Purpose: Severe obesity has been considered a relative contraindication to orthotopic liver transplantation (OLT) at many centers. We present a single-center experience on OLT outcomes in severely obese patients.
Methods: Retrospective analysis of primary OLT over the last two years at our institution was performed. Severe obesity was defined as a body mass index (BMI) of $> 34 kg/m^2$. Non-obese recipients with a BMI $< 30 kg/m^2$ were used as controls.
Results: Sixteen severely obese patients underwent OLT. Thirty non-obese liver recipients were used as controls. The average BMI in the obese group was 39.4 kg/m^2 (range 34.1–42.8 kg/m^2) versus 25.3 kg/m^2 (15.3–29.9 kg/m^2) in the controls. Patient survival was 100% in the severely obese patients (9 of whom had one-year survival data available). One-year survival was 28/30 (93.3%) in the control patients. The average operative time was 431 minutes (270–630 minutes) in the obese and 423 minutes (248–896 minutes) in the non-obese patients. The average length of hospital stay was 15 days (8–52 days) in the obese and 16.2 days (7–57 days) in the non-obese group. The average length of ICU stay was 5.19 days (3–10 days) in the obese compared to 6.6 days (2–45 days) in the non-obese patients. The average length of time until post-operative extubation was 3.81 days (2–9 days) in the obese compared to 3.17 days (1–9 days) in the control group. Biliary complications were noted in 3/16 (18.8%) obese compared to 13/30 (43%) non-obese patients. Cardiac complications occurred in 2/16 (12.5%) obese compared to 3/30 (10%) non-obese patients. Overall infections occurred in 6/16 (37.5%) obese compared to 11/30 (36.7%) non-obese patients. Wound infections were diagnosed in 4/16 (25%) obese compared to 1/30 (3.33%) non-obese patients. Only the higher incidence of wound infections in the obese patients was found to be statistically significant ($p = 0.043$).
Conclusions: Severe obesity (defined as BMI $> 34 kg/m^2$) did not influence one-year survival after OLT. Operative time, hospital stay, ICU stay, and period of intubation were not different between the groups. Cardiac, biliary, and overall infectious complications showed no significant difference. Post-operative wound infections were more common in the severly obese patients.

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Liver Transplantation in Severly Obese Patients: A Single Center Experience

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24 Weeks of Treatment for Hepatitis C Genotype 4 May Be Sufficient

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Purpose: Hepatitis C Genotype 4 (HCV4) is prevalent among people from the Middle Eastern. At present, the recommendation is to treat with pegylated interferon plus weight based ribavirin for 48 weeks, with an expected sustained virologic response (SVR) of about 42%. The purpose of our study was to evaluate in a retrospective manner our experience with 24 weeks of therapy for HCV4, and compare the SVR from our study with that of other studies.
Methods: A retrospective case-analysis study was conducted at Brooklyn Medical Group NY, an outpatient multi-specialty clinic affiliated with NY Methodist Hospital. We analyzed the charts of all the patients, who were treated for HCV4. Patient demographics; type, duration and complications of treatment; serum alanine transaminase (ALT) and viral load at different stages of therapy were recorded.
Results: There were 4 patients with HCV4. All were male from the Middle East. Average age at the start of treatment was 43.7 years (range 38 to 50 years). Baseline viral load averaged 764,494 IU/ml (range 17,200 to 1,955,376 IU/ml) and mean ALT was 77 U/L (range 69 to 93 U/L). One patient had failed previous therapy. Three treatment naïve patients were treated for 24 weeks or less. Viral load was undetectable in these three patients at 12 weeks, 24 weeks and 6-months post-treatment (SVR 100%). Average ALT at the end of treatment was 44 U/L. In one these 3 patients, treatment was stopped before 24 weeks due to complications at 18 weeks (depression and hypothyroidism). The treatment varied: 1 patient was treated with peginterferon alfa-2b (1.5 mcg/kg/week) and ribavirin (1200 mg/day); while the other 2 patients were given interferon alpha-2b (3 million units

three times/week) and ribavirin (1200 mg/day). Baseline liver biopsy was done in 2 of these patients. Both had grade 3/4 and stage 3/4 fibrosis.
The 4th patient had previously failed interferon alfa-2b plus ribavirin therapy. He was treated for 48 weeks with peginterferon alfa-2a (180 mcg/week) and ribavirin (1200 mg/day). Despite a 2-log drop in HCV4 at 12 weeks, the virus was detectible at 48 weeks. This patient didn't have liver biopsy.
Conclusions: In this small group of treatment-naive patients with HCV4, we found SVR of 100% after 24 weeks of combination therapy. The possibility that treatment-naïve HCV4 pts can be treated for only 24 weeks should be further evaluated.

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Recurrent Hepatitis C after Living Donor Liver Transplantation Detected by Tc-99m GSA Liver Scintigraphy

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Purpose: Recurrence of hepatitis C after living donor liver transplantation was investigated using technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (Tc-99m-GSA) liver scintigraphy.
Methods: A 55-year-old woman with cirrhosis due to chronic hepatitis C underwent liver transplantation with a graft from her husband. Scintigraphy was used to determine the hepatic uptake ratio of the tracer corrected for disappearance from the blood, as well as the maximal removal rate of the tracer by hepatocytes, as parameters of hepatic functional reserve.
Results: Conventional liver function parameters and the graft volume (computed tomography) were almost unchanged up to 18 months after transplantation. Serum HCV RNA was elevated from 3 months after transplantation, and was 2-fold higher at 12 months compared with 6 months. At 18 months postoperatively, liver biopsy showed an increase of histologic activity, and there was also evidence of recurrent hepatitis C. The corrected hepatic uptake ratio and maximal removal rate were decreased at 3 months postoperatively, and thereafter remained low.
Conclusions: The decrease of scintigraphic parameters at 3 months after transplantation suggested recurrent hepatitis C affecting the graft. Tc-99m-GSA liver scintigraphy is a useful noninvasive method for evaluating graft functional reserve.

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Comparison of Limited and Anatomical Hepatic Resections for Hepatocellular Carcinoma with Hepatitis C Virus

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Purpose: The long-term outcome after resection of hepatocellular carcinoma is influenced by factors related to the tumor and the underlying liver disease. The optimum extent of surgical resection, which can be limited or anatomical, is another important factor but is still controversial.
Methods: Among 247 patients with hepatitis C virus infection who underwent curative resection of hepatocellular carcinoma between 1992 and 2003, 213 patients underwent limited resection and 34 patients underwent anatomic resection of at least 1 liver segment with complete removal of the portal territory containing the tumor. The clinical characteristics, operative results, and long-term survival of these two groups were compared.
Results: The patients receiving limited resection had significantly worse preoperative liver function than the patients undergoing anatomic resection. The mortality and morbidity rates after limited and anatomic resection were not significantly different. Disease-free survival and overall survival were similar after both types of resection, as were the incidence and pattern of intrahepatic tumor recurrence.
Conclusions: In patients with hepatitis C virus infection and hepatocellular carcinoma, anatomic resection shoud not be routinely performed. In patients with a limited hepatic functional reserve, resection of the tumor with preservation of liver parenchyma may take priority over wide resection.

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Failure To Show for Initial Consultation in Patients Referred for Evaluation of Hepatitis C

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Purpose: There are many impediments to the successful treatment of patients with chronic hepatitis C infection. These include potential factors present during each step of the referral, consultative, evaluation, treatment and follow-up segments. In the recent past, I have been impressed with a seemingly high "no-show" rate when patients are referred for initial evaluation of hepatitis C infection. This rate has seemed out of proprtion to the "no-show" rate for patients referred for evaluation of other gastroenterologic/hepatologic problems. This study aimed to prospectively investigate whether this problem actually exists.
Methods: From 10/3/03 through 5/6/05, the number of new patients referred to a single gastroenterologist in an outpatient office setting were prospectively tabulated. The physician was part of a 5 member single-specialty gastroenterology group, in a semi-rural community. The practice members make themselves available to care for patients with all insurance plans commonly carried by residents in their catchment area, including Medicare and Medicaid. The number of "no-shows" were compared between patients referred for initial evaluation of hepatitis C, and those referred for "all other" gastroenterologic/hepatologic diagnoses.
Results: Over the study period, 543 new patients were scheduled for initial office consultation. Of these, 66 were referred for evaluation of hepatitis C, and 477 were referred for evaluation of "all other" diagnoses. The rate of "not-showing" for initial consultation was $12/66 = 18.2\%$ for patients presenting for evaluation of hepatitis C versus $37/477 = 7.8\%$ for patients referred for evaluation of "all other" diagnoses, ($p = 0.01$ by Fischers exact test; odds ratio $= 2.65$).
Conclusions: The results from this prospective investigation confirm the suspicion that patients who are referred for evaluation of hepatitis C are significantly less likely to show for their initial office consultation, than patients referred for a combination of "all other" gastroenterlogic/hepatologic diagnoses. Many potential factors may be responsible for this phenomenon and in this regard, further study is ongoing.

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Detection of Hepatitis B Virus Surface Antigen in Hepatitis B Vaccine Recipients

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Purpose: Some reports of HBsAg positivity soon after HBV vaccination have been mentioned in the literature. To study the duration of HBsAg persistence in blood after HBV vaccination in volunteers.
Methods: Thirty two healthy HBsAg negative volunteers were recruited in the study. A written consent was taken from all. HBsAg in blood of these volunteers was tested by a commercially available kit (Bioelisa HBsAg BIOKIT, SA, Spain) on day 2, 4, 6, 9, and 12 after an intramuscular injection of 20 ug of recombinant Hepatitis B vaccination.
Results: The volunteers (19 M and 13 F) had a mean age of 26.65 ± 2.42 years. On day 2 HBsAg was positive in 18 (56.25%) volunteers. Of these 18 volunteers 6 (33.33%) remained positive on day 4. Two volunteers who were negative on day 2 were also positive on day 4 [Total HBsAg positivity on day $4 = 8$ (44.44%)]. Out of these eight volunteers 4 were still positive

on 6th day and out of these four only two were positive on day 9. None of these volunteers were positive for HBsAg on day 12.
Conclusions: HBsAg after 9 days of HBV Vaccination can be falsely positive in some individuals. It is therefore recommended that individuals who have been recently vaccinated with HBV vaccine should be enquired of the same if an asymptomatic patient is detected to be HBsAg positive.

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Hepatic Venous Pressure Gradient Predicts the Severity of Cirrhosis

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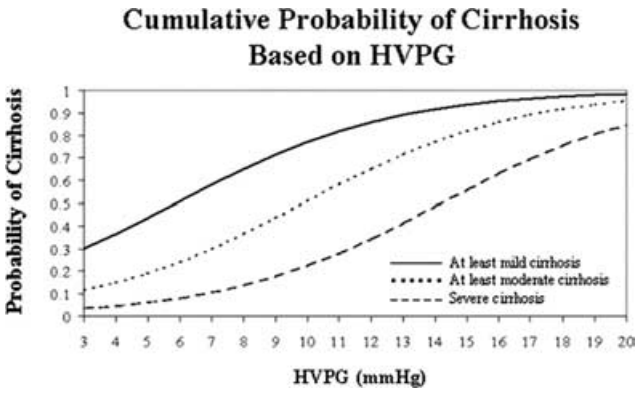
Purpose: Liver biopsy is the gold standard for establishing cirrhosis, but may provide inadequate tissue in some patients. The purpose of this study was to determine whether the hepatic venous pressure gradient (HVPG) predicts the presence and severity of cirrhosis.
Methods: Patients with liver disease who had undergone HVPG measurements were identified at two Boston teaching hospitals. Patients were excluded if they lacked a liver biopsy or the slides could not be obtained, if there was an elapsed time between liver biopsy and HVPG measurement of >12 months, or if the patient had undergone a shunt, TIPS or liver transplantation prior to completion of both the liver biopsy and the HVPG measurement. Clinical, laboratory, and HVPG data were collected and biopsies were staged for the degree of fibrosis using the Laennec scoring system, a modification of METAVIR, which sub-classifies cirrhosis as mild, moderate or severe.

Laennec Scoring System of Liver Biopsies

Score	Description
0	No definite fibrosis
1	Minimal fibrosis (no septa or a rare thin septum; may have portal expansion or mild sinusoidal fibrosis)
2	Mild fibrosis (occasional thin septa)
3	Moderate fibrosis (moderate thin septa; up to incomplete cirrhosis)
4A	Mild cirrhosis, definite or probable
4B	Moderate cirrhosis (at least 2 broad septa)
4C	Severe cirrhosis (at least one very broad septum or many minute nodules)

Results: A total of 32 patients met inclusion and exclusion criteria. Univariate logistic regression identified HVPG and platelet count as independent predictors of cirrhosis. When a proportional odds model was applied, the magnitude of the effect of HVPG on fibrosis score was described by the estimated OR of 1.34 (95% CI 1.12–1.61). Additionally, the model demonstrated that as the HVPG increased, so did the probability of having more histologically advanced cirrhosis. [figure 1]



Conclusions: HVPG measurement predicts cirrhosis, with higher HVPG measurements correlating with more advanced cirrhosis. Therefore, when the diagnosis of cirrhosis is in question, an elevated HVPG measurement can support the diagnosis.

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Trends in Biopsy and Treatment Rates in Patients with Chronic Genotype 2 & 3 Hepatitis C Infection over a Five-Year Period

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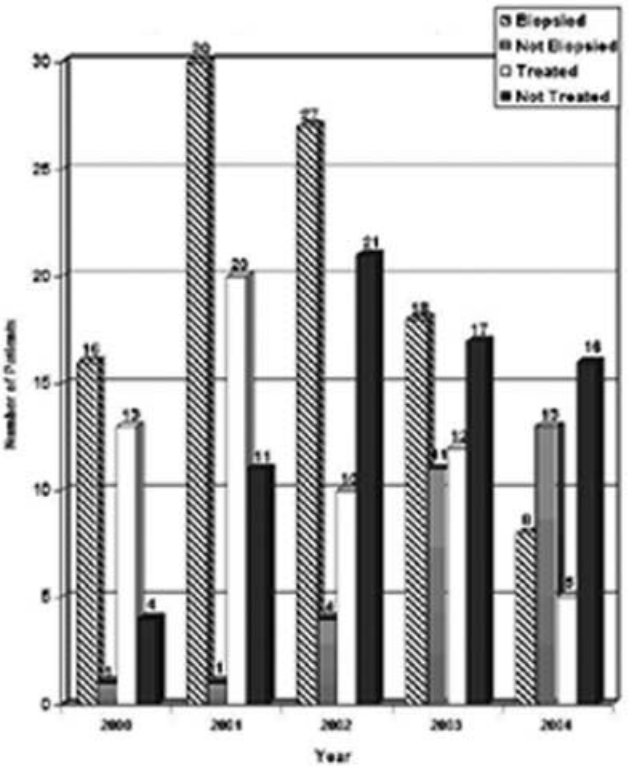
Purpose: Patients with hepatitis C virus–genotype 2 or 3 (HCV 2/3) have a sustained virologic response (SVR) of about 80% when treated with pegylated interferon plus ribavirin and thus it is common to undergo treatment without liver biopsy. The aim of our study was to determine changes in liver biopsy and treatment patterns in patients (pts) with HCV 2/3 over the past 5 years at our institution.
Methods: We retrospectively reviewed the charts of patients with HCV 2/3 seen at our institution between Jan 2000 and March 2004. Data collected included pt demographics, risk factors for HCV, liver biopsy results, history of previous HCV treatment, reasons for not treating, and SVR.
Results: There were 129 pts seen with HCV 2/3. The mean age was 48 (range 26–82) with 61% men. 79 pts (60%) had a history of IV drug use (IVDU) and 23 (18%) had a history of transfusion before 1992. 12 (9.2%) were co-infected with HIV and 3 (2.3%) with HBV. 14 pts (11%) were previously treated for HCV without SVR. Overall, 60 pts (46%) were treated. Reasons for not treating included pt refusal (46.4%), medically not suitable for treatment (31.9%) or lost to follow-up (21.7%). Reasons for medically unsuitability included: minimal disease on biopsy (stage 0–1 fibrosis) in 12 pts, or contraindication to treatment including significant co-morbidity or psychiatric history in 6 pts, active IVDU in 1 pt and decompensated cirrhosis in 2 pts. 99 (77%) pts had a liver biopsy (Fig. 1) of which 51 pts (51.5%) underwent treatment. Of the 60 pts that began treatment, 38 (63%) completed



the course. Overall, by an intent to treat analysis, SVR was achieved in 30 (50%) pts. Of those pts completing treatment, SVR was achieved in 50 pts (79%).
Conclusions: The majority of pts with HCV 2/3 had a liver biopsy, however the proportion of pts who had a liver biopsy has declined since 2001. Despite the advancements in available therapies, the proportion of pts with HCV 2/3 being treated has remained relatively constant. SVR was achieved in 79% of pts, similar to that achieved in pivotal trials. [figure 1]

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A "Fishy" Cough: Hepatobronchial Fistula Due to a Pyogenic Liver Abscess

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Purpose: A hepatobronchial fistula is an anatomic communication between the liver parenchyma and the bronchial tree. Major causes include contamination from the biliary tract secondary to obstruction, trauma, or pyogenic liver abscess. We report a case of persistent, productive "fishy" cough resulting from a hepatobronchial fistula in a patient with a chronic, recurrent hepatic abscess.
Case Report: A 49-year-old white male presented to the emergency department complaining of three days of progressive fever, chills, and a cough productive of "fishy" tasting sputum. The patient had a history of Billroth II gastrectomy, open cholecystectomy, and chronic recurrent hepatic abscess refractory to multiple courses of intravenous antibiotics, ultrasound-guided percutaneous drainage, and wedge resection. Previous intra-operative tissue samples were negative for malignancy and cultures were negative for aerobic, anaerobic, fungal, and acid-fast organisms. On admission, the patient underwent radiographic evaluation with a CT scan, demonstrating a residual 8 cm septated hepatic abscess and a fistulous tract communicating with the bronchial tree. A pigtail drain was placed under CT guidance and the patient was empirically started on ceftriaxone, ciprofloxacin, and metronidazole. Cultures of the aspirate later grew multiple organisms to include: *Clostridium perfringes*, *Klebsiella pneumoniae*, and *Enterococcus faecalis*. At four week follow-up, the patient reported termination of symptoms and CT scan demonstrated near-complete resolution of the abscess. The patient was continued on the same antibiotic regimen and assessed serially with CT scans to assure complete resolution of the abscess.
Discussion: Pyogenic hepatic abscesses are rare and seldom communicate with the pleural space, owing to the tough membranous barrier provided by the diaphragm. As a result, very few cases have been reported in the literature. Historically, surgical drainage of the abscess and correction of the fistulous tract have been the mainstays of therapy. However, in recent decades authors have reported success with CT and ultra-sound guided drainage followed by long-term intravenous antibiotics—the technique chosen for our patient. Although rare, the presentation of cough with peculiar tasting symptom in a patient with known hepatic abscess should raise suspicion for a hepatobronchial fistula.

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Four-Dimensional Ultrasonogaraphy for Therapeutic Radiofrequency Ablation for Hepatocellular Carcinoma

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Purpose: Studies to evaluate the tumor vascularity in HCC have been done extensively with various imaging modalities because the finding of the vasularity is helpful to evaluate the biological features of the tumor. In the present study, we investigated whether four-dimensional real-time flow imaging is useful to display the accurate position of percutaneous radiofrequency ablation:RFA needle in the tumor and evaluated the efficacy of RFA therapy in patients with HCC.
Methods: Seventeen patients with 20 HCC lesions (13 men and 4 women, aged 37 to 83 years with a mean age of 61.9years), admitted to our Aichi Medical University Hospital between March 2003 and June 2004, were enrolled to the present study. Their diagnosis was confirmed by dynamic CT and celiac angiography. Based on Child-Pugh score, 11 patients was diagnosed as grade A, and 6 patients as grade B. All patients enrolled showed hypervascular enhancement of HCC on contrast-enhanced US and/or dynamic CT. The diameters of tumors were 1.1–2.0 cm in 6 nodules, 2.1–3.0 cm in 10, 3.1–5.0 cm in 4, respectively. US imaging We used VOLUSON 730 (GE Medical Systems, Milwaukee) for RFA therapy with a convex array as US system. 4D Real-time refers here to the display of 3-dimensional moving images composed of 3 orthogonally intersecting scans in the transverse, longitunal and horizontal planes. RF ablation was carried out under a real-time US guidance. We used a radiofrequency generator with 200 W power connected to a 17-gauge perfusion needle (Radionics Inc., Burlington, MA).
Results: It was possible to obtain accurate position of cool-tip needle and to perform RFA procedure in all 17 HCC patients with 20 nodules using 4D real-time VOLUSON 730 US machine. We confirmed by various angles that the needle was inserted into the center of tumor nodule. The simultaneous study before RFA therapy showed the inflow of arterial blood and tumor stai And importantly it appeared that 4D real-time US provided much perceptible information on the spatial relationship between RFA needle and the target lesion, and resulted in accurate therapeutic efficacy for percutaneous RFA procedure.
Conclusions: We experienced the treatment of 17 patient with HCC by RFA using 4D real-time ultrasound system. Application of this menthod allowed a more accuraye cauterization of the tumor.

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Reasons Why Patients Choose Expectant Management in CHC Infection and Changes in Satisfaction over Time

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Purpose: To assess reasons for the informed decision to choose expectant management for CHC infection and subsequent patient satisfaction.
Methods: A retrospective open access clinic-based chart review was completed on all patients. The reasons for expectant treatment by patient were recorded. A follow-up telephone communication consisting of a structured questionnaire was made at least one year after initial consultation was done. Patients were asked about their current health status and satisfaction with their initial decision.
Results: A total of 446 patient charts were reviewed. Out of these, 115 (26%) patients made an informed choice for expectant management after consultation. The majority [n = 105 (91%)] were genotype 1A/1B. Reasons given by patients for choosing expectant management were: absence of symptoms [n = 51 (44.3%)]; concerns about adverse effects [n = 25 (21.7%)]; medical contraindications [n = 23 (20.0%)]; social circumstances preventing effective treatment [n = 11 (9.6%)]; and doubts about efficacy [n = 5 (4.3%)]. Patients expressed concern about the adverse effects of conventional treatment that they had observed in contacts undergoing treatment. Medical reasons included depression, anxiety, morbid obesity, malignancy, and seizures. Social circumstances precluding treatment included alcohol or substance abuse, inadequate support systems, and lack of insurance. After at least one year, 75 patients were successfully contacted. Fifty-eight patients (77.3%) were comfortable with their decision and wished to remain expectantly followed. Eight patients (10.7%) were moderately satisfied but were considering conventional treatment. Nine patients (12%) expressed dissatisfaction with their decision. Two of these had since started conventional treatment, while one died while awaiting transplant.
Conclusions: The majority of patients remained satisfied with their initial informed decision to be followed expectantly. Reasons for their decision included the asymptomatic nature of infection, concern regarding adverse effects and efficacy, medical contraindications, and social circumstances preventing optimal treatment. Based on our findings, we recommend that

candidates for interferon treatment continue to be educated regarding efficacy and adverse effects. In addition, patients with unstable social conditions preventing treatment should be closely monitored for resolution of those issues.

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Correlation of Histological Severity between Genotype 3 and Others in HCV Chronic Hepatitis

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Purpose: Genome heterogeneity may be related to the wide variability of clinical and pathological features in hepatitis C virus (HCV) related chronic liver disease. The aim of this study is to see the significance of hepatitis C genotypes in relation to the severity of liver disease and to determine if the histological activity index (HAI) and fibrosis are more severe in genotype 3 than others.
Methods: Fifty-one consecutive liver biopsies of naïve patients with hepatitis C were evaluated. Serologic HCV-RNA was verified by RT-PCR and genotyping by direct sequencing. Grading of necroinflammatory and staging of fibrosis were hisologically assessed by Metavir scoring system. The disease activity was graded as minimal (A1), moderate (A2) and severe (A3). The extent of fibrosis was marked as absent (F0), mild (F1), moderate (F2) and severe (F3). Results were analyzed using t-test.
Results: 28/51 (51%) were genotype 3 almost all from South Asia and 23/51 (45%) were non-genotype 3 from a mixed ethnic group mostly native born Americans. There were 23/51 (45%) males and 28/51 (55%) females. The mean age of the patients were 45.1 (age range of 26–65). There were 14/28 (50%) males and 14/28 (50%) females in genotype 3 with a mean age of 41. There were 9/23 (39%) males and 14/23 (61%) females in non-genotype 3 with a mean age of 49.2. The mean activity score was 1.178 in genotype 3 and 1.434 in non-genotype 3 (p 0.085). The mean fibrosis score was 1.964 in genotype 3 and 2.000 in non-genotype 3 with a (p 0.46)
Conclusions: There was no statistically significant difference between histological activity and fibrosis between genotype 3 and others. Genotype 3 is histologically similar to other genotypes in severity. Genotype is not useful in predicting the severity of hepatitis C related liver disease.

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Preoperative Regional Maximal Removal Rate of Technetium-99m-galactosyl Human Serum Albumin (GSA-Rmax) Is Useful for Making a Final Decision on Surgical Procedure

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Purpose: For safe hepatic resection, the preoperative estimation of hepatic functional reserve in the predicted remnant liver may be more important than that in the entire liver. The purpose of this study was to find the minimal GSA-Rmax in the predicted remnant liver (GSA-RL) using functional imaging that predicts postoperative hepatic failure and, by so doing, avoid this complication.
Methods: One hundred and seventy-eight patients were admitted for elective hepatectomy. Conventional liver function, and 15 min retention rate of indocyanine green (ICGR15) were carried out preoperatively. The GSA-Rmax was calculated according to a radiopharmacokinetic model and then, using the SPECT images, we calculated the regional GSA-Rmax in the predicted residual liver (GSA-RL), depending on the operative procedures. The volume of the predicted residual liver (LV-RL) was calculated on the basis of CT images.
Results: Surgical procedures consisted of 98 sub-segmentectomy cases, 41 mono-segmentectomy cases, 31 di-segmentectomy cases and 8 tri-segmentectomy cases. The preoperative LV-RL correlated well with the GSA-RL in patients with normal liver however, there was no such correlation in those with chronic hepatitis or cirrhosis. Postoperative major complications such as hepatic failure, hyperbilirubinemia, bleeding (requiring re-operation), ascites, liver abscess, bile leakage and pleural effusion were recorded for 45 patients after subsegmentectomy, 25 patients after monosegmentectomy and 23 patients after di- and tri-segmentectomies. Fourteen patients had more than one complication. All of 7 postoperative hyperbilirubinemia occurred in the patients with GSA-RL < 0.15. Two patients died of postoperative liver failure one to two months after the operation. These two patients GSA-RL values were 0.078 and 0.090, respectively and severe discrepancies between the GSA-Rmax in the remnant liver and ICGR15.
Conclusions: Our data suggest that GSA-RL might be a practical and reliable diagnostic method for estimating the postoperative functioning hepatocyte volume and useful for making a final decision on surgical procedure, regarding the extent of liver resection in order to avoid postoperative hyperbilirubinemia or hepatic failure.

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Histological Acute Alcoholic Hepatitis Does Not Impair Survival after Liver Transplant

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Purpose: Clinical acute alcoholic hepatitis(AAH) is a contraindication for liver transplantation whereas the prevalence of histological AAH in patients undergoing transplantation is unknown. We investigated the prevalence of histological AAH in liver explants from alcoholics undergoing primary liver transplantation, and its association with post transplant outcomes.
Methods: A retrospective cohort study was designed of 1100 primary liver transplant recipients between 1984 and 2002. 144 recipients with liver failure due to alcoholic cirrhosis alone were compared with 116 randomly chosen non-alcoholic transplant recipients, matched for year of transplantation. Data on pre/post transplant drinking behavior and survival was recorded. The explanted livers were reviewed by a blinded pathologist for steatosis and Mallory bodies and graded on severity.
Results: All alcoholic patients had prolonged alcohol use (>50 g/day) prior to transplantation, with a mean abstinence period of 21 (0–156) months. Histological AAH was seen in 22% of explants from alcoholics compared with 4% in the control explants. Less than 6-months abstinence pre-transplant was significantly associated with histological AAH ($p = 0.05$ Odds ratio 2.3 (1.0–5.6)). After transplantation, survival among alcoholic recipients did not differ between subjects with or without histological AAH ($p = 0.39$) or when all alcoholic recipients were compared with non-alcoholic controls ($p = 0.13$). Neither histological AAH in the explant ($p = 1.00$) nor abstinence period prior to transplantation ($p = 0.96$) predicted alcohol relapse. A Cox Proportional Hazards Model failed to demonstrate an association between the following variables and post-transplant survival: steatosis ($P = 0.64$), Mallory bodies ($P = 0.84$), duration of abstinence pre-transplant ($P = 0.82$), alcohol relapse post transplant ($P = 0.71$), recipient gender ($P = 0.69$), or recipient age ($P = 0.08$).
Conclusions: The prevalence of histological acute alcoholic hepatitis in explants taken from patients with alcoholic cirrhosis is higher than previously recorded. Abstinence duration less than 6 months correlated with histopathological AAH. Histological AAH in the explant did not adversly effect transplant outcomes. Histological AAH should not prevent selection for liver transplantation.

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HBV Genotype Distribution Differs in Acute Hepatitis from Chronic Hepatitis in Japan

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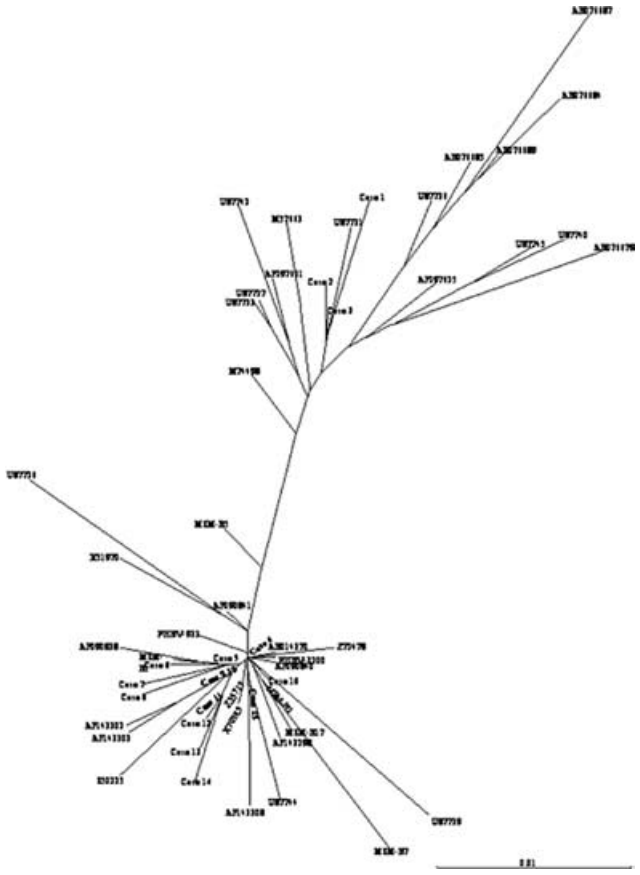
Purpose: Recently genotype A which is rare in the patients in chronic hepatitis B was frequently noted in patients with acute hepatitis B. To investigate their clinical and virological features, we studied the acute hepatitis B patients in the past 5 years.
Methods: 98 patients with acute hepatitis B and 80 patients with chronic hepatitis B admitted to our hospital between 1998 and 2003 were studied.
Results: Genotype A was not found in chronic hepatitis but was frequently noted in acute hepatitis (18.4%) ($p < 0.001$). Comparison of the clinical features of acute hepatitis between the two major genotypes, A and C, homosexual and heterosexual with multiple partners were frequently seen among genotype A patients. On the other hand, infection from steady partner showed a tendency to be more in genotype C. Acute hepatitis B caused by genotype A was more likely to progress to chronic infection than genotype C, significantly. Phylogenetic analysis of genotype A revealed that almost all strains from homosexual men belonged not to the African type A' but to the western type A. [figure 1]



Conclusions: Genotype A has increased recently among Japanese acute hepatitis B, and it may be related to promiscuous intercourse in high risk group. Prophylactic efforts against hepatitis B virus infection should be reconsidered from the view point of prevention from genotype A prevailing.

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Fat or Fiction: Ultrasound Diagnosis of Fatty Liver in Patients with Chronic Liver Disease

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Purpose: Hepatic steatosis (or fatty liver) is common in the United States and frequent in patients with chronic hepatitis C (CHC), where it may lead to disease progression and hinder response to HCV therapy. Therefore, it is important to recognize fatty liver. Liver biopsy confirms the degree of fat, inflammation and fibrosis, but is invasive. Hepatic ultrasound is well-tolerated, non-invasive and provides good information. It is commonplace to trust the results of an ultrasound suggesting fatty liver, but there are conflicting reports on its accuracy. Therefore, we retrospectively examined liver biopsies and compared the histologic results to the ultrasound interpretations. We selected patients with chronic liver disease, primarily CHC, in order to evaluate the accuracy of ultrasound in identifying fatty liver in a typical clinical setting.
Methods: Liver biopsies were reviewed on 131 patients who had a random liver biopsy performed for evaluation of chronic liver disease (89% had CHC). The biopsies were graded for fat (grades 0–3), inflammation (grades 0–4) and fibrosis (stages 0–4). Ultrasound interpretations were grouped into 3 categories- 'normal', 'fatty liver' and 'non-specific', and then compared to histologic results.
Results: A 'normal' ultrasound interpretation was correct in excluding significant fat (grades 2–3) 95.8% of the time, but 25% had some fat (grades 1–3) on biopsy, representing false negatives. Furthermore, 37.5% had significant fibrosis (stages 2–4) and 8.3% had significant inflammation (grades 2–4). A 'fatty liver' interpretation was only correct in identifying some fat on biopsy in 36.4% and significant fat in 11.4%, yielding many false positives. In addition, 47.7% had significant fibrosis and 18.2% had significant inflammation. A 'non-specific' interpretation was associated with 25.6% significant fat, 53.8% significant fibrosis and 23.1% significant inflammation. The sensitivity of ultrasound for detecting fat ranged from 32.0–88.2 and the specificity ranged from 40.4–65.4, depending on the degree of fat on biopsy and the sonographic interpretation considered to be significant.
Conclusions: Ultrasound is inaccurate for diagnosing hepatic steatosis in patients with chronic liver disease; echogenic alterations are more likely to be the result of fibrosis or inflammation in this setting. Therefore, in patients with chronic liver disease, the ultrasound diagnosis of fatty liver is more 'fiction' than 'fat'.

