up, the complete withdrawal of IS in HCV LT recipient remains safe and beneficial to patients, because it reduces the IS-related morbidity and increases the quality of life. The impact on HCV disease recurrence is less marked than after 3.5years.

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#### **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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**Interferon-alpha therapy does not modulate hepatic expression of classical type I interferon inducible genes.** Meier V, Mihm S, Ramadori G. J Med Virol. 2008 Sep 23;80(11):1912-1918  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18814253&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18814253&dopt=Abstract)

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. Treatment with interferon-alpha(2) (IFN-alpha(2)) can induce viral clearance and marked biochemical and histological improvement. IFN-alpha(2) treatment has been shown to stimulate the expression of type I IFN regulated genes in peripheral blood mononuclear cells (PBMCs) of hepatitis C patients; however, whether it affects hepatic expression remains unknown. **This study thus aimed** at comparing hepatic gene expression with particular emphasis on type I IFN inducible genes in patients with chronic hepatitis C before and during an IFN-alpha(2) monotherapy. Responsiveness to IFN-alpha(2) therapy was monitored by determining serum and hepatic viral load. Differential gene expression analysis was performed by two different techniques, namely suppression subtractive hybridization (SSH) and differential display (DD). Expression of two prototype type I IFN regulated genes was quantified in further PBMC and liver samples. Among different genes found to be up-regulated during an effective, that is, virus clearing, IFN-alpha treatment, only a single one was identified which can be accounted to type I IFN responsive genes. Parallel quantitative real time PCR analyses demonstrated significant induction of the type I IFN regulated genes MxA and PKR in PBMC, but not in the liver. Taken together, while IFN-alpha treatment leads to the induction of type I IFN regulated genes in PBMC, such an induction appears not to occur in the liver of hepatitis C patients. The mechanism by which IFN-alpha treatment causes viral clearance might be independent of hepatic activation of type I IFN regulated genes.

**Relation between serum levels of cell-free DNA and inflammation status in hepatitis C virus-related hepatocellular carcinoma.** Iida M, Iizuka N, Sakaida I, et al. *Oncol Rep.* 2008 Oct;20(4):761-5

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18813815&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18813815&dopt=Abstract)

**Our study** revealed that the level of circulating cell-free DNA (cfDNA) is increased in the serum of patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). To gain insight into the mechanism underlying this phenomenon, we examined the association between cfDNA levels and various clinicopathological factors in 96 patients with HCV-related HCC and 99 non-HCC patients with HCV. Using pooled DNA microarray data, we profiled the expression patterns of inflammatory cytokine genes in 14 primary tumors from the group of HCC patients. We found that there were positive associations between the cfDNA level, aspartate aminotransferase levels and the number of leukocytes and neutrophils in patients with HCV-related HCC but not in non-HCC patients with HCV. The serum cfDNA level was not associated with other clinicopathological factors in HCC or non-HCC patients. A cluster analysis based on the inflammatory cytokine gene data revealed that HCCs with a high serum cfDNA level had increased levels of several inflammatory cytokine genes, suggesting that the serum cfDNA level is associated with the inflammatory status in primary tumors in HCV-related HCC.

**Sperm ultrastructure and meiotic segregation in a group of patients with chronic hepatitis B and C.** Moretti E, Federico MG, Giannerini V, Collodel G. *Andrologia.* 2008 Oct;40(5):286-91

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18811918&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18811918&dopt=Abstract)

Little is known about the effect of chronic hepatitis B and hepatitis C on sperm quality. In this study, we analysed sperm quality from selected patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections. Semen samples were examined by light and transmission electron microscopy (TEM). TEM data were elaborated with a mathematical formula able to indicate a fertility index and the presence of the three main sperm pathologies: apoptosis, immaturity and necrosis. Meiotic chromosome segregation was investigated by fluorescence in situ hybridisation carried out on sperm nuclei, using probes for chromosomes 18, X and Y. Despite normal sperm concentration, we observed reduced motility. TEM analysis highlighted that 35.7% of patients showed generally good semen quality. However, significantly higher values of apoptosis and necrosis, compared with controls, were observed, demonstrating spermatogenetic alterations. Regarding meiotic segregation, we found an incidence of disomies similar to that observed in control samples, whereas diploidy resulted higher in HCV patients, without reaching statistical significance.

**In conclusion**, sperm quality in the studied group was not impaired; however, apoptosis and necrosis resulted out of normal range and the fertility index was significantly lower in HCV- and HBV-infected patients versus controls.

