



HEPATITIS C July 2004

1: AAOHN J. 2004 May;52(5):210-7; quiz 218-9.

Comment on:

AAOHN J. 1999 May;47(5):217-22; quiz 223-4.

Hepatitis C: an update for occupational health nurses.

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Hepatitis C is no longer an emerging dilemma. It is a significant public health problem with life altering complications. Occupational health nurses have the responsibility to their employees to be up to date on the latest treatment modalities so they can accurately advise their clients should an exposure occur.

Occupational health nursing practice needs to focus on employee education related to Occupational Safety and Health Administration's Blood Borne Pathogens Standard and the latest in safety devices through regular yearly in-services.

PMID: 15152719 [PubMed - indexed for MEDLINE]

2: AIDS Patient Care STDS. 2004 Apr;18(4):239-45.

Hepatitis C treatment eligibility in an urban population with and without HIV coinfection.

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In an urban referral clinic, 182 hepatitis C-infected adults including 110 (60%) with HIV coinfection were evaluated for pegylated interferon and ribavirin therapy. Overall, only 33% were eligible for treatment. Considering all patients together, the major barriers to treatment were nonadherence with the evaluation process (23%), refusal of treatment (10%), active substance abuse (9%), and medical contraindication (8%). There was a trend toward a higher rate of treatment eligibility in HIV coinfecting patients (39% vs. 25%; $p = 0.07$), who were significantly more likely to be adherent with the evaluation process compared to those with hepatitis C alone (86% vs. 63%; $p = <0.001$). Acceptance of antiviral therapy for hepatitis C was similar between eligible persons with and without HIV. These findings highlight the need to develop interventions to improve adherence and to manage substance abuse and other comorbidities in order to maximize the impact of interferon and ribavirin therapy on urban patients with hepatitis C.

PMID: 15142354 [PubMed - indexed for MEDLINE]

3: Am J Gastroenterol. 2004 May;99(5):873-7.

Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin.

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BACKGROUND: Sudden hearing loss has been reported on standard interferon (IFN)-alpha2 therapy. This is the first report on the occurrence of sudden hearing loss in six cases of chronic hepatitis C in temporal relation to treatment with pegylated (PEG)-IFN alfa2a or b/ribavirin combination therapy. Three patients were treated in an ongoing randomized placebo-controlled trial comparing the addition of 200 mg amantadine or placebo to the combination of 180 microg PEG-IFN alpha2a (PEGASYS, Roche, Basel, CH)/wk and 1-1.2 g ribavirin/d (COPEGUS, Roche, Nutley, USA) in de novo patients infected with HCV genotype 1. Sudden hearing loss and tinnitus developed on day 1 and after 4, 23, 25, 36, and 40 wk of treatment, respectively. **CONCLUSIONS:** Sudden hearing loss may occur in about 1% of patients on PEG-IFN/ribavirin combination therapy. This rate was not different to that observed in an untreated population. Possible mechanisms involved include direct ototoxicity of IFN, autoimmunity, and hematological changes. In contrast to published cases on auditory disability due to standard IFN, hearing loss did not fully resolve after discontinuation of therapy with PEG-IFN. On the other hand, symptoms did not worsen on continued treatment. Therefore, the decision whether to continue or to stop the treatment when signs of ototoxicity appear is based on the clinical judgment of the treating physician.

PMID: 15128353 [PubMed - indexed for MEDLINE]

4: Am J Gastroenterol. 2004 May;99(5):866-72.

Treatment of chronic hepatitis C virus in the virginia department of corrections: can compliance overcome racial differences to response?

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OBJECTIVE: Chronic hepatitis C virus (HCV) is common in the correctional setting and there are few data on the use of interferon (IFN)/ribavirin(RVN) combination therapy in this population. Given the high proportion of African Americans (AA) in correctional facilities, which may be associated with reduced response rates, the correctional setting allows a unique opportunity to compare the response rates of AA to Caucasians (CA). The present study describes our experience of treating HCV in the inmate population of the Virginia Department of Corrections.

METHODS: Of the 119 inmates evaluated between 1998 and 2000, a retrospective analysis of 59 consecutive inmates (mean age 41, 83% male, 55% CA, 73% genotype

(GT)1, and 41% with advanced fibrosis) who underwent HCV therapy with IFN a-2b (3 MU TIW) and RVN (1,000-1,200 mg/d) under direct observation was performed.

Patients were followed by telemedicine and the primary endpoint was sustained virologic response (SVR) defined as an undetectable HCV RNA at least 24 wk after completion of therapy. **RESULTS:** All but one patient completed at least 12 wk of therapy and no patient required dose reduction. By wk 24, 34 inmates (58%) responded (negative HCV RNA) which was higher in CA compared to AA (70%vs 40%;

p= 0.037). Although overall SVR was higher in CA compared to AA (41%vs 28%; p= ns), we observed no difference in SVR when comparing only GT 1 CA to AA (33%vs 29%).

CONCLUSIONS: HCV can be effectively treated in the correctional setting with response rates similar to, if not better than the published literature. In this controlled setting of direct observational therapy, we observed similar SVR in CA and AA.

PMID: 15128352 [PubMed - indexed for MEDLINE]

5: Am J Gastroenterol. 2004 May;99(5):860-5.

Clinical significance of elevated alpha-fetoprotein (AFP) in patients with chronic hepatitis C, but not hepatocellular carcinoma.

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BACKGROUND: Although elevated serum alpha-fetoprotein (AFP) is often seen in patients with chronic hepatitis C (CHC), its prevalence, risk factors, and clinical significance remain to be determined. **AIMS:** The present study assessed the frequency of, the risk factors for, and the clinical significance of elevated AFP in patients with CHC, but not hepatocellular carcinoma. **METHODS:** This retrospective study utilized systematic chart review and statistical analyses to investigate 357 U.S. patients with CHC from a university medical center and a regional veteran administration medical center. **RESULTS:** The prevalence of elevated serum AFP (i.e., ≥ 10.0 microg/L) was 23.0%, including 15.3% (28/183), 24.5% (25/102), and 42.0% (29/69) in patients with chronic hepatitis C and stage 0-II, III, and IV hepatic fibrosis, respectively. After adjusting for age, HCV load, and hepatic steatosis, stage III/IV fibrosis, elevated aspartate aminotransferase (AST), and prolonged prothrombin time as measured by international normalized ratio (INR) remained independently associated with elevated serum AFP in these patients. A serum AFP level of 15.0 microg/L was 22.8% sensitive and 94.5% specific for stage III/IV fibrosis. **CONCLUSIONS:** In patients with chronic hepatitis C, 23.0% had elevated serum AFP that is independently associated with stage III/IV hepatic fibrosis, elevated level of AST, and prolonged INR.

PMID: 15128351 [PubMed - indexed for MEDLINE]

6: Am J Gastroenterol. 2004 May;99(5):855-9.

Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study.

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The risk of sexual transmission of hepatitis C virus (HCV) infection was evaluated among 895 monogamous heterosexual partners of HCV chronically infected

individuals in a long-term prospective study, which provided a follow-up period of 8,060 person-years. Seven hundred and seventy-six (86.7%) spouses were followed for 10 yr, corresponding to 7,760 person-years of observation. One hundred and nineteen (13.3%) spouses (69 whose infected partners cleared the virus following treatment and 50 who ended their relationship or were lost at follow-up) contributed an additional 300 person-years. All couples denied practicing anal intercourse or sex during menstruation, as well as condom use. The average weekly rate of sexual intercourse was 1.8. Three HCV infections were observed during follow-up corresponding to an incidence rate of 0.37 per 1,000 person-years. However, the infecting HCV genotype in one spouse (2a) was different from that of the partner (1b), clearly excluding sexual transmission. The remaining two couples had concordant genotypes, but sequence analysis of the NS5b region of the HCV genome, coupled with phylogenetic analysis showed that the corresponding partners carried different viral isolates, again excluding the possibility of intraspousal transmission of HCV. Our data indicate that the risk of sexual transmission of HCV within heterosexual monogamous couples is extremely low or even null. No general recommendations for condom use seem

required for individuals in monogamous partnerships with HCV-infected partners.
PMID: 15128350 [PubMed - indexed for MEDLINE]

7: Am J Gastroenterol. 2004 Apr;99(4):636-44.

Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study.

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OBJECTIVES: Fibrotic severity, biochemical indices of poor liver function, and sporadic transmission are independent predictors of liver complications among people with chronic hepatitis C. After accounting for these factors, we tested whether interferon treatment or the treatment response reduces the rate of liver cancer, liver-related death or transplantation, and other liver complications during extended follow-up. **METHODS:** Liver clinic cohort of 455 patients with histologically proven chronic hepatitis C was followed prospectively for median 9 yr (IQ 6, 11 yr); 384 received interferon, 343 completed a treatment course. Liver complications were assessed in relation to treatment and treatment response in univariate and multivariate models, and survival to onset of liver-related complications was determined. **RESULTS:** The annual incidence of total liver complications was 1.5% in treated and 2.9% in untreated patients and appeared quasilinear throughout 9-yr follow-up. Interferon treatment did not influence the rate of liver complications. However, the rate of complications increased exponentially with transition of the treatment response from sustained viral response (SVR), through response-relapse to nonresponse (or no treatment). By univariate analysis, response to interferon treatment was a significant predictor of complications. After adjustment for fibrosis score, serum albumin concentration and mode of transmission in a multivariate model, treatment response just failed to reach significance ($p=0.058$) as a predictor of outcome. **CONCLUSIONS:** Response to antiviral therapy, and particularly SVR, appears to reduce liver complications in chronic hepatitis C. However, in the absence of an antiviral treatment response, a course of interferon does not reduce risks of liver cancer or liver failure.

Review, Multicase

PMID: 15089895 [PubMed - indexed for MEDLINE]

8: Am J Hematol. 2004 Jun;76(2):107-13.

Use of alveolar carbon monoxide to measure the effect of ribavirin on red blood cell survival.

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A major side effect of ribavirin (RBV) treatment is anemia. While this anemia is thought to result from increased RBC turnover, RBC survival has not been determined in subjects receiving RBV due to the complexity of the techniques commonly used to quantitate RBC life span. We recently described a simple, rapid, non-invasive technique that utilizes measurements of alveolar carbon monoxide (CO) concentration to determine RBC survival. In the present report, this method was employed to assess RBC survival in patients receiving RBV for hepatitis C. Each of the 31 measurements of RBC survival in 12 subjects with RBV-associated anemia was below the lower limit of normal (77 days), and the average survival (46 ± 14 days) in these subjects was only about 38% of that of healthy controls (122 ± 23 days). Five hepatitis C patients not undergoing RBV treatment had normal RBC survivals (112 ± 17 days). While the mean reticulocyte percentage was significantly elevated in subjects treated with RBV, 59% of these measurements fell within the limits of normal. We conclude that

RBV-associated anemia consistently is associated with reduced RBC survival as determined from breath CO measurements and that this reduced survival frequently is not associated with an elevated reticulocyte count.

