Insulin resistance is associated with liver fibrosis in non-diabetic chronic hepatitis C patients.

J Hepatol. 2005 Jan; 42(1):41-6.
Muzzi A, Leandro G, Rubbia-Brandt L, James R, Keiser O, Malinverni R, Dufour JF, Helbling B, Hadengue A, Gonvers JJ, Mullhaupt B, Cerny A, Mondelli MU, Negro F; Swiss Hepatitis C Cohort Study.

Background/Aims: Liver steatosis is a frequent finding in chronic hepatitis C. An association has been suggested between steatosis and fibrosis progression rate, but the pathogenetic mechanisms linking fatty infiltration and collagen deposition are unknown.
Methods: We measured the levels of insulin resistance (as HOMA score) and leptin in 221 non-diabetic chronic hepatitis C patients, to assess their impact on liver steatosis and fibrosis, relative to other factors, using a multivariable logistic regression.
Results: When all 221 patients were considered, steatosis was associated with excessive alcohol intake, genotype 3, and serum HCV RNA level, whereas fibrosis was associated with HOMA score and age. In 152 patients infected with genotype non-3, steatosis was associated with alcohol abuse and HCV RNA level, and fibrosis with HOMA score and age. In the 69 patients with genotype 3, steatosis and fibrosis were associated with each other. The association between fibrosis and HOMA score held also when 22 obese patients were excluded from the analysis. Levels of insulin resistance were not correlated with the presence of steatosis.
Conclusions: Thus, insulin resistance (but not leptin) may play a role in fibrogenesis in chronic hepatitis C patients infected with genotype non-3.

Hepatitis newswire in February 2005

Vaccinations for waste-handling workers. A review of the literature.

Waste Manag Res. 2005 Feb; 23(1):79-86.
Tooher R, Griffin T, Shute E, Maddern G.

A review of the literature relating to the need for vaccination against infectious disease in the solid waste industry was conducted, focusing on hepatitis A, hepatitis B and tetanus. Databases (Medline, PreMedline, EMBASE, CINAHL, Current Contents, Cochrane Database, HTA Database, DARE, OSHROM) were searched up to and including August 2003. Articles were included in the review if they reported the prevalence of immunity to hepatitis A, hepatitis B or tetanus in solid waste workers or the incidence of clinical infection with any of these diseases. Papers about hazardous or medical waste, incineration or other infectious diseases were excluded. Forty-four papers constituted the evidence database. Only one paper studied the prevalence of antibodies to hepatitis A and hepatitis B in solid waste workers compared with sewage plant workers and office workers, and no difference was found between these groups of workers. There was some evidence to support a theoretical risk of infection with hepatitis A, B and tetanus; however, no studies could be found of the risk of these diseases in solid waste workers. No single cases of these diseases being acquired occupationally in solid waste management were identified in the literature. Workers in the solid waste industry may theoretically be at increased risk of acquiring infectious diseases occupationally. However, at present no studies could be found which have documented this risk.

Histological changes in the liver of morbidly obese patients: correlation with metabolic parameters.

Obes Surg. 2005 Feb; 15(2):228-37.
Wolf AM, Busch B, Kuhlmann HW, Beisiegel U.

Background: Obesity is a major risk factor for fatty liver disease. The purpose of this study was: 1) to determine the degree of steatosis, inflammation and fibrosis in liver biopsies of morbidly obese patients in relation to their body fat distribution and metabolic status, and 2) to examine the course of liver enzyme changes with surgically-induced weight loss.
Methods: The study population included 179 morbidly obese bariatric surgical patients (82% female, 18% male, mean age 39+/-0.7 (SEM) years, BMI 52+/-0.6 kg/m(2), excess body weight 80+/-1.8 kg). All patients tested negative for hepatitis and HIV. Liver biopsies were taken intra-operatively. Hepatic enzyme activities were measured along with lipid parameters, fasting glucose, insulin and leptin.
Results: Liver biopsies showed that 47% of morbidly obese females and 85% of males had >30% of hepatocytes filled with fat droplets. Clinically significant hepatic steatosis was associated ($P<0.01$) with: a) metabolic aberrations, i.e.hyperlipidemia, hyperglycemia, b) male gender, c) abdominal adiposity, and d) elevated hepatic aminotransferase activities. Hepatic inflammation was found in 47% of females and 55% of males, and 'moderate' fibrosis occurred in 12% of males and 6% of females. Postoperatively, the activity of hepatic aminotransferases declined after an initial increase in response to weight loss, with normalization of values occurring at an excess weight loss of 50% ($P<0.0001$).
Conclusion: The majority of morbidly obese patients have >30% steatosis of the liver. The incidence of steatosis is higher for males than females, possibly due to their visceral obesity and associated metabolic aberrations.

Triple antiviral therapy with amantadine for IFN-Ribavirin nonresponders with recurrent posttransplantation hepatitis C.

Transplantation. 2005 Feb 15; 79(3):325-9.
Bizollon T, Adham M, Pradat P, Chevallier M, Ducerf C, Baulieux J, Zoulim F, Trepo C.

Background: HCV reinfection after liver transplantation is universal and has an accelerated course with a high risk of progression to cirrhosis. It is now established that combination therapy with interferon (IFN) alpha and ribavirin may achieve a sustained virological response in 20% of transplanted patients. However, the optimal therapy for nonresponders remains an unresolved issue. We conducted a pilot study to determine the efficacy and safety of triple antiviral therapy in IFN-ribavirin nonresponders with recurrent chronic hepatitis C.
Methods: Twenty-four nonresponders to the IFN-ribavirin combination were enrolled in this pilot study. Patients were treated with IFN-alpha (3 million units three times a week subcutaneously with ribavirin [800-1,000 mg daily]) and amantadine 200 mg daily for 48 weeks. The primary end point was the loss of HCV RNA 6 months after the end of treatment.
Results: Median age was 50 years; 72% were men and 82% had genotype 1. The median interval between the end of combination therapy and enrollment was 11 months. Twenty-four patients started therapy, but five (21%) withdrew due to side effects, including two with anemia.On an intent-to-treat basis, 18 patients (75%) had a biochemical response and 9 (37%) had a virologic response at the end of triple antiviral therapy. Eight of these nine patients (33%) had a sustained virological response. The mean METAVIR score improved from A 2.2 F2.1 before treatment to A

1.2 F1.9 in sustained virological responders. In virological nonresponders, inflammatory activity did not change, but fibrosis worsened. Several patients required treatment with erythropoietin for anemia. Triple therapy was well tolerated and neither increased the frequency nor severity of side effects.
Conclusion: Our results show that triple antiviral therapy for 48 weeks induced a sustained virological response in 33% of IFN-ribavirin nonresponders with recurrent hepatitis C.