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Functional Significance of the Proliferating Bile Ductules in Primary Biliary Cirrhosis -Increased Expressions of Caveolin -1 and -2-

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Purpose: Bile ductular proliferation is noted in diverse human liver diseases, particularly in primary biliary cirrhosis (PBC) and obstructive jaundice. Caveolins, caveolin-1 (CAV-1) and caveolin-2 (CAV-2) are Ca^{-++} and cholesterol-binding proteins involved in the regulation of several intracellular processes including cholesterol transport. The aim of the present study is to clarify how CAV-1 and -2 are expressed by immunohistochemical and Western blot analyses in human liver biopsy specimens from patients with PBC.
Methods: Surgical liver biopsy specimens were obtained under laparoscope from 13 patients with PBC (12 females and 1 male, mean age 53.4 years, Scheur's stageI∼II; 6 cases, stageIII; 7). As controls, wedge biopsy specimens were obtained from normal portions of the livers of 10 patients (2 females and 8 males, mean age of 57.3 years) who underwent surgical resection for metastatic liver carcinomas. Indirect immunohistochenical staining was performed on consecutive serial sections using anti-CAV-1, anti-CAV-2 specific antibody as primary antibody and horseradish peroxidase (HRP)-conjugated anti-IgG as secondary antibody. Four-micrometer sections were cut from paraffin blocks of formalin-fixed liver tissues, deparaffinized with xylene and dehydrated by graded ethanol solutions. Bile ductules were identified by immunostaining of CK-6. Western blotting was conducted using fresh control and PBC liver tissues.
Results: In control liver, the specific immunopositive reactions for CAV-1 and -2 were hardly detected on the bile ducts and ductules. In PBC, the

immunopositive reactions for CAV-1 and -2 were increased on the proliferating bile ductules in the stageII and III of PBC, but sparsely noted on the interlobular bile ducts in the stageIof PBC. Particularly, the epithelial cells of the proliferating bile ductules at the interface between the portal tract and the lymphocytes-infiltrated parenchymal area were intensely immunostained for CAV-1 and -2. These results were confirmed by Western blot analysis.
Conclusions: The increased expressions of CAV-1 and -2 in the proliferating bile ductular epithelial cells in PBC may be related to the homeostatic control of cholesterol transport in the regenerating bile ductules in response to the obliterative immunodestruction of the down-stream interlobular bile ducts in PBC.

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Comparison of Pegylated Interferon alfa-2a and alfa-2b in Combination with Ribavirin in Obese Patients with Chronic Hepatitis C

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Purpose: Obesity (body mass index (BMI) > 30) is a negative predictor of response to HCV treatment. Two pegylated interferons (PEG-IFN) are available for treatment of chronic hepatitis C (CHC). One is administered in a fixed weekly dose (PEG-IFN alfa-2a) and the other in a weight-based weekly dose (PEG-IFN alfa-2b). It is hypothesized that weight-based dosing of PEG-IFN may be superior to fixed dosing on treatment response rate in obese patients. However, no prospective, controlled efficacy data are available.
Aim: To determine if weight-based dosing of PEG alfa-2b is superior to fixed dose PEG alfa-2a in terms of sustained virologic response (SVR) rates in obese patients with CHC.
Methods: We conducted a retrospective analysis of our database of PEG treated patients at the Little Rock VA. We included 31 treatment naïve patients with BMI>30 who received either form of PEG in combination with ribavirin. PEG alfa-2a dose was 180 μg/week and PEG alfa-2b dose was 1.5 μg/kg/week plus ribavirin 800–1200 mg/day according to weight and genotype.
Results: SVR data is noted in table. Age, gender, race, and baseline HCV RNA were similar between the 2 groups.

SVR in Patients with BMI >30

	PEG-IFN alfa-2a	PEG-IFN alfa-2b	p-value
SVR			
all patients	6/13 (46%)	8/18 (44%)	>0.05
HCV genotype 1	2/9 (22%)	6/14 (43%)	>0.05
HCV genotype 2 or 3	4/4 (100%)	2/4 (50%)	>0.05

Conclusions: There was no difference in SVR rates between obese patients with CHC who were treated with either PEG-IFN alfa-2a or PEG-IFNalfa-2b. Further prospective studies are warranted.

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No Difference in Efficacy and Tolerability between Pegylated Interferon alfa-2a *vs.* alfa-2b in Combination with Ribavirin in Treatment of Naïve Patients with Chronic Hepatitis C

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Purpose: Two pegylated interferons (PEG-IFN) are currently available for treatment of chronic hepatitis C (CHC): PEG-IFN alfa-2a and PEG-IFN alfa-2b. No prospective, controlled efficacy data are available comparing sustained virologic response (SVR) rates between the two approved PEG-IFN.
Aim: To determine if there was any difference in SVR between the 2 PEG-IFN in treatment naïve CHC patients.
Methods: We conducted a retrospective analysis of our database of CHC patients treated with PEG-IFN at the Little Rock VA (n = 60). We included treatment naïve CHC patients who received either form of PEG-IFN + ribavirin and had follow-up of at least 18 months for genotype 1 (n = 40) and 12 months for genotype 2 or 3 (n = 20). Dose of PEG-IFN alfa-2b was 1.5 μg/kg/week and PEG-IFN alfa-2a was 180 μg/week + ribavirin 800–1200 mg/day according to weight and genotype.

Table 1: SVR

	PEG-IFN alfa-2a	PEG-INF alfa-2b	p-value
SVR			
all patients	11/22 (50%)	17/38 (45%)	>0.05
HCV genotype 1	4/13 (31%)	9/27 (33%)	>0.05
HCV genotype 2/3	7/9 (78%)	8/11 (73%)	>0.05

Results: SVR data and side-effects are noted in table. Age, gender, race, BMI and baseline HCV RNA were similar between the 2 groups.

Table 2: Side Effects

	PEG-IFN alfa-2a	PEG-IFN alfa-2b	p-value
Side-Effects			
neutropenia	5/22 (23%)	7/38 (18%)	>0.05
thrombocytopenia	3/22 (14%)	4/38 (11%)	>0.05

Conclusions: There was no difference in SVR rates between PEG alfa-2b and PEG alfa-2a in CHC naïve patients (overall and by genotype). The frequency of side-effects was similar between the two. Further prospective studies are warranted.

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Improving Sustained Response Rates in Hepatitis C Non-Responders by Combining PEG-INF alfa 2b with INF alfa 2b and RBV

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Purpose: PEG-interferon and Ribavirin (RBV) combination therapy is the current standard of care due to its improved sustained virologic response rate (SVR) over IFN alfa 2b and RBV combination therapy. It is felt that the improved SVR is related to sustained levels of interferon in the body. Protein peggylation does come with a price, as the viral activity of PEG-interferon-alfa 2b (PEG) is only 28% that of Interferon-alfa-2b (INF) and the viral activity of PEG-interferon-alfa-2a is 7% that of Interferon-alfa-2a. It is hypothesized that a combination of the longer acting peggylated interferon with the shorter acting more virally active interferon may offer high viral activity as well as sustained pressure on the virus and improve sustain response rates particularly in previous non-responders (NR).
The aim of this study was to prospectively evaluate the use of a combination of PEG and INF, along with RBV in the treatment of Hepatitis C patients who have been non-responders to at least six months of INF ± RBV therapy.
Methods: Patients eligible for the study received PEG at 1.0ug /kg SQ every Saturday and INF was dosed at 3 mil units (< 90kg) or 5 mil units (≥ 90 kg) SQ every Monday, Wednesday, and Friday. RBV was given at doses of 12–15 mg/kg/day. Treatment duration was for 48 weeks and NR were defined as having detectable HCV RNA at 24 weeks.
Results: A total of 10 patients were enrolled in the study; six had cirrhosis, seven were genotype-1, and nine were previous combo treatment NR. Initial response rates were 80%(8/10) and the SVR was 30%(3/10). Two of the five

relapsers were re-treated for 60 weeks and both of these patients became sustained responders bringing the overall SVR rate up to 50%. Dose reductions of PEG/INF were not required and only one patient had a dose reduction in RBV. No serious adverse events were noted.
Conclusions: The combination of PEG/INF/RBV in the schedule and doses outlined above can be given safely. Initial and sustained response rates to this combination therapy in previous non-responders are very good particularly if treatment extends beyond 48weeks. Longer duration of treatment beyond 48 weeks may be needed in patients at high risk for relapse such as previous non-responders or relapsers to therapy, cirrhotics, patients with high viral load and genotype-1, and those who's HCV RNA takes longer than 12 weeks to become undetectable. If larger studies confirm these results, this could be a method to maximize the effects of interferon in the treatment of non-responders.

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Prophylactic Tips for Large Gastric Varices: A Pilot Study with Four-Year Prospective Experience

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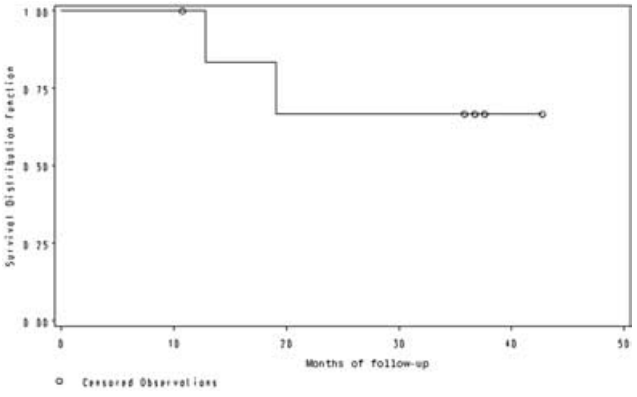
Purpose: Cirrhotic patients with large fundal gastric varices have high morbidity and mortality. We sought to determine the role of TIPS as primary prophylaxis for bridging such patients to liver transplantation.
Methods: Among 147 consecutive patients evaluated in the Stanford University pretransplant hepatology clinic, we identified 9 patients with large fundal gastric varices (LFGV) and high-risk characteristics. Seven (78%) patients underwent TIPS, and were followed for a mean of 28 months (range, 10.7–42.8 months).
Results: At the end of the follow-up period, 2 (28.6%) patients had undergone liver transplantation and 2 (28.6%) had died. One patient died from gastrointestinal bleeding and the other succumbed to severe hepatic decompensation complicated by intracranial bleeding. The other 3 patients remain on the transplant list with no episodes of gastrointestinal hemorrhage. [figure 1]Four patients required one TIPS revision each, at a mean of 168 days from the time of the initial procedure. These outcomes compare favorably with published morbidity and mortality rates of patients with LFGV.



Conclusions: TIPS may be useful as a bridge to liver transplantation for patients with large gastric varices. A randomized controlled trial is warranted.

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Liver Transplantation for Hereditary Hemochromatosis–A Single Center Experience

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Purpose: Herditary hemochromatosis (HH) is a systemic disease that can lead to cardiac and liver failure requiring organ transplantation. Long-term results of orthoptic liver transplantation (OLT) for HH have been disappointing due to an increased mortality from cardiac and infectious complications. The aim of this study is to report the outcomes of OLT for HH from a single transplant program.
Methods: A retrospective chart review was performed on patients transplanted for iron overload at the University of Nebraska Medical Center between 1985 and 2004. Patients were diagnosed with HH if three of the following four criteria were present: iron saturation greater than 65%, C282Y mutation, liver biopsy consistent with iron overload and explant histopathology confirming excess iron deposition. The following outcomes were recorded: prevalence of hepatocellular carcinoma (HCC), episodes of rejection, post-transplant diabetes mellitus and sepsis, cardiac complications post-OLT, graft and patient survival and cause of death.
Results: 16 patients were transplanted during this period. There were 13 males and 3 females. Median age was 58.8 years at OLT. HCC was present in 3 patients, of whom two were diagnosed pre-OLT due to elevated alfa-feto protein levels. Acute rejection occurred in 11 patients, all of whom responded to steroid boluses and one who developed chronic rejection. Diabetes developed in 10 patients and 6 patients developed post-transplant sepsis. Two patients were retransplanted for chronic rejection and hepatic artery thrombosis. Cardiac complications occurred in 10 patients post-OLT (cardiac arrest n = 1; arrhythmias n = 2; MI n = 5; pericarditis n = 1; aortic stenosis n = 1) with 4 patients dying from cardiac related causes. Cumulative incidence of graft failure was 0% at 1 year and 14% at 5 years (95% CI 0–45%). Overall survival at 1 year was 94% (95% CI 82–100%) and at 5 years was 75% (95% CI 61–86%).
Conclusions: Despite the encouraging one year survival for patients transplanted for HH, 5 year survival was disappointing compared to patients undergoing OLT for other indications. Infections, although frequent, were not responsible for mortality in this small series of patients. Cardiac related causes accounted for the death in all 4 patients. Cardiac disease remains an important cause of morbidity and mortality in patients undergoing OLT for HH. Consideration for combined cardiac and liver transplantation may need to be entertained for this high risk group.

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Non-Invasive Predictors of Advanced Liver Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

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Purpose: Patients with nonalcoholic fatty liver disease (NAFLD) require a liver biopsy to definitively establish the presence of advanced fibrosis. The purpose of this study was to determine whether non-invasive parameters could accurately predict advanced fibrosis in this cohort.
Methods: We retrospectively reviewed the records of 57 consecutively biopsied patients with NAFLD. Data recorded included demographic features, medical history, and clinical laboratory studies. Liver biopsy specimens were staged and graded by an individual pathologist according to the original Brunt system. Continuous and categorical variables were evaluated by univariate analysis, and statistically significant variables were included in multiple logistic regression models.
Results: Of the 57 NAFLD liver biopsies, 30 (52.6%) had advanced fibrosis (stages 3 + 4). Univariate analysis indicated that those individuals with advanced liver fibrosis had significantly lower platelets and albumin levels (Table 1). These patients were also more likely to have type 2 diabetes mellitus and AST/ALT ratios greater than 1.0 ($p < 0.05$). Multiple logistic regression models indicated that the Odds Ratios for advanced fibrosis were 8.9 and 10.3 for individuals with diabetes mellitus and AST/ALT ratio > 1.0, respectively. A model using the combined presence of type 2 diabetes mellitus and AST/ALT ratio > 1.0 demonstrates an AUROC of 0.81.

Table 1. Comparisons of Study Patients with NAFLD According to Degree of Fibrosis

Features	Advanced Liver Fibrosis (N = 30)	Non-Advanced Liver Fibrosis (N = 27)	P-value
Age (yr)	54.0 ± 9.6	49.6 ± 10.9	0.070
Gender (%M)	53	52	1.000
BMI (kg/m2)	40.9 ± 10.14	37.2 ± 10.0	0.321
ALT (U/L)	81.8 ± 52.1	118.8 ± 69.7	0.029
AST (U/L)	74.0 ± 36.8	61.6 ±27.0	0.292
AST/ALT ratio	1.04	0.61	0.001
Type 2 Diabetes (% present)	77.0	22.7	0.006
Platelets (bil/L)	197.0 ± 73.0	253.0 ± 87.5	0.027
Albumin (g/dl)	4.11 ± 0.44	4.32 ± 0.39	0.038

Conclusions: This data suggests that non-invasive models may allow gastroenterologists to accurately predict advanced liver fibrosis in NAFLD patients. The best model is one based on the combined presence of type 2 diabetes mellitus and an AST/ALT ratio > 1.0.

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Treatment of Hepatitis C Infected Substance Abusers within a Community-Based, Outpatient Methadone Maintenance Program

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Purpose: To demonstrate the feasibility of Hepatitis C virus treatment of HCV-infected substance abusers within a community-based, outpatient methadone maintenance program.

Methods: In an effort to expand the treatment options to community-based methadone maintenance pts within a behavioral health agency, an HCV evaluation and treatment program was initiated. After HCV antibody testing and counseling, pts were screened for suitability for IFN-based tx (stable medical/psychiatric/substance abuse disease). These pts received a physician evaluation, lab (± biopsy evaluation), and IFN-based tx with lab monitoring and on-site psychiatric services.

Results: Using an intention-to-treat analysis, 15 pts on methadone maintenance therapy started a course of combination tx for chronic HCV liver disease. Demographically pts were 67% male, with mean age of 45, mean baseline ALT of 107, and 73% genotype I with a mean HCV viral load of 2,800,000 IU/ml. Mean biopsy stage was 2.4 with a mean grade of 2.4. All pts had had at least 3 months abstinence from illicit drugs prior to the initiation of tx. 8/15 (53%) had known psychiatric illness; 7 of these were diagnosed with depression.

All 15 pts were treated with PEG-IFN and RBV for 24–48 wks dependent on genotype. Only one pt withdrew from tx, due to intolerance of PEG-IFN. 93% of those completing 12 wks of tx (N = 14) had an early virological response (2-log drop in HCV RNA level). Later 3 pts had a recurrence of virus, leading to discontinuation of tx prior to its intended duration. 10 pts completed a full course of tx; 9 of these pts had undetectable HCV RNA (ETR 60%). 6 months post-tx, 5/15 (33%) had a sustained virological response; 2 pts had recurrence of virus, and 2 others pts remain in follow-up. 2 pts with preexisting depression experienced worsening of symptoms; temporary reduction of PEG-IFN dosage successfully reduced depressive symptoms for one of these pts. 3 other pts developed depressive symptoms. Therapy was generally well-tolerated, with side-effects similar to pts who are not on methadone. Upward titration of methadone dosage reduced side-effects in most pts. There were no serious adverse events.

Conclusions: HCV-infected pts on methadone therapy can be safely and effectively treated for HCV. Due to the enhanced ability to monitor for psychiatric decompensation and substance abuse relapse, this therapy can be effectively delivered within the setting of a community-based, outpatient methadone maintenance program.

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Is NASH Triggered by a Leaky Gut?

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Purpose: The pathophysiology of non-alcoholic steatohepatitis(NASH) has not been clearly delineated, but there appears to be a "two hit" mechanism. Based on animal studies, one of the proposed second hit mechanisms is oxidative stress triggered by endotoxin. Increased intestinal permeability has been shown to be a source of endotoxemia and oxidative stress in alcoholics. We aim to determine whether patients with NASH have intestinal hyperpermeability and whether leaky gut can differentiate simple steatosis from NASH in obese patients.

Methods: Patients were recruited from the Bariatric surgery center or Nutrition clinic at Rush. Steatosis and NASH were diagnosed by liver biopsy using Brunt criteria. Intestinal permeability was measured using urinary excretion of poorly absorbed sugars (lactulose, sucrose, mannitol and sucralose). To determine whether patients had increased susceptibility to leakiness, the permeability test was repeated after aspirin challenge (1300mg ASA). Urinary sugars were measured by gas chromatography. Small bowel permeability was defined by the Lactulose/Mannitol (L/M) ratio and whole gut permeability was defined by sucralose excretion. Median values for sugar excretion were compared between all groups using Kruskal-Wallis and between each group using Mann-Whitney tests.

Results: There was no statistically significant difference between patients with steatosis (n = 6) and NASH (n = 10) in regards to demographics, BMI, AST, AP, bilirubin, or cholesterol. ALT levels were significantly higher in patients with NASH (98) *vs.* steatosis (55). (p = 0.021). Small bowel permeability (median L/M ratio) was similar between groups pre and post aspirin. Whole gut permeability (sucralose excretion) was similar between groups at baseline, control 0.0245, steatosis 0.0323 and NASH 0.0328. (p = 0.873). However, patients with NASH had a significant increase in whole gut permeability with aspirin challenge, 0.0613, compared to both controls, 0.0283 (p = 0.006) and steatosis 0.0405 (p = 0.023). In contrast, patients with steatosis had no increased susceptibility to leakiness with aspirin compared to controls.

Conclusions: Our data indicate that patients with NASH are susceptible to colonic leakiness as they have an exaggerated response to aspirin challenge. This susceptibility should result in increased endotoxemia and oxidative stress in these patients. Therefore, avoidance of factors that may deleteriously affect intestinal permeability, such as NSAIDs, is strongly suggested in those at risk for NASH.

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A Randomized Controlled Trial of Consensus Interferon with or without Zinc for Chronic Hepatitis C Patients with Genotype 2

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Purpose: Additive effect of zinc supplementation on the treatment of chronic hepatitis C by interferon was demonstrated in hepatitis virus genotype 1b and high viral load. This study focused on the patients with genotype 2 which is more sensitive to interferon than genotype 1b, treated by consensus interferon with or without zinc.

Methods: We randomized 83 patients with chronic hepatitis C to consensus IFN (CIFN) 18MIU 6 times/week for 4 weeks, followed by CIFN 18MIU 6 times/week for further 20 weeks given in combination with polaprezinc 300 mg/day (regimen A, n = 41) or as monotherapy (regimen B, n = 42).

Results: Thirty-one patients in regimen A and 33 patients in regimen B completed this trial; the other patients withdrew because of side effects or a transfer to another hospital. No additional side effects of polaprezinc were noted. Sustained biochemical response, defined as normal aminotransferase level at the end of the 6 months post treatment observation, was 68 and 69%,

and sustained virological response, defined as undetectable HCV-RNA at the end of the 6 months post treatment observation, was 54 and 67% for regimen A and B, respectively.
Conclusions: Combination of CIFN treatment with zinc did not enhance the effect of CIFN as shown by biochemical, virological criteria.

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Risk Factors for Bacterial Infections in Cirrhotic Patients

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Purpose: Cirrhotic patients with bacterial infection have a significantly higher mortality than uninfected cirrhotic patients in many studies,which indicates that bacterial infection is a poor prognostic factor in cirrhotic patients. Thus, it is important to investigate and eliminate the risk factor for bacterial infection in cirrhotic patients. This study was performed to evaluate the risk factors for infections in patients with liver cirrhosis.
Methods: The medical records of 674 consecutive admissions with liver cirrhosis hospitalized at the Division of Gastroenterology and Hepatology of Chungang University Yongsan Hospital were retrospectively reviewed between January 2002 and December 2004. The collected data included etiology, severity and complications of cirrhosis, blood test results on admission, isolated pathogenic organism, site of infection and prognosis.
Results: Bacterial infections developed in 188 patients (27.9%) and 66 (35.1%) of these developed nosocomial infections. The patients with infection have a higher mortality rate than patients without infection (17.6% vs 5.8%). Gram-negative bacterial strains were the most frequently isolated pathogens, in 62 of the 81 strains isolated. Univariate analysis revealed significant differences between the groups with and without infections with regard to advanced Child-Pugh class, ascites, hepatic encephalopathy, gastrointestinal bleeding, gastroesophageal varices, decompensated liver function, total protein, albumin, total bilirubin, total cholesterol, prothrombin time and activated partial thromboplastin time. Multivariate analysis revealed advanced Child-Pugh class ($p = 0.017$; odds ratio, 0.566; 95% CI, 0.356–0.902), gastrointestinal bleeding ($p = 0.003$; odds ratio, 3.973; 95% CI, 1.577–10.011), low serum albumin ($p = 0.001$; odds ratio, 2.525; 95% CI, 1.440–4.427) and low serum cholesterol ($p = 0.003$; odds ratio, 1.008; 95% CI, 1.003–1.013) as the independent factors contributing to the development of infections.
Conclusions: The present study indicated to need attention should be directed to gram-negative bacterial infections in advanced cirrhotic patients with gastrointestinal bleeding and low serum albumin and cholesterol levels.

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CD34 Expression in Hepatocellular Carcinoma and Chronic Liver Diseases

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Purpose: Angiogenesis is known to be essential for the progression of hepatocellular carcinoma (HCC). However, the relationship between the occurrence of HCC and angiogenesis has been not elucidated. CD34 have been used for the detection of active angiogenesis in malignant tumors including HCC.
Methods: 38 specimens of liver tumor which were obtained from patients including 6 cases of HBV-associated chronic liver diseases, 30 cases of HCV-associated, 1 case of glycogen storage disease, and 1 case of liver disease with unknown etiology by US-guided fine-needle target biopsy were embedded in paraffin, and cut into 4-micrometer-thick sections. These sections were immunostained with anti-CD34 monoclonal antibodies. The standard avidin-biodin-peroxidase complex technique was applied for immunostaining. The CD34 labeling index (LI) was measured.
Results: CD34 staining patterns in cases without HCC were all negative or minimal. On the other hand, many of cases with HCC showed focal or diffuse staining pattern. The sensitivity and specificity of focal or diffuse CD34 staining for HCC was 76.9% and 100%. In 72% of cases, we could distinguish HCC from non-HCC area within the same specimen by CD34 staining. In a view of relationship between CD34 staining pattern of obtained tumor tissues and clinical variables of patients, platelet counts was significantly lower in cases with diffuse staining than in cases with negative and minimal staining ($p < 0.05$). The level of alfa-fetoprotein (AFP) tended to be correlated with the intensity of CD34 staining, and the AFP level of cases with diffuse CD34 staining was significantly higher than that with minimal CD34 staining ($p < 0.05$). In 34 patients with advanced stages, CD34 LI of 16 patients with progression to HCC within 5 years (HCC group) was significantly higher than that of 18 patients without HCC (non-HCC group)($P = .0199$). Moreover, in the same patients, the cumulative incidence of HCC was significantly higher in the patients of CD34 LI$\geq$12 ($n = 16$) than of CD34 LI<12 ($n = 18$)($P = .009$).
Conclusions: These results indicate that evaluating the CD34 expression in chronic liver disease is very useful in predicting the HCC development and diagnosis of HCC.

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Hepatitis D Is an Important Cause of Decompensation in HBV Related Chronic Liver Disease in India

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Purpose: To study the extrinsic causes and methods of decompensation in hepatitis B related chronic liver disease.
Methods: 78 patients of CLD-B; 13 compensated and 65 recently (< 3 months) decompensated were included. ACLF was defined as acute deterioration in liver function over a period of 2–4 weeks in a pre-existing patient of CLD. Patients with alcohol intake > 20 g/day, concomitant HCC, chronic liver disease due other causes, HIV positivity or severe co-morbid conditions were excluded. Serological tests including IgM anti HAV, IgM anti HEV, HBsAg, HBeAg, Anti HBe, IgM anti HBc, Anti –HCV, IgM Anti–delta, HIV 1&2. HBV DNA was quantified.
Results: 68 patients were followed-up; 56 were ACLF and 12 were compensated liver disease. Patients with ACLF presented alone or in combination as jaundice, ascites or variceal bleed in 78%, 61% and 11% patients respectively. ACLF patients had higher AST, ALT, bilirubin, CPT score and lower serum albumin than compensated CLD patients. IgM anti HBc was significantly higher in ACLD ($p < 0.001$) but median HBV DNA was comparable to compensated CLD patients {(12 (0.5–1129) *vs.* 1.7 (0.5–3809) pg/ml)}. The most common extrinsic causes of decompensation were Hepatitis E in 17.8% of patients followed by Hepatitis D in 14.2% cases. Hepatitis A in 3.5% and Hepatitis C in 1.8% were other minor causes of decompensation. Reactivation of HBV was the cause in about 63% patients.
Conclusions: Besides reactivation of HBV**,** and superinfection by Hepatitis E, Hepatitis D infection is an important cause of recent decompensation and acute-on chronic liver failure in India.

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Interferon and Ribavirin Combination Therapy in Chronic Hepatitis C: Predictors of Sustained Viral Response

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Purpose: To determine the predictors of SVR in Ribavirin and Interferon alpha combination therapy.
Methods: A retrospective chart analysis was done in 228 patients treated for Hep C between (2000–2005) and 137 charts were excluded. The exclusion criteria included patients with liver transplant, HIV or other forms of hepatitis, autoimmune diseases, on immunosuppressant, poor compliance, age >70 and any other cause of chronic liver disease.Data collected from 91 charts were analyzed.Apart from demographic variables, information was collected on initial viral count, genotype, patient type, stage and grade of liver disease, alcohol use and treatment types. The primary outcome variable, Sustained viral response was defined as viral count < 600 six months after 1 year of treatment.
Results: The mean age of total sample (N = 91) was 49.15±7.14 years. 73.3% were men, 63.7% were Caucasians, 23.1% African Americans and 13.2% were Hispanics. Distributions of Genotypes 1, 2,3, and 4 were 70.3%, 19.8%, 3.3%, and 2.2% respectively. The distributions of patient types were 73.6% Naives, 16.5% were non-responders (NR) and 7.7% were relapsers (R). 60.4% of the patients had SVR. Univariate analysis showed that SVR was significantly correlated with patient type [chi sq 5.9, p 0.015], race [chi sq 5.9, p 0.052] and alcohol use [chi sq 3.65, p 0.056]. SVR was also significantly correlated with early viral response (EVR) [0.875, p < 0.001]. SVR did not have correlation with age, weight, smoking, stage and grade of liver disease, and treatment type. Although the genotypes differed in the initial viral count [F 3.18, p < 0.001], they did not show differences in SVR. A secondary observation made in this study is that the reason for incomplete treatment (<1 year) was 30.2% non-response to treatment and 25.5% as a result of side effects.
Conclusions: In our study race, alcohol intake, patient type and early viral response showed significant correlation with sustained viral response to ribavirin and interferon alpha combination therapy. Identification of these variables might provide help in improving treatment outcomes and pretreatment counseling.Further studies are needed to confirm this findings.

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Epidemiology of Chronic Hepatitis B Infection in South Bronx Community Hospital

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Purpose: Prior study reported that prevalence of hepatocellular carcinoma (HCC) and portal hypertension from chronic hepatitis B virus (HBV) infection was 44% among Hispanics and 28% among Blacks. Since our institution predominantly serves these populations therefore we retrospectively studied the epidemiology of HBV infection in our community.
Methods: We reviewed medical records all patients age ≥18 years with chronic HBV infection who had been evaluated at the clinics affiliated with Bronx Lebanon Hospital Center between January 1, 2002 and December 31, 2004.
Results: 167 patients with chronic HBV infection were identified with mean age of 40 years (range 18–81). Of these, 82 (49%) patients were males. 103 (62%) were African-Americans, 60 (36%) Hispanics and 4 (2%) others. Majority of the patients were covered by health insurance (127, 76%). Comorbidities included HIV (23, 14%), HCV (8, 5%), HIV and HCV (4, 2%). Of the 16 patients with liver cirrhosis, 9 (56%) were found to be decompensated and 1 (6%) had HCC. Among 68 patients who had HBeAg status known, 23 (34%) had positive HBeAg. Of 78 patients with alpha-fetoprotein (AFP) known, 69 (88%) had AFP level less than 10 ng/mL. Liver imaging study for HCC screening was performed in 80 (48%) patients. 12 (7%) patients underwent HBV treatment. Among 155 patients who were not treated, 107 (69%) had alanine aminotransferase (ALT) level less than upper limit of normal (ULN) without evidence of liver cirrhosis. 48 patients were not eligible for HBV treatment for the following reasons: 20 (42%) were active injection drug or heavy alcohol users, 17 (35%) were non-compliant with visits during the evaluation period and 11 (23%) did not have health insurance coverage.
Conclusions: In the South Bronx, nearly half of our patients underwent HCC screening. More than half of patients with liver cirrhosis were decompensated. Most of our patients were not considered to be candidates for treatment because of normal ALT levels and potentially modifiable social factors. Recognition and management of the identified factors may increase rate of HCC screening and HBV treatment.

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Liver Dysfunction in Patients with Inflammatory Bowel Disease

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Purpose: The prevalence of liver dysfunction in inflammatory bowel disease (IBD) varies across studies. Little is known about the relationship between liver dysfunction and IBD activity. In IBD patients we sought to 1) determine the prevalence of liver dysfunction, defined by abnormal serum levels of aspartate aminotransferase, alanine aminotransferase and/or alkaline phosphatase; 2) determine the prevalence of chronic liver disease; and 3) clinically compare patients with and without liver dysfunction.
Methods: IBD patients seen for the first time at Mayo Clinic Rochester from 1/1/00 to 12/31/00 were identified. Medical records were abstracted for gender, age, IBD subtype, extent and activity, medications, history of liver disease, and liver biochemistries. Chi-square, student t-test or rank tests were used as appropriate.
Results: We identified 544 patients with available hepatic biochemistries. Abnormal liver tests were found in 159 (29%), of whom 81% had no specific diagnosis. Primary sclerosing cholangitis (PSC) was present in 4% of all patients, and in 14% of those with liver dysfunction. Other liver diseases were autoimmune hepatitis (n = 2), fatty liver (n = 1), hepatitis C (n = 1), portal or hepatic vein thrombosis (n = 2) and metastatic cancer (n = 1). The prevalence of liver dysfunction was 27% for those with active IBD and 36% for those in remission (p = 0.06). Patients with and without liver dysfunction did not differ with regards to gender, age or subtype of IBD, but were less likely to be on oral 5-aminosalicylate (5-ASA) agents (35% *vs.* 51%, p < 0.001). 5-ASA did not modify or confound the effect of IBD activity in liver dysfunction. The use of other medications did not differ between groups. Follow-up liver tests were obtained in 118 patients (74%) with liver dysfunction. Abnormalities persisted in 39 (32%), with PSC being diagnosed in 15 (38%).
Conclusions: Liver dysfunction was detected in 29% of IBD patients. Surprisingly, we found no association between liver dysfunction and IBD activity. Patients with liver dysfunction were less likely to be on 5-ASA. One-third of those with abnormal liver tests had persitent abnormalities, and PSC was present in a significant proportion of them. Abnormal liver tests should not be attributed to active IBD. Rather, they should be monitored and work-up should be undertaken if liver dysfunction persists, even if IBD is active.

