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Hepatitis B and C: prevalence and social factors associated with

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APASL Abstracts, Bali 2005

APASL/Poster/Abstract/1
Expression of co-inhibitory molecules in PBMC from chronic hepatitis C patients

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We reasoned that B7-H1 and B7-H4, co-inhibitory molecules, may be involved in the defective T cell immunity to hepatitis C virus (HCV) in chronic hepatitis C (CHC) patients. First, we measured the expression profiles of B7-H1 and B7-H4 in unstimulated or stimulated PBMCs with PHA or LPS by FACS. The percentage of B7-H1-expressing unstimulated CD4+, CD8+ T cells, B cells, and monocytes was significantly increased in CHC patients compared to normal donors. However, B7-H4 expression appeared considerably high only in CD19+B cells and monocytes from CHC patients. In contrast, B7-H1 and B7-H4 expression in stimulated CD4+ and CD8+ T cells with PHA were upregulated in normal donors rather than in CHC patients, implying that a proliferating activity of T cells was inhibited by unknown mechanisms. We also examined the expression of regulatory molecules associated with tolerance such as immunoglobulin-like transcript 3 (ILT3), ILT4, TGF-β3, and indolamine 2,3-deoxygenase (IDO). Expression of all these genes was upregulated in CHC patients untreated with IFN-a/ribavirin compared with normal donors. The findings of high expression of co-inhibitory molecules, B7-H1 and B7-H4, and regulatory molecules associated with tolerance suggest that these molecules may be involved in the pathogenesis of chronic hepatitis C.

2
Abstract withdrawn

APASL/Poster/Abstract/3
Endoscopic mucosal resection of a long Barrett's esophagus with intramucosal cancer in a patient with decompensated HCV liver cirrhosis (Child–Pugh B) and esophageal varices (grade I)

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Endoscopic mucosal resection (EMR) has emerged as a viable alternative form of curative therapy to surgery for early esophageal cancers, especially in patients with a high surgical risk. One of the limitations of EMR is coexisting esophageal varices. We describe a case of intramucosal cancer in a 10-cm long segment Barrett's esophagus arising in a 63-year-old patient with esophageal varices (grade I) due to hepatitis C liver cirrhosis (Child–Pugh B). Early Barrett's cancer and esophageal varices were diagnosed during his pre-liver transplantation evaluation. To qualify for liver transplantation listing, the Barrett's cancer had to be treated but he was deemed to have too high a surgical risk on account of his cirrhosis and as such was referred for treatment with EMR. Prior to EMR, the portal system was decompressed by transjugular intrahepatic portosystemic shunting (TIPS). Complete ablation of Barrett's esophagus was then successfully achieved with circumferential EMR using the newly introduced multi-band ligation (MBL) technique (Duette Multi band mucosectomy kit - CE0123, Cook Ireland Ltd., Ireland) supplemented by snare resection using a 30-mm Erlangen-type polypectomy snare made of monofilament 0.28-mm-thick stainless-steel wire (Medwork, Germany) in five sessions. The total number of resected mucosa pieces was 25 and the size ranged from 0.3 to 2.4 cm^2. Histological evaluation revealed high-grade intraepithelial neoplasia (HGIN) and well-differentiated intramucosal cancer (IMC) (pT1 m2; G2). Bleeding from a small varix occurred only once during the first EMR session, and was controlled immediately by intravariceal injection with 0.5 ml of the *N*-butyl-2-cyanoacrylate (Histoacryl®): Lipiodol® mixture (0.5 ml: 0.8 ml). During the entire follow-up of 4 months, no recurrence of Barrett's esophagus or malignancy was observed. The patient is currently doing well and is awaiting liver transplantation.

APASL/Poster/Abstract/4
Long-term safety and efficacy of *N*-butyl-2-cyanoacrylate injection for bleeding fundal varices using a standardized injection technique

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Introduction: The tissue glue *N*-butyl-2-cyanoacrylate (CA) has been successfully used in many countries for the treatment of gastric fundal variceal (FV) bleeding. However, significant rebleeding rates and serious complications including embolism have been reported, which hinders approval in the US. **Aims:** To analyze the long-term safety and efficacy of CA for FV bleeding using a standardized injection technique and regimen. **Methods:** (1) 0.5 ml CA was mixed with 0.8 ml Lipiodol. (2) To minimize the risk of embolism, not more than 1.0 ml of CA–Lipiodol mixture was injected into fundal varices at any one time and repeated if necessary until hemostasis was achieved. (3) Simultaneous obliteration of all tributaries was carried out. (4) Endoscopy was repeated after 4 days to check for patent varices by palpation method to prevent rebleeding. **Results:** Fighty-eight patients with FV underwent endoscopic

obliteration with CA from 1994 to 2003. Eleven presented with active bleeding and 47 had elective sessions. Cirrhosis was present in 54 patients and non-cirrhotic portal fibrosis in 4. Initial hemostasis and eradication were achieved in all patients. The total number of sessions was 1.3 ± 0.5. The total volume of CA was 3.7 ± 2.3 ml. The cumulative rebleeding free rate at 1-, 3- and 5-year periods was 97.9, 93.9 and 78.0%, respectively. The cumulative survival rate at 1-, 3- and 5 year periods was 75.1, 51.7 and 40.8%, respectively. There was no procedure-related complication. Rebleeding free rate was not influenced by the type of FV or by liver function. However, mortality rate was significantly related to Child–Pugh class. **Conclusion:** Endoscopic obliteration with CA is safe and effective for treatment of bleeding FV. The side effects can be minimized by the standardized injection technique and regimen. Future studies of primary prophylaxis for gastric fundal varices with CA are warranted to prevent early mortality.

APASL/Poster/Abstract/5

May three to four months' treatment with pegylated interferon and ribavirin for chronic hepatitis C be an alternative basic therapy?

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Following the case of a woman, 60 years old with chronic C hepatitis, treated with interferon thrice a week and ribavirin 1000 mg daily, one can stop the therapeutic program after 4 weeks of treatment. When her qualitative serological marker was checked for its HCV RNA, the result was negative. These data suggest that it may be possible to treat chronic hepatitis C in a shorter time. Another reason is that Interferon is too expensive for our people. Based on these data, I tried to treat the patients in two groups: the first group consisted of those with type I virus and the other group had those with the other genotype virus. The first group was treated for 3 months and then the qualitative HCV RNA was checked. While we waited for the results from the laboratory, which took a month's time, the patients were still being treated. If the result was negative, it meant that the virus was negative in 3 months of treatment, but I still continued the treatment for a month then. The second group, which was of the other genotype, was treated with the regimen for 2 months and the qualitative HCV RNA was checked. While we waited for the results, the patients were still under treatment for a month. If the HCV RNA was negative, the patients still followed their regimen of treatment for 1 month. I realize there is the danger of relapse, but for economic reasons, treating the first group (genotype I) for 4 months and the second group for 3 months, is reasonable as an alternative basic therapy for chronic hepatitis C, particularly for a poor country. Certainly this study needs a longer time and many more patients.

APASL/Poster/Abstract/6

Liver diseases in private hospitals in Jakarta

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Background: Liver disease can be drug induced, caused by viral or bacterial infection, fatty infiltration, malignancy, etc. Hepatitis can be acute or chronic. Hepatitis may be drug induced or caused by viral or bacterial infection. **Patients and Methods:** This is a retrospective study. All data from the medical records of the liver disease patients related to viral hepatitis infection in three hospitals in Jakarta (Abdi Waluyo, Pluit, and St. Carolus) from the year 2001 to 2003 were included in this study. Incomplete data were excluded. Diagnosis of patients was made on the basis of history of illness, physical examination, supporting laboratory (liver function tests), liver ultrasound or CT-scan examination, and liver biopsy for chronic liver disease/hepatoma. The diagnosis of viral hepatitis infection was made according to the results of viral serological marker (IgM anti HAV, HBsAg, IgM anti-HBc, HBeAg, total anti-HCV, IgM anti-HCV) examinations. **Results:** There were 278 data of liver disease related to viral hepatitis infection patients from the year 2001 to 2003. The most frequent liver disease was acute hepatitis (55.39%). The characteristics of the patients were male (64.75%), mean age 39.38 ± 17.21 years old and Javanese (24.10%). In acute hepatitis, there was no correlation with sex ($P > 0.05$). The male patient was more frequent in the chronic hepatitis, liver disease, and hepatoma groups ($P < 0.001$). The mean age in the acute hepatitis group was less than in the chronic hepatitis, liver cirrhosis and hepatoma groups ($P < 0.001$). The hepatitis A viral infection was the most frequent cause of acute hepatitis in 121 patients (85.21%). The hepatitis C viral infection was the most frequent cause of chronic hepatitis (63.89%), liver cirrhosis (53.33%), and hepatoma/HCC (60%). **Conclusion:** The most frequent liver disease is acute hepatitis.

APASL/Poster/Abstract/7

Endoscopic retrograde cholangio pancreatography (ERCP) examination in patients with biliary obstruction due to common bile duct (CBD) stone

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Background: Biliary obstruction can be caused by CBD stone, CBD stricture, cholangio carcinoma, etc. In this study, we wanted to assess the role of ERCP examination (diagnostic and therapeutic) in cases with CBD stone. **Patients and Methods:** All patients with common bile duct stone found in ERCP examination from 2000 to 2004 were included in this study. This is a retrospective study, using the patients' medical records from Cipto Mangunkusumo Hospital and St. Carolus Hospital. **Results:** We found 67 patients with biliary obstruction due to CBD stone from 138 ERCP examinations. The most frequent complaint was jaundice in 44 (65.67%) patients. The most frequent age group is 40–49 years (29.85%). The biliary stones were found both in the CBD and the gall bladder in 18 (26.87%) patients. Sphincterotomy and stone extraction were done in 31 (46.27%) patients. Mechanical lithotripsy was done in 2 patients. Stenting was done in 17 (25.37%) patients. The failure of therapeutic ERCP was found in 13 (19.40%) patients. **Conclusion:** We frequently found CBD stones in biliary obstruction with ERCP examination. Therapeutic ERCP was successful in 80.60% of patients.

APASL/Poster/Abstract/8

Efficacy of analog of schizandrine C in management of acute viral hepatitis

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Background: Acute viral hepatitis is still the main health problem in many countries all over the world, including Indonesia, because of high incidence, morbidity, and mortality rates. Until now, there is no specific treatment for acute viral hepatitis. Management therapy is carried out by giving rest, a sufficient-calorie diet, and avoiding hepatotoxic drugs. Nowadays, scientists are interested in using alternative medicines such as herbal plants or phytopharmacy, which is already known as medicine for healing the liver after trauma or infection (hepatoprotector). **Objective:** To determine the efficacy of analogue of schizandrine C on acute viral hepatitis patients. **Patients and Methods:** This study was a double-blind controlled study. Sample was adapted based on simple randomization. Subjects were inpatients with acute viral hepatitis in Dr. Moh. Hoesin General Hospital, Palembang during July–December 2004, with age range 15–65 years; clinically, they had acute viral hepatitis A and B features, positive serologic markers (IgM anti-HAV for hepatitis, acute viral hepatitis A, HBsAg and IgM anti-HBc for acute viral hepatitis B) and agreed to participate in this study. **Results:** We had 39 acute viral hepatitis patients, 36 patients were included in the study and three patients dropped out. Out of 36 patients, 32 patients had acute viral hepatitis A, and 4 patients had acute viral hepatitis B. Subjects are divided into two groups by simple randomization; each group included 18 patients, composed of 16 acute viral hepatitis A patients and two acute viral hepatitis B patients. There were no significant differences on database characteristics of both groups ($P > 0.05$). Improvement on liver function parameters showed significant differences in both groups in the second, third and fourth weeks after treatment ($P < 0.05$). At the end of the fourth week, in group I, SGOT and SGPT levels declined and were 94.56% and 95.79%, respectively, and almost all patients achieved clinical improvement except for 1 patient who still had jaundice. In group II, SGOT and SGPT levels declined and were 79.29% and 83.80%, respectively, and eight patients still had jaundice, two of them with nausea, one patient with vomitus and one patient with epigastric pain. During this study period, there were no side effects found on using analogue of schizandrine C or worsening of the course of acute viral hepatitis patients in both groups. **Conclusions:** Analogue of schizandrine C improved the clinical healing and recovery period and also liver function parameters in acute viral hepatitis patients.

APASL/Poster/Abstract/9

Multistage stratified random sampling of HbsAg in rural area of Pagar Alam South Sumatra, Indonesia

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Background: The data available in gastroenterohepatology division of internal medicine department of Dr. Moh. Hoesin Hospital Palembang showed that hepatitis, liver cirrhosis and hepatoma patients with HBsAg positive mostly come from Pagar Alam town, South Sumatra, Indonesia. Therefore, the research was carried out in that town in order to know the prevalence and risk factors influencing the cause of hepatitis B in that particular area. **Methods:** A cross-sectional study was carried out from May to October 2004 in Pagar Alam, a mountainous area 350 km from Palembang. The subjects of the research were 1000 people taken by using the multi-stage stratified random sampling technique. **Results:** Mean age of the respondent was 38.9 years (range 65–72 years old), mostly 30 years old; the youngest was 17 and the oldest one was 95 years old. They had the following characteristics: female 52.1% (521 people), farmers 49.4% (494 people), elementary graduate, Basemah ethnic 62% (628 people). A total of 1000 subjects were examined: 71 people suffered from HBsAg positive (7.1%), 42 of them had HBsAg positive and 19 subjects had families with positive HBsAg. There were 71 subjects with HBsAg positive; the male to female ratio was 7.16%:6.9% but was not significant statistically. In terms of occupation 10.6% (67 subjects), had one permanent job, and most of them were junior high school graduates (11.5%). Pagar Alam ethnics have a 1.8-fold risk of getting infected by hepatitis B compared to other ethnics ($P = 0.04$). There was no statistically significant correlation among specific anamnesis, injection and tranfusion history and positive HBsAg ($P = 0.146$ and 0.146). The history of subjects with fever and icteric symptom and subjects with family jaundice history show a significant relation to positive HBsAg examination ($P = 0.03$ and 0.02). Multiple heterosexual subjects and drug users had a statistically significant relationship with hepatitis B prevalence in Pagar Alam ($P = 0.002$ and 0.001). Based on physical examination, there were 27 subjects suffering from icteric eyes (2.72%) and 54 subjects with hepatomegaly (5.4%). The HBeAg positive were 59.16% of HBsAg positive patients. **Conclusion:** Prevalence of HBV (positive HBsAg) was 7.1% in Pagar Alam. Risk factors of HBsAg positive in Pagar Alam were poor socioeconomics status and knowledge, HBV positive family members, sexual behavior, and drug user.