PMID: 15164374 [PubMed - indexed for MEDLINE]

9: Am J Med. 2004 Jun 1;116(11):749-52.

Accelerated decline in lung function and impaired reversibility with salbutamol in asthmatic patients with chronic hepatitis C virus infection: a 6-year follow-up study.

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PURPOSE: Chronic hepatitis C virus (HCV) infection may have adverse effects on pulmonary function in patients with chronic obstructive pulmonary disease. This prospective study was designed to determine whether chronic HCV infection affects decline in lung function and airway responses to salbutamol in asthmatic patients. **METHODS:** Interferon alpha (6 MIU three times a week for 6 months) was given to 55 HCV-positive asthmatic patients, 18 of whom had a virologic response to interferon. Pre- and postbronchodilator forced expiratory volume in 1 second (FEV(1)) and reversibility with salbutamol or oxitropium at years 1, 3, and 6 after interferon therapy were examined. **RESULTS:** We found a significant decrease in pre- and postbronchodilator FEV(1) from year 1 to years 3 and 6 only in interferon nonresponders. Reversibility with salbutamol at years 3 and 6 was significantly lower in interferon nonresponders than in HCV-negative patients ($P < 0.0001$) and interferon responders ($P < 0.0001$). Moreover, there was a steep decline in reversibility with salbutamol during the follow-up period only in interferon nonresponders. In contrast, reversibility with oxitropium at years 3 and 6 was significantly higher in interferon nonresponders than in HCV-negative patients and interferon responders, and there was a steep increase in reversibility with oxitropium only in interferon nonresponders. In addition, declines in the diffusing capacity of the lung for carbon monoxide during follow-up were significantly greater in interferon nonresponders than in HCV-negative patients and interferon responders. **CONCLUSION:** Chronic HCV infection is associated with an accelerated decline in lung function and impaired reversibility with salbutamol among asthmatic patients who do not respond to interferon therapy.

Publication Types:

Clinical Trial

PMID: 15144911 [PubMed - indexed for MEDLINE]

10: Antivir Ther. 2004 Apr;9(2):275-86.

Meta-analysis of mutations in the NS5A gene and hepatitis C virus resistance to interferon therapy: uniting discordant conclusions.

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BACKGROUND: Hepatitis C virus genotype 1B responds poorly to treatment with interferon, in contrast to the more interferon-sensitive genotypes 2 and 3. Studies on combination therapy regimens with PEG-interferon and ribavirin report sustained response rates that generally do not exceed 50%, in contrast to sustained response rates of 80% for genotype 2 and 3. In Japan, a correlation was found between the number of mutations in an 'interferon sensitivity determining region' (ISDR) and outcome of interferon treatment in genotype 1B-infected patients. However, an ongoing controversy on the existence of an ISDR in non-Japanese isolates resulted, as non-Japanese studies failed to confirm this association. The present study approached this issue by carrying

out a meta-analysis of ISDR sequences and response to interferon treatment. METHODS: Twenty-seven studies were included, reporting 1351 ISDR sequence data of genotype 1B-infected patients and their virological response to interferon treatment. Both summary statistics and individual patient data were used systematically to explore the association between ISDR mutations and response to interferon. RESULTS: The ISDR effect on response was universally present but appeared to be stronger in Japan, with a relative risk of 5.73 for mutant viruses as compared to 4.66 for non-Japanese isolates. High interferon dose, in Japan administered more frequently, was associated with an increase in response rate only among patients infected with mutant isolates. Interaction between dose and ISDR type was confirmed in a logistic regression model. After stratifying for dose, differences in response rate between Japanese and non-Japanese patients were no longer present. CONCLUSION: This study puts an end to a longstanding controversy by confirming the universal existence of an ISDR in genotype 1B-infected patients. Apparent discrepant findings from Japanese and non-Japanese studies can be explained by differences in dosing regimens and a dose-dependent differential effect of ISDR mutations on response to treatment. Publication Types:

Meta-Analysis

PMID: 15134190 [PubMed - indexed for MEDLINE]

11: Arch Virol. 2004 May;149(5):1015-26. Epub 2004 Jan 29.

Phylogenetic conservation of the stem-loop III structure of the 5' untranslated region of Hepatitis C virus RNA among natural variants in samples collected from Southern India.

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The stem-loop III (SLIII) structure within the 5' untranslated region has been shown to be critical for internal initiation of translation of Hepatitis C virus (HCV). Using 'Single Strand Conformation Polymorphism (SSCP)' of the SLIII region we have investigated for natural mutations and demonstrated presence of some non-covariant changes in certain sub-domains. However, overall SLIII-RNA structure was found to be phylogenetically conserved. Additionally, by SSCP analysis we have determined the genotype of 50 HCV isolates collected from Southern India, 25 random samples were confirmed by DNA sequencing. Results showed the prevalence of genotype 1 in this part of India.

PMID: 15098115 [PubMed - indexed for MEDLINE]

12: Can J Public Health. 2004 May-Jun;95(3):188-92.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in a Northern Alberta population.

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OBJECTIVE: To describe the demographics and estimate the prevalence of hepatitis C virus (HCV) in a cohort of Human Immunodeficiency Virus (HIV) positive patients in Northern Alberta. METHODS: A cross-sectional (prevalence) study was performed on a cohort of HIV-positive patients. HCV testing was not widely available until December 1989, and the more sensitive, second generation immunoassay was not available until 1992. To reduce the effect of testing bias, we restricted consideration of HCV status to patients first seen January 1, 1992 onward. RESULTS: Forty-four percent of patients in the whole cohort were tested for HCV (564/1,276) and 62% (505/809) of patients entered since January 1, 1992 were tested for HCV. During the period January 1, 1992-December 31, 1999, the prevalence of HCV in our cohort of northern Alberta HIV-positive patients was at

least 37.9% (307/809) and was 60.8% (307/505) among those who were tested for HCV in 1992 or later. The mean age of the co-infected group was 33.6 years, 66.1% were male, 91.2% were injection drug users (IDUs), 56.8% were Caucasian, and 40.0% were Aboriginal. A statistically significant difference was found between the HCV-negative cohort, the HCV co-infected cohort, and the HCV-untreated cohort for the following variables: risk behaviour, gender, ethnic status, death, occurrence of an AIDS-defining illness ($p < 0.0001$), and mean baseline CD4 cell count ($p = 0.002$). CONCLUSION: A high proportion of the HIV-infected IDUs was co-infected with HCV. Compared to the HCV-negative group, the co-infected group appears to have had less advanced HIV disease. This is likely a reflection of more recent HIV infection in the HCV co-infected group. PMID: 15191121 [PubMed - indexed for MEDLINE]

13: Cancer Lett. 2004 May 10;208(1):75-9.

Codon 72 polymorphism of P53 gene does not affect the risk of cirrhosis and hepatocarcinoma in HCV-infected patients.

Leverì M, Gritti C, Rossi L, Zavaglia C, Civardi E, Mondelli MU, De Silvestri A, Silini EM.

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Chronic hepatitis C virus (HCV) infection is the most frequent cause of progressive liver disease and liver cancer in the West. The p53 tumor suppressor gene is known to play an important role in carcinogenesis of different tissues being involved in gene transcription, DNA synthesis and repair and somatic mutations of p53 are common in primary liver cancer. The p53 gene displays a common genetic Arg/Pro polymorphism at codon 72 with functional significance, that has been investigated as risk factor in several cancer models. We analyzed p53 codon 72 polymorphism in a group of 340 HCV-infected subjects at different stages of disease, including 84 hepatocellular carcinoma patients. No association between codon 72 genotypes and disease severity or liver cancer was observed.

PMID: 15105048 [PubMed - indexed for MEDLINE]

14: Clin Exp Immunol. 2004 Jun;136(3):507-12.

Kinetics of soluble tumour necrosis factor (TNF)-alpha receptors and cytokines in the early phase of treatment for chronic hepatitis C: comparison between interferon (IFN)-alpha alone, IFN-alpha plus amantadine or plus ribavirin.

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We have previously studied the effect of three different treatment regimens with interferon (IFN)-alpha alone or in combination with amantadine or ribavirin on viral kinetics in the first month of therapy. To understand the regulation of cytokine immune response during early inhibition of HCV replication, we analysed the longitudinal profile of proinflammatory markers (soluble TNFRs), of type 1 cytokines [IFN-gamma and interleukin (IL-12)], and of a type 2 cytokine (IL-10). Twenty-two chronic hepatitis C patients received daily therapy for 6 months. Sera were collected at baseline, at 6, 12, 24, 30 and 48 h and at the 3rd, 7th, 15th and 30th days of treatment. All cytokines and receptors were evaluated by enzyme linked immunosorbent assay (ELISA). At baseline, a correlation was found between the two soluble TNFRs ($P < 0.0001$) and between the soluble TNFRs and ALT

levels ($P < 0.003$), as shown previously. Regardless of the type of treatment, lower levels of soluble TNFR-p75 were present from day 3 in patients who had significant virus decay at day 30 ($P < 0.01$). Baseline IL-10 levels correlated with TNFR-p75 ($P < 0.01$) and with treatment response ($P < 0.05$) and a significant IL-10 reduction from baseline was observed from day 3 among

responders, irrespective of the type of treatments ($P < 0.05$). IL-12 and IFN-gamma levels did not differ according to treatment or outcome. These findings suggest a pivotal role for IL-10 in orchestrating the antiviral immune response. Its early decline can favour the shift from a Th2 to a Th1 immune response, which has been shown to be associated with a long-term virological response to treatment.

PMID: 15147353 [PubMed - indexed for MEDLINE]

15: Clin Exp Immunol. 2004 Jun;136(3):501-6.

Thymic volume is associated independently with the magnitude of short- and long-term repopulation of CD4+ T cells in HIV-infected adults after highly active antiretroviral therapy (HAART).