**Gene expression profile of Huh-7 cells expressing hepatitis C virus genotype 1b or 3a core proteins.** Paziienza V, Clément S, Pugnale P, et al. *Liver Int.* 2008 Sep 18; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18803589&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18803589&dopt=Abstract)

**BACKGROUND:** The liver disease expression in chronic hepatitis C patients is variable and may partially depend on the sequence of the infecting viral genotype. **AIM:** To identify some hepatitis C virus (HCV) genotype-specific virus-host interactions potentially leading to clinically significant consequences. **Methods:** We compared the gene expression profile of Huh-7 cells transiently

expressing the core protein of HCV genotype 1b and 3a using microarray technology. **RESULTS:** Thirty-two genes were overexpressed in Huh-7 transfected with the HCV genotype 1b core protein and 57 genes in cells transfected with the genotype 3a core protein. On the other hand, we found 20 genes downregulated by core 1b and 31 genes by core 3a. These included genes involved in lipid transport and metabolism, cell cycle, immune response and insulin signalling. **CONCLUSION:** The expression of HCV core proteins of different genotypes leads to a specific gene expression profile. This may account for the variable disease expression associated with HCV infection.

**Liver insulin-like growth factor 2 methylation in hepatitis C virus cirrhosis and further occurrence of hepatocellular carcinoma.** Couvert P, Carrie A, Paries J, et al. World J

Gastroenterol. 2008 Sep 21;14(35):5419-27

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18803353&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18803353&dopt=Abstract)

**AIM:** To assess the predictive value of the insulin-like growth factor 2 (Igf2) methylation profile for the occurrence of Hepatocellular Carcinoma (HCC) in hepatitis C (HCV) cirrhosis. **METHODS:** Patients with: (1) biopsy-proven compensated HCV cirrhosis; (2) available baseline frozen liver sample; (3) absence of detectable HCC; (4) regular screening for HCC; (5) informed consent for genetic analysis were studied. After DNA extraction from liver samples and bisulfite treatment, unbiased PCR and DHPLC analysis were performed for methylation analysis at the Igf2 locus. The predictive value of the Igf2 methylation profile for HCC was assessed by Kaplan-Meier and Cox methods. **RESULTS:** Among 94 included patients, 20 developed an HCC during follow-up (6.9 +/- 3.2 years). The methylation profile was hypomethylated, intermediate and hypermethylated in 13, 64 and 17 cases, respectively. In univariate analysis, two baseline parameters were associated with the occurrence of HCC: age (P = 0.01) and prothrombin (P = 0.04). The test of linear tendency between the three ordered levels of Igf2 methylation and probability of HCC occurrence was significant (Log Rank, P = 0.043; Breslow, P = 0.037; Tarone-Ware, P = 0.039). **CONCLUSION:** These results suggest that hypomethylation at the Igf2 locus in the liver could be predictive for HCC occurrence in HCV cirrhosis.

**Activation of central nervous system inflammatory pathways by interferon-alpha:**

**relationship to monoamines and depression.** Raison CL, Borisov AS, Majer M, et al. Biol Psychiatry. 2008 Sep 16; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18801471&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18801471&dopt=Abstract)

**BACKGROUND:** Interferon (IFN)-alpha has been used to study the effects of innate immune cytokines on the brain and behavior in humans. The degree to which peripheral administration of IFN-alpha accesses the brain and is associated with a central nervous system (CNS) inflammatory response is unknown. Moreover, the relationship among IFN-alpha-associated CNS inflammatory responses, neurotransmitter metabolism, and behavior has yet to be established. **METHODS:** Twenty-four patients with hepatitis C underwent lumbar puncture and blood sampling after approximately 12 weeks of either no treatment (n = 12) or treatment with pegylated IFN-alpha 2b (n = 12). Cerebrospinal fluid (CSF) and blood samples were analyzed for proinflammatory cytokines and their receptors as well as the chemokine, monocyte chemoattractant protein-1 (MCP-1), and IFN-alpha. Cerebrospinal fluid samples were additionally analyzed for monoamine metabolites and corticotropin releasing hormone. Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale. **RESULTS:** Interferon-alpha was detected in the CSF of all IFN-alpha-treated patients and only one control subject. Despite no increases in plasma IL-6, IFN-alpha-

treated patients exhibited significant elevations in CSF IL-6 and MCP-1, both of which were highly correlated with CSF IFN-alpha concentrations. Of the immunologic and neurotransmitter variables, log-transformed CSF concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), were the strongest predictor of depressive symptoms. Log-transformed CSF concentrations of IL-6, but not IFN-alpha or MCP-1, were negatively correlated with log-transformed CSF 5-HIAA ( $r(2) = -.25, p < .05$ ). **CONCLUSIONS:** These data indicate that a peripherally administered cytokine can activate a CNS inflammatory response in humans that interacts with monoamine (serotonin) metabolism, which is associated with depression.