Immunomodulating and anti-apoptotic action of ursodeoxycholic acid: where are we and where should we go?

European Journal of Gastroenterology & Hepatology. 17(2):137-140, February 2005.
Bellentani, Stefano

Ursodeoxycholic acid (UDCA) is currently used in clinical practice worldwide not only for the dissolution of cholesterol gallstones, but also, mainly, to treat patients with chronic cholestatic liver diseases. However, the mechanisms of action of UDCA at the hepatocyte and cholangiolyte levels are still not completely understood. Much progress has been made from the first concept that the only mechanism of action of this bile acid was its choleretic action. One of the most fascinating mechanisms of action that was evoked for UDCA is its immunomodulating and anti-apoptotic action, which could, in part, be explained by its interaction with the glucocorticoid nuclear receptor at the hepatocyte level. Glucocorticoids, whose prototype is dexamethasone, are the major ligands of the glucocorticoid receptor. The biological effects of glucocorticoids are driven by a multiple-step reaction including binding of the steroid to the glucocorticoid receptor, DNA binding, receptor transformation, nuclear translocation and either positive or negative gene transactivation. In this issue of the journal, Weitzel and co-workers clearly demonstrated that the binding of UDCA to the glucocorticoid receptor is unspecific. Therefore, the anti-inflammatory, cytoprotective and anti-apoptotic actions of UDCA should be due not only to the mild interaction with the glucocorticoid receptor, but also to transactivation or transrepression of different cytoplasmic proteins that are involved in the survival pathway.

Liver steatosis is an independent risk factor for treatment failure in patients with chronic hepatitis C.

Eur J Gastroenterol Hepatol. 2005 Feb;17(2):149-53.
Thomopoulos KC, Theocharis GJ, Tsamantas AC, Siagris D, Dimitropoulou D, Gogos CA, Labropoulou-Karatza C.

Objectives: Hepatic steatosis is a common feature of chronic hepatitis C. The purpose of this study was to determine factors related to the presence of steatosis and to define the role of steatosis in the response to antiviral treatment in chronic hepatitis C patients.
Methods: We retrospectively analyzed all patients with chronic hepatitis C treated in a 5 year period in our department. Patients were included in the study only if a pretreatment liver biopsy specimen was available for evaluation. All patients treated either with interferon in combination with ribavirin, or with pegylated interferon in combination with ribavirin were included irrespectively of their response (early, end of treatment and/or sustained) to antiviral therapy.
Results: A total of 116 patients with chronic hepatitis C were included in the study with a mean age of 45.5+/-14.1 years. Steatosis was present in 52 patients (44.8%). On univariate analysis age, P=0.04 and body mass index >/=25, P=0.004 were correlated with the presence of steatosis and on multivariate analysis only body mass index >/=25, P=0.032. Advanced fibrosis was not found associated with steatosis. Sixty patients out of 116 (51.7%) had sustained virological response (SVR). In particular 42 out of 64 patients with no steatosis (65.6%) had SVR compared to 20 out of 52 patients (38.4%) with any degree of steatosis (P=0.009). Patients with genotype 2 or 3 had a more favourable outcome compared to patients with 1 or 4 genotypes, 63.2% vs 49.2%, P=0.032. Also increased age (P=0.0001), gamma glutamyltransferase (GGT) (P=0.029), no history of intravenous drugs use (P=0.001) and advanced fibrosis on pretreatment biopsy (P=0.046) were correlated with treatment failure. On multivariate analysis significant independent association with SVR was found with the presence of steatosis on pretreatment biopsy (P=0.004), increased GGT (P=0.005) and genotype (P=0.017).
Conclusion: antiviral treatment was found to be associated only to the body mass index of the patients and to be a strong independent factor for treatment failure.

A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors.

Transfusion. 2005 Feb; 45(2):254-64.
Busch MP, Glynn SA, Stramer SL, Strong DM, Caglioti S, Wright DJ, Pappalardo B, Kleinman SH; NHLBI-REDS NAT Study Group.

Background: Estimates for human immunodeficiency virus (HIV)-1 and hepatitis C virus (HCV) transfusion-transmitted risks have relied on incidence derived from repeat donor histories and imprecise estimates for infectious, preseroconversion window periods (WPs).
Study Design and Methods: By use of novel approaches, WPs were estimated by back-extrapolation of acute viral replication dynamics. Incidence was derived from the yield of viremic, antibody-negative donations detected by routine minipool nucleic acid testing (MP-NAT) of 37 million US donations (1999-2002) or from sensitive/less-sensitive HIV-1 enzyme immunoassay (S/LS-EIA) results for seropositive samples from 6.5 million donations (1999). Incidences and WPs were combined to calculate risks and project yield of individual donation (ID)-NAT.
Results: The HIV-1 WP from presumed infectivity (1 copy/20 mL) to ID-NAT detection was estimated at 5.6 days, and the periods from ID to MP-NAT detection and from MP-NAT to p24 detection at 3.4 and 6.0 days, respectively; corresponding estimates for HCV were 4.9, 2.5, and 50.9 days (the latter represents period from MP-NAT to HCV antibody detection). The HIV-1 incidence projected from MP-NAT yield or from S/LS-EIA data was 1.8 per 100,000 person-years, resulting in a corresponding HIV-1 transfusion-transmitted risk of 1 in 2.3 million. The HCV incidence from MP-NAT yield was 2.70 per 100,000 person-years with a corresponding risk of 1 in 1.8 million donations. Conversion from MP-NAT to ID-NAT was projected to detect two to three additional HIV-1 and HCV infectious units annually.
Conclusions: MP-NAT yield and S/LS-EIA rates can accurately project transfusion risks. HCV and HIV-1 risks, currently estimated at 1 per 2 million units, could be reduced to 1 in 3 to 4 million units by ID-NAT screening.

Autoimmune hazards of hepatitis B vaccine.

Autoimmun Rev. 2005 Feb; 4(2):96-100.
Girard M.

According to Hippocratic tradition, the safety level of a preventive medicine must be very high, as it is aimed at protecting people against diseases that they may not contract. This paper points out that information on the safety of hepatitis B vaccine (HBV) is biased as compared to classical requirements of evidence-based medicine (EBM), as exemplified by a documented selectivity in the presentation or even publication of available clinical or epidemiological data. Then, a review is made of data suggesting that HBV is remarkable by the frequency, the severity and the variety of its complications, some of them probably related to a mechanism of molecular mimicry leading to demyelinating diseases, and the others reproducing the spectrum of non-hepatic manifestations of natural hepatitis B. To be explained, this unusual spectrum of toxicity requires additional investigations based upon complete release of available data.