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Age is one of the main factors involved in the rapidity and the magnitude of CD4(+) T cell repopulation in human immunodeficiency virus (HIV)-infected patients on highly active antiretroviral treatment (HAART). Improved thymic function has been suggested as the main factor associated with CD4(+) T cell restoration after HAART. This work was undertaken to determine, among host factors, the predictor variable at baseline involved in the magnitude of short- and long-term recovery of CD4(+) T cells after HAART. HIV-RNA levels and CD4(+) T cell numbers were determined in 54 HIV-infected adults at baseline and at weeks 4, 12, 48 and 96 after HAART. T cell subpopulations were determined by flow cytometry, thymic volume by computed tomography, T cell receptor excision circle (TREC)-bearing cells by quantitative polymerase chain reaction (PCR) and interleukin (IL)-7 levels by enzyme linked immunosorbent assay at baseline. The phenotype of patients' isolates was determined by infecting GHOST cells expressing CCR5 and CXCR4. The possible interference of phenotype with thymic function was also analysed. Baseline thymic volume was associated independently with the magnitude of short- and long-term recovery of CD4(+) T cells after HAART, despite the patients' viral phenotype. The measurement of thymic volume before therapy may predict the magnitude of T cell increase. This result could have important clinical implications not only in HIV-infected patients, but also in other scenarios of T cell depletion such as bone marrow transplantation and chemotherapy.

PMID: 15147352 [PubMed - indexed for MEDLINE]

16: Clin Gastroenterol Hepatol. 2004 May;2(5):440-3.

Differential efficacy of corticosteroids and interferon in a patient with chronic hepatitis C-autoimmune hepatitis overlap syndrome.

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The chronic hepatitis C-autoimmune hepatitis (AIH) overlap syndrome has been described in the literature, but to date appropriate therapy remains controversial. We report on a 28-year-old woman with hepatitis C-AIH overlap syndrome. The patient was infected with HCV genotype 1b and had laboratory and immunologic findings of AIH type 2 such as increased Igs and a high titer of antibodies against liver-kidney microsomes. Initial liver biopsy specimen demonstrated end-stage liver fibrosis due to chronic hepatitis. After long-lasting corticosteroid treatment, only partial remission was achieved. In contrast, short-term antiviral therapy with interferon-alpha2b in combination with ribavirin was followed by complete biochemical and virologic remission. However, 15 months later, a relapse of AIH was observed. After restarting

corticosteroid treatment, transaminase levels completely normalized. Surprisingly, in this patient with overlap syndrome, short-term interferon therapy induced complete remission of chronic HCV infection and regression of severe liver fibrosis.

Publication Types:

Case Reports

PMID: 15118984 [PubMed - indexed for MEDLINE]

17: Clin Gastroenterol Hepatol. 2004 May;2(5):432-9.

Impact of highly active antiretroviral therapy on the spectrum of liver disease in HCV-HIV coinfection.

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BACKGROUND & AIMS: Hepatitis C virus (HCV) coinfection is common in patients with human immunodeficiency virus (HIV) infection. The mortality associated with HIV has decreased dramatically with the introduction of highly active antiretroviral therapy (HAART). However, the impact of HAART, including protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors (NRTIs), and non-NRTIs (NNRTIs), on the spectrum of HCV-related liver disease remains unclear. The purpose of this retrospective analysis is to determine the impact of PI and NNRTI use on liver histological characteristics in patients with stable HIV-HCV coinfection (n = 101) compared with HIV-uninfected controls with HCV infection (n = 302). **METHODS:** The majority of coinfecting patients were men (75%), African American (82%), and had genotype 1 HCV (91%). Mean HIV load was

1.52 log copies/mL, 48% had undetectable HIV RNA and a mean CD4 count of 528 cells/microL, and 11% had a CD4 count < 200 cells/microL. Both mean alanine aminotransferase (ALT) level (83 U/L; 54% had a normal ALT level) and Knodell Histological Activity Index score (7.04; 33% had advanced fibrosis) were similar to those of our control population. Ninety-three percent of patients were administered a mean of 3 antiretroviral medications: NRTIs in 98%, NNRTIs in 45%, and PIs in 54%. **RESULTS:** There were no significant differences in biochemical or histological parameters between patients administered or not administered PIs or NNRTIs. **CONCLUSIONS:** In this uncontrolled retrospective analysis, we were unable to show a significant impact of either PI or NNRTI use on the spectrum of liver disease.

PMID: 15118983 [PubMed - indexed for MEDLINE]

18: Clin Gastroenterol Hepatol. 2004 May;2(5):425-31.

Effectiveness of interferon alpha-2b and ribavirin combination therapy in the treatment of naive chronic hepatitis C patients in clinical practice.

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BACKGROUND & AIMS: Studies in many diseases have shown that efficacy in clinical trials often does not translate into effectiveness in clinical practice. The aims of this study were to determine the rate of sustained virological response (SVR) and the factors associated with SVR in therapy naive chronic hepatitis C patients treated with interferon alpha-2b and ribavirin combination therapy at a university outpatient clinic. **METHODS:** The medical records of 153 consecutive chronic hepatitis C patients treated between June 1998 and May 2001 were reviewed. **RESULTS:** The mean subject age was 44 years, 64% were men, 85% were white, 56% had HCV genotype 1, and 21% had cirrhosis on biopsy. The overall SVR rate was 42% (29% in genotype 1/4; 65% in genotype 2/3). Side effects resulted

in interferon or ribavirin dose reductions in 22% of patients and premature termination of treatment in 10%. The SVR rate was significantly higher in the 102 patients who received >80% of the recommended dose and duration of therapy compared with the 51 patients who did not (53% vs. 20%, $P = 0.00008$). HCV genotype, subject race, and adherence were independently associated with SVR ($P < 0.01$). Although the incidence of side effects and medication adherence was similar in blacks and whites, adherent blacks had a significantly lower SVR rate (14% vs. 58%, $P < 0.01$). CONCLUSIONS: Despite the inclusion of a broader spectrum of patients and less frequent monitoring, combination antiviral therapy in our treatment-naïve chronic hepatitis C patients was of similar efficacy to that reported in large multicenter trials. In addition, our data show that medication adherence is an important predictor of SVR in an academic clinical practice.

PMID: 15118982 [PubMed - indexed for MEDLINE]

19: Clin Infect Dis. 2004 Jun 1;38 Suppl 5:S398-401.

Addressing the need for treatment paradigms for drug-abusing patients with multiple morbidities.

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Persons who use and abuse drugs are at risk for multiple morbidities that involve addiction, bloodborne infectious diseases, and sexually transmitted diseases, in addition to psychiatric illness and social instability. Infectious diseases acquired as a result of drug use can diffuse into non-drug using populations through other high-risk behaviors. Drug users also have substantial comorbidities from noncommunicable diseases and complications that can affect virtually every organ system in the body. Diagnosis of comorbidities and complications associated with drug abuse usually occurs late in the disease course, particularly for persons who are disenfranchised and have limited or no access to medical care. Medical management of these comorbid conditions constitutes a significant challenge. Directly observed therapy (DOT) can be useful but needs to conform to the needs of the targeted treatment population for full efficacy. DOT may have its greatest impact with drug users destabilized by cocaine or methamphetamine use but has yet to be fully investigated in this patient population.

PMID: 15156429 [PubMed - indexed for MEDLINE]

20: Curr Opin Infect Dis. 2004 Jun;17(3):193-8.

Immune responses in hepatitis C: is virus or host the problem?

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PURPOSE OF REVIEW: Hepatitis C virus is an RNA virus that usually establishes persistent infection in its host. As an important cause of cirrhosis and hepatocellular carcinoma worldwide, hepatitis C is a growing public health concern. Despite recent advances in therapy, most people infected with the virus can expect lifelong infection. In the minority of those exposed and who spontaneously clear virus, a robust hepatitis C virus-specific T cell response of T helper 1 type correlates with resolution. The longevity of this response in the recovered state and the potential for hepatitis C virus-specific T cells to protect against future infection are critical parameters for vaccine design.

RECENT FINDINGS: The literature of the past year dissected components of protective immunity to hepatitis C and emphasized the importance of the CD4 helper response in both the expansion and maintenance of hepatitis C

virus-specific CD8(+) T cells. Other important studies examined how the virus interacts with immune cells to subvert both innate and adaptive immune responses in acute and chronic infection. SUMMARY: Defining the essential components of protective immunity against a highly mutable virus like hepatitis C underpins successful vaccine design. By understanding viral and host factors which influence hepatitis C virus-specific T cell maintenance and function, we are better equipped to devise immunomodulatory therapies and vaccines which induce robust and lasting immunity.

Publication Types:

Review

Review, Tutorial

PMID: 15166820 [PubMed - indexed for MEDLINE]

21: Epidemiol Infect. 2004 Jun;132(3):409-15.

The prevalence and the risk behaviours associated with the transmission of hepatitis C virus in Australian correctional facilities.

Hellard ME, Hocking JS, Crofts N.

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This study measured the prevalence and the risk factors associated with HCV antibody-positive prisoners. A total of 630 prisoners completed a questionnaire about risk behaviours associated with HCV transmission and were tested for HCV antibody from a blood test. Of these 362 (57.5%) prisoners were HCV antibody positive. A total of 436 (68.8%) prisoners reported ever injecting drugs and 332 reported injecting drugs in prison. HCV-positive prisoners were more likely to have injected drugs (OR 29.9) and to have injected drugs in prison during their current incarceration (OR 3.0). Tattooing was an independent risk factor for being HCV positive (OR 2.7). This is the first study conducted on prisoners that has identified having a tattoo in prison as a risk factor for HCV. Injecting drugs whilst in prison during this incarceration was also a risk factor for HCV. Our results show prisoners who injected drugs outside of prison continue to inject in prison but in a less safe manner.

PMID: 15188710 [PubMed - indexed for MEDLINE]

22: Gastroenterology. 2004 May;126(5):1302-11.

Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study.

Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ; Proactive Study Group.