**Three cases of successful tryptophan add-on or monotherapy of hepatitis C and IFNalpha-associated mood disorders.** Schaefer M, Winterer J, Sarkar R, et al. *Psychosomatics*. 2008 Sep-Oct;49(5):442-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18794514&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18794514&dopt=Abstract)

**BACKGROUND:** Interferon-alpha (IFN(alpha))-associated mood disorder is a major complication of treatment for chronic hepatitis C. **METHOD:** The authors report on three patients infected with chronic hepatitis C showing severe depressive symptoms during or after IFN(alpha) treatment. Because patients had lowered tryptophan blood levels and did not respond to antidepressants, they received tryptophan up to a dosage of 1,000 mg/day as mono- or add-on treatment. **RESULTS:** Tryptophan, used as augmentation or monotherapeutic treatment, led to a significant improvement of depressive symptoms in all three patients. **CONCLUSION:** A tryptophan deficit seems to be involved in the pathophysiology of persistent mood changes during and after IFN(alpha) treatment.

**A recombinant replication-competent hepatitis C virus expressing Azami-Green, a bright green-emitting fluorescent protein, suitable for visualization of infected cells.** Hou W, Aoki C, Yu L, et al. *Biochem Biophys Res Commun*. 2008 Sep 8; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18786508&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18786508&dopt=Abstract)

The hepatitis C virus (HCV) production system consists of transfecting the human hepatoma cell line Huh7 with genomic HCV RNA (JFH1). To monitor HCV replication by fluorescence microscopy, we constructed a recombinant HCV clone expressing Azami-Green (mAG), a bright green fluorescent protein, by inserting the mAG gene into the nonstructural protein 5A (NS5A) gene; the resultant clone was designated JFH1-hmAG. The Huh-7.5.1 (a subclone of Huh7) cells transfected with JFH1-hmAG RNA were found to produce cytoplasmic NS5A-mAG, as readily visualized by fluorescence microscopy, and infectious virus, as assayed with the culture supernatant, indicating that JFH1-hmAG is infectious and replication-competent. Furthermore, the replication of this virus was inhibited by interferon alpha in a dose-dependent manner. **These results suggest** that JFH1-hmAG is useful for studying HCV life cycle and the mechanism of interferon's anti-HCV action and for screening and testing new anti-HCV drugs.

**High values of CXCL10 serum levels in mixed cryoglobulinemia associated with hepatitis C infection.** Antonelli A, Ferri C, Fallahi P, et al. *Am J Gastroenterol*. 2008 Sep 4; [Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18775023&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18775023&dopt=Abstract)

**OBJECTIVES:** No study has evaluated circulating CXCL10 in patients with mixed cryoglobulinemia (MC) and hepatitis C virus (HCV) chronic infection. The aim of this study is to

measure interferon-inducible protein 10 (CXCL10/IP-10), interferon-gamma (IFN-gamma), and tumor necrosis factor alpha (TNF-alpha) (Th1 cytokines) in a series of cryoglobulinemic patients and to correlate this parameter to the clinical phenotype. **METHODS:** Serum CXCL10, IFN-gamma, and TNF-alpha were assayed in 102 patients with hepatitis C-associated cryoglobulinemia (MC + HCV), in 102 sex- and age-matched patients with type C chronic hepatitis without cryoglobulinemia (HCV+), and in 102 sex- and age-matched controls. **RESULTS:** Cryoglobulinemic patients showed significantly higher mean CXCL10 serum levels than controls ( $P < 0.0001$ ) or HCV+ patients ( $P < 0.0001$ ) (397 +/- 132 pg/mL, 92 +/- 53 pg/mL, 280 +/- 149 pg/mL, respectively). Moreover, CXCL10 was significantly increased in 30 cryoglobulinemic patients with active vasculitis compared to those without it (460 +/- 104 pg/mL vs 369 +/- 139 pg/mL, respectively;  $P < 0.001$ ). Both groups of MC + HCV patients with or without active vasculitis had serum CXCL10 significantly higher than HCV+ patients ( $P < 0.001$ ,  $P = 0.02$ , respectively). IFN-gamma levels were not significantly different in MC + HCV than in HCV+ patients or controls. Serum TNF-alpha levels were significantly higher in MC + HCV than in HCV+ patients or controls (median [interquartile range]: 12.0 [9.8], 5.7 [5.4], 1.3 [2.1] pg/mL, respectively;  $P < 0.0001$ ). **CONCLUSIONS:** The study demonstrates high CXCL10 and TNF-alpha serum levels in patients with hepatitis C-associated cryoglobulinemia. Moreover, in MC + HCV patients, increased CXCL10 levels were significantly associated with the presence of active vasculitis.