"Strong reasons make strong actions" - The antiviral efficacy of NS3/4A protease inhibitors.

Hepatology. 2005 Feb 18; 41(3):671-4.
Lemon SM, Yi M, Li K.

Background: Novel, potent and well-tolerated hepatitis C (HCV) drugs are still needed. BILN 2061 is a potent and specific inhibitor of HCV serine protease in vitro. Pre-clinical toxicology data and studies in healthy volunteers supported the administration of BILN 2061 to patients with HCV infection.
Methods: The antiviral efficacy, pharmacokinetics and tolerability of 25, 200 and 500 mg bid BILN 2061 given as monotherapy for two days in 31 patients infected with chronic genotype 1 HCV infection and with minimal liver fibrosis (Ishak score 0-2) were assessed in a placebo controlled double blind pilot study. In two, subsequent, placebo controlled studies of similar design, 200 mg bid BILN 2061 was administered for two days to 10 patients with advanced liver fibrosis (Ishak score 3-4) and to 10 patients with compensated cirrhosis (Ishak 5-6).
Results: Viral RNA reductions of 2-3 log10 copies/mL were achieved in most of the patients. There was a trend towards a higher number of patients receiving 500 mg BILN 2061 achieving a viral RNA reduction >3 log10 copies/mL as compared to patients receiving 25 mg BILN 2061. Advanced fibrosis or compensated cirrhosis did not affect the antiviral efficacy of BILN 2061. BILN 2061 was well tolerated in all studies.
Conclusions: BILN 2061 is a well tolerated and very active compound, which reduced serum viral RNA concentrations after two days of treatment in patients infected with genotype 1 HCV independent from the degree of fibrosis. Nevertheless further clinical trials are on hold pending resolution of animal toxicity issues.

Hepatitis C virus genotype distribution in China: Predominance of closely related subtype 1b isolates and existence of new genotype 6 variants.

J Med Virol. 2005 Feb 15; 75(4):538-49.
Lu L, Nakano T, He Y, Fu Y, Hagedorn CH, Robertson BH.

To determine hepatitis C virus (HCV) genotype distribution in China, a total of 148 HCV RNA positive serum samples were collected from nine geographic areas and subjected to RT-PCR followed by direct DNA sequencing and phylogenetic analysis of the core, E1, and NS5B regions. HCV was genotyped in 139 (93.9%) samples. Among them subtype 1b was the most predominant [66% (92/139)] followed by 2a [14% (19/139)]. Of 92 subtype 1b isolates, 35 (38%) and 30 (33%) formed two clusters, designated groups A and B. Group A was prevalent throughout China, while group B was predominant in the central and southern regions. In three cities in the Pearl River Delta, subtype 6a replaced 2a as the second most predominant subtype, and in Kunming (southwest) multiple HCV genotypes/subtypes were present. New variants of HCV genotype 6 were discovered in three samples from Kunming and one in Guangzhou in the Pearl River Delta.

Significance of hepatitis B core antibody as the only marker of hepatitis B infection.

Enferm Infecc Microbiol Clin. 2005 Feb; 23(2):80-5.
Colomina-Rodriguez J, Gonzalez-Garcia D, Burgos-Teruel A, Fernandez-Lorenz N, Guerrero-Espejo A.

Introduction: Little is known about the clinical significance of the "anti-HBc alone" serological profile (absence of HBsAg and anti-HBs) in HBV infections. The objective of the present study was to estimate the prevalence of the anti-HBc alone immunological profile and the clinical-epidemiological characteristics of patients with this profile.
Methods: Prospective, cross-sectional, descriptive study performed in 2002 and including patients with anti-HBc alone (HBsAg-negative, anti-HBs-negative and anti-HBc-positive). All the cases identified underwent the following microbiological tests: IgM anti-HBc, HBeAg, anti-HBe, anti-HDV, anti-HCV, anti-HIV, as well as HBV-DNA testing by qualitative nested-PCR. Furthermore, studies of serum biochemical parameters, blood counts and coagulation, as well as a clinical-epidemiological interview were performed in all patients.
Results: Among 3900 patients studied, 195 (5%) presented the anti-HBc alone profile (48% were > 65 years old). Residual anti-HBs (< 10 mUI/mL) was found in 44% of cases and 33% were anti-HBe positive. HCV or HIV coinfection were seen in 38% and 8%, respectively. HBV-DNA was detected in 4.2% (5/120) of cases. Epidemiologically, detection of anti-HBc alone was casual in 60% of patients, whereas the remaining cases had a history of chronic liver disease (82% of these were anti-HCV positive). In a high percentage (63%) the transmission mechanism of HBV infection was unknown (11% intravenous drug abuser, 10% surgery, 6% transfusions).
Conclusion: The anti-HBc alone pattern is a frequent finding, particularly in patients > 65 years old and in HCV or HIV coinfected patients. Although HBV-DNA was detected in a small percentage of cases, this test could be indicated in certain clinical situations (liver disease, coinfection, donors). Furthermore, this profile seems to be related with HCV infection; hence, we consider anti-HCV detection necessary in all patients with anti-HBc alone.

Hepatocyte steatosis is an important predictor of response to interferon (IFN) monotherapy in Japanese patients infected with HCV genotype 2a: Virological features of IFN-resistant cases with hepatocyte steatosis.

J Med Virol. 2005 Feb 15; 75(4):550-8.
Akuta N, Suzuki F, Suzuki Y, Sezaki H, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H.

The role of hepatocyte steatosis in interferon (IFN) resistance is still unclear, especially in patients infected with hepatitis C virus (HCV) genotype 2a. The present study was conducted in 364 consecutive non-cirrhotic naive patients infected with genotype 2a, who were evaluated for the severity of steatosis and response to IFN monotherapy after a 24-week median duration of therapy. The patients were examined for factors associated with steatosis and treatment efficacy according to the grade of steatosis. Early viral kinetics was also evaluated in 64 patients for predictors of response to therapy. Nine IFN-resistant patients were assessed for the relationship between amino acid sequence of HCV core region/NS5A and severity of steatosis. Multivariate analysis identified two independent factors associated with steatosis; serum ferritin >/=200 mug/l and body mass index >/=25.0 kg/m(2). The sustained virological response rate in patients with high-grade steatosis was significantly lower than in the low-grade group. Study of early viral kinetics showed a significantly lower cumulative HCV-RNA negative rate for the high-grade than low-grade steatosis group. Sequence analysis of HCV core region/NS5A in IFN-resistant patients with or without steatosis failed to identify steatosis-specific amino acid substitutions associated with resistance. This study of HCV genotype 2a suggested that steatosis is associated with excess iron storage, and that it is an important predictor of efficacy of IFN monotherapy. Further large-scale studies are warranted to examine the role of amino acid substitutions on IFN resistance specific for steatosis.

