

# Caring Ambassadors Hepatitis C Program Newsletter

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## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Safety and efficacy of peginterferon alpha plus ribavirin in patients with chronic hepatitis C and coexisting heart disease.** Durante-Mangoni E, Iossa D, Pinto D, De Vincentiis L, Ragone E, Utili R. Dig Liver Dis. 2011 May;43(5):411-5.

<http://www.ncbi.nlm.nih.gov/pubmed/21310673>

**BACKGROUND:** Chronic hepatitis C patients with coexisting heart disease are often denied antiviral treatment due to safety concerns. However, this is not evidence-based. **AIMS:** To evaluate safety and efficacy of pegylated interferon and ribavirin in chronic hepatitis C patients with heart disease. **METHODS:** Patients with overt heart disease (ischaemic heart disease, prior mechanical heart valve replacement, chronic arrhythmias and cardiomyopathy) and chronic hepatitis C were treated with standard pegylated interferon/ribavirin doses for standard duration. Cardiovascular safety was monitored by electrocardiography, echocardiography and measurement of troponin and B-type natriuretic peptide. **RESULTS:** Twenty-three patients (65.2% male, median age 57 years, 47.8% genotype 1) were treated. Three patients (13%) suspended treatment prematurely; 52% obtained sustained virological response, 39% relapsed, 9% were non-responders. No serious adverse event was observed. Post-treatment clinical examination, electrocardiography and echocardiography did not show any sign of progression of the pre-existing heart disease. **CONCLUSIONS:** Treatment with pegylated interferon/ribavirin may be safely offered to carefully selected chronic hepatitis C patients with coexisting, clinically significant heart disease. In these patients, the outcome of antiviral treatment overlaps that observed in other patient subgroups.

**Closure of Ascites Leaks with Fibrin Glue Injection in Patients with End-Stage Liver Disease.** Sadik K, Laibstain S, Northup PG, Kashmer D, Bonatti HJ. J Laparoendosc Adv Surg Tech A. 2011 May 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21612447>

**BACKGROUND:** Ascites leaks (AL) in patients with end-stage liver disease (ESLD) are associated with significant morbidity and mortality regardless if they are medically or surgically managed. **PATIENTS AND METHODS:** In a pilot study, 14 ESLD patients with AL underwent treatment with fibrin glue injection around the leak after failing conservative therapy. The end point of this study was the cessation of AL in the short term and the maintenance of a leak-free abdomen in the long term, allowing for medical optimization of the patients.

**RESULTS:** Median age of the 10 men and 4 women was 50 (range 26-67) years. Underlying

ESLDs were chronic hepatitis C (n=5), alcoholic LD (n=2), cryptogenic cirrhosis (n=2), and miscellaneous (n=5). There were six leaking incisions posthernia repair (three umbilical and three inguinal), two leaking/ruptured umbilical hernias, four leaking paracentesis sites, one leaking Jackson-Pratt (JP) drain canal, and one leaking laparoscopic trocar site. Average AL volume per day was 1000 (range 400-2000) mL. All leaks were immediately resolved with a 3-5 mL fibrin glue injection. Five recurred and required a second injection (four within 24 hours). Mental status improved in 7 patients (West Haven Criteria: grade II to I [n=6], grade III to I [n=1]). Median model of end-stage liver disease scores improved from 23 (range 8-33) to 20 (range 14-26). There were no infections, bleeds, or other injection-related complications. Average follow-up for these patients was 441.6 days (range 2-852). Five patients underwent liver transplant (LT) median 15 (range 4-270) days postinjection; 2 of them died. Another 3 patients died (2 from sepsis and 1 from metastatic cancer). **CONCLUSION:** Fibrin glue injection for the control of AL is a simple and safe bedside procedure that quickly controls AL, allowing for patient recovery in anticipation of further care.

**Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children.** Rodrigue JR, Balistreri W, Haber B, et al. *Hepatology*. 2011 May;53(5):1468-75. doi: 10.1002/hep.24248.

<http://www.ncbi.nlm.nih.gov/pubmed/21351116>

**The aim of this study** was to prospectively assess the quality of life (QOL), behavioral/emotional functioning, and cognitive status of children undergoing treatment for hepatitis C virus (HCV) infection. In all, 114 children (5 to 18 years old) enrolled in a multisite randomized clinical trial (Peds-C) to evaluate peginterferon alpha 2a (PEG 2a) with ribavirin (RV) or with placebo (PL) completed several standardized measures prior to treatment and at 24 weeks, 48 weeks, 6 months following treatment, and at two annual follow-up visits. After 24 weeks of treatment, mean physical QOL scores declined significantly for both groups from baseline to 24 weeks of treatment ( $F = 5.8$ ,  $P = 0.004$ ), although scores remained in the average range. There were no significant time or group effects for behavioral/emotional or cognitive functioning. Three children (5%) in the PEG 2a + RV group and no children in the PEG 2a + PL group had a clinically significant increase in depression symptoms. For those children who received 48 weeks of treatment, there were no significant time or group effects on any of the outcome measures ( $P > 0.05$ ). A majority of children in both the PEG 2a + RV and PEG 2a + PL groups experienced no clinically significant change in physical QOL, behavioral adjustment, depression, or cognitive functioning during or after treatment. **CONCLUSION:** Overall QOL and psychosocial functioning are not deleteriously impacted by PEG 2a + RV or PL treatment of children with HCV.

**Patient-care practices associated with an increased prevalence of hepatitis C virus infection among chronic hemodialysis patients.** Shimokura G, Chai F, Weber DJ, et al. *Infect Control Hosp Epidemiol*. 2011 May;32(5):415-24.

<http://www.ncbi.nlm.nih.gov/pubmed/21515970>

**OBJECTIVE:** To identify patient-care practices related to an increased prevalence of hepatitis C virus (HCV) infection among chronic hemodialysis patients. **DESIGN:** Survey. **SETTING:** Chronic hemodialysis facilities in the United States. **PARTICIPANTS:** Equal-probability 2-stage cluster sampling was used to select 87 facilities from all Medicare-approved providers treating 30-150 patients; 53 facilities and 2,933 of 3,680 eligible patients agreed to participate.

**METHODS:** Patients were tested for HCV antibody and HCV RNA. Data on patient-care practices were collected using direct observation. **RESULTS:** The overall prevalence of HCV infection was 9.9% (95% confidence interval [CI], 8.2%-11.6%); only 2 of 294 HCV-positive patients were detected solely by HCV RNA testing. After adjusting for non-dialysis-related HCV risk factors, patient-care practices independently associated with a higher prevalence of HCV infection included reusing priming receptacles without disinfection (odds ratio [OR], 2.3 [95% CI, 1.4-3.9]), handling blood specimens adjacent to medications and clean supplies (OR, 2.2 [95% CI, 1.3-3.6]), and using mobile carts to deliver injectable medications (OR, 1.7 [95% CI, 1.0-2.8]). Independently related facility covariates were at least 10% patient HCV infection prevalence (OR, 3.0 [95% CI, 1.8-5.2]), patient-to-staff ratio of at least 7 : 1 (OR, 2.4 [95% CI, 1.4-4.1]), and treatment duration of at least 2 years (OR, 2.4 [95% CI, 1.3-4.4]).

**CONCLUSIONS:** This study provides the first epidemiologic evidence of associations between specific patient-care practices and higher HCV infection prevalence among hemodialysis patients. Staff should review practices to ensure that hemodialysis-specific infection control practices are being implemented, especially handling clean and contaminated items in separate areas, reusing items only if disinfected, and prohibiting mobile medication and clean supply carts within treatment areas.

**Prevalence of liver disease in veterans with bipolar disorder or schizophrenia.** Fuller BE, Rodriguez VL, Linke A, Sikirica M, Dirani R, Hauser P. *Gen Hosp Psychiatry*. 2011 May-Jun;33(3):232-7. Epub 2011 May 6.

<http://www.ncbi.nlm.nih.gov/pubmed/21601719>

**OBJECTIVE:** To assess the prevalence of three liver diseases [hepatitis C virus (HCV), nonalcoholic fatty liver disease and alcohol-induced cirrhosis] in patients (veterans) with/without schizophrenia/schizoaffective disorder and bipolar disorder. **METHODS:** A retrospective electronic chart review of Veterans Integrated Services Network 20 facilities from January 1, 2001 to December 21, 2006 selected patients to one of two groups: schizophrenia/schizoaffective disorder or bipolar disorder. Patients in both groups were compared with veterans in an equal-sized random sample from the same data set of veterans without psychiatric diagnoses. Logistic regression models evaluated risk for overall liver diseases as well as HCV, nonalcoholic fatty liver disease and alcoholic-induced cirrhosis. **RESULTS:** Patients with schizophrenia (n=6521) had a higher prevalence of liver disease [22.4% versus 3.2%; odds ratio (OR)=8.73]; HCV (16.5% versus 1.9%; OR=10.21); and alcohol-related cirrhosis (1.6% versus 0.4%; OR=4.09) than matched controls. Patients with bipolar disorder (n=5319) had a higher prevalence of liver disease (21.5% versus 3.5%; OR=7.58); HCV (15.5% versus 2.1%; OR=8.60); and alcohol-related cirrhosis (1.6% versus 0.4%; OR=3.82) than matched controls. Risk factors for liver disease in patients with schizophrenia (versus matched controls) included diabetes (OR=1.29), hypertension (OR=1.27), HIV (OR=3.54), substance use disorder (SUD) (OR=2.28), alcohol use disorder (OR=3.05) and schizophrenia (OR=2.74). Risk factors for development of liver disease for patients with bipolar disorder: diabetes (OR=1.40), HIV (OR=3.66), SUD (OR=2.68), alcohol use disorder (OR=3.22) and bipolar disorder (OR=2.27). **CONCLUSIONS:** This study in veterans shows that the presence of mental illness and its comorbidities represents a significant risk factor for the diagnosis of liver disease, including HCV and alcohol-related cirrhosis.