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BACKGROUND & AIMS: Combination therapy with interferon alpha (IFN-alpha) and ribavirin (RBV) or pegylated IFN-alpha (PEG-IFN-alpha)/RBV for chronic hepatitis C virus (HCV) infection often causes anemia, prompting RBV dose reduction/discontinuation. This study assessed whether epoetin alfa could maintain RBV dose, improve quality of life (QOL), and increase hemoglobin (Hb) in anemic HCV-infected patients. METHODS: HCV-infected patients (n = 185) on combination therapy who developed anemia (Hb < or = 12 g/dL) were randomized into a U. S. multicenter, placebo-controlled, clinical trial of epoetin alfa, 40,000 U subcutaneously, once weekly vs. matching placebo. The study design used an 8-week, double-blind phase (DBP) followed by an 8-week, open-label phase (OLP), in which placebo patients were crossed over to epoetin alfa. RESULTS: At the end of the DBP, RBV doses were maintained in 88% of patients receiving epoetin alfa vs. 60% of patients receiving placebo (P < 0.001). Mean QOL scores at the end of the DBP improved significantly on all domains of the Linear Analog Scale Assessment (LASA) and on 7 of the 8 domains of the Short Form-36, version

2 (SF-36v2). Mean Hb increased by 2.2 +/- 1.3 g/dL (epoetin alfa) and by 0.1 +/- 1.0 g/dL (placebo) in the DBP (P < 0.001). Similar results were demonstrated in patients who switched from placebo to epoetin alfa in the OLP. Epoetin alfa was well tolerated; the most common adverse effects were headache and nausea. CONCLUSIONS: Epoetin alfa maintained RBV dose and improved QOL and Hb in anemic

HCV-infected patients receiving combination therapy.

Publication Types:

Clinical Trial

Multicenter Study

Randomized Controlled Trial

PMID: 15131791 [PubMed - indexed for MEDLINE]

23: Hum Pathol. 2004 May; 35(5):636-8.

Severe steatosis as the initial histologic manifestation of recurrent hepatitis C genotype 3.

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Steatosis is a common finding that is seen in patients with both chronic hepatitis C and alcoholic liver disease; however, the extent of involvement in the former is generally minimal to mild. We present 2 patients who underwent live donor liver transplantation for end-stage liver disease that was caused by chronic hepatitis C (genotype 3) and alcohol abuse. Both patients presented with liver allograft dysfunction, with liver biopsy findings of moderate to marked steatosis. Exclusion of a relapse of alcohol use required intense questioning of both the patients and their families. A definitive diagnosis of recurrent hepatitis C was established by viral markers with institution of the proper therapy and resolution of graft dysfunction. We conclude that recurrent hepatitis C, particularly genotype 3, may present with severe steatosis. Recognition of this phenomenon is important, and confirmation with viral markers is necessary to provide optimal patient care.

Publication Types:

Case Reports

PMID: 15138942 [PubMed - indexed for MEDLINE]

24: Int J Cancer. 2004 Jun 20; 110(3): 380-5.

Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy.

Talamini R, Montella M, Crovatto M, Dal Maso L, Crispo A, Negri E, Spina M, Pinto A, Carbone A, Franceschi S.

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HCV has been associated with NHL, but the evidence from case series and case-control studies is not totally consistent. Between 1999 and 2002, we conducted a hospital case-control study on the association between HCV, HBV and NHL in 2 areas of Italy where HCV infection is relatively frequent. Cases (n = 225, median age 59 years) were consecutive patients with a new diagnosis of NHL admitted to local specialized and general hospitals. Controls (n = 504, median age 63 years) were patients with a wide spectrum of acute conditions admitted to the same hospitals as cases. HCV prevalence was 19.6% among NHL cases and 8.9%

among controls (adjusted OR = 2.6, 95% CI 1.6-4.3). The ORs for HCV were similar for low-grade and intermediate-/high-grade B-cell NHL (3.2 and 2.4, respectively) as well as for nodal and extranodal NHL (2.7 and 2.6, respectively). Positivity for HBsAg was found in 3.8% of cases and 0.9% of

controls (OR = 4.1, 95% CI 1.2-14.4). An elevated OR was also found for history of hepatitis C (OR = 4.7, 95% CI 2.3-9.5). History of blood transfusion before 1990 was associated with HCV positivity among controls but not with NHL risk. In conclusion, HCV infection was associated with an increase in NHL risk, and the fraction of NHL cases attributable to HCV was 12.4% (range 6.3-18.5%). Copyright 2004 Wiley-Liss, Inc.
PMID: 15095303 [PubMed - indexed for MEDLINE]

25: J Bone Joint Surg Am. 2004 May;86-A(5):1065-76.
Transmission and prevention of occupational infections in orthopaedic surgeons.
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Microorganisms are transmitted in hospitals mainly by contact, droplet, and airborne routes. Orthopaedic surgeons have a substantial occupational risk of contracting a blood-borne infection because of frequent handling of sharp instruments and objects during operative procedures. Aerosolization means the formation of aerosols and droplets when blood or other body fluids are mechanically disturbed. Smaller particles (<5 microm) will remain suspended in air. Pathogens that can survive in these small airborne particles may cause infection if they are inhaled. Aerosol-generating procedures in patients with tuberculosis or severe acute respiratory syndrome (SARS) may facilitate airborne transmission. The Hospital Infection Control Practices Advisory Committee and the Centers for Disease Control and Prevention have established guidelines for isolation precautions in hospitals.

Publication Types:

Review

Review, Tutorial

PMID: 15118055 [PubMed - indexed for MEDLINE]

26: J Clin Virol. 2004 Jun;30(2):175-82.

Improved detection of HCV Infection in hemodialysis patients using a new HCV RNA qualitative assay: experience of a transplant center.

Khan N, Aswad S, Shidban H, Aghajani M, Mendez R, Mendez R, Comanor L.
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BACKGROUND: Hepatitis C virus (HCV) is frequently a silent infection in hemodialysis (HD) patients with a prevalence of 8-10%. Improving HCV detection in this population prior to transplantation is critical both for infection control and optimal patient care. OBJECTIVES: To assess the current HCV testing practice of the National Institute for Transplantation (PCR testing of enzyme immunoassay (EIA) positive HD patients) by evaluating a subset of EIA positive and EIA negative samples with the VERSANT HCV RNA Qualitative Assay based on transcription mediated amplification (HCV Qual (TMA)) (sensitivity < or = 9.6 IU/ml) and in-house PCR (HCV Qual (PCR)) (sensitivity approximately 149 IU/ml). STUDY DESIGN: 2321 HD patients were screened by Abbott HCV EIA 2.0. A subset of

80/169 EIA positive samples and 100/2152 EIA negative samples were tested by both assays. TMA/PCR discordant samples were genotyped. RESULTS: PCR and TMA gave concordant results in 67/80 (83.8%) of EIA positive samples. 11/80 (14.7%) were reactive by HCV Qual (TMA), but not by HCV Qual (PCR); 2/80 (2.7%) were reactive by HCV Qual (PCR), but not by HCV Qual (TMA). 2/100 (2%) EIA negative samples were reactive and 95/100 (95%) were non-reactive by both assays. Three (3%) were only HCV Qual (TMA) reactive. 11/14 TMA+/PCR-samples with sufficient volume were genotyped. CONCLUSIONS: HCV Qual (TMA) identified active HCV infection in more EIA positive and EIA negative patients than HCV Qual (PCR) and

should be part of our testing algorithm.

Publication Types:

Multicenter Study

PMID: 15125874 [PubMed - indexed for MEDLINE]

27: J Dermatol. 2004 Apr; 31(4):293-8.

Diabetes and hepatitis frequency in 140 lichen planus cases in Cukurova region.

Denli YG, Durdu M, Karakas M.

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The aim of the present study was to determine the Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and diabetes mellitus (DM) frequencies in lichen planus (LP) cases in our region. We performed a retrospective review of records from all cases that were diagnosed with LP at the our department between 1997 and 2002. The results were compared with the control group (any type of dermatosis other than LP). The 260 LP cases included 108 (41.5%) males and 152 (58.5%) females aged between 5 and 78 years. The clinical distribution of the lesions were 127 (48.8%) with skin lesions and 133 (51.2%) with oral mucosal lesions. The duration of disease ranged from 1 to 240 months. In 140 of 260 LP cases, hepatitis serology and pre-prandial blood glucose were examined. We found HBV positivity in 24 (17.1%) cases, Anti-HCV positivity in 7 (5%) cases, and DM in 22 (15.7%) cases. The control group included 116 (41.4%) males and 164 (58.6%) females. Their ages ranged between 10 and 82 years. In this group, we found HBV positivity in 20 (7.1%), Anti-HCV positivity in 4 (1.4%), and DM in 20 (7.1%) cases. We believe that the co-association of LP with HCV is significant and this co-association ratio indicates variance depending on clinical attributes of the lesions and racial characteristics of the patients. Although we found co-associations between HBV and LP or DM and LP, we believe that further studies are necessary to determine if they are significant.

PMID: 15187324 [PubMed - indexed for MEDLINE]

28: J Gen Virol. 2004 Jun; 85(Pt 6):1521-31.

Identification of novel hepatitis C virus-specific cytotoxic T lymphocyte epitopes by ELISpot assay using peptides with human leukocyte antigen-A*2402-binding motifs.

Hakamada T, Funatsuki K, Morita H, Ugajin T, Nakamura I, Ishiko H, Matsuzaki Y, Tanaka N, Imawari M.

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The human leukocyte antigen (HLA)-A*2402 is common in Asians. The authors attempted to identify epitopes for HLA-A*2402-restricted, hepatitis C virus (HCV)-specific CD8(+) T cells by an enzyme-linked immunospot (ELISpot) assay using peripheral blood CD8(+) T cells from HLA-A*2402-positive hepatitis C patients and synthetic HCV peptides based on HLA-A*2402-binding motifs and the amino acid sequence of type 1b HCV. Ten novel epitopes were identified in five of seven HLA-A*2402-positive patients with acute or short-term chronic HCV infection (<3 years), but in none of four with longer-term chronic infection (>10 years). Only one of the ten epitopes proved to be definitely HLA-A*2402-restricted. Another epitope was identified in one of two HLA-A*2402-negative acute hepatitis C patients. In two of the six patients with positive CD8(+) T cell responses, the targeted epitopes were multiple. The same epitope was targeted in two patients. When patients with unresolved acute HCV infection were treated with alpha interferon, peripheral blood HCV-specific CD8(+) T cells decreased with resolution of the hepatitis. In conclusion, CD8(+) T cell responses to HCV infection are heterogeneous. One definite HLA-A*2402-restricted and ten probably non-HLA-A*2402-restricted epitopes were

identified. Patients with short-term HCV infection are suitable for searching for novel HCV epitopes, but peripheral blood HCV-specific CD8(+) T cells decrease markedly after loss of antigenic stimulation.
PMID: 15166436 [PubMed - indexed for MEDLINE]

29: J Gen Virol. 2004 Jun;85(Pt 6):1497-507.

Characterization of the genome and structural proteins of hepatitis C virus resolved from infected human liver.