**Regulatory polymorphisms in the interleukin-18 promoter are associated with hepatitis C virus clearance.** An P, Thio CL, Kirk GD, et al. J Infect Dis. 2008 Oct 15;198(8):1159-1165  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18781864&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18781864&dopt=Abstract)

The immune response is critical in determining the outcome of hepatitis C virus (HCV) infection. Interleukin (IL)-18 is a pivotal mediator of the Th1/Th2-driven immune response. Two IL-18 promoter polymorphisms (-607C/A and -137G/C) and their haplotypes were known to affect IL-18 expression. We examined the role played by these polymorphisms in determining HCV clearance or persistence. Genotyping was performed among African American injection drug users with HCV clearance ([Formula: see text]) or HCV persistence ([Formula: see text]) and among European Americans with hemophilia who were mainly infected through plasma transfusion. Among injection drug users, IL18 -607A (odds ratio [OR], 3.68 [95% confidence interval {CI}, 1.85-7.34]) and IL18 -137C (OR, 2.33 [95% CI, 1.24-4.36]) were significantly associated with HCV clearance. A haplotype carrying -607A and -137C (OR, 4.53 [95% CI, 1.77-11.6]) was also strongly associated with viral clearance. No association was found among those with hemophilia. **These results suggest** that IL18 promoter polymorphism may affect the outcome of HCV infection in certain groups.

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## HIV/HCV COINFECTION

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**Impact of HIV on Genomic Variability in the 5'UTR of HCV in Indian Patients with HCV/HIV Co-Infection.** Chaudhary A, Kukreti H, Pasha ST, et al. Intervirology. 2008 Sep 10;51(4):224-229  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18781077&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18781077&dopt=Abstract)

**BACKGROUND:** The impact of HIV on hepatitis C virus (HCV) genome during HCV/HIV co-infection is poorly understood. The present study was intended to unveil nucleotide sequence variability in the 5'-untranslated region (5'UTR) of HCV in co-infected cases. **METHODS:** Automated nucleotide sequencing of the 5'UTR of HCV from both mono- and co-infected cases

was performed. **RESULTS:** Data analysis revealed deletion of a continuous stretch of 12 nucleotides (nt 240-251) from domain IIIc in 20% co-infected cases, but no long-stretch deletion was observed in HCV from mono-infected cases. On the contrary, there was no insertion in the 5'UTR of HCV from co-infected cases, but there were insertions in domain II and III (3 mononucleotides and 2 dinucleotides) of the 5'UTR in mono-infected cases. **CONCLUSION:** Since domain III is known to be important for binding of 40S ribosomal subunit, deletion of a single stretch of 12 nucleotides in HCV from co-infected cases observed in the present study may have implications during HCV replication with or without HIV infection. Although this is the first report on genomic heterogeneity in the 5'UTR of HCV from HCV/HIV co-infected Indian patients, it would be worthwhile to study if similar changes are observed in other genes of HCV during co-infection.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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**Treatment with silybin-vitamin E-phospholipid complex in patients with hepatitis C infection.** Falasca K, Ucciferri C, Mancino P, et al. J Med Virol. 2008 Sep 23;80(11):1900-1906 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18814253&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18814253&dopt=Abstract)

**The aim** of this study was to evaluate the hepatoprotective and anti-inflammatory effects of silybin-phospholipids and vitamin E complex (SPV complex), by determining cytokine patterns and various markers of liver disease. Forty Caucasian patients with chronic HCV infection were recruited and divided into two groups: 30 were treated with SPV complex for 3 months, while the other 10 did not receive any treatment. Ten other subjects without HCV infection but with steatotic diagnosis were recruited and treated with SPV complex. Biochemical and hepatic principal parameters were investigated at 0 (T0) and 3 months (T3). The group of HCV patients treated showed an improvement trend of hepatic indices and viral load, and had a significant and persistent reduction of ALT (P = 0.02) and AST serum level (P = 0.01). In this group cytokines showed a statistically significant increase of IL-2 (P = 0.03) and IL-6 were significantly reduced (P = 0.02) at T0 and T3. After the treatment the group of hepatic steatotics showed a significant decrease in ALT (P = 0.02), AST (0.008), gammaGT (0.004) alkaline phosphatase (0.05), total cholesterol (P = 0.03), fasting glucose (P = 0.008), insulinemia (0.0006), HOMA value (0.002) and C-reactive protein (CRP; 0.04). There was a significant reduction of IFN-gamma, TNF-alpha, and IL-6 (P = 0.02, 0.05 and 0.04, respectively). **The data suggest** that the SPV complex exerts hepatoprotective, anti-inflammatory and antifibrotic effects. This new compound may therefore be useful in clinical practice in patients with chronic hepatitis C who cannot undergo conventional antiviral therapy.