**Open-label, ascending dose, prospective cohort study evaluating the antiviral efficacy of Rosuvastatin therapy in serum and lipid fractions in patients with chronic hepatitis C.**

Patel K, Jhaveri R, George J, et al. *J Viral Hepat.* 2011 May;18(5):331-7. doi: 10.1111/j.1365-2893.2010.01310.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20367801>

HMG CoA reductase inhibition suppresses in vitro HCV replication through depletion of cellular sterol proteins such as geranylgeraniol. Our aims were to prospectively evaluate the changes in serum and lipid fraction HCV RNA with Rosuvastatin in non-responder (NR) patients with CHC. A total of 11 patients with CHC genotype-1 received Rosuvastatin at 20 mg qd (weeks 0-4), 40 mg qd (weeks 5-12), with 4 week follow up. Lipid fractions were separated by a sucrose density gradient ultracentrifugation, HCV RNA determined at wks 0, 2, 4, 8, 12, 16 in serum, and in selected very low- (VLDF) to high-density (HDF) lipid fractions. A reduction in LDL and total cholesterol (TC) was not accompanied by significant decline in HCV RNA. At baseline, there was an inverse correlation between HDL and HCV RNA ( $\rho = -0.45$ ,  $P = 0.036$ ). At 20 mg, there was correlation between change ( $\Delta$ ) in TG and  $\Delta$  HCV RNA ( $\rho = 0.75$ ,  $P = 0.007$ ),  $\Delta$  ALT and  $\Delta$  TC ( $\rho = -0.64$ ,  $P = 0.03$ ) and  $\Delta$  LDL ( $\rho = -0.67$ ,  $P = 0.02$ ). At 40 mg,  $\Delta$  TG maintained a positive correlation with  $\Delta$  HCV RNA ( $\rho = 0.65$ ,  $P = 0.03$ ). There was a group difference for HCV RNA in relation to lipid fractions ( $P = 0.04$ ) but not study time intervals ( $P = 0.17$ ); mean log HCV RNA was greater in VLDF compared to HDF ( $5.81 \pm 0.59$  vs  $5.06 \pm 0.67$ ,  $P = 0.0002$ ) with no other differences to study time intervals ( $P = 0.099$ ). Short-term Rosuvastatin monotherapy is not associated with significant changes in serum or lipid fraction HCV RNA in NR patients. HCV co-localizes with the lowest density lipid fractions in serum.

**The hepatitis C self-management programme: a randomized controlled trial.** Groessl EJ, Weingart KR, Stepnowsky CJ, Gifford AL, Asch SM, Ho SB. *J Viral Hepat.* 2011

May;18(5):358-68. doi: 10.1111/j.1365-2893.2010.01328.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20529203>

Chronic hepatitis C (HCV) infection afflicts millions of people worldwide. While antiviral treatments are effective for some patients, many either cannot or choose not to receive antiviral treatment. Education about behavioural changes like alcohol avoidance and symptom management, in contrast, is universally recommended, particularly in HCV-infected persons from disadvantaged groups where liver risk factors are most prevalent. Self-management interventions are one option for fostering improved HCV knowledge and health-related quality of life (HRQOL). One hundred and thirty-two patients with VA with HCV (mean age of 54.6, 95% men, 41% ethnic minority, 83% unmarried, 72% unemployed/disabled, 48% homeless in last 5 years) were randomized to either a 6-week self-management workshop or an information-only intervention. The weekly 2-h self-management sessions were based on cognitive-behavioural principles and were adapted from an existing self-management programme that has been efficacious with other chronic diseases. HCV-specific modules were added. Outcomes including HRQOL, HCV knowledge, self-efficacy, depression, energy and health distress were measured at baseline and 6 weeks later. Data were analysed using ANOVA. When compared to the information-only group, participants attending the self-management workshop improved more on HCV knowledge ( $P < 0.001$ ), HCV self-efficacy ( $P = 0.011$ ), and SF-36 energy/vitality ( $P = 0.040$ ). Similar trends were found for SF-36 physical functioning ( $P = 0.055$ ) and health distress ( $P = 0.055$ ). Attending the self-management programme improved disease knowledge and HRQOL 6 weeks later in this disadvantaged population. The intervention can improve the

health of people with hepatitis C, independent of antiviral therapy. Future research will study longer-term outcomes, effects on antiviral treatment and costs.

**Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy.** Sasadeusz JJ, Dore G, Kronborg I, Barton D, Yoshihara M, Weltman M. *Addiction*. 2011 May;106(5):977-84. doi: 10.1111/j.1360-0443.2010.03347.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21205057>

**AIMS:** To evaluate the efficacy, safety and adherence to hepatitis C (HCV) therapy in patients attending tertiary hepatitis clinics who are receiving opioid replacement therapy. **DESIGN:** A non-randomized, open-label study. Participants were treated with pegylated interferon alpha-2a and weight-based ribavirin for 24 weeks (genotype non-1, n = 31) or 48 weeks (genotype 1, n = 22). **SETTING:** Four tertiary hospital hepatitis clinics in Australia. **PARTICIPANTS:** Fifty-three patients with chronic HCV who were receiving opioid replacement therapy. **MEASUREMENTS:** Patients were monitored for virological response, adverse events and adherence. They were also screened for psychiatric illness prior to and throughout the study utilizing two validated instruments: the Mini International Neuropsychiatric Interview (MINI) and Beck Depression Interview (BDI)-II. **FINDINGS:** The overall sustained virological response (SVR) rate was 57% (71% genotype non-1 versus 36% genotype 1), and was similar in active injectors (63%) and non-injectors (53%). The psychological profile of patients based on validated instruments did not change on therapy. The pattern and frequency of adverse effects were comparable to non-opioid replacement patients. Eighty-five per cent of patients were adherent to therapy by 80/80/80 criteria and only two patients who had an end-of-treatment response relapsed, one of whom was not an active injector. **CONCLUSIONS:** Patients on opioid replacement therapy, even if they continue to inject actively, can achieve comparable sustained virological response rates to other populations with pegylated interferon alpha-2a and ribavirin therapy, suffer no excess rates of adverse effects or psychological complications and have good adherence to therapy.

**Diagnosis of depression in former injection drug users with chronic hepatitis C.** Scott JD, Wang CC, Coppel E, Lau A, Veitengruber J, Roy-Byrne P. *J Clin Gastroenterol*. 2011 May-Jun;45(5):462-7.

<http://www.ncbi.nlm.nih.gov/pubmed/21293293>

**GOALS:** This study seeks to define the performance characteristics of 2 common depression screening tests and how psychiatric diagnoses affect adherence to treatment. **BACKGROUND:** Hepatitis C virus is common in former injection drug users (IDU). Many former IDUs have depression, which may complicate treatment, and are often denied therapy. **STUDY:** Ninety patients with chronic hepatitis C virus and reported IDU were recruited from a Hepatology Clinic in Seattle. Subjects completed the Beck Depression Inventory (BDI) and Patient Health Questionnaire-9 (PHQ-9) before antiviral therapy. A psychiatrist administered the Mini International Neuropsychiatric Interview as the "gold standard." Adherence was measured by self-report of missed doses. **RESULTS:** The BDI and PHQ-9 were highly correlated ( $r=0.75$ ). Using a BDI score of  $\geq 20$  and a PHQ-9 score of  $\geq 10$ , 39% and 52%, respectively, were misclassified as being depressed, as compared with the Mini International Neuropsychiatric Interview. Maximal sensitivity (85.7%) and specificity (82.6%) was achieved using a BDI score cutoff of 31, with an area under the curve of 0.82. For the PHQ-9, a cutoff of 14 yielded the best sensitivity (85.7%) and specificity (73.9%) with an area under the curve of 0.84. Adherence to

least 80% of medications was achieved by the majority. **CONCLUSIONS:** Subjects reported good adherence and outcomes despite a high level of psychiatric comorbidity. The BDI and PHQ-9 were highly correlated but both tended to overdiagnose depression. A high score on BDI or PHQ-9 should not be the sole basis for withholding treatment. These patients should be evaluated by a psychiatrist to make an informed decision.

**Psychiatric and Substance Use Disorders among Methadone Maintenance Patients with Chronic Hepatitis C Infection: Effects on Eligibility for Hepatitis C Treatment.** Batki SL, Canfield KM, Ploutz-Snyder R. *Am J Addict.* 2011 Jul;20(4):312-8. doi: 10.1111/j.1521-0391.2011.00139.x. Epub 2011 May 31.

<http://www.ncbi.nlm.nih.gov/pubmed/21679262>

We set out to describe the prevalence and severity of psychiatric and substance use disorders (SUDs) in methadone maintenance treatment (MMT) patients with chronic hepatitis C virus (HCV) infection and to measure the impact on HCV-treatment eligibility. Psychiatric disorders, SUDs, and HCV-treatment eligibility were assessed in 111 MMT patients prior to a controlled trial of HCV treatment. Lifetime and current diagnosis rates, respectively, were: any non-SUD Axis I disorder: 82% and 57%, any mood disorder: 67% and 35%, any anxiety disorder: 63% and 22%, any psychotic disorder: 11% and 9%. Antisocial personality disorder was present in 40%. A total of 56% met criteria for current SUDs. A total of 66% received psychiatric medications prior to HCV treatment; over half were receiving antidepressants. Despite psychiatric and substance use comorbidity, only 15% of patients were ineligible for HCV treatment: 10% due to failure to complete the evaluation, and 5% due to psychiatric severity. Substance use did not lead to ineligibility in any participant. Multiple logistic regression showed the Beck Depression Inventory contributed significantly to predicting HCV treatment eligibility. Most MMT patients were ineligible for HCV treatment despite current SUD and non-SUD diagnoses. Depression severity may be a more significant predictor of HCV treatment eligibility than is substance use.