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Mild-Moderate Alcohol Consumption Does Not Enhance Liver Fibrosis Progression in Patients with Chronic Hepatitis C Virus (HCV)

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Purpose: Previous studies have suggested that regular ETOH use may lead to more rapid progression of chronic HCV. These studies focused on patients who consumed excessive amounts of ETOH (>6gms/day) and implied that any amount of ETOH may be deleterious to patients with chronic HCV. The present study is a retrospective, although detailed analysis assessing the impact of ETOH consumption on liver fibrosis in patients with chronic HCV.

Methods: 474 patients with well characterized chronic HCV followed at our Center were enrolled. All patients underwent a baseline liver biopsy, serum HCV RNA level (Roche Amplicor) and genotype. Liver biopsy was staged according to the criteria of Knodell. system. Questions regarding a range of risk factors to estimate the date of infection as accurately as possible along with detailed history of ETOH use according to the Skinner Alcohol Examination Questionnaire were obtained during a one-on-one interview. Patients were grouped according to mean lifetime daily ETOH (<1drink, 1–3drinks, 3–8drinks, >8drinks) and HCV duration (<10yrs, 10–29yrs, 30–39yrs, > or = 40yrs). A one-way ANOVA statistical analysis and linear regression were used to compare mean fibrosis with daily ETOH intake among each HCV group.
Results: The mean age of the group was 50 years, 58% were male and 71% Caucasian. The median duration of HCV infection was 27 years. Mean ETOH use was 3.2 drinks ± 8.8/day; mean fibrosis score 2 ± 1.5 and this increased stepwise with the duration of infection. For every level of ETOH consumption a broad range of fibrosis was observed. For each fibrosis stage (no fibrosis through cirrhosis), no relationship to ETOH use was observed. At least 40% of patients in each fibrosis group consumed <1drink/day. An increase in fibrosis was observed in patients who consumed 5–6 drinks/day, although this relationship fell short of significance ($p = 0.08$).
Conclusions: The consumption of mild-moderate ETOH (up to 3 drinks/day) appeared to have no effect on the development of fibrosis in patients with chronic HCV. Recommending that patients with chronic HCV must remain completely abstain of ETOH for fear of developing cirrhosis therefore appears unnecessary. These data suggest that other factors, likely genetic, are more likely to affect fibrosis progression than ETOH consumption.

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Depression and Sustained Viral Response in Patients with Hepatitis C

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Purpose: To examine the incidence of depression associated with interferon (IFN)-based therapies in patients with chronic hepatitis C viral (HCV) infection. We also assessed the relationship between sustained viral response (SVR) rates and the development of IFN-induced depression.
Methods: Patients with HCV were recruited from two, separate sites (Baltimore and Bethesda, MD). In the Baltimore study, patients with HCV were evaluated for symptoms of depression prior to and during therapy with interferon (IFN) and ribavirin (N = 39). Weekly psychometric testing [Beck Depression Inventory] and standardized psychiatric interview indicated that IFN-induced major depression (MDD) developed in 13 of 39 patients (33%). Patients who became depressed were treated mostly with the antidepressant citalopram [a selective serotonin reuptake inhibitor (SSRI)]. Similarly, in the Bethesda study, patients were monitored for symptoms of depression before and during pegylated IFN and ribavirin therapy (N = 60). Serial testing [Center for Epidemiological Studies Depression Scale] and standardized clinical evaluation revealed that 23 of 60 patients (38%) developed IFN-induced MDD. As in Baltimore, the patients who developed depression were treated predominantly with citalopram.
Results: At both study sites, end-of-treatment response (ETR) and SVR rates were significantly higher in the patients who developed MDD during IFN therapy, as compared with those who did not.

	Baltimore		Bethesda	
HCV Patients	ETR (%)	SVR (%)	ETR (%)	SVR (%)
MDD	61.5	38.5	65.0	56.5
non-MDD	26.9	11.5	21.6	16.2

Conclusions: Results from these two studies (N = 99) suggest that IFN-induced depression may be a predictor of a positive response to antiviral therapy and may be an indication of optimal dosing. Patients who developed MDD were treated with SSRIs, which alleviated IFN-induced MDD and allowed continuation of therapy. Antidepressants may have permitted patients to remain on optimal antiviral therapy dosing and increase their chances of viral clearance. More research regarding the effects of depression and antidepressant use on antiviral responsiveness is needed. However, our results show that with regular monitoring, early symptom detection, and appropriate treatment intervention, patients who develop depression during HCV treatment can successfully complete a course of IFN therapy and achieve SVR.

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Predictive Factors for the Distant Recurrence of Hepatocellular Carcinoma after Radiofrequency Ablation of Hepatocellular Carcinoma

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Purpose: Radiofrequency ablation (RFA) therapy for hepatocellular carcinoma (HCC) has made good local control possible. After the local control, however, distant recurrences are frequently observed in remnant liver. In this study the efficacy of RFA is evaluated and predictive factors for the distant recurrence are revealed.
Methods: 135 patients with initial HCC who underwent RFA in our hospital (Male/Female = 100/35) were selected for this study. After transecatheter airterial embolization, RFA was performed under the real-time CT guided. Safety margins of more than 5mm around tumors were confirmed by dynamic CT after the RFA with all those patients. The mean age is 66.9 years old, HBV/HCV/HBV+HCV/NBNC = 10/109/1/15, Child-Pugh(A/B/C) = 96/35/4, the average follow-up period is 21.8 months (3–54months). We studied local and distant recurrence rates, predictive factors for the distant recurrence of HCC, and treatment performed for the recurrence.
Results: After RFA for the initial HCC, survival rates are 84.5%, 82.4% and 62.8% for two, three and four years respectively. The recurrence rates after RFA are 5% and 12% in two and four years respectively for local, and 41.4% and 67.7% in two and four years respectively for distant. RFA could be performed again for 76% of the patients with distant recurrence. The study of predictive factors for cumulative distant recurrence rates by Kaplan-Meier method shows significant high recurrence rates in cases of initial multi-occurrence, low albumin level, high AST level, low platelet count and low prothrombin time (PT). The predictive factors for cumulative distant recurrence after RFA by Cox proportional hazard regression model are low albumin level and high AST level.
Conclusions: While RFA enables good local control for the initial HCC without remarkably worsening liver functions, distant recurrences in remnant liver are observed at high rates in the cases with low albumin, platelet and PT level. Low albumin and high AST level are predictive factors for the distant recurrence, and it is possible to control distant recurrence by caring nutrition and lowering AST after RFA.

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Association between Antioxidant Use and the Prevalence and Severity of Steatosis and Fibrosis in Patients with Chronic Hepatitis C Virus Infection

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Purpose: Oxidative stress is increased in patients with chronic hepatitis C virus (HCV) infection and may be involved in the pathogenesis of this

disease. Therefore, antioxidant therapy may be beneficial for the treatment of HCV-associated liver disease. The aims of the present study were to compare the prevalence and severity of steatosis and fibrosis among patients who were and those who were not taking antioxidants.

Methods: Consecutive patients undergoing liver biopsy were prospectively identified and were interviewed by a research assistant who obtained detailed demographic and clinical data, as well as information on the use of antioxidants (vitamin C and E). Steatosis was scored according to the percent of hepatocytes involved as none (no steatosis), mild (<33%), moderate (33%–66%), or severe (>66%) using the Brunt system; fibrosis was scored on a scale from 0–4.

Results: Of the 577 patients enrolled, current antioxidant use was reported by 241 subjects (41.8%). Overall, 336 (58.2%) were not taking any antioxidants, 99 (17.2%) used vitamin C only, 62 (10.7%) used vitamin E only, and 80 (13.9%) were taking both vitamin C and E. The prevalence of steatosis of any grade (42.3% vs 60.1%, $p < 0.001$), moderate-severe steatosis (15.8% vs 24.7%, $p = 0.009$), and stage 3/4 fibrosis (23.7% vs 34.5%, $p = 0.005$) were significantly lower in patients who were taking antioxidants as compared to those who were not taking these supplements. The lower odds of steatosis (OR = 0.46; 95% CI, 0.31–0.69) and stage 3/4 fibrosis (OR = 0.68; 95% CI, 0.42–0.94) among patients who were taking antioxidants remained significant even after adjusting for age, gender, race, alcohol use, diabetes, BMI, triglycerides, and HCV genotype. However, the prevalence of steatosis (45.0% vs 42.4% vs 38.7%, $p = 0.75$) and stage 3/4 fibrosis (31.3% vs 19.2%, vs 21.0%, $p = 0.14$) among patients who were taking both vitamin C and E was not significantly different from those who were taking vitamin C alone or vitamin E alone.

Conclusions: Antioxidant use was associated with a significantly lower prevalence and severity of steatosis and fibrosis among patients with chronic HCV infection. However, we found no evidence of a synergistic effect among patients taking both vitamin C and E as compared to those who were only taking one of these supplements. Randomized controlled trials to evaluate the beneficial effect of antioxidants are warranted in patients with chronic HCV infection.

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Impact of Ethnicity and Antioxidant Use on the Prevalence and Severity of Steatosis in Patients with Chronic Hepatitis C Virus Infection

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Purpose: Both ethnicity and antioxidant use may affect the prevalence of steatosis among patients with nonalcoholic steatohepatitis. Although steatosis is a common histologic finding in patients with chronic hepatitis C virus (HCV) infection, it is unclear if ethnicity or antioxidant use influence steatosis formation. The aim of the present study was to determine the impact of ethnicity and antioxidant use on the prevalence and severity of steatosis in patients with chronic HCV infection.

Methods: Prior to liver biopsy, patients were interviewed by a research assistant who obtained detailed demographic and clinical data, as well as information on the use of antioxidants (vitamin C and E). Steatosis was scored according to the percent of hepatocytes involved as none (no steatosis), mild (<33%), moderate (33%–66%), or severe (>66%) using the Brunt system; fibrosis was scored on a scale from 0–4.

Results: 577 were patients enrolled, including 185 non-Hispanic whites, 234 non-Hispanic blacks, 139 Hispanics, and 19 who self-reported their ethnicity as other. Among whites, blacks, Hispanics, and other ethnic groups, respectively, there were significant differences in the prevalence of steatosis of any grade (56.2% vs 43.6% vs 64.0% vs 47.4%, $p = 0.001$), moderate/severe steatosis (21.1% vs 14.5% vs 31.7% vs 21.1%, $p = 0.001$), and stage 3/4 fibrosis (31.4% vs 20.9% vs 42.4% vs 36.8%, $p < 0.001$). Antioxidant use was reported by 241 subjects (41.8%); 99 (17.2%) used vitamin C only, 62 (10.7%) used vitamin E only, and 80 (13.9%) were taking both vitamin C and E. Patients taking antioxidants had a lower prevalence of steatosis of any grade (42.3% vs 60.1%, $p < 0.001$), moderate/severe steatosis (15.8% vs 24.7%, $p = 0.009$), and stage 3/4 fibrosis (23.7% vs 34.5%, $p = 0.005$) compared with those who were not taking these supplements. Overall, the steatosis grade was strongly correlated with fibrosis stage ($r = +0.56$, $p < 0.001$) and this varied from +0.42 to +0.76 across ethnic groups ($p < 0.01$ for all groups). Ethnicity and antioxidant use remained independently associated with both steatosis and fibrosis after adjusting for age, gender, alcohol use, diabetes, BMI, triglycerides, and HCV genotype.

Conclusions: There were marked ethnic differences in the prevalence and severity of steatosis and fibrosis among patients with chronic HCV infection, with the prevalence being highest in Hispanics and lowest in blacks. In this population, antioxidant use was associated with a significantly lower prevalence and severity of steatosis and fibrosis. Randomized controlled trials to evaluate the beneficial effect of antioxidants are warranted in patients with HCV infection.

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Fulminant Hepatic Failure Secondary to Low Dose Amiodarone

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Purpose: Amiodarone is a commonly used antiarrhythmic medication. Abnormal liver function are frequently reported with its use, however clinically symptomatic disease is rare. Toxic effects are well described with high dosages, there have only been a few case reports of low dose amiodarone and fulminant liver failure. We report a rare case of a patient who developed fatal fulminant hepatic failure with low dose oral amiodarone.

Case Report: 70 years old male admitted to the hospital with symptoms of anorexia, nausea, and generalized weakness for several days. He had history of coronary artery disease, ischemic cardiomyopathy with ejection fraction of 25% and Diabetes Mellitus. Amiodarone 200 mg was started 11 months ago for nonsustain ventricular tachycardia. Medications included atenolol, enalapril, atrovastatin, and Metformin. No history of recent alcohol, recreational or herbal drug use. Exam revealed a somnolent, normotensive, afebrile, non icteric patient, in no distress. Cardiopulmonary exam revealed bibasilar crackles. Abdominal exam was normal.

Lab data showed, ALT 1821U/L, AST 1424U/L, total bilirubin of 5 mg/dl, direct bilirubin of 3.4 mg/dl, and ALP 269U/L, Hb 6g/dl, WBC of 17.9(81% neutrophils) BUN 90 mg/dl and creatinine 5.7 mg/dl. Blood cultures were negative. Hepatitis A, B and C profiles were negative. Chest X-ray showed pleural effusions bilaterally with cardiomegaly. Despite discontinuing the amiodarone patient's condition worsened rapidly. He developed multiple organ failure, and died on the third hospital day. Autopsy showed centrilobular hemorrhagic necrosis with cholestasis and ductal inflammation consistent with drug induced hepatitis.

Discussion: Amiodarone is widely used for treatment of ventricular and supraventricular arrhythmia. When long term amiodarone therapy is used potential drug toxicity must be considered. Acute hepatic failure is a rare complication of Amiodarone therapy. Our patient had acute hepatic failure without any identifiable cause and the autopsy was consistent with drug toxicity. An exclusive ischemic cause of acute hepatitis seemed to be unlikely as there was no documented precipitating event. Whether additional factors contributed to the hepatitis cannot be ruled out. The patient did have ischemic cardiomyopathy and the literature shows amiodarone toxicity is more common in patients with congestive heart failure with a low ejection failure.

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Interferon alfa/ Ribavirin Combination Therapy in Mixed Hepatitis C Virus (HCV) Genotype Infection

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Purpose: Response rate to interferon alfa/ ribavirin combination therapy in various HCV genotypes has been widely reported. To this date response rate in mixed HCV genotype infections has not been reported. We report our experience of interferon alfa/ ribavirin combination therapy in our patients with mixed HCV genotype infection.
Methods: A retrospective analysis of 65 patients with mixed HCV genotype infection (mixed 3a/3b 30 pts, 3a/2a 5pts 3b/2a 5 3a/2b 5, 1a/3a 10. 1a/3b 6 1a/2a 4 patients.) treated with interferon alfa/ ribavirin combination therapy was carried out. Those with mixed 3a/3b, 3a/2a, 3b/2a, 3a/2b were treated with 24 weeks of combination therapy whereas patients with 1a/3a, 1a/3b, 1a/2a, mixed infections had received 48 weeks of combination therapy. Sustained viral response (SVR) was assessed at 24 weeks after stopping the treatment.
Results: SVR in mixed 3a/3b, 3a/2a, 3b/2a, 3a/2b, 1a/3a, 1a/3b, 1a/2a, was 50%, 40%, 40%, 40%, 20%, 16.6% and 0% respectively.
Conclusions: Lower SVR to interferon alfa/ Ribavirin combination therapy was noted in mixed HCV genotype infections.

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Is C Reactive Protein (CRP) a Useful Test in Distinguishing Steatosis from Steatohepatitis in Patients with Non Alcoholic Fatty Liver Disease (NAFLD)?

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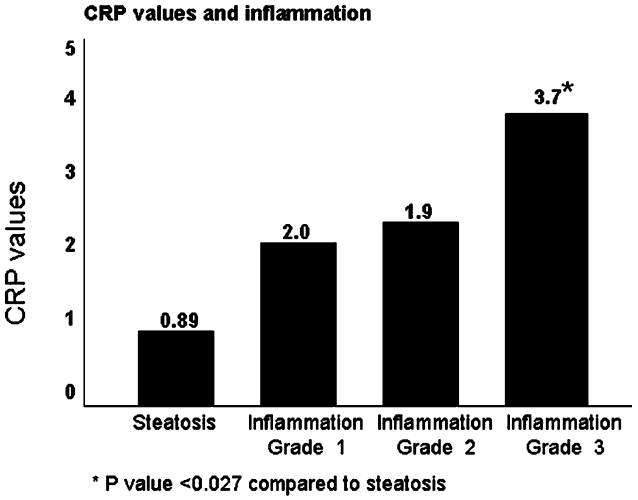
Purpose: NAFLD encompasses a spectrum of liver diseases ranging from fat accumulation in the liver (steatosis), inflammation, cell necrosis (steatohepatitis) and cirrhosis. Steatohepatitis is a progressive disease leading to cirrhosis, whereas steatosis has a benign course. There are no clinical or biochemical markers to distinguish steatosis from steatohepatitis. CRP is a widely available blood test that has been used as a marker of systemic inflammation. The aim of our study is to determine if CRP can be used to distinguish steatosis from steatohepatitis.
Methods: CRP values (ultraquant, normal < 0.3 mg/dl) were measured in 44 patients with NAFLD and 8 controls with chronic hepatitis C virus (HCV) infection who underwent liver biopsy in the same period. Liver function tests, fasting insulin levels, glucose and lipid profile were also obtained. The liver biopsies in patients with NAFLD were graded based on percentage of steatosis, inflammation and fibrosis as per published guidelines. Biopsies of 8 HCV patients were graded and staged by Knodell scoring system. Insulin resistance was calculated by QUICKI.
Results: Results are shown in table 1 and figure 1. CRP values were higher in patients with steatohepatitis compared to patients with simple steatosis. The values were highest in patients with severe inflammation. There were no differences in transaminases, insulin resistance, and lipid levels between the groups of patients.

Clinical and Biochemical Profile

	Steatosis (n = 8)	Steatohepatitis (n = 36)	HCV (n = 8)	p value
Age	48.5 ± 12	47.8 ± 12	46.6 ± 6	NS
BMI	31.9 ± 4.2	31.3 ± 7.9	32.1 ± 9.7	NS
AST	36.3 ± 16	48.7 ± 21	42.3 ± 14	NS
ALT	65.8 ± 30	73.3 ± 36	59.5 ± 31	NS
CRP	0.86 ± 1.5	2.19 ± 3.0	0.52 ± .4	0.08
QUICKI	0.322	0.311	0.318	NS



[figure 1]
Conclusions: C reactive protein appears to be a useful marker to distinguish steatohepatitis from steatosis. Studies with a larger number of patients are needed to clarify whether it can be used as a substitute for liver biopsy.

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Profile of Liver Involvement among Adult Patients in Dengue Virus Infection

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Purpose: Little data are available on liver involvement in adult patients with dengue virus infection.
Methods: During a recent outbreak in India, we looked for evidence of liver dysfunction among adult patients with dengue fever, dengue hemorrhagic fever and dengue shock syndrome. Diagnosis of dengue infection was based on presentation, during the outbreak, with fever of short duration and thrombocytopenia.
Results: Forty five patients [median age 33 (range 7–65) years; 29 male; 39 adult; 23 dengue fever, 15 dengue hemorrhagic fever and 7 dengue shock syndrome] were studied. Median platelet count was 34×10^9/L ($9–99 \times 10^9$). Seven patients (15%) had jaundice, 11 (24%) hepatomegaly and nine clinically-detectable ascites; none had splenomegaly. Twelve (27%) patients had hyperbilirubinemia. Serum alanine and aspartate aminotransferase activities were elevated in 43 (96%) patients each; 5-fold elevated levels were more frequent in severe disease. Hypoalbuminemia was found in 31/41 (76%) patients. Seven patients died, including two with acute liver failure.
Conclusions: Our data show that liver injury is common in adult patients with dengue virus infection. Further studies are needed to determine the mechanism of liver injury in this disease.

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Effect of BMI on Survival after Liver Transplant: A Single Center Experience

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Purpose: Orthotopic liver transplant has become an accepted modality for the treatment of end stage liver disease. The increase prevalence of obesity in the United States has resulted in an increased number of obese recipients as well as obese donors. Questions have emerged on whether these recipients with less than ideal body weights have increased morbidity and mortality.

Aims: 1. To determine whether BMI affects patient survival and post-surgical complication rate.
2. To assess the effect of BMI on renal function after liver transplant.
3. To determine whether survival rate changes in patients who develop co-morbid conditions (i.e. diabetes, hypertension) after transplant.
Methods: A retrospective database of all adult patients undergoing first time liver transplant at our center from 1995 to 2002 was established. The database was divided into patients with BMI < 30 kg/m^2 (low) and patients with BMI > 30 kg/m^2 (high). The groups were evaluated for survival, post surgical complications, and worsening renal function which was defined as renal transplant, dialysis or 3 consecutive creatinines over 1.8 mg/dL.
Results: From 1995 to 2002, 309 adult patients underwent first time liver transplant, of which 264 patients had BMI measurements. The mean BMI of the patients was 27.9 kg/m^2. In comparing patients with low and high BMI, the post-surgical complication rate was not significantly different between the two groups. Additionally, worsening renal function was not significantly different between the two BMI groups. On univariate analysis, development of diabetes adversely affected post-transplant survival ($p = 0.02$). However, on multivariate analysis, which included the development of hypertension, diabetes, and the presence of obesity, no conditions significantly affected post-transplant survival. Finally, when looking at survival rates between the two BMI groups, there is worse 3 year survival for the high BMI group ($p = 0.03$) while after 3 years post-transplant, there was a better survival for the high BMI group ($p = 0.09$).
Conclusions: In our experience with liver transplant, obesity did not affect the post-surgical complication rate. This was different than previously published reports from other single center studies. The development of diabetes post-transplant adversely affects patient survival. Patients who are obese have poorer short term survival, but appear to have better long term survival although continued follow-up of these patients is necessary to confirm this conclusion.

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Anemia during Ribavirin Treatment for Hepatitis C: Can Creatinine Clearance Predict the Risk of Anemia and Response to Erythropoietin Treatment

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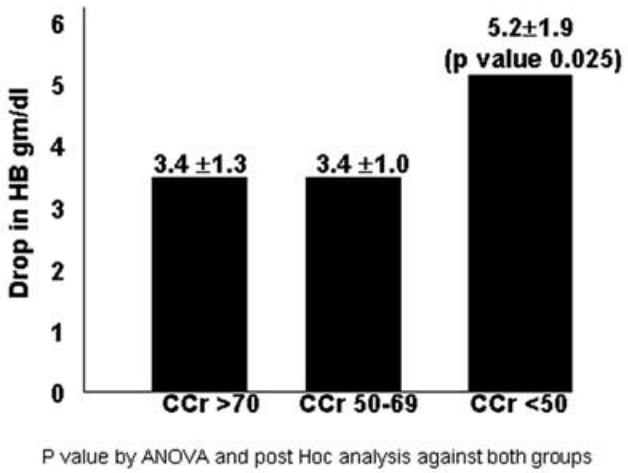
Purpose: There is paucity of data on the incidence of ribavirin induced anemia and effectiveness of erythropoietin in patients with preexisting renal insufficiency (RI). The **aim** of this study is to determine whether pre treatment creatinine clearance can predict the occurrence of anemia and response to erythropoietin.
Methods: 46 patients (15 females, mean age 53.8 yr (range 44–71) with HCV infection after liver transplant were enrolled in the study. The antiviral regime comprised of pegylated interferon alpha 2b (1 microgram/kg/week) and 800 mg ribavirin. Weekly monitoring of hemoglobin and hematocrit was done. Erythropoietin alpha (procrit^{TM}) 40,000 units was given for a decrease in hemoglobin level of < 10 gm/dl or a drop in hemoglobin > 3gms if patients had prior heart disease or are symptomatic. The erythropoietin was continued in weekly doses till an improvement in hemoglobin was noted or continued throughout treatment if hemoglobin remained stable. Creatinine clearance (CCr) was calculated by using modified diet in renal disease formula (MDRD1).
Analysis: To determine whether CCr predicted anemia, patients were divided into three groups: those with CCr$>$ 70ml/mt, CCR between 50–70ml/mt, and CCr $<$ 50 ml/mt (*severeRI*).
Results: Occurrence for anemia in each CCR group is shown in the table.
Response to Erythropoietin alpha: Twenty patients (45%) required erythropoietin alpha and of these 9 patients had dose reduction in ribavirin. There were 11 (55%) patients who has improvement in hemoglobin by at least 1 gm/dL on erythropoietin, five (25%) remained stable and four (20%) patients had further drop in hemoglobin.The response to erythropoietin was similar in all groups of patients.

	Drop HB <1gms	Drop HB 1–3 gms	Drop HB 3–5 gms	Drop HB>5	P value
CCr≥70	17%	26%	48%	9%	
CCr 50–69	0%	38%	56%	6%	
CCr<50	29%	14%	14%	49%	0.05*

P value indicates difference in Drop $>$ 5 gms.



[figure 1]
Conclusions: Severe RI (CCR $<$50 ml/mt) is associated with marked decrease ($>$5 gms) in hemoglobin levels. Erythropoietin (40000 units weekly) stabilizes the hemoglobin levels in majority of patients even in those with severe RI.

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Hepatitis C Treatment Eligibility and Outcomes in Patients with Psychiatric Illness

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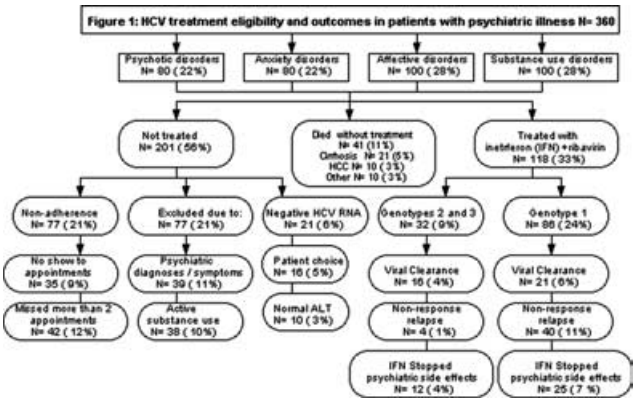
Purpose: This report describes the existing status of Hepatitis C Virus (HCV) treatment eligibility, utilization and outcomes in a large sample of patients with HCV and co-morbid psychiatric illness. This would serve as a first step toward the facilitation of HCV treatment in psychiatric populations.
Methods: Our sample was derived from the sequential screening of all admissions ($N = 3470$) to an inpatient psychiatric service at a VA medical center from 1998 to 2002. HCV treatment evaluation and outcomes were tracked in 360 HCV (+) patients. The patient's primary psychiatric admission diagnoses included one of the following: substance use disorders (alcohol, cocaine, marijuana); anxiety disorders; affective disorders (depression, bipolar) or psychotic disorder (schizophrenia).
Results: As illustrated in Figure 1, more than 2/3 of patients did not receive HCV treatment due to: non-adherence, active psychiatric symptoms and active substance use. Eleven percent died from HCV complications. Sustained virologic response (SVR) was achieved in 31% of those treated with interferon-α (IFN) and ribavirin (RBV). Patients with psychotic or anxiety disorders were less likely to achieve SVR (p¨0.002) and

more likely to have neuropsychiatric adverse effects from IFN treatment ($p < 0.004$) when compared with patients with affective or substance use disorders.



Conclusions: HCV infection in patients with psychiatric illness was associated with significant mortality. IFN-based therapy combined with RBV can be safely administered to patients with HCV and psychiatric illness. However, many patients with HCV and psychiatric illness were found ineligible for HCV treatment due to their psychiatric illness, and non-adherence to the evaluation process leading to HCV treatment was substantial. Our results highlight the need to develop better management and therapeutic approaches to engage, manage and successfully administer HCV treatments to patients with psychiatric illness. [figure 1]

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Outcomes of Gastric Variceal Bleed: Results of Sclerotherapy with N-Butyl 2 Cyanoacrylate

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Purpose: To study the incidence and outcomes following NBC sclerotherapy of GV bleed.
Methods: Retrospective analysis of case records of 1436 patients who underwent endoscopy for PHTN from March 2000 to March 2005. GV were classified according to Sarin's classification. Outcomes with respect to primary hemostasis ie., bleeding control within first 24 hrs of endoscopy, rebleed ie., bleed after the first 24 hrs of endoscopy & in-hospital mortality were analyzed.
Results: The incidence of GV in patients with PHTN was 220/1436 (15%) and of these, 50 (22.7%) had bled. Mean age of patients with bleeding GV was 50 ±11 years, and 30/50 (60%) were males. The main etiology of PHTN in bleeders was hepatitis C in 34 (68%), followed by HBV and NBNC in 6 (12%) patients respectively; IGV-I were observed in 22 (44%), GOV-I in 16 (32%) and GOV-II in 15 (30%). A comparison of bleeding and non bleeding GV revealed that IGV-I was seen in 22/50 (44%) patients who bled as compared to 39/170 (23%) who never bled ($p < 0.003$).
Primary hemostasis was achieved with NBC in all patients. Rebleed occurred in 7 (14%) patients. Secondary hemostasis with repeat NBC sclerotherapy was achieved in 3 (43%); 2 (28.5%) patients died after repeat sclerotherapy and one each during TIPSS and surgery. Treatment failure related mortality rate was 4/50 (8%).
Conclusions: GV were observed in 15% patients presenting with portal hypertension and bleed occurred in 22.7%. There was an increased risk of bleed from IGV-1. NBC was effective in controlling GV bleed. In hospital mortality in patients with bleeding GV was 8%.

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Predictors of Early Rebleeding Following Endoscopic Control of Variceal Bleeding

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Purpose: Early rebleeding is a major complication of variceal hemorrhage. Factors associated with early rebleeding after endoscopic control of the initial bleeding episode are not fully clarified.The aim of this study was to examine the frequency of early rebleeding, and to investigate factors related to its occurrence.
Methods: Acute variceal bleeding was controlled in by endoscopic intervention in 846 patients (662 males, 184 females, mean age 52.6 years). All patients received antibiotic prophylaxis, and were followed for the occurrence of early rebleeding for 5 days or till discharge.
Results: Early rebleeding occurred within the first 5 days in 82 patients (9.7%). Rebleeding was successfully re-controlled endoscopically in 37 (45.1%) (significantly less than in 764 of 918 patients (83.2%) with initial bleed (OR 6.03, 95%CI 3.7, 9.64). Rebleeding was related to severity of liver disease (none of Child A patients rebled, *vs.* 4.6% of Child B and 13.5% of Child C patients, $p < 0.05$, Child C vs Child B OR 3.2 [1.77,6.01]). Rebleeding mortality occurred more in rebleeding Child C patients compared to Child B (62.3% vs 15.4% respectively, OR 9.1, [1.87, 44.3]). Earlier endoscopic intervention for managing the initial bleed was associated with significantly less re-bleeding (rebleeding occurred in 20 of 363 patients (5.5%) in whom endoscopy was done within 3 hours of admission, vs 26 of 264 (9.8%) with endoscopy between 3 and 6 hours, and 36 of 219 (16.4%) with endoscopy >6 hours, $p < 0.05$). Patients with gastric varices injected with tissue adhesive had more rebleeding than patients with esophageal varices managed with either sclerotherapy or band ligation (25 of 161 patients (15.5%) *vs.* 57 of 685 patients (8.3%); OR 2.03, [1.22, 3.36]). Rebleeding was significantly related to the presence of encephalopathy, ascites, initial diagnosis of SBP in ascitic patients, renal impairment on admission, the presence of HCC, and the number of blood units needed to achieve hemodynamic stability before the initial endoscopic intervention. It was not related to method of initial management of esophageal varices, (banding *vs.* sclerotherapy), and was not related to age, sex, whether first or recurrent attack, and endoscopic description of varices.
Conclusions: Early rebleeding is a serious risk following control of bleeding from varices, and carries high mortality. Further preventive measures are needed for high risk patients to ensure prevention of early rebleeding.

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Non-Alcoholic Fatty Liver Disease in an Area of Nothern Italy: Incidence and Main Clinical and Histological Aspects

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Purpose: The incidence of NASH in pts with abnormal transaminases has not been clearly defined. The purpose of this prospective study was to determine the incidence of NASH in asymptomatic pts with abnormal ALT referred for evaluation to five Hepatology Units in nothern Italy.
Methods: In the period from January to December 2003, pts (18–60 years old) with persistently abnormal ALT levels, normal US and alkaline phosphatase were studied. The diagnosis of NASH was based on: (1) a weekly intake of less than 40 g of ethanol (evaluated using codified questionnaires and modalities) (2) exclusion of all other liver diseases such as drug induced and autoimmune hepatitis, hemochromatosis, Wilson's disease, PBC, PSC 3) exclusion of hepatitis B or C infection 4) abnormally high plasma aminotransferase levels for at least 6 months 5) no exposure to known toxins such as pesticides or other xenobiotics. All pts with NASH underwent a liver

biopsy (scored according to Brunt EM et al Am J Gastroenterol 1999; 94: 2476–84).
Results: We evaluated 553 with abnormal ALT. NASH was found in 33 pts (6%). This population included 27 males with a median age of 40.2 years (range 27–60), BMI of 26.8 ± 1.9 (range 24–30) and 6 females with a median age of 40.7 (range 34–57), BMI 25.8 ± 1.7 (range 23–29). Four pts had hypertension, two hyperlipidemia, one patient had hyperlipidemia and hypertension. In 26 pts we found no co-morbidity. Clear obesity was found only in two pts, while none claimed to have recent weight loss. Grade of necroinflammation (grade1/grade2/grade3) was found in 8/4/4 pts respectively. Fibrosis score (1/2/3/4) was reported in 8/4/2/2 pts respectively. Liver histology was normal or near normal in 12 pts. Liver biopsy specimens were insufficient for histology in 5 pts.
Conclusions: In the setting of unexplained chronic liver transaminase abnormalities, NASH is found in 6% of our patients. A great proportion of pts with NASH present a normal or near normal liver histology. Cirrhosis was found in 6% of our population with NASH. Non alcoholic steatohepatitis can also occur in lean male and female pts without associated conditions.