**The impact of diet on liver fibrosis and on response to interferon therapy in patients with HCV-related chronic hepatitis.** Loguercio C, Federico A, Masarone M, et al. Am J Gastroenterol. 2008 Sep 11; [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18786125&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18786125&dopt=Abstract)

**BACKGROUND AND AIMS:** A deranged metabolic status and alcohol intake may trigger induction and progression of chronic hepatitis C virus (HCV) liver disease. The aim of this study was to evaluate whether dietary composition affects the severity of liver damage and response to therapy in patients with HCV-related chronic hepatitis. **METHODS:** We enrolled 1,084 patients with biopsy-proven HCV-related chronic hepatitis (432 treated with interferon plus ribavirin) and 2,326 healthy subjects in this prospective study conducted in a university hospital. Dietary habits

were recorded in enrolled individuals, and their alcohol consumption was evaluated with a questionnaire (AUDIT). Body mass index, and plasma levels of blood glucose, nitrogen, creatinine, cholesterol, and triglycerides were also measured. All individuals underwent routine liver tests and HCV genotyping. **RESULTS:** At study onset, there were no differences in metabolic status or alcohol consumption between patients and controls. About 50% of each group was overweight, and about 60% consumed alcohol. Patients and controls had similar dietary habits. Intake of carbohydrates, lipids and polyunsaturated fatty acids, and alcohol consumption were independent factors of liver damage at histology (logistic regression analysis). Some dietary components (unsaturated fatty acids, iron, zinc, vitamin A, and niacin) and alcohol intake differed significantly ( $P < 0.05$  and  $P 0.01$ , respectively; univariate analysis) between responders and nonresponders to interferon therapy. Genotype, age, body mass index, steatosis, and fibrosis were independent predictors of therapy outcome ( $P < 0.02$ ; multivariate analysis). **CONCLUSIONS:** The severity of HCV-related chronic hepatitis depends on a variety of factors. Our results show that dietary composition is related to the extent of liver damage. Although traditional risk factors independently affected treatment response, some dietary components were associated with nonresponse to therapy in our patients. This suggests that HCV patients may benefit from instructions regarding their diet.

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## EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Discordance between biochemical markers of liver activity and fibrosis (Actitest((R))-Fibrotest((R))) and liver biopsy in patients with chronic hepatitis C.** Fontanges T, Bailly F, Trepo E, et al. Gastroenterol Clin Biol. 2008 Sep 3; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18775614&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18775614&dopt=Abstract)

**INTRODUCTION:** The purpose of this clinical trial was to determine in routine practice and in comparison with liver biopsy the limitations of two blood tests, Actitest((R)) and Fibrotest((R)), for the evaluation of hepatic activity and fibrosis in patients with chronic hepatitis C. **METHODS:** Routine blood tests, Actitest((R)) and Fibrotest((R)), and liver biopsy were performed in 96 patients with chronic hepatitis C attending routine outpatient clinics. Receiver operating characteristics (ROC) curves were used to assess the diagnostic value of the biochemical tests in comparison with the METAVIR classification. **RESULTS:** The study population was predominantly male (63.5%) with a mean age of 48 years; 83.3% of the patients had genotype 1 hepatitis C virus infection. Treatment status was naive (62.5%), nonresponders (17.7%), relapsers (7.3%), or unknown (12.5%). The comparison of F0-F2 versus F3-F4 estimated the negative predictive value at 92% and the positive predictive value at 52% for a cut-off of 0.455. Discrepancies in activity score were more frequently due to a higher score of the biochemical test compared to biopsy (18 cases out of 19). Discrepancies for fibrosis were observed in 18 patients with a higher score for biochemical test in eight and a higher score for liver biopsy in 10 cases. A significant increase of gamma-glutamyl-transferase (GGT) ( $p=0.0001$ ) and alanine aminotransferase (ALT) ( $p<0.0001$ ) was observed in case of biochemical test overestimation of activity, and a significant increase of alpha2-macroglobulin ( $p=0.006$ ) and GGT ( $p=0.018$ ) in case of biochemical test overestimation of fibrosis. **CONCLUSION:** This prospective study confirms the good diagnostic value of biochemical tests for necrotico-inflammatory activity and fibrosis as compared with the histological analysis of liver biopsy. Clinicians must interpret Actitest((R)) and Fibrotest((R)) results with caution in patients with a significant elevation of ALT, and/or GGT and/or alpha2-macroglobulin which could

overestimate hepatic injury.