APASL/Poster/Abstract/10

Utility of serum α-fetoprotein in predicting survival of patients diagnosed with hepatocellular carcinoma

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Introduction: Hepatocellular carcinoma (HCC) represents the third most common cancer in the Philippines. α-fetoprotein (AFP) is a widely used marker to screen for early HCC. Its role in predicting survival has not been established. **Objective:** The aim of this study is to determine the utility of AFP in predicting survival among patients with HCC. **General Study Design:** Prospective cohort. **Participants:** All patients from 1997 to 2004 who were referred to our clinic due to liver mass and underwent liver biopsy were analyzed and followed up. **Analysis:** Demographic data, tumor characteristics and Child–Pugh Classification were analyzed and correlated with AFP levels using multivariate analysis. Patients were classified into Group I (AFP < 10 ng/ml) and Group II (AFP > 10 ng/ml). Kaplan–Meier method of analysis was used to determine the survival difference. **Results:** One hundred and four patients were included. Demographic data and tumor characteristics of the two groups were comparable. Group I ($N = 25$) had 1-, 3- and 5-year survival rates of 88%, 65% and 65%, respectively. Group II ($N = 63$) had a 1-, 3- and 5-year survival rates of 79%, 44% and 20%, respectively ($P = 0.60$). Furthermore, substratifying patients based on treatment showed no significant difference in survival rates between Group I and Group II ($P = 0.60$). **Conclusions:** sAFP is not a good predictor for survival of patients with HCC. Furthermore, it does not correlate with patient or tumor characteristics.

APASL/Free Paper/Abstract/11

Titers of antibody to Hepatitis B surface antigen after the implementation of expanded program on immunization in Cicalengka subdistrict Bandung

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To evaluate the immunologic response and the long-term protection provided by a Biofarma's yeast-derived recombinant Hepatitis B (HB) vaccine that was implemented by Expanded Program on Immunization since 1995, we examined titers of antibody to Hepatitis B surface antigen (anti-HBs) on 61 children aged 9–66 months old who were recipients of that vaccine in Cicalengka subdistrict Bandung West Java. Our sample consisted of 31 (50.8%) males and 30 (49.2%) females. All of the subjects had received three doses of intramuscular HB vaccine according to the recommended dose and schedule (the last dose was given at age 6). These subjects were divided into six age groups, i.e. 9, 18, 30, 42, 54 and months old, respectively. Blood samples were examined for anti-HBs using the Immulite Diagnostic Kit (Enzyme-linked immunosorbent assay). Mothers' HBsAg status were unknown. The geometric means of anti-HBs titers (GMTs) were calculated by taking the log of anti-HBs titers for each subject and then taking the antilog of the mean of these values. There was a high significant difference of the GMTs in all groups with the values 539.6, 62.0, 30.2, 119.7, 132.5 and 11.6 mIU/ml, respectively ($F = 5.998$; $P < 0.001$). A further analysis by the Duncan's mean difference test showed that significant groups were the first compared to the sixth group. To assess the association between the duration after immunization and antibody titers using the cubic regression formula, we had obtained the GMT's estimate of each group as 592.2, 44.7, 44.2, 108.1, 122.9 and 12.3 mIU/ml, respectively ($r = 0.585$; $P < 0.001$). The GMTs of anti-HBs after HB vaccination by Expanded Program on Immunization had fluctuated during 5 years after the last dose; seroprotective level had been obtained in 100% of the first group and 55% of the sixth group. However, all of the subjects with no protective anti-HBs titers remained protected against acute infection as well as chronic Hepatitis B carrier. It seems that immunologic memory remains intact up to 5 years after immunization.

APASL/Free Paper/Abstract/12
Association of Hepatitis C infection among thalassemic children with number of blood unit transfusions after donor blood screening in Hasan Sadikin General Hospital Bandung

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Introduction: Donor blood screening test for HCV antibody by third generation ELISA is widely used. However, there is still a window period during which a donor can be infected, but still have a negative screening test. The positive predictive value of this test is only 50–61% in patients who are at low risk for HCV infection. With PCR, this window period is reduced approximately to 12 days. **Objectives:** To find the association of HCV infection with the number of blood unit transfusions, and prevalence of hepatitis C infection in thalassemic children receiving screened donor blood. **Patients and Methods:** This was an analytic cross-sectional study. Sixty-seven children receiving third generation ELISA screened donor blood were examined for HCV antibody using UBI EIA 4.0 consecutively. The study was conducted in Hasan Sadikin General Hospital, Bandung, from January to March 2004. The prevalence of Hepatitis C was presented in percentage, and the association of HCV infection with the number of unit transfusions was presented using logistic regression analysis. **Results:** There was an association between the quantities of transfused blood and positive HCV antibody ($P < 0.001$). The magnitude of association was 1.08 for each blood unit transfusion. The prevalence of Hepatitis C in thalassemic children receiving third generation ELISA-screened blood was 22.4% (95% CI 12.4–32.4%). Comparison with the prevalence of HCV infection from previous studies before and after the advent routine screening for HCV using third generation ELISA (50.8% and 22.4%, respectively) showed significant difference by χ^2 ($P < 0.001$). **Conclusion:** There is an association between HCV infection and the number of blood unit transfusions, and donor blood screening test with third generation ELISA will decrease the prevalence of Hepatitis C infection among thalassemic children.

APASL/Free Paper/Abstract/13
Eupatilin, a pharmacologically active flavone derived from *Artemisia asiatica*, suppresses death receptor-mediated hepatocyte apoptosis

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Background: In cholestasis, bile acids induce hepatocyte apoptosis primarily via activating death receptor (DR)-mediated pro-apoptotic signaling cascades. Eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone), an active ingredient of *Artemisia asiatica*, has anti-oxidative and anti-inflammatory activities, and exhibits cytoprotective effects against experimentally-induced gastrointestinal, hepatic and pancreatic damage. **Objectives:** This study was conducted to examine if Eupatilin might modulate DR-mediated hepatocyte apoptosis. **Methods:** Huh-BAT cells, a human hepatocellular carcinoma cell line stably transfected with a bile acid transporter, were used in this study. Hepatocyte apoptosis was quantified using DAPI staining, and its signaling cascades were explored by immunoblot. MAPK signals were evaluated using immunoblot and their selective inhibitors. **Results:** Eupatilin significantly attenuated DR-mediated hepatocyte apoptosis, which was either induced by bile acid or TRAIL. Specifically, Eupatilin diminished bile acid-induced caspase 8 cleavage and subsequent activation of its downstream pro-apoptotic signals. The reduced caspase 8 activation was not due to the modulation of TRAIL-R2/DR5 expression levels. Instead, Eupatilin attenuated bile acid-induced activation of pro-apoptotic MAPKs including p38 MAPK and JNK. In particular, the Eupatilin-mediated inhibition of bile acid-induced JNK activation was responsible for the attenuation of caspase 8 cleavage. Contrary to Eupatilin, *N*-acetylcysteine, an anti-oxidant, did not affect the bile acid-induced pro-apoptotic signals. **Conclusions:** The results demonstrate that Eupatilin attenuates DR-mediated hepatocyte apoptosis by decreasing bile acid-induced pro-apoptotic JNK activation, independent of its anti- oxidative function. Therefore, Eupatilin might be therapeutically efficacious in a variety of human liver diseases associated with cholestasis.

14
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APASL/Poster/Abstract/18
Coadministration of albumin and furosemide for the treatment of cirrhosis patients with ascites and hypoalbuminemia
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Introduction: Hypoalbuminemia in cirrhosis patients often results in sufficient fluid accumulation to mandate diuretic therapy but is often resistant to diuresis. Studies have suggested that hypoalbuminemia itself diminishes the amount of albumin-bound furosemide and diminishes furosemide delivery to the ascending limb of the loop of the Henle. Therefore, administration of mixtures of albumin and furosemide may enhance diuretic and natriuretic responses. **Objectives:** The aim of this crossover study was to investigate whether albumin/furosemide mixture could increase the diuretic and natriuretic action of furosemide. **Patients and Methods:** Eleven patients with cirrhosis and ascites (age, 54.4 ± 16.5 years; Child–Pugh score, 10.2 ± 0.9; Child–Pugh class B/C, 2/9; serum albumin, 2.1 ± 0.4 g/dl; serum bilirubin, 1.3 ± 0.7 mg/dl; serum creatinine, 0.9 ± 0.3 mg/dl; serum ALT, 58.0 ± 27.3 IU/L) were enrolled in the study. Sodium balance was maintained throughout the study with a metabolic diet. All patients received spironolactone, but administration of all other diuretic agents was discontinued. Each patient received all of the following two treatments intravenously: (1) 40 mg of furosemide, (2) 40 mg of furosemide and 25 g of albumin premix *ex vivo*. **Results:** Both furosemide alone and albumin/furosemide mixture increased urine volume significantly as compared with each basal state (673 ± 254 ml/24 h vs 2273 ± 969 ml/24 h, $P<0.05$; and 818 ± 338 ml/24 h vs 3009 ± 907 ml/24 h, $P<0.05$). The volumes of urine between the two groups were of statistical significance ($P<0.05$). Sodium excretions were significantly increased in both groups, compared with each basal state (35.0 ± 22.1 mEq/24 h vs 161.5 ± 86.3 mEq/24 h, $P<0.05$; and 34.3 ± 20.5 mEq/24 h vs 192.0 ± 106.6 mEq/24 h, $P<0.05$). The amounts of sodium excretion between the two groups were of statistical significance ($P<0.05$). **Conclusions:** Albumin enhanced the diuretic and natriuretic effects of furosemide in cirrhosis patients with ascites and hypoalbuminemia. Therefore, the coadministration of albumin and furosemide for the treatment of cirrhosis patients with ascites and hypoalbuminemia should be consider clinically.

19
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20
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21
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APASL/Poster/Abstract/22
Prevalence of HCV genotype
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Background: Hepatitis C virus (HCV) genotypes are distributed differently depending on geography and etiology of infection. The incidence of HCV isolates found in clinical practice is of great clinical significance to the treatment of HCV infected patients as different subtypes may respond unequally to therapy. **Objectives:** To evaluate the prevalence of HCV genotypes in Vietnamese patients. Comparison of serum virus loads among patients infected with Hepatitis C Virus genotypes 1, 2, and 6. **Methods:** A total of 327 HCV RNA-positive patients with chronic hepatitis were enrolled (male 57.5%, female 42.5% with mean age of patients 47.9 ± 10.58 years) from April 2004 to January 2005. HCV genotypes were determined by LiPA (Bayer Corporation). At the same time, we collected 229 random serums in this group to perform Branched DNA for HCV RNA quantification. **Results:** Genotypes 1 and 6 were the commonest genotypes, followed by type 2, while the rare genotype 3 was found in a lone patient. Genotype 1 was seen in 58.4% (type 1: 5.8%; 1a: 6.4%; 1a/1b: 0.3%; 1b: 45.9%) genotype 6a in 23.9%, genotype 2 in 13.1% (type 2: 1.5%; type 2a/2c: 11.6%), and genotype 3b in 0.3%. 14 samples (4.3%) were unclassified. We then performed sequencing based on 5′UT with the Trugene system, identified genotype 1 (two cases), 1b (two cases), 2a (one case), 2c (one case), and 6a (eight cases) but not typed by LiPA. In all, 229 patients had viral loads. HCV genotypes 1, 2, and 6 had quantities of HCV above 2×10^6 copies/ml in 91, 18, and 32 cases, and below 2×10^6 copies/ml in 46, 15, and 27 cases, respectively. We observed no significant difference in virus load between patients infected with genotypes 1, 2, and 6 ($P>0.05$). **Conclusions:** Our study indicated that HCV genotypes 1 and 6 are common in Vietnam, while subtype 1b is the most common. A unique genotype 3b was detected in our patients. There is no relationship between HCV genotype and viremia levels. The TruGene system, a direct sequencing method, is more efficient in the identification of the HCV genotype.

23
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24
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APASL/Plenary/Abstract/25
Genotype C HBV has two subgroups with distinct epidemiological and virological characteristics
H. L. Y. Chan, S. K. W. Tsui, C. H. Tse, E. Y. T. Ng, T. C. C. Au, L. Yuen, A. Bartholomeusz, K. S. Leung, K. H. Lee, S. Lorcarnini and J. J. Y. Sung
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Background: Genotype C hepatitis B virus (HBV) is associated with more aggressive disease and possibly higher risk of hepatocellular carcinoma than genotype B HBV in Asia. **Objectives:** We aimed to investigate the characteristics of HBV genotype C subgroups in Hong Kong and its relationship

with HBV genotype C in other parts of Asia. **Methods:** Full-genome nucleotide sequences of 49 HBV genotype C isolates from Chinese chronic hepatitis B patients were compared with the sequences of 69 HBV genotype C isolates and 12 genotype non-C isolates in GenBank database. Phylogenetic analysis was performed to define the subgroups of HBV genotype C based on >4% heterogeneity of the entire HBV genome. **Results:** Eighty percent of patients in Hong Kong belonged to a subgroup predominantly found in Southeast Asia (Vietnam, Thailand, Myanmar and Southern China) designated as HBV genotype Cs and the remaining 20% of patients belonged to another subgroup predominantly found in the Far East (Korea, Japan and Northern China) designated as HBV genotype Ce. Overall, the number of differences in nucleotide sequence between HBV genotype Cs and HBV genotype Ce was $4.2 \pm 0.3\%$. Both genotypes Cs and Ce have over 8% nucleotide difference from other HBV genotypes. Comparing HBV genotype Cs and HBV genotype Ce among patients in Hong Kong, HBV genotype Cs was associated with a higher tendency to develop basal core promoter mutations (80% vs 50%, $P = 0.14$), C at nucleotide 1858 (95% vs 0%, $P < 0.001$) and fewer precore stop codon mutation (5% versus 50%, $P = 0.002$). On comparing with the reference amino acid sequences of other HBV genotypes, lysine at amino acid 85 in the terminal protein region of the polymerase gene was most specific for HBV genotype Cs, while lysine at amino acid 143 in the terminal protein region was most specific for HBV genotype Ce. **Conclusions:** We have identified two subgroups of genotype C HBV, namely genotypes Ce and genotype Cs, which have different epidemiological distributions and virological characteristics. Further research is required to investigate the clinical outcome associated with these two genotype C HBV subgroups.

26
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27
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APASL/Poster/Abstract/28
Prevalence of hepatitis C virus infection in health care workers
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Objectives: To investigate the prevalence of hepatitis C virus (HCV) infection in health care workers who work in Prof. Dr. R. D. Kandou Manado General Hospital and Bethesda Hospital in Tomohon. **Methods:** This is a descriptive study of 3 months (July–October 2002). Diagnosis of HCV infection was based on positive antibody of HCV by Entebe Dipstick Anti HCV. **Results:** We found 14 of 239 subjects (5.9%) infected by HCV. Distribution rates of HVC on medical nurses and non-medical nurses were 11 and 3, respectively ($P > 0.05$). Two (2.9%) and nine (13.0%) subjects, respectively, who worked in the ward and intensive care room were infected by HCV ($P < 0.005$). Four (3.6%) of 110 subjects who worked for <5 years, and 10 (7.8%) subjects who worked for >5 years were infected by HVC. The relationship between duration of working as nurse and prevalence of HVC infection was not significant statistically ($P > 0.05$). Nevertheless, there was a tendency of increased risk of HVC infection in health care workers who had worked >5 years as nurses. We did not find a relationship between contact frequency with prevalence of HVC infection, but subjects who worked >5 times with needlesticks showed 2.3 times higher transmitted HCV than those who had worked <5 times with needlesticks. There was a significant difference on health care workers who had worked >5 times with needlesticks with duration of working >5 years $P < 0.01$. **Conclusions:** There was no difference of HCV infection in medical nurses and non-medical nurses. We did not find a relationship between HCV infection and duration of working as nurse. Nevertheless, this study found a relationship between nurses who worked in the ward and intensive care room. **Suggestions:** Health care workers should universally take precautions during their duties in the hospital.