**Efficacy of re-treatment with pegylated interferon plus ribavirin combination therapy for patients with chronic hepatitis C in Japan.** Oze T, Hiramatsu N, Yakushijin T, et al. *J Gastroenterol.* 2011 May 3. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21538029>

**BACKGROUND:** It is still not known which patients with chronic hepatitis C who failed to respond to previous pegylated interferon (Peg-IFN) plus ribavirin therapy can benefit from re-treatment. **METHODS:** Seventy-four patients (HCV genotype 1, n = 56, genotype 2, n = 18) were re-treated with Peg-IFN plus ribavirin. **RESULTS:** On re-treatment, the sustained virologic response (SVR) rate was 41% for genotype 1 and 56% for genotype 2. With genotype 1, the factors associated with an SVR were previous treatment response and the serum hepatitis C virus (HCV) RNA level at the start of re-treatment. Patients with a  $\geq 2$ -log decrease in HCV RNA at week 12 (partial early virologic response, p-EVR) in previous treatment had significantly higher SVR rates than those without these decreases ( $p < 0.001$ ); no patient without a p-EVR in the previous treatment attained an SVR with re-treatment (0/16). All patients with  $< 5 \log(10)$  IU/ml of HCV RNA at the start of re-treatment attained an SVR (6/6), while only 33% (15/45) of those patients with  $\geq 5 \log(10)$  IU/ml of HCV RNA attained an SVR ( $p < 0.01$ ). Among the patients with relapse in the previous treatment, those who attained an SVR on re-treatment required a longer duration of re-treatment than the duration of the previous treatment (re-treatment,  $63.8 \pm 13.0$  weeks vs. previous treatment,  $53.9 \pm 13.5$  weeks,  $p = 0.01$ ). **CONCLUSIONS:** Re-

treatment of genotype 1 patients should be limited to patients with a p-EVR in the previous treatment and a low HCV RNA level at the start of re-treatment. In re-treatment with Peg-IFN plus ribavirin, longer treatment duration can contribute to increasing the anti-viral effect.

**Efficacy of pegylated interferon- $\alpha$ 2a monotherapy in Japanese children with chronic hepatitis C.** Tsunoda T, Inui A, Etani Y, et al. *Hepatol Res.* 2011 May;41(5):399-404. doi: 10.1111/j.1872-034X.2011.00789.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21518401>

**AIM:** There is little information available on the efficacy of pegylated interferon (PEG IFN) therapy for children with chronic hepatitis C. The aim of this study was to evaluate the efficacy and tolerability of PEG IFN- $\alpha$ 2a monotherapy for children infected by chronic hepatitis C virus (HCV). **METHODS:** From 2004-2006, we conducted a prospective, open-label, multicenter study of 22 patients aged 4-18 years, including eight with genotype 1 and 14 with genotype 2. None had previously received IFN. The patients were treated with s.c. PEG IFN- $\alpha$ 2a at a dose of 3  $\mu$ g/kg once a week for 48 weeks. Rapid virological response (RVR) was defined as: undetectable serum HCV RNA at week 4; early viral response (EVR) as a 2 or more log reduction or undetectable serum HCV RNA at week 12; and sustained viral response (SVR) as undetectable serum HCV RNA at 24 weeks after the cessation of treatment. **RESULTS:** SVR was achieved in 10 (45%) of the 22 patients (three with genotype 1, seven with genotype 2). Retrospectively, the patients with SVR included five with RVR (one with genotype 1, four with genotype 2) and five with EVR (two with genotype 1, three with genotype 2). PEG IFN- $\alpha$ 2a monotherapy was well tolerated, except in one patient in whom alanine aminotransferase activity flared (>500 IU/L) during treatment. **CONCLUSION:** The efficacy of PEG IFN- $\alpha$ 2a monotherapy in children is similar to that for adults, while tolerability seems to be better in children than in adults.

**Efficacy and safety of peginterferon  $\alpha$ -2a (40 kD) plus ribavirin among patients with chronic hepatitis C and earlier treatment failure to interferon and ribavirin: an open-label study in central and Eastern Europe.** Husa P, Oltman M, Ivanovski L, Reháč V, Messinger D, Tietz A, Urbanek P. *Eur J Gastroenterol Hepatol.* 2011 May;23(5):375-81.

<http://www.ncbi.nlm.nih.gov/pubmed/21502923>

**OBJECTIVE:** To assess the safety and efficacy of 48 weeks of re-treatment with peginterferon  $\alpha$ -2a (40 kD) plus ribavirin in previously treated hepatitis C virus (HCV) genotype 1 patients. **METHODS:** HCV genotype 1 patients previously treated with conventional interferon with or without ribavirin were assigned to 48 weeks of treatment with peginterferon  $\alpha$ -2a (40 kD; 180  $\mu$ g/week) plus ribavirin (recommended dose: 1000/1200 mg/day) in this open-label trial conducted in central and Eastern Europe. The primary efficacy endpoint was sustained virological response (SVR, HCV RNA <50 IU/ml) after 24 weeks of untreated follow-up. Early virological response (EVR) was defined as an undetectable HCV RNA or at least 2-log drop at week 12. **RESULTS:** A total of 154 of the 203 (76%) treatment-experienced genotype 1 patients completed the treatment. Overall, 113 patients (56%) achieved an EVR, 107 (53%) had an end-of-treatment response and 63 patients (31%) achieved an SVR [including 38% (40/105) of those with an earlier breakthrough or relapse and 24% (21/88) of those with earlier nonresponse]. Among patients with an EVR, 47% (53/113) achieved an SVR (positive predictive value=47%), compared with 3% (1/34) of patients without an EVR (negative predictive value=97.1%). Rates

of SVR were higher in patients without cirrhosis (54/169, 32%), with a baseline viral load of 800 000 IU/ml or less (29/68, 43%) and younger than 40 years of age (36/77, 47%).

**CONCLUSION:** The combination of peginterferon  $\alpha$ -2a (40 kD) plus ribavirin produced an overall SVR rate of 31% in difficult-to-treat genotype 1 patients who had not responded to the previous treatment with conventional interferon plus ribavirin.

**Th17 cells are increased with severity of liver inflammation in patients with chronic hepatitis C.** Chang Q, Wang YK, Zhao Q, Wang CZ, Hu YZ, Wu BY. *J Gastroenterol Hepatol*. 2011 May 18. doi: 10.1111/j.1440-1746.2011.06782.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21592230>

**BACKGROUND AND AIM:** As a newly identified subset of T helper cells, T-helper 17 cells (Th17) are major mediators of inflammation-associated disease. Some reports have revealed significantly increased Th17 cells in HBV-infected patients, and a recent study has demonstrated that HCV-specific Th17 cells can be induced in vitro and regulated by TGF- $\beta$ . This study attempted to characterize the role of Th17 cells in the disease progression of chronic hepatitis C (CHC). **METHODS:** The current study enrolled 53 patients with CHC and 23 healthy controls, in which the circulating and liver-infiltrating Th17 cells were monitored. **RESULTS:** We found that CHC patients had increased proportions of both circulating and liver-infiltrating Th17 cells compared to healthy individuals, and both measures of Th17 cells were correlated with severity of liver inflammation. We further demonstrated that the HCV-specific Th17 cells were correlated with liver damage but not HCV viral replication. **CONCLUSIONS:** Such a correlation between the severity of liver damage of CHC and Th17 cells illustrated in this study shed some light to the understanding of the pathogenesis of CHC.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**T Helper Type 1/T Helper Type 17-Related Cytokines in Chronic Hepatitis C Patients before and after Interferon and Ribavirin Therapy.** Fathy A, Ahmed AS, Metwally L, Hassan A. *Med Princ Pract*. 2011;20(4):345-9. Epub 2011 May 11.

<http://www.ncbi.nlm.nih.gov/pubmed/21576995>

**OBJECTIVE:** This study examined the T helper (Th) 1/Th17-related cytokines, interferon (IFN)- $\gamma$  and interleukin (IL)-17 in the serum of biopsy-proven chronic hepatitis C patients before and after IFN and ribavirin therapy to address whether or not viral clearance is related to Th1/Th17 cytokines. **SUBJECTS AND METHODS:** The serum levels of IFN- $\gamma$  and IL-17 were assayed by ELISA on 26 patients with chronic hepatitic C virus (HCV) infection before the start and 3 months after treatment with pegylated IFN- $\alpha$  plus ribavirin and compared with sera from 15 normal control subjects. **RESULTS:** IFN- $\gamma$  and IL-17 levels are higher in the serum of patients with chronic hepatitis than in normal controls and these elevated levels were not directly correlated ( $r = -0.01$ ,  $p = 0.96$  for IFN- $\gamma$  and  $r = -0.08$ ,  $p = 0.66$  for IL-17) to the viremic state of the HCV infection. In contrast to IL-17, IFN- $\gamma$  showed significant reduction after 12 weeks of treatment with pegylated IFN plus ribavirin. However, IFN- $\gamma$  and IL-17 serum levels were not significantly ( $p = 0.19$  and  $p = 0.70$ , respectively) different among responders and nonresponders for pegylated IFN plus ribavirin therapy. **CONCLUSION:** Our findings suggest that the combined treatment with pegylated IFN- $\alpha$  and ribavirin downmodulates the secretion of key cytokine IFN- $\gamma$  as early as 12 weeks after treatment in infected patients. These findings could

encourage new exciting possibilities for immune-based interventions with the aim of restoring functional antiviral T cell responses combined with improved viral clearance.

**Single nucleotide polymorphism at exon 7 splice acceptor site of OAS1 gene determines response of hepatitis C virus patients to interferon therapy.** El Awady MK, Anany MA,

Esmat G, et al. J Gastroenterol Hepatol. 2011 May;26(5):843-50. doi: 10.1111/j.1440-1746.2010.06605.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21182542>

**BACKGROUND AND AIM:** Response to interferon therapy and disease progression in hepatitis C virus (HCV) infected patients differs among individuals, suggesting a possibility of a contribution of host genetic factors. 2'-5'-oligoadenylate synthetase 1 (OAS1), an important component of the innate immune system with a proven antiviral function, may therefore have a relationship with the response to interferon therapy and clinical course of HCV disease. Our aim was to determine the frequency of single nucleotide polymorphism (SNP) at exon 7 splice acceptor site (SAS) of the OAS1 gene in relation to the interferon response and status of HCV infection. **METHODS:** A 203 bp fragment containing exon 7 SAS was amplified in 70 HCV chronic patients and 50 healthy controls. SNP was examined using restriction fragment length polymorphism (RFLP) genotyping method. Correlations of SNP genotypes with response to interferon and clinical status of patients were statistically analyzed. Results: There was an increasing trend of response from AA to AG to GG genotypes (P = 0.007). Genotype AA was associated with non-response to interferon and higher degree of liver fibrosis (P = 0.05).