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Polymorphism of T-Cell Receptor Gamma Microsatellite and the Susceptibility of Hepatocellular Carcinoma

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Purpose: T-cells play a critical role in the immunological surveillance network against cancer formation. Activation of T-cells is initiated by binding of T-cell receptors (TCR) with antigen epitopes. Polymorphism of TCR-γ microsatellite (short tandem repeats, STR) marker has been found to be associated with early-onset colorectal cancer. The aim of this study was to elucidate the relationship of TCR-γ STR genetic polymorphism and hepatocellular carcinoma (HCC).
Methods: A total of 192 chronic hepatitis B or C carriers with HCC and liver cirrhosis were enrolled in this study. The other 192 sex-matched cirrhotic patients without HCC were recruited as controls. Their TCR-γ STR polymorphisms at loci D7S1818 and D7S2206 were detected by polymerase chain reaction. Dietary habits and other possible risk factors for HCC were also assessed by a structured questionnaire.
Results: Neither genotype nor allele of TCR-γ STR was found to be related to the susceptibility of HCC. However, after grouping the 20 genotypes of TCR-γ STR of D7S1818 into a high TCR-γ STR group (one or both alleles $\geq$ 13 in repeated number of GATA) and a low TCR-γ STR group (both alleles $<$ 13 of repeated number), we demonstrated the former had a higher risk of HCC than the latter, in subjects younger than 60 years old (67.5% *vs* 42.8%, $p = 0.006$). This finding remains true after adjustment for dietary habits (OR: 2.72, 95% CI: 1.29–5.75).
Conclusions: TCR-γ STR polymorphism may be associated with the susceptibility of early-onset HCC. The viral hepatitis-associated cirrhotics with high TCR-γ STR may have T-cell dysfunction and increase the risk of HCC at a younger age.

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Characteristics and Problems of Randomized Controlled Trials on Hepato-Pancreatic Surgery

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Purpose: The randomized controlled trial (RCT) is an important research method, providing the highest evidence and playing a pivotal role in the performance of evidence-based medicine. However, RCTs on hepato-pancreatic surgery have been performed less frequently than RCTs in other fields. I examined the characteristics of RCTs for hepatic and pancreatic surgery in comparison with RCTs for other surgical fields to propose breakthrough.
Methods: A retrieval of studies was performed through MEDLINE to identify prospective RCTs on hepato-pancreatic surgery and other surgeries including gastrectomy, colectomy, and mastectomy in the last decade. I analyzed eligible RCTs using the following items: study design, publication year, geographical area, sample size, multicenter study, and impact factor.
Results: One hundred and eleven papers on hepatectomy and 44 papers on pancreatectomy were eligible for review. Studies comparing surgical technique or methods have composed the majority of the RCTs involving hepatectomy and pancreatectomy. About half of the RCTs on hepatectomy have been performed in East Asia, while most of the RCTs on pancreatectomy in the Western countries. The average sample number of RCT on hepatectomy is significantly smaller than those in other fields. Moreover, multicenter studies are less frequently performed on hepatectomy compared with pancreatectomy. The average impact factors for RCTs on hepatectomy and pancreatectomy are similar.
Conclusions: Promoting the organization of multicenter studies would be the best way to increase the number and sample size of RCTs on hepatectomy. Adequate RCTs observing the Consolidated Standards of Reporting Trials statements such as estimation of sample size are necessary to obtain reliable evidence.

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Detection of Precore Mutants of Hepatitis B Virus by Ligase Chain Reaction (LCR) in the Patients of Chronic Liver Diseases

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Purpose: Hepatitis B is one the most important cause of chronic hepatitis. Several recent studies have been shows that mutants of hepatitis B virus have important clinical and therapeutic implications of the many mutants described, mutations involving the precore region which suppresses expression of HBeAg have substantial clinical significance. The most sensitive and specific method of detecting these mutants is nucleotide sequencing. Ligase chain reaction is an alternative, simple and reliable method of detecting precore mutants. The study was designed with the following.
Objectives: To detect the precore mutant with a point mutation from G to A at nucleotide 83 in the precore region using Ligase chain reaction (LCR), and to study the clinical and biochemical profile of patients harboring HBV precore mutations and their comparison with those infected by wild type HBV and finally to compare the course of illness and clinical outcome due to precore mutation with that of wild type HBV.
Methods: 104 patients of serologically proven HBV chronic liver disease, which included cases of chronic hepatitis (90), Cirrhosis of liver (8) and HCC (6), were inducted in the study.
Results: The cases were evaluated on the basis of history, clinical examination, liver function profile and serological test of HBV infection (HBsAg, anti HBc (Total), HBeAg using commercially available Elisa Test. Those cases, which were HBsAg +ve, HBeAg –ve & HBV DNA +ve were subjected to LCR.18 cases out of the total 104 cases were serologically suspected as precore mutants. These serologically suspected cases were subjected to LCR. 15 out of total 18 (83.3%) were positive for LCR conforming the presence of precore mutants, which were also confirmed by direct sequencing. The sequencing data analyzed showed that 7/15, (46.6%) of the cases were infected predominantly by the mutant form of the virus while the remaining 8/15, (53.3%) of the cases showed the presence of mixed infection with the wild and the mutant form of the virus.
Conclusions: The present data suggests that precore mutations is seen in 14.4% of the patients of Asian Indian origin suffering from chronic liver disease and the disease is more symptomatic and aggressive in patients with the mutant form of the virus as compared with the wild form of the virus.

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No Association between Mannose-Binding Lectin Gene Polymorphisms in Patients with Chronic Hepatitis B and Spontaneously Recovered among Iranian Population

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Purpose: To determine the frequency of codon +57(G to A) and position +4 (C to T) of non-translated region mannose-binding lectin (MBL) gene polymorphisms in chronic hepatitis B subjects, spontaneously recovered subjects and healthy controls.
Methods: In a case-control study, we examined 100 (27female and 73 male) unrelated patients with Chronic hepatitis B and 100 (24female and 76 male) spontaneously recovered patients referred to RCGLD, and 100 healthy controls (70 female and 30 male) which all had been matched by sex and age. DNA extraction with salting-out method was performed on blood samples. MBL gene polymorphisms were determined by PCR-RFLP and SSP-PCR methods.
Results: Considering codon +57 the A/A genotype was not detected in either chronic hepatitis B patients or the spontaneously recovered ones. The frequency of A allele was estimated as 0.5% in chronic hepatitis B and 0.5% in spontaneously recovered patients. In the meanwhile the frequency of T allele at position +4 (C to T) of non-translated region was measured as 13.5% and 17.5% in chronic hepatitis B and spontaneously recovered patients, respectively. The occurrence of the codon +57 and position +4(C to T) of non-translated region polymorphisms in patients with chronic hepatitis B infection did not differ significantly from that in patients with spontaneously recovered infection or controls. (p value >0.05).

Table. Distribution of MBL Genotypes in the Studied Population

Polymorphisms	Healthy Controls N (%)	Spontaneous recovered HBV N (%)	Chronic HBV N (%)
Position +4 (C to T)			
C/C	75 (75)	68 (68)	74 (74)
C/T	24 (24)	29 (29)	25 (25)
T/T	1 (1)	3 (3)	1 (1)
Codon +57			
G/G	90 (90)	99 (99)	99 (99)
G/A	9 (9)	1 (1)	1 (1)
A/A	1 (1)	0 (0)	0 (0)
Total	100	100	100

Conclusions: Our findings do not show any association between codon +57 and position +4 promoter polymorphisms of the MBL gene with persistent HBV infection in Iranian population which may be because of the variation in ethnicity.

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Tumor Necrosis Factor-alpha (TNF-alpha) Gene Promoter Polymorphisms in Patients with Chronic HBV and Spontaneously Recovered among Iranian Population

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Purpose: The aim of present study was to examine whether TNF- alpha gene promoter polymorphisms (−308G/A, −857C/T, −863C/A, −1031T/C) are associated with the clearance of HBV infection in chronic HBV patients and spontaneously recovered subjects.
Methods: We investigated −308, −857, −863, −1031 TNF-alpha polymorphisms in 100 patients with chronic HBV infection, 100 subjects who had spontaneously recovered from acute HBV infection, and 100 healthy controls. Genomic DNA was obtained from peripheral blood leukocytes by standard phenol-chloroform extraction. The −308G/A, −857C/T, −863A/C, and −1031C/T polymorphisms in the promoter region of TNF-a gene were detected by PCR-RFLP.
Results: Our finding have shown that the frequency of −308A, −857C, −863A and −1031C alleles were 0.12, 0.835, 0.21 and 0.245 in chronic HBV patients, respectively; 0.13, 0.775, 0.185 and 0.25 in spontaneous recovered subjects and 0.105, 0.84, 0.13 and 0.16 in healthy controls. As shown in the table below our data suggest no significant difference among chronic HBV patients, spontaneous recovered subjects, and healthy controls considering the four evaluated TNF-alpha promoter polymorphisms (p value > 0.05).

Distribution of TNF-Alpha Genotypes in Chronic HBV Patients, Sopontaneously Recovered Subjects and Healthy Controls

	Chronic HBV patients N (%)	Sopontaneously recovered subjects N (%)	healthy controls N (%)
−308 A/A	2 (2)	2 (2)	1 (1)
−308 A/G	20 (20)	22 (22)	19 (19)
−308 G/G	78 (78)	76 (76)	80 (80)
−857 C/C	70 (70)	60 (60)	71 (71)
−857 C/T	27 (27)	35 (35)	26 (26)
−857 T/T	3 (3)	5 (5)	3 (3)
−863 A/A	4 (4)	4 (4)	5 (5)
−863 A/C	34 (34)	29 (29)	16 (16)
−863 C/C	62 (62)	67 (67)	79 (79)
−1031 C/C	5 (5)	5 (5)	6 (6)
−1031 C/T	39 (39)	40 (40)	20 (20)
−1031 T/T	56 (56)	55 (55)	74 (74)

Conclusions: In contrast to other studies, these findings suggest no association between the TNF-alpha promoter polymorphisms and the development of chronic HBV infection in Iranian population, which probably ethnic differences could lead to different results.

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Postresectional Adjuvant Intraportal Chemotherapy Improves Survival of Patients with TNM Stage I and II Hepatocellular Carcinoma

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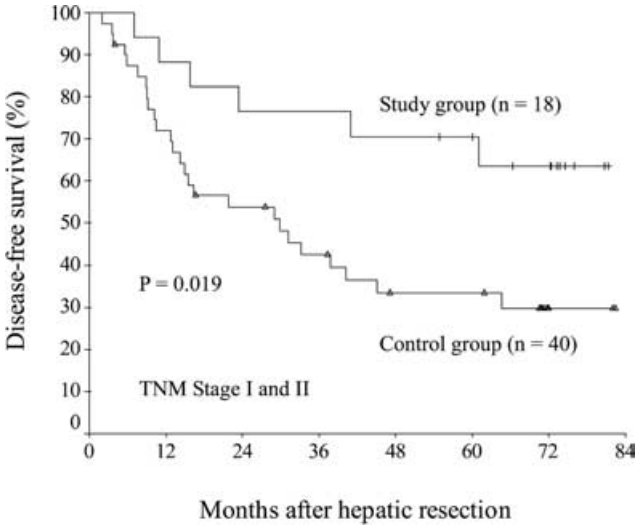
Purpose: Hepatic resection for hepatocellular carcinoma (HCC) carries a high postresectional recurrence rate. Tumor portal vein invasion is considered the major cause of recurrence. Adjuvant intraportal infusion chemotherapy (IPIC) was initiated in an effort to improve postresectional survival.
Methods: During June 1998 to May 1999, 28 HCC patients who underwent curative hepatic resection (study group) were placed on a protocol of postoperative IPIC daily for 2 days with 5-fluorouracil (650 mg/m^2), leukovorin (45 mg/m^2), doxorubicin (10 mg/m^2), and cisplatin (20 mg/m^2). Treatment was repeated every 3 weeks for a total of six cycles. Patient outcomes were compared with those of 66 matched HCC patients (control group) who underwent resection with no adjuvant therapy. The two groups were matched for age, gender, liver function status and tumor TNM stage.
Results: Adjuvant chemotherapy started 5–24 days after operation. The study group patients received an average of 5.2 cycles of chemotherapy.

Twenty patients (71%) experienced adverse events related with IPIC treatment, mainly upper abdominal pain, vomiting and myelosuppression. The median follow-up in the study group was 74 months. The 5-year disease-free and overall survivals of the study group were 44.6% and 60.7%, respectively. In subgroup analysis of patients with TNM stage I and II disease, the tumor recurrence rates were significantly lower in the study group (33.3%) than those in the control group (65.0%) ($P = 0.025$); the 5-year disease-free and overall survivals of the study group (70.6% and 83.3%, respectively) were significantly better than those of the control group (33.4% and 46.9%, respectively) ($P < 0.05$).



Conclusions: This study indicates that early postoperative IPIC is feasible in HCC patients with good liver functional reserve. Comparing to those of matched controls, adjuvant IPIC decreased the tumor recurrent rate and improved survival in patients with TNM stage I and II disease. The survival advantages demonstrated in this study justifies a selection of patients for future trials. [figure 1]

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Clinical Features of Hepatocellular Carcinoma in Patients with Mutant p53 and/or Mismach Repair Genes

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Purpose: There have been great advanced made in hepatic surgery, but the prognosis of the hepatocellular carcinoma (HCC) patients after curative resection remains poor. One of the most important reasons is the high recurrence rate. There are two types of intrahepatic recurrences. One is intrahepatic metastasis and the other is multicentric occurrence.If analysis of the molecular aspect of HCC could be used as a prognostic indicator of recurrence and the type of recurrence, it could greatly improved the prognosis of patients. In molecular biology, recent advances also have identified various genetic abnormalities important in hepatocarcinogenesis. In this respect, one of the best studied genes is the p53 tumor suppressor gene. And several studies have demonstrated that there may be a casual role for microsatellite instability in hepatocarcinogenesis. We report on a close correlation between mutations in either the p53 or mismatch repair gene (hMSH2 gene) and clinical features such as survival and recurrences.
Methods: We obtained tissue samples from 79 HCC patients by surgically curative resection. After extraction of DNA, SSCP was performed to screen the hMSH2 and p53 genes for variant sequences. Then we identified the mutations by the direct sequencing method.
Results: hMSH2 gene mutations were detected in 12 patients (15.2%) and p53 gene mutations in 14 patients (17.7%). There was a significant reduction in the value that we observed for 50% survival in the group with mutations of p53 and/or hMSH2 (mutation-positive group) (34 months) in comparison with the value for the group with mutations neither gene (mutation-negative group) (98 months) ($p < 0.05$). In the mutation-positive group, a high portion of the patients (88.0%) showed recurrence; of these only 13.6% experienced multicentric recurrence, but there were 59.1% that experienced intrahepatic metastasis. In the mutation-negative group, 42.6% experienced intrahepatic recurrences; only 13.6% experienced intrahepatic metastasis and almost one half of the others that experienced multicentric occurrence.
Conclusions: We found that the presence of either a p53 or an hMSH2 gene mutation in HCC patients could lead to the poor outcome. And we also obtained the convincing evidence that mutation of either gene could be value in the prediction of HCC recurrent patterns.

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Liver Biopsy Is Necessary To Accurately Diagnose the Severity of Chronic Hepatitis B

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Purpose: Hepatitis B (HBV) practice guidelines include viral load, HBeAg (eAg) status, Alanine aminotransferase (ALT) and histology for patient management. Little histological data exists for those with low viral load (LVL), normal ALT, and negative HBeAg since disease progression is felt to be rare.
AIM: Compare histological disease in HBV patients.
Methods: A cross sectional study of sequential HBV infected patients referred to our center was performed. Inclusion criteria: (1) measurable HBV DNA (Taqman Real Time PCR); (2) no co-infections; (3) immune competent; (4) no prior antiviral treatment; (5) liver biopsy. Low viral load (LVL) was defined as $<10^5$ copies/ml and high viral load (HVL) as $>10^5$ copies/ml. METAVIR scores were categorized using the following combined histological severity definitions: Normal (grade 0/stage 0); Mild (grade 1 $\pm$ stage 1); Moderate (grade 2 $\pm$ stage 2); and Severe (grade 3–4 $\pm$ stage 3–4). Patients were then categorised into 3 groups based on ALT and Viral load. Group A: normal ALT/LVL; Group B: normal ALT/HVL; Group C: abnormal ALT/HVL. Demographics, Body mass index (BMI), ethanol use and eAg status were determined.
Results: 23 patients met inclusion criteria of which 11 were women and 12 men.Race:18 Asians (Vietnamese 13, Korean 1, Combodian 1, Chinese 2, Taiwanese1), Hispanic 2, African Descent 3. Age range 30–71 (mean 50). Groups: A: N = 11 (all HBeAg negative); B: N = 8; C: N = 4. Group histology results by eAg status: B: eAg+ (n = 2) 1/2 mild, 1 moderate, eAg neg. (n = 2) both severe; C: eAg+ (n = 4), $\frac{3}{4}$ severe, 1/3 moderate, eAg neg. 2/3 severe, 1/3 moderate.
Significant alcohol intake in 1 Group C patient with cirrhosis, all others denied significant alcohol use. All patients below 40 years (n = 6) had mild to moderate disease.

Histology vs Viral Load

	A	B	C
HISTOLOGY	%	%	%
Normal	10	0	0
Mild	45	14	0
Moderate	27	28	20
Severe	18	58	80

Conclusions: ALT, viral load and eAg status can be unreliable in predicting HBV disease progression. High rates of histologically worrisome disease was observed in our patients with LVL or HVL and normal ALT regardless of eAg status. Therefore, a liver biopsy should be considered in all HBV infected patients with detectable viremia, even low level viremia. These results need to be confirmed in a larger cohort.

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High Dose Daily Consensus Interferon and Ribavirin Is an Effective Option in Chronic Hepatitis C Patients Who Are Nonresponders to Peg-Interferon and Ribavirin

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Purpose: The majority of nonresponder and relapser patients with chronic hepatitis C are unable to achieve a sustained virologic response (SVR) with the combination of PEG-Interferon (PEG-IFN) and ribavirin (RBV), especially those who have genotype 1 and advanced disease. Consensus interferon (Interferon alfacon-1, CIFN) is a bio-optimized alfa interferon that exhibits increased in-vitro antiviral activity than the naturally occurring alfa interferons 2a and 2b. Improved response rates have been reported with high-dose CIFN therapy and RBV for patients who have failed to respond to PEG-IFN/RBV.
Aim: Evaluate efficacy and safety of high-dose daily CIFN and RBV in HCV patients who failed therapy with PEG-IFN/RBV.
Methods: Patients who had been treated with PEG-IFN/ RBV for HCV but did not obtain a SVR were eligible for treatment if they: 1) tolerated treatment with PEG-IFN / RBV, and 2) had advanced liver disease. Patients were given 27 ug of CIFN daily and RBV 400 mg BID during the first four weeks, followed by 18 ug daily and ribavirin 400 mg BID daily for the next eight weeks. At 12 weeks, CIFN was decreased to 15 ug daily while RBV was increased to 1,000–1,200 mg daily for 36 weeks.
Results: Thirty-two patients have been enrolled in the study, 76% male with a mean age of 52 years old. 94% had genotype 1. 22% of patients had stage 2 fibrosis.78% had stage 3–4 fibrosis of which 39% of patients had cirrhosis.70% of patients were nonresponders. 20 patients (62.5%) have achieved an early virologic response (EVR) at 12 weeks. 16 patients (52%) were undetectable at 24 weeks and 8 patients (43%) achieved an End-of-Treatment response (EOT). In an Intention to treat analysis, (ITT) of the 12 patients who have completed 72 weeks of treatment, 7 patients discontinued therapy, 5 patients achieved an EOT (41%), 3 of these patients (25%) have achieved a Sustained Virological Response (SVR). 6 patients were dose reduced and 3 patients stopped therapy due to adverse effects.

Treatment Response

HCV RNA VIRAL LOAD	WK 12 (N = 32)	WK 24 (N = 29)	WK 48 (N = 23)	SVR (N = 12)
> 2 LOG Decrease	66%	–	–	–
Undetectable	34%	52%	35%	25%

Conclusions: For HCV patients with advanced histologic disease who had previously failed therapy with PEG-IFN and RBV, the combination of high-dose CIFN and RBV is a well-tolerated and effective option. Although our numbers are small, 25% of patients achieved a SVR.

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Clinical Utility of AFP-L3% in Early Detection of Hepatocellular Carcinoma

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Purpose: AFP-L3 is an isoform of alpha-fetoprotein (AFP) from malignant liver cell, which is the *Lens culinaris* agglutinin (LCA)-reactive fraction. To determine the clinical utility of AFP-L3% as an early cancer biomarker of HCC in a high risk population, a prospective and double-blinded study was conducted in North America.
Methods: AFP-L3% is the ratio of AFP-L3 against total AFP. AFP-L3% can be measured by using an automated analyzer, the LiBASys (Liquid-phase Binding Assay System), manufactured by Wako Pure Chemical Industries.
Results: A total of 440 patients with chronic hepatitis or liver cirrhosis related to hepatitis B or hepatitis C infection were enrolled in this study. Thirty-nine subjects had developed clinically verifiable HCC during the study. AFP-L3% was significantly associated with the development of HCC on multiple logistic regression analysis ($p = 0.001$). The risk of HCC, given an AFP-L3% elevation, was 40.0% (95%CI: 26.4%−53.6%). The risk of HCC, given an AFP-L3% below the cutoff, was 4.9% (95%CI: 2.7%−7.0%). The relative risk for developing HCC within the next 21 months after an initial AFP-L3% elevation was 8.2 (95%CI 4.7–14.3). The average and median lead times between the first elevated AFP-L3% and radiological demonstration of cancer were 205 and 130 days, respectively (ranging from 0–619 days). HCC patients exhibiting a tumor doubling time of less than 90 days had significantly higher AFP-L3% values ($p = 0.0066$).
Conclusions: The AFP-L3% is a useful cancer biomarker in early detection of HCC. An early elevation of AFP-L3% in patients blood offers a unique early warning for HCC in high risk patients.

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Peginterferon Alfa-2b and Ribavirin Treatment Response among Hispanic Veterans with Chronic Hepatitis C Genotype 1

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Purpose: The response rate to interferon-based therapies is variable among patients from different ethnic backgrounds. Hepatitis C (HCV) is a public health problem in Puerto Rico, with an increased prevalence at subpopulation studies. Hispanics are usually infected with HCV genotype 1 strain, are commonly underrepresented in clinical trials, and their response to treatment modalities is comparable to those of African American (AA) origin.
To establish the rate of sustained virological response (SVR) to Peginterferon Alfa-2b and Ribavirin in a group of Veteran Hispanic treatment-naïve patients chronically infected with HCV genotype 1.
Methods: A retrospective analysis was performed from 2002–2005 in one-hundred and four (104) HCV infected Hispanic patients enrolled at the San Juan VA Medical Center. Patients were treated using weight based peginterferon and Ribavirin. Sustained viral response (defined as undetectable virus 6 months after completion of therapy) and side effects were recorded. A multivariable analysis was performed using several prognostic factors to determine an association with SVR.
Results: There was a male predominance 101/104 (97.1%) with a mean age of 52.7 years old. The most common genotype was 1a (65.4%). According to BMI, 79% of them were overweight or obese. At least 19/104 (18.3%) had DM. Fibrosis stage 3 and 4 was evident in 35.3% (18/51). Early discontinuation was observed in 27/104 (25.9%) most due to side effects. A total of 81/104 (77.9%) completed their treatment. Breakthrough infection was observed in 9.8% (8/81). When patients with an early discontinuation are excluded from analysis, the SVR was 28.4% (23/81); while the SVR for those intended to be treated was only 22% (23/104). There was no statistical difference between SVR, age, the presence of DM, BMI, pre-treatment viral load, and/or histology staging.
Conclusions: A large proportion of our patients have advance stage liver fibrosis and a predominance of genotype 1a. One fourth of those intended to receive treatment have an early drop-out. This population also experienced

an increased rate of breakthrough infection during the course of treament. Overall, Hispanic veterans with genotype 1 have a lower sustained virological response to the standard combination therapy. This SVR is comparable to that observed in AA's, but lower than reported for white American descendents. It appears that ethnicity may affect the treatment outcome of this subpopulation.

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Is Low Serum HDL the First Marker for Insulin Resistance in Early Stage Hepatitis C?

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Purpose: HepatitisC (HCV) is believed to cause insulin resistance and non-insulin dependent diabetes (NIDDM) through expression of TNF-α. This association is observed regardless of the stage of liver disease. It is also known that advanced cirrhosis causes impaired glucose tolerance regardless of etiology. Insulin resistance has been implicated in the progression of liver fibrosis and decreased sustained virologic response to interferon therapy. Insulin resistance is also known to be a risk factor for metabolic syndrome. We examined the relationship between insulin resistance in early HCV patients and the appearance of risk factors for metabolic syndrome.
Methods: A prospective sample of 42 HCV patients [mean MELD score of 7.5 ± 4.2*(sd)*] was examined at our University teaching hospital. Patients had no history of NIDDM. Data were collected on patient's age, gender, waist circumference, BP, BMI, race, clinical labs including fasting HDL, triglycerides, glucose and insulin, HCV risk factors and drug treatment for HCV. Data were analyzed by normal BMI *vs.* elevated BMI, by Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) and by fasting insulin using student t-tests, chi-square analysis, multiple linear and logistic regression analysis.
Results: Patient age ranged from 30–87 years [mean $= 5 \pm 13$*(sd)* yrs]; 71% were male. Insulin resistance was found in 76%(33/42) of patients (HOMA-IR used). Eleven patients (26%) had impaired glucose tolerance and 21 (50%) had NIDDM. Patients with insulin resistance had a 61-fold increased risk of low HDL ($P = .025$) and the effect was greatest in males (116-fold increase likelihood). No association between insulin resistance and other parameters of metabolic syndrome was observed. These findings were independent of patient's BMI.

Results

Variable	Specificity	Sensitivity	ROC Area	P-value
High glucose	96%	0%	.8698	>0.50
High waist	50%	50%	.5000	>0.050
High TG	83%	60%	.7722	>0.050
High BP	93%	50%	.7238	>0.050
Low HDL	73%	93%	.9075	0.0001

Conclusions: (1) Low HDL is the earliest marker for insulin resistance in patients with early HCV 2) HCV causes insulin resistance regardless of patient's BMI. The identification of low HDL in early HCV suggests that an accurate and simple clinical marker for insulin resistance may be available so that intervention with insulin sensitizing therapies is initiated at the earliest.

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Efficacy and Safety of Selective Internal Radiation Spheres (SIR-spheres) To Treat Patients with Unresectable Hepatocellular Carcinoma (HCC) and Liver Cirrhosis

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Purpose: Selective internal radiation spheres (SIR-spheres) is currently FDA approved for treatment of inoperable tumors from primary colorectal cancer that have spread to the liver. The purpose of this study was to evaluate the efficacy and safety of the SIR-spheres to treat patients with unresectable hepatocellular carcinoma (HCC) and liver cirrhosis.
Methods: This is a case series of 10 patients (8 males, 2 females) with HCC and liver cirrhosis who have been treated with at least one session of SIR-spheres. Baseline lab tests along with abdominal CT or MRI 3–12 weeks prior to the first treatment with SIR-spheres. Follow-up CT or MRI was done within 12 weeks after treatment and repeated as indicated.
Results: Patients age range was 51–80 years (mean 68.1 ± 11.1) with Child-Pugh scores between 5 to 8 (Child's class A). Two patients had small multifocal lesions and a total of 13 hepatic lesions were present in the other 8 patients. All patients were treated with at least 1 session of SIR-spheres with 4 patients having 2 sessions. Additional tumor therapy following SIR-spheres included chemoembolization in 3, radiofrequency ablation in 2, and surgical resection in 1 patient. Based upon follow-up imaging, tumor shrinkage occurred in 6/10 with tumor burden reduction between 20–52% in 4/10 patients. Liver failure with subsequent death occurred in 4/10 patients of which 3 had experienced progression of liver tumor prior to liver failure. One other patient died from extra hepatic carcinomatosis despite hepatitic response. One patient has had surgical resection of the tumor and 4 patients continue to be monitored.
Conclusions: Treatment with SIR-spheres is safe in patients with extensive HCC and liver cirrhosis. Tumor shrinkage occurred in 60% of patients. In some patients tumor burden can be decreased substantially to enable curative resection to be performed. Further data need to be collected on safety and efficacy of SIR-spheres in treating patients with HCC.

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Change of Serum Ghrelin Concentration According to Severity of Hepatosteatosis

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Purpose: Recently, ghrelin was reported to be associated with insulin resistance. Nonalcoholic fatty liver disease (NAFLD) is a condition in which insulin resistance relatively plays a pivotal role. The aim of this study was to evaluate change of serum ghrelin concentration according to severity of hepatosteatosis.
Methods: Sixty five apparently normal male adults who underwent health screen examinations were classified into three groups, Group I: normal liver (27 subjects), Group II: mild fatty liver (24 subjects) and Group III: moderate to severe fatty liver (14 subjects), according to ultrasonographic findings of liver. We analyzed the association between serum ghrelin concentration and severity of hepatosteatosis by ANOVA test. And the independent correlation between serum ghrelin concentration and insulin resistance related factors, HOMA (homeostatic model assessment), BMI (body mass index), WC (waist circumference), HC (hip circumference), WHR (waist to hip circumference ratio) were analyzed by multiple linear regression analysis.
Results: Serum ghrelin concentration tended to decrease according to severity of hepatosteatosis (Group I: 230.9±94.3, Group II: 195.2±97.2, Group III: 164.3±71.4 pmol/L). But this was statistically insignificant ($p = 0.081$). The independent correlation between serum ghrelin concentration and insulin resistance related factors were not observed.
Conclusions: Our study did not prove the correlation between insulin resistance related factors and serum ghrelin concentration in NAFLD according to severity of hepatosteatosis. However, we found tendency to decrease of

serum ghrelin concentration according to severity for hepatosteatosis. So, further studies were required for certification these correlations.

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Thyroid Dysfunction in Patients with Chronic Hepatitis C Treated with Pegylated Interferon alpha Therapy

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Purpose: Thyroid dysfunction has been reported in patients with chronic hepatitis C treated with interferon therapy. We prospectively studied this hypothesis in our patients with chronic hepatitis C on pegylated interferon alpha therapy and attempted to determine if autoimmune mechanisms play a role in the etiology of the thyroid dysfunction in these patients.
Methods: 39 patients (18 males and 21 females) aged 18–55 years with chronic hepatitis C were treated with pegylated interferon alpha. Thyroid stimulating hormone (TSH) and free thyroxine (free T4) levels were obtained on all patients prior to therapy. Antibodies to the microsomal and thyroglobulin receptor were obtained for baseline evaluation in all patients. All patients were euthyroid prior to beginning interferon therapy. TSH and free T4 levels were monitored on a monthly basis for the duration of the therapy. If the TSH or free T4 increased above or reduced below the normal range of the laboratory values during treatment, microsomal and thyroglobulin receptor antibodies were obtained to evaluate for development of autoimmune thyroid dysfunction.
Results: Of the 39 patients in our study, 4 patients (3 females, 1 male) had past history of hypothyroidism and one in this group had preexistent antithyroglobulin and anti-microsomal antibodies, 2 patients (both females) had past history of hyperthyroidism and one had preexistent anti-thyroid antibodies. 9 out of 39 patients (8 females and 1 male, 23%) showed changes in their thyroid function activity during treatment. Of these 8 patients became clinically hypothyroid and 1 patients became thyrotoxic and later became hypothyroid. Of the hypothyroid group 1 patient developed new antithyroglobulin antibody while the other showed increase in the level of preexisting anti-thyroglobulin and anti-microsomal antibodies. The patient that became hypothyroid following a thyrotoxic course also developed new thyroglobulin and microsomal antibodies. Therefore, 2 of 9 patients (22%) with thyroid dysfunction during the interferon therapy developed microsomal or thyroglobulin receptor autoimmune antibodies.
Conclusions: Patients on pegylated interferon therapy for treatment of chronic hepatitis C develop thyroid dysfunction. There appears to be a female predominance to this phenomenon. All patients become hypothyroid with or without preceding hyperthyroidism. This may be associated, but not entirely explained by the development of thyroglobulin and microsomal antibodies.