Nielsen SU, Bassendine MF, Burt AD, Bevitt DJ, Toms GL.

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In the absence of satisfactory cell culture systems for hepatitis C virus (HCV), virtually all that is known about the proteins of the virus has been learned by the study of recombinant proteins. Characterization of virus proteins from patients with HCV has been retarded by the low virus titre in blood and limited availability of infected tissue. Here, the authors have identified a primary infection in a liver transplanted into an immunodeficient patient with chronic HCV. The patient required re-transplant and the infected liver, removed 6 weeks after the initial transplant, had a very high titre of HCV, 5×10^9 International Units (IU) per gram of liver. The density distribution of HCV in iodixanol gradients showed a peak at $1.04 \text{ g} \times \text{ml}^{-1}$ with 73 % of virus below $1.08 \text{ g} \times \text{ml}^{-1}$. Full-length HCV RNA was detected by Northern blotting and the ratio between positive- and negative-strand HCV RNA was determined as 60. HCV was partially purified by precipitation with heparin/Mn(2+) and a single species of each of the three structural proteins, core, E1 and E2, was detected by Western blotting. The molecular mass of core was 20 kDa, which corresponds to the mature form from recombinant sources. The molecular mass of glycoprotein E1 was 31 kDa before and 21 kDa after deglycosylation with PNGase F or endoglycosidase H. Glycoprotein E2 was 62 kDa before and 36 kDa after deglycosylation, but E2-P7 was not detected. This was in contrast to recombinant sources of E2 which contain E2-P7.

PMID: 15166434 [PubMed - indexed for MEDLINE]

30: J Immunol Methods. 2004 Apr;287(1-2):91-9.

The use of class-I HLA tetramers for the detection of hepatitis C virus NS3-specific CD8(+) T cells in patients with chronic infection.

Lopez-Labrador FX, He XS, Berenguer M, Cheung RC, Wright TL, Greenberg HB. Department of Medicine (Gastroenterology and Hepatology), Stanford University School of Medicine, CA 94305, USA. fxlopez@teleline.es

BACKGROUND/AIMS: New methods to detect virus-specific T-cell responses have recently been developed. Several human leukocyte antigen (HLA)-peptide tetramers for the detection of hepatitis C virus (HCV)-specific CD8(+) T cells are under evaluation. METHODS: Evaluation of one HLA class I-tetramer (HCVNS3-2) for the detection of HCV NS3-specific CD8(+) T cells in a series of 38 HLA-A2(+) chronically infected patients. RESULTS: Almost half (42%) of the patients had detectable NS3-specific CD8(+) T cells. The frequencies of such cells ranged from 0.01% to 0.22% of total CD8(+) T cells. No significant differences in clinical features or mean viral load were detected between patients with or without tetramer + CD8(+) T cells. CONCLUSIONS: The tetramer HCVNS3-2 may be very useful for the study of the HCV-specific CD8(+) immune response. Combination of this reagent with other tetramers based on other HCV peptides may help in the understanding of the immune response to the virus. However, a panel of tetramers based on several parts of the HCV polyprotein may be a mandatory requirement to explore the whole breadth of the CD8(+) T-cell response against HCV and to detect that response in the majority of patients with chronic infection.

PMID: 15099758 [PubMed - indexed for MEDLINE]

31: J Infect Dis. 2004 May 15;189(10):1846-55. Epub 2004 Apr 26.
Clearance of hepatitis C viremia associated with cellular immunity in the absence of seroconversion in the hepatitis C incidence and transmission in prisons study cohort.

Post JJ, Pan Y, Freeman AJ, Harvey CE, White PA, Palladinetti P, Haber PS, Marinos G, Levy MH, Kaldor JM, Dolan KA, Ffrench RA, Lloyd AR, Rawlinson WD; Hepatitis C Incidence and Transmission in Prisons Study (HITS) Group. Department of Pathology, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia. j.post@unsw.edu.au

Understanding the earliest virological and immunological events in acute hepatitis C virus (HCV) infection may provide insight into the determinants of protective immunity. Four cases of HCV viremia with subsequent viral clearance, but without biochemical hepatitis or anti-HCV seroconversion, are reported from a prospective cohort study of prison inmates. Two of the subjects who developed sustained viremia were assessed for production of interferon (IFN)- gamma, by use of the enzyme-linked immunospot (ELISPOT) method and by assessment of HCV cytotoxic T lymphocyte (CTL) activity, CD4 lymphocyte proliferative responses, HCV load, and genotype. After 2-6 months of viremia, all 4 subjects cleared serum HCV RNA. Specific cellular responses were detected in both of the subjects who were assessed, and production of IFN- gamma was demonstrated in one subject.

All subjects had weak, but consistent, serological reactivity against HCV nonstructural proteins on immunoblot testing, despite repeatedly nonreactive HCV ELISA tests. These cases highlight the potential for cellular immune responses against HCV to facilitate viral clearance, responses that may model those required for effective HCV vaccination.

PMID: 15122521 [PubMed - indexed for MEDLINE]

32: J Trauma. 2004 Apr;56(4):867-72.

Analysis of occupational exposures associated with emergency department thoracotomy.

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BACKGROUND: Although previous studies have examined the cost effectiveness of emergency department thoracotomy (EDT), provider risk has not been included in these analyses. This study examined the costs associated with provider exposure to human immunodeficiency virus (HIV) and hepatitis from percutaneous injury during EDT. **METHODS:** A decision tree describing the occupational risks and costs associated with EDT was created. Exposed providers undergo initial counseling, evaluation, and HIV postexposure prophylaxis and treatment as recommended by the

Centers for Disease Control. Costs are reported from a health care system perspective in year-2000 dollars. The following prevalences were assumed: HIV (7.1%), hepatitis C (18%), and provider percutaneous injury rate (10%). Sensitivity analyses were performed by varying the prevalence of disease and the probability of seroconversion. **RESULTS:** According to the authors' model assumptions, the probability is 0.00004 for HIV and 0.0027 for chronic hepatitis C seroconversion. The total additional cost per thoracotomy associated with an exposure is dollars 1,377. **CONCLUSIONS:** Emergency department thoracotomy is associated with important provider medical risks. Future analyses of EDT should include these factors in reports on the value of this procedure.

PMID: 15187755 [PubMed - indexed for MEDLINE]

33: J Viral Hepat. 2004 May; 11(3):271-6.

Single nucleotide polymorphism of the MxA gene promoter influences the response to interferon monotherapy in patients with hepatitis C viral infection.

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

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The biological activity of interferon (IFN) is mediated by the induction of intracellular antiviral proteins, such as 2'-5' oligoadenylate synthetase, dsRNA-activated protein kinase and MxA protein. Among these, MxA protein is assumed to be the most specific surrogate parameter for IFN action. This study was performed to elucidate whether a single nucleotide polymorphism (SNP) (G/T at nt-88) in the promoter region of the MxA gene influences the response to IFN therapy in patients with chronic hepatitis C virus (HCV) infection.

Polymorphisms of the MxA gene in 235 HCV patients were determined by polymerase chain reaction-restriction fragment length polymorphism. The frequency of SNP was compared between sustained-responders (n = 78) and nonresponders (n = 157),

as determined by biochemical and virological responses to IFN. Multivariate analysis showed that among all patients, HCV genotype, HCV RNA level and the SNP of the MxA gene were independent and significant determinants of the outcome of IFN therapy [odds ratio 3.8 (95% confidence interval 2.0-7.0), $P < 0.0001$; 0.27 (0.15-0.50), $P < 0.0001$; 1.8 (1.0-3.4), $P = 0.0464$, respectively]. Furthermore, among patients with a low viral load ($< \text{or} = 2.0 \text{ Meq/mL}$), MxA-T-positive patients were more likely to show a sustained response compared with MxA-T-negative patients [2.87 (1.3-6.3); 62% vs 36%; $P = 0.0075$]. Our findings suggested that the SNP of the MxA gene is one of the important host factors that independently influences the response to IFN in patients with chronic HCV infection, especially those with a low viral load.

PMID: 15117331 [PubMed - indexed for MEDLINE]

34: J Viral Hepat. 2004 May; 11(3):268-70.

Infection with human herpes virus type 8 in an area at high prevalence for hepatitis C virus infection in southern Italy.

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The Campania Region is a geographical area of southern Italy characterized by high incidence rates of hepatocellular carcinoma and of classic Kaposi's sarcoma. Epidemiological investigations carried out among different population groups in this region have found high prevalence rates of both hepatitis C virus (HCV) and human herpesvirus type 8 (HHV-8). To assess co-infection rates of HCV and HHV-8, we carried out a cross-sectional seroepidemiological study prevalence in Pomigliano d'Arco, a Health District of Campania located 20 km away from Naples. The overall rate of HCV/HHV-8 co-infection was 3.1%, 3.5% among men and 2.7% among women. No difference emerged in the HCV/HHV-8 co-infection rates according to seropositivity for HCV infection, either overall (Mantel Haenszel odds ratio = 1.2, 95% CI: 0.6-2.6) or when the analysis was stratified by gender. These findings support the hypothesis that in Campania common routes of transmission are rarely shared by HCV and HHV-8 infections. Local factors may result in different epidemiological patterns for these two viral infections.

However, our findings have important public health implications, especially in Mediterranean countries where HCV and HHV-8 infections are endemic.

PMID: 15117330 [PubMed - indexed for MEDLINE]

35: J Viral Hepat. 2004 May; 11(3):257-62.

Does an 'autoimmune' profile affect the clinical profile of chronic hepatitis C?
An Italian multicentre survey.

Stroffolini T, Colloredo G, Gaeta GB, Sonzogni A, Angeletti S, Marignani M,
Pasquale G, Venezia G, Craxi A, Almasio P.
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Nonorgan-specific autoantibodies (NOSA) are common in patients with chronic hepatitis C virus infection. It is unclear whether serological markers of autoimmunity segregate in a cohort of cases with more severe liver damage. We assessed the relationship between NOSA and demographic, biochemical and histological features in 502 subjects with anti-HCV positive, HCV-RNA positive, HBsAg negative chronic hepatitis consecutively referred to four Italian liver units. Percutaneous liver biopsy was performed in all subjects. A single pathologist scored the biopsies using histology activity index classification. The overall prevalence of positivity for any NOSA was 36.9%. Antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomal antibodies were found in 15.7, 27.3 and 2.2% of cases. Multivariate analysis showed that gamma-globulin >2 g/dL was the only independent predictor of the likelihood of NOSA positivity (OR, 2.1; 95% CI, 1.3-3.4). No other clinical (age, gender, ALT, HCV genotype) or histological features (grading and staging score, bile ductular damage) were linked to NOSA. Antiviral therapy in 155 subjects with NOSA did not cause any adverse events related to autoimmunity during and after treatment. The presence of NOSA in patients with chronic HCV hepatitis is not related to specific demographic features and has no impact on the biochemical and histological profile of the liver disease at presentation and the response to antiviral treatment.