Multivariate analysis showed this SNP as independent and a significant determinant of the outcome of interferon therapy (odds ratio 4.913 [95% confidence interval 1.365-8.2], P = 0.006).

**CONCLUSIONS:** This is the first study to show a significant association between the functional SNP at exon 7 SAS of OAS1 gene and the viral response to interferon in chronic HCV patients. Patients with AA genotype were associated with progressive HCV disease and viral resistance to interferon therapy. This OAS SNP is a potential bio-marker to predict IFN response in chronic hepatitis C patients.

**Inhibition of Hepatitis C Virus 3a genotype entry through Glanthis Nivalis Agglutinin.**

Ashfaq UA, Masoud MS, Khaliq S, Nawaz Z, Riazuddin S. Virol J. 2011 May 20;8:248.

<http://www.ncbi.nlm.nih.gov/pubmed/21599979>

Hepatitis C Virus (HCV) has two envelop proteins E1 and E2 which is highly glycosylated and play an important role in cell entry. Inhibition of virus at entry step is an important target to find antiviral drugs against HCV. Glanthis Nivalis Agglutinin (GNA) is a mannose binding lectin which has tendency for specific recognition and reversible binding to the sugar moieties of a wide variety of glycoproteins of enveloped viruses. **RESULTS:** In the present study, HCV pseudoparticles (HCVpp) for genotype 3a were produced to investigate the ability of GNA to block the HCV entry. The results demonstrated that GNA inhibit the infectivity of HCVpp and HCV infected serum in a dose-dependent manner and resulted in 50% reduction of virus at  $1 \pm 2$   $\mu$ g concentration. Molecular docking of GNA and HCV glycoproteins (E1 and E2) showed that GNA inhibit HCV entry by binding N-linked glycans. **CONCLUSION:** These results demonstrated that targeting the HCV glycans is a new approach to develop antiviral drugs against HCV.

**Hepatitis C virus targets the T cell secretory machinery as a mechanism of immune evasion.** Petrovic D, Stamataki Z, Dempsey E, et al. *Hepatology*. 2011 Jun;53(6):1846-53. doi: 10.1002/hep.24327. Epub 2011 May 2.

<http://www.ncbi.nlm.nih.gov/pubmed/21452285>

T cell activation and the resultant production of interleukin (IL-2) is a central response of the adaptive immune system to pathogens, such as hepatitis C virus (HCV). HCV uses several mechanisms to evade both the innate and adaptive arms of the immune response. Here we demonstrate that liver biopsy specimens from individuals infected with HCV had significantly lower levels of IL-2 compared with those with other inflammatory liver diseases. Cell culture-grown HCV particles inhibited the production of IL-2 by normal peripheral blood mononuclear cells, as did serum from HCV-infected patients. This process was mediated by the interaction of HCV envelope protein E2 with tetraspanin CD81 coreceptor. HCV E2 attenuated IL-2 production at the level of secretion and not transcription by targeting the translocation of protein kinase C beta (PKC $\beta$ ), which is essential for IL-2 secretion, to lipid raft microdomains. The lipid raft disruptor methyl- $\beta$ -cyclodextrin reversed HCV E2-mediated inhibition of IL-2 secretion, but not in the presence of a PKC $\beta$ -selective inhibitor. HCV E2 further inhibited the secretion of other cytokines, including interferon- $\gamma$ . Conclusion: These data suggest that HCV E2-mediated disruption of the association of PKC $\beta$  with the cellular secretory machinery represents a novel mechanism for HCV to evade the human immune response and to establish persistent infection.

**Expression profiles of genes associated with viral entry in HCV-infected human liver.**

Nakamuta M, Fujino T, Yada R, et al. *J Med Virol*. 2011 May;83(5):921-7. doi:

10.1002/jmv.22042.

<http://www.ncbi.nlm.nih.gov/pubmed/21412800>

Recent studies have demonstrated that several cellular factors are involved in entry of hepatitis C virus (HCV) into host cells. Detailed gene expression profiles of these factors in HCV-infected livers have not been reported for humans. Transcriptional levels of LDL receptor (LDLR), CD81, scavenger receptor class B type I (SR-BI), claudin-1, and occludin genes in liver samples from patients with chronic hepatitis C were investigated. Serum levels of LDL-cholesterol (LDL-C) and HCV core antigen were also evaluated, and expression of claudin-1 and occludin were immunohistochemically analyzed. Compared with normal liver, transcription of LDLR and claudin-1 genes was significantly suppressed ( $P < 0.0001$ ) and occludin transcription was significantly up-regulated in HCV-infected livers ( $P < 0.0001$ ). Significant positive correlations were found for LDLR versus occludin, LDLR versus claudin-1, occludin versus claudin-1, and CD81 versus SR-BI in HCV-infected ( $P = 0.0012$ ,  $P < 0.0001$ ,  $P = 0.0004$ , and  $P < 0.0001$ , respectively) and normal livers ( $P < 0.0001$ ,  $P = 0.0051$ ,  $P < 0.0001$ , and  $P < 0.0001$ , respectively). Positive correlation was observed between serum levels of HCV core antigen and LDL-C ( $P = 0.0147$ ), with their levels negatively correlated to LDLR ( $P = 0.0270$  and  $P = 0.0021$ , respectively). Immunohistochemically, hepatocellular expression of claudin-1 and occludin was increased in HCV-infected livers. Different levels of expression were demonstrated at the mRNA and protein levels for occludin and claudin-1 in HCV-infected and normal livers. Correlation of elements associated with viral entry was comparable in HCV-infected and normal livers.

**Hepatic Akt expression correlates with advanced fibrosis in patients with chronic hepatitis C infection.** Huang JF, Chuang YH, Dai CY, et al. *Hepatology*. 2011 May;41(5):430-436. doi: 10.1111/j.1872-034X.2011.00786.x. Epub 2011 Apr 19.

<http://www.ncbi.nlm.nih.gov/pubmed/21504518>

**AIM:** Hepatitis C virus (HCV) proteins can activate the PI3K/Akt pathway which is involved in multiple cellular functions such as inflammatory cell activation and liver fibrosis. The aim of the present study was to elucidate the correlation between Akt expression and liver fibrosis staging in chronic hepatitis C (CHC) patients. **METHODS:** Paraffin-embedded liver sections from 133 consecutive treatment-naïve CHC patients were recruited. The expression features of Akt were analyzed using immunohistochemical methods and the results were compared with histological, virological and biochemical profiles. **RESULTS:** The 73 patients with high Akt expression carried higher histological activity index scores ( $6.52 \pm 2.5$  vs  $5.62 \pm 2.4$ ,  $P = 0.04$ ) and advanced fibrosis (72.7% vs 26.3%,  $P < 0.01$ ) than other 60 patients with low Akt expression. The high Akt expression showed a significant incremental trend dependent on fibrosis stages, from 33.3% of F0 to 85.7% of F4 ( $P = 0.005$ ). Akt expression was not correlated with degrees of steatosis and virological features of HCV infection, such as viral load and genotypes. Multivariate logistic regression analysis showed advanced fibrosis was the most significant factor associated with high Akt expression (odds ratio = 3.16). **CONCLUSION:** Hepatic Akt expression correlated with advanced liver fibrosis in CHC patients.

**Hepatitis C virus core protein induces fibrogenic actions of hepatic stellate cells via toll-like receptor 2.** Coenen M, Nischalke HD, Krämer B, et al. *Lab Invest*. 2011 May 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21537327>

Hepatic stellate cells (HSCs) represent the main fibrogenic cell type accumulating extracellular matrix in the liver. Recent data suggest that hepatitis C virus (HCV) core protein may directly activate HSCs. Therefore, we examined the influence of recombinant HCV core protein on human HSCs. Primary human HSCs and the human HSC line LX-2 were stimulated with recombinant HCV proteins core and envelope 2 protein. Expression of procollagen type I  $\alpha$ -1,  $\alpha$ -smooth muscle actin, cysteine- and glycine-rich protein 2, glial fibrillary acidic protein, tissue growth factor  $\beta$ 1, matrix metalloproteinases 2 (MMP2) and 13, tissue inhibitor of metalloproteinases 1 and 2 was investigated by real-time PCR. Intracellular signaling pathways of ERK1/2, p38 and, jun-amino-terminal kinase (JNK) were analyzed by western blot analysis. Recombinant HCV core protein induced upregulation of procollagen type I  $\alpha$ -1,  $\alpha$ -smooth muscle actin, MMP 2 and 13, tissue inhibitor of metalloproteinases 1 and 2, tissue growth factor  $\beta$ 1, cysteine- and glycine-rich protein 2, and glial fibrillary acidic protein mRNA expression, whereas HCV envelope 2 protein did not exert any significant effect. Blocking of toll-like receptor 2 (TLR2) with a neutralizing antibody prevented mRNA upregulation by HCV core protein confirming that the TLR2 pathway was involved. Furthermore, western blot analysis revealed HCV-induced phosphorylation of the TLR2-dependent signaling molecules ERK1/2, p38 and JNK mitogen-activated kinases. Our in vitro results demonstrate a direct effect of HCV core protein on activation of HSCs toward a profibrogenic state, which is mediated via the TLR2 pathway. Manipulating the TLR2 pathway may thus provide a new approach for antifibrotic therapies in HCV infection

**Genetic determinants in hepatitis C virus-associated mixed cryoglobulinemia: role of polymorphic variants of BAFF promoter and Fcγ receptors.** Gragnani L, Piluso A, Giannini C, et al. *Arthritis Rheum.* 2011 May;63(5):1446-51. doi: 10.1002/art.30274.