Hepatitis newswire in March 2005

The experience of interferon-based treatments for hepatitis C infection.

Qual Health Res. 2005 May; 15(5):635-46.
Hopwood M, Treloar C.

Clinical trials of interferon-based treatments for hepatitis C infection show decrements in patients' health-related quality of life due to side effects of therapy. The impact of side effects on patients' overall quality of life still remains unclear. To explore this issue, the authors interviewed people living in New South Wales, Australia, who had undergone treatment for hepatitis C. Their aim in this article is to report participants' experiences of treatment side effects. In Australia, this information is important, because a new interferon-based regimen has been adopted as the mainstay of hepatitis C treatment, and it is predicted that many more people will seek treatment. The authors argue for further qualitative research to enhance knowledge of the impact of this therapy.

Risk of transmission of hepatitis B virus from anti-HBc positive cadaveric organ donors: a collaborative study.

Transplant Proc. 2005 Mar; 37(2):1238-9.
De Feo TM, Poli F, Mozzi F, Moretti MP, Scalamogna M; Collaborative Kidney, Liver and Heart North Italy Transplant program Study Groups.

Organ donors with a serologic profile of recovered (HBsAg negative and/or anti-HBc IgG positive) hepatitis B virus infection (HBV) have been reported to transmit HBV to recipients. In Italy, up until 2002, anti-HBc determination was not mandatory. We retrospectively evaluated the incidence of HBV transmission among recipients transplanted with organs from anti-HBc positive donors from 1997 to 1999. Anti-HBc was screened in 886 available sera among 964 HBsAg and anti-HCV negative donors. HBV transmission was evaluated in 325 kidney, liver, and heart recipients according to their pretransplant HBV serum profile. Of 210 anti-HBc positive donors, 185 were anti-HBc positive/anti-HBs positive and 25 anti-HBc positive/anti-HBs negative with a prevalence of 20.8% and 2.8%, respectively. One hundred seven sera (51%) were collected from donors after transfusion of blood components, the remainder were either before transfusion or from nontransfused donors. The 210 anti-HBc positive subjects donated 356 kidneys, 117 livers and 117 hearts, among whom follow-up is presently available for 251 kidney, 61 liver, and 25 heart recipients. No HBV transmission was observed independent of the recipient immunological profile among the kidney or heart recipients. In liver recipients, no transmission was reported in recovered or vaccinated patients, while a high incidence (43%) of de novo hepatitis was observed among naive patients. In conclusion, there does not seem to be a risk of transmitting HBV through anti-HBc positive transplants in heart and kidney recipients; only naive liver recipients are at high risk of HBV infection.

Reactogenicity profile of a combined hepatitis A and B vaccine in clinical practice: a naturalistic study in adult travellers.

Vaccine. 2005 Mar 31; 23(19):2465-9.
Vilella A, Dal-Re R, Simo D, Puente J, Diez C, Garcia-Corbeira P, Bayas JM.

A prospective observational naturalistic study was conducted to assess the reactogenicity of the combined hepatitis A and hepatitis B (HAB) vaccine in a real-life setting. All healthy candidates for HAB vaccination attending an adult vaccination centre between October 1998 and February 2000 were invited to participate in the study. A follow-up diary card was provided to subjects to record local and general symptoms during a 4-day follow-up. Intensity was graded from 1 to 3. Redness was recorded as presence or absence. Fever was defined as axillary temperature >/=37.5 degrees C and grade 3 >39.0 degrees C. For all other symptoms, grade 3 was defined as an adverse reaction preventing normal everyday activities; 998 subjects (74% females), mean age (+/-S.D.) of 23 years (+/-4.5) (range: 11-54 years) agreed to participate. At first immunization 92% were <30 years old. Grade 3 pain and swelling was recorded in 1.2% and 0.3% of local symptom sheets completed, respectively; 438 subjects received the HAB vaccine alone (group 1) whereas 560 received at least one concomitant vaccine (group 2). In 45%, 27%, 18% and 10% of subjects the HAB vaccine was coadministered with 1, 2, 3 or 4 to 6 vaccines (mainly Td adult-type, typhoid, MMR and IPV vaccine). Grade 3 pain and swelling were recorded in 1.2% & 0.3% of symptom sheets (SS), respectively. In group 1, any fever and grade 3 fever was recorded in 3.5% and 0.1% of SS. Group 1 versus 2 had a lower risk for any fatigue (P=0.0002; OR=0.617) and any malaise

(P=0.0076; OR=0.693) but not for grade 3 symptoms. In conclusion, our study showed that the HAB vaccine is well tolerated in adults either alone or coadministered with other vaccines in the routine clinical practice.

Prevalence of gallbladder disease among persons with hepatitis C virus infection in the United States.

Hepatology. 2005 Mar 15.
Bini EJ, McGready J.

Although cirrhosis is a known risk factor for gallstones, little is known about gallbladder disease (GBD) in individuals with hepatitis C virus (HCV) infection. We determined the association between chronic HCV infection and GBD in a representative sample of adults in the United States. Data on HCV infection and GBD were available for 13,465 persons 20 to 74 years of age who participated in the Third National Health and Nutrition Examination Survey. The presence of GBD (gallstones or cholecystectomy) was determined using abdominal ultrasonography, and HCV infection was assessed via a positive HCV antibody test and a positive HCV RNA test. Overall, 1.6% of adults (95% CI, 1.1-2.1) had chronic HCV infection and 12.5% (95% CI, 11.3-13.7) had GBD. After adjusting for potential confounding variables, the odds of gallstones (OR = 3.20; 95% CI, 1.08-9.45) and cholecystectomy (OR = 4.57; 95% CI, 1.57-13.27) among HCV-positive men was significantly higher compared with HCV-negative men. In contrast, the adjusted odds of gallstones (OR = 2.55; 95% CI, 0.58-11.25) and cholecystectomy (OR = 0.70; 95% CI, 0.21-2.37) among HCV-positive women was not significantly higher. The odds of GBD increased significantly with the severity of liver disease as assessed via elevated serum bilirubin levels and low levels of serum albumin and platelets. In conclusion, chronic HCV infection was strongly associated with GBD among men but not women in the United States, and GBD was more common in adults with severe liver disease.

Natural history of hepatitis C virus infection in adult renal graft recipients.