**Intrafamilial transmission of hepatitis C virus: Infection of the father predicts the risk of perinatal transmission.** Indolfi G, Bartolini E, Azzari C, et al. J Med Virol. 2008 Sep

23;80(11):1907-1911

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18814243&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18814243&dopt=Abstract)

**The aims** of the present study were to evaluate in a cohort of mothers infected with hepatitis C virus (HCV) the prevalence of HCV infection of their sexual partners, the influence of infection of the partners on perinatal transmission, and whether this influence is mediated by other well known risk factors for perinatal transmission. Forty-nine consecutive mothers infected with HCV who transmitted infection to their offspring and, as a control group, 557 consecutive mothers infected with HCV who did not transmit infection, together with their children and the fathers of the children who were also the sexual partners of the mothers were evaluated. History of intravenous drug use was significantly more frequent in women with partners infected with HCV than in women with partners not infected [115/180 (63.9%) vs. 87/401 (21.7%); relative risk (RR): 6.38, 95% confidence intervals (CI): 4.34-9.39,  $P < 10^{-3}$ ]. HCV infection was more frequent in the partners of mothers who transmitted perinatally HCV [23/49 (46.9%) vs. 174/557 (31.2%); RR: 1.95, 95%CI: 1.08-3.51,  $P = 0.03$ ]. Multivariate analysis demonstrated that paternal HCV infection is not a risk factor per se for perinatal HCV transmission, but its role is dependent on maternal intravenous drug use [adjusted RR: 1.23 (95%CI: 0.44-3.39,  $P = 0.6$ )]. **In conclusion**, the present study shows that partners of mothers infected with HCV with a history of intravenous drug use were at a higher risk of HCV infection. HCV infection of the father seems to be associated with perinatal transmission but this relationship is dependent on maternal history of intravenous drug use.

**Incidence and Risk Factors for Hepatocellular Carcinoma After Solid Organ**

**Transplantation.** Hoffmann CJ, Subramanian AK, Cameron AM, Engels EA Transplantation.

2008 Sep 27;86(6):784-790

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18813102&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18813102&dopt=Abstract)

**BACKGROUND:** Solid organ transplant recipients commonly are infected with hepatitis viruses, are immunosuppressed, and have other potential hepatocellular carcinoma (HCC) risk factors. **METHODS:** We studied de novo HCC incidence arising after transplant using U.S. registry data (223,660 recipients, 1987-2005). We used proportional hazards regression to identify HCC risk factors and calculated standardized incidence ratios (SIRs) to compare HCC risk with that in the general population. **RESULTS:** Based on 74 cases reported by transplant centers to the registry, HCC incidence was 6.5 per 100,000 person-years among kidney, heart, and lung (non-liver) recipients and 25 per 100,000 person-years among liver recipients. Hepatocellular carcinoma incidence among non-liver recipients was independently associated with hepatitis B surface antigenemia (hazard ratio [HR] 9.7, 95% confidence interval [CI] 2.8-33), hepatitis C virus (HCV) infection (HR 6.9, 95% CI 2.5-19), and diabetes mellitus (HR 2.8, 95% CI 1.2-6.6). Among liver recipients, HCC incidence was associated with advancing age ( $P < 0.001$ ), male sex (HR 4.6, 95% CI 1.4-16), HCV infection (HR 3.1, 95% CI 1.3-7.2), and diabetes mellitus (HR 2.7, 95% CI 1.2-6.2). Among non-liver recipients, overall HCC incidence was similar to the general population (SIR 0.8) but elevated among those with HCV (3.4) or hepatitis B surface antigenemia (6.5). Hepatocellular carcinoma incidence among liver transplant recipients was elevated overall (SIR 3.4) and especially among those with HCV (5.0) or diabetes mellitus (6.2). **CONCLUSIONS:** Hepatocellular

carcinoma incidence is elevated among liver transplant recipients and subsets of non-liver recipients. These risk factors indicate the need for improved control of viral hepatitis after solid organ transplantation.

**Differences between two real-time PCR based assays (RealTime HCV, COBAS AmpliPrep/COBAS TaqMan) and one signal amplification assay (VERSANT HCV RNA 3.0) for HCV RNA detection and quantification.** Vermehren J, Kau A, Gärtner BC, et al. J Clin Microbiol. 2008 Sep 17; [Epub ahead of print]  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18799708&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18799708&dopt=Abstract)