<http://www.ncbi.nlm.nih.gov/pubmed/21538321>

**OBJECTIVE:** Mixed cryoglobulinemia (MC) is a hepatitis C virus (HCV)-related immune complex disorder. Only some HCV-infected patients develop MC, which suggests that the genetic background of the host plays a key role. This study was undertaken to evaluate the contribution of host genetic factors in the pathogenesis of HCV-associated MC (HCV-MC) by analyzing allelic variants of low-affinity Fcγ receptor (FcγR) genes and BAFF promoter.

**METHODS:** FcγR polymorphisms (FCGR2A 131 R/H, FCGR2B 232 I/T, FCGR3A 176 V/F, and FCGR3B NA1/NA2) and BAFF promoter polymorphism -871 C/T were analyzed in 102 patients with HCV-MC and 108 patients with HCV without MC, using polymerase chain reaction-based techniques. **RESULTS:** A higher prevalence of -871 T/T homozygosity (31% versus 16%;  $P = 0.001$ ) and a greater frequency of T alleles of the BAFF promoter (80% versus 57%;  $P = 0.004$ ) were found in the HCV-MC group than in the HCV group. A significant increase in serum BAFF concentration was significantly associated with the higher frequency of the T allele in HCV-MC (mean  $\pm$  SD  $4.12 \pm 1.29$  versus  $2.09 \pm 0.81$  ng/ml;  $P < 0.0005$ ). The distribution of the FcγR genotypes was not significantly different. In the 21 HCV-MC patients treated with rituximab, the response was strictly related to F allele homozygosity (significantly reduced in 5 of 5 patients with the FCGR3A F/F genotype versus 4 of 16 with V/V or V/F;  $P < 0.0005$ ). **CONCLUSION:** These results indicate the importance of host genetic background in the development of HCV-MC, suggesting that mechanisms enhancing Ig production and B cell survival may play a relevant role. Genetic FcγR variants seem to be crucial to the effectiveness of rituximab therapy.

**Distinct Functions of NS5A in HCV RNA Replication Uncovered by Studies with the NS5A Inhibitor BMS-790052.** Fridell RA, Qiu D, Valera L, Wang C, Rose RE, Gao M. *J Virol.* 2011 May 18. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21593143>

BMS-790052, targeting non-structural protein 5A (NS5A), is the most potent hepatitis C virus (HCV) inhibitor described to date. It is highly effective against genotype 1 replicons and also displays robust genotype 1 anti-HCV activity in the clinic (Gao, M., R. E. Nettles, et al., 2010. *Nature* 465:96-100). BMS-790052 inhibits genotype 2a JFH1 replicon cells and cell culture infectious virus with EC(50)s of 46.8 and 16.1 pM, respectively. Resistance selection studies with the JFH1 replicon and virus systems identified drug-induced mutations within the N-terminal region of NS5A. F28S, L31M, C92R and Y93H were the major resistance mutations identified; the impact of these mutations on inhibitor sensitivity was very similar between the replicon and virus. The C92R and Y93H mutations negatively impacted fitness of the JFH1 virus. Second site substitutions at NS5A residue 30 (K30E/Q) restored efficient replication of the C92R viral variant, thus demonstrating a genetic interaction between NS5A residues 30 and 92. By using a trans-complementation assay with JFH1 replicons encoding inhibitor-sensitive and inhibitor-resistant NS5A proteins, we provide genetic evidence that NS5A performs two distinct functions in HCV RNA replication: a cis-acting function that likely occurs as part of the HCV replication complex, and a trans-acting function that may occur outside of the replication complex. The cis-acting function is likely performed by basally phosphorylated NS5A, while the trans-acting function likely requires hyperphosphorylation. Our data indicate that BMS-790052

blocks the cis-acting function of NS5A. Since BMS-790052 also impairs JFH1 NS5A hyperphosphorylation, it likely also blocks the trans-acting function.

**Estimation of inhibitory quotient using a comparative equilibrium dialysis assay for prediction of viral response to hepatitis C virus inhibitors.** Mo H, Yang C, Wang K, et al. *J Viral Hepat.* 2011 May;18(5):338-48. doi: 10.1111/j.1365-2893.2010.01314.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20456634>

The relationship of inhibitory quotient (IQ) with the virologic response to specific inhibitors of human hepatitis C virus (HCV) and the best method to correct for serum protein binding in calculating IQ have not been addressed. A common method is to determine a fold shift by comparing the EC(50) values determined in cell culture in the absence and presence of human serum (fold shift in EC(50) ), but this method has a number of disadvantages. In the present study, the fold shifts in drug concentrations between 100% human plasma (HP) and cell culture medium (CCM) were directly measured using a modified comparative equilibrium dialysis (CED) assay for three HCV protease inhibitors (PIs) and for a novel HCV inhibitor GS-9132. The fold shift values in drug concentration between the HP and CCM (CED ratio) were ~1 for SCH-503034, VX-950 and GS-9132 and 13 for BILN-2061. These values were ~3-10-fold lower than the fold shift values calculated from the EC(50) assay for all inhibitors except BILN-2061. Using the CED values, a consistent pharmacokinetic and pharmacodynamic relationship was observed for the four HCV inhibitors analysed. Specifically, an approximate 1 log(10) reduction in HCV RNA was achieved with an IQ close to 1, while 2-3 and greater log(10) reductions in HCV RNA were achieved with IQ values of 3-5 and greater, respectively. Thus, use of CED to define IQ provides a predictive and quantitative approach for the assessment of the in vivo potency of HCV PIs and GS-9132. This method provides a framework for the evaluation of other classes of drugs that are bound by serum proteins but require the presence of serum for in vitro evaluation.

**Inhibition of full length Hepatitis C Virus particles of 1a genotype through small interference RNA.** Ansar M, Ashfaq UA, Shahid I, et al. *Virology*. 2011 May 2;8:203.

<http://www.ncbi.nlm.nih.gov/pubmed/21535893>

**BACKGROUND:** Hepatitis C virus (HCV), a member of the Flaviviridae family of viruses, is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Currently, the only treatment available consists of a combination of Pegylated interferon alpha (INF- $\alpha$ ) and ribavirin, but only half of the patients treated show a sufficient antiviral response. Thus there is a great need for the development of new treatments for HCV infections. RNA interference (RNAi) represents a new promising approach to develop effective antiviral drugs and has been extremely effective against HCV infection. **RESULTS:** This study was design to assess or explore the silencing effect of small interference RNAs (siRNAs) against full length HCV particles of genotype 1a. In the present study six 21-bp siRNAs were designed against different regions of HCV structural genes (Core, E1 and E2). Selected siRNAs were labeled as Csi 301, Csi 29, E1si 52, E1si 192, E2si 86 and E2si 493. Our results demonstrated that siRNAs directed against HCV core gene showed 70% reduction in viral titer in HCV infected liver cells. Moreover, siRNAs against E1 and E2 envelop genes showed a dramatic reduction in HCV viral RNA, E2si 86 exhibited 93% inhibition, while E1si 192, E2si 493 and E1si 52 showed 87%, 80%, and 66% inhibition respectively. No significant inhibition was detected in cells transfected with the negative control siRNA. **CONCLUSION:** Our results suggested that siRNAs targeted against

HCV structural genes efficiently silence full length HCV particles and provide an effective therapeutic option against HCV infection.

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## HIV/HCV COINFECTION

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**Hepatitis C virus (HCV) treatment uptake and changes in the prevalence of HCV genotypes in HIV/HCV-coinfected patients.** Medrano J, Resino S, Vispo E, et al. *J Viral Hepat.* 2011 May;18(5):325-30. doi: 10.1111/j.1365-2893.2010.01309.x.  
<http://www.ncbi.nlm.nih.gov/pubmed/20456635>

The efficacy of current hepatitis C therapy in HIV/HCV-coinfected patients is largely dependent on HCV genotype. The annual prevalence of HCV genotypes/subtypes and their influence on HCV clearance with antiviral treatment were examined in a dynamic cohort of HIV/HCV-coinfected patients followed up in Madrid since 2000. Patients entered the cohort at first visit and left the cohort when HCV clearance was achieved with HCV therapy or when follow-up was interrupted for any reason, including death. A total of 672 HIV/HCV-coinfected patients constituted the cohort. The mean follow-up time was 5.5 years, corresponding to 4108 patient-years. Mean age at entry was 37 years, and 73% were men and 86% were intravenous drug users. Overall distribution of HCV genotypes was as follows: 57.1% HCV-1 (1a: 29.2%, 1b: 20.4%, unknown: 7.6%), 1.3% HCV-2, 25.4% HCV-3 and 15.9% HCV-4. A total of 274 (40.8%) patients were treated with peginterferon-ribavirin, of whom 116 (42.3%) achieved HCV clearance following 1-3 courses of therapy. The proportion of HCV-1/4 rose from 71.7% in 2000 to 76.8% in 2008, whereas the proportion of HCV-2/3 fell from 28.1% in 2000 to 23.2% in 2008. The yearly prevalence increased for HCV-1 (R(2) : 0.92, b: 0.59, P < 0.001) and HCV-4 (R(2) : 0.77, b: 0.33, P < 0.005) and conversely diminished for HCV-3 (R(2) : 0.94, b: -0.82, P < 0.001). **In summary**, the prevalence of HCV-1 and HCV-4 has increased over the last decade in HIV/HCV-coinfected patients, whereas conversely it has declined for HCV-3, in association with the wider use of HCV therapy (41%) in this population.