Publication Types:

Multicenter Study

PMID: 15117328 [PubMed - indexed for MEDLINE]

36: J Viral Hepat. 2004 May;11(3):251-6.

Serum immunoglobulins predict the extent of hepatic fibrosis in patients with chronic hepatitis C virus infection.

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Recently, we documented that immunoglobulins stimulate the proliferative activity of rat hepatic stellate cells in vitro. The aim of the present study was to determine whether there is any association between serum immunoglobulin levels and hepatic fibrosis in patients with chronic hepatitis C virus (HCV) infection. Charts from 116 patients with biochemical, serologic, virologic and histologic evidence of chronic hepatitis C infection and serum immunoglobulin levels (IgA, IgG, IgM and total) were reviewed. The mean (+/-SD) age of the study population was 46 +/- 11 years and 67 (58%) were male. There were significant correlations between serum IgA ($r = 0.39$, $P = 0.00001$), IgG ($r = 0.49$, $P = 0.000002$) and total ($r = 0.51$, $P = 0.000003$) immunoglobulin levels and the stage of hepatic fibrosis. When serum immunoglobulin levels were included into logistic regression analysis with variables known to be associated with advanced disease (male gender, age >40 years at onset of infection, duration of infection beyond 20 years and concurrent alcohol abuse) only IgA, IgG and total immunoglobulin levels ($P < 0.05$, <0.05 and <0.005 , respectively) emerged as independent predictors of hepatic fibrosis. Our data indicate a strong association between serum immunoglobulin levels (IgA, IgG and total) and hepatic fibrosis in patients with HCV infection. This finding supports the need to further investigate whether immunoglobulins independently promote disease progression in patients with chronic HCV infection.

PMID: 15117327 [PubMed - indexed for MEDLINE]

37: J Viral Hepat. 2004 May; 11(3):243-50.

Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection.

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Interferon alpha and ribavirin (RBV) combination therapy is associated with decreases in haemoglobin (Hb) concentrations and anaemia. The aim of this analysis was to better characterize the magnitude and frequency of Hb changes and risk factors. This retrospective analysis evaluated treatment-related changes in Hb in 677 patients who participated in either of two interferon alpha-2b plus RBV studies for chronic hepatitis C virus (HCV) infection. Study 1 included 192 interferon alpha-naive patients randomized to receive RBV 1000-1200 mg/day plus interferon alpha-2b 3 million IU daily or three times weekly for 48 weeks. Study 2 included 485 interferon alpha-experienced patients randomized to receive RBV 1000-1200 mg daily plus interferon alpha-2b 3 million IU daily or three times weekly for 4 weeks, followed by three times weekly dosing for 44 weeks. More than 50% of all patients experienced a decrease in Hb $>$ or $=$ 30 g/L. Women were 4.4 times as likely as men to experience a Hb level of $<$ 100 g/L; however, men were at a 40% higher risk to experience a Hb decline of $>$ 30 g/L from baseline. Daily use of interferon alpha-2b did not impact the magnitude of Hb decrease. In this pooled analysis, RBV dose reduction resulted in increases in Hb concentration of approximately 10 g/L. Lower baseline creatinine clearance, higher baseline Hb levels and increased age were independently associated with increased risk of Hb decreases of $>$ 27.7%. Lower baseline weight was not associated with increased risk of Hb decrease. Substantial Hb decreases occur frequently with interferon alpha/RBV combination therapy. Sex, the magnitude of the Hb decline and renal function are potentially important factors to consider in patients receiving RBV. Further research is needed to determine the impact on virological response and to develop strategies to manage the medical consequences.

Publication Types:

Clinical Trial

Randomized Controlled Trial

PMID: 15117326 [PubMed - indexed for MEDLINE]

38: J Viral Hepat. 2004 May; 11(3):225-35.

Polymorphisms of NS5B protein relates to early clearance of hepatitis C virus by interferon plus ribavirin: a pilot study.

Kumagai N, Takahashi N, Kinoshita M, Tsunematsu S, Tsuchimoto K, Saito H, Ishii H.

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Although randomized trials have shown enhancement of efficacy for combination therapy with interferon (IFN) alpha-2b and ribavirin compared with IFN monotherapy as first-line treatment for chronic hepatitis C, infection with genotype 1b and high viremia are still associated with significantly low response rates compared with non-1 genotypes and low viremia. We analysed amino acid sequences of the viral RNA-dependent RNA polymerase (RdRP) or nonstructural protein 5B (NS5B), responsible for ribavirin misincorporation into RNA products in patients with genotype 1b-related chronic hepatitis C and high viremia, and examined the relationship between such RdRp polymorphisms, and the initial decline in viral load induced by combination therapy with IFN-alpha and ribavirin. Substitution of glutamic acid to lysine at the 124th position (E124K) and of isoleucine to valine at the 85th position (I85V) were found to be closely

associated with a potent decline of viral load and viral clearance at 8 weeks of treatment (five of five patients, coincidence rate 100%). In conclusion, our results suggest that the polymorphisms of E124K and I85V identified in NS5B protein are crucial for early viral clearance in patients with genotype 1b and high viremia by combination therapy with IFN and ribavirin, and that detection of amino acid sequence motifs might enable prediction of clinical efficacy.
PMID: 15117324 [PubMed - indexed for MEDLINE]

39: J Viral Hepat. 2004 May;11(3):206-16.

Effects of interferon and ribavirin combination therapy on CD4+ proliferation, lymphocyte activation, and Th1 and Th2 cytokine profiles in chronic hepatitis C. Marinho RT, Pinto R, Santos ML, Lobos IV, Moura MC.

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We studied the relationship between immunological markers such as CD4+ proliferation, cytokines profile and lymphocyte activation markers in patients with chronic hepatitis C, having different responses to interferon (IFN) and ribavirin (RBV) treatment. A prospective study of 20 patients was conducted, six had received IFN-alpha-2b alone and 14 IFN in combination with RBV. The proliferative immune responses of peripheral blood mononuclear cells to hepatitis C virus peptides and the lymphocyte activation markers (CD25+, CD38+ and CD69+) were assessed before treatment, at 1 week, and 1, 3 and 6 months of treatment. Cytokines interleukin (IL)-2, IFN-gamma, IL-4 and IL-10 were determined in supernatants before onset of treatment and at 1 and 6 months thereafter. Stimulation indices (SI) were higher in the sustained responders (SR), in comparison with those with no response (NR), before treatment (5.2 +/- 3.7 to 3.3 +/- 1.9, P = 0.028) and also at 6 months (7.8 +/- 1.9 to 4.1 +/- 1.2, P = 0.021). Patients with SR also had high SI to NS3 when compared with those with transitory response or no response (NR) (4.9 +/- 2.5 and 3.3 +/- 1.1, P = 0.033). At 1 month, SR had higher supernatant IL-2 than those with NR (133.8 +/- 119.2 to 56.0 +/- 89.3 pg/mL, P = 0.023) and lower levels of IL-10 (13.8 +/- 10.1 and 167.1 +/- 272.0 pg/mL, P = 0.023) in response to NS3. Combination therapy induced a higher percentage of the lymphocyte activation markers CD69+ and CD38+. In conclusion, we found that SR is associated with higher CD4+ proliferation particularly in response to the NS3 region, promoting a T-helper (Th)1/Th0 profile of cytokines, and that combination therapy induced a higher percentage of lymphocyte activation than therapy with IFN alone.

PMID: 15117322 [PubMed - indexed for MEDLINE]

40: J Viral Hepat. 2004 May;11(3):198-205.

Prevention of hepatitis C virus infection.

Kew M, Francois G, Lavanchy D, Margolis H, Van Damme P, Grob P, Hallauer J, Shouval D, Leroux-Roels G, Meheus A; Viral Hepatitis Prevention Board.

South African Medical Research Council/Cancer Association of South Africa/University Molecular Hepatology Research Unit, Department of Medicine, University of the Witwatersrand, and Johannesburg Hospital, Johannesburg, South Africa.

In spite of advances made in our understanding of the biology of the hepatitis C virus (HCV), the epidemiology and natural history of HCV infection, and the treatment of chronic hepatitis C, the development and worldwide implementation of a comprehensive prevention and control strategy remains necessary. A World Health Organization informal consultation with the Viral Hepatitis Prevention Board was convened and met in Geneva, Switzerland, 13-14 May 2002, to review epidemiological and public health aspects of HCV infection, and the various prevention and control strategies that are currently in place. Based on the presentations and discussions, a number of specific recommendations were made,

which should be considered in conjunction with previously published recommendations.

Publication Types:

Review

Review, Tutorial

PMID: 15117321 [PubMed - indexed for MEDLINE]

41: J Viral Hepat. 2004 May;11(3):191-7.

Epoetin alfa treatment for acute anaemia during interferon plus ribavirin combination therapy for chronic hepatitis C.

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Infection with the hepatitis C virus (HCV) remains chronic in 75% of infected individuals, in whom it can cause liver inflammation and progressive fibrosis leading to cirrhosis in 20% of patients. A sustained viral response (SVR) to HCV therapy, i.e. undetectable plasma HCV RNA 6 months after the end of treatment, leads to permanent eradication of the virus in 98.3% of patients. The current treatment of choice is combination therapy with pegylated interferon alfa (PEG-IFN alfa), 2a or 2b, and ribavirin (RBV), which achieves an SVR in 54-56% of patients. In patients with HCV genotype 1, RBV doses of 1000-1200 mg/day are associated with a higher SVR than 800 mg/day (51 vs 40%). However, RBV also causes dose-dependent reversible haemolytic anaemia that, in combination with the myelosuppressive effects of PEG-IFN, results in a mean drop in haemoglobin (Hb) level of 3.7 g/dL within 4 weeks. Conventionally, this acute anaemia has been managed with RBV dose reductions. However, this may result in a decreased SVR rate. Alternatively, this anaemia can be managed with administration of epoetin alfa at 40 000 IU once weekly. In a randomized placebo-controlled trial, treatment with epoetin alfa has been shown to raise Hb levels and maintain RBV doses. Furthermore, the increase in Hb level was associated with improved quality of life. Anaemia in patients treated with interferon plus RBV combination therapy can be managed effectively and safely with once weekly epoetin alfa without sacrificing optimal dosing of RBV.