APASL/Poster/Abstract/29
Platelet count/spleen diameter ratio: can it predict the presence of varices in patients with cirrhosis of liver?
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Introduction and Objective: Ratio of platelet count and spleen diameter has recently been proposed as a predictor of the presence of esophageal varices in patients with cirrhosis. This study was carried out to evaluate the predictive value of this ratio for the presence of varices. **Patients and Methods:** One hundred and one patients with established cirrhosis and no history of variceal bleed were included. Diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic features. Data on physical examination, hematological, biochemical, and abdominal ultrasound examination were recorded for all patients. All patients underwent upper GI endoscopy. Varices were recorded as low- and high-grade. The presence of varices on EGD was correlated with platelet count/spleen diameter ratio. **Results:** Total number of cased included were 101, 54 of whom were males and 47 were females. Mean age of patients was 52.48 (± 11.11) years. Thirty-five patients were in Child–Pugh class A, 49 in Child class B and 17 patients in Child class C. Esophageal varices were seen in 65 patients while 36 patients had no varices. High-grade varices were seen in 15 patients and 50 patients had low-grade varices. Mean value of platelet count/spleen diameter in patients with varices was 798.09 compared to 617.08 in those without varices. Value of platelet count/spleen diameter ratio was not significantly different among patients with and without varices ($P = 0.117$). **Conclusions:** The ratio of platelet count/spleen diameter cannot be used to predict the presence of esophageal varices.

APASL/Poster/Abstract/30
Value of quantitative HCV RNA in management of chronic hepatitis C patients with genotypes 2 and 3
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Introduction and Objective: Viral load of hepatitis C virus is used to predict early viral response in genotypes 1 and 4. Its value in

predicting response in genotypes 2 and 3 is still questionable. This study was carried out to assess the value of quantitative PCR in genotypes 2 and 3 in predicting response to therapy. **Patients and Methods:** Patients with positive HCV RNA and genotypes 2 and 3 were included. Baseline liver function tests, complete blood count, clotting profile, viral load and liver biopsy were carried out. Viral load was checked by quantitative HCV RNA in all patients before commencing therapy. All patients were treated with standard interferon α-2b with ribavirin for 6 months. Patients with completed therapy were checked for sustained viral response 6 months after completion of treatment. Correlation between sustained viral response (SVR) and baseline viral load was determined using Student's *t*-test and χ^2 test. **Results:** Of the 55 patients included, six patients were of genotype 2 while 49 had virus of genotype 3. Male to female ratio was 1.11:1 (29/26). Mean baseline viral load was 4.8 million copies/ml. Fifty patients completed the treatment. Sustained viral response was seen in 31 patients while 19 patients were positive for HCV RNA 6 months posttherapy. Viral load at start of therapy was not significantly different in those with SVR compared to those with no response to therapy ($P = 0.478$). **Conclusion:** Viral load of hepatitis C virus at start of therapy is not predictive of response to combination therapy in patients with viral genotypes 2 and 3.

31
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APASL/Poster/Abstract/32
Real-time virtual sonography, an integrated system of computer tomography with ultrasound images: value in radiofrequency ablation guidance

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Background: Recently, the real-time visualization system that combines ultrasound cross section and CT has been invented and introduced into the clinical practice of hepatology. The system, Real-time Virtual Sonography, can display the same cross sectional view of US image with CT in real-time fashion using CT volume data. **Purpose:** We examined the feasibility and safety of percutaneous radiofrequency (RF) ablation guided by Real-time Virtual Sonography for hepatic malignancies.
Subjects and methods: Between September 2004 and November 2004, nine patients with 15 nodules have been treated using Real-time Virtual Sonography. The patient population included seven men and two women, with a mean age of 65.6 years. RF ablation was used to treat primary liver cancer in seven patients (78%); two patients (23%) were treated for metastatic lesions from colorectal adenocarcinoma ($n = 1$), and rectal carcinoid ($n = 1$). The maximum diameter of nodules ranged from 1.0 to 5.0 cm (mean ± SD; 1.8 ± 1.3 cm). Real-time Virtual Sonography can display a multi planar reconstruction (MPR) image, which indicates the same cross section as ultrasound image from the CT volume data in real time. The system is composed of an ultrasound scanner with probe, a PC that generates MPR image from CT volume data and magnetic positioning unit that detects the position of probe. During ultrasound scanning, the PC detects the position of probe by the using magnetic positioning sensor. After that, the PC generates an MPR image from the CT volume data and display. As a result, it became possible to compare ultrasound image with MPR image in real time. The cool-tip needle RF system was used for RF ablation. **Results:** The relationship between a tumor and surrounding vessels was easily recognized by referring to the image of virtual sonography in all nodules. The synergic effect which not only virtual MPR image helps understanding of US image but US helps understanding of CT image affected. The overall success rate in puncturing lesions that were unrecognized by US was 100%. Complete tumor necrosis was achieved in a single session in 13 lesions (86%), while two sessions were required for the remaining two lesions (14%). No serious side effects or procedure-related complications were observed. **Conclusion:** In our experience of 15 hepatic malignancies, Real-time Virtual Sonography-guided RF ablation could be used safely and successfully for hepatic masses. It even made possible treatment of hepatic nodules poorly defined on B-mode US.

APASL/Plenary/Abstract/33
Changes of expression of Toll-like receptors 2 and 4 in HepG2 cells before and after hepatitis B virus infection

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Background: Toll-like receptors (TLR) have been identified to mediate cell stimulation by microbial antigens. The recent discovery of the TLR family has focused attention on the disease processes as TLR mediate pathogen recognition and immune activation. However, only TLR2 and TLR4 were shown to transmit lipopolysaccharide (LPS) effects via immune signal transmittal. Recent publications show that regulation of TLR2, TLR4 and their associated downstream pathways are both involved and crucial for LPS tolerance. Regulation of TLR2 and TLR4 can affect a mechanism to modify LPS responses in patients with chronic endotoxemia due to liver diseases. However, more evidence has shown that endotoxin/lipopolysaccharide from the gut playsan important role in liver damage in chronic hepatitis patients. **Objective:** In order to explore the roles of TLR2 and TLR4 in hepatocyte damage after hepatitis B virus infection, and to discover whether LPS can affect hepatocytes without immuno-mechanism pre- and post-HBV infection, we detected the changes of TLR2 and TLR4 expression in human hepatocyte lines using HepG2 cells and 2.2.15 cells. **Methods:** HepG2 cells are most similar to normal human hepatocytes and 2.2.15 cells are HepG2 cells infected with HBV. We selected these two cell lines to study the differences of TLR2 and TLR4 expression between HepG2 cells before and after HBV infection. In this research, both HepG2 and 2.2.15 cells were stimulated with 1 μg/ml, 10 μg/ml, 100 μg/ml, 1 mg/ml and 10 mg/ml LPS. Then the expressions of proteins of TLR2 and TLR4 were examined by immunohistochemistry (IHC), the mRNA was examined by reversal transcription-polymerase chain reaction (RT-PCR), apoptosis was examined by flow cytometry (FC), and the expressions of HBsAg and HBeAg of 2.2.15 cells were tested with Abbott kits. **Results:** IHC and RT-PCR analysis revealed that TLR2 and TLR4 expressions were detected in both HepG2 and 2.2.15 cells. Moreover, without immune activation, TLR2 and TLR4 expressions were higher when the concentrations of LPS were higher. FC analysis revealed that no apoptosis was detected in HepG2 cells stimulated with LPS in this research, but apoptosis was detected in 2.2.15 cells when treated with the same factors. Furthermore, the apoptosis ratios increased with the increase in

concentrations of LPS. When concentrations of LPS were 1 μg/ml, 10 μg/ml, 100 μg/ml, 1 mg/ml and 10 mg/ml, the apoptosis ratios were 1.94%, 3.03%, 3.50%, 3.72% and 5.30%, respectively. Abbott analysis revealed that expressions of HBsAg and HBeAg of 2.2.15 cells stimulated with LPS were lower than those not stimulated with LPS ($P<0.05$). **Conclusions:** HBV can affect expressions of TLR2 and TLR4 in HepG2 cell lines. LPS can lead 2.2.15 cells to apoptosis but not HepG2 cells. Although LPS cannot damage normal hepatocytes, it might aggravate hepatocyte damage when their microenvironment is changed by HBV infection. Therefore, we feel the mechanism involved in this phenomenon needs to be identified through more research.

APASL/Poster/Abstract/34

Serum ALT levels do not correlate with response to interferon–ribavirin combination in patients with chronic hepatitis C

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Introduction and Objective: A significant proportion of individuals with chronic hepatitis C virus (HCV) infection have persistently normal alanine aminotransferase (ALT) levels. This study was conducted to see the effect of baseline ALT in chronic hepatitis C patients on response to interferon–ribavirin combination therapy. **Patients and Methods:** Patients with positive anti HCV and HCV RNA by PCR with no signs of decompensated liver disease were included. Depending on baseline ALT, patients were divided in two groups. One group with ALT below the upper normal limit and a second group with raised ALT (>1.5 times the upper limit of normal value). Both groups were treated with interferon and ribavirin therapy. All patients were evaluated for sustained viral response (SVR) at 6 months after treatment completion with HCV RNA by PCR. Both groups were compared for response to therapy with the χ^2 test. **Results:** The total number of patients was 70, 25 patients with normal ALT and 45 patients with ALT above the upper normal limit. Male to female ratio was 1.1:1 (37/33). Mean age was 35.61 (± 10.59) years. Sixty-three patients completed treatment. Sustained viral response (SVR) was seen in 35 patients. Comparison of patients with normal ALT and those with raised ALT revealed 13 of 25 patients with normal ALT and 22 of 45 patients with raised ALT. Difference in SVR in the two groups was not significant ($P=0.679$). When patients with raised ALT were sub-classified, a significantly better response was seen in patients with ALT twice the upper normal limit. ($P=0.021$). **Conclusions:** Patients with normal ALT level have a good response to combination therapy, equivalent to those with a raised ALT level.

APASL/Free Paper/Abstract/35

Cost–benefit analysis of living-donor liver transplantation (LDLT) timing in hepatocellular carcinoma patient within Milan criteria: an outcome-oriented decision analysis

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Background: Liver transplantation (LT) is the optimal treatment of hepatocellular carcinoma (HCC) and living-donor liver transplantation (LDLT) is an alternative way to overcome donor shortage. However, there are several problems for LDLT, such as the frequent complications and injury to the donor. Therefore, it is important to decide the timing of LDLT for HCC patients. **Aim:** The aim of this study is to determine the economical effects of LDLT for HCC patients with a Markov-based decision analytic model according to the times of LDLT. **Method:** (1) Between January 1994 and October 2004, 230 HCC patients within Milan criteria treated by resection and/or local ablation therapy were enrolled. We analyzed their liver functions and tumor parameters when there was HCC recurrence. (2) A Markov model was constructed simulating the natural history of HCC patients within Milan criteria. We compared the data following three strategies according to the times when LDLT was selected (''LDLT at first'' was defined as LDLT at the time of HCC diagnosis, ''LDLT at recurrence'' was defined as that when HCC was initially resected/ablated, and LDLT was performed at the time of recurrence with a strategy that did not select liver transplantation (No LT). Transition probabilities and all costs were drawn from published data. Simulation and analysis were performed using TreeAge pro 2004. **Results:** (1) Out of 230 HCC patients, 104 patients (45%) showed recurrence of HCC during the follow-up period. The number of patients within Milan criteria at recurrence and second recurrence were 81 patients (79%). (2) When we analyzed this model using our recurrence data, the life expectancy of each of the strategies was as follows: 9.9 years for LDLT at first, 9.6 years for LDLT at recurrence and 6.8 years for No LT. Incremental cost-effectiveness ratio (ICER) was $46,232 for LDLT at first and $34,864 for LDLT at recurrence, when we compared these with No LT. **Conclusion:** Primary local therapy and following LDLT at HCC recurrence is the cost-effective strategy for HCC patients within Milan criteria.

36

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APASL/Poster/Abstract/41

EGCG and resveratrol protect human hepatocytes (Hep G2 and Chang liver cells) from oxidative stress

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Backgrounds and Objectives: Increasing evidence regarding free-radical generating agents and the inflammatory process suggests that accumulation of reactive oxygen species (ROS) can involve hepatotoxicity, and direct oxidative injury serves as a general trigger for apoptosis in the liver. Although the underlying mechanisms remain incompletely understood, it is widely accepted that oxidative stress also plays a critical role in liver fibrogenesis. In this study, the protective effects of the antioxidants, epigallocatechin-3-gallate (EGCG) and resveratrol on oxidative stress in human hepatocyte Hep G2 and Chang liver cells were investigated. **Methods:** Cytotoxicity was measured by MTT assay. Intracellular oxidative activity was detected in dihydrodichloro-fluorescein diacetate (DCF-DA) loading cells by fluorescent spectrophotometer. GSH/GSSG ratio was measured with commercially available kit according to the manufacture's instructions. The lipid peroxidation and protein carbonylation assay kits were used to analyze oxidation damage to lipids and proteins. Cell cycle was analyzed by flow cytometry. The expression of cell cycle-related nuclear factors was analyzed by Western blotting. **Results:** Exposure to a concentration of 200 μM hydrogen peroxide or 500 mM ethanol induced cytotoxicities to hepatocytes, as shown by cell toxicity assay. Hydrogen peroxide and ethanol administration induced increases of ROS generation, lipid peroxidation and protein carbonylation either by enhancing the production of oxygen-reactive species and/or by decreasing the level of endogenous antioxidants. EGCG and resveratrol were found to reduce the ROS generation, lipid peroxidation and protein carbonylation in oxidative-stressed cells. They also prevented hepatocytes from depletion of GSH. Flow cytometric analysis revealed that both EGCG and resveratrol protect the cells from oxidative stress-induced cell death in appropriate conditions but Western blot analysis demonstrated that addition of EGCG and resveratrol upon oxidative-stressed cells led to marked reduction of mitotic Cdk (Cdk1). **Conclusions:** EGCG and resveratrol could prevent Chang liver and Hep G2 cells from oxidative damages of lipids and proteins caused by hydrogen peroxide or ethanol. They might inhibit the proliferative capacities of Chang liver and Hep G2 cells but protect them from oxidative stress-induced cell death.

42
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APASL/Poster/Abstract/43
Hepatitis B virus-neutralizing anti-pre-S1 human antibody fragments from large naïve antibody phage library

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We report the construction of a large nonimmunized phage antibody library in single-chain variable region fragment (scFv) format, which allowed the selection of antibodies that neutralize hepatitis B virus (HBV). We generated 1.1×10^{10} independent scFv clones using the cDNA of functional variable (V) gene segments of heavy and light chains purified from the peripheral blood mononuclear cells of 50 nonimmunized human donors. Using BIAcore, we selected two clones that recognized pre-S1 and neutralized pre-S1- and HBV binding of Chang liver cells. Clone G10 had the highest affinity ($K_D = 1.69 \times 10^{-7}$ M), which was higher than that of clone 1E4 that was generated previously from a heavy chain-shuffled antibody library. The off-rates of clones were within $10^{-3}\,s^{-1}$ as determined by BIAcore and are comparable to those of antibodies derived from a secondary immune response. In the inhibition assays of pre-S1 and virus binding to Chang liver cells using fluorescence-activated cell sorting and the polymerase chain reaction, G10 had better neutralizing activity than 1E4. The new phage library may be a valuable source of antibodies with reasonable affinities to different targets, and the anti-pre-S1 antibody fragment G10 may be a good candidate for immunoprophylaxis of HBV infection.