Hepatitis C Virus (HCV) RNA detection and quantification is the key diagnostic tool for the management of hepatitis C. Commercially available HCV RNA assays are calibrated to the HCV genotype 1-based WHO standard. Significant differences between assays have been reported. However, it is unknown which assay matches the WHO standard best and little is known about sensitivity and linear quantification of non-genotype 1 specimens. Two real-time RT-PCR based assays (RealTime HCV [RealTime HCV], COBAS Ampliprep/COBAS Taq Man HCV [CAP/CTM]) and one signal amplification based assay (VERSANT HCV RNA 3.0 [bDNA]) were compared for quantification of clinical genotype (gt) 1-5 specimens (n=65). Mean differences for RealTime HCV in comparison to bDNA and CAP/CTM were for gt1, -0.02 and 0.72; gt2, -0.22 and 0.03; gt3, -0.27 and -0.22; gt4, -0.19 and -1.27; and gt5, -0.03 and 0.09 log<sub>10</sub> IU/mL HCV RNA, respectively. The lower detection limit for RealTime HCV and CAP/CTM was 16.8 and 10.3 IU/mL, respectively for the WHO standard and in the range of 4.7-9.0 and 3.4-44.4 IU/mL for clinical specimens of gt 1-6 samples, respectively. Direct comparison of the two assays using high-titer samples of the WHO standard (code 96/798) yielded slightly lower quantification for RealTime HCV (-0.2 log<sub>10</sub> at 1.500 IU/mL and -0.3 log<sub>10</sub> at 25.000 IU/mL) and higher quantification for CAP/CTM (0.3 log<sub>10</sub> at 1.500 IU/mL and 0.2 log<sub>10</sub> at 25.000 IU/mL). Finally, all three tests were linear between 4.0 x 10<sup>3</sup> and 1.0 x 10<sup>6</sup> IU/mL (correlation coefficient >=0.99). **In conclusion**, real-time PCR based assays showed comparable, linear HCV RNA quantification and sensitive detection of all genotypes with exception of genotypes 1 and 4. Previously reported differences of absolute quantification of genotype 1 samples were confirmed and may be explained by different calibrations to the WHO standard.

**Diagnoses of, and deaths from, severe liver disease due to hepatitis C in England between 2000 and 2005 estimated using multiple data sources.** Mann AG, Ramsay ME, Brant LJ, et al. Epidemiol Infect. 2008 Sep 16;:1-6  
[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18796172&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18796172&dopt=Abstract)

**SUMMARY** Matching individuals reported to a sentinel surveillance scheme for hepatitis C between 2000 and 2005 to individuals with a hospital episode for hepatitis C-related liver disease in the same hospitals, we estimated that the number of cases of hepatitis C-related end-stage liver disease in these English hospitals was 42% (597/419) higher than Hospital Episode Statistics (HES) would indicate. Further, matching records of hepatitis C-related deaths in HES to death certificates, we estimated that, between 2000 and 2005, the true number of deaths from hepatitis C-related end-stage liver disease was between 185% (353/124) and 257% (378/106) higher than the number recorded in routine mortality statistics. We provide estimates of under-recording that can be used to modify existing models of disease burden due to hepatitis C and provide a simple approach to improve the monitoring of trends in severe hepatitis C-related morbidity over time.

**Preoperative assessment of the risk factors that help to predict the prognosis after living donor liver transplantation.** Yoshida R, Iwamoto T, Yagi T, et al. World J Surg. 2008 Sep 16;

[Epub ahead of print]

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18795246&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18795246&dopt=Abstract)

**BACKGROUND:** The purpose of this study was to analyze various risk factors and to assess the preoperative risk score, which can predict the prognosis after living donor liver transplantation (LDLT). **METHODS:** From February 2002 to August 2007, 84 adult to adult living donor liver transplantation donors and recipients were analyzed. First, the donor, recipient, and intraoperative factors were examined by univariate and multivariate analyses. We then gave a score of one point for each significant marginal factor (total point scores were called "risk score") and each risk score was examined by univariate analyses. **RESULTS:** Recipients with the donor age 50 years or older, Model for End-Stage Liver Disease (MELD) score ( $\geq 21$ ), and hepatitis C virus-positive status had a significantly poor survival. Recipients between the risk score of 0 vs. scores of 2 + 3 ( $p < 0.001$ , log-rank) and risk score of 1 vs. scores of 2 + 3 ( $p = 0.003$ , log-rank) had significantly different survival. **CONCLUSIONS:** Preoperative assessment of the risk score might help to predict recipient outcomes after living donor liver transplantation.

**Prevalence of hepatitis C infection and risk factors in hospitalized diabetic patients: results of a cross-sectional study.** Cadranel JF, Di Martino V, Lambrey G, et al. Eur J Gastroenterol Hepatol. 2008 Sep;20(9):829-36

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**OBJECTIVES:** Although there may exist a nosocomial risk of hepatitis C virus (HCV) infection in patients with type 1 or type 2 diabetes, this risk has not been fully investigated thus far and its magnitude is unknown. The aim of this multicenter cross-sectional study was to evaluate the prevalence of, and risk factors for, hepatitis C infection in consecutive hospitalized patients with diabetes and to assess the nosocomial risk and magnitude of HCV infection in these patients.