**Somatic symptoms and the association between hepatitis C infection and depression in HIV-infected patients.** Yoon JC, Crane PK, Ciechanowski PS, et al. *AIDS Care.* 2011 May 11:1-11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21562994>

Studies of depression and hepatitis C virus (HCV) infection in HIV-infected patients have been contradictory and often not addressed key differences between HCV-infected and uninfected individuals including substance use. This cross-sectional observational study from the University of Washington HIV cohort examined associations between HCV, symptoms, and depression in HIV-infected patients in routine clinical care. Patients completed instruments measuring depression, symptoms, and substance use. We generated depression severity scores and used linear regression to examine the relationship with HCV accounting for demographic and clinical characteristics. We conducted sensitivity analyses in which we removed depression somatic symptom items (e.g., fatigue) from depression scores, and sensitivity analyses in which we also adjusted for nondepression somatic symptom items to examine the role of somatic and nonsomatic symptoms in the association between depression and HCV. Of 764 HIV-infected patients, 160 (21%) were HCV-infected. In adjusted analysis, HCV-infected patients had worse depression severity (p=0.01) even after adjusting for differences in substance use. HCV remained associated with depression severity in secondary analyses that omitted the depression somatic

patient health questionnaire-9 (PHQ-9) items ( $p=0.01$ ). However, when nondepression somatic symptoms were included as covariates in multivariate analyses, HCV was no longer associated with depression ( $p=0.09$ ).

**Low-density lipoprotein receptor genotyping enhances the predictive value of IL28B genotype in HIV/hepatitis C virus-coinfected patients.** Pineda JA, Caruz A, di Lello FA, et al. AIDS. 2011 May 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21572301>

**OBJECTIVE:** The aims of this study were to appraise the predictive value of variations in a single nucleotide polymorphism (SNP) in the low-density lipoprotein receptor (LDLR) gene for sustained virological response (SVR) to pegylated interferon (Peg-IFN) plus ribavirin (RBV), as well as to analyze the relationship between LDLR genotype and other predictors of SVR, particularly IL28B genotype, in patients coinfecting with HIV and hepatitis C virus (HCV).

**METHODS:** 184 HIV/HCV-coinfecting, treatment-naïve patients with chronic HCV infection, who received Peg-IFN plus RBV were included. Variations in the SNP rs14158 and rs12979860 were tested by Taqman PCR assay. **RESULTS:** 28 (38%) patients with rs14158 TT/TC and 61 (55%) with CC ( $p = 0.028$ ) achieved SVR. The rates of SVR in patients with rs14158 TT/TC and with CC harboring HCV 1-4 were 20% and 41% ( $p = 0.020$ ), respectively, and, in those with HCV genotype 2-3, 75% and 84% ( $p = 0.513$ ), respectively. Patients with rs14158 CC showed less commonly plasma HCV-RNA load  $\geq 600000$  IU/mL (57% vs. 71%,  $p = 0.047$ ) and lower likelihood of relapse (13% vs. 30%,  $p = 0.023$ ). In patients with HCV genotype 1-4, the rates of SVR according to the combination of IL28B/LDLR genotypes were: CC/CC = 69%; CC/non-CC: 30%; non-CC/CC: 25%; non-CC/non-CC: 14% ( $p < 0.001$ ).

**CONCLUSIONS:** Variations in rs14158 are associated with SVR to Peg-IFN plus RBV in HIV/HCV-coinfecting patients harboring HCV genotype 1-4. LDLR and IL28B genotypes seem to have a synergistic effect on SVR. The combined use of LDLR and IL28B genotypes in routine clinical practice could enhance the predictive value of IL28B genotype alone.

**Safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B and/or C virus coinfection.** Rockstroh J, Tepller H, Zhao J, et al. HIV Med. 2011 May 22. doi: 10.1111/j.1468-1293.2011.00933.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21599819>

**OBJECTIVE:** The aim was to examine the long-term safety and efficacy of raltegravir in patients with HIV-1 and hepatitis B virus (HBV) and/or hepatitis C virus (HCV) coinfection in three double-blind, randomized, controlled Phase III studies. **METHODS:** In STARTMRK, treatment-naïve patients received raltegravir 400 mg twice a day (bid) or efavirenz 600 mg at bedtime, both with tenofovir/emtricitabine. In BENCHMRK-1 and -2, highly treatment-experienced patients with multi-drug resistant virus and prior treatment failure received raltegravir 400 mg bid or placebo, both with optimized background therapy. Patients with chronic HBV and/or HCV coinfection were enrolled if baseline liver function tests were  $\leq 5$  times the upper limit of normal. HBV infection was defined as HBV surface antigen positivity for all studies; HCV infection was defined as HCV RNA positivity for STARTMRK and HCV antibody positivity for BENCHMRK. **RESULTS:** Hepatitis coinfection was present in 6% (34 of 563) of treatment-naïve patients (4% HBV only, 2% HCV only and 0.2% HBV+HCV) and 16% (114 of 699) of treatment-experienced patients (6% HBV only, 9% HCV only and 1% HBV+HCV). The incidence of drug-related adverse events was similar in raltegravir recipients

with and without hepatitis coinfection in both STARTMRK (50 vs. 47%) and BENCHMRK (34 vs. 38.5%). Grade 2-4 liver enzyme elevations were more frequent in coinfecting vs. mono-infected patients, but were not different between the raltegravir and control groups. At week 96, the proportion of raltegravir recipients with HIV RNA <50 HIV-1 RNA copies/mL was similar between coinfecting and mono-infected patients (93 vs. 90% in STARTMRK; 63 vs. 61% in BENCHMRK). **CONCLUSION:** Raltegravir was generally well tolerated and efficacious up to 96 weeks in HIV-infected patients with HBV/HCV coinfection.

**IL28B gene polymorphisms and viral kinetics in HIV/hepatitis C virus-coinfecting patients treated with pegylated interferon and ribavirin.** Rallón NI, Soriano V, Naggie S, et al. AIDS. 2011 May 15;25(8):1025-33.

<http://www.ncbi.nlm.nih.gov/pubmed/21505315>

**BACKGROUND:** A single nucleotide polymorphism (SNP) upstream of the IL28B gene (rs12979860) predicts sustained virological response (SVR) to peginterferon-ribavirin therapy in chronic hepatitis C patients. There is scarce information regarding the influence of this IL28B SNP on early viral kinetics during therapy, particularly in patients coinfecting with HIV, in whom treatment response is lower than in hepatitis C virus (HCV)-mono-infected patients. **METHODS:** We selected 196 HIV/HCV-coinfecting individuals who had completed a course of peginterferon-ribavirin therapy, and a validated outcome for SVR. Association of IL28B SNPs with rapid, early and end-of-treatment virological responses [rapid virological response (RVR), early virological response (EVR) and end of treatment virological response, respectively] was assessed in univariate and multivariate analyses. **RESULTS:** Rate of SVR in the study population was 54%. Frequency of the IL28B CC genotype was 44%. The distribution of HCV genotypes was as follows: HCV-1 57%, HCV-2 1%, HCV-3 30% and HCV-4 12%. Compared to CT/TT, the CC genotype was associated with significantly higher rates of all on-treatment viral outcomes, after adjusting for other predictors of viral response as serum HCV-RNA, HCV genotype and liver fibrosis staging. IL28B CC genotype kept its predictive power of SVR in patients who did not achieve RVR or cEVR. The association between IL28B SNP and viral kinetics and treatment outcomes was significant only for HCV genotypes 1 and 4. **CONCLUSION:** IL28B CC genotype is a strong predictor of virological response to therapy in HIV/HCV-coinfecting patients. This effect is mediated by an increase in viral clearance during the first 12 weeks of treatment and is mainly seen in patients infected with HCV genotypes 1 and 4.

**Impact of IL28B polymorphisms on response to peginterferon and ribavirin in HIV–hepatitis C virus-coinfecting patients with prior nonresponse or relapse.** Labarga P, Barreiro P, Mira JA, et al. AIDS. 2011 May 15;25(8):1131-3.

<http://www.ncbi.nlm.nih.gov/pubmed/21537116>

IL28B polymorphisms predict treatment response in chronic hepatitis C. However, no information exists in prior treatment failures. A total of 62 HIV/hepatitis C virus (HCV) patients who completed retreatment with peginterferon- $\alpha$ /ribavirin were examined, of whom 25 (40%) had been cured. Predictors of response [odds ratio, OR (95% confidence interval, CI)] were HCV genotypes 2/3 [16.1 (2.7-90.9)], prior relapse [9.6 (1.5-62.4)] and ribavirin plasma trough concentrations at week 4 [4.9 (1.3-18.4)]. IL28B-CC only predicted response in prior nonresponders carrying HCV genotypes 1/4 [25.1 (1.9-337)].

**Treatment of hepatitis C virus (HCV) infection in patients coinfecting with HIV in the HIV Outpatient Study (HOPS), 1999-2007.** Vellozzi C, Buchacz K, Baker R, et al. *J Viral Hepat.* 2011 May;18(5):316-24. doi: 10.1111/j.1365-2893.2010.01299.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20367803>

Liver disease due to hepatitis C virus (HCV) infection is a leading cause of non-AIDS-related morbidity and mortality in patients infected with HIV. We assessed the frequency of and predictors for initiation of treatment for HCV infection among patients coinfecting with HCV/HIV enrolled in the HIV Outpatient Study (HOPS) during 1999-2007. We included patients with confirmed HCV infection, at least 1 year of subsequent follow-up, and no evidence of prior HCV treatment. We assessed predictors of HCV treatment initiation using Cox proportional hazards analyses. During 1999-2007, 103 (20%) HOPS patients coinfecting with HCV/HIV initiated HCV treatment during a median of 4.3 years of follow-up (interquartile range: 2.7, 6.7). In multivariable analysis, non-Hispanic black race/ethnicity (hazard ratio HR] 0.3; 95% confidence interval [CI] = 0.2, 0.6) was independently associated with a lower likelihood of HCV treatment. Elevated alanine aminotransferase (ALT; HR 3.5; 95% CI = 2.2, 5.6) and CD4+ cell count  $\geq$ 500 cells/mm<sup>3</sup> (HR 1.8; 95% CI = 1.2, 2.8) at the start of observation were independently associated with higher likelihood of HCV treatment. For patients starting observation in 1999-2001, 2002-2004 and 2005-2007, 5%, 11% and 21% of patients initiated treatment during the first year of follow-up, respectively. Between 1999 and 2007, despite a stable low fraction of patients coinfecting with HCV/HIV initiating treatment for HCV infection, an increasing proportion initiated treatment within the first year after the infection was confirmed. Treatment of HCV infection in patients coinfecting with HCV/HIV should be considered a priority, given the increased risk of accelerated end-stage liver disease.