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Human Telomerase Reverse Transcriptase (h-TERT) as Regulator of Telomerase Activity in Indian Hepatocellular Carcinoma

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Purpose: Telomerase is a ribonuleoprotein that acts as reverse transcriptase. The protein adds the hexanucleotide repeats $(TTAGGG)_n$ on the ends of telomeres and is essential for cellular immortality. It is a multimeric enzyme and composed of three subunits: (1) h-TERC, (2) h-TEP1, and (3) h-TERT. h-TERT is essential for *in vivo* activity of telomerase and has been identified as the catalytic subunit of human telomerase.
Objective: To investigate whether telomerase activity is related to h-TERT mRNA expression in hepatocellular carcinoma (HCC) and non-HCC tissues.
Methods: Patients of hepatocellular carcinoma (HCC) coming to the Liver Clinic of our Institute were included in the study. Clinical history and examination was done in all patients. Diagnosis of HCC was made by USG/CECT/MRI/AFP and confirmed by imaging guided FNAC. FNAC samples of 17 HCC patients (Group 1) and liver biopsy samples of 15 chronic hepatitis patients (Group 2) without HCC were taken. Total RNA extracted by using acid guanidinium thiocyanate phenol-chloroform extraction method. cDNA generated and h-TERT was amplified using cDNA as template. Telomerase activity was measured using a telomeric repeat amplification protocol (TRAP assay).
Results: There were 14 (82.3%) males and 3 (17.7%) females (mean age 57.63 ± 9.68 yrs; 32–72 yrs) in group I, 13 patients (76.47%) were positive for HBsAg, 1 (5.88%) for anti-HCV and 3 patients (17.65%) negative for both HBsAg and anti-HCV. In group 2, 11 (73.33%) were males and 4 (26.67%) females (mean age 41.2 ± 9.57 yrs; 27–58 yrs), 8 patients (53.33%) were positive for anti-HCV and 7 (46.67%) for HBsAg. h-TERT mRNA was expressed in 15 (88.24%) of 17 HCC samples (12 HBsAg +ve and 3 –ve for both the viral markers). These 15 (88.24%) h-TERT positive patients were also positive for telomerase, showing high level of positive correlation between the two. Telomerase and h-TERT mRNA were not present in any of the chronic hepatitis tissue samples.
Conclusions: Telomerase is strongly expressed in HCC but not in chronic hepatitis liver biopsy samples. Also, the h-TERT mRNA was detected in all tissues that were telomerase positive and it was undetected in all tissues that were telomerase negative. Thus, h-TERT may be used as an important target for cancer drug development.

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The Increased Risk for Non-Alcoholic Fatty Liver Disease (NAFLD) in Indian Immigrants with Type 2 Diabetes Mellitus

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Purpose: NAFLD, the most prevalent liver disease in the US, is associated with obesity, type 2 diabetes mellitus, insulin resistance, and hyperlipidemia. The aim of this study is to assess the prevalence of biochemical NAFLD in immigrants from the Indian subcontinent, where the incidence of type 2 diabetes and dysmetabolic syndrome is rapidly increasing (Chitturi and George. NAFLD/NASH is not just a western problem: some perspectives on NAFLD/NASH from the east. Fatty Liver Disease: NASH and Related Disorders. Blackwell Publishing. Massachusettes. 2005. Pp. 218).
Methods: In this retrospective study, we reviewed data from the initial visits of 200 patients with type 2 diabetes to assess the prevalence of NAFLD (ALT>40 u/L) and its relation to BMI and hemoglobin A_{1c} in Caucasians ($n = 104$), African Americans ($n = 34$), and Indians (immigrants from the Indian subcontinent; $n = 31$). In addition, we used the ratio of aspartate to alanine aminotransferases (AST/ALT) to evaluate the severity of fibrosis across the three ethnic groups. Patients with history of hepatitis or alcohol use (>20 g/day) were excluded.

Table 1: Prevalence of NAFLD (% with ALT>40 u/L)

	African Americans	Caucasians	Indians
Overall Prevalence	5.9	23.1	29.0
BMI: <25	N/A*	14.3	16.7
25–30	2.3	15.6	30.1
>30	8.7	33.3	N/A*
HbA1c: <6.0	2.0	13.3	1.7
6.0–8.0	3.3	19.6	36.8
>8.0	12.5	32.6	11.1

*No patients in this category displayed abnormal ALT.

Results: See Tables 1 and 2.

Table 2: Prevalence of Increased Fibrosis

	African Americans	Caucasians	Indians
% with AST/ALT > 1.0	38.2	34.6	22.6

Conclusions: In Indian immigrants with type 2 diabetes, the prevalence of NAFLD:

(1). is greater than in Caucasians or African Americans.
(2). is greater at lower BMI levels. A BMI of 25–30 in Indians poses nearly the same risk for NAFLD as a BMI>30 in Caucasians.
(3). increases dramatically as HbA_{1c} rises above 6.0, while a similar increase in Caucasians occurs only with $HbA_{1c}>8.0$.

Therefore, BMI alone may not be a good risk indicator for NAFLD in Indians; the waist-hip ratio may be preferable. Conversely, an AST/ALT ratio greater than 1.0, which may indicate an increased level of fibrosis, is less prevalent in Indians than in the other ethnic groups. Overall, tigher standards for control of diabetes are necessary to reduce the risk for NAFLD. These observations are based on a small number of patients, and our studies are in progress.

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A Pilot Study of Hepatitis C Non-Responders Treated with a Combination of Parental Vitamin B-12 along with Pegylated Interferon α 2b and Ribavrin

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Purpose: The current treatment of naïve Hepatitis-C patients has a response rate that results in a large number of non responders. Recent experiments have shown that vitamin B12 (cyanocobolamin) inhibited HCV internal ribosomal entry site (IRES)-dependent translation of a reporter gene *in vitro*. This inhibition is selective for the HCV IRES in the presence of cap-dependent RNA, and is specific for HCV IRES relative to other viral IRES. At high cobalamin (B12) concentrations, reduced viral translation may result in concentrations of viral proteins that are inadequate for replication and packaging, and may effect the virologic response *in vivo.* We conducted a pilot study to assess the efficacy of treatment with pegylated interferon α 2b, ribavirin and vitamin B12 in patients with hepatitis-C, prior non-responders to standard therapy not limited to pegylated interferon and ribavirin.
Methods: Thirty one patients with normal baseline vitamin B-12 levels were enrolled at the University of Connecticut Health Center liver diseases clinic. Patients received vitamin B-12 (1000 μg subcutaneous) at baseline and at week 24, along with weekly pegylated interferon α 2b and daily weight-based Ribavirin (800–1400 mg daily). The primary end point was a sustained virologic response (SVR).

Response Ratio with Reference to Prior Treatment

Interferon only	Interferon + Ribavirin	Pegylated Interferon + Ribavirn
0/2	4/16	2/11

Responders/ Treatment, SVR pending 2 patients.

Results: The median age was 50 years, 74% were men, 74% were genotype 1 and 38% were previous pegylated interferon and ribavirin non responders. Twenty six (83%) completed at least 24 weeks of treatment, and twenty five (80%) went on to complete 48 weeks of treatment. Eighteen patients (58%) had an early virological response (EVR) at week 24. Fourteen patients (45%) showed an end of treatment response (EOT), while six patients (21%) had a sustained virological response (SVR). Four of the six patients (66%) were genotype 1. SVR for two patients is pending.
Conclusions: Our results show that Vitamin B-12 along with current standard treatment induced an SVR of 21% in previous Hepatitis-C non responders. In pegylated interferon with ribavirin non responder subgroup the SVR was 18% compared to 25% in interferon and ribavirin non responders subgroup.

Response by Genotype

Genotype 1	Genotype 2	Genotype 3	Genotype 4
4/22	1/5	1/1	0/1

Responders/Number of patients, SVR pending 2 patients.

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Cholangitis Complicating Percutaneous Radio-Frequency Ablation [RFA] of Liver Metastases

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Purpose: RFA is becoming increasingly popular as a non surgical method for ablating primary or metastatic liver tumors. The reported complication rate for RFA varies between 2 to 10%. We report an unusual complication following RFA.
Case: A 75 year old female with colon cancer metastatic to the liver, underwent RFA of three hepatic lesions in one session. Her baseline liver biochemistries prior to RFA were normal. The RFA treatment was itself uneventful. However, four weeks later the patient presented with jaundice and biliary colic. Her bilirubin increased to 4.2 mg/dl (normal <1.0), alkaline phosphatase 326 U/L (normal <126), AST 223 U/L (normal <39) and, ALT 247 U/L (normal <59). CT scan showed markedly dilated bile ducts. One metastatic lesion was in contiguity to one of the dilated bile ducts. Wheareas the baseline CT scan showed three liver metastases but no dilation of the bile ducts. ERCP revealed a dilated bile duct containing debris. A sphincterotomy was performed and the bile duct was cleared off necrotic debris and blood clots. Patient liver enzymes returned to baseline post-ERCP.
Discussion: Since one metastatic lesion was adjacent to a bile duct, we hypothesize that the RFA caused necrosis of both the tumor and the biliary duct. This allowed subsequent sloughing of necrotic debris and blood clots into the biliary duct resulting in obstructive cholangitis. Obstrucive cholangitis is an unusual complication following RFA.

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Relationships of Hepatic Histology to Metabolic, Inflammatory and Viral Parameters in Chronic HCV Infection

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Purpose: Hepatic steatosis is commonly associated with chronic hepatitis C infection (HCV). The purpose of this study was to determine the associations between hepatic histology, and metabolic, inflammatory and viral parameters.
Methods: This was a cross-sectional study of 31 hepatitis C infected subjects prior to HCV treatment, 21 male and 10 female, of whom 21 were HCV/HIV co-infected and 9 were HCV mono-infected. The infection was genotype I in 22 cases. Serum HCV RNA, soluble TNF receptors I and II (sTNFRI, II), fasting triglycerides, HDL-cholesterol, glucose and insulin levels were measured. Insulin resistance (IR) was calculated by HOMA. Body composition measures included BMI, body fat and fat free mass by bio-impedance analysis (BIA), and anthropometric measures of fat distribution. Liver biopsies were evaluated using a 4-point scale for disease activity (grade), and a 6-point scale for fibrosis (stage). Steatosis was measured using NIDDK 4-point scale plus a quantitative percent area estimate of macro and microvesicular fat. Data was analyzed by the general linear model method and by multiple regression, using steatosis, steatohepatitis, disease activity

and fibrosis as dependent variables; and metabolic, inflammatory, HCV viral parameters and HIV as independent variables.
Results: HIV infection was associated with greater area of steatosis ($p = 0.07$), greater waist:hip ratio ($p = 0.04$), thinner thigh skinfolds ($p = 0.006$). Steatosis was directly associated with serum insulin level ($p = 0.04$), HOMA ($p = 0.05$), sTNFR II ($p = 0.02$). Grade was related to HCV RNA ($p = 0.04$), AST ($p = 0.004$), total body fat ($p = 0.07$). Disease stage was associated directly with sTNFR II ($p = 0.0001$), and AST ($p = 0.07$), and inversely with HDL. By multiple regression steatosis was associated with increased sTNFR I and II, grade was related to IVDU, HCV viral load, gender, and stage was related to sTNFR II, HCV viral load, and glucose.
Conclusions: Multiple factors affect hepatic histology in subjects with chronic HCV infection. While HCV viral load affects disease activity, the metabolic syndrome and TNF may be related to steatosis and fibrosis.

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African-Americans with Genotype-1 with Chronic Hepatitis C Respond Poorly to Pegylated-Interferon and Ribavirin Combination Treatment as Compared to Caucasians

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Purpose: African-Americans (AA) with chronic hepatitis C (CHC) have a lower response to interferon (IFN) monotherapy as well as standard IFN and ribavirin combination therapy than Caucasians (Cau). Recent data suggests AA patients with CHC demonstrate a lower response to pegylated-interferon (PEG-IFN) and ribavarin combination therapy as well. Our aim was to determine and compare the sustained virologic response (SVR) rates in AA and Cau patients treated with PEG-IFN and ribavarin therapy for CHC.
Methods: This is a retrospective study consisting of consecutive patients seen and treated for CHC between March 2001 and February 2003. All patients included had measurable HCV RNA by polymerase chain reaction (PCR) assay and were treatment naïve. We treated 139 patients with PEG-IFN and ribavarin for 24 to 48 weeks. Treatment was discontinued in those with less than a 2 log drop in HCV RNA at week 24; however those with a greater than 2 log drop or negative HCV RNA were treated for 48 weeks. The primary end point was an SVR defined as a negative PCR for HCV RNA six months after completion of therapy. Variables affecting the treatment outcome such as ethnicity, gender, viral load, genotype, stage of fibrosis, pre- treatment ALT and 12 week PCR results were analyzed.
Results: Of the 139 patients (AA = 95, Cau = 44) treated, genotype was available for 130 patients. Genotype 1 was seen in a significantly higher proportion of AA (n = 78, 86%) compared to Cau (n = 27, 69%, $p = <0.008$). Mean age in both groups was 49–50 years. There were no statistically significant differences between the viral load and stage of fibrosis between AA and Cau. However, ALT values were found to be lower in AA ($p = <0.02$). Overall, SVR was higher in Cau (30%) as compared to AA (19%) ($p = <0.01$). Only 14% of AA compared to 32% of Cau with genotype 1 achieved an SVR ($p < 0.001$). However, the SVR in both AA and Cau with genotype 2 and 3 was 50%. In addition to genotype, stage of fibrosis ($p = <0.001$), baseline viral load ($p<0.003$) and a negative PCR at week 12 ($p = <0.0001$) significantly influenced the SVR in AA and Cau.
Conclusions: African-American patients with genotype 1 CHC have a lower treatment response to PEG-IFN and ribavarin combination therapy compared to Caucasian patients. In addition, we noted that a lower baseline viral load, lower stage of fibrosis and negative 12 week PCR are associated with an improved SVR in AA patients with CHC.

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Hepatocellular Carcinoma (HCC): Outcome of Patients Treated with Trans Arterial Chemoembolization (TACE) at the Universtiy of Illinois at Chicago (UIC)

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Purpose: Surgical approaches remain the only curative option for HCC but they are possible in only a minority of patients. The purpose of this study was to analyze the outcome of 38 patients treated with TACE at UIC.
Methods: Information about all patients with HCC treated at UIC since 1998 was retrospectively collected by electronic chart review. Statistical Analysis was performed utilizing the SAS Biostatistical software.
Results: A Total of 194 patients were identified. Of these, 38(19.6%) underwent at least one hepatic artery chemoembolization alone or with other interventions such as ethanol ablation (5), systemic chemotherapy (5), radiofrequency ablation (RFA) (3), or as a bridge to transplantation (2). The tumor size ranged between 2–15 cm. The stage distribution of the patients was: Stage I: 4, Stage II: 16, Stage III: 7, and Stage IV: 11. Almost half of the patients belonged to early stages (I-II) but could not receive surgical treatment due to comorbidities or logistic barriers to transplantation. The median survival for the whole cohort was 17 months, 95% confidence interval (95% CI) 12–24 months. The median survival for the TACE group was 25 months, 95% CI 10 -35 months. The survival of the TACE group seems better than the historically reported 12 months for HCC but this may be due in part to selection of patients with better prognostic features for this treatment modality. Most patients did not have documentation of response, which precluded meaningful recurrence analysis. Of interest, one of the patients who underwent liver transplant following TACE was found to have no evidence of tumor in the explanted liver. This was a very atypical patient who survived from 1999 and past her transplant in 2003 maintained with multiple procedures (TACE, ethanol and RFA). Even though the possibility of a complete pathological remission of a tumor with very low aggressive potential exists, misdiagnosis cannot be excluded. One more patient treated with a combination of RFA, TACE five times followed by chemotherapy has had a survival of over 7 years. This patient had two 2cm biopsy proven tumors but could not undergo transplant due to cardiovascular disease.
Conclusions: TACE with or without other local modalities appears to be a reasonable therapeutic alternative for selected patients with HCC where surgery is contraindicated.

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Fulminant Hepatic Failure Secondary to Lamotrigine

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Purpose: Lamotrigine is a triazine derivative which inhibits release of glutamate (an excitatory amino acid) and inhibits voltage-sensitive sodium channels, which stabilizes neuronal membranes. It is often used in the treatment of primary seizure disorders. Lamotrigine metabolism occurs primarily in the liver by glucuronic acid conjugation. We report a case of lamotrigine induced hepatic necrosis, and fulminant liver failure one month after initation of this drug.
33 year-old Jamaican male with history of Hepatitis C, HIV with CD4 count of 250 c/UL and alcohol abuse presented to outlying hospital with seizures after a drinking binge. After being treated in the intensive care unit for delerium tremens with benzodiazepines, he was discharged on lamotrigine and multi-vitamins with minerals which he took daily leading up to our hospitalization. While home, he began developing jaundice over the next three weeks. He denied illicit drug or resumption of alcohol use, drinking bush tea, eating mushrooms, anti-retroviral therapy, travel, exposure to animals, sick contacts, or new rash.
On presentation to our hospital three weeks after the recent discharge, he was encephalopathic and jaundiced. He had leukocytosis (wbc of 38,000 u/l) with mild eosinophilia(3%). The patient had a total bilirubin of 18 mg/dl, rising to 35 mg/dl (18 mg/dl direct bilirubin) over the next two weeks. Records from the outlying hospital show total bilirubin at time of discharge to be less than 3 mg/dl.
During this hospitalization, the aspartate aminotransferase and alanine aminotrasferase were in a 4:1 ratio (120:29)U/l. Prothrombin time was elevated at 19.2 seconds which did not correct with vitamin K therapy.

Serologic workup for acute decompensation of chronic liver diseases such as Hepatitis A, B, and C was negative.
Liver biopsy showed acute hepatitis with lobular dissaray, hepatocyte dropout minimal steatosis, consistent with drug or toxin exposure. Special stains for herpes virus and cytomegaloviruses were negative.
During the hospital course the patient developed renal failure requiring dialysis. Following a three week intensive care unit course, the patient improved and was discharged home.
Conclusions: This patient developed fulminant liver failure manifested as severe, acute cholestasis which was temporally related to lamotrigine use. Our case reveals a rare adverse effect of a commonly used neuro-psychiatric medication.

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Hepatocellular Carcinoma (HCC): Outcome of Patients Treated Surgically at the University of Illinois at Chicago (UIC)

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Purpose: Surgical approaches remain the only curative option for HCC. The two main procedures available are resection and liver transplantation. The purpose of this study was to analyze the outcome of 36 patients treated surgically with curative intent at the UIC.
Methods: Information about all patients with HCC treated at UIC since 1998 was retrospectively collected by electronic chart review. Statistical Analysis was performed utilizing the SAS Biostatistical software.
Results: A Total of 194 patients were identified. The distribution of the stages was: 18 (9.2%) were Stage I, 65(33.5%) stage II, 44(22.7%) stage III, 60(30.9%) stage IV and 7(3.6%) had unclear stage. Of these, 36 (18.6%) underwent surgical therapies with curative intent. Eleven (5.7% of the total), underwent resection and 25 (12.9%), transplant. Using the Wilcoxon statistical test, the median survival time for these patients was 37 months with 95% confidence interval (CI 95%) 30–42 months. In patients treated with non surgical therapies the median survival was 12 months (CI 95% 8–17 months) $p < 0.0001$. The median survival for patients undergoing transplant was 38 months (CI 95% 31–58) and it was 26 months (CI 95% 1–37) for the resection group. The median time to recurrence for all surgically treated patients was 33 months (CI 95% 22–37 months). There was no significant difference in the recurrence time between transplant and resection groups. Recurrence was treated with a second surgical procedure, ethanol ablation, chemoembolization or systemic chemotherapy.Even though the percentage of patients potentially eligible for surgery (stages I and II combined) was 44.1%, less than half of these received either one. The inferior median survival of the patients treated with palliative modalities is probably explained at least in part by a more advanced median stage as well as other comorbidities that precluded surgery. Survival seemed better in patients treated with transplant than in those treated with resection; however these results should be taken with caution because of the wide confidence interval.
Conclusions: HCC continues to carry a very poor prognosis. Patients who are able to undergo surgical resection or transplant have the longest survival but most patients are not eligible for these interventions.

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Neutropenia Associated with Pegylated Interferon Treatment for Chronic Hepatitis C: A Single Center Experience

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Purpose: Pegylated interferon (p-IFN) and ribavirin (RBV) are currently the standard of care for the treatment of chronic hepatitis C. Bone marrow suppression is a side effect of interferon and the degree of neutropenia may differ based on the type of p-IFN used.
Aim: To determine the incidence of neutropenia in patients treated with p-IFN alpha 2a *vs.* p-IFN alpha 2b and ribavirin at a single center.
Methods: 63 patients with HCV treated between Jan 2003 and Apr 2004 were analyzed. Patients were treated with p-IFN 2a (180 mcg/wk)+ RBV(1000 mg/day <75kg, or 1200 mg if >75kg) **(Group 1, n = 36)** or p-IFN 2b (1.5 mcg/kg/week) +RBV (13 mg/kg/day) **(Group 2, n = 27).** Complete blood counts (CBC) with absolute neutrophil count (ANC) were measured at baseline, weeks 2, 4, 6, 12, 18, and 24 and as clinically indicated thereafter. Grade 3 neutropenia was defined as ANC <750 cells/ mm^3, grade 4 neutropenia was defined as ANC <500 cells/ mm^3. Statistical analysis was performed using the one-tailed Chi square with Yates correction.
Results: Baseline white blood cell counts were equivalent between the two groups (6.10 *vs.* 6.26 /UL), and initial ANC prior to therapy was 3235 cells/ mm^3 in group 1 and 3148 cells/ mm^3 in Group 2. Neutropenia at week 4 in Group 1 was 6% vs 0% in Group 2 (NS). Treatment with granulocyte colony stimulating factor (G-CSF) was started in 12 patients (19%): 7 patients in the p-IFN alpha 2a group and 5 patients in the p-IFN alfa 2b group. Grade 3 and 4 neutropenia was noted in both groups (Table 1).

Table 1. Baseline Characteristics (N = 63)

Proportion of Patients,%	Gp 1 (n = 36) Peg 2a	Gp 2 (n = 27) Peg 2b	p-value
Age (years)	48	48.5	NS
Gender (female)	52.9	44.8	NS
Race (non-white)	20.6	17.2	NS
Genotype-1	67.7	51.7	NS
Weight lbs (kg)	164.1 (74.5kg)	187.0 (85 kg)	0.026
Baseline hemoglobin (g/dl)	14.1	14.7	NS
Pts treated with G-CSF	7	5	NS
Ave nadir ANC (cells/mm3)	882	1010	NS
Grade 3 neutropenia (ANC <750)	8 (22%)	10 (37%)	NS
Grade 4 neutropenia (ANC <500)	8 (22%)	1 (4%)	P = 0.043

Conclusions: Neutropenia is commonly seen in patients treated with p-IFN. Grade 4 neutropenia was observed more often in patients treated with p-IFN alpha 2a *vs.* p-IFN alfa 2b.This may be attributable to differences in bone marrow toxicity between interferons however the effect of weight on bone marrow toxicity needs to be further assessed.

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Hepatocellular Carcinoma Occurring in a Patient with Crohn's Disease Treated with Both Azathioprine and Infliximab

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Purpose: In this report, we describe a case of hepatocellular carcinoma and focal hepatic glycogenosis (FHG) occurring in a non-cirrhotic Crohn's disease patient who has been treated with both azathioprine and infliximab.
Case Report: A 28-year-old, non-cirrhotic female with history of fistulizing Crohn's disease was hospitalized for further evaluation of fever prior to undergoing routine maintenance infusion of infliximab. She had been experiencing rectal pain for two weeks prior to admission. Admission labs were significant for anemia with a hemoglobin level of 8.8 g/dl, thrombocytosis, and a positive leukocyte esterase on her urinalysis. Chemistry was unremarkable with normal hepatic panels, amylase, and lipase. Because there was a concern for perianal abscess, a CT of abdomen and pelvis with oral and IV contrast was performed, that revealed a perianal fluid collection, moderate

thickening of the sigmoid colon, and an incidental finding of a 2-cm hypodensity in the right lobe of the liver. A fine needle aspiration of the liver mass revealed hepatocellular carcinoma and focal hepatic glycogenosis without cirrhosis. Viral serologies were negative. Surgery service was consulted and the patient underwent a total proctocolectomy with permanent end ileostomy followed by segmentectomy of the liver lesion as an outpatient.
Conclusion: To the best of our knowledge, this is the first case of hepatocellular carcinoma occurring in the abscence of hepatic cirrhosis in a Crohn's disease patient who has been treated with both azathioprine and infliximab. Although a direct causal relationship cannot be established, it is possible that infliximab may have been a contributing factor in its pathogenesis in addition to azathioprine. Further studies will be needed to better understand the role of various immunosuppresants on the development of FHG and hepatocellular carcinoma in non-cirrhotic patients.

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Immune Response to Influenza Vaccine in Adult HCV Patients Receiving Peginterferon and Ribavirin Therapy

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Purpose: Influenza virus infection may cause significant complications in patients with chronic liver disease from hepatitis C virus infection (HCV) (1). Patients with advanced liver disease due to HCV and those who are post-liver transplantation have an impaired response to influenza vaccination (2). Whether influenza vaccination is effective in patients with HCV who are undergoing therapy with peginterferon and ribavirin is unknown. We performed a pilot study to assess the immune response to influenza vaccine in patients with HCV infection on interferon (HCV/IFN) therapy in comparison to HCV controls not on therapy.
Methods: HCV/IFN pts (n = 22) and HCV controls (n = 9) were administered the standard dose of the 2004–05 inactivated trivalent vaccine (A/MOSCOW/10/99[H3N2]; A/NEW CALEDONIA/20/99[H1N1]; B/HONG KONG/330/2001). Antibody responses to each of 3 components of the vaccine were measured at baseline and after 6 weeks by hemagglutination inhibition.
Results: Vaccination was tolerated with no side effects observed. Initial results show the rate of seroconversion to ≥ 2 of the 3 vaccine antigens to be greater in HCV controls than in HCV/IFN patients, 78% vs 41%, $p = 0.085$.
Conclusions: This trend toward statistical significance suggests that patients with HCV on interferon treatment could have an impaired immune response to the influenza vaccine and merits further investigation. We are currently in the process of completing serologic analysis of the final 10 control cases not included in this abstract.

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Correction of Both Hepatic and Brain Lysosomal Glycosaminoglycan Storage Using a Single Gene Transfer Vector in a Murine Model of Mucopolysaccharidosis VII

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Purpose: Lysosomal storage disorders (LSDs) are chracterized by cellular accumulation of glycosaminoglycans (GAGs), due to the deficiency of GAG-degrading enzymes. Mucopolysaccharidosis type VII (MPS-VII) is caused by β-glucuronidase (GUSB) deficiency, inherited as autosomal recessive trait. GAG accumulation affects the liver, spleen, cornea and bones, as well as the brain. GUSB is secreted into plasma and endocytosed by cells via the mannose-6-phosphate receptor. Thus, hepatic GUSB expression following gene therapy results in "cross-correction" of all abdominal viscera. However, brain lesions are not ameliorated, because GUSB does not cross the blood-brain barrier. Our purpose was to test if recombinant simian virus 40 (rSV40) vectors would not only transduce the abdominal viscera, but also cross the blood-brain barrier to transduce neural cells.
Methods: The T-antigen gene of the SV40 genome was replaced with human GUSB encoding sequences. The recombinant viral genome was transfected into COS-7 cells for packaging the vector (SV-GUSB). Viral titer was determined by infecting primary MPS VII mouse skin fibroblasts and staining for GUSB activity. MPS-VII micewere injected with SV-GUSB (10^7 rfu). Serial serum GUSB levels were measured. Mice were sacrificed at intervals after the injection. GUSB expression, GUSB activity and histological clearance of GAG deposits was examined in various tissues.
Results: Two weeks after SV-GUSB injection, serum GUSB activity increased from undetectable levels to 40–150% of normal. Southern blot analysis showed transduction of multiple organs (liver > spleen > kidney > lung > brain), but not spermatozoa. All abdominal viscera were repleted with GUSB in two weeks. In addition, a significant number of brain cells, including neural cells and microglia exhibited GUSB activity and clearance of the GAG deposits in two months. Molecular analysis showed integration of the transgene into the host genome along with life-long expression.
Conclusions: rSV40 vectors are the first gene transfer vehicles that permit efficient correction of LSD lesions in both abdominal organs and the brain after intravenous administration. This integrating, non-immunogenic vector can be administered repeatedly and is an attractive vehicle for comprehensive gene therapy of MPS-VII.

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Seroprevalence of Hepatitis A; a Community Clinic Experience

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Purpose: The Center of Disease Control (CDC) Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994 found serological evidence of prior exposure to Hepatitis A virus (HAV) of 37.4% in the US general population. Some studies from urban settings have shown higher seroprevalence rates. The seroprevalence of anti-HAV antibodies in a community is important in assessing the need for vaccination against HAV in high-risk individuals. This study was designed to determine the incidence of HAV seropositivity in a typical midwestern community clinic setting.
Methods: In a prospective study, 399 patients were screened for evidence of prior exposure to HAV with anti-hepatitis A antibody (IgG), over a 3year period from July 2002 to June 2005. Patients with prior immunization history were excluded. There were 252 (63%) males and 147(37%) females comprising 283 (71%) Caucasians, 56(14%) African Americans, 44(11%) Asians and 16(4%) people of other races. Their ages ranged from 20 years to 79 years with a mean of 47 years. The main reason for testing was to determine the need for vaccination in high-risk individuals, which included healthy travelers 20 (5%), patients with chronic viral hepatitis 291(73%), other chronic liver diseases 48(12%) and HIV 40 (10%).
Results: Of the 399 subjects studied, 127(31.8%) were positive (*vs.* NHANES III 37.4%%). The127 seropositive subjects included 53(42%) Caucasians, 26(20%) African Americans, 34(27%) Asians and 14(11%) people of other races. Subset analysis of each ethnic group revealed the lowest incidence of seropositivity in Caucasians of 53/283 (18%) compared to 29% ($p < 0.001$) in NHANES III. In the African American group 26/56 (46%) were positive and for the Asian group 34/44 (77%), while the highest incidence was among people of other races who were mainly immigrants from developing countries with 14/16 (88%) testing positive.

Conclusions: The incidence of HAV seropositivity in a midwestern community clinic is comparable to NHANES III although with different population demographics. The seropositivity rates varied widely among different ethnic groups, thus one's ethnic background may be important when individualizing vaccination strategies for hepatitis A in our community.

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MELD Score vs Child Score in Predicting the Outcome of Elective Abdominal Surgical Procedures in Patients with Cirrhosis

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Purpose: The aim of this study is to evaluate the outcome of patients with cirrhosis undergoing elective abdominal surgery and to compare the capacity of the Child-Turcotte-Pugh (CTP) and Model for End Stage Liver Disease (MELD) scores to predict that outcome.
Methods: We conducted a chart review of patients with cirrhosis who underwent general anesthesia between January 1999 and December 2004 at Emory University Hospital and Emory Crawford Long Hospital. Patients with documented cirrhosis undergoing elective abdominal surgery were included. Patients undergoing liver transplantation or other surgical procedures involving the liver were excluded. Patients with evident extrahepatic cholestasis were excluded as well.
Results: A total of 617 charts were screened. After the inclusion and exclusion criteria were applied, 66 procedures performed on 62 patients were identified. The mean MELD score was 9.4 ± 3.3, the mean CTP score was 7.3 $\pm$ 1.5. Twenty (30.3%) patients were classified as CTP class A, 40 (60.6%) as class B and 6 (9.1%) as class C. The most common procedures were hernia repair (21, 31.8%), cholecystectomy (17, 25.7%), and diagnostic laparoscopy/laparotomy (15, 22.8%). One patient (1.5%) died of pneumonia in the postoperative period. Signs of decompensated liver disease (hepatic encephalopathy, new ascites, variceal hemorrhage) in the postoperative period were noted in 5 patients (7.6%). There was no statistically significant difference in the CTP or MELD scores between patients who developed signs of decompensation and those who did not. Nine patients (13.6%) developed postoperative transaminase elevation (at least twice the baseline value). The patients with postoperative transaminase elevation had a higher baseline MELD (12.3 ± 3.9 vs 9.1 ± 2.6, $p = 0.004$), but not a higher CTP score (7.7 ± 2.2 vs 7.4 ± 1.5, $p = 0.68$).
Conclusions: Our data suggests that elective abdominal procedures in patients with cirrhosis appear to be relatively safe, with a low risk of liver-related complications. The MELD score correlates better than the CTP score with postoperative transaminase elevation. This may reflect an acute injury to the liver in the perioperative period. More studies are needed to better define the roles of the CTP and MELD scores in predicting the outcome of elective surgical procedures in patients with cirrhosis.

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Symptoms of Sjögren's Syndrome in Patients with Primary Biliary Cirrhosis Improve after Liver Transplantation

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Purpose: PBC is a slowly progressive cholestatic liver disease that predominantly affects middle-age women. Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disorder frequently associated with PBC with a high prevalence in the United States. Characteristic symptoms of SS include dry eyes, dry mouth, dry cough, arthralgias, fatigue and Raynaud's phenomenon. To date, no studies have evaluated the outcome of these symptoms after transplantation.
Aim: The aim of this study was to determine the outcome of SS symptoms in patients with PBC after liver transplantation.
Methods: This is a retrospective cohort study in 57 patients with PBC who underwent OLT at UCSF between August 1988 and September 2003. Questionnaires were administered to 40 patients who consented to participate in this study. The subjects ranked symptoms of dry eyes, dry mouth, dry skin, dry cough, Raynaud's phenomenon, GERD, pruritus and fatigue before and after transplantation according to a simple objective severity scale (0–1, 2–3 and 4–5). Data were expressed as mean difference score (DS) and compared using the Wilcoxon signed-rank test.
Results: The group consisted of 5 men and 35 women. A high prevalence of SS symptoms were present in this group of patients before OLT. The most commonly reported SS symptoms were Raynaud's ($20/40 = 50\%$), dry eyes ($19/40 = 48\%$), arthralgias ($19/40 = 48\%$), dry mouth ($15/40 = 38\%$), and dry cough ($8/40 = 20\%$). 63% of patients reported dry skin, which may occur in either PBC or SS. The most commonly reported PBC symptoms were pruritus ($36/40 = 90\%$) and fatigue ($33/40 = 83\%$). Most patients reported improvement in their symptoms after liver transplantation with the exception of GERD, which did not change (pre-32.5% vs post-32.5%, $DS = 0$). The most clinically significant findings were the improvement after transplantation of dry eyes ($DS = -2$; $p = 0.0254$), dry skin ($DS = -1$; $p = 0.0366$) and Raynaud's ($DS = -2$; $p = 0.0055$). As anticipated, there was significant improvement after transplantation in the major PBC-related symptoms of pruritus ($DS = -4$; $p < 0.0001$) and fatigue ($DS = -2$; $p < 0.0001$).
Conclusions: SS symptoms are very common in patients with PBC and may have a significant negative impact on quality of life. These symptoms may improve after liver transplantation, although the mechanism for improvement is unclear. These results, which require confirmation by prospective study, suggest an important positive impact of liver transplantation on SS symptoms in PBC.