APASL/Free Paper/Abstract/44
Is Gilbert syndrome really more prevalent in schizophrenic patients?

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Background: Controversy exists on the issue of serum bilirubin in schizophrenia. Although the majority of published studies have demonstrated high prevalence of unconjugated hyperbilirubinemia in schizophrenic patients, none of these studies have investigated the *UGT1A1*28* polymorphism (a genotypic marker of GS in Caucasians). The aim of our study was to analyze both serum bilirubin and GS genotype in schizophrenic patients. **Methods:** Our study was performed on 88 patients with schizophrenia (56 males, median age = 39 years, 32 females, median age = 45.5 years) and 110 healthy age and sex-matched controls. Standard serum biochemical tests and *UGT1A1*28* polymorphism were determined in all subjects. **Results:** Substantially lower serum bilirubin levels were detected in schizophrenic patients than in controls ([median; 25–75% range], total population: 6.6; 4.9–8.5 vs 12.2; 9–15.6 μM/l, $P < 0.001$; males: 7.1; 4.8–9.4 vs 12.9; 9–16.8 μM/l, $P < 0.001$; females: 6.1; 5.0–7.4 vs. 10.3; 8.4–13.5 μM/l, $P < 0.001$). Similarly, the prevalence rates of GS genotype and bilirubinemia >17 μM/l were also markedly low in all schizophrenic patients vs controls (TATA box 7/7 = 9.1% vs 16.3%, $P = 0.196$ [not significant presumably due to low numbers of subjects], and 2.3% vs. 18.2%, $P < 0.001$, respectively). **Conclusions:** Patients with schizophrenia do not have higher prevalence of either the common *UGT1A1* polymorphism or hyperbilirubinemia above 17 μM/l. In contrast, they exhibit substantially lower levels of serum bilirubin levels. Since bilirubin is a potent antioxidant it seems that low levels of serum bilirubin may predispose patients to oxidative stress-mediated diseases such as schizophrenia.

APASL/Poster/Abstract/45
Prevalence and factors associated with insulin resistance among patients with non-alcoholic fatty liver: a prospective study

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Objective: To determine prevalence of insulin resistance among patients with fatty liver. **Methods:** The study employed a cross-

sectional survey design among adult patients with fatty liver seen at Cardinal Santos Medical Center for executive check up from September 2003 to September 2004 using a non-probability, purposive, prospective sampling. Ultrasound was utilized to detect patients with non-alcoholic fatty liver disease (NAFLD) who would be prospectively recruited using purposive sampling. Baseline sociodemographic and clinical data were collected. Insulin resistance (IR) was measured using the homeostatic model assessment for insulin resistance (HOMA-IR). Descriptive statistics was then employed to describe the cases and prevalence of insulin resistance was computed. **Results:** Of the 24 patients with NAFLD recruited for the study, 15 (67%) were shown to have insulin resistance (IR) as computed by HOMA-IR. Variables noted to be significant and confirmed using correlation coefficient by linear regression in contributing to IR among these patients included waist circumference ($P<0.009$), waist-to-hip ratio ($P<0.003$) and fasting insulin levels ($P<0.001$). **Conclusion:** Based on the initial data, prevalence of insulin resistance among patients with NAFLD was high at 62.5%. Factors associated with insulin resistance among patients with NAFLD include higher fasting insulin levels, bigger waist circumference and waist-to-hip ratio.

APASL/Poster/Abstract/46
Hepatitis E in rural England

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Introduction: Hepatitis E (HEV) is rare in developed countries and was previously thought to be confined to travelers returning from endemic areas. Recently there have been reports from a number of developed countries of HEV infection in non-travelers. However, the epidemiology of autochthonous (locally acquired) HEV infection (aHEV) in the developed world is unclear. **Objectives:** To evaluate the incidence and natural history of aHEV infection in Cornwall UK. **Methods:** Eighty-seven patients with unexplained hepatitis were tested for HEV over a 6-year period by HEV IgM serology and/or RT-PCR RNA assays. A case of HEV infection was defined as an ALT > 500 U/l and strongly positive HEV IgM serology (test: cut-off ratio > 5) or HEV PCR positive. **Results:** A total of 7/87 of patients tested was found to have aHEV infection, giving an incidence of 2.9 cases/million population/year. None of the cases had traveled to an endemic area. All patients were middle-aged or elderly (median age 63, range 48–81 years), and males were more commonly affected (M:F ratio 5:2). The range of expression of aHEV varied from asymptomatic anicteric disease to severe hepatitis requiring in-patient care. All patients recovered within 6 weeks except for one patient who died of an unrelated cause. None were vegetarian and two had regular contact with uncooked pork, including daily exposure in one patient who works as a butcher. All cases were caused by genotype III HEV, and in two cases the HEV RNA bore close sequence homology to genotype III HEV RNA isolated from a UK pig. **Conclusions:** The incidence of aHEV is 2.9/million/year. Unlike endemic HEV it causes a hepatitic illness in the middle-aged and elderly. The mode of transmission remains to be determined, but could be a zoonosis from a pig reservoir. aHEV is a Public Health issue in the UK.

APASL/Free Paper/Abstract/47
The expression of CD 137(4-1BB) and serum concentration of soluble 4-1BB (s4-1BB) in patients with hepatocellular carcinoma

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Background/Aims: The 4-1BB, a member of the TNF receptor superfamily, is expressed on activated T cells and antigen presenting cells. 4-1BB generates costimulatory signals, which involve T cell activation and proliferation, and tumor suppression. s4-1BB, which is generated by proteolytic cleavage or alternative splicing, inhibits biological activities of 4-1BB. High circulating levels of s4-1BB have been suggested to suppress immune response and this finding was observed in hematologic malignancy. In this study, we investigated expression of 4-1BB on peripheral blood mononuclear cell (PBMC) and serum concentration of s4-1BB in patients with hepatocellular carcinoma (HCC) and in healthy controls. We also analyzed correlations between s4-1BB concentrations and clinical characteristics of HCC patients. **Methods:** 4-1BB expressions on PBMC from 23 HCC patients and 24 healthy controls were analyzed by flow cytometry after stimulation with CD3. Serum levels of s4-1BB were measured by an enzyme-linked immunosorbent assay. **Results:** The expression of 4-1BB was significantly lower on PBMC of HCC patients than that of healthy controls ($10.35 \pm 5.3\%$ vs $23.08 \pm 6.73\%$; $P<0.01$). PBMC with $CD4^+4\text{-}1BB^+$ of HCC patients was higher than that of controls ($36.6 \pm 12.9\%$ vs $21.9 \pm 4.3\%$. $P<0.01$). But, PBMC with $CD8^+4\text{-}1BB^+$ was not different between HCC patients and controls ($30.2 \pm 13.1\%$ vs $25.3 \pm 12.1\%$; $P=0.18$). Serum level of s4-1BB was significantly higher in HCC patients than in healthy controls (4455 ± 2194 pg/ml vs 1575 ± 990 pg/ml). There was no difference in expression of 4-1BB and serum levels of s4-1BB according to the Child–Pugh classification. The s4-1BB levels in HCC patients were correlated with AFP levels ($r=0.64$; $P<0.01$). **Conclusions:** We have demonstrated low expression of 4-1BB and high level of s4-1BB in patients with HCC. These results suggest that poor costimulatory effects of 4-1BB may be associated with escape of immune surveillance in patients with HCC.

48
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APASL/Poster/Abstract/49
Association of hepatic fibrosis or inflammation with serum iron indices and hepatic iron concentration in patients with nonalcoholic fatty liver disease

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Background/Objectives: Nonalcoholic fatty liver disease (NAFLD) may progress to advance liver disease. Increased iron is suspected to enhance hepatic injury associated with NAFLD. The aims of this study are to evaluate the relation of serum iron indices and hepatic iron concentration (HIC) with hepatic fibrosis or inflammation, and to assess whether the increased HIC is an independent predictor of progression to liver fibrosis. **Methods:** The clinicodemographic, laboratory and

histopathological data on 31 subjects with a final diagnosis of NAFLD seen between July 2001 and March 2004 at our hospital were analyzed. Liver biopsy specimens were graded according to methods described by Brunt et al. Hepatic iron concentration was available in 25 NAFLD patients. **Results:** Liver biopsy specimens showed grade 1 and 2 inflammations in 12 (38.7%)patients and grade 3 inflammation in 2 (6.6%). It revealed stage 1 fibrosis in 10 (32.3%) patients and stage 2 fibrosis in 12 (38.7%). Advanced fibrosis (stage 3) was observed in 2 (6.6%) patients, but there was no cirrhosis. HIC and hepatic iron index (HII) were 1426–1188 μg/g dry weight and 0.79–0.69 μg/g/age. Serum ferritin and body mass index (BMI) were associated with hepatic inflammation (correlation coefficient = 0.591, 0.428, P value < 0.05, Spearman's correlation analysis). Serum ferritin, BMI and AST/ALT ratio were associated with hepatic fibrosis (correlation coefficient = 0.497, 0.437, 0.456, P value < 0.05, Spearman's correlation analysis). But, multivariate analysis did not identify serum ferritin, BMI, transferrin saturation, HIC as an independent predictor of hepatic fibrosis or inflammation (multiple logistic regression model). **Conclusions:** Hepatic iron accumulation had no correlation with the degree of hepatic inflammation or fibrosis. Thus, hepatic iron may not be an independent predictor of hepatic fibrogenesis in patients with NAFLD.

APASL/Poster/Abstract/50

Clevudine therapy for 24 weeks reduced serum HBV DNA levels and increased ALT normalization rates further than 12-week clevudine therapy

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Background: In a phase II clinical study (Hepatology 24;40:652A), clevudine 30 mg QD for 12 weeks was well tolerated and produced a potent antiviral activity during the dosing period and maintained a viral suppression through 24 weeks after the end of dosing. **Objectives:** The primary objectives of the study were to evaluate the safety and tolerability and to assess the antiviral activity of 24-week treatment with clevudine 30 mg QD. Biochemical and serological responses were also assessed. **Method:** All of 21 eligible patients received clevudine 30 mg QD for 24 weeks and were followed up for another 24 weeks off therapy. Eligible patients were HBeAg-positive chronic hepatitis B patients who had previously received placebo in the previous phase II 12-week treatment study and whose HBeAgs were not seroconverted to anti-HBe. The antiviral activity was defined as median log10 decrease from the baseline. **Results:** Median decreases from baseline in serum HBV DNA were 4.65 and 1.96 log10 copies/ml at week 24 (the end of treatment) and week 48(24 weeks off therapy), respectively. Analysis of individual data showed that serum HBV DNA levels were below the lower limit of detection (300 copies/ml) by Amplicor PCR assay in 19%, 57%, 19% and 0% at weeks 12, 24, 34 and 48, respectively. ALT levels were normalized in 67% at week 24 and the ALT normalization rates further increased after the cessation of therapy up to 81% at week 34 and then slightly decreased thereafter to 75% at week 48. The rates of HBeAg loss were 24 and 20% at weeks 24 and 48, respectively. Genotypic analysis did not show any mutation at the HBV *pol* domain except one (rt 183V/I); however, it was not associated with a viral breakthrough. **Conclusion:** Clevudine 30 mg treatment for 24 weeks was well tolerated with an excellent safety profile and exhibited more potent antiviral activity and a higher ALT normalization rate than 12-week treatment with durable vial suppression and normalization of ALT levels at week 24 off therapy.

APASL/Poster/Abstract/51

Estimation of intravenous frusemide-induced natriuresis for early detection of refractory ascites

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Background: Ascites is a common major complication of cirrhosis. About 5–10% patients of ascites eventually becomes refractory. Identification of patients who are refractory usually requires several weeks of observation with diuretics. **Objective:** To exploremethods for earlier detection of refractory ascites. **Materials and Methods:** This study is a prospective study. Consecutive patients of cirrhosis with ascites were included in the study, which was carried out during the period from January 2001 to January 2003. All the patients were kept on low sodium diet and all diuretics were withdrawn for 3 days. Then 24- h urinary sodium was estimated. Patients having 24-h urinary sodium excretion less than 50 mmol were included in the study. Eighty milligrams frusemide was then injected intravenously. Urine was collected for 8 h for measurements of sodium and < 50 mmol were suspected refractory ascites group and > 50 mmol were responsive group. Both the groups were followed with oral diuretics therapy. **Results:** A total of 30 patients of cirrhosis with ascites, 24 male and six female, were included in the study. Cirrhosis was related to hepatitis B virus in 22 patients, hepatitis C virus in two patients and six patients were non-B, non-C related. All the patients were in Child B and C grade. The intravenous injection of frusemide was not associated with any adverse effect. There were no significant differences between two groups for age, sex, etiology of liver disease and Child–Pugh score. At the end of the study, 24 patients were detected as responsive ascites and six patients were detected as refractory ascites with oral diuretics. But the prediction was 27 and three with frusemide injection. **Conclusion:** The present study showed that 50% of patients with refractory ascites could be identified reliably by this method. The availability of a simple test that can be administrated in a day care unit. We recommend further study of a larger group with this test.

52

Abstract withdrawn

APASL/Poster/Abstract/53

Interventional US on liver diseases, diagnostic, and treatment

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Many liver diseases, diagnosed by ultrasound or by clinicians, need more information for an accurate final diagnosis and adequate treatment as well. As Color Doppler, 3D and 4D not always could provide an accurate diagnosis, interventional

US (IUS) is the procedure of choice. For these purposes, various types of needles and procedures are available which are convenient for the patients as well as for the operator. In Graha Medika Medika hospital, during the last years, IUSs were performed in 24 liver diseases, 22 HCC, six cysts and 31 abscesses. The samples were sent to pathologists for histological or cytological study or both. More accurate treatment or surgery could then be realized. During US follow-up after treatment or surgery with conventional US, color Doppler and/or 3D/4D, a second or more IUS could be performed, as needed, before arriving at final complete healing. In conclusion, performing IUS is necessary to establish an accurate final diagnosis and treatment with convenient techniques that areeconomical and could replace surgery.