**Treatment for hepatitis C virus with pegylated interferon- $\alpha$  plus ribavirin induces anti-atherogenic effects on cardiovascular risk biomarkers in HIV-infected and -uninfected patients.** Masiá M, Robledano C, López N, Escolano C, Gutiérrez F. *J Antimicrob Chemother.* 2011 May 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21622971>

**OBJECTIVES:** We investigated the influence of hepatitis C virus (HCV) therapy with pegylated interferon- $\alpha$  plus ribavirin on cardiovascular disease risk through the serial measurement of several laboratory markers in HCV-monoinfected and HCV/HIV-coinfecting patients. **METHODS:** In a longitudinal study, biomarkers of inflammation, coagulation and oxidative stress were measured during and after therapy. **RESULTS:** A total of 56 patients were included; 32 (57.1%) were HCV/HIV coinfecting and 24 (42.9%) were HCV monoinfected. Compared with baseline, during HCV therapy there was a significant decrease in the concentrations of matrix metalloproteinase-9 ( $P < 0.001$ ), intercellular cell adhesion molecule-1 (ICAM-1) ( $P \leq 0.01$ ) and oxidized low-density lipoproteins ( $P = 0.002$ ). In contrast, levels of vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 and fibrinogen increased during treatment. After treatment discontinuation, levels of ICAM-1, VCAM-1 and tumour necrosis factor- $\alpha$  were significantly lower compared with baseline, a change restricted to patients with sustained virological response. Decreases in transaminases and HCV-RNA from baseline correlated positively with the decrease in ICAM-1 concentration 6 months after treatment discontinuation. Changes in biomarkers were similar in HIV-infected and -uninfected patients. **CONCLUSIONS:** Treatment for HCV induces different changes in several cardiovascular risk biomarkers, most being anti-atherogenic effects, although only the anti-

atherogenic effects remain after treatment discontinuation in patients with sustained virological response.

**Correlation between FIB4, liver stiffness and metabolic parameters in patients with HIV and hepatitis C virus co-infection.** Bruno R, Sacchi P, Cima S, et al. Dig Liver Dis. 2011 Jul;43(7):575-8. Epub 2011 May 19.

<http://www.ncbi.nlm.nih.gov/pubmed/21596630>

**BACKGROUND/AIMS:** Assessment of liver fibrosis is crucial in HIV/HCV coinfecting patients, in whom metabolic disturbances are frequent. Aims of this study were to analyse the association of two non-invasive liver fibrosis evaluation methods, liver stiffness measurement and FIB4, and their correlation with metabolic parameters. **METHODS:** This was a single centre cross-sectional study. All patients underwent biochemical and virological assessment, FIB4 score, HOMA and transient elastography. **RESULTS:** Seventy-five patients were evaluated. Liver stiffness values positively correlated with FIB4 ( $R=0.62$ ;  $p<0.0001$ ). By ROC curve analysis the optimal cut-off for liver stiffness to identify high FIB4 was calculated as 10.1kPa. The area under the ROC curve was 0.78 (95%CI 0.78-0.94, sensitivity 83.3%, specificity 80.7%). Liver stiffness values positively correlated with HOMA score ( $R=0.31$ ;  $p=0.006$ ). **CONCLUSIONS:** The combination of two non invasive tools provide a useful system for the assessment of fibrosis evolution in patients with HIV-HCV coinfection.

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#### EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

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**Irritability: an underappreciated side effect of interferon treatment for chronic hepatitis C?** Blacklaws H, Gardner A, Usher K. J Clin Nurs. 2011 May;20(9-10):1215-24. doi: 10.1111/j.1365-2702.2010.03494.x. Epub 2011 Mar 3.

<http://www.ncbi.nlm.nih.gov/pubmed/21371144>

**AIM AND OBJECTIVES:** The research literature was reviewed with the aim of answering the question 'is irritability an underappreciated side effect of interferon and ribavirin treatment for hepatitis C'. **BACKGROUND:** The majority of information regarding interferon treatment identifies depression as the main psychological side effect. However, clinical observation and patient reports suggest that irritability, not depression, is the predominant side effect. **DESIGN:** The literature review included research and discussion papers. Data bases were searched using the keywords interferon and hepatitis C in combination with one of the following: side effects, depression, mood alteration/change, irritability, anger, impulse control, psychiatric side effects or neuropsychiatric side effects. **RESULTS:** The review revealed a gap in the literature regarding interferon-related irritability. Whereas depression was well researched and described, irritability was afforded little research time. However, where irritability was assessed, it was found to occur to a significant degree. Issues identified were difficulty defining and categorising irritability; lack of irritability-specific assessment tools and failure of depression rating scales to adequately discern irritable mood; and the confounding effect of physiological side effects on mood alteration. Relevance to clinical practice. Underappreciation and underrecognition of irritability have implications for clinical practice. Good research is the foundation for evidence-based practice; therefore, the possibility exists that, based on current research evidence, patients may not be receiving a standard care that adequately addresses the entirety of the side effect spectrum. **CONCLUSION:** Irritability is an underappreciated psychological side effect of interferon therapy. Although irritability is recognised as a side effect of interferon, there is considerable

discordance between clinical observation, patient reports and research evidence as reported in the literature.

**Partnering urban academic medical centers and rural primary care clinicians to provide complex chronic disease care.** Arora S, Kalishman S, Dion D, et al. *Health Aff (Millwood)*. 2011 Jun;30(6):1176-84. Epub 2011 May 19.

<http://www.ncbi.nlm.nih.gov/pubmed/21596757>

Many of the estimated thirty-two million Americans expected to gain coverage under the Affordable Care Act are likely to have high levels of unmet need because of various chronic illnesses and to live in areas that are already underserved. In New Mexico an innovative new model of health care education and delivery known as Project ECHO (Extension for Community Healthcare Outcomes) provides high-quality primary and specialty care to a comparable population. Using state-of-the-art telehealth technology and case-based learning, Project ECHO enables specialists at the University of New Mexico Health Sciences Center to partner with primary care clinicians in underserved areas to deliver complex specialty care to patients with hepatitis C, asthma, diabetes, HIV/AIDS, pediatric obesity, chronic pain, substance use disorders, rheumatoid arthritis, cardiovascular conditions, and mental illness. As of March 2011, 298 Project ECHO teams across New Mexico have collaborated on more than 10,000 specialty care consultations for hepatitis C and other chronic diseases.

**Immunological/virological peripheral blood biomarkers and distinct patterns of sleeping quality in chronic hepatitis C patients.** de Almeida CM, de Lima TA, Castro DB, et al. *Scand J Immunol*. 2011 May;73(5):486-95. doi: 10.1111/j.1365-3083.2011.02518.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21231952>

The rationale of this study we intended to investigate whether the peripheral blood immunological/virological biomarkers were associated with distinct patterns of sleeping quality in patients with chronic hepatitis C (HCV). Distinct well-established indexes/scores were used to categorize the sleeping quality of HCV patients, including the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale and Fatigue Severity Scores. Our findings demonstrated that HCV patients classified as 'good sleeper' displayed an enhanced frequency of circulating CD8(+) T cells, lower frequency of activated (CD69(+)) neutrophils and eosinophils but enhanced frequency of activated lymphocytes besides lower seric levels of IL-4/IL-8/IL-10 but higher levels of IL-12, besides lower HCV virus load and lower anti-HCV IgG levels. In contrast, HCV patients classified as 'poor sleeper' displayed enhanced levels of activated neutrophils and eosinophils but lower frequency of activated lymphocytes, higher seric levels of IL-6/TNF- $\alpha$ /IL-10 but lower levels of IL-12 besides higher HCV virus load and increased anti-HCV IgG levels. Positive correlation was further confirmed by the relationship between the leucocyte activation status, the cytokine levels, the HCV viral load and the anti-HCV IgG reactivity with the PSQI indexes. Analysis of cytokine signature curves demonstrated that lower frequency of IL-10 was observed in HCV patients classified as 'good sleepers', whereas enhanced frequency of IL-6 was found HCV patients classified as 'poor sleepers'. **In conclusion**, our data suggest that immunological biomarkers (leucocytes activation status and seric cytokines levels) are likely to be associated with sleeping quality patterns in HCV patients, suggesting their putative use for clinical monitoring purposes.

**Current strategies for managing providers infected with bloodborne pathogens.** Turkel S, Henderson DK. *Infect Control Hosp Epidemiol.* 2011 May;32(5):428-34.

<http://www.ncbi.nlm.nih.gov/pubmed/21515972>

**BACKGROUND:** In 1991 the Centers for Disease Control and Prevention issued guidelines to reduce risks for provider-to-patient transmission of bloodborne pathogens. These guidelines, unchanged since 1991, recommend management strategies for hepatitis B e antigen-positive providers and for providers infected with human immunodeficiency virus; they do not address hepatitis C virus (HCV)-infected providers. **OBJECTIVE:** We summarized current state practices and surveyed state health departments to determine (1) whether state policies have been modified since 1991; (2) whether state laws require prospective notification of patients and/or expert review panels to manage infected providers; (3) the frequency with which infected-providers issues come to the attention of state health departments; and (4) how state health departments intervene. **METHODS:** We reviewed the 50 states' laws and guidelines to determine current practices and conducted a structured telephone survey of all state health departments. **RESULTS:** Whereas only 19 states require infected providers to notify patients of the providers' bloodborne pathogen infection, these 19 states require notification under highly varied circumstances. Only 10 of 50 state health department officials identified these issues as requiring significant departmental effort. No state law or guideline incorporates information about providers' viral burdens as part of the risk assessment. Only 3 of 50 states have modified policies or laws since initial passage, and only 1 of 50 discusses the management of HCV-infected providers. **CONCLUSIONS:** These results identify a need for incorporating contemporary scientific information into guidelines and also suggest that infected-provider issues are not occurring commonly, are not being detected, or are being managed at levels below the state health department.