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Frequency and Biochemical Expression of Hemochromatosis (HFE) Gene Mutations in 1029 Blood Donors in Iran

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Purpose: To determine the frequency and biochemical expression of the hemochromatosis associated mutations, C282Y and H63D, in Iranian adult population
Methods: We investigated the frequency of the C282Y/H63D HFE gene mutations in a group of 1029 randomly selected Iranian blood donors as well as transferrin saturation (TS), serum iron and serum ferritin (SF) levels. DNA extraction with salting-out method was performed on blood samples and the analysis of HFE gene mutations was performed by PCR amplification followed by digestion with RsaI and BclI restriction enzymes.
Results: No homozygote for the C282Y mutation was found. Heterozygosity for the C282Y mutation was 0.2%, while homozygosity and heterozygosity for the H63D mutation were 1.6% and 19.6%, respectively. There was no compound heterozygote for the C282Y/H63D mutation. These data resulted in allele frequencies of 0.1% and 11.3% for C282Y and H63D mutations, respectively. Serum iron and TS were not affected from the type of C282Y and H63D mutations. However, there was a trend toward higher SF levels in men with H63D heterozygotes and homozygotes genotypes in comparison with wild type ($P = 0.06$).
Conclusions: This study shows low allele frequency for C282Y and H63D mutations in Iran. These results also suggest that there is not any strong association between HFE gene mutations and iron, TS and ferritin level among Iranian population. The genetic screening for the HFE gene mutations in Iran is not recommended until the true prevalence of other mutations in all hemochromatosis genes will be established.

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Heme Oxygenase-1 mRNA Expression in Chronic Hepatitis B

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Purpose: Heme oxygenase(HO)-1, a stress-responsive enzyme, has previously been shown to prevent inflammation-related apoptotic liver damage as well as protect grafts from ischemia/reperfusion injury. In addition, recent studies showed HO-1 had anti-fibrogenic effect and had close relation with pathogenesis of NASH. The aim of this study was to investigate the HO-1 mRNA expression in chronic hepatitis B and evaluate the relation between the apoptosis and/or fibrosis and HO-1 expression.
Methods: Reverse transcriptase-polymerase chain reaction was used to identify intrahepatic expression of HO-1 in liver biopsy specimens from twenty four patients with chronic hepatitis B (CHB). In addition, TUNEL method was used to determine the degree of apoptosis and histologic activity index (HAI) and ALT were measured.
Results: Intrahepatic mRNA expression of HO-1 was demonstrated in 5 cases, all of those cases were stage 4 histologically (Figure). There were no associations between HO-1 expression and apoptosis index. Moreover, there were no associations between HO-1 mRNA expression and serologic activity including ALT.

Conclusions: This study suggests HO-1 is an anti-fibrogenic protein indirectly as showing that HO-1 mRNA is expressed in chronic hepatitis B, for the most part, in cirrhotic stage. However, studies on the association between the HO-1 expression and apoptotic liver injury in CHB will be warranted. [figure 1]

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Hemochromatosis and Transferrin Receptor-2 Gene Mutations in Iranian Patients with Chronic Hepatitis C

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Purpose: to determine frequency of hemochromatosis gene mutations (C282Y, H63D and S65C) and transferring receptor-2 (TfR2) gene mutation (Y250X) in patients with chronic hepatitis C and healthy controls and to evaluate the effect of these mutations on ferritin level
Methods: we investigated the frequency of these mutations in 149 patients and 149 age- and sex-matched healthy controls. DNA extraction with salting-out method was performed on blood samples and afterwards, mutation detection based on PCR-RFLP method was done. C282Y, H63D, S65C and Y250X mutations were sought in all subjects by digestion of PCR products with RsaI, BclI, HinfI and MaeI restriction endonucleases, respectively. Ferritin level was measured in all subjects.
Results: There were no C282Y, S65C and Y250X mutations in either patients or controls.29 (19.5%) patients and 30(20.1%) controls were heterozygote for H63D mutation, and 3 (2%) patients and 4 (2.7%) controls were homozygote for it. The H63D allele frequency was 11.7% and 12.7% in patients and controls, respectively. We did not detect any significant difference in ferritin level among patients with H63D mutation and the ones without it.
Conclusions: There is no difference in the frequency of hemochromatosis gene mutations (C282Y, H63D and S65C) between patients with chronic hepatitis C and healthy controls among Iranian population. Besides we did not detect any TfR2 gene mutation (Y250X) in our patients. These mutations may either have a recent founder population or be associated with chronic hepatitis C only among the Caucasians.

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A Comparison of Sustained Viral Response in Patients with Chronic Hepatitis C Virus (HCV) Treated with Peginterferon Alfa-2a (Peg2a) Versus Peginterferon Alfa-2b (Peg2b) and Ribavirin

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Purpose: Pegylated interferon (pIFN) is superior to non-pegylated interferon across all genotypes. There are two available pIFNs available, but there is little head to head data comparing efficacy of these two treatment regimens.
Aim: To evaluate treatment efficacy of the two available pIFNs and ribavirin (RBV) regimens.
Methods: Interferon-naïve patients with chronic HCV treated consecutively at a single center between 2001 and 2003 formed this retrospectively and prospectively collected data set. Patients received either Peg2a 180 μg/wk or Peg2b1.5 μg/kg/wk, combined with ribavirin (RBV), per preference of the treating physician. RBV was administered either as a standard 800 mg dose in 20% of patients, or a weight-based (WB) dose in 80% (Peg2a: 1000 mg for patients $<$75 kg and 1200 mg for $\geq$75 kg. Peg2b: 13 mg/kg). Genotype 1 or 4 (G1,4) patients were treated 48 weeks, while genotypes 2 or 3 (G2,3) were treated 24 weeks. The treatment protocols for dose reduction or discontinuation were identical across patients treated, regardless of regimen used. The primary endpoint was sustained virologic response (SVR), defined as undetectable serum HCV RNA ($<$50 IU/mL) 24 weeks post treatment.
Results: Eighty-five patients with G1,4 (n = 51) and G2,3 (n = 34) were included in the analysis; 38 received Peg2a (WB RBV n = 32, flat RBV n = 6) and 47 received Peg2b (WB RBV n = 36, flat RBV n = 11). Early discontinuation for any reason occurred in 9/38 (24%) Peg2a and 8/47 (17%) Peg2b recipients (NS). Groups were well matched for age, weight, race, fibrosis, genotype and baseline viral load. SVR rates were greater in Peg2b compared with Peg2a (77% vs 47%; p = 0.007). See Table.

Table 1: Virologic Response Rates

	Peg2a		Peg2b	
Time point	G1,4	G2,3	G1,4	G2,3
Wk 24	19/28 (67%)	9/10 (90%)	19/23 (83%)	22/24 (92%)
Wk 48	17/23 (74%)	5/10 (50%)*	16/19 (84%)	22/24 (92%)*
Wk 72	13/28 (46%)#		14/23 (61%)#	
Relapse rate	28%	40%	23%	0%

* p = 0.014; # p = 0.40.

Conclusions: Sustained virologic response was higher in Peg2b treated patients compared with Peg2a. While both regimens suppressed virus well, relapse rates were higher with the Peg2a regimen. These results require confirmation in other studies.

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Antigenic Variations of Core Protein among Different Genotypes of Hepatitis C Virus

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Purpose: Antibodies against core antigen are reliable markers of virus replication, since their presence is found to be closely associated with the presence of specific mRNA. Hence the aim of the present study was to evaluate antigenic variations of 120 amino acids of core gene among 1a, 1b, 3a and 3b genotypes.
Methods: Serum samples of 120 patients who were anti HCV positive by 3rd EIA, 50 subjects were negative for all hepatitis markers.

Viral RNA extraction was carried out by QIAamp viral RNA kit followed by RT-PCR using core primes. The 120 amino acids of core gene were Cloned in BamHI and Eco RI sites of P^{ET21} expression system (Novogen). Gene was transformed in BL21 DE3 cells. Gene expression was induced by the addition of isopropyl-b-D-thiogalactopyranoside (IPTG). The bacteria were harvested after 6 h after IPTG activation. Cell lysates were subsequently prepared for protein purification. The purified 100 ng of core antigens were coated to a microtiter plates and tested with the patient's samples.

Results: The amino acid sequences of the recombinant protein used from different genotypes in the ELISA were compared with each other. The sequence of genotype 1a differing from that of genotype 3b by 13 of 120 amino acids (11% divergence), from that of genotype 3a by 9 amino acids (7.5% divergence) and 1b by 6 amino acids (5% divergence). All the four recombinant proteins were tested with 120 anti HCV positive samples and it was observed that all four proteins did not pick up any negatives ($n = 50$) showing 100% specificity, and had > 97% sensitivity. The protein 1a was the most sensitive and had a sensitivity of 99%. There was a close correlation observed between reactivity to the core protein of type 1a, 1b, 3a & 3b, with correlation coefficients of 1.289, 1.176, 1.201 and 1.154 respectively.

Conclusions: i) The structural antibody would appear much earlier and more persistently than antibodies against the non structural region and hence can be used as a good diagnostic marker.

ii) It was observed that by using just one structural recombinant antigen, a significant correlation between our EIA and commercial 3rd EIA was noted.

iii) Although slight amino acid difference was observed in the proteins among different genotypes, there was no significant difference was observed in the specificity and sensitivity of the test result.

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Use of Erythropoietin Increases the Likelihood of Achieving Viral Clearance in HCV Infected Patients Treated with Pegylated Interferon and Ribavirin

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Purpose: The current standard of treatment for hepatitis C (HCV) is pegylated interferon (pegIFN) and ribavirin (RBV). The latter causes hemolytic anemia. Dose reduction of RBV has been reported to have a negative impact on sustained virologic response (SVR). Erythropoietin (EPO) is used for the treatment of RBV induced anemia in an estimated 8–10% of cases. While several studies have suggested that the use of EPO allows for maintenance of the appropriate dose of RBV, no study has shown that it is correlation to SVR.

Aim: To assess the use of EPO in a clinical hepatology practice and its effect on treatment outcomes in HCV pts.

Methods: A data base of 87 treatment naïve HCV pts between 2001–2004 were evaluated for this study. Of these, 48 were genotype 1 (G-1), while the remainder were genotype 2 and 3 (G-2,3). Of the pts, 54% were male and 84% were Caucasian. SVR was defined as viral clearance 24 wks beyond the end of therapy by a negative qualitative PCR (<50 IU/mL). Pts were treated with either pegIFN alpha 2a or 2b, for either 24 (G-2,3) or 48 wks (G-1). The mean RBV dose in the EPO group was 1062 mg and 1017 mg in the non-EPO group. The decision to use EPO was based upon either hemoglobin (Hb) <10 mg/dL or Hb<12 mg/dL associated fatigue or dyspnea. Dose given was 40,000 units SQ weekly. Dose reduction of RBV by 200–400mg was the standard for individuals not receiving EPO if Hb fell below 10 mg/dL, followed by dose escalation once stable.

Results: Baseline Hb was 14.3 mg/dL. The mean weight in the EPO group was 77.65 kg, vs 79.42 kg in the others. A total of 26% required EPO. Of the G-1 patients, 50% received EPO. Of those in the EPO group, 65% were female. RBV dose reductions in G1 were required in 8% of pts receiving EPO *vs.* 40% in those not ($p = 0.04$). A total of 26% of pts in the EPO group discontinued early vs 16% in the non-EPO group either for side effects or for non response (NR). See TABLE

Table 1: SVR Results Based on Use of Erythropoietin (EPO)

Group	EPO		NO EPO		P value
Response	SVR	NR	SVR	NR	
All Genotypes	20	3	37	27	$P = 0.019$
G-1	11	2	13	22	$P = 0.008$

Conclusions: The use of EPO was associated with fewer dose reductions of RBV in HCV patients undergoing therapy. EPO was associated with higher SVR rates in all genotypes, including G-1 patients. The use of EPO appears to be justified as adjuvant therapy for anemia in HCV patients undergoing treatment with pegIFN and RBV.

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Molecular Genotyping of Hepatitis B Virus (HBV) Using Restriction Fragment Length Polymorphism (RFLP) Analysis of HBV Surface (S) Gene in HBV-Related Liver Disease Patients from New Delhi, India

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Purpose: Genotypes of HBV have now been identified that appear to have distinct clinical and pathological importance. Information regarding the prevalence of HBV genotypes and their clinical correlation in HBV-related liver disease patients from Northern India is scanty.

Methods: Total of 58 cases of serologically and PCR positive HBV-related liver disease patients were enrolled for the study which were analysed for HBV genotypes by PCR RFLP method.

Results: Majority of the cases, irrespective of the disease type, had evidence of circulating HBV genotype D infection (56/58, 96.5%) as revealed by PCR-RFLP analysis. Also, 2 cases (3.4%) had Genotype A infection. All the cases with genotype A infection belonged to Chronic Hepatitis B subset of the patients studied.

Conclusions: Genotype D infection seems to be widespread in Northern India. Genotype D is causing Acute Viral Hepatitis, Chronic Hepatitis B (CHB), Cirrhosis, Hepato-cellular carcinoma and Fulminant Hepatic Failure. Genotype A was associated only with CHB cases.

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Complications from Transjugular Liver Biopsy: An Analysis of 1000 Procedures

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Purpose: Transjugular liver biopsy (TLB) is an invasive diagnostic procedure extremely useful in assessing liver disease in all kinds of coagulopathy patients. We have analysed the type of complications from this technique, considering all the steps involved, including jugular, cardiac and liver catheterization.

Methods: We analysed retrospectivly 1000 TLB, performed in 14 years. 350 were achieved with TJ Henriksen aspiration needle, and 650 with TruCut needle.

Results: The complications that we observed were: carotid punction in 28 patients (2,8%), that did not preclude the liver biopsy; cervical haematoma in 12 patients (1,2%), without arterial puncture; transient auricular arrythmia in 15 patients (1,5%), that did not need pharmacological intervention or suspending the procedure; lumbar pain in inferior vena cava catheterization (without dissection) in 3 patients (0,3%); right hipocondrial pain in distal catheterization of hepatic veins, pre biopsy, in 5 patients (0,5%); ascitic fluid recovery in aspirative biopsy in 2 patients (0,2%); hemobilia in 1 patient

(0,1%), with pain, hyperamilasemia and oozing from the papilla; convulsion during lydocaine anesthesia in 1 patient (0,1%). In 8 patients, the access was from left jugular vein.
We did not have any complications related to the usual premedication (25–50 mg, iv, meperidine), to contrast allergy or to inadverted puncture of any cardiac afluent.
Conclusions: Even in serious and delicate conditions that the candidates for this procedure present, the complication rate, 6,7%, is exceptionally low, and generally quite benign and of minor importance. This suggests TLB as an extremelly useful and safe tool in assisting acute or chronic severe liver disease patients.

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Histologic and Liver Biochemistry Improvement in Patients with Non-Alcoholic Steatohepatitis (NASH) after 12 Months of Treatment with S-Adenosyl Methionine (SAMe)

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Purpose: Hepatic steatosis and oxidative stress are key factors in the pathogenesis of NASH. SAMe prevents fat deposition and glutathione depletion in the liver. Oral SAMe restored hepatic glutathione content in humans with chronic liver disease. The aim is to determine the efficacy of SAMe in reducing histologic inflammation and fibrosis, and improving liver biochemistry in patients with biopsy-proven NASH.
Methods: Patients with biopsy-proven NASH who did not have other known liver diseases, and did not consume >20 gm of alcohol per week, or take vitamin E, betaine, or ursodeoxycholic acid, were given SAMe (*Nature Made*, Pharmavite Corporation) 1,600 mg daily for 12 months (mos). Their liver enzymes and weight were recorded every 3 mos until end of treatment; liver biopsy was done at month 12 and compared with their pre-treatment biopsy. A single pathologist, who was blinded, reviewed the liver biopsies and graded the following NASH histologic variables: macrovesicular steatosis, ballooning and disarray, lobular inflammation, portal tract inflammation, Mallory's hyaline, acidophil bodies, glycogenated nuclei, lipogranulomas, and hepatocellular iron; overall necroinflammatory grade and fibrosis stage were also recorded.
Results: 8 subjects were enrolled; 1 withdrew because of breast cancer and 1 removed due to recurrent irritable bowel symptoms. 6 completed the study; 4 females and 2 males, BMI>30 in 4 and >25 in 2. All subjects lost weight but <10% from baseline. Necroinflammatory grade decreased (dec) in 3 of 6; fibrosis stage also dec in 3 of 6; none worsened after treatment. All had improvements in NASH histologic variables; 2 improved in 6 of 9 variables. Transaminases normalized in 4, with a mean dec in AST of 110 IU/L and ALT of 136 IU/L; 1 had near normalization, and 1 remained unchanged. Subjects were >92% compliant over the study period. The drug was considered "well-tolerated" by all, with a mean self-reported rate of 98%. Most side effects occurred during the first half of the study, and the most common were nausea, diarrhea, bloating and dyspepsia.
Conclusions: In this pilot study, 12 mos. of treatment with SAMe 1,600 mg daily resulted in histologic and liver biochemistry test improvements in a majority of subjects with biopsy-proven NASH, despite <10% weight loss. SAMe was safe and well-tolerated by all patients.

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Results of Liver Secondaries Treated by Radiofrequency Ablation

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Purpose: Radiofrequency ablation (RFA) is a new percutaneous tissue ablative therapy. We present our experience of RFA in liver secondaries.
Methods: Using Berchtold (Tuttlingan, Germany) RF generator (35–50 watt output); 1500–2000 watts energy/ cc tumour was delivered according to the size of liver secondaries.
Between February 2001 and December 2004, 49 patients (32 men) aged 44 to 72 years (man 59 years) had RFA of 177 liver secondaries from: Gall bladder = 12; colorectal = 22; Breast = 10; carcinoid/ neuroendocrine = 3 and stomach = 2 cancers. Lesions were sized < 3 cm in 44; 3–4 cm in 89 and >4 cm in 44. RF needle was placed US guided in 46, CT guided in 1 and at an open Surgery in 2 patients.
Follow up was by contrast enhanced CT scan.
Results: There was no procedure related mortality. All patients were discharged within 24 hours except two. There was no major morbidity. There were 6/49 (12%) minor morbidity (self limiting ascites = 2, self limiting pleural effusion = 4).
Efficacy: Complete necrosis was seen in all (100%; 44/44) of lesions up to 3 cms size and 34.8% (31/89) of lesions 3–4 cms in size. Recurrence at completely treated site, at mean follow up of 12 months was 7/75 (9.3%). On more than 6 months follow up, 31/43 (72%) patients developed new hepatic metastases and 23/43 (53%) patients also had systemic metastases.
Survival: 26 patients (53%) are alive and being followed. One year survival was 49% and 2 year survival was 12%
Conclusions: RFA is safe and effective local tissue ablative method for liver secondaries. More randomized controlled trials are required to ascertain efficacy of RFA in improving quality of life and/or survival in patients with liver secondaries.

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Critical Analysis of Radiofrequency Assisted Liver Resection

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Purpose: Radiofrequency (RF) tumor ablation is a well established local ablative procedure. Recently newer applications of RF have been suggested. RF can be used for performing hepatectomies safely. We analysed our 8 cases of segmental liver resection, using radiofrequency energy.
Methods: We performed RF aided liver resection using Berchtold (Germany) RF generator in eight cases of.
Carcinoma of the Gallbladder (Segment IVb and V or wedge resection); n = 5.
Liver metastasis from Gastric carcinoma (Segment III); n = 1.
Liver metastasis from colonic malignancy (Segment V); n = 1;
Suspected carcinoma of gallbladder, Xanthogranulomatous cholecystitis (Segment IVb and V); n = 1.
RF energy was used to coagulate 1 cm columns of liver parenchyma in a continuous row. Subsequent liver transaction was bloodless and it also coagulated the small bile ducts. Any additional bleeding point was directly treated with RF needle.
Results: There was no procedure related mortality. Blood loss varied between 5–20 ml except 100 ml in one case of bleeding from segment 3 artery. No patient required blood transfusion. There was no procedure related early morbidity. 3/8 (37%) patients had liver or sub diaphragmatic abscess in the late postoperative period (>2 weeks post op).
Three patients had post procedure abscess formation. Two patients had developed liver abscess in segment 8, far away from operated site. Both these patients had bactobilia due to biliary stent or bilioenteric anastomosis. Third patient of Carcinoma Gall bladder had associated pyocele.
At median, follow up of 1 year (6–24 months) all patients are alive with no locoregional recurrence, except one patient who had died of unrelated cause.
Conclusions: RF energy can be safely used for liver resection. It should be avoided in patients with overt local sepsis due to bactobilia (due to biliary stent or bilioenteric anastomosis) or pyocele.

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Frequency of Nonalcoholic Fatty Liver Disease, Nonalcoholic Steatohepatitis and Degree of Hepatic Steatosis in African American Patients

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Purpose: To evaluate degree and distribution of hepatic steatosis in African American (AA) patients who had liver biopsies over a period of five years
Methods: A search in the pathology registry was performed for the presence of fat in liver biopsies. Of 320 liver biopsies performed from1999 to 2003, 61 had fatty infiltration. Each biopsy was assessed by an expert pathologist. Patient records, imaging studies and laboratory tests were analyzed. The severity of steatosis was graded based on the percent of hepatocytes demonstrating fat as follows: Grade 1: <5%, Grade 2: 5–33%, Grade 3: 33–66%, Grade 4: >66%. Steatohepatitis was assessed by using guidelines by brunt et al. Fisher's exact test and ANOVA were used.
Results: There were 320 liver biopsies that were reviewed. A total of 61 biopsies were found to have steatosis. The mean age was 49 years and 55% of the patients were male. Fifty six of the 61 patients were African American. The mean Body Mass Index (BMI) in those AA patients was found to be 30. Majority had chronic hepatitis C (78%). Grade 1 steatosis was found in 16 patients, grade 2 in 22 patients, grade 3 in 14 patients and 9 patients had grade 4 steatosis. Alcoholic Steatohepatitis was present in 2 (4%) patients. The degrees of fat infiltration in the two patients with alcoholic steatohepatitis were 50% and 80%. Four patients fulfilled the criteria for the diagnosis of NAFLD (No history of alcohol use and had negative workup for causes of abnormal liver function test). All four patients had simple steatosis without any inflammation. The frequency of NAFLD in our study population was found to be less than 2%. Non alcoholic steatohepatitis (NASH) wasn't found in any of our study population. Dyslipidemia was found in all four patients with steatosis. Two of the patients were Diabetic. The mean values of AST, ALT, INR, Platelet count and BMI were compared amongst the four groups by using ANOVA test. There was no statistically significant difference when those variables were compared by the degree of steatosis.
Conclusions: NAFLD has a low prevalence in African Americans. NASH was not found in any of the AA patients seen at our institution. The severity of fatty infiltration didn't appear to have an impact on the severity of hepatic inflammation. BMI had no direct correlation to the degree of fatty infiltration in our study.

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Ophthalmic Findings in Chronic Hepatitis C (CHC) Patients Treated with Pegylated-Interferon (PIFN) and Ribavirin (RBV)

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Purpose: Retinal changes have been described in 18–86% of CHC patients receiving interferon alfa2a/2b. There is paucity of data on ophthalmic changes in CHC patients on PIFN+RBV.
Methods: Baseline eye exams were performed in 108 CHC patients treated with PIFN+RBV for 24–48 weeks. In a subcohort of 57 patients, visual acuity, tonometry, slit lamp and fundus examinations were done before, during and after therapy. Visual field testing, gonioscopy, color vision testing and fundus photography ± angiography were done, if indicated. Statistical comparisons between patients who developed retinopathy, Group A (GpA) versus those that did not, Group B (GpB) were performed (Student t test, $p < 0.05$).
Results: Patient Characteristics: mean age 49.7y (26–68), male 53/57, Caucasian 86%, African American 12.5%, smoking status−50% active smokers, 25% ex-smokers; hypertension 37%, diabetes 14%, hypercholesterolemia 14%, thrombo-embolic events−0%, vasculitis−1.7%, epogen use−26%, advanced fibrosis/ cirrhosis 37%, genotype 1–82% and high viral load−65%. GpA and GpB were statistically similar. **Laboratory data**: Hgb, Platelets, WBC, ALT, Albumin, Bilirubin and INR were similar in the two groups.
Retinopathy, cotton wool spots (CWS) and/or intraretinal hemorrhage (IRH) developed in 16 of 57 (28%) patients 1 to 9 months after start of therapy and in the majority (11) within 3 months. 12 patients had CWS, 3 had CWS+IRH and 1 had IRH. Treatment was continued in 15 of 16 patients with resolution in 9 (all had CWS only) during or shortly after completion of therapy. 3/4 patients with IRH continued to have stable eye changes (normal visual acuity) after completion of therapy; eye exam in the fourth patient is pending. Therapy was stopped in only 1 patient with complete resolution within 2 months. **Visual and ocular symptoms**: GpA: 9/16 (itching, blurring, floaters, diplopia). GpB: 15/41 (blurring, diplopia, eye pain, redness, grittiness). Dry eye syndrome was noted in 6 GpB patients, 2 at baseline and 4 during therapy.
Conclusions: (1) Retinopathy developed in 28% of patients treated with PIFN+RBV. (2) 44% patients with retinopathy were asymptomatic. (3) Conversely, 62.5% of patients with visual and ocular symptoms had no retinopathy. (4) CWS remained stable or resolved despite continued therapy. (5) IRH persisted after completion of therapy, however did not affect vision. (6) Retinal changes developed early during PIFN+RBV therapy.

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Treatment of Hepatitis C: Clinical Experience at a VA Medical Center

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Purpose: Chronic HCV infection is highly prevalent in the VA population but its treatment may be compromised by ETOH/drug use, psychiatric contraindications, and co-morbid conditions. Response rates and adherence to treatment have been reported to be lower in this population.
AIMS: To describe the clinical experience of treating patients infected with hepatitis C at a single VAMC.
Methods: Retrospective review of naive veteran pts with HCV infection treated with combination Pegylated interferon α (either 2b or 2a) + Ribavarin (Riba). All patients had their genotype determined at entry. Initiation of treatment was decided by a gastroenterologist but the administration and follow-up was closely monitored by a nurse practitioner under his/her direct supervision. Sustained virological response (SVR) was assessed 6-months after discontinuation of therapy in those with end of treatment response on an ITT and completion of therapy analysis.
Results: A total of 186 pts (115 Peg-Ifn 2b; 71 Peg-Ifn 2a) had completed treatment, were 6-mo beyond discontinuation of treatment, and could be evaluated for SVR. The average age was 51.
The overall SVR for all genotypes was 43.5% with a discontinuation rate of 26.9%. The discontinuation rate was independent of Interferon type.

SVR Rates on ITT & (Completed Treatment)

	PEG IFN 2b	PEG IFN 2a	Overall
SVR all Genotypes	38.3% (53.7%)	52.1% (68.5%)	43.5% (59.6%)
SVR Genotype 1	30.1% (44.4%)	36.6% (51.7%)	32.1% (46.7%)
SVR non-Genotype 1	72.7% (84.2%)	73.3% (88.0%)	73.1% (86.4%)
Discontinuation Rate	28.7%	23.9%	26.9%

There were no significant overall differences between the two forms of Peg-Ifn regarding SVR. Analysis of weight showed a slightly higher BMI for non-SVR in the Peg-Inf 2a group (29.3) *vs.* Peg-Inf 2b group (28.6). ($p = NS$) Side effects were the cause of discontinuation in 62% of cases whereas other causes (non-compliance, financial/work-related issues, etc) represented 32%. Three patients discontinued therapy due of liver decompensation.

Conclusions: 1. Even in a tightly monitored environment the SVR for all genotypes was lower than those reported in the literature but higher than previously reported in other VA populations. Side effects or reasons other than no-response accounts for a 27% discontinuation rate.
2. There is a trend for slightly lower SVR in higher BMI patients treated with Peg-Inf 2a *vs.* Peg-Inf 2b.
3. Intense monitoring results in higher SVR than previously reported in this population.

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MELD Score as a Predictor of Esophageal Varices Re-Bleeding Risk

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Purpose: Upper gastrointestinal bleeding secondary to esophageal varices in patients with end-stage liver disease (ESLD) is unpredictable with approximately 30% of these having at least one event. The 1-year risk of re-bleeding could be as high as 70%. The severity of underlying liver disease has been previously identified as a risk factor for re-bleeding, therefore we conducted an analysis of MELD score among patients with history of variceal bleeding and no bleeding in an effort to identify those at highest risk of re-bleeding based on this new parameter.
Aim: To establish an association between the severity of MELD score and the risk of re-bleeding in patients with ESLD.
Methods: Retrospective data analysis of patients with ESLD that presented to our institution with at least one episode of UGI bleeding (UGIB) from 1997 to 2002. There were 94 patients with complete database which we matched to 71 patients with ESLD and no history of bleeding (NUGIB).
Results: A total of 166 patients with ESLD were evaluated. Of those, 94 had at least one episode of variceal bleeding. The mean age was 55.7 years. Etiologies of liver disease included ETOH: 100, ETOH/HCV: 34, HCV: 13, Co-Infection: 4, and Other: 15. The MELD score among patients with history of UGIB and NUGIB was 11.5 *vs.* 14.8 ($p = 0.08$) and CTP score of 7.93 *vs.* 8.4 ($p = 0.13$). There was no age difference among groups. ($p =$ NS) Subgroup analysis of patients with history of UGIB who had further episodes of UGIB *vs.* those with only one episode of UGIB showed a MELD score of 14.9 in the rebleeding *vs.* 11.9 in the non-rebleeding groups ($p = 0.04$) and a CTP score of 8.59 *vs.* 7.52 ($p = 0.013$). The likelihood ratio for a repeat bleeding episode in the MELD >14 group was 1.54.

MELD Score and Rebleeding

	Bleeding < 1	Bleeding > 2
MELD > 14	20	17
MELD < 14	40	16
TOTAL	60	33

Sensitivity: 52%; Specificity: 67%; Likelihood ratio: 1.54.

Conclusions: 1. Analysis of ESLD patients with history of variceal bleed *vs.* re-bleed showed a statistically significant higher MELD score in the re-bleeding group when compared to patients with only one episode of bleeding. However, it appears that MELD score is not a good overall predictor of index variceal bleeding in patients with ESLD as previously shown for CTP score.
2. Patients with a MELD score over 14 were 50% more likely of having two or more UGI bleeding episodes.
3. We propose that history of variceal bleeding and a MELD score >14 might identify those patients at risk of variceal re-bleeding.

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A Crossover Retrospective Chart Review Evaluating Hospitalizations Associated with the Use of Rifaximin vs Lactulose in the Management of Patients with Hepatic Encephalopathy

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Purpose: Hepatic encephalopathy (HE) is a common condition among patients with liver disease, leading to repeated hospitalizations at an average daily cost of $6,230. This chart review compared the number and duration of hospitalizations associated with a discharge diagnosis of HE among patients treated first with lactulose and then rifaximin.
Methods: This study was a single-center, crossover, retrospective chart review of 145 patients diagnosed with HE. All patients received lactulose (30 cc bid) for ≥6 months then rifaximin (400 mg tid) for ≥6 months. Charts were reviewed to compare patients' last 6 months on lactulose therapy and first 6 months on rifaximin therapy. The primary endpoint was the number of hospitalizations a patient had during each 6-month therapy period. Hospitalizations were assigned 2005 dollar value based on inflation-adjusted Healthcare Cost Utilization Project (H-CUP) 2002 data for HE. Secondary endpoints were length of hospitalization, HE grade, presence of asterixis, patient reported medication compliance, and side effects severity during each therapy period.
Results: The number of hospitalizations was significantly lower during the period of rifaximin therapy compared with lactulose (mean 0.5 vs 1.6, respectively, $P < 0.001$). During the rifaximin therapy period, patients spent significantly less time in the hospital (mean time 3.14 days) than during the lactulose period (mean time 12.52 days, $P < 0.001$). Compared with the lactulose therapy period, HE grade was significantly lowered following rifaximin therapy ($P < 0.001$). Significantly fewer patients had asterixis at the end of the rifaximin therapy period compared with the end of the lactulose period ($P < 0.001$), as well as fewer diarrhea, flatulence, and abdominal pain side effects ($P < 0.001$). Medication compliance was significantly higher with rifaximin therapy compared with lactulose ($P < 0.001$). Using H-CUP data, the reductions in occurrences and duration of hospitalizations realized with rifaximin therapy resulted in an average cost savings of $67,559 per patient.
Conclusions: After 6 months of rifaximin therapy, HE grade was significantly lowered compared with the prior 6 months of lactulose therapy. Subsequently, hospitalizations were fewer and shorter during the rifaximin therapy period compared lactulose, resulting in substantially lower costs. Based on these results rifaximin should be considered as first-line therapy for HE.