APASL/Poster/Abstract/54

The role of zinc, copper, ratio Cu/Zn, and lymphocytes in liver cirrhotic and hepatocellular carcinoma patients

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Background: Hypozincemia has been described in many chronic liver diseases including liver cirrhotic (LC) and hepatocellular carcinoma (HCC). The hypozincemia is always followed by hypercopperemia and the ratio Cu/Zn increased as the malignant process prediction. The hypozincemia has a place in immune function impairment and encephalopathy caused by a malnutrition status. The hallmark of protein–calorie deficiency and zinc deficiency are thymic atrophy and lymphopenia. **Objective:** Exploring hypozincemia and the increase in ratio Cu/Zn as the predictor of malignant process in HCC and LC patients. Studying the role of hypozincemia and lymphopenia as predictors of immune function impairment and encephalopathy. **Design:** A cross-sectional study was conducted with subjects from inpatient and outpatient Gastroentero-hepatology Department, Dr. Sardjito Hospital, Yogyakarta, Indonesia. The study was carried out from March to August 2004. Diagnosis of LC is performed by ultrasound and clinical examination, and diagnosis of HCC is performed by α-fetoprotein, ultrasound and fine needle biopsy. Measuring of zinc and copper serum by spectrophotometer atom absorber (SAA). Hepatic encephalopathy was predicted by numeric connection test (NCT). Data were analyzed with computer system (*t*-test, Wilcoxon rank test, and linear regression). **Results:** Total LC patients are 20 (four patients Child–Pugh A; six patients Child–Pugh B; 10 patients Child–Pugh C). Total HCC patient are 15. There is no difference of age and sex between HCC and LC patients ($P > 0.05$). The decreasing of zinc serum in LC patients is significantly heavier than in HCC(LC 48.97 ± 8.74 μg/dl; HCC 35.89 ± 40.45 μg/day; $P = 0.012$; normal Zn = 50–150 μg/dl). The increasing of copper serum in LC patients is not different compared with HCC patients (LC 131.99 ± 24.85 μg/day; HCC 126.50 ± 32.75 μg/day; $P > 0.05$; normal Cu = 100–200 μg/dl). The ratio Cu/Zn in KHS is significantly higher than in LC patients (8.57 vs 3.15; $P < 0.05$; cut off 1.15). The total lymphocyte counts in LC and HCC patients are not different statistically ($P > 0.05$), but the leucocyte count in HCC is higher than in LC (12.9 vs 7.8; $10^3/mm^3$: $P = 0.26$). By non parametrical analysis, there are correlations between lymphopenia–hypozincemia and increasing Cu–lymphopenia both in LC and HCC patients, with $P < 0.05$. There are correlations between hypozincemia-encephalopathy and increasing of NCT-hypozincemia in LC patients, with $P < 0.05$. **Conclusions:** Our data indicate that hypozincemia and increasing of ratio Cu/Zn may occurr in LC and HCC patients as a predictor of malignant process. Decreasing immune function may be predicted by lymphopenia combined with hypozincemia, and occurring of encephalophaty may be correlated with hypozincemia too.

APASL/Poster/Abstract/55

Detection of hepatitis B virus DNA on filter paper: comparison between serum and whole blood

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Hepatitis B virus infection is still a major public health problem in Indonesia. More than 11 million people have been infected by this virus. To provide good treatment for HBV infection, as the first step we need to detect HBV DNA. However, detection of HBV DNA can be done only in big cities because geographical limitations have caused some difficulties in transporting blood samples in Indonesia. The goal of this study is to prove that HBV DNA can be detected from serum or a whole blood sample that is dried on filter paper, which makes it easier to transport a specimen to the laboratory. We examined 20 serum and whole blood samples with positive HBV DNA. These samples had been quantified with COBAS AMPLICOR HBV Monitor reagent and dripped on filter papers. We used Nested-PCR method for detection of HBV DNA. A comparison was made between serum and blood samples. Out of 20 specimens, we got 100% positive results on serum and 75% on whole blood, with the quantitative result lying between log 2 and >log 5. In conclusion, examination of HBV DNA with the Nested-PCR method on filter paper was better when using serum than when using whole blood samples.

56

Abstract withdrawn

57

Abstract withdrawn

APASL/Free Paper/Abstract/58

Malaria with hyperbilirubinemia in Minahasa, Indonesia

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Background: Malaria remains the most important parasitic disease in the world, including Indonesia. In Minahasa, North Sulawesi, jaundice is the most frequent presentation found in severe malaria patients. **Objectives:** To explore the features of malaria patients with hyperbilirubinemia, and its correlation with other complications. **Methods:** A retrospective study was performed by collecting data of severe malaria patients treated at the Bethesda Hospital and Gunung Maria Hospital in Minahasa, North Sulawesi from January 1991 until December 2000. Statistical analysis was carried out using the *z* test, χ^2 test and *t*-test for regression. **Results:** In the period of 10 years, there were 271 severe malaria patients treated at these two hospitals.

Of 271 severe malaria patients, 209 patients (77.1%) had total bilirubin level > 1 mg/dl and 147 patients (54.2%) fulfilled WHO criteria for jaundice (total bilirubin level > 3 mg/dl). Total bilirubin level ranged from 1.01 to 36.40 mg/dl with mean value 6.64 mg/dl. Mean conjugated bilirubin level was 3.99 mg/dl and mean unconjugated bilirubin level was 2.65 mg/dl. Malaria with hyperbilirubinemia was frequently accompanied with renal dysfunction/acute renal failure (56.9%). Mean SGOT level was 57.8 IU/l and mean SGPT level was 37.9 IU/l. Mean alkaline phosphatase level was 176.5 IU/l. There were significant positive correlations between total bilirubin level and SGOT, SGPT, alkaline phosphatase, creatinine levels, parasite count ($P < 0.05$) and significant negative correlation between total bilirubin level and platelet count ($P < 0.05$). There was no correlation between total bilirubin level and level of consciousness (GCS), hemoglobin level and reticulocyte count ($P > 0.05$). Mortality rate was 17.2% (36/209). There was no correlation between total bilirubin level and mortality rate, although the highest mortality rate was found among patients with total bilirubin level > 10 mg/dl (32.6%) and those with three or more complications (40.4%). There was no significant difference in the efficacy of parenteral quinine and artemether used in treating severe malaria patients (86.8% vs 86.2%; $P > 0.05$). **Conclusions:** Malaria with hyperbilirubinemia/jaundice is the most common complication of severe malaria patients in Minahasa, Indonesia. Total bilirubin level correlates positively with SGOT, SGPT, alkaline phosphatase, creatinine levels and parasite count, but it correlates negatively with platelet count. Liver parenchymal disorder and cholestasis seem to play a more important role compared with hemolysis in the development of jaundice in severe malaria patients. More than 50% of hyperbilirubinemia patients develop accompanying acute renal failure. The mortality rate of hyperbilirubinemia patients is 17.2%.

APASL/Poster/Abstract/59

Protective effect of captopril and losartan against liver cell injury induced by paracetamol, CCL_4, and ethanol in rats

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Background: ACE-inhibitor and angiotensin receptor blockers have been shown to be protective against ischemia-reperfusion injury in various tissues including heart and liver. **Aim:** The present study was aimed to evaluate whether inhibition of renin-angiotensin system (RAS) by captopril and losartan also protective against liver cells injury induced toxic dose of paracetamol, CCl_4, and ethanol. **Methods:** Fifty four male Sprague-Dawley rats of 200–250 g BW were devided into 3 groups of 18 rats. The first group was given a single dose of paracetamol 2500 mg/kg p.o, the second group received a single dose of CCl_4 2 mg/kg p.o, and the third group received a four days administration of 10 ml/kg/d of ethanol solution with escalating concentration (35%, 50%, 60%, and 70%). Each group was further devided into 3 subgroups each receiving pretreatment with aquadest (10 ml/kg/d) for 3 days (control group), captopril 2 mg/kg/d for 3 days, or losartan 4 mg/kg/d for 3 consecutive days prior to paracetamol or CCl_4. For those receiving ethanol, captopril and losartan were given for 4 days. One day after administration of the toxic substances, laparotomy was performed under pentobarbital anesthesia. Blood samples were withdrawn from vein cava for the measurement of SGOT and SGPT level representing the parameter of liver inuury. The liver was excised for MDA measurement as the parameter of oxidative stress. One way ANOVA or Krusskal-Wallis were applied (as appropriate) for between group comparison. **Results:** Mean ± SD of SGOT, SGPT, and liver MDA levels in control (Ctl) and captopril- and losartan protected groups are shown in the following table:

Groups Subgroups	Paracetamol			CCl4			Ethanol		
	Ctl	Capt	Los	Ctl	Capt	Los	Ctl	Capt	Los
SGOT	212.8	100.2*	102.8*	285.2	179.6*	144.5*	116.3	91.7*	90.8*
(U/l) ± SD	54.3	10.2	7.8	39.5	18.4	45.3	2.6	5.4	8.6
SGPT	216.3	71.7*	90.2*	272.2	161.0*	156.9*	58.6	46.6*	46.5*
(U/l) ± SD	63.8	14.4	34.6	3.8	47.8	40.9	2.9	4.3	4.4
MDA ± SD	24.4	16.7*	15.9*	47.9	26.1*	27.4*	34.1	18.9*	20.0*
(nmol/ml)	3.5	1.9	3.3	9.1	4.8	2.4	5.9	3.3	2.7

*$P < 0.05$ versus respective control groups.

Conclusions: Reduction of SGOT and SGPT levels indicated that captopril and losartan have protective effects against liver injury induced by paracetamol, CCl_4, or ethanol. Reduction of MDA levels suggests that this protective effect is (at least partly) mediated by antioxidant effects RAS-inhibition.

APASL/Free Paper/Abstract/60

Protective effect of renin–angiotensin system inhibition on ischemic reperfusion of the liver

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Aim of the Study: Inhibition of the renin–angiotensin system (RAS) by ACE-inhibitors or angiotensin receptor blocker (ARB) has been widely used in the treatment of myocardial infarction. In the following study, the influence of RAS blockade on ischemic reperfusion injury of the liver was evaluated as a preliminary model to further learn the role of RAS in liver failure such as that encountered during multiple organ failure. **Methods:** Thirty male Wistar rats weighing 200–250 mg were divided into five groups of six rats. Ischemic reperfusion was performed by a 30-min ligation of the portal vein followed by 30 reperfusions *in situ*. All procedures were performed under anesthesia with intraperitoneal injection of penthobarbital sodium (60 mg/kg). ALT and AST were measured from the plasma before and after ischemia as indicators of liver damage. Malondialdehyde (MDA) and superoxide dismutase (SOD) were assayed from liver homogenate after the reperfusion period, and were taken as the parameters of free radical attack. The control group underwent ischemic reperfusion without previous treatment. Treated groups received Captopril 2 mg/kgBW/day, Benazepril 0.1 mg/kg BW/day, Valsartan 4 mg/kgBW/day or *N*-acetyl cystein (NAC) 15 mg/kgBW/day for three consecutive days before the procedure. **Results:** The table shows the results of ALT, AST, MDA and SOD.

	Control		Captopril		Benazepril		Valsartan		NAC	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
ALT	54.46	**348.5**	42.55	**60.03**	65.69	**83.84**	82.86	**75.27**	55.53	**62.90**
± SE	6.57	33.99	7.49	5.78	7.85	8.09	6.02	5.49	3.33	9.43
AST	23.01	**306.25**	31.8	**41.34**	56.61	**67.85**	72.97	**67.22**	31.81	**39.36**
± SE	2.12	17.18	5.52	5.53	7.90	16.32	4.0	6.11	3.62	4.90
MDA		11.64		7.24		8.21		9.03		9.83
± SE		0.65		0.64		0.79		0.57		0.66
SOD		19.52		11.60		12.99		17.86		12.80
± SE		1.34		1.50		1.80		1.92		1.91

It is concluded that 1. ACE-inhibitor and ARB reversed the increase of ALT and AST after ischemic-reperfusion to a value approaching baseline level. 2. The reduction of MDA and SOD suggests that the protective effect of ACE-I and ARB is mediated by the antioxidant effect of these substances.

APASL/Free Paper/Abstract/61

Functional roles of ubiquitin hybrid genes in hepatoma cell proliferation and apoptosis

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Using the cDNA microarray method, we found that the ubiquitin–ribosomal protein hybrid genes, *Uba80* and *Uba52*, were preferentially expressed in hepatocellular carcinomas compared with corresponding nontumor samples. This overexpression seems to be correlated with tumor cell proliferation (cell-cycle progression). However, the ubiquitin hybrid genes are further overexpressed during tumor cell apoptosis induced by various apoptogenic agents. Cells that ectopically overexpress Uba80 or Uba52 show a higher susceptibility to apoptosis and are even occasionally induced to apoptosis when cultured in the absence of apoptogenic agents. Apoptogenic insults enhance the nuclear targeting of ubiquitin–nibosomal proteins and elicit the aggregation of ubiquitin proteins in the nucleus during the early stage of apoptosis. However, further insult results in a decrease in histone ubiquitination, and, subsequently, to the abnormal ubiquitination of the nuclear envelope, and a change to an apoptotic cell morphology during the late stage of apoptosis. Each fused nibosomal protein may function as a carrier for rapid nuclear targeting and is localized in nucleoll. These results suggest that ubiquitin hybrid genes may be associated with tumor cell proliferation, but are further targeted during apoptosis and are responsible for the abnormal ubiquitination of the nuclear envelope instead of nucleosomal histones.

62

Abstract withdrawn

APASL/Free Paper/Abstract/63

Characteristic clinical features of sarcomatoid hepatocellular carcinoma: a suggestion of a different carcinogenic process from trabecular type of hepatocellular carcinoma

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Background/Aims: Although the histological characteristics of sarcomatoid type of hepatocellular carcinoma (scHCC) have been occasionally reported, the clinical features of patients with scHCC are still unclear. Thus, in this study, we analyzed the clinical and radiological features of scHCC, comparing it with trabecular HCC (trHCC), which is the most common histological type, to get an insight into the biology of it. **Methods:** Fifteen patients with scHCC who were diagnosed at our institution from August 1997 to August 2004 were the subjects. Their clinical and radiological features were compared with those of 96 patients with trHCC diagnosed histologically from January to December 2004. **Results:** The age and gender of patients with scHCC were not different from those with trHCC. The etiologies of underlying chronic liver disease were not different between scHCC and trHCC (HBV; HCV; NBNC; 80%:7%:13% vs. 70%:19%:11%; $P > 0.05$). Sarcomatoid HCC associated with liver cirrhosis infrequently compared with trHCC (13% vs. 81%; $P < 0.01$). Serum α-fetoprotein (AFP) levels of patients with scHCC were much lower than those of patients with trHCC (median: 9.9 vs. 17.1 ng/ml; $P < 0.05$). The size of scHCC was much larger than that of trHCC (9.4 ± 4.9 vs. 4.1 ± 2.8 cm in diameter; $P < 0.001$). At the time of diagnosis, scHCC also associated more frequently with extrahepatic metastases compared with trHCC (47% vs. 4%; $P < 0.01$). However, the frequency of portal vein invasion in scHCC is not significantly different from that of trHCC. Consequently, patients with scHCC appeared to have much shorter survival periods than patients with trHCC ($P < 0.01$). **Conclusions:** Sarcomatoid HCC presents as a larger-sized tumor that produces less AFP, more frequently associating with extrahepatic metastases and resulting in a shorter survival period than trHCC. A majority of scHCC seems to arise from an underlying non-cirrhotic liver, suggesting pathogenic mechanisms of scHCC that are different from those of trHCC.