Transplant Proc. 2005 Mar; 37(2):940-1.
Aroldi A, Lampertico P, Montagnino G, Lunghi G, Passerini P, Villa M, Campise M, Cesana BM, Ponticelli C.

Aim: To study the natural history of hepatitis C virus infection in renal transplantation, 464 HbsAg negative patients were prospectively studied from 1989.
Methods: AntiHCV was tested by ELISA II and HCVRNA by Amplicor HCV RNA tests.
Results: Two hundred nine patients were antiHCV positive (C+). HCVRNA was confirmed in 89% of C+ patients. Compared with the 255 anti-HCV negative (C-), C+ had undergone longer periods of dialysis (P = .0001), were more transfused (P = .01), and included more retransplants (P = .002). Immunosuppression was azathioprine (AZA) plus steroids in 133 and cyclosporine (CsA) in 331 patients. Liver biopsy showed chronic active hepatitis in 50, cirrhosis in 8, and fibrosing cholestatic hepatitis in 2 patients. Histologic progression of liver disease was confirmed in 18 of 26 patients. The causes of death in 84 patients (51 C+ vs 33 C-) were cardiovascular disease in 49%, sepsis in 13%, liver failure in 14%, neoplasia in 21%, and hepatocarcinoma in 2%. The 14-year patient survival was 75% in C+ and 86% in C- (P = .002). By multivariate analysis, age (>40) (P = .001) and C+ (P = .019) correlated with a worse patient survival. If patients were stratified according to age (<40 vs >/=40), younger C+ patients had a lower survival probability (P = .03). The 14-year graft survival was 44% in C+ vs 60% in C- patients (P = .001) but pure graft survival was similar (68% in C+ vs 72% in C-) (P = .13).
Conclusion: The presence of C+ significantly reduced both patient and graft survival in the long-term with liver failure being the second most frequent cause of death.

Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients.

Gastroenterology. 2005 Mar; 128(3):636-41.
Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, Corpas R, Cruz M, Grande L, Vazquez L, Munoz-De-Rueda P, Lopez-Serrano P, Gila A, Gutierrez ML, Perez C, Ruiz-Extremera A, Suarez E, Castillo J.

Background & Aims: We evaluated the effect of insulin resistance and viral factors on sustained virological response in patients with chronic hepatitis C treated with peginterferon plus ribavirin.
Methods: Patients (n=159; 94 men; age, 41.7 +/- 11.1 years) with chronic hepatitis C (genotype 1, n=113; non-1 genotype, n=46) received treatment with interferon plus ribavirin. Serum levels of leptin and insulin were measured, and the insulin resistance index (HOMA-IR: homeostasis model of assessment) and body mass index were calculated.
Results: A sustained virological response was associated with lower age, insulin resistance index, body mass index, and gamma-glutamyltranspeptidase and serum leptin levels. There was no association with viral load, sex, type of interferon, or cholesterol levels. A sustained virological response was achieved in 43.4% (46/113) of genotype 1 and 89% (32/36) of genotype 2 and 3 (P=.0001) patients. Necroinflammatory activity and steatosis were not associated with the sustained virological response rate. Multivariate regression analysis indicated that the independent variables related to sustained virological response were genotype (odds ratio, 3.57; 95% confidence interval, 1.49-8.3; P=.001), insulin resistance index (odds ratio, 1.82; 95% confidence interval, 1.08-3.06; P=.012), and fibrosis (odds ratio, 1.36; 95% confidence interval, 1.01-1.84; P=.029). A sustained virological response in patients with genotype 1 and insulin resistance (HOMA-IR > 2) occurred in 23 of 70 (32.8%; 95% confidence interval, 21.9%-43.9%) patients, vs. 26 of 43 (60.5%; 95% confidence interval, 45.9%-75.1%) genotype 1 patients without insulin resistance (P=.007; odds ratio, 3.12, 95% confidence interval, 1.42-6.89).
Conclusions: Insulin resistance, fibrosis, and genotype are independent predictors of the response to antiviral therapy in chronic hepatitis C patients treated with peginterferon plus ribavirin.

Quantitative detection of serum HBV DNA levels employing a new S gene based cPCR assay.

Arch Virol. 2005 Mar; 150(3):481-91. Epub 2004 Nov 18.
Changotra H, Sehajpal PK.

Hepatitis B virus (HBV) infection is a major public health problem and a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Worldwide, there are about 350 million carriers of this pathogen and India bears the second highest carrier pool in the world. Early diagnosis and measurement of viral load in hepatitis B patients is very helpful for the better management of this disease. The existing methods for viral quantification are either cumbersome or expensive. Since viral replication correlate well with HBV DNA levels a new sensitive, reliable and cost effective competitive PCR assay has been developed for quantifying the viral load in the serum of hepatitis B patients. The S gene based cPCR assay was able to detect as low as 100 genome equivalent/ml of HBV DNA from human serum and was applied to determine viral load among inactive and chronic hepatitis B carriers demonstrating the usefulness of the developed test.

Dramatic decline in acute hepatitis B infection and disease incidence rates among adolescents and young people after 12 years of a mass hepatitis B vaccination programme of pre-adolescents in the schools of Catalonia (Spain).

Vaccine. 2005 Mar 18; 23(17-18):2181-4.

Salleras L, Dominguez A, Bruguera M, Cardenosa N, Batalla J, Carmona G, Navas E, Taberner JL.

The aim of the study was to describe the impact of hepatitis B vaccination and disease incidence in adolescents and young people 12 years after the launching of a mass hepatitis B vaccination of pre-adolescents in schools. Vaccination coverage was assessed using administrative and serological data. Infection trends were evaluated by means of seroepidemiological surveys. High levels of vaccination coverage and vaccine-induced immunity were achieved. The resulting low proportions of susceptible adolescents and young people have undoubtedly contributed to the substantial reduction in the prevalence of hepatitis B infection in the 15-24 years age group (0.9 per 100 in 2001 versus 9.3 per 100 in 1986) and in the reported incidence of hepatitis B cases (80% reduction). Over the last 3 years, the declining trend seems to have been halted, although 35% of cases reported during this period corresponded to immigrants.

Comparative long term immunogenicity of two recombinant hepatitis B vaccines and the effect of a booster dose given after five years in a low endemicity country.

Pediatr Infect Dis J. 2005 Mar; 24(3):213-8.

Duval B, Gilca V, Boulianne N, De Wals P, Masse R, Trudeau G, De Serres G.

Background: Few data are available concerning the long term immunogenicity of the pediatric doses of hepatitis B vaccines given to preteenagers. The long term effect of the booster dose in teenagers is unknown. We evaluated the immunogenicity of 2 pediatric hepatitis vaccines after primary vaccination and after a booster dose.