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Retrospective Analysis of Chronic Hepatitis C and Autoimmunity

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Purpose: To assess the influence of age, sex, genotype and histological profile of liver in patients with autoimmune chronic Hepatitis C (HCV) and to demonstrate the variation of effectiveness of anti-viral therapy in autoimmune positive and negative patients in respect to sex, genotype and histological profile
Methods: This retrospective study was conducted in fifty biopsy proven chronic hepatitis C patients in the hapatology clinic at Coney Island Hospital, Brooklyn, New York. Designated pathologist scored the biopsy results using METAVIR scoring system. Thirty patients received the antiviral treatment. Sustained viral response is defined as viral load less than 50 IU/ml on Roche Amplicor method after six months of treatment. Results were analyzed by using Chi- Square and independent t-test.
Results: The overall prevalence of auto-immunity was 42%. Mean age of autoimmune positive and negative patients was 44.57 and 46.62 years respectively ($p = 0.47$). 38% of male and 62% of female were found to have autoimmune positive HCV ($p = 0.79$). Majority of patients had genotype 3a and 50% were found to have autoimmune antibody positive. However presence of autoimmunity is not significantly influenced by genotype ($p = 0.44$). Presence of autoimmunity did not affect the severity of the histological profile both in activity score ($p = 0.86$) and in fibrosis score ($p = 0.99$). Genotype was significantly related to treatment response in the autoimmune positive patients ($p = 0.02$) but lacks significant response in negative patients ($p = 0.31$). On the other hand, gender difference showed little variation in treatment response but failed to demonstrate statistically significant difference in outcome whether autoimmune positive ($p = 0.15$) or negative ($p = 0.36$).

Autoimmunity played no role in histological profile of the liver and the treatment response. The *p* value of activity scores in the autoimmune positive and negative groups are 0.35 and 0.36 while the *p* value of fibrosis score are 0.16 and 0.42 respectively.
Conclusions: Increasing prevalence of autoimmunity is observed in HCV patients. The autoimmune positive and negative groups are not different by age, sex, genotype and histological profile. The outcome of treatment in autoimmune positive and negative groups is independent of sex and histological profile. However, the presence of genotype 3a and autoimmunity revealed a better prognosis. Further study in large population is needed for clinical application of this conclusion

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Advanced Hepatoma—Role of Transarterial Chemoembolization (TRCE)

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Purpose: Hepatocellular carcinoma is an aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis. It is typically diagnosed late in the course of patients with chronic liver disease, with the median survival following diagnosis of approximately 6 to 20 months. Hepatocellular carcinoma generally occurs in patients with cirrhosis. Curative options, such as liver transplantation, hepatic resection, and percutaneous alcohol injection, are applicable to a minority of cases. Because systemic chemotherapy and radiation therapy provide dismal results, transarterial chemoembolization (TACE) remains an approach to antagonizing the cancer growth in most patients. Although most tumors show an extensive necrosis after TACE, the beneficial effect on survival has not been properly substantiated, so that its application still remains a matter of debate.Although the mainstay of therapy is surgical resection, several other treatment modalities may also have a role.
Methods: 81 year lady was hospitalised 18 months ago with anemia, weakness and abdominal distention. She was diagnosed to have cirrhosis, HepatitisC and hepatic mass. She was found to have both esophageal and gastric varices. Biopsy of the hepatic mass was reported as hepatocellular carcinoma-pseudoglandular varient. There were two hepatic lesions measuring 6cm and 5cm in the right lobe. She was referred to hepatic surgical unit. She had transarterialchemoembolisation. with adriamycin and 5FU twice with good results. Patient tolerated well. She is being followed at primary physcian's office on regular basis.She is taking propranonol and diuretics. She lives alone with only imited assistance.
Results: The above case illustrates the effective role TRCE in her case with advanced liver disease with large hepatomas.
Conclusions: TACE is an effecive palliative treatment which should be considered in patients who are not candidates for surgical treatment. It can offer good palliation in selected patients.

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A Placebo Controlled Double Blind Clinical Trial of the Efficacy of Hepavirin in Viral Hepatitis B

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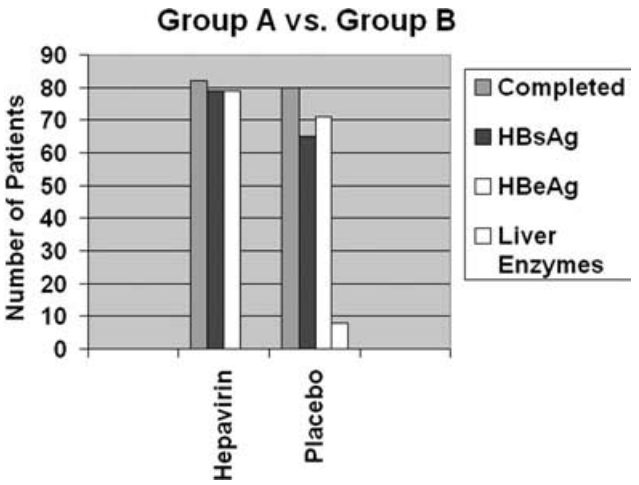
Purpose: The drug hepavirin is a new polyherbal formulation consisting of phyllanthus amarus. Treatment of hepatitis B carriers is expensive.The study was conducted (a) to study the natural profile of hepatitis B in initial 4 weeks of the disease and (b) to evaluate the efficacy of Hepavirin in hepatitis B viral infection and in liver functions.
Methods: 200 patients of serologically proven acute hepatitis B (100 patients in each group A and B) of all the age groups were included in the study. Detailed history, physical examination and investigations like Hb, TLC, DLC, ESR, Platelet count, Serum bilirubin, SGPT, SGOT, Serum Proteins, HBSAg, HBeAg, IgM-Anti HBcAb were recorded. All patients received 1 tablet of hepavirin 500 mg thrice a day; in group A and of the placebo in group B for a total of 4 weeks. All patients were clinically monitored weekly at 0, 16 and 24 weeks.
Results: At the end of 24 weeks 82 patients (82%) in the drug group and 80 (80%) in the placebo group completed the trial. Clinical symptomatic improvement and return of SGPT and SGOT to normal was significantly faster with the drug than with the placebo. 79 (96.3%) patients receiving the drug and 65 (81.2%) receiving placebo cleared HBsAg from their sera ($p < 0.001$). HBeAg was cleared from 79 (96.3%) patients receiving drug and 71 (88.7%) patients receiving placebo ($p < 0.001$). Liver enzymes were raised in 8 patients in the placebo group as compared to 0 patients in the Hepavirin group which is significant.



Conclusions: Hepavirin administration results in significantly faster($p < 0.005$) symptomatic and serologically clearing of antigens and normalization of liver enzymes than placebo in acute hepatitis B. [figure 1]

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Predicting Relapse to Pegylated Interferon and Ribavirin Therapy According to First HCV RNA Negativity

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Purpose: Although current HCV antiviral treatment algorithms reliably predict virologic nonresponders at TW12, a method to identify potential relapsers remains unclear. We sought to determine whether available clinical data could predict those patients likely to experience relapse.
Methods: 52 consecutive treatment naïve chronic HCV genotype 1 patients received PEG/ribavirin therapy (weight based) for 48 weeks. Therapy was stopped in those patients who did not achieve EVR (greater than 2 log decline) at TW 12 or viral negativity at TW 24. Liver biopsies were performed within one year of therapy and were scored by an individual pathologist (Ishak). We assessed HCV RNA levels (Bayer Versant quantitative with reflex TMA qualitative) at TW 4, 8, 12, 16, 20, 24, 48 and at week 24 follow-up. We examined factors (BMI, baseline viral load, and fibrosis stage) that might affect relapse rate. We also assessed whether late virologic response (HCV RNA positive at TW 12 and negative at TW 24) or duration of viral negativity were associated with subsequent relapse. We used two sample t-tests and the Wilcoxon rank sum tests to assess significance. All data were expressed according to ITT analysis.
Results: The mean age was 49 yrs (range, 33–71), 57% men; 81% Caucasian, 13% AA, 6% Asian. The SVR rate was 44% (23/52) and relapse rate was 13% (7/52). 6/52 discontinued treatment prematurely. The median baseline viral level for SVR was 1,275,000 IU and 1,490,000 IU for relapsers

($p = 0.90$). The mean time to viral negativity was 15.5 weeks for those patients who achieved SVR and 22.3 weeks in those who relapsed ($p < 0.001$). No relapser became viral negative before TW 20. There was a trend toward higher mean BMI and among relapsed compared to SVR patients. The mean BMI in patients with an SVR was 25.5 (range, 21.3–32.5), and 27.7 (range 23.7–32.7) for relapsers ($p = 0.096$). 7/23 (30%) of SVR patients and 2/7 (28%) of relapsers had advanced fibrosis or cirrhosis ($p = 0.89$). 16/52 (30%) genotype 1 patients failed to achieve EVR or viral negativity at TW 24.
Conclusions: (1) The rate of virologic relapse is directly related to time to first HCV RNA negativity. (2) Relapsers have a shorter duration of viral negativity during therapy than do sustained responders on a 48-week treatment regimen. (3) These findings corroborate recent reports suggesting that extending HCV antiviral therapy from 48 to 72 weeks lowers relapse rates in the cohort of patients with a late virologic response.

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Methotrexate (MTX)-Induced Hepatotoxicity in Patients with Psoriasis: Are Serial Liver Biopsies Needed?

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Purpose: 1.Evaluate the impact of MTX on liver biopsies in patients with Psoriasis 2. Determine the impact of serial liver biopsies on patient management.
Methods: Single center, retrospective analysis of liver biopsies performed on patients with Psoriasis receiving MTX. Liver biopsies were assessed for MTX toxicity using the Roenigk criteria
Results: Between 01/1990–12/2004, 18 patients with psoriasis receiving MTX therapy underwent 29 liver biopsies. Mean age of patients was 68 years (range 48–85). All patients were males. Median MTX dose was 2050 mg (mean 3163 mg). None of these biopsies was done before MTX initiation. Four biopsies showed changes of Grade 2(out of 4) MTX toxicity (all patients had concomitant risk factors for non alcoholic steatohepatitis). All other biopsies were normal or showed minimal changes (Grade1 out of 4 changes). Based on liver biopsy findings, MTX was stopped 2 patients (11%) who showed progression from Grade 1 to grade 2 on serial liver biopsies (both with significant risk factors for non alcoholic steatohepatitis with hyperlipidemia and morbid obesity). Treatment was stopped in another patient with normal liver biopsy but mild persistent elevation of bilirubin. None of the biopsies showed cirrhosis or advanced fibrosis
Conclusions: No cases of advanced hepatic fibrosis were found in 18 patients undergoing MTX therapy. Serial liver biopsies resulted in change of treatment in 11% of patients(all with concomitant risk factors for non alcoholic fatty liver disease(NAFLD)). Patients with risk factors for liver disease, including NAFLD, should have pre-MTX liver biopsies, and only these patients considered for repeat biopsies during continued MTX therapy. Dermatology and GI/Hepatology Departments should revise current practice guidelines for patients with psoriasis beginning MTX therapy.

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Radiofrequency Ablation (RFA) in Patients with Non-Resectable Hepatocellular Carcinoma

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Purpose: Primary hepatocellular carcinoma is the seventh most common cause of cancer in men and ninth most common in woman. Nearly 500,000 patients per year worldwide are diagnosed with hepatocellular carcinoma. While surgery is the only chance for cure, the tumor grows rapidly and the diagnosis is usually made late in the disease. It is estimated that less than 10% of patients with hepatocellular carcinoma are candidates for curative resective surgery. In addition, the minority of patients with hepatocellular carcinoma are candidates for liver transplantation given the large size and/or the multiplicity of tumors noted on presentation. Laparoscopic RFA provides a minimally invasive means of thermally debulking hepatomas as adjunctive therapy to chemotherapy and/or as a "bridge" to hepatic transplantation.
Methods: From 3/99 to 5/05, we treated 48 patients (30 men, 18 women) with non-resectable hepatocellular carcinoma using laparoscopic RFA. All procedures were done under general anesthesia using laparoscopic ultrasound assistance employing the RITA laparoscopic RFA probes. The 48 patients with a mean age ($\pm$ SD) of 63.0 ± 11.3 years were from varied ethnic backgrounds: 19 Asian/Pacific Islanders, 16 Caucasians, 2 African-Americans and 11 others. Twenty-three patients had HCV while 4 patients had HBV.
Results: Forty-one patients received one laparoscopic RFA treatment session while 7 patients received 2 treatment sessions. A total of 94 individual lesions were treated by laparoscopic RFA (mean 2.0 lesions per patient, range 1 to 5 lesions per patient). The largest lesion mean diameter per patient was 3.5 ± 1.7 cms (range 1.4 to 10 cms); while the aggregate tumor mean diameter per patient was 5.8 ± 3.6 cms (range 1.4 to 16 cms). The vast majority of patients was hospitalized for only 2 days and experienced symptomatic improvement and computed tomographic documented palliation of tumor size. Given the marked improvement and, in some virtually complete CT resolution of tumor mass, 11 of 48 patients (24%) underwent subsequent successful liver transplantation, two of whom had no evidence of residual hepatoma in the explanted liver.
Conclusions: Laparoscopic RFA is a substantial addition to our armamentarium for palliation of hepatocellular carcinoma. In some patients, RFA can substantially debulk and in some patients eradicate hepatoma such that patients can either be bridged or downstaged to become acceptable candidates for hepatic transplantation.

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Hepatitis C Genotype 1 Treatment Picture in the Real World: Where Are Our Patients Failing?

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Purpose: Clinicians treating patients with genotype 1 Chronic Hepatitis C (CHC) using pegylated interferon and ribavirin are faced with several challenges. Despite advances in therapy and use of growth factors, a majority of these patients do not achieve a sustained virologic response (SVR). We postulated that side effects play an important role in the discontinuation of therapy especially during the early weeks of treatment in clinical practice. Our aim was to explore the nature and frequency of adverse events that led to premature termination of combination therapy at our tertiary referral center.
Methods: Medical records were reviewed on consecutive CHC genotype 1 patients who initiated 48 weeks of standard pegylated interferon (alpha 2a or alpha 2b) in combination with weight based ribavirin therapy. Data on the reasons for therapy discontinuation (constitutional, organic, psychiatric side effects) and response (early virologic, end of treatment, or sustained) was recorded and treatment was discontinued if early virologic response (EVR) was not obtained.
Results: Overall on 100 patients with genotype 1 EVR was 60%, end of treatment response was 40%, and SVR was 28%. In the first 12 weeks 33 patients did not achieve an EVR and 7 patients discontinued therapy due to side effects. Of the 60 patients with EVR, in the next 36 weeks 8 patients did not achieve an end of treatment response and 12 patients discontinued therapy due to side effects. Overall, of the 19 patients who discontinued therapy 6 patients had psychiatric side effects (major depression, suicidal ideations, or psychosis), 4 patients had organic side effects (recalcitrant cytopenias or retinopathy) and 9 patients had various constitutional symptoms as the prominent reason for discontinuing therapy.

Conclusions: In our clinical practice 19% of genotype 1 patients discontinued treatment during a planned 48-week course of standard combination therapy. Among those who discontinued therapy 7/19 (37%) patients did so prior to achieving an EVR versus an unexpected 12/19 (63%) patients post-EVR. Constitutional and psychiatric side effects prompted discontinuation in 5/7 (71%) patients pre-EVR versus 10/12 (83%) patients post-EVR.
Our study shows that constitutional and psychiatric side effects are the major cause of discontinuation of therapy even after EVR. Continued post-EVR vigilance and proactive management of side effects may significantly reduce patient drop-out and improve SVR.

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Combination Therapy for Genotype I Hepatitis C—Can We Accurately Identify Predictors of Response?

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Purpose: Current evidence suggests that more than 50% of patients with genotype 1 chronic hepatitis C (CHC) who undergo combination treatment with pegylated interferon (PIN) and ribavirin do not achieve sustained virologic response (SVR). Our aim was to retrospectively identify patient-related and biohistochemical factors that predict improved outcomes for genotype 1 CHC patients outside of registration trials.
Methods: Medical records were reviewed on consecutive genotype 1 patients who initiated PIN (alpha 2a or 2b) in combination with weight based ribavirin therapy. Treatment was discontinued on patients who did not have a 2 log drop after 12 weeks. Patient demographics, alcohol use, diabetes history, prior therapy (non-PIN and ribavirin), and antidepressant use was recorded. Baseline biohistochemical data on HAI and fibrosis score, viral load, hematocrit, platelet count, liver enzymes, and transferrin saturation was recorded.
Results: Complete data was available on 102 patients with genotype 1 with an overall SVR of 28%. The factors that positively influenced SVR on multivariate analysis were: no prior therapy ($p = 0.005$, OR 21.04), Ishaak fibrosis score <3 ($p = 0.027$, OR 4.48), pre-treatment viral load $<500{,}000$ IU/ml ($p = 0.011$, OR 4.31), and none/minimal alcohol use ($p = 0.042$, OR 3.82). Age <40 ($p = 0.04$) and total billirubin <1.0 ($p = 0.0001$) reached statistical significance in univariate analysis. The remaining variables showed a favorable trend that did not meet statistical significance (Table 1).

Table 1. Factors With a Favorable SVR Trend

Factor	SVR (%)	P-Value
Transferrin Sat < 35% / > = 35%	35.6 / 15.6	0.200
Normal AST, ALT / Abnormal	33.3 / 21.8	0.395
Hematocrit>40 / < = 40	30.5 / 22.7	0.665
No Prior Antidepressants / Prior Use	31.7 / 16.7	0.316
Caucasian / Non-Caucasian	32.4 / 20.6	0.496
No Diabetes / Diabetes-II	31.3 / 16.7	0.405
Modifying Antidepressants / Not	48.3 / 20.0	0.067

Conclusions: Patients with low hepatic fibrosis, viral load, alcohol use and those with no prior therapy had an improved SVR with combination therapy in a multivariate analysis of our CHC genotype 1 cohort. Age <40 and total billirubin <1.0 made a significant positive impact on SVR in univariate analysis. We suggest that treatment-naive younger genotype 1 CHC patients with a low viral load and fibrosis score may have the highest response rates and should be considered for therapy earlier in their disease presentation.

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Restless Legs Syndrome Diminishes Quality of Life in Chronic Liver Disease

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Purpose: Restless Legs Syndrome (RLS) is a clinical syndrome that affects approximately 10% of the general population. RLS can be debilitating and lead to reduced quality of life. We have previously shown that RLS is more prevalent in patients with chronic liver disease (CLD). The impact of RLS on quality of life (QoL) of CLD patients has not previously been assessed. We prospectively evaluated the impact of: 1. RLS on the QoL in CLD patients; 2.The severity of liver disease on the presence of RLS.
Methods: CLD patients presenting to an outpatient Hepatology clinic were queried for presence of RLS using validated RLS survey tools. Patients found to have RLS were then contacted by telephone and the Johns Hopkins RLS Quality of Life Questionnaire was administered. The main outcome measure was the score on the RLSQoL questionnaire, a validated instrument that measures quality of life on a scale of 0 (poor quality) to 100 (good quality). This scale includes daytime somnolence, ability to concentrate, social activity impairment, sexual health and work productivity. MELD and Child's score were determined in patients based on chart review. Mann-Whitney rank sum test was used to compare MELD scores and Chi square to compare Child's class in RLS and non-RLS groups.
Results: Of 141 CLD patients surveyed, 86 were found positive for RLS. Of those positive for RLS, 34 (40%) self-reported risk factors including kidney disease (9), iron deficiency (19), and/or neuropathy (22). We were able to contact 76/86 RLS positive CLD patients for RLSQoL questionnaire and 74 RLS patients responded (2 refused). Average calculated RLSQoL score was 68, which reflects moderate diminished QoL and RLS severity. MELD score was available in 64/86 RLS positive patients and 37/55 RLS negative patients. Mann-Whitney rank sum test showed no significant difference ($p = 0.90$) in MELD score between RLS positive (Median 6) and RLS negative patients (Median 7). Further, there was no significant difference in the Childs class between the RLS and non-RLS groups (see table).

Child's Class–RLS

Child's class	with RLS (%)	without RLS (%)	P VALUE
A	73.25	70.91	NS
B	13.95	16.36	NS
C	5.81	3.64	NS

Conclusions: RLS occurs with a surprisingly high prevalence in patients with liver disease and results in significantly diminished quality of life, with an average QoL score of 68 on a 0–100 scale. Presence of RLS in CLD patients is not directly related to the severity of their underlying liver disease. The cause for increased prevalence of RLS in liver patients is unknown and warrants further investigation.

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Can Use of Growth Factors Enhance SVR to Combination Antiviral Therapy for Hepatitis C amongst Veterans?

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Purpose: Previous studies have suggested that sustained virologic response (SVR) to interferon alpha and ribavirin antiviral therapy in the VA population is less than half of that achieved in randomized controlled trials using similar therapies. Most of these studies attribute this lack of response to high drop out rates and comorbidities. The use of growth factors to enhance outcomes and minimize drop out rates in the veteran population has not been examined. Our aim was to assess the SVR to pegylated alfa (PEG) interferon combined

with weight adjusted ribavirin in veterans who received adjunctive therapy with erythropoietin as needed for anemia.
Methods: A retrospective review of a cohort receiving combination antiviral therapy with either PEG interferon 2a or 2b and weight based ribavirin was performed. Eighty consecutive patients who met the approved guidelines for treatment with PEG interferon and ribavirin were offered therapy. During therapy erythropoietin support was initiated if the hemoglobin value dropped to 11 gm and if patient was symptomatic. Demographics, laboratory, and histologic parameters were compared to determine predictors of SVR using Chi square and logistic regression analysis.
Results: The mean age of the cohort was 49.9 ± 5.02. The average BMI was 28.9 ± 4.78. 84.8% (67/79) of patients were Caucasian, 11.4% (9/79) were African Americans, and 3.8% (3/79) were Hispanic. Genotype 1 comprised 69.6% of the cohort, whereas 27.8% were genotype 2 or 3 and one patient was genotype 4. 32.4% of the cohort had advanced fibrosis (stage 3 or 4). The SVR in the 71 veterans who had completed therapy was 63.4%. The SVR for Genotype 2 and 3 (87.5% and 83.3%) was significantly higher than the SVR for genotype 1 (52.1%) ($p = 0.04$). SVR was not significantly associated with Age, BMI, race, presence of DM, advanced fibrosis, and erythropoietin use by chi square or logistic regression analysis. 46.8% of the cohort received adjunctive support with erythropoietin.
Conclusions: Higher than expected response rates can be achieved with combination antiviral therapy using PEG interferon and Ribavirin in a veteran population when erythropoietin is used to mitigate the dose reduction or discontinuation.

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Ethnic Differences in Cryptogenic Cirrhosis in Patients Undergoing Liver Transplantation

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Purpose: Studies suggest a substantial number of patients with cryptogenic cirrhosis have nonalcoholic steatohepatitis, and that it is more frequent among minorities. We used the Scientific Registry of Transplant Recipients (SRTR) to determine the ethnic distribution of patients listed and transplanted for cryptogenic cirrhosis (CC) compared to alcoholic cirrhosis (AC) or alcoholic cirrhosis with Hepatitis C (AHC), which represent common disorders for which minorities are listed for transplant.
Methods: The SRTR was used to determine the proportion of patients of different ethnicities added to the registry or transplanted from 1/1/1990 to 12/31/2004 with CC, AC, or AHC. Chi square analysis tested whether there were differences in the ratio of various ethnic groups listed or transplanted for CC compared to AC or AHC.
Results: 9,560 patients were added to the registry with a diagnosis of CC, of which 77% were White, 14% Latino, 5% Black, 3% Other. Patients with AC or AHC ($n = 23{,}767$) included 79% White, 14% Latino, 5% Black, 2% Other. Chi square analysis revealed a greater percentage of Latinos listed on the registry with CC compared to Whites ($p = 0.009$). There was no difference in the percentage of Blacks *vs.* Whites ($p = 0.49$) or Blacks *vs.* Latinos ($p = 0.38$) listed with CC.
6,597 patients were transplanted for CC. The ethnic distribution included 79% White, 12% Latino, 6% Black, 3% Other. Patients transplanted with AC or AHC ($n = 12{,}382$) included 82% White, 11% Latino, 5% Black, 2% Other. A greater percentage of Blacks ($p < 0.001$) and Latinos ($p = 0.009$) were transplanted for CC compared to Whites who were more frequently transplanted for AC or AHC. There was no statistically significant difference between Blacks and Latinos ($p = 0.08$) transplanted for cryptogenic cirrhosis.
Chi square analysis also suggested a greater percentage of Latinos with CC were listed for transplant compared to Whites but were less likely transplanted for CC than Whites ($p < 0.001$). There was no statistically significant difference between Blacks and Whites ($p = 0.687$).
Conclusions: In the SRTR, there was an increased prevalence of CC in Latinos compared to Whites which may reflect differences in advanced liver disease and NASH in this ethnic group. Additionally, although Latinos were more likely to be added to the registry with a primary diagnosis of CC, they were less likely to be transplanted for CC than Whites. A better understanding of these differences is necessary, with future studies exploring the potential reasons for this disparity.

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Effect of Needle Biopsy in the Outcome of Hepatocellular Carcinoma (HCC)

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Purpose: Diagnosis of HCC can usually be made by a combination of radiographic appearance and Alpha Fetoprotein levels. However, many patients still require a needle biopsy for pathological diagnosis. There have been several anecdotal reports of needle track tumor seeding after a biopsy but not enough evidence to document a connection. In this study we have attempted to answer the question about whether needle biopsy has an impact in HCC survival or risk of recurrence
Methods: Information about all patients with HCC treated at UIC since 1998 was retrospectively collected by electronic chart review. Statistical analysis of the data was done to correlate the clinical and pathological size of the tumor, nodal involvement and presence of metastasis. SAS Biostatistical software was used.
Results: The database included a total of 194 patients, from these, 61 patients had documentation of having had a needle biopsy. Multivariate analysis was done. The variables most strongly correlated with survival were clinical stage, receiving surgical treatment (resection or transplant) and having a recurrence. The unadjusted survival analysis showed that the hazard ratio of death for patients whom had had a needle biopsy was 1.381 (Chi square 2.864. $p = 0.0906$). The adjusted survival analysis, controlling for clinical stage and surgical treatment, revealed a hazard ratio of death of 1.057 (Chi-square 0.0809; $p = 0.776$). However, controlling for whether a patient experienced a recurrence, patients who received a needle biopsy had a hazard ratio of death of 1.89 (chi-square 6.2116; $p = 0.0127$). All other covariates (diagnosis age, stage and type of treatment) were found to be not significant after controlling for biopsy status and recurrence status. The non-significant trend of correlation between having had a needle biopsy and increased probability of death disappears after adjustment by stage and treatment type, and may suggest a confounding effect. The significant effect of biopsy on survival after adjusting for recurrence may be due to a tendency to take smaller tumors directly to surgical resection and reserve biopsy for larger tumors. However, it raises the question of whether the detrimental effect of biopsy is related to systemic dissemination of disease as opposed to a local recurrence.
Conclusions: In this multivariate analysis, needle biopsy seems to predict survival when controlling by recurrence.

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Detection of Focal Hepatic Lesions in Patients with Liver Cirrhosis Undergoing Transplant Evaluation: Ultrasound Versus Magnetic Resonance Imaging

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Purpose: Ultrasound imaging (U/S) and magnetic resonance imaging (MRI) are used extensively in the clinical practice to detect focal lesions in the liver. The purpose of this study is to determine the sensitivity of MRI compared to U/S in detecting focal hepatic lesions in patients with end stage liver disease undergoing liver transplant evaluation.

Methods: This was a retrospective study of patients with decompensated cirrhosis undergoing liver transplant evaluation. As part of the routine liver transplant evaluation at our institution, patients undergo imaging of the liver with both U/S and MRI. Identified lesions are then managed as appropriate based on clinical relevance. Patients were selected who had imaging with both U/S and MRI within the same month and identified lesions were evaluated for clinical significance requiring further management.
Results: From March, 2003 to May, 2005, a total of 268 patients underwent liver transplant evaluation. A total of 147 patients (93 males; 54 females) met the inclusion criteria for the study including imaging using both U/S and MRI with one month time period. There were 34 (23%) patients with focal lesions identified on imaging. Of these, 16 (47%) patients were identified by both U/S and MRI, 17 (50%) were identified by only MRI, and 1 (3%) was identified by only U/S (McNemar's $p < .0002$). Sensitivity was 50% and 97% with a NPV of 87% and 99% on U/S and MRI, respectively. Two lesions identified as cysts not requiring further follow-up. The other 32 (94%) lesions were all clinically significant that resulted in a change in management of the patient.
Conclusions: Prevalence of focal liver lesions in patients with end stage disease was 23% with 94% of these having clinical significance requiring a change in management. Imaging with MRI was significantly superior to U/S in identification of focal liver lesions including clinically relevant lesions. In this population with end stage liver disease undergoing liver transplant evaluation, recognizing potentially malignant liver lesions is critical in the management of these patients. Further studies to correlate lesions identified on imaging with pathology are needed.

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Ophthalmologic Complications Occuring during Treatment of Chronic Hepatitis C Infection with Pegylated Interferon

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Purpose: Ophthalmologic disorders are among the reported complications of pegylated interferon (IFN); however, there is little data on the frequency, associated symptoms, duration of onset, or whether either of the available forms of IFN put patients at higher risk for these complications. The aim of this study is to assess the incidence and nature of ophthalmologic complications from the use of IFN in the treatment of chronic HCV.
Methods: Charts for patients treated for chronic HCV between December 2002 and May 2005 were retrospectively reviewed. Patients were treated with ribavirin in combination with either IFN alfa-2a or alfa-2b. Ophthamologic complications were defined as either vision changes reported by the patient or findings on dilated eye examination including cotton wool spots, retinal hemorrhages, or optic neuropathy. Any visual symptom prompted immediate treatment cessation until the patient could be evaluated by an ophthamologist.
Results: A total of 294 patients, including 285 men and 9 women, were treated with IFN. Of these, 173 were treated with IFN alfa-2b while 121 received alfa-2a. In 23 of these patients ophthalmologic complications occurred and treatment was discontinued. Twelve patients complained of visual changes, 5 of which had observable ophthalmologic lesions. Of the remaining 7 without findings, treatment was resumed in 4 without sequelae, while it was not resumed in the other 3. Fifteen patients had findings on eye examination. Cotton wool spots were the most frequently observed lesion ($n = 11$), followed by optic neuropathy ($n = 4$). Among those with cotton wool spots only one reported symptoms, while all those with optic neuropathy were symptomatic. The earliest visible changes on eye exam were observed in a patient with a previously normal eye exam who began treatment 4 weeks prior. Of the patients receiving IFN alfa-2a, 7 (5.7%) had findings on exam; whereas 8 (4.6%) of those treated with IFN alfa-2b had detectable lesions.
Conclusions: Ophthalmologic complications were observed in 7% of patients receiving IFN. Five percent had lesions on exam. These complications can lead to blindness, are often asymptomatic, and can occur as soon as one month after treatment initiation, thus supporting the need for baseline and follow-up eye examinations. Vision changes alone do not preclude treatment continuation. There does not appear to be a significant difference between IFN alfa-2a and alfa 2b with regards to these complications.

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Spectrum of Advanced Liver Disease in a Tertiary Care Institution

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Purpose: In population based studies, the rise of HCV infection has surpassed alcoholic liver disease (ALD) as the most common cause of chronic liver disease. However, it is unknown if HCV is becoming the dominant cause of advanced liver disease. The aim of this study was to determine the distribution of etiologies in a cohort of patients presenting with advanced liver disease.
Methods: A retrospective review of patients presenting with advanced liver disease defined as the presence of endoscopically identified esophageal or gastric varices for the period between January 1999 and December 2002. Etiologies of hepatic injury were identified from the clinical record and laboratory database. Patients were excluded if their disease could be attributed to more than one cause (i.e. alcohol & HCV) or had a non-hepatic cause of portal hypertension. Patients were grouped according to etiology: (1) HCV (2) ALD (3) hepatitis B (HBV) and (4) other (cryptogenic cirrhosis, non-alcoholic fatty liver disease, autoimmune hepatitis, portal vein thrombosis).
Results: A total of 411 patients were identified as having either esophageal and/or gastric varices. The mean age was 56.1 years (range 19–89). There were 275 males (66.9%) and 136 females (33.1%). The proportions of females in those with HCV and ALD were similar although women were predominant in non-viral, non-alcohol related disease group compared to other diagnoses (59.4% *vs.* 24.3%, $p < 0.0001$). Etiology of liver disease differed in those older than 65 years of age compared to younger patients for all diagnostic categories ($p < 0.0001$) with ALD being more prevalent than HCV in older patients ($p = 0.0120$). Race was evenly distributed amongst groups. Hepatitis C represented the single most common etiology (42.1%) followed by alcohol (29.9%), other predominantly non-viral, non-alcohol diagnoses (20.0%), and hepatitis B (8.0%).
Conclusions: Etiology of liver disease drastically differs in those older than 65 years of age compared to younger patients. Higher prevalence of ALD rather than HCV in elderly population alludes to different risk behavior pattern between the two groups (i.e., intravenous drug use more common in younger patients). For patients younger than 65 years of age**,** HCV is the major cause of cirrhosis and burden of complications of cirrhosis attributable to HCV infection should be expected to rise as this population ages.