APASL/Free Paper/Abstract/64

Effects of long-term ribavirin monotherapy on progression of liver cirrhosis and occurrence of hepatocellular carcinoma in patients with chronic hepatitis C

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Background/Aims: Although ribavirin (RBV) has been used for the treatment of chronic hepatitis C (CHC) in combination of interferon (IFN), the efficacy and safety of long-term RBV monotherapy remain to be clarified. In this study, we evaluated the clinical outcomes of long-term RBV monotherapy in terms of progression of liver cirrhosis (LQ and occurrence of hepatocellular carcinoma (HCC). **Methods:** Sixty-five CHC patients (37 CH and 28 LC of Child–Pugh class A) with serum alanine aminotransferase (ALT) level >2 upper limit of normal (ULN) over 6 months, who did not respond or relapsed following IFN-(X therapy, were administered RBV at a dose of 900–1200 mg/day and followed up for >12 months (median 47; range 12–88 months). Female patients aged <45 and patients with hemoglobin levels <10 g/dl were excluded. We compared the cumulative occurrence rates of decompensation and HCC according to the response to RBV monotherapy. **Results:** Serum ALT levels of 40 patients (62%) were <2 ULN (responders); those of the other 25 (38%) were ~ 2 ULN (non-responders) at 12 months following RBV monotherapy. Female gender appeared to be more common in responders ($P < 0.05$). However, there were no differences in age, duration of therapy, percentage of LC, initial ALT, albumin, bilirubin levels and Child–Pugh scores between the responders and non-responders. The cumulative occurrence rates of decompensation at 1, 3 and 5 years tended to be lower in responders than in non-responders (8.3%, 25% and 25% vs. 21%, 32% and 40%; $P = 0.07$). The cumulative occurrence rates of HCC at 1, 3 and 5 years were

significantly lower in responders than in non–responders (2.5%, 5.8% and 5.8% vs. 14%, 29% and 39%; $P<0.05$). During follow-up periods, five patients (81/6) need to reduce the dosage of ribavirin because of hemolytic anemia. **Conclusion:** Long-term RBV monotherapy may retard the progression of LC and reduce occurrence of HCC in patients with chronic hepatitis C who arc responsive to the therapy.

APASL/Young Investigator/Abstract/65

Different cut-off values of serum α-fetoprotein should be used for the diagnosis of hepatocellular carcinoma in accordance with the etiology of associated chronic liver disease

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Background/Aims: Although α-fetoprotein (AFP) has been regarded as a useful serologic marker of hepatocellular carcinoma (HCC), the usefulness of it is limited because of frequent elevation of serum AFP levels in patients with chronic liver disease (CLD), which is commonly associated with HCC. Serum AFP levels of patients with CLD have been reported to be different in relation to the etiology of CLD, affecting the specificities of serum AFP in diagnosing HCC. Thus, in this study, we evaluated the efficacies of serum AFP in the diagnosis of HCC in accordance with the etiology of associated CLD. **Methods:** A total of 443 consecutive patients with HCC (340 HBV, 43 HCV, 57 NBNC, 3 HBV+HCV) were the subjects; 552 patients with liver cirrhosis (LC) were also examined as non–tumor controls (359 HBV, 42 HCV, 143 NBNC, 8 HBV+HCV). Using serum AFP levels measured at the time of diagnosis, the sensitivities and specificities of serum AFP in diagnosing HCC were calculated and compared in accordance with the etiology of associated CLD. **Results:** Serum AFP levels in HBV-associated HCC were significantly higher than those in HCV-associated HCC or NBNC HCC. ($P<0.00$ 1) Moreover, serum AFP levels of patients with LC were also significantly different in relation to the etiology ($P<0.001$) The calculated cut-off values of serum AFP in diagnosing HBV-associated HCC, where the specificities were over 95%, were 400 ng/ml; l00 ng/ml in HCV-associated HCC and 20 ng/ml in NBNC HCC. At the cut-off level of serum AFP, the sensitivities were 44%, 33% and 49%, respectively. **Conclusion:** HBV infection frequently associates with elevated serum AFP levels, compared with HCV infection or other causes of CLD. Therefore, different cut-off values of serum AFP should be used for the diagnosis of HCC, in accordance with the etiology of associated CLD.

APASL/Young Investigator/Abstract/66

The effects of long-term continuous administration of lamivudine in patients with YMDD mutants of genotype C hepatitis B virus: in relation to type of YMDD variants

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Background/Aim: Prolonged lamivudine (LAM) therapy frequently associates with YMDD mutants of hepatitis B virus (HBV). The long-term outcome of patients with YMDD mutations is not clear so far, especially when they are treated with lainivudine continuously. We analyzed the effects of long-term continuous LAM therapy in patients with YMDD mutants of genotype C HBV. **Method:** Out of 92 with viral resistance during prolonged larnivudine therapy, 82 patients with the YMDD mutant (63 CK 19 LC; 47 YIDD, 20 YVDD and 15 mixed) were administered lamivudine continuously at a dose of 100 mg/day and followed for >12 months (median, range; 61, 16–96 months). The cumulative rates of serum ALT normalization, negative serum HBV-DNA and loss of serum HBeAg were calculated. The clinical, biochemical and virological features were compared, especially in relation to the type of YMDD variant. **Result:** The 1-, 2- and 3-year cumulative rates of normal serum ALT were 41%, 82% and 90% and those of negative serum HBV-DNA were 27%, 59% and 80%, respectively Moreover, 5%, 13% and 27% of patients with YMDD mutants lost their serum HBeAg at 1, 2 and 3 years following the appearance of the YMDD mutant, respectively During the periods of follow-up, two patients (2.4%) underwent liver transplantation because of serious decompensation, two patients (2.4%) developed hepatocellular carcinoma and four patients (4.9%) died of liver-related complications. There were no differences of age, gender, initial serum ALT, HBV-DNA levels and HBeAg-positivity ,in accordance with the type of YMDD variants (YIDD, YVDD and mixed type). Also, the cumulative rates of normal serum ALT, negative serum HBV-DNA and loss of serum HBeAg were not different among the three groups of YMDD variants. **Conclusion:** Long-term continuous LAM therapy gives a substantial proportion of patients with the YMDD mutant favorable viral responses. However, the type of YMDD variant may not influence the clinical outcomes induced by the continuous LAM therapy.

67

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APASL/Poster/Abstract/68

Efficacy of oral branched-chain amino acid supplement in liver cirrhosis

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Background/Aim: Nutritional supports with branched-chain amino acids (BCAA) might prevent disease progression in patients with liver cirrhosis. We investigated the efficacy of oral BCAA supplementation in patients with liver cirrhosis. **Materials and Methods:** Thirty-eight cirrhotic patients, from January 2001 to July 2003, prescribed oral BCAA supplementation for more than 12 months, were included retrospectively. We compared the parameters associated with cirrhotic complications such as incidence of HCC, laboratory data, Child–Pugh score, number of admissions and mortality rate, with parameters in those who had not received BCAA (control group, $N=100$). **Results:** Mean age of the patients was 51.7 ± 10.2 Y/O and the male–female ratio was 29:9. Average follow-up period and duration of oral supplementation with BCAA in these patients

were 16.6 ± 5.8 months and 12.8 ± 4.6 months, respectively. There were no differences in baseline characteristics. In the patients group, the total number of HCC was less frequent (BCAA vs not BCAA = 0/38:6/100), but no statistical significance was noted. Cirrhotic patients with oral BCAA supplementation had higher serum albumin (3.3 ± 0.5 mg/dl vs 2.8 ± 0.6 mg/dl, $P<0.001$) and a lower Child–Pugh score (7.7 ± 2.1 vs 9.7 ± 2.9, $P<0.001$) than those in the control group. Although statistically not significant, the BACC group showed more improvement with PT(change of PT, − 1.85 mg/dl vs − 0.27 mg/dl, $P<0.439$) and T.B(change of BT, 0.2 mg/dl vs 3.3 mg/dl, $P<0.121$) than the control group. **Conclusions:** Oral BCAA supplementation would prevent cirrhotic progression and trend to a decreased risk of HCC. But a long term, prospective, randomized study, to clarify the effects of oral BCAA supplementation, is warranted.

69
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APASL/Poster/Abstract/70
Does Celecoxib have anti cancer activity against hepatocellular carcinoma cells? A case report
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Objectives: To report the possibility that celecoxib has anti cancer activity against hepatocellular carcinoma cells. **Materials:** A man, 58 years old and weighing 51 kg, was clinically diagnosed with hepatocellular carcinoma (HCC), based on the pain he was suffering, a mass in the right upper quadrant of his abdomen and a weight loss of about 11 kg in 3 months. The clinical pathology: Hb 13.7 gr%, leucocytes at 11 600 cells/ml, thrombocytes at 214 000 cells/ml, albumin 4.2 gr%, globulin 3.7 gr%, γ-globulin15.2%, HBsAg negative, anti HBs positive, anti HCV negative and AFP 62, PIVKA II >2000. Sonography showed a mass that was hyper and hypoechoic, with a diameter of more than 6 cm. He had comorbidity with hypertensive heart disease, treated with one tablet 40 mg propranolol at night, 10 mg nifedipin at dawn, and tablets of 25 mg captopril and 25 mg hydrochlorothiazide in the morning. The HCC was treated with celecoxib 100 mg twice a day,and after 6 months of treatment, his weight increased to 61 kg and he was without limited activity. In the 13 months of treatment, he is still alive, with normal activity. **Results:** Now, in the 13 months of the celecoxib treatment, the patient is still alive, with 57 kg body weight and normal activity. **Conclusion:** Perhaps celecoxib has activity against HCC cells;this needs further confirmation.

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APASL/Poster/Abstract/80
Durability of effectiveness after cessation of lamivudine treatment in patients with chronic hepatitis B
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Objective: To investigate the durability of effectiveness after cessation of lamivudine treatment in HbeAg-positive CHB patients and HbeAg-negative CHB patients, as well as the factors influencing it. **Methods:** Fifty-nine HBeAg-positive CHB patients who met the cessation criteria of lamivudine therapy (defined as total duration ≥ 12 months and HBeAg seroconversion maintained ≥ 6 months) and 29 HBeAg-negative CHB patients (total duration ≥ 24 months) were included in the study. HBVDNA (Lightcycler, Roche), and biochemical parameters (Architect Ci8200, Abbott) were tested at months 1–4, 6, 9, and 12 of year 1, and every 6 months thereafter. Relapse was defined as HBVDNA ≥ 10^4 copies/ml. The endpoint of the study was relapse. The statistical analysis was performed by the software SPSS for windows 10.0. **Results:** 1. For HBeAg-positive CHB patients, the duration of lamivudine treatment was 12-60 months (median 23 m). During follow-up 20 patients relapsed, all the relapses occurring within 18 months after cessation of lamivudine, The cumulative relapse rates (Kaplan–Meier method) were 22.0%, 27.2%, 31.3% and 36.3% at months 3, 6, 12 and 24, respectively; the ratios of cumulative relapse cases to all relapse cases at months 4, 6 and 12 were 75.0%, 80.0% and 90.0%, respectively. The ages of the relapse cases were significantly higher than those of the nonrelapse cases (36.7 ± 15.6 years, 22.7 ± 9.3 years, $P = 0.039$). The relapse rate of patients aged ≤ 18y was significantly lower than that of patients aged >18 years, 6.7% (1/15) vs. 43.2% (19/44), $P<0.01$; for patients whose treatment duration was <18 months, the overall relapse rate was 66.7% (6/9); for those ≥ 18 months, the cumulative relapse rates at months 3, 6, 12 and 24 were 18.0%, 20.0%, 24.8% and 30.4%, respectively. 2. For HBeAg-negative CHB patients, the treatment duration of lamivudine was 24–42 months (median 27 m).Of these patients, 12 relapsed, 11 (91.7%) relapses occurring within 18 months after cessation of lamivudine. The cumulative relapse rates at months 3, 6, 12 and 24 were 17.2%, 21.2%, 41.5% and 47.4%, respectively; the ratios of cumulative relapse cases to all relapse cases at months 4, 6 and 12 were 41.7%, 50.0% and 83.3%, respectively. The durability of effectiveness has no association with age and duration of treatment. **Conclusion:** 1. The dur-

ability of effectiveness after cessation of lamivudine treatment in patients with HBeAg-positive chronic hepatitis B is different from that of those with HBeAg-negative CHB. 2. For patients with HBeAg-positive chronic hepatitis B, the durability of effectiveness after cessation of lamivudine treatment is associated with age and duration of treatment. It was especially noted that the relapse rate of patients aged ≤ 18 years was significantly lower than that of patients aged >18 years. 3. For patients with HBeAg-positive chronic hepatitis B, it is recommended that the duration of lamivudine therapy should be ≥ 18 months. 4. Follow-up was essential after cessation of lamivudine and biochemical analysis and HBVDNA should be tested periodically within 18 months, especially within the first 4 months. For patients with HBeAg-negative chronic hepatitis B, the follow-up period should be properly prolonged.

81
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82
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APASL/Poster/Abstract/84
The brain natriuretic peptide and diastolic dysfunction of cirrhosis with ascites

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Background: Cirrhotic cardiomyopathy is generally defined as subnormal ventricular response to stress, and subtle cardiac abnormalities have been described in patients with cirrhosis. Especially, diastolic dysfunction can be seen in cirrhotic cardiomyopathy. Natriuretic peptide hormones have been reported to be sensitive markers of early cardiac disease. We evaluated the relationship between brain natriuretic peptide (BNP) and cardiac diastolic function in cirrhosis with ascites. **Methods:** Prospectively, eight patients of cirrhosis with ascites and four patients of hepatitis without cirrhosis as controls were enrolled in this study. Each patient was examined for determination of serum BNP level, which was followed by echocardiography within 3 days. **Results:** Between cirrhosis and hepatitis without cirrhosis, there were significant differences of ALT, albumin, prothrombin time and platelets. But, there were no significant differences of serum BNP level and diastolic dysfunction of echocardiogram. Correlation between BNP and diastolic dysfunction of heart was not seen in this study. Among 12 cases, five were alcohol-related liver diseases and seven were not alcohol-related liver diseases. Between alcohol-related liver disease and alcohol-unrelated liver disease, there were no significant differences of BNP level and diastolic dysfunction. **Conclusion:** BNP of cirrhosis showed an increased tendency compared to that of hepatitis without cirrhosis butit was not significant. The relationship between serum BNP level and cardiac diastolic dysfunction of echocardiogram was not seen in this study.

APASL/Poster/Abstract/85
The associations between polymorphisms of some candidate genes and outcomes of hepatitis B virus infection

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The outcomes of HBV infection are thought to be correlated with the individual immune status and HBV-specific cellular immune response. The immune-related genes may play important roles in conquering viral replication and clearing the viral infection. SNPs (single nucleotide polymorphisms), which can serve as genetic markers, may influence the expression and function of the genes. 253 cases of self-limited HBV infection and 308 cases with persistent HBV infection from patients of Chinese HAN ethnicity were enrolled in this study. The ratio of male to female in the persistent HBV group was much higher than that of self-limited infected subjects ($P = 0.001$). The average age of self-limited infected patients was much more than that of persistent HBV infected patients ($P < 0.001$). A panel of nine SNPs in seven important genes was determined by allele-specific PCR. The distribution of MxA -88 SNP genotypes was not in accord with the Hardy–Weinberg equilibrium. This might have been caused by technical problems and will be re-analyzed later. As the multiplicative logistic model was used to exclude the influence of age and sex, the distribution of genotypes of MTP H297Q in the self-limited HBV infection group is higher than that in the persistent HBV infection group (OR of CC genotype is 1.80, 95% CI: 1.011–1.769, $P = 0.042$). As the dominant/recessive logistic model was used, the dominant G allele of OAS1 3′UTR, the dominant T allele of MTP-493 and the dominant G allele of MTP H297Q in the self-limited group were much higher than those in the persistent group (OR is 0.37, 0.13 and 0.53, respectively; 95% CI 0.164–0.814, 0.026–0.666 and 0.285–0.995, respectively). These results implied for the first time that the polymorphism of these genes might be involved in determining the outcomes of HBV infection. The combination of several SNPs could serve as the predictor for the evolution of HBV infection, leading to new therapeutic methods for HBV infection.