Methods: A prospective 15-year follow-up study of the immunogenicity of 2 hepatitis B vaccines was initiated in 1995 in Quebec City, Canada. One year apart, 1129 children 8-10 years old received Engerix-B 10 microg (EB), and 1126 received Recombivax-HB 2.5 microg (RB) vaccine after a 0-, 1-, 6-month schedule. After 5 years, one-third of the 2 cohorts were randomly selected. A booster dose of EB 10 microg or RB 5 microg was administered according to the vaccine used in the primary immunization. Antibodies were measured before, 1 month after and 1 year after the booster injection.

Results: Before the booster dose, anti-HB surface antibody (HBs) was detected in 94.7% of the EB subjects and in 95.2% of the RB subjects ($P = 0.85$). The geometric mean titer (GMT) was higher in the EB than in the RB group (252 mIU/mL versus 66 mIU/mL, $P < 0.0001$). One month after the booster, 99.7% of subjects in the EB group and 99.6% in the RB group had a detectable anti-HBs, and 99.0 and 99.3%, respectively, had anti-HBs > or =10 mIU/mL. The anti-HBs GMT was 113,201 mIU/mL in the EB and 16,623 mIU/mL in the RB groups ($P < 0.0001$). One year after the booster, 99.3% of subjects in the EB group and 100% in the RB group had detectable anti-HBs, and 97.9 and 98.5% respectively, had anti-HBs > or =10 mIU/mL. The anti-HBs GMT was 14,028 mIU/mL in the EB and 3437 mIU/mL in the RB group ($P < 0.0001$).

Conclusions: The immunity persists for at least 5 years after the primary vaccination with both pediatric vaccines in 99% of children vaccinated at the age of 8-10 years. It confirms that no booster is needed at that point.

Sarcoidosis in patients with chronic hepatitis C virus infection: Analysis of 68 cases.

Medicine (Baltimore). 2005 Mar;84(2):69-80.

Ramos-Casals M, Mana J, Nardi N, Brito-Zeron P, Xaubet A, Sanchez-Tapias JM, Cervera R, Font J; for the HISPAMEC Study Group.

We describe the clinical characteristics, the patterns of association, and the role of antiviral therapies in patients with sarcoidosis associated with chronic hepatitis C virus (HCV) infection. Sixty-eight patients were included in the current study, 56 cases identified in the literature search plus 12 unpublished cases from our department. In 50 HCV patients, sarcoidosis appeared after starting antiviral therapy. Antiviral therapy associated with triggered sarcoidosis consisted of alpha-interferon monotherapy in 20 cases and combined therapy with alpha-interferon and ribavirin in 30. Sarcoidosis appeared during the first 6 months after starting therapy in 66% of patients. The clinical picture of sarcoidosis included predominantly pulmonary disease in 38 (76%) patients and cutaneous sarcoidosis in 30 (60%). Antiviral therapy was discontinued in 60% of patients and continued or adjusted in 14%, while sarcoidosis appeared after completed therapy in the remaining cases. Specific therapy for sarcoidosis was started in only 21 patients, mainly with oral corticosteroids. The outcome of patients was detailed in 46 cases: remission or improvement was observed in 38/46 (83%) patients, stabilization of sarcoidosis in 5/46 (11%), and reactivation of sarcoidosis after an initial improvement in 3/46 (6%). Finally, 18 treatment-naive HCV patients presented sarcoidosis, with 14/18 (87%) patients presenting with pulmonary involvement and 8/18 (44%) with cutaneous involvement.In summary, sarcoidosis may be observed in HCV patients in 2 different situations: triggered by antiviral therapy (in 75% of cases) and unrelated to treatment. Sarcoidosis during antiviral therapy may present mainly as cutaneous or pulmonary disease, with a benign, uncomplicated evolution in more than 85% of cases. However, more complicated cases are observed, especially in HCV patients with preexisting sarcoidosis and/or with previous antiviral treatment. Clinicians should be aware of the possibility that sarcoidosis may initially manifest or be reactivated during or shortly after treatment with antiviral therapy in patients with chronic HCV infection.

Differential dynamics of the peripheral and intrahepatic cytotoxic T lymphocyte response to hepatitis B surface antigen.

Virology. 2005 Mar 15;333(2):293-300.

Isogawa M, Kakimi K, Kamamoto H, Protzer U, Chisari FV.

The distribution and dynamics of the cytotoxic T lymphocyte (CTL) response to hepatitis B surface antigen (HBsAg) were studied in mice after intramuscular DNA immunization and after hepatic infection by a recombinant adenovirus that expresses the hepatitis B virus genome (Ad-HBV). CTLs specific for HBsAg accumulate preferentially in the spleen after DNA immunization but are primarily intrahepatic after Ad-HBV infection. The secondary CTL response to Ad-HBV in DNA-primed mice is characterized by rapid depletion of effector CTLs from the spleen, and their expansion in the liver where they cause hepatitis, secrete interferon gamma (IFNgamma), and inhibit HBV gene expression. Suppression of HBsAg synthesis is accompanied by disappearance of intrahepatic IFNgamma-producing CTLs and their reaccumulation in the spleen. The data suggest a possible explanation for the paucity and functional deficiency of HBV-specific CTLs in the periphery during chronic HBV infection, and that the severity of infection can be worsened by a preexisting CTL response if neutralizing antibody is not also present.

Hepatitis C virus viral recurrence and liver mitochondrial damage after liver transplantation in HIV-HCV co-infected patients.

J Hepatol. 2005 Mar;42(3):341-9.

Duclos-Vallee JC, Vittecoq D, Teicher E, Feray C, Roque-Afonso AM, Lombes A, Jardel C, Gigou M, Dussaix E, Sebagh M, Guettier C, Azoulay D, Adam R, Ichai P, Saliba F, Roche B, Castaing D, Bismuth H, Samuel D.

Background/Aims: As life expectancy in HIV-HCV co-infected patients improves, end stage liver disease requiring liver transplantation (LT) may become an emerging problem. We report the Paul Brousse Hospital experience of transplantation for end stage cirrhosis in HIV-HCV co-infected patients.
Methods: Seven consecutive HIV-HCV co-infected patients were transplanted between December 1999 and December 2002 for end stage liver disease due to HCV. All patients were treated by highly active antiretroviral therapy (HAART), HIV plasma viral load was <400copies/ml and median CD4 lymphocyte count was 306cells/mm(3) (range, 103-510) before LT. At the time of evaluation (March 2003), the median follow-up was 21 months (range, 4-40).
Results: Two patients died, 4 and 22 months, respectively after LT. At the last biopsy, METAVIR score was staged F4 in two patients, F3 in two, and F1 in one. Microvesicular steatosis was noted in nearly all patients. The ratio of mitochondrial to nuclear DNA was low in three of four patients examined as compared with the amount of liver mtDNA found in eight HIV-negative, HCV-infected controls (P=0.01).
Conclusions: A significant defect in the activity of the respiratory chain complex IV was noted in all five patients studied. Mitochondrial hepatotoxicity and severe HCV recurrence occur in HIV-HCV co-infected patients after LT.