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Plasma Factor VII May Increase the Sensitivity and Specifiicity of the APRI Score in Seperating Mild and Significant Fibrosis in Patients with Hepatitis C

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Purpose: Separating mild from significant fibrosis is an important step in the decision making process in treating and evaluating the prognosis of HCV patients. Liver biopsy remains the gold standard. The APRI*. is a recently proposed index (Wai et al. Hepatology; 38:518–526) that we have found to be accurate in both a retrospective and prospective study of patients with HCV undergoing liver biopsy at our institution. Cutoffs of ≤ 0.42 and ≥ 1.2 accurately identified patients with mild and significant fibrosis (Snyder et al

Gastroenterol 126:A-304, Snyder et al Am J Gastroenterol 99 S100–101). Rodríguez-Iñigo et al, found that the percentage of hepatocytes expressing Factor VII was significantly lower in stage 4 liver fibrosis patients than in stage 3, stage 2, stage 1 and stage 0 patients ($P < 0.001$). (Blood Coagulation & Fibrinolysis, 12:193). We hypothesized that addition of Facto VII measurement might enhance the sensitivity of the APRI.

*APRI = AST/ULN × 100/platelets(109/L)

Methods: The patients studied were 19 patients with chronic HCV undergoing pretreatment liver biopsies. Patients were excluded if they had received anti-viral treatment within the last year, if they were co infected with HBV or HIV, or had an organ transplants. All patients had blood drawn on the day of the biopsy. The Factor VII assay was run on the STA-R instrument (Diagnostic Stago Parsippany, NJ.) The APRI was calculated. The liver biopsies were read blindly by one pathologist using the Ludwig Batts criteria for staging of fibrosis. Analysis was performed using Insightful Miner 2 software (Insightful Corporation Seattle, WA.).

Results: One patient had an inadequate biopsy and two other patients did not have Factor VII measured because of inadequate specimen. Based on the biopsy results, there were 13 patients with significant fibrosis (F2–F4) and 5 patients with mild fibrosis (F0-F1). By logistic regression, the APRI had a sensitivity of 84.6% and a specificity of 60%. The combination of the APRI and Factor VII resulted in an improved sensitivity of 100% and a specificity of 100% in separating patients with significant fibrosis from patients with mild fibrosis.

Conclusions: Factor VII measurement may improve the sensitivity and the specificity of the APRI score in separating mild and significant fibrosis in patients with HCV. A larger number of patients is needed to evaluate this further.

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Post-Transplant Lymphoproliferative Disorder (PTLD): The Great Mimic in Liver Transplantation (LTx)

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Purpose: PTLD complicates all organ transplantation but the diversity of clinical presentation is often unappreciated, and may delay diagnosis. Therefore the current aim is to chronicle the clinical spectrum, histopathology and outcome of PTLD in LTx, and to relate these variables to the prior level of immunosuppression.

Methods: Retrospective analysis of LTx database at the Medical University of South Carolina 1–1990 through 5–2005.

Results: PTLD occurred in 23/621 (3.7%) LTx patients, 13m + 11f, mean age 43y (7mo-61y), interval 3 wks to 11y (mean 33mo) post-LTx.

Clinical Presentation: Common ($n \geq 1$)

Lymphadenopathy 5 (diffuse 3, focal 2)

Necrotic liver mass 5 (biliary stricture 1)

Lymphomatous ascites 3 (chylous 1)

Monoclonal gammopathy 2

Uncommon (1 each)

Skin nodules, biloma, hemolysis, breast mass, tonsillar lymphoma, malignant hydronephrosis, gastroduodenal ulceration, multiorgan failure

Of these: 1 patient had sequential Hodgkin and non-Hodgkin lymphoma, 1 diffuse Hodgkin lymphoma with persistent amyloidosis, 2 Burkitt's lymphoma, 1 large cell T cell lymphoma.

EBV infection was implicated in 13 (57%); 6 (26%) patients had steroid-resistant rejection and received antilymphocyte antisera. PTLD responded to treatment in 13 (57%) patients but led to death in 7 (30%) patients who did not respond; 3 patients are still under treatment.

Conclusions: PTLD, which is relatively common in LTx, has a diverse spectrum of clinical and histopathologic presentations that mimic other diseases. A low threshold of suspicion is needed to diagnose PTLD. Remission can occur with treatment in more than half the patients but there is also a high rate of fatality. Whereas EBV and antilymphocyte therapy may predispose to PTLD, these risk factors are not invariable.

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Differences in the Evaluation and Management of Hepatitis C Patients Seen by Gastroenterologists Compared to Hepatologists

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Purpose: The current study is a retrospective analysis of patients with HCV seen at a integrated health care system to determine differences in the management of patients seen by a gastroenterologist *vs.* a hepatologist.

Methods: The database of an integrated health care system was queried to identify hepatitis C patients. Between 1977 to present, 7588 patients over the age of 18 were identified who were hepatitis C antibody positive. Of these, 1793 patients were seen by 1of 5 hepatologists and 1696 were seen by 1 of 7 gastroenterologists. 150 patients seen by a hepatologist were randomly chosen and compared to 150 randomly chosen patients seen by a gastroenterologist. Chart reviews were performed on all 300 patients and data was collected on demographics including age, gender, alcohol use, route of transmission, HCV genotype and rates and results of liver biopsy. Data was collected on therapy including whether treatment was offered or accepted, rates of completion and dose adjustment, use of antidepressants and growth factors and rates of sustained virologic response (SVR). Differences were assessed using Fisher's exact test.

Results: Patients did not differ between the 2 groups by demographics including age, gender, social practices (alcohol and drugs), and genotype. Hepatologists were more likely to perform liver biopsy (55% v. 30%: $p < 0.001$) and hepatologists were more likely to perform the liver biopsy themselves (83% v. 40%: $p < 0.001$). Rates of bridging and fibrosis were comparable between the two groups (15% v. 17%). Gastroenterologists were at least as likely to offer therapy to their patients as hepatologists (72% v. 59%: $p = 0.091$). However, patients offered therapy by hepatologists were more likely to accept than patients offered therapy by gastroenterologists (80% v. 51%: $p < 0.001$) and more patients seen by hepatologists ended up receiving treatment (47% v. 37%: $p = 0.08$). There was no difference in the use of growth factors (3% v. 8%) and anti-depressants (20% v. 17%) between the groups. There were no difference in SVR between patients treated by hepatologists (41%) and those treated by gastroenterologists (38%: $p = 0.760$).

Conclusions: Hepatitis C patients seen by hepatologists were more likely to undergo a liver biopsy than those seen by gastroenterologists. Both gastroenterologists and hepatologists offered therapy at comparable rates but patients seen by a hepatologists were more likely to accept treatment. The rates of SVR were no different between the two groups.

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Endoscopic Argon Plasma Coagulation for the Treatment of Portal Hypertensive Gastropathy: Short Term Effects on Chronic Blood Loss

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Purpose: Argon plasma coagulation (APC) has been used to treat chronic blood loss from gastric antral vascular ectasia. Its role in the management of chronic blood loss and anemia in patients with portal hypertensive gastropathy (PHG) is not settled. The purpose of this study was to evaluate the use of APC for the treatment of chronic blood loss and iron deficiency in patients with PHG.

Methods: The study included 30 patients (17 post-menopausal females and 13 males, mean age 50.7 years) with liver cirrhosis, iron deficiency anemia and severe PHG diagnosed endoscopically. All had hemoglobin <10 gm/dl, with no active bleeding from varices within the previous 6 months. 18 patients had obliterated varices following endoscopic therapy, with the last session more than 6 months before inclusion, and 12 patients had varices that had not bled previously (7 grade 1 and 5 grade 2). Patients had APC sessions with multiple brief pulses delivered to all areas of visible angioectasias or red spots. Endoscopy was repeated after 3 weeks, and further sessions were performed as needed. Patients receiving blood transfusion or iron therapy

within the preceding 3 months were not included in the study. Response was assessed by change in hemoglobin and serum iron parameters over the following 2 months after completion of the sessions.
Results: APC was delivered in 1 session to 24 patients (16 fundal, 5 body, and 3 antral). Six patients had diffuse PHG with ectasia, 5 requiring 3 sessions and 1 patient requiring 4 sessions of APC. Hemoglobin, MCV, serum iron, and tranferrin saturation increased significantly over the following 2 months in all patients.
Conclusions: APC is a safe procedure for the management of PHG. Short term result show favorable response in controlling chronic blood loss and iron deficiency. Whether these results are sustained over longer periods is to be evaluated.

Mean Hemoglobin & Iron Profile

	Pre APC	1 Month	2 Months	p
Hemoglobin (gm/dL)	8.10 ± 0.95	8.86 ± 0.93	9.68 ± 1.07	<0.05
MCV (fl)	75.93 ± 3.45	78.06 ± 3.39	80.33 ± 3.95	<.0.05
Serum Iron (mcg/dL)	45.83 ± 6.18	58.56 ± 7.62	71.46 ± 12.3	<0.05
Total Iron Binding Capacity (mcg/ dL)	496.4 ± 21.1	482.4 ± 94.8	441.6 ± 31.2	ns
Transferrin saturation (%)	9.29 ± 1.66	12.66 ± 1.98	16.4 ± 3.41	<0.05

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Methionine Breath Test and Serum Clearance as a Diagnostic Tool in Chronic Liver Disease

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Purpose: It is well known that there is impaired methionine metabolism in patients with alcoholic and non-alcoholic liver disease (at a lesser level) due to defective hepatic mitochondrial oxidation. Patients with these liver disorders have hypermethionemia, prolonged methionine half life, and decreased plasma methionine clearance. The evaluation of hepatic mitochondrial function normally involves time consuming and composite testing. Despite extensive investigational efforts, there is no widely accepted investigational or diagnostic test to directly assess liver function. **Aims:** To assess the efficacy of methionine breath testing and serum clearance testing as tools for the diagnosis of liver disease in humans.
Methods: The non-radioactive ^{13}C-Methionine Breath Test was performed in healthy subjects (n = 10), patients with documented non-alcoholic steatohepatitis (n = 8), and alcoholic hepatitis (n = 5). Study subjects were recruited from General Clinical research Center at University of Louisville, and informed consent was obtained with IRB approved forms. After an overnight fast of 8hrs, vitals were obtained and initial evaluation was performed by one of the principal investigators, then baseline breath sample was obtained in commercially available sealed packed kit supplied by Metabolic Solution Inc. Later, subjects were asked to drink 200 mg of non-radioactive ^{13}C-Methionine dissolved in water, and 40 minutes later another breath sample was obtained. Both samples were sent to Metabolic Solutions Inc for analysis.
Results: Preliminary data from patients with severe alcoholic hepatitis/cirrhosis and non-alcoholic steatohepatitis with advanced disease showed reduced exhalation of non-radioactive ^{13}C as compared to normal control, but data for compensated liver disease have indeterminate findings.
Conclusions: It appears that the Methionine Breath Test may be useful in diagnosing and assessing improvement in progression of different stages of liver impairment. Further large scale studies are required to prove the efficacy of this non-invasive test in evaluation of hepatic mitochondrial function.

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N-2-butyl-cyanoacrylate for Gastric Varices—A Study To Determine Its Optimal Technique, Immediate and Long-Term Efficacy and Complication Rates

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Purpose: Fundal and isolated gastric varices are at high risk of bleeding and are a life-threatening complication of portal hypertension. Management of bleeding gastric varices has not been standardized but it has recently it has been shown that Cyanoacrylate injection therapy is safe with results comparable to patients treated with TIPS. Cyanoacrylate injection therapy becomes particularly relevant in Pakistan as TIPS or Liver transplant is not easily available. Our study was done to (1) evaluate the immediate and long-term efficacy of cyanoacrylate injection therapy (2) to evaluate the efficacy of injection of smaller amounts of cyanoacrylate at the time of initial endoscopoic examination with reinjection on an as needed basis only. This was expected to decrease the cost of the procedure significantly.
Methods: A prospective study conducted at the endoscopy unit of two tertiary care centers from January 2002 to December 2004. The data was collected by a formal questionnaire from the medical records and follow-up was done by outpatient visits, surveillance endoscopy, telephone calls and interviews of the patients. The data was analyzed using the SPSS 10.0 software.
Results: 38 patients underwent cyanoacrylate injection therapy for isolated gastric varices. 27 patients had bleeding gastric varices or signs of recent bleeding while 8 patients had elective Cyanoacrylate injection therapy. In 15 patients a 2:1 ratio of lipoidal and cyanoacrylate was used. In 6 patients 1:1, 3 patients a 3:1and in 2 patients a 4:1 ratio of the two agents was used. 1 patient had no lipoidal injected with 2 cc of cyanoacrylate being used. There was one mortality during the therapy session but all others were noted to have excellent post-procedure hemostasis. Amongst the 18 patients followed long-term, the cumulative rebleeding rates at 3, 6, 12 and 24 months were 6%, 12%, 18% and 24%. All the patients who rebled were controlled with repeat cyanoacrylate injection. 2 patients expired during the follow-up period due to unrelated causes.
Conclusions: (1) Cyanoacrylate injection remains an effective modality for control of bleeding from isolated gastric varices. (2) Smaller amounts of cyanoacrylate can also be effective in achieving good results with significant cost savings and lower risk of complications. (3) The overall complication rate is low and acceptable in a setting where TIPS or Liver Transplant is not a viable option.

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Demographics of Hepatocellular Carcinoma and Association with Alcohol Intake and Presence of Diabetes Mellitus among US Veterans. A Cross Sectional Analysis

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Purpose: Incidence of hepatocellular carcinoma (HCC) is on the rise in the US and around the world. In the US population rate of occurrence has doubled in the past two decades. The most common etiologies for HCC include viral hepatitis C and B, alcohol (ASH), non alcoholic steatohepatitis (NASH) and hemochromatosis (HC). Alcohol doubles the risk of HCC in chronic hepatitis C patients. The impact of NASH and ASH on HCC is largely unclear.
Methods: A database has been created to prospectively evaluate the interactions of HCV and DM/ metabolic syndrome in a population of male US veterans. Here we present the demographic data for a consecutive case series

of HCC patients and assess the prevalence of DM and alcohol abuse among veterans diagnosed with HCC.
Preliminary analysis of this data is presented.
Cross sectional analysis was performed on 53 veterans with diagnosis of HCC by biopsy or liver lesion with elevated AFP >500. Demographic clinical and laboratory data including viral hepatitis serologies, alcohol use, and presence of DM were evaluated.
SPSS version 13 was used for the statistical analysis.
Results: Of the 53 male veterans with diagnosis of HCC 50.9% were white, 18.9% were black and 22.6% were hispanic. For the entire cohort mean age (years) was 64.68 ± 2.68 (95%CI). 69.8% of patients had HCV, 57% were HBV cAb positive, while 4% had HBV sAg, 36.5% had HCV and evidence of exposure to B (cAb and/or sAg positivity), 5.8% of patients had NASH only, 20.8% had ASH only. 3.8% had HC. DM occured in 52.83% of this patient population and 64.15% of the patients had history of significant alcohol use. 32% of patients in this cohort had both DM and alcohol abuse as part of their history. Frequency of DM and/or alcohol abuse is found to be 84.9%. The mean $HgbA_{1c}$ among those with DM was 7.2 ± 0.61 (95%CI).
Conclusions: HCC in our veteran population is mostly related to HCV. A large proportion of veterans with HCC also have alcohol abuse and DM as comorbid conditions. Further studies are needed to evaluate the impact of alcohol and diabetes on the oncogenesis in the setting of HCC.
While our cohort is too small to show the statistical significance, we plan further investigations to evaluate the impact of ASH and NASH on oncogenesis in the setting of HCC, potentially modifiable contributors to this fatal disease.

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High Prevalence of Occult Hepatitis B in Patients with Advanced Liver Disease and Patients with Hepatitis C

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Purpose: Several reports indicated the higher prevalence of occult hepatitis B infection in patients with chronic hepatitis C, and that occult HBV might influence the clinical and biochemical features, and the severity of disease. This has not been studied among Egyptian patients with chronic HCV infection due to HCV genotype 4.
Aim: to evaluate the presence of HBV-DNA in HBsAg negative patients with chronic liver disease, and to correlate its presence with HCV infection, and with severity of liver disease.
Methods: 224 HBsAg negative patients with liver disease and 227 HBsAg negative and HCV negative individuals without liver disease had serum HBV-DNA tested using nested PCR by specific primers of surface antigen. All procedures were performed in duplicate. Patients were: 185 HCV genotype 4 positive (86 with liver cirrhosis, 58 with chronic hepatitis, 41 with persistently normal ALT) and 39 HCV negative (14 with liver cirrhosis and 25 with chronic active hepatitis).

Results: HBV-DNA was positive among 53 of 100 patients with liver cirrhosis (54% in HCV+ve vs 43% in HCV-ve, ns). Of these, 5 were serongative for all HBV markers. Similarly, in CAH, the prevalence of HBV-DNA did not differ among patients with and without HCV infection.

Group	#	HBV-DNA +ve
HCV+ve cirrhosis	86	
HCV+ve CAH	58	47 (54.6%)
HCV+ve PNALT	41	7 (12.1%)
HCV+ve Total	185	3 (7.3%)
HCV-ve cirrhosis	14	57 (30.8%)
HCV-ve CAH	25	6 (42.9%)
HCV-ve Total	39	1 (4%)
Liver Disease Total	224	7 (17.9%)
Control	227	2 (0.8%)

HBV was more prevalent among patients with liver disease than controls ($p < 0.001$, OR45, 95%CI: 11.59–382), among patients with HCV infection than controls ($P < 0.001$, OR50.1, 95%CI: 12.8–427)), and among patients with advanced than mild liver disease (cirrhosis vs CAH $p < 0.005$, OR8.78, 95%CI 3.4–25.2). No significant biochemical differences were observed among HBV-DNA positive or negative patients with similar stages of liver disease, and the Child-Pugh score and clinical indications of severity were similar among HBV-DNA positive and negative patients with cirrhosis.
Conclusions: Occult hepatitis B is highly prevalent among patients with hepatitis C and with liver disease compared to control, and the prevalence increases with advanced liver disease. Among patients with similar degree of liver disease the presence of HBV-DNA is not associated with increased markers of disease severity. The role of occult hepatitis B in the progression of liver disease remains to be identified in future studies.

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Pegylated Interferon alpha-2a (Pegasys) Versus Pegylated Interferon alpha-2b (Pegintron) in the Treatment of Chronic Hepatitis C Infection

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Purpose: Hepatitis C infection is a major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma. Highest overall end of treatment response (ETR) and sustained viral response (SVR) in chronic hepatitis C infection have been achieved with weekly sub-cutaneous injections of pegylated interferon alpha and ribavirin. However there have been no trials comparing Pegasys versus Pegintron in the treatment of chronic hepatitis C infection, when combined with standard doses of ribavirin. We conducted a retrospective study comparing the two drugs for the treatment of chronic hepatitis C infection.
Methods: 42 naïve hepatitis C patients from the Overton Brooks VAMC were divided into two groups, based on treatment with weekly subcutaneous injections of Pegintron (weight based regimen) or Pegasys (180 mcg). There were 32 patients in the Pegintron group and 10 patients in the Pegasys group. Both groups were treated with standard dose of ribavirin. Duration of treatment was 48 weeks for genotype 1 and 24 weeks for genotype 2 or 3. Both groups were matched for age, sex, weight, body mass index (BMI) race, and genotype. Outcomes were compared for ETR and SVR.
Results: There was no significant difference in ETR (70% *vs.* 71.9%, $P>0.99$), or in SVR (40% *vs.* 53.1%, $P = 0.47$) in both the groups. *P* values for covariates; weight, BMI, race, genotype, were tested by linear and logistic regression methods based on drug used and outcomes (ETR and SVR), and were not significant. *P* value for age was only significant (0.03) for ETR (Irrespective of drug used, greater the age, better the response) but not for SVR (0.5).
Conclusions: In naive patient with chronic hepatitis C infection, combination of Pegasys and ribavirin is no different than combination of Pegintron and ribavirin in achieving ETR and SVR

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A Case of Multiple Bile Duc Hamartomas (Von Meyenburg Complexes) with Suspicion for Malignant Transformation

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Purpose: Multiple bile duct hamatrtomas (Von Meyenburg complexes–VMC) are benign malformations of the bile ducts due to abscence of persistent remodeling of the embryonic bile duct network. It presents as diffuse, small, cystic lesions consisting of deformed bile ducts. VMC can be confused with metastatic disease on imaging studies and histologic examination

is usually required for diagnosis. Although VMC is thought to be innocuous, malignat transformation has been reported.
Methods: A 71 year old female with a 5-year history of right upper quadrant abdominal pain was found on abdominal CT scan to have multiple hypodense liver lesions. Routine labs were normal and the work up for chronic liver disease was negative. There was no evidence of primary malignancy elsewhere on imaging and endoscopic studies as well. A CT-guided biopsy was obtained from one of the lesions and it showed bile duct hamartomas. The patient presented to our clinic 3 years later with recurrent abdominal pain. A MRI of abdomen showed multiple small cysts throughout the liver and a 1.0 × 1.5 cm focus in the left lobe concerning for dysplastic nodule. The repeat liver function tests were normal, tumor markers CEA and AFP were normal, but CA 19–9 was elevated at 38 U/ml. A follow up MRI 2 months later showed unchanged size of the dysplastic nodule but another one 6 months later was much less suspicious for a dysplastic nodule. The absence of malignant transformation was also confirmed on a total body PET scan which did not show any abnormal focus of hypermetabolism, including in the liver. The follow up CA 19–9 showed levels of 119 U/ml and later 83.7 U/ml but since this tumor marker can be elevated in a wide variety of benign biliary diseases, we did not feel that this was due to malignat transformation of the bile duct hamartomas in the abscence of any other clinical, laboratory, and imaging data to support this.
Conclusions: Von Meyenburg complexes are seen frequently in the liver and are generally benign lesions. Although neoplastic transformation has been reported, a causative relationship has never been proven. We present our case to increase the awareness for possibility of malignant transformation and to emphasize the importance of following disease progression. In addition, VMC should be considered in the differential diagnosis of metastatic liver disease where histologic evaluation can help to avoid misdiagnosis.

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Safety and Tolerability of Double-Dose Peginterferon alfa-2b and Weight-Based Ribavirin for Non-Responders with Hepatitis C

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Purpose: Patients with hepatitis C who did not clear HCV RNA on interferon + ribavirin have only a 10–12% chance of a sustained viral response if they are subsequently treated with peginterferon + ribavirin. We have recently concluded the RENEW trial, comparing re-treatment with standard doses of peginterferon alfa-2b (PEG-2b) and ribavirin to re-treatment with a double dose of PEG-2b and ribavirin. The aim of this analysis was to compare the safety and tolerability of doubling the dose of PEG-2b while using weight-based ribavirin dosing.
Methods: There were 100 academic and community sites in the US. Particpants never cleared HCV RNA during previous interferon/ribavirin treatment. They were randomized to 48 wk of PEG-2b 1.5 or 3.0 mcg/kg/wk + ribavirin 12–15 mg/kg/day (800–1400 mg/day), stratified for sex, race, genotype, and fibrosis. Treatment was discontinued at 24 wk if HCV RNA was positive. Doses were reduced 33% for toxicity, based on modified NCI criteria. Growth factors were not allowed. The efficacy endpoint was SVR; safety endpoints were rates of dose reduction and discontinuation.
Results: 704 patients were confirmed to have started treatment, 352 in each group. Patients were 91% genotype 1, 70% male, 40% F3/4, and 16% Afr-Amer. Final analysis of efficacy is pending. Although there was a slightly higher frequency of dose reduction on the higher dose of PEG-2b, the rates of discontinuation were the same (Table). There were no clinically significant differences in the frequencies of fatigue, myalgia, nausea, depression, leukopenia, or thrombocytopenia.
Conclusions: (1) Among patients who never cleared HCV RNA on previous interferon +ribavirin, the safety/tolerability profile of PEG-2b 3.0 mcg/kg/wk, with ribavirin 12–15 mg/kg daily, is comparable to that of PEG-2b 1.5 mcg/kg/wk. (2) High-dose antiviral treatment is a safe strategy for patients with hepatitis C who are resistant to standard treatment.

Adverse Events

	1.5 mcg/kg	3.0 mcg/kg	P
Dose red. in first 12 wk	25%	33%	0.02
Dose reduction overall	37%	45%	0.04
D/C for adverse event	11%	13%	NS
D/C overall	35%	36%	NS
WBC at wk 24 (billion/L)	3.3	3.2	NS
Plts at wk 24 (billion/L)	162	159	NS

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Increased S-Adenosylhomocysteine (SAH) May Predispose to TNF Liver Injury in Human Alcoholic Liver Disease (ALD)

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Purpose: There are several potential mechanisms by which chronic alcohol may sensitize the liver to tumor necrosis factor (TNF) liver injury. SAH is a product of methionine in the transmethylation pathway, and is a competitive inhibitor of most methyltransferases. *In vitro* studies and *in vivo* animal studies have shown that elevated SAH, decreased s-adenosylmethionine (SAMe), and a low SAMe/SAH ratio are key elements sensitizing hepatocytes to damage from TNF in the setting of chronic alcohol exposure. There has not yet been an *in vivo* study documenting abnormal SAH metabolism in human subjects with chronic stable ALD.
Aim: Demonstrate any differences in SAH, SAMe, and SAMe/SAH ratios in stable ALD patients compared with non-alcoholic subjects.
Methods: Blood samples were collected in EDTA vacutainers from stable cirrhotic ALD subjects (n = 5) who had been abstinent from alcohol for at least one year, as well as from non-alcoholic volunteers (n = 10). Plasma concentrations of SAH and SAMe were assayed by reverse-phase HPLC by a modified method of Merali et al. (2000). SAMe and SAH were detected using a Waters 2487 absorbance detector at 254 nm. Standard solutions of SAMe and SAH were prepared in 4% MPA. An internal standard, S-adenosylethionine (SAE), was added to all samples and standard solutions to a concentration of 100 nmol/ml.
Results: Averaged values for cirrhotic patients, versus non-alcoholic volunteers, indicate elevated plasma levels of SAH in cirrhotics (3.54 nmol/ml, SD ± 1.31 versus 2.20 nmol/ml SD ± 0.46; $p < 0.05$), decreased levels of SAMe (0.12 nmol/ml, SD ± 0.05 versus 0.17 SD ± 0.01; $p < 0.05$), and a decreased SAMe/SAH ratio (0.048 ± SD 0.032 versus 0.079 ± 0.017; $p < 0.05$).
Conclusions: These data document significantly elevated SAH, as well as significantly decreased SAMe levels and SAMe/SAH ratios, in human subjects with ALD. This supports previous *in vitro* human cell line studies and *in vivo* animal studies implicating elevated SAH and depleted SAMe as mechanisms leading to TNF sensitization in hepatocytes in the setting of alcoholism. Although there are studies demonstrating that blocking TNFa can prevent alcohol-induced hepatocellular damage, future studies may examine whether liver damage can be prevented by reducing SAH levels or blocking hepatocyte exposure to SAH in the clinical setting of alcoholism.

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Histopathologic Features of Hepatic Steatosis in Patients with Hepatitis C Virus Genotype 3 Infection

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Purpose: Steatosis is frequently associated with chronic hepatitis C virus (HCV) infection. Studies have suggested steatosis associated with HCV genotype 3 infection may result from a viral etiology, evidenced by regression of steatosis following successful antiviral therapy. Histopathologic features that may distinguish viral from metabolic steatosis in this setting have not been well characterized. The aim of this study was to identify histopathologic features associated with HCV genotype 3 infection that may be attributable to viral steatosis in contrast to metabolic steatosis.
Methods: Liver biopsies from 26 treatment-naïve patients with chronic HCV infection were evaluated, including patients infected with genotypes 1 (n = 8), 2 (n = 10), and 3 (n = 8). Histopathologic features including the type, severity, and zonal distribution of steatosis, lobular inflammation, portal inflammation, and fibrosis in all biopsies were evaluated by a single pathologist who was blind to the clinical status of each patient. Clinical and demographic information was obtained from the medical record.
Results: Patient age, gender, race, weight, mean ALT levels, fibrosis stage, and necroinflammatory grade did not differ between genotypes. Genotype 1 patients had higher HCV RNA levels compared with genotypes 2 and 3 (p = 0.003). Overall, 13 patients (genotype 1, n = 4; genotype 2, n = 3; and genotype 3, n = 6) had significant macrovesicular steatosis (grades 2/3 and 3/3). The distribution of steatosis in genotype 3 patients was predominantly centrilobular, involving zones 2 and 3 (5/6, 83%), while steatosis occurring in genotype 1 and 2 patients was nonzonal (7/7, 100%; p = 0.005). Genotype 1 and 2 patients tended to have increased portal inflammation compared with genotype 3 patients (56% *vs.* 25%, p = 0.06). Increasing ALT levels correlated with lobular inflammation in genotype 3 patients (r = 0.76, p = 0.03) and with portal inflammation in both genotype 2 (r = 0.78, p = 0.01) and genotype 3 patients (r = 0.76, p = 0.03).
Conclusions: Patients infected with HCV genotype 3 have a predominantly centrilobular (zones 2 and 3) distribution of steatosis, while steatosis in genotypes 1 and 2 appeared nonzonal. Histopathologic differences in patterns and distribution of steatosis among different HCV genotypes may help in identifying features associated with viral versus metabolic hepatic steatosis.

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Hepatitis B and C Viral Markers among Family Members of Patients with Advanced Liver Disease and Occult Hepatitis B

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Purpose: The risk of infectivity of HBV is high among unvaccinated family members of HBsAg +ve patients. The risk among family members of patients with occult HBV remains unknown. The aim of this study was to examine the HCV and HBV serological markers and viral status of immediate family members of HBsAg –ve patients with liver cirrhosis.
Methods: 100 HBsAg –ve patients with Child C cirrhosis agreed to provide 4 consenting unvaccinated family members each for testing for markers of HBV and HCV infection, and biochemical and clinical parameters of liver disease. Patients and family members were tested for HBsAg, anti-HBs, anti-HBc, anti-HCV, HCV-RNA by PCR, and had serum HBV-DNA tested using nested PCR by specific primers of surface antigen.
Results: Family members were 25 spouses, 268 offsprings and 107 siblings. 86 Patients were +ve for HCV, 53 were HBV-DNA +ve (48 sero+ve and 5 sero-ve) and 17 were anti-HBc +ve and HBV-DNA-ve. Among the 400 family members tested, 122 had antibodies to HCV (30.5%), 49 were HBsAg +ve HBV-DNA +ve (12.25%), 13 (3.25%) had occult hepatitis B (all anti-HBc +ve). HCV +ve patients had 32% of their relatives +ve for HCV vs 21.4% of the relatives of HCV –ve patients (ns), and 13% of their relatives +ve for HBsAg vs 3.6% of the relatives of HCV-ve patients (p = 0.05). Patients with occult hepatitis B had 18.9% of their relatives HBV-DNA +ve vs 11.7% of the relatives of HBV-DNA –ve patients. Patients –ve for HBV and HCV markers had none of their relatives +ve for any HBV markers. HBV markers were not different among siblings, spouses and offsprings (HBsAg +ve in 16.8%, 10.1% and 16% respectively, ns; occult HBV in 6.5%, 1.9% and 4% respectively, ns). Spouses had significantly higher prevalence of HCV (56%) compared to siblings and offsprings (28% and 28.7% respectively). 58 Of 99 relatives +ve for HCV (58.6%) had biochemical and clinical indications of asymptomatic liver disease, vs 25 of 252 HCV negatives (10%) and 12 of 49 with HBsAg +ve(25%).
Conclusions: Family members of patients with HBsAg –ve chronic liver disease are at higher risk of being +ve for HCV than HBV. This risk is higher if the patient is HCV +ve than occult hepatitis B +ve, and is highest if both are positive. The routes of infection need be further studied. The high prevalence of HBsAg positivity in relatives vs occult infection is indicative that occult HBV is a stage in the disease progress of HBV infection.

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Improved SVR Rates in Southeast Asians with Chronic Hepatitis C Treated with PEG-Interferon and Ribavirin

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Purpose: To describe our HCV treatment experience with Southeast Asian (SEA) patients.
Methods: Retrospective cross sectional study of all SEA patients seen at a single center between 2001–2004. Inclusion criteria: 1. patients self identified as SEA (Vietnam, Cambodia, Laos, and Thailand) 2. Detectable quantitative HCV RNA (IU/ml) 3. Treatment naive 4. No coinfections. Genotype (GT) was done using the INNO-Lipa assay. High viral load (HVL) was defined as >600,000 IU/ml. All patients in cohort received standard PEG/RBV dosing. Patients were categorized as non-responders(NR), early virologic response (EVR), end of treatment response (ETR), relapse, and sustained virologic response (SVR). Standard patient pre-treatment demographics were collected. METAVIR histologic scoring was utilized.
Results: 25 SEA patients were identified; 11 were not treated (8 are still being evaluated; 2 were lost to follow up; 1 refused treatment) 1 is in the midst of therapy. The study cohort consisted of 13 patients that completed management. Age range was 19–67(mean 52). BMI range was19–31 (mean 24). EVR, ETR, relapse, and SVR rates are seen in the table.
6 patients with HVL achieved 83% SVR. 7 patients with a low viral load achieved 86% SVR. 3 of 13 patients discontinued treatment. 2 of whom still achieved SVR (1 stopped after 20 weeks due to psychosis had GT6, LVL, and stage 2 histology. 1 stopped after 5 weeks had GT1b, LVL, and refused biopsy). The patient that relapsed stopped at 24 weeks after developing influenza had GT6, HVL, and stage 3 histology. 5 patients required dose reductions (1 NR, 1 relapse, 3 SVR). Growth factors were used in 2 patients (1 relapse, 1 SVR). 1 patient with cirrhosis relapsed (GT1b,HVL).

Virologic Response

	N	EVR	ETR	Relapse	SVR
Total	13	100%	92%	15%	85%
GT 1	6	100%	100%	17%	83%
GT 2	4	100%	100%	0%	100%
GT 6	3	100%	67%	33%	67%

Conclusions: SEA patients have high rates of response to PEG/RBV treatment independent of genotype and viral load. Larger prospective studies are needed to confirm these findings.