**Electronic matching of HIV/AIDS and hepatitis C surveillance registries in three states.**

Speers S, Kleven RM, Vonderwahl C, et al. *Public Health Rep.* 2011 May-Jun;126(3):344-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21553662>

**OBJECTIVES:** Both HIV and hepatitis C virus (HCV) can be transmitted through percutaneous exposure to blood in similar high-risk populations. HCV and HIV/AIDS surveillance databases were matched in Colorado, Connecticut, and Oregon to measure the frequency of co-infection and to characterize coinfecting people. **METHODS:** We defined a case of HCV infection as a person with a reactive antibody for hepatitis C, medical diagnosis, positive viral-load test result, or positive genotype reported to any of three state health departments from the start of each state's hepatitis C registry through June 30, 2008. We defined a case of HIV/AIDS as a person diagnosed and living with HIV/AIDS at the start of each state's respective hepatitis C registry through June 30, 2008. HIV/AIDS and hepatitis C datasets were matched using Link King, public domain record linkage and consolidation software, and all potential matches were manually reviewed before acceptance as a match. **RESULTS:** The proportion of reported hepatitis C cases co-infected with HIV/AIDS was 1.8% in Oregon, 1.9% in Colorado, and 4.9% in Connecticut. Conversely, the proportion of HIV/AIDS cases co-infected with hepatitis C was consistently higher in the three states: 4.4% in Oregon, 9.7% in Colorado, and 23.6% in Connecticut. **CONCLUSIONS:** Electronic matching of registries is a potentially useful and efficient way to transfer information from one registry to another. In addition, it can provide a measure of the public health burden of HIV/AIDS and hepatitis C co-infection and provide insight into prevention and medical care needs for respective states.

**Breaking Bad News: The Patient's Viewpoint.** Munoz Sastre MT, Sorum PC, Mullet E. Health Commun. 2011 May 17:1-7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21598151>

The objective of this study was to ascertain how patients judge the acceptability of physicians' communication of bad news. Two hundred forty-five adults, who had in the past received bad medical news, indicated the acceptability of physicians' conduct in 48 vignettes of giving bad news to patients. Vignettes were all combinations of five factors: level of bad news (infection with hepatitis C, cirrhosis of the liver, or liver cancer); request or not to the patient to come with spouse or partner; attempt or not by the physician to find out the patient's expectations about the test results; presence or absence of emotional supportiveness; and provision or not of complete and understandable information. In addition, nine physicians rated the same vignettes. Quality of information and emotional supportiveness explained more than 95% of the variance in patients' acceptability judgments, while the degree of badness of the news had no impact. In addition, for patients, low emotional supportiveness could not be fully compensated by high quality of information, nor the inverse. Physicians, in contrast, responded as if such compensations were possible. Physicians must appreciate that patients expect high levels of both empathy and information quality, no matter how bad the news.

**Hepatitis C virus infection among adolescents and young adults --- Massachusetts, 2002--2009.** Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2011 May 6;60(17):537-41.

<http://www.ncbi.nlm.nih.gov/pubmed/21544042>

Hepatitis C virus (HCV) infection is a major cause of liver disease and hepatocellular carcinoma in the United States. Of the estimated 2.7--3.9 million persons with active HCV infection, most were born during 1945--1964 and likely were infected during the 1970s and 1980s, before the advent of prevention measures. Nationwide, rates of acute, symptomatic HCV infection declined during 1992--2005 and then began to level. Declines also were observed in rates of newly reported HCV infection in Massachusetts. Although these declines were evident among reported cases overall in Massachusetts during 2002--2006, an increase was observed among cases in the 15--24 year age group. In response to this increase, the Massachusetts Department of Public Health (MDPH) launched a surveillance initiative to collect more detailed information on cases reported during 2007--2009 among this younger age group and to examine the data for trends through 2009. This report describes results of both efforts, which revealed continued increases in rates of newly reported HCV infection among persons aged 15--24 years. These cases were reported from all areas of the state, occurred predominantly among non-Hispanic white persons, and were equally distributed among males and females. Of cases with available risk data, injection drug use (IDU) was the most common risk factor for HCV transmission. The increase in case reports appears to represent an epidemic of HCV infection related to IDU among new populations of adolescents and young adults in Massachusetts. The findings indicate the need for enhanced surveillance of HCV infection and intensified hepatitis C prevention efforts targeting adolescents and young adults.

**Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy.** Hung CH, Lee CM, Wang JH, Hu TH, Chen CH, Lin CY, Lu SN. *Int J Cancer*. 2011 May 15;128(10):2344-52. doi: 10.1002/ijc.25585.

<http://www.ncbi.nlm.nih.gov/pubmed/20669224>

There is strong evidence linking chronic hepatitis C virus (HCV) infection and Type 2 diabetes mellitus (DM). Recent studies have suggested that DM is associated with increased risk of developing hepatocellular carcinoma (HCC). The aim of our cohort study was to assess whether DM influence the incidence of HCC in chronic hepatitis C patients treated with interferon (IFN)-based antiviral therapy. A total of 1,470 chronic hepatitis C patients treated with IFN or pegylated-IFN plus ribavirin therapy were enrolled. Of them, 253 (17%) patients had DM at entry. Evaluation of HCC incidence was performed by Kaplan-Meier method and Cox proportional hazards analysis. Patients with baseline DM were significantly older and had higher body mass index, serum transaminase levels and fibrosis scores and lower platelet counts compared to non-DM subjects. Sustained virological response (SVR) was achieved in 160 (63%) of DM and 867 (71%) of non-DM patients ( $p = 0.008$ ). During a median follow-up period of 4.3 years, HCC developed in 21 (8.3%) of DM and 66 (5.4%) of non-DM patients ( $p = 0.017$ ). However, DM was not an independent covariate by Cox proportional hazards analysis. In a subgroup analysis, DM (hazard ratio, 4.32; 95% confidence interval, 1.23-15.25;  $p = 0.023$ ) was an independent predictor of HCC in the SVR patients without baseline cirrhosis, despite a low HCC incidence. **In conclusion**, DM has a selective impact on HCC development among chronic hepatitis C patients after IFN-based therapy. DM may increase the HCC risk in chronic hepatitis C without cirrhosis after eradication of HCV.

**Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era.** Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H, Maehara Y. *World J Surg*. 2011 May;35(5):1072-84. <http://www.ncbi.nlm.nih.gov/pubmed/21468888>

**BACKGROUND:** The present study was conducted to clarify the causes of recent improvement of outcomes after hepatectomy in patients with hepatitis C (HC)-related hepatocellular carcinoma (HCC). **METHODS:** From 1990 to 2006, 323 curative liver resections for HC-HCC were performed in our department. The patients were divided into two groups: early period (1990-1999:  $n=221$ ) and the late period (2000-2006:  $n=102$ ). Prognostic factors were determined to clarify the cause of the survival improvement in the modern era. **RESULTS:** The overall survival rates for the patients in the early and late periods were 54.9 and 70.3% at 5 years, respectively ( $P=0.0005$ ). There was no difference in the recurrence-free survival rates between the two groups, although both survival without recurrence ( $P=0.0003$ ) and survival after recurrence ( $P=0.0063$ ) were significantly better in the late period than in the early period. Patients with better liver function, patients with interferon (IFN) therapy and patients with subsegmentectomy were selected more frequently, and the incidence of blood transfusion was decreased in the late period below the level recorded in the early period. For recurrent HCC, lipiodolization decreased and local ablation therapy increased in the late period. The independent prognostic factors for overall survival were preoperative serum levels of albumin and alanine aminotransferase, histological liver cirrhosis, tumor size, intrahepatic metastasis, histological

grade, blood transfusion, and IFN therapy. **CONCLUSIONS:** In HC-HCC, survival was improved in the late period of the present study. Selection of patients with good liver function, no blood transfusion with reduction of blood loss, anti-hepatitis C virus therapy with IFN, and introduction of local ablation therapy for HCC recurrence may be related to the improved survival.

**Risk factors for hepatocellular carcinoma in a cohort infected with hepatitis B or hepatitis**

**C.** Walter SR, Thein HH, Gidding HF, Amin J, Law MG, George J, Dore GJ. *J Gastroenterol Hepatol.* 2011 May 26. doi: 10.1111/j.1440-1746.2011.06785.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21615789>

**BACKGROUND AND AIM:** The incidence of hepatocellular carcinoma (HCC) has increased in Australia in recent decades, a large and growing proportion of which occurs among a population chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). However, risk factors for HCC among these high-risk groups require further characterisation.

**METHODS:** We conducted a population based cohort study using HBV and HCV cases notified to the New South Wales (NSW) Health Department between 2000 and 2007. These were linked to cause of death data, HIV/AIDS notifications and hospital records. Proportional hazards regression was used to identify significant risk factors for developing HCC. **RESULTS:** Two-hundred and forty-two and 339 HCC cases linked to HBV (n = 43,892) and HCV (n = 83,817) notifications, respectively. For both HBV and HCV groups, being male and increasing age were significantly associated with risk of HCC. Increasing comorbidity score indicated high risk while living outside urban areas was associated with lower risk. Hazard ratios for males were two to three times those of females. For both HBV and HCV groups, cirrhosis, alcoholic liver disease and the interaction between the two were associated with significantly and considerably elevated risk. **CONCLUSION:** This large population-based study confirms known risk factors for HCC. The association with older age highlights the potential impact of HBV and HCV screening of at-risk groups and early clinical assessment. Additional research is required to evaluate the impact of improving antiviral therapy on HCC risk.