**PATIENTS AND METHODS:** Consecutive hospitalized patients with diabetes seen in 11 French hepatogastroenterology and diabetology departments were studied. The prevalence of anti-HCV antibodies was compared with that observed in healthy blood donors and individuals seen during routine medical checkup. Diabetic patients with anti-HCV antibodies were compared with patients without anti-HCV antibodies for assessment of risk factors. **RESULTS:** In total 1561 patients were studied. Independent risk factors for HCV infection were assessed through multivariate analysis. Thirty-three patients (2.11%) had anti-HCV antibodies and 21 (63.70%) had HCV identified risk factors. The prevalence of HCV infection was higher in patients with diabetes than in blood donors (0.08%) or healthy controls (0.20%) ( $P < 0.001$ ). Multivariate analysis identified four independent risk factors for HCV infection: blood transfusion before 1991 [odds ratio (OR)=2.88,  $P=0.033$ ], intravenous drug use (OR=21.37,  $P=0.012$ ), treatment in a hepatogastroenterology center (OR=4.17,  $P=0.002$ ) and a high number ( $>2$ ) of previous admissions since the onset of diabetes (OR=2.52,  $P=0.039$ ). **CONCLUSION:** A nosocomial source of HCV infection in hospitalized diabetic patients is suggested by the increased risk of HCV infection associated with the number of hospitalizations. This may account for at least 36% of cases of HCV infection.

**Hepatitis C virus infection in South Australian prisoners: seroprevalence, seroconversion, and risk factors.** Miller ER, Bi P, Ryan P. *Int J Infect Dis.* 2008 Sep 12; [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18790659&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18790659&dopt=Abstract)

**OBJECTIVES:** To determine entry antibody seroprevalence and seroconversion to hepatitis C virus (HCV) and associated risk factors in newly incarcerated prisoners. **METHODS:** Males and females entering South Australian prisons completed risk factor surveys and were offered HCV-antibody testing. Participants completed additional surveys and, if HCV-negative at last test, underwent further antibody tests at 3-monthly intervals for up to 15 months. Data were analyzed using univariate and multivariate techniques. **RESULTS:** HCV seroprevalence among 662 prison entrants was estimated at 42%. Previous injecting history was highly prevalent at entry (64%) and both community and prison injecting independently predicted entry HCV status. Tattooing was not an important risk factor. While community exposure could not be ruled out, three seroconversions were noted in 148 initially HCV-seronegative individuals occurring in a median 121 days - 4.6 per 100 person-years. Prison injecting was infrequently reported, but HCV-seropositive participants were significantly more likely to commence IDU in prison than seronegative participants ( $p=0.035$ ). **CONCLUSIONS:** Entry HCV seroprevalence in South Australian prisoners is extremely high and may have contributed to a 'ceiling effect', minimizing the observable seroconversion rate. Greater frequency of injecting among those already infected with HCV represents a significant threat to other prisoners and prison staff.

**Morphologic features resembling transplant rejection in core biopsies of native livers from patients with Hepatitis C.** Souza P, Prihoda TJ, Hoyumpa AM, Sharkey FE. *Hum Pathol.* 2008 Sep 12; [Epub ahead of print] [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list\\_uids=18790517&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?tmpl=NoSidebarfile&db=PubMed&cmd=Retrieve&list_uids=18790517&dopt=Abstract)

Morphologic differentiation of recurrent Hepatitis C from transplant rejection is a major problem in posttransplant liver biopsies. Although biopsies of the native livers from patients with Hepatitis C are known to display bile duct damage, other morphologic features similar to those seen in rejection, such as endotheliitis, portal eosinophils, and pericentral fibrosis, are not generally acknowledged. To determine the frequency with which features morphologically similar to rejection might be present, we examined 50 cases of core-needle biopsy from the native livers of patients with Hepatitis C for the presence of the following: bile duct damage, portal eosinophils, portal or central vein endotheliitis, ductopenia, vascular obliteration, pericentral fibrosis, and pericentral mononuclear cell infiltrate. Biopsy specimens with other concurrent disease processes were excluded. The frequency of each morphologic feature was as follows: bile duct damage (30%), portal eosinophils (42%), portal endotheliitis (20%), central vein endotheliitis (0%), pericentral mononuclear cell infiltrate (14%), ductopenia (2%), atrophic-looking bile ducts (2%), vascular obliteration (0%), and pericentral fibrosis (10%). Bile duct damage and portal endotheliitis were both more common with higher grade hepatitis (Fisher exact test,  $P = .001$ ). None of the morphologic parameters correlated with biopsy stage, viral genotype, or liver function tests. **We conclude** that features similar to those found in acute rejection are common in Hepatitis C, whereas features resembling chronic rejection are less frequent. This study provides quantitative data that supports the need to interpret these features with great caution in posttransplant liver biopsies from patients with recurrent Hepatitis C who are suspected of rejection.