Serum lipid profile and hepatic steatosis of adult beta-thalassaemia patients with chronic HCV infection.

Eur J Gastroenterol Hepatol. 2005 Mar;17(3):345-50.

Siagris D, Kouraklis-Symeonidis A, Christofidou M, Lekkou A, Papadimitriou C, Arvaniti V, Thomopoulos K, Tsamandas A, Zoumbos N, Labropoulou-Karatza C.

Objectives: The aim of this study was to evaluate the serum lipid profile and to assess the prevalence of hepatic steatosis in adult beta-thalassaemic patients with chronic hepatitis C virus (HCV) infection.
Methods: Thirty-five adult HCV infected, multi-transfused, beta-thalassaemia patients (beta-HCV patients), 63 otherwise normal patients with chronic HCV infection (HCV patients) and 54 beta-thalassaemia patients without chronic viral hepatitis (beta patients) were studied. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, viral markers and liver histology were evaluated.
Results: Serum total cholesterol, HDL-C and LDL-C were found at significantly lower levels in beta-HCV and beta patients than in HCV patients. Triglyceride levels were significantly lower in the HCV group compared with the beta group. Nine (25.7%) of the 35 beta-HCV patients had mild hepatic steatosis. Thirteen (23.6%) of 55 HCV patients presented mild and 4/55 (7.3%) moderate hepatic steatosis. None of the beta group presented steatosis. When we compared beta-HCV and HCV patients with steatosis, we found that beta-HCV patients had a lower degree of steatosis (11.1+/-7% vs 22.9+/-17.2%, P=0.021). Multivariate logistic regression analysis showed that the only independent predictor associated with hepatic steatosis in beta-HCV and HCV patients was genotype 3a (OR, 3.61; 95% CI, 1.22-10.71, P=0.021).
Conclusions: Adult beta-thalassaemia patients, compared to other patients with chronic HCV infection, present lower cholesterol levels (total cholesterol, HDL, LDL) and similar frequency but a lower degree of hepatic steatosis. This difference in the degree of steatosis is most likely due to the higher prevalence of genotype 3a in the non-beta-thalassemia group.

Hepatitis C reactivation in patients with chronic infection with genotypes 1b and 2c: a retrospective cohort study of 206 untreated patients.

Gut. 2005 Mar; 54(3):402-6.

Rumi MG, De Filippi F, La Vecchia C, Donato MF, Gallus S, Del Ninno E, Colombo M.

Background: We previously described hepatitis reactivation in two carriers of the hepatitis C virus (HCV) genotype 2c. AIM: To assess the relationship between HCV genotypes and risk of hepatitis reactivation, we studied the course of aminotransferases in patients infected with the two relevant genotypes in Italy.
Patients: A cohort of 100 patients with genotype 2c chronic hepatitis and 106 with genotype 1b were subjected to surveillance.
Methods: Hepatitis reactivation was defined as an alanine aminotransferase (ALT) value >/=400 IU/l or a maximum/minimum ALT ratio value of >/=8.
Results: Over a period of 71 (24-144) months, one or more flares of ALT (201-2200 IU/l, 6-90 months' duration) occurred in 31 patients with genotype 2c and in eight patients with genotype 1b (rates of flares: 55.6 per 1000 person years for genotype 2c v 15.0 for genotype 1b; P = 0.001). On repeat biopsy, hepatic fibrosis increased by more than 2 points in 10/16 patients examined either during or after an ALT flare compared with 7/36 flare free patients (63% v 19%; P = 0.003). Hepatitis flares were significantly associated with genotype 2c (odds ratio 6.48 (95% confidence interval 2.57-16.35)) but not with sex, age, modality or duration of infection, baseline ALT values or histological severity of hepatitis, hepatitis other than HCV, or reinfection.
Conclusions: Genotype 2c carriers are at high risk of hepatitis reactivation, suggesting that virus genetic heterogeneity is important in the natural history of HCV, questioning the linearity of hepatic fibrosis progression during hepatitis C.

Association of Helicobacter species with hepatitis C cirrhosis with or without hepatocellular carcinoma.

Gut. 2005 Mar; 54(3):396-401.

Rocha M, Avenaud P, Menard A, Le Bail B, Balabaud C, Bioulac-Sage P, de Magalhaes Queiroz DM, Megraud F.

Background and Aims: Recent studies have suggested that bacterial coinfection with Helicobacter species in patients already infected with hepatitis C virus (HCV) could be involved in the development of cirrhosis and hepatocellular carcinoma (HCC). A retrospective cross sectional study was performed in order to explore the association between Helicobacter species and HCV associated liver diseases.
Methods: The presence of Helicobacter species was tested by polymerase chain reaction on liver samples from four groups of patients.
Results: Helicobacter 16S rDNA was found in only 4.2% of liver samples from control patients (n = 24) and in 3.5% of liver samples from patients with non-cirrhotic chronic hepatitis C (n = 29) while it was found in 68.0% of liver samples from patients with HCV positive cirrhosis without HCC (n = 25) as well as in 61.3% of cirrhotic liver samples from patients with HCV positive cirrhosis and HCC (n = 31). In addition, when the HCC tumour tissue was

tested (n = 21), 90.5% of samples were positive. DNA from Helicobacter pylori- and Helicobacter pullorum-like organisms was found.
Conclusions: There is an association between the presence of Helicobacter species DNA in the liver and hepatitis C cirrhosis, with or without HCC. Indeed, the presence of these bacteria could be the result of structural changes in the liver. Alternatively, Helicobacter species could be a co-risk factor in HCV chronic liver diseases. This result warrants prospective studies to determine the possible causal role of these bacteria in the progression of chronic hepatitis C.

Vascular cell adhesion molecule-1 (VCAM-1) plays a central role in the pathogenesis of severe forms of vasculitis due to hepatitis C-associated mixed cryoglobulinemia.

J Hepatol. 2005 Mar; 42(3):334-40.
Kaplanski G, Maisonobe T, Marin V, Gres S, Robitail S, Farnarier C, Harle JR, Piette JC, Cacoub P.