86
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APASL/Free Paper/Abstract/87
Hepato renal Syndrome in late extrahepatic obstructive jaundice after internal drainage in experimental rats

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Delayed extrahepatic obstructive jaundiced patients undergoing internal biliary drainage have an increased risk of acute ischemic renal dysfunction that ends in renal failure, with potentially high morbidity and mortality. The aim of this study was to investigate the significance of acute ischemic renal failure caused by ANF and ET-1 balance disturbance after internal biliary drainage (ID) in an experimental animal model of delayed extra hepatic obstructive jaundice. Adult male Wistar rats (weight: 190–220 g and age: 20–24 weeks), $n = 20$ (five pairs) rats were used: first pair (four rats) for control (C), second pair for sham operation (SO), third , fourth, and fifth pair of rats for bile duct ligation (BDL). The third pair was used as BDL control (BDLC), second laparotomy was performed on the fourth pair for ID to perform

a stenting choledocho-duodenostomy in the 14 days after BDL and the fifth pair underwent a second laparotomy to perform ID in the same way in 35days after BDL. In the 38days after BDL, all the 20 Wistar rats were sacrified. All the Wistar rats were assigned to the systemic blood ANF and ET-1 investigation with Enzyme linked immunoabsorbent assay (ELISA), and renal parenchymal ANF and ET-1 investigation with immunohistochemistry staining (HIS). The concentration of ANF and ET-1 in systemic blood and renal parenchyma in the first, second, and fourth pairs was balance (in normal value), but the concentration of ET-1 in renal glomeruli was higher than the normal value ($P = 0.0001$) and the concentration of ANF in renal glomeruli was much lower than the normal value ($P = 0.0001$) in the fifth pair. The data from this experimental animal study was evidence that delayed extrahepatal obstructive jaundice internal drainage caused disturbance of the ANF and ET-1 balance and triggered acute ischemic renal failure.

88
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APASL/Free Paper/Abstract/92

HBV genes induce cytotoxic T lymphocyte response upon adeno-associated virus (AAV) vector delivery into dendritic cells

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Objective: The hepatitis B virus (HBV) has been an expanding problem throughout the world and it remains difficult to treat. Immunotherapeutic approaches may offer new, effective treatments. The study is to show that multiple HBV genes delivered by recombinant adeno-associated virus (AAV) virus into dendritic cells (DC) are able to elicit a strong antigen-specific and MHC class I-restricted CTL response. **Methods:** Three recombinant AAV type 2 vectors, which carry one of HBV S, C or X genes, were used to transduce professional antigen-presenting DC for the purpose of stimulating cytotoxic T lymphocytes (CTL) *in vitro*. Monocytes, isolated from 10 healthy donors or seven chronic hepatitis B patients, were pulsed by rAAV-HBV-S, X, C or 293 lysate as control at the first day of isolation, then the DC were cultured for 7 days *in vitro*. The transcription and expression of HBV-S, C or X genes were analyzed by reverse transcription-polymerase chain reaction (RT-PCR) or intracellular staining fluorescence-actived cell sorter (FACS), respectively. **Results:** It was found that all three recombinant AAV/HBV antigen viruses could load DC at approximately 90% transduction efficiency. Most importantly, all three AAV-loaded DC stimulated rapid, antigen-specific and major histocompatability complex (MHC)-restricted CTL. *In vitro*, these CTL killed (30–50%) synthetic antigen-positive autologous targets as well as Hep3B liver cell targets. In comparing the three antigens, it was found that AAV/HBV-C-derived CTL consistently had the highest killing efficiency. **Conclusion:** These data suggest that AAV/HBV antigen gene-loading of DC may be useful for immunotherapeutic protocols against hepatitis B virus infection and that the HBV C antigen may be the most useful for this purpose.

APASL/Free Paper/Abstract/93

The effective infection of recombinant adeno-associated virus on hepatic oval cells *in vitro*

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Objective: Hepatic oval cells, the progenitors for liver regeneration, are ideal target cells for gene therapy. As one of the main gene therapy vectors, adeno-associated virus (AAV) has shown the high ability to infect differentiated liver cells. This study is to evaluate the infection efficiency and gene expression on hepatic oval cells *in vitro*. **Methods:** Two marker genes, neomycin (neo) or green fluorescence protein (GFP) were constructed into AAV type 2 vector and packaged into rAAV-neo or rAAV-GFP virus in 293 cells. Hepatic oval cells were isolated from rats fed with choline-deficient diet supplement with 0.1% (w/w) ethonine for 6 weeks and identified by electromicrology, immunohistochemistry, RT-PCR, Western blot and cell differentiation. The cultured hepatic oval cells were infected by rAAV-Neo virus or rAAV-GFP virus at the MOI of 25. The rAAV-Neo virus-infected cells and uninfected control cells were selected by 100 μg/ml G418 after 3 days of infection for 6 days and reduced to 50 μg/ml thereafter. The rAAV-GFP virus-infected cells and the control cells were observed by both fluorescence microscope and fluorescence-activated cell sorter (FACS) for GFP expression. **Results:** Electron microscope, immunohistochemistry, RT-PCR and Western blot results showed the isolated cells had the characteristics of mature hepatocytes, bile duct cells, fetal liver cells and stem cells and could differentiate under appropriate circumstances. So these cells were hepatic oval cells. There were no obvious phenotypic changes after hepatic oval cells were infected either by rAAV-Neo or by rAAV-GFP. Under G418 selection, about 80% of the cells infected by the rAAV-Neo virus could survive while the uninfected control cells gradually died out, which indicated that the infection efficiency of rAAV-Neo on hepatic oval cells was around 80%. The rAAV-GFP virus-infected oval cells showed a green fluorescence signal after 4 days of infection by fluorescence microscope. The infection efficiency was 93.5% by FACS analysis. **Conclusion:** Hepatic oval cells could be infected by recombinant adeno-associated virus significantly, with the efficiency above 80%.

APASL/Plenary/Abstract/94

Real-time PCR determines extracellular matrix mRNA levels in experimental rat liver fibrosis

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Objectives: To study the expression of procollagen I mRNA, TIMP-1 mRNA and CTGF mRNA in bile duct occlusive rat liver fibrosis by real-time PCR. **Methods:** (1) One hundred male SD rats weighing 150–200 g were randomly divided into five

groups: sham-operation group, bile duct occlusive fibrosis model group, silymarin (SIL) treatment group (intragastric gavage of SIL 50 mg/kg/day), Pentoxifyline (PTX) treatment group (intragastric gavage of PTX 16 mg/kg/day) and SIL/PTX combination treatment group (intragastric gavage of SIL 50 mg/kg/day and PTX 16 mg/kg/day). (2) Total RNA was extracted from frozen rat liver tissue by using TRIzol reagent and was reverse transcribed to cDNA. (3) The mRNA levels of procollagen I, TIMP-1 and CTGF were determined by real-time PCR (TaqMan technique). For each sample, the mRNA levels of procollagen I, TIMP-1 and CTGF were normalized by GAPDH mRNA. **Results:** After 6 weeks of bile duct occlusion (BDO), the model group displayed 14-, 7- and 8-fold increases for procollagen I mRNA, TIMP-1 mRNA and CTGF mRNA, respectively. After treatment with SIL, PTX and a combination of both, fibrous septa became discontinuous and thinner. Compared with the model group (procol-I mRNA: 1.54 ± 0.29; TIMP-1 mRNA: 4.08 ± 1.36; CTGF mRNA:24.14 ± 5.08), SIL could downregulate the expression of procol-I mRNA (0.59 ± 0.15), TIMP-1 mRNA (1.49 ± 0.60) and CTGF mRNA (6.43 ± 2.01). The difference between the SIL group and the model group is statistically significant ($P < 0.05$). PTX could also downregulate the expression of procol-I mRNA (0.68 ± 0.18) and CTGF mRNA (8.12 ± 2.27); however, it upregulated TIMP-1 mRNA (6.16 ± 2.14) significantly. Procollagen I mRNA level and CTGF mRNA level in the combination group were similar to the monotherapy groups ($P < 0.05$), although TIMP-1 mRNA level in the combination group was lower than that in the PTX group ($P < 0.05$). **Conclusions:** We conclude that in rat fibrosis induced by bile duct occlusion, SIL or PTX could attenuate hepatic fibrosis by downregulating procollagen I and CTGF mRNA expression. However, there is no further benefit of combination therapy, perhaps because of the upregulation of TIMP1 by PTX.

APASL/Free Paper/Abstract/95

Hepatic hemodynamic change after percutaneous radiofrequency ablation of hepatocellular carcinoma

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Objective: Radiofrequency thermal ablation (RFA) is a minimally invasive treatment widely used for the treatment of liver neoplasms. The purpose of this study was to evaluate the changes in hepatic hemodynamics after percutaneous RFA treatment of hepatocellular carcinoma using pulsed Doppler sonography. **Materials and Methods:** Between April 2004 and November 2004, 40 subjects with hepatocellular carcinoma (1.2–4.3 cm in diameter, 1–3 nodules) were treated by RFA. The RFA was performed percutaneously using a monopolar cooled-tip electrode needle under US guidance with local anesthesia. Hepatic hemodynamic change was examined in each patient 2 days before and after the RFA. The statistical analysis was performed on hemodynamic measurements recorded in the fasting state by pulsed Doppler sonography. The time-averaged velocity and cross-sectional area of the portal vein and maximum velocity of the hepatic artery were recorded. Portal vein blood flow was calculated. Hepatic venous flow was classified into normal or abnormal patterns. **Results:** In the ablation zone, hepatic arterial velocity was significantly elevated after RFA, compared to pre-treatment level (35.5 cm/s vs 26.4 cm/s), $P < 0.05$, while portal vein flow and hepatic venous flow were not significantly altered. In the non-ablated zone, there was no significant change in the hepatic hemodynamics before and after RFA. **Conclusion:** RFA-treated zone had elevated hepatic arterial velocity. But in the non-ablated zone, no significant change was observed in the hemodynamics of artery, portal and hepatic veins, indicating that RFA is a safe and minimally invasive treatment, with no untoward effect on hepatic hemodynamics outside the locoregional area.

96
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APASL/Free Paper/Abstract/98

Combination therapy of intra-arterial 5-flourouracil and systemic interferon hepatocellular carcinoma with portal venous invasion

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Background: Hepatocellular carcinoma (HCC) with portal venous invasion (PVI) presents an ominous prognosis. The combination of intra-arterial 5-fluorouracil (FU) and systemic interferon was recently reported to be effective against HCC with PVI, although only in small-sized pilot studies. **Methods:** One hundred and sixteen patients with HCC with PVI received IFN (5 000 000 U intramuscularly on days 1, 3, and 5 of each week) and 5-FU (500 mg into the hepatic artery on days 1 through 5 of the first and second week of each 4-week cycle). The therapy was terminated at the end of the first cycle in case of progressive disease, or repeated for at least three cycles otherwise, when the response to treatment was evaluated by Eastern Cooperative Oncology Group criteria. The survival was compared with that of historical controls ($n = 42$). **Results:** Nineteen (16%) patients showed a complete response, and the other 42 (36%) showed a partial response. The untoward effects were limited to controllable nausea and appetite loss. The survival rates at 12 and 24 months among patients overall were 34% and 18%, respectively, in contrast to 15% and 5% among the historical controls. Survival rates at 12 and 24 months were 81% and 59% among complete responders, respectively, and 43% and 18% among partial responders. **Conclusions:** The combination therapy with 5-FU and IFN was safe, and substantially improved survival among the complete responders.

99
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100
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APASL/Poster/Abstract/101

Efficacy of glycyrrhizin in the treatment of non-alcoholic steatohepatitis

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Stronger Neo-Minophagen C (SNMC) is a registered Japanese medicine in the form of an intravenous injecting solution, which contains 0.2% glycyrrhizin, a major saponin component in an aqueous extract from licorice roots. SNMC has proven effective in improving serum transaminase levels in patients with chronic viral hepatitis. We used SNMC in the treatment of non-alcoholic steatohepatitis (NASH). Five NASH patients (two males and three females, aged 48 ± 6 years) received SNMC (Minophagen Pharmaceutical Co., Tokyo, Japan, 40 ml/day) alone intravenously three times/week for 3 months or more. NASH was diagnosed clinically on the basis of the laboratory data and histological findings in the liver. Both the alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (r-GTP) levels (mean, IU/l) significantly improved from 112 and 89 before SNMC treatment, respectively, to 49 and 55 after treatment, respectively ($P<0.01$). Serum ferritin levels (mean, ng/ml) also significantly improved from 210 before, to 116 after SNMC treatment ($P<0.01$). NASH, which is characterized by fatty change associated with necroinflammation, occasionally progresses to cirrhosis and hepatic failure. Oxidative stress may contribute to the progression of NASH. We have found that SNMC increases the levels of glutathione in human lymphocytes, thereby decreasing oxidative stress of the body (Antiox Redox Signal, 2:687, 2000). The present data clearly indicate that SNMC improves the levels of ALT, r-GTP, and serum ferritin as a marker of oxidative stress (Liver, 2001; 21:295) in NASH patients. In conclusion, the decrease in oxidative stress may be one mechanism that accounts for the therapeutic effects of SNMC on NASH.

102
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103
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APASL/Free Paper/Abstract/104
Time course of cell-cycle-related proteins in rat hepatic stellate cells isolated from dimethynitrosamine-induced hepatic fibrosis
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DMN (dimethynitrosamine)-induced rat liver cirrhosis model appears appropriate for the study of the early events of hepatic fibrosis. Hepatic stellate cells (HSCs) are the primary cellular source of the matrix components in liver fibrosis. This study was designed to decipher the expression pattern of the cell cycle and apoptosis regulatory proteins in HSCs during DMN-induced rat hepatic fibrosis. Six-week-old female Sprague–Dawley rats were intraperitoneally injected 10 μl of DMN/kg body weight, 3 consecutive days a week for 4 weeks. The animals were sacrificed in the first, second, third and fourth weeks and HSCs were purified. The expression of cell-cycle control proteins such as CDK2, CDK4, cdc2, cyclin B, cyclin D, cyclin E and apoptosis-related proteins (bcl-2 and Fas) was examined by Western blotting. The proliferation and apoptosis fractions of the isolated HSCs were examined by flow cytometry. The portions of S-phase cells and apoptotic cells dramatically increased in the first week and rose again in the fourth week. Expression pattern of cyclins, CDKs, PCNA, Fas and bcl-2 was diverse. Cyclin A, cyclin D and PCNA showed increased expression in the first week but cyclin B steadily increased up to the fourth week. The expression of other cyclins and CDKs remained unchanged or decreased slightly. Bcl-2 and Fas were increased from the first week until the fourth week. The HSCs in DMN-induced rat hepatic fibrosis had a high proliferation rate in the early stage of fibrosis, with high apoptotic activity. These early events were correlated with increased cyclin A and D expression and increased Fas expression.