Publication Types:

Review

Review, Tutorial

PMID: 15117320 [PubMed - indexed for MEDLINE]

42: J Virol. 2004 Jul;78(13):7257-63.

Human monoclonal antibody to hepatitis C virus E1 glycoprotein that blocks virus attachment and viral infectivity.

Keck ZY, Sung VM, Perkins S, Rowe J, Paul S, Liang TJ, Lai MM, Fong SK.

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Human antibodies elicited in response to hepatitis C virus (HCV) infection are anticipated to react with the native conformation of the viral envelope structure. Isolation of these antibodies as human monoclonal antibodies that block virus binding and entry will be useful in providing potential therapeutic reagents and for vaccine development. H-111, an antibody to HCV envelope 1 protein (E1) that maps to the YEVRNVSQVYH sequence and is located near the N terminus of E1 and is able to immunoprecipitate E1E2 heterodimers, is described. Binding of H-111 to HCV E1 genotypes 1a, 1b, 2b, and 3a indicates that the H-111 epitope is highly conserved. Sequence analysis of antibody V regions showed evidence of somatic and affinity maturation of H-111. Finally, H-111 blocks HCV-like particle binding to and HCV virion infection of target cells, suggesting the involvement of this epitope in virus binding and entry.

PMID: 15194801 [PubMed - indexed for MEDLINE]

43: J Virol. 2004 Jul;78(13):6995-7003.

Immunization with hepatitis C virus-like particles induces humoral and cellular immune responses in nonhuman primates.

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We have previously reported the production of hepatitis C virus-like particles (HCV-LP) using a recombinant baculovirus containing the cDNA of the HCV structural proteins (core, E1, and E2). These particles resemble the putative HCV virions and are capable of inducing strong and broad humoral and cellular immune responses in mice. Here we present evidence on the immunogenicity of HCV-LP and the effects of novel adjuvant systems in a nonhuman primate model, the baboon. Three groups of four baboons were immunized with HCV-LP, HCV-LP and adjuvant AS01B (monophosphoryl lipid A and QS21), or HCV-LP and the combination of AS01B and CpG oligodeoxynucleotides 10105. After four immunizations over an 8-month period, all animals developed HCV-specific humoral and cellular immune responses including antibodies to HCV structural proteins and gamma interferon(+) (IFN-gamma(+))CD4(+) and IFN-gamma(+))CD8(+) T-cell responses. The

immunogenicity of HCV-LP was only marginally enhanced by the use of adjuvants. The overall HCV-specific immune responses were broad and long lasting. Our results suggest that HCV-LP is a potent immunogen to induce HCV-specific humoral and cellular immune responses in primates and may be a promising approach to develop novel preventive and therapeutic modalities.

PMID: 15194776 [PubMed - indexed for MEDLINE]

44: J Virol. 2004 Jun;78(12):6151-61.

Lack of phenotypic and functional impairment in dendritic cells from chimpanzees chronically infected with hepatitis C virus.

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Dendritic cells (DCs), which are potent antigen-presenting cells (APCs), are used as adjuvants for the treatment of cancer and infectious diseases in human and nonhuman primates, with documented clinical efficacy. The hepatitis C virus (HCV)-chimpanzee model is the best available model for testing the immunotherapeutic effects of DCs in the setting of a chronic infection, as chimpanzees develop a persistent infection resembling that seen in humans. However, several reports have suggested that DCs derived from chronically infected individuals or nonhuman primates are functionally compromised. As a prelude to clinical studies, we evaluated whether functionally mature DCs could be generated in chimpanzee plasma by good manufacturing practice using CD14(+) mononuclear precursors from chronically infected chimpanzees. DCs generated in a medium with HCV-negative plasma and treated with a defined cocktail of cytokines or a CD40 ligand trimer matured fully, as measured by the induction of CD83 expression and the upregulation of costimulatory molecules. Furthermore, the expression of CCR7 was induced, suggesting an acquisition of migration capacity. Mature DCs were capable of stimulating allogeneic T cells, antigen-specific memory CD4(+) T cells, and HCV-specific CD8(+)-T-cell clones. In all cases, there was no evidence of HCV infection in DCs. Furthermore, these DCs maintained their phenotype and APC function after cryopreservation. Finally, no discernible differences were noted between DCs derived from HCV-infected and uninfected chimpanzees. In summary, precursor cells from HCV-infected chimpanzees are fully

capable of differentiating into functional, mature DCs, which can now be reproducibly prepared for investigations of their immunotherapeutic potential in the setting of chronic HCV infection.

PMID: 15163708 [PubMed - indexed for MEDLINE]

45: J Virol. 2004 Jun; 78(11):5867-74.

Hepatitis C virus persistence after spontaneous or treatment-induced resolution of hepatitis C.

Pham TN, MacParland SA, Mulrooney PM, Cooksley H, Naoumov NV, Michalak TI. Molecular Virology and Hepatology Research, Faculty of Medicine, Health Science Centre, Memorial University, St. John's, Newfoundland, Canada A1B 3V6.

It is presumed that resolution of hepatitis C, as evidenced by normalization of liver function tests and disappearance of hepatitis C virus (HCV) RNA from serum, as determined by conventional laboratory assays, reflects virus eradication. In this study, we examined the expression of the HCV genome in the sera, peripheral blood mononuclear cells (PBMC), and, on some occasions, monocyte-derived dendritic cells (DC) long after resolution of hepatitis C by using a highly sensitive reverse transcription (RT)-PCR-nucleic acid hybridization (RT-PCR-NAH) assay. The samples obtained from 16 randomly selected patients (5 with spontaneous and 11 with treatment-induced resolution), monitored for up to 5 years, were studied by qualitative and semiquantitative RT-PCR-NAH and by real-time RT-PCR to detect the HCV RNA positive strand. The replicative HCV RNA negative strand was examined in PBMC after culture with a T-cell proliferation stimulating mitogen. The findings show that HCV RNA was carried in the convalescent-phase sera and/or PBMC in all 16 individuals investigated. Also, DC from six of seven patients were reactive for the HCV genome. Importantly, traces of the HCV RNA negative strand, suggesting progressing virus replication, were detected in the majority of mitogen-stimulated PBMC, including four samples collected 5 years after recovery. Sequencing of the HCV 5' untranslated region fragment revealed genotype 1b in four of nine individuals examined and genotypes 1a and 2a in three and two patients, respectively. These results imply that HCV RNA can persist at very low levels in the serum and peripheral lymphoid cells and that an intermediate replicative form of the HCV genome can persist in PBMC for many years after apparently complete spontaneous or antiviral therapy-induced resolution of chronic hepatitis C.

PMID: 15140984 [PubMed - indexed for MEDLINE]

46: J Virol Methods. 2004 Jun 1; 118(1):23-31.

Application of the trak-C HCV core assay for monitoring antiviral activity in HCV replication systems.

Cagnon L, Wagaman P, Bartenschlager R, Pietschmann T, Gao T, Kneteman NM, Tyrrell DL, Bahl C, Niven P, Lee S, Simmen KA.

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The Ortho trak-C immunoassay has recently established detection of the HCV core antigen as a viable indirect marker of HCV replication in clinical samples. In this study, trak-C is used to monitor HCV replication in three pre-clinical models: the cellular HCV replicon system, transient transfection of HCV genomes, and the murine Alb-uPa/SCID HCV infection model. All of these systems utilize full-length HCV genomes that direct the expression of core, facilitating its detection with monoclonal antibodies. When performed with purified protein, the assay detects HCV core with a lower limit of detection at 1.5pg, and exhibits linear detection up to 100pg. When assaying extracts prepared from Huh-7 clone 21-5 cells harboring a full-length HCV replicon, core is detectable from as few as 63 cell equivalents. The assay was used to determine the sensitivity of Huh

21-5 cells to the antiviral effects of interferon (IFN). Inhibition by IFN-alpha using core detection was comparable to that observed using branched-DNA (bDNA 3.0) detection of HCV RNA. Replication of transfected full-length HCV 1a Con1 genomes in Huh-7 cells was also detectable using the trak-C assay. Finally, in the transgenic murine HCV infection model, the course of viral amplification was detected from serum using trak-C with kinetics similar to those observed with RNA detection. Given its ease of use and the lack of requirement for RNA purification, the trak-C assay has several advantages over RNA-based methods of viral monitoring.

PMID: 15158065 [PubMed - indexed for MEDLINE]

47: Jpn J Infect Dis. 2004 Apr;57(2):49-51.

Markers for transfusion-associated hepatitis in north Indian blood donors: prevalence and trends.

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Transfusion-associated hepatitis is a great problem in developing countries including India due to endemic hepatitis infections and a lack of voluntary donors, trained personnel, and funds. The prevalence of post-transfusion hepatitis B and C in India is about 1-5% and 1%, respectively. A total of 128,589 blood donors were screened for hepatitis B surface antigen (HBsAg) and 76,089 donors were screened for anti-hepatitis C virus (HCV) from 1997 - 2002. Data were tabulated annually. Out of the total 83.6% were replacement donors. Our study concluded that the prevalence of HBsAg and antibodies for HCV ranged between 1.7 - 2.2% and 0.25 - 0.9%, respectively among all of the donors. Seropositivity was definitely higher in replacement donors than in voluntary donors. Based on these results, we recognize an urgent need to establish a non-remunerated voluntary donor base in India. A stringent deferral system should be developed. The use of sensitive laboratory tests and the addition of core antigen (anti-HBc) to the mandatory screening test list would further reduce the incidence of post-transfusion hepatitis.

PMID: 15118208 [PubMed - indexed for MEDLINE]

48: Kaohsiung J Med Sci. 2004 Apr;20(4):151-9.

Relationship of oral lichen planus to hepatitis C virus in southern Taiwan.

Chung CH, Yang YH, Chang TT, Shieh DB, Liu SY, Shieh TY.