Background/Aims: To better characterize the molecules involved in leukocyte tissue infiltration during hepatitis C-mixed cryoglobulinemia (HCV-MC)-associated vasculitis.
Methods: The involvement of ELAM, ICAM-1 and VCAM-1 was evaluated in 36 patients with HCV-MC vasculitis using three different approaches: concentrations of soluble forms by specific ELISA, tissue expression by immunohistochemistry on patients nerve biopsies, endothelial expression by FACS analysis, on cells activated in vitro by cryoprecipitates purified from HCV-MC patients.
Results: Concentrations of sVCAM-1 were significantly elevated in the serum of HCV-MC patients compared to HCV patients without MC, the highest concentrations being found in severe vasculitis. VCAM-1 expression was detected on blood vessels from nerve biopsies performed in patients with severe vasculitis. When added to endothelial cells in vitro, HCV-MC patients cryoprecipitate induced VCAM-1 but also ELAM and ICAM-1 expression possibly through a mechanism due to the C1q complement fraction interaction with endothelial cells, since C1q was consistently present in the cryoprecipitates.
Conclusions: VCAM-1 is mainly involved in the pathogenesis of HCV-MC-associated severe vasculitis and may be a potential interesting therapeutic target.

Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance.

J Hepatol. 2005 Mar; 42(3):329-33.
Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Francavilla R, Pastore G.

Background/Aims: Interferon (IFN) monotherapy significantly reduces the chronicity rate of acute hepatitis C (AHC) but optimal regimen and treatment timing remain undefined. The aim of this study was to assess the efficacy of a 6-month course of pegylated IFN (PEG-IFN) alpha-2b monotherapy in AHC patients and to investigate if IFN treatment initiated after 12 weeks from clinical presentation, still achieved a high response rate.
Methods: Sixteen AHC patients still viremic after 12 weeks from the onset were treated with PEG-IFN alpha-2b (1.5mcg/kg once weekly) for 6 months and followed for at least 12 months. Response to therapy was defined as normal ALT values and undetectable HCV RNA (<50IU/ml) at the end of therapy, after 6 (sustained response) and 12 months follow-up (long-term response).
Results: At the end of treatment, HCV RNA was undetectable in 15/16 patients while ALT normalized in 14/16 patients. After 6 and 12 months follow-up, 15/16 patients (94%) showed virological and biochemical response.
Conclusions: A 6-month course of PEG-IFN alpha-2b is effective in inducing resolution of AHC in 94% of patients. Our results provide a rationale for delaying treatment for 12 weeks, targeting only patients who fail to clear the virus spontaneously and truly requiring therapy without loss of efficacy.

Quasispecies heterogeneity within the E1/E2 region as a pretreatment variable during pegylated interferon therapy of chronic hepatitis C virus infection.

J Virol. 2005 Mar; 79(5):3071-83.
Chambers TJ, Fan X, Droll DA, Hembrador E, Slater T, Nickells MW, Dustin LB, Dibisceglie AM.

A series of 29 patients undergoing treatment for chronic hepatitis C virus (HCV) genotype 1 infection with pegylated alpha-2a interferon plus ribavirin were studied for patterns of response to antiviral therapy and viral quasispecies evolution. All patients were treatment naive and had chronic inflammation and fibrosis on biopsy. As part of an analysis of pretreatment variables that might affect the outcome of treatment, genetic heterogeneity within the viral E1-E2 glycoprotein region (nucleotides 851 to 2280) was assessed by sequencing 10 to 15 quasispecies clones per patient from serum-derived PCR products. Genetic parameters were examined with respect to response to therapy based on serum viral RNA loads at 12 weeks (early viral response) and at 24 weeks posttreatment (sustained viral response). Nucleotide and amino acid quasispecies complexities of the hypervariable region 1 (HVR-1) were less in the responder group in comparison to the nonresponder group at 12 weeks, and genetic diversity was also less both within and outside of the HVR-1, with the difference being most pronounced for the non-HVR-1 region of E2. However, these genetic parameters did not distinguish responders from nonresponders for sustained viral responses. Follow-up studies of genetic heterogeneity based on the HVR-1 in selected responders and nonresponders while on therapy revealed greater evolutionary drift in the responder subgroup. The pretreatment population sequences for the NS5A interferon sensitivity determinant region were also analyzed for all patients, but no correlations were found between treatment response and any distinct genetic markers. These findings support previous studies indicating a high level of genetic heterogeneity among chronically infected HCV patients. One interpretation of these data is that early viral responses are governed to some extent by viral factors, whereas sustained responses may be more influenced by host factors, in addition to effects of viral complexity and diversity.

Lamivudine monotherapy for spontaneous severe acute exacerbation of chronic hepatitis B.

J Gastroenterol Hepatol. 2005 Mar; 20(3):426-32.

Tsubota A, Arase Y, Suzuki Y, Suzuki F, Sezaki H, Hosaka T, Akuta N, Someya T, Kobayashi M, Saitoh S, Ikeda K, Kumada H.

Background: Severe acute exacerbations of chronic hepatitis B virus (HBV) infection can spontaneously occur and rapidly progress to fatal hepatic failure. The purpose of the present paper was to identify factors that could influence the rapid progression of liver disease to hepatic failure, and assess the effects of lamivudine on serious disease.

Methods: Twenty-five patients with spontaneous severe acute exacerbation (accompanied by jaundice and coagulopathy) were consecutively treated with lamivudine. Their clinical outcomes were compared with those of 25 lamivudine-untreated patients, as historical controls.

Results: Six lamivudine-treated patients (24%)and seven controls (28%) rapidly developed hepatic failure. Lamivudine monotherapy did not significantly prevent progression to hepatic failure. Multivariate analysis identified baseline serum bilirubin >/=6 mg/dL (odds ratio [OR]: 5.61; 95% confidence interval [CI]: 1.66-21.61; $P = 0.018$), pre-existing cirrhosis (OR: 4.52; 95%CI: 1.26-30.42; $P = 0.034$), and baseline prothrombin time <40% (OR: 3.75; 95%CI: 1.03-43.86; $P = 0.045$) as independent determinants of the event. Of the aforementioned patients with hepatic failure, three lamivudine-treated patients (50%) and two controls (29%) survived ($P > 0.15$). However, lamivudine induced a sustained normalization of liver function and inhibited the development of cirrhosis in survivors.

Conclusions: Lamivudine monotherapy conferred no significant protection against rapid progression of the disease to hepatic failure, but it resulted in long-term benefits. Lamivudine combined with other drugs could be more beneficial for patients with the aforementioned risk factors.