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Oral lichen planus (OLP) is a relatively common skin and oral disease that manifests as a mucous reaction to a variety of etiologic factors, including autoimmune disease, drug reaction, diabetes mellitus (DM), hypertension, hepatitis C virus (HCV), urolithiasis, psychogenic factors, and bacterial infection. The purpose of this study was to investigate the relationship between HCV infection and OLP as there is a high prevalence of HCV infection in Taiwan. A total of 1,075 subjects aged at least 15 years participated in the study. The total prevalence of OLP was 3% (32/1,075). OLP was significantly associated with DM (odds ratio, OR, 3.09) and HCV (OR, 2.05). Atrophic-erosive OLP (13/32) and reticular OLP (21/32) were significantly associated with HCV and DM, respectively. Logistic regression analysis showed that elevation of alanine aminotransferase (ALT) significantly increased the risk of atrophic-erosive OLP. We concluded that OLP is significantly associated with HCV and DM in southern Taiwan, particularly in HCV patients with elevated serum ALT levels and atrophic-erosive OLP.

PMID: 15191216 [PubMed - indexed for MEDLINE]

49: Medicine (Baltimore). 2004 May;83(3):176-87.

Habitual betel quid chewing and risk for hepatocellular carcinoma complicating cirrhosis.

Tsai JF, Jeng JE, Chuang LY, Ho MS, Ko YC, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY.

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This case-control study aimed to assess the independent and interactive role of habitual betel quid chewing and known risk factors for hepatocellular carcinoma (HCC). Subjects enrolled included 210 pairs of sex- and age-matched cirrhotic patients with HCC, patients with cirrhosis alone, and healthy controls.

Information on risk factors was obtained through serologic examination of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV), and a standardized personal interview with a structured questionnaire. Multivariate analysis indicated that betel quid chewing (odds ratio [OR], 5.81; 95% confidence interval [CI], 2.26-14.94); HBsAg (OR, 37.98; 95% CI, 19.65-73.42); and anti-HCV (OR, 47.23; 95% CI, 18.86-118.25) were independent risk factors for HCC when HCC patients were compared with healthy controls. Using patients with cirrhosis alone as a reference group, multivariate analysis indicated that only betel quid chewing (OR, 1.69; 95% CI, 1.04-2.76) and HBsAg (OR, 1.54; 95% CI, 1.01-2.37) were independent risk factors for HCC. There was an additive interaction between betel quid chewing and the presence of either HBsAg (synergy index, 5.22) or anti-HCV (synergy index, 1.35). Moreover, a higher risk of HCC was associated with a longer duration of betel quid chewing and a larger amount of betel quid consumed (each p(for trend) < 0.0001). In conclusion, betel quid chewing is an independent risk factor for cirrhotic HCC. There is an additive interaction between betel quid chewing and chronic hepatitis B and/or hepatitis C virus infection.

PMID: 15118544 [PubMed - indexed for MEDLINE]

50: Proc Natl Acad Sci U S A. 2004 May 18;101(20):7705-10. Epub 2004 May 10. Neutralizing antibodies to hepatitis C virus (HCV) in immune globulins derived from anti-HCV-positive plasma.

Yu MY, Bartosch B, Zhang P, Guo ZP, Renzi PM, Shen LM, Granier C, Feinstone SM, Cosset FL, Purcell RH.

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The role of humoral immunity in hepatitis C virus (HCV) infections is uncertain. Nevertheless, there is increasing evidence for neutralizing antibodies to HCV in the serum or plasma of chronically infected individuals. Immune globulins prepared by ethanol fractionation of plasma had long been considered safe until a commercial immune globulin product, Gammagard, prepared from plasma from which

units containing anti-HCV had been excluded, transmitted HCV to recipients. Studies suggested that the exclusion might have removed neutralizing antibodies from the plasma and hence compromised the safety of the resulting immune globulins. In the present study, by using chimpanzees and a recently validated in vitro system based on neutralization of infectious HCV pseudoparticles, we found broadly reactive neutralizing and protective antibodies in experimental immune globulin preparations made from anti-HCV-positive donations. Neutralizing antibodies were also found in Gammagard lots made from unscreened plasma that did not transmit hepatitis C but not in Gammagard lots, which were prepared from anti-HCV-screened plasma, that did transmit hepatitis C. The results provide an explanation for the mechanism by which the safety of this product was compromised. Immune globulins made from anti-HCV-positive plasma and containing

broadly reactive neutralizing antibodies may provide a method of preventing HCV infection.

PMID: 15136748 [PubMed - indexed for MEDLINE]

51: Prog Neuropsychopharmacol Biol Psychiatry. 2004 May;28(3):591-7.

High prevalence of the hepatitis C virus infection among the inpatients of schizophrenia and psychoactive substance abuse in Japan.

Nakamura Y, Koh M, Miyoshi E, Ida O, Morikawa M, Tokuyama A, Nagano T, Honda Y,

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Prevalence of anti-HCV antibody in 1193 hospitalized patients (848 males and 345 females) in psychiatric department was investigated. Overall prevalence ratio was 9.1%, indicating significantly higher than that of healthy blood donors. In the classification of ICD-10, the prevalence of the inpatients diagnosed in schizophrenia group and psychoactive substance use group accounted for 6.2% and 13.8%, respectively. However, adequate reasons such as sanitary issues were not found to account for the high prevalence. Only the age of the patients could account for the high prevalence in the schizophrenic group. In the psychoactive substance abuse group, the sanitary issues might be a major cause of the very high prevalence of anti-HCV antibody, while other factors such as dysfunction of the immune system might be considered to account for it.

PMID: 15093967 [PubMed - indexed for MEDLINE]

52: Trans R Soc Trop Med Hyg. 2004 Jun;98(6):367-72.

A higher than expected recovery rate from hepatitis C infection amongst adolescents: a community study in a hepatitis C-endemic township in Taiwan.

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This study investigated the prevalence of antibody to hepatitis C virus (anti-HCV), evaluated clinical manifestations of hepatitis C, and explored the risk factors amongst adolescents in an HCV-hyperendemic area in Taiwan. In December 1999, 713 students aged 13-16 years from Taishi township, in central Taiwan, were enrolled in a screening program for anti-HCV and alanine transaminase (ALT) status. Fourteen participants (M/F = 6/8) were positive for anti-HCV. Eight of the 14 later proved to be negative for HCV RNA, and they demonstrated relatively low sample rate/cut-off rate (S/CO) ratios (1.05-11.83) for anti-HCV tests. All HCV RNA negative cases had normal serum ALT levels. The other six (43%) seropositive students demonstrated HCV viraemia and greater S/CO ratios (25.66-77.49). Two of these six participants had elevated serum ALT levels. Compared to anti-HCV-negative subjects, anti-HCV-positive students exhibited significantly greater rates of exposure to one or more of the following: blood transfusion, tattooing, and earlobe piercing. This study group has a greater prevalence (2%) of anti-HCV than the general Taiwanese population at the same age. The study also reveals a lower rate (43%) of chronicity of HCV infection than that reported in the literature.

PMID: 15099993 [PubMed - indexed for MEDLINE]

53: Transfusion. 2004 Jul;44(7):1067-71.

Hepatitis C core antigen in Polish blood donors.

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BACKGROUND: The goal of this study was to evaluate the feasibility of adopting

the HCV core antigen ELISA (HCVcAg) for routine screening of Polish blood donors. STUDY DESIGN AND METHODS: A total of 133,279 donor samples were tested by ORTHO HCVcAg. All repeatedly reactive (RR) samples were tested by neutralization test for confirmation, RIBA HCV for anti-HCV, and by Cobas Amplicore for HCV RNA. All donations were tested for ALT level. RESULTS: The HCVcAg test specificity was 99.94 percent. In total, 1499 donations (1.12%) were initially reactive and 124 (0.09%) were RR. Antibodies to HCV were found in 22 out of 124 donors and HCV RNA was detected in 19 out of 22. In 10 out of the 19 HCV-RNA-positive donors, the HCVcAg neutralization test was positive. Among the 102 HCVcAg RR/anti-HCV-negative donors, there were 6 neutralization-test-positive individuals, and all were HCV RNA positive. Elevated ALT level was observed in one of them. During the follow-up studies of three HCVcAg RR/HCV-RNA-positive donors, seroconversion was observed 5 to 7 weeks after the initial HCVcAg-positive result. In all, HCVcAg results became negative once antibodies to HCV were detected. CONCLUSION: The HCVcAg test proved to be feasible for routine screening in the Polish Blood Transfusion Service. Six HCVcAg RR/anti-HCV-negative donors were identified. The calculated residual risk in this study of donors in the preseroconversion window was 45 per million. Mandatory testing of every blood and plasma donation for HCVcAg or HCV RNA was recommended as of January 2, 2002.
PMID: 15225249 [PubMed - indexed for MEDLINE]

54: Transplantation. 2004 Jun 15;77(11):1755-60.
Role of replicative senescence in the progression of fibrosis in hepatitis C virus (HCV) recurrence after liver transplantation.
Trak-Smayra V, Contreras J, Dondero F, Durand F, Dubois S, Sommacale D, Marcellin P, Belghiti J, Degott C, Paradis V.
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BACKGROUND: Although hepatitis C virus (HCV) recurrence is almost universal after orthotopic liver transplantation (OLT), the impact of viral infection on liver graft is highly variable and difficult to predict. Because of the possible relationship between replicative senescence (RS) and the accelerated development of liver fibrosis, we aimed to assess the potential role of RS in the severity of HCV-related chronic hepatitis recurrence after OLT. METHODS: One hundred three liver biopsies from 56 patients receiving transplants for HCV-related cirrhosis were studied, including 30 revascularization biopsies and 52 and 21 biopsies performed during and beyond the first year of OLT, respectively. The presence of senescent cells in liver grafts was assessed by the senescence-associated beta-galactosidase (SA-beta-Gal) staining method. Chronic hepatitis was defined by fibrosis stage and necrotico-inflammatory activity grade using the METAVIR score. RESULTS: A total of 34 of the 103 (33%) frozen liver biopsies displayed SA-beta-Gal-positive cells, including 6 (20%) of the revascularization biopsies, 14 (34%) of the biopsies performed within the first year, and 10 (46%) of the biopsies performed beyond 1 year of follow-up. The presence of senescent cells in revascularization biopsies was significantly associated with the degree of ischemic necrosis at time of OLT ($P = 0.01$) and hepatitis C recurrence in the first year after OLT ($P = 0.05$). Furthermore, the presence of RS in the biopsy performed within the first year was associated with further development of fibrosis ($P = 0.05$). CONCLUSIONS: These data show that RS has a significant impact upon the course of liver transplantation, especially in the long-term progression of fibrosis observed in HCV-infected patients.
PMID: 15201678 [PubMed - indexed for MEDLINE]