105
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APASL/Free Paper/Abstract/108
Prognostic determinants of survival and effect of transarterial chemoembolization in patients with hepatocellular carcinoma
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Introduction: The aim of the present study was to identify independent prognostic markers for survival in patients of hepatocellular carcinoma (HCC) and cirrhosis of liver and to evaluate the effect of transarterial chemoembolization (TACE) on overall survival. **Methods:** We conducted a study on 50 patients with HCC and cirrhosis where baseline characteristics and follow-ups were available. The diagnosis of HCC was established by ultrasound, computerized tomography, magnetic resonance imaging, histologic or α-fetoprotein levels. Survival rates were calculated by means of the Kaplan–Meier method. Univariate analyses of the effect of different characteristics were based on comparison of survival by the log-rank test. Statistically significant variables were introduced into a multivariate Cox's proportional-hazard regression analysis. Survival curves were compared using different classification systems (Child's Class, CLIP, Okuda, BCLC). Because TACE was performed in 21 patients, its effect on survival was also analyzed. **Results:** Males were 78%, median age 51 years(range 13–70 years). Median follow-up was 7.5 months (range 2–26 months). HCV was the etiology in 50%. At the time of analysis of data, 23 patients had died (46%) and 21 (42%) had undergone TACE. Overall survival rates at 2, 6, 12 and 22 months were 98% (95% Cl, 97–99%), 78% (95% Cl, 72–84%), 45% (95% Cl, 37–53%) and 26% (95% Cl. 16–36%), respectively. Univariate analyses showed that etiology ($P=0.0001$), sex ($P=0.01$), tumor type ($P=0.02$), hepatomegaly ($P=0.04$), portal vein thrombosis ($P=0.05$), hemoglobin ($P=0.06$), age ($P=0.07$), splenic varices ($P=0.09$) and serum levels of alkaline phosphatase ($P=0.09$) and CLIP scoring ($P=0.0004$) were significantly related to survival. The multivariate Cox regression model showed that hepatitis C etiology ($P=0.009$) and portal vein thrombosis ($P=0.061$) were independent prognostic determinants of survival. In addition, patients, 21 (42%) of whom were offered TACE, also yielded a beneficial effect on the survival in the total population (relative risk (RR), 1.95; 95% CI, 0.84–

4.54) and showed improved 1-year survival compared with those who were not offered TACE (57% vs 37%). **Conclusion:** Hepatitis C as the etiology of HCC is associated with poor prognosis. Portal vein involvement adversely affects survival. TACE influences favorably 1-year survival. The CLIP scoring system seems to be a better choice in our patients.

APASL/Poster/Abstract/109
Pyogenic liver abscess in Southeast Asian patients
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Background: Liver abscess (LA) can cause significant morbidity and the organisms vary between different regions. **Objective:** This study assesses the characteristics of LA in Southeast Asian patients. **Material and Methods:** Patients treated for LA (1999–2004) were identified and retrospectively reviewed. **Results:** Forty-two patients (mean age 47.6 years (range 22–79 years), male = 38%, 91%) were treated for 49 episodes of LA. Two patients (post-Whipple's and diabetes, respectively) had recurrent abscesses. Predisposing factors were diabetes (47.7% (known diabetes 31% and newly diagnosed 16.7%)) and biliary pathologies (21.4%). The most common manifestations were fever (95.6%) and abdominal pain (69%). LA was located at the right lobe (80%), left lobe (11%) and both lobes (9%). Eighty-one percent had a solitary abscess. The commonest organisms isolated were *Klebsiella* (46.8%) and *Mellioidosis* (21.3%). No organisms (cryptogenic) were isolated in 21.3%. *Klebsiella* abscess patients were older (54.9 vs. 38.1 years old, $P = 0.021$) and more likely to have diabetes (93.3% vs. 6.7%, $P = 0.005$) compared to patients with cryptogenic abscesses. Mellioidosis patients were more likely to have diabetes compared to patients with cryptogenic abscess (90% vs. 10%, $P = 0.000$) and other organisms (81.8% vs. 18.2%, $P = 0.039$). Others organism-related abscesses were more likely to have biliary pathologies. Sixty-six percent required aspirations of the abscess and 33% need a drainage catheter inserted. Complications were seen in 37%, with 12.2% needing intensive care admissions. All responded to antibiotics with or without drainage. There was no mortality associated with LA. **Conclusions:** *Klebsiella* and *Mellioidosis* are common organisms causing pyrogenic LA in Southeast Asian patients. Both *Klebsiella* and *Mellioidosis* abscesses were associated with diabetes. Other organisms group was more likely to have biliary pathologies. All responded to treatment with antibiotics with or without drainage/aspiration.

APASL/Poster/Abstract/110
Characteristics of hepatitis C in Negara Brunei Darussalam
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Introductions: A combination therapy for chronic hepatitis C (CHCV) has improved the treatment outcome. The patients' and viral characteristics are important predictors of the response. We aim to assess these characteristics in our patients. **Methods:** CHCV patients (positive serum RNA) followed up in the hepatology clinics were identified and retrospectively reviewed. **Results:** There were 81 patients (male ($n = 67\%$, 83%)) with a mean age of 41.3 ± 10.9 years (range 25–80 years). Fifty-six percent were ≤ 40 years old. The etiologies of CHCV were intravenous drug use (IDU) – 55.6%, hemodialysis related – 13.6% and others – 13.6%. Unknown etiology accounted for 17.3%. The associated factors for disease progression were hepatitis B co-infection ($n = 3\%$, 3.7%) and history of alcohol use ($n = 15\%$, 18.5%). All were negative for HIV. Serum ALT was persistently elevated in 61.5%, fluctuating in 20% and persistently normal in 18.5%. Genotype testing ($n = 14$) showed genotype 1 ($n = 5\%$, 35.7%), genotype 2 ($n = 1\%$, 7.1%), genotype 3 ($n = 8\%$, 57.1%) and genotype 4 ($n = 2\%$, 14.3%). Two patients had dual genotypes (genotypes 2/4 and 1/4, respectively). Liver biopsy was carried out in 42% ($n = 34$), showing grade (1.9 ± 0.91/4) and stage (1.9 ± 0.98/4). Compared to non-IDU patients, more IDU patients were 40 years old (75.6% vs. 30.6%, $P < 0.001$) with favorable genotypes (80% vs. 25%, $P = 0.052$), although not significant. There were no differences between the genders, except that female patients had more unfavorable genotypes ($P = 0.040$). **Conclusions:** Our results show that our patients have favorable factors such as low co-infection rate, alcohol use, mild histological activities and favorable genotypes. Majority of the IDU patients were younger than 40 years old and had favorable genotypes. There were no differences in the serum ALT and histological activities.

APASL Bali/Poster/Abstract/111
Hepatitis C in Negara Brunei Darussalam: response to combination therapy
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Introductions: Treatment of chronic hepatitis C (CHCV) has improved with combination therapy. Currently, there is debate regarding treatment of CHCV in intravenous drug users (IDU). We review our experience with combination therapy in CHCV patients.
Methods: All patients who had completed at least one course of combination therapy (>6 months of therapy) and had longer than 6 months of follow-up were identified and reviewed.
Results: There were 28 patients (22 males, mean age of 40.7 ± 9.9 years old) who completed one course of treatment (standard IFN/ribavirin, $n = 23$ and pegylated IFN/ribavirin, $n = 5$). IDU accounted for 61% of the etiology. All IDU were undergoing drug rehabilitation before treatment. The end of the treatment biochemical response was 93%. The overall sustained viral response (SVR) was 64.3%. Comparing IDU with others (non-IDU), there was no difference in treatment response (64.7% vs. 63.6%, $P = 0.954$). IDU patients were younger (37.2 ± 6.7 vs. 46.2 ± 11.7 years old, $P = 0.025$) and had higher pretreatment serum alanine aminotrasferase (ALT) ($P = 0.790$). Responders had significantly higher pretreatment ALT ($P = 0.018$). Overall side effects of treatment were seen in 64% (flu-like symptoms 58.3%, hematological 50% and depressive related 8%).
Conclusions: Our response rates for combination therapy are comparable with published data. There was no difference in treatment response rate between the IDU and non-IDU. This suggests that the CHCV-infected IDU should be offered treatment whenever possible after rehabilitation.

112
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113
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114
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APASL/Poster/Abstract/115
Correlation between the degree of hepatic disfunction and the degree of cognitive deficits in patients with liver cirrhosis
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Background: Cirrhotic patients may present a degree of cognitive alterations, which is related to the degree of hepatic dysfunction. The number connection test (NCT) and digit symbol test (DST) have been used to assess the degree of cognitive deficits in liver cirrhosis. However, the test may potentially be attributed to the education level and age, although some authors found their role insignificant. **Methods:** In order to find the relationship between the degree of hepatic dysfunction as assessed by Child–Pugh score and the degree of cognitive deficits as assessed by percentage of increase of NCT score or percentage of decrease of DST score with respect to age and education level predicted score, a cross-sectional analytic study was conducted among cirrhotic patients in several hospitals in Denpasar. A normal control group was selected to set the formula for age and education level predicted NCT or DST score. Spearman's corelation test was used to assess the relationship between variables. **Results:** A total of 97 cirrhotic patients, aged 51.96 ± 11.15, male 84.5%, female 15.5% and 40 normal controls, aged 49.18 ± 10.53, male 50%, female 50%, were involved in this study. The mean NCT, DST and Child–Pugh score of cirrhotic patients were 106.24 ± 75.56, 21.62 ± 9.41 and 7.87 ± 1.63, respectively. The mean NCT and DST of normal controls were 42.95 ± 13.62 and 42.81 ± 9.23, respectively. The formula for predicted NCT score is $48.256+(0.343 \times \text{age})-(6.987 \times \text{education level})$ and that for predicted DST is $49.423-(0.336 \times \text{age})+(3.119 \times \text{education level})$. Child–Pugh score was positively and significantly correlated with percentage of increase of NCT score ($R = 0.221$; $P = 0.029$), and also Child–Pugh score was negatively and significantly correlated with percentage of decrease of DST score ($R = -0.328$; $P = 0.001$). **Conclusion:** In liver cirrhosis, the degree of hepatic dysfunction was correlated with the degree of cognitive deficits.

APASL/Poster/Abstract/116
The seroepidemiological investigation of hepatitis B in Chinese over 3-years-old
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Objective: In order to know about the epidemic situation of hepatitis B and the effect of hepatitis B vaccine, which was brought into the Expanded Program on Immunization from 1992, and provide the theoretical basis for prevention and control of hepatitis B in China. **Methods:** (1) A total of 62 029 specimens were selected from the sampling of the Investigation of Nutrition and Health in Chinese residents in 2002. (2) HBsAg, anti-HBs and anti-HBc in blood samples were detected using ELISA reagents and revised by SPRIA and Abbott ELISA reagents. (3) The software used for the analysis of the data above is SAS 8.2. **Results:** (1) The standardized prevalence rate of HBsAg, anti-HBs and anti-HBc is 9.09%, 37.48% and 50.04% in humans aged over 3-years-old and 5.03%, 45.33% and 29.10% in children from 3 to 12 years, respectively. (2) The prevalence rate of HBsAg and HBV in urban areas is 4.61% and 43.51%, respectively. Comparing with 1992 (HBsAg 8.08% and HBV 59.46%), the rate of HBsAg has declined to 42.95% and the rate of HBV has declined to 26.82%. The prevalence rate of HBsAg and HBV in villages is 9.41% and 56.77%, respectively. Comparing with 1992 (HBsAg 10.49%), the rate of HBsAg has declined to 27.63%. (3) In humans aged over 3-years-old, comparing with 1992 (HBsAg 9.75%), the rate of HBsAg (5.28%) in the vaccinated area has declined to 45.85%, while the rate of HBsAg (9.51%) in the unvaccinated area has not obviously changed. (4) The prevalence rate of HBsAg and HBV in the vaccinated children from 3 years to 12 years is 3.63% and 26.88%, respectively. Comparing with 1992 (HBsAg 10.22–11.27% and HBV 52–55%), the rate of HBsAg and HBV has declined by 64–68% and 40–52%, respectively. In the vaccinated children from 3 to 12 years, the prevalence rate of HBsAg in the urban areas is 1.96%, but the rate of HBsAg in villages is 6.65%. In the unvaccinated children, the prevalence rate of HBsAg and HBV is 11.19% and 47.03%, respectively. **Conclusion:** The results reveal that some changes have happened in the epidemic character of hepatitis B in China and suggest that since the hepatitis B vaccine was brought into the expanded program on immunization (EPI) from 1992, the prevalence rate of the HBsAg and HBV, especially in the children from 3 years to 12 years, has obviously declined.
Note: The final data should be the result of further analysis.

APASL/Poster/Abstract/117
Aetiology of cirrhosis in a tertiary referral centre in Sri Lanka
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Introduction: Alcoholic liver disease is widely believed to be the commonest cause of cirrhosis in Sri Lanka. However, with the rising prevalence of obesity and diabetes, non-alcoholic steatohepatitis (NASH) is increasingly being diagnosed. Despite being situated in an intermediate to high transmission region, the prevalence of both hepatitis B ($<2\%$) and C ($\leq 1\%$) is low in our population. **Aims:** To study the aetiology of cirrhosis in a tertiary referral centre in Sri Lanka. **Methods:** We analysed the database of outpatients with cirrhosis maintained since 2001, reviewing records with regard to aetiology. A diagnosis of cirrhosis was established on clinical, biochemical and radiological evidence, and confirmed histologically when required. A detailed alcohol and drug history was obtained from all cirrhotic patients. Hepatitis B and C serology, iron and copper studies, and an autoimmune screen were also performed. **Results:** Records of 101 patients were analysed (male:female = 78:23, mean age 38.3 years (SD 17.5)). The aetiology of cirrhosis was as follows: alcohol 64 patients (63.4%, male:female = 60:4), cryptogenic 24 (23.8%, male:female = 12:12), chronic hepatitis B four (all males), autoimmune hepatitis four (all females), Wilson's disease two (both females), previously diagnosed NASH two (one male, one female), and chronic hepatitis C one (male). The prevalence of diabetes was 45% among patients with cryptogenic cirrhosis compared to 27% among patients with other causes. **Conclusions:** Alcohol remains the commonest cause of cirrhosis in our patients. Cryptogenic cirrhosis was the second commonest cause overall, and the commonest among females. The high prevalence of diabetes among patients with

cryptogenic cirrhosis suggests an aetiology of previously undetected NASH.

APASL/Poster/Abstract/118

Effects of fatty liver and related factors on the efficacy of combination antiviral therapy in patients with chronic hepatitis C

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Hepatic steatosis is a histological feature in patients with chronic hepatitis C and adversely affects the virologic response rates to anti-HCV therapy. This study is to investigate whether the fatty liver and related factors have an impact on the efficacy in chronic hepatitis C treated with peginterferon and ribavirin, and the associations between HCV genotyping and fatty liver. Ninety patients received, subcutaneously, 180 μg peginterferon α-2a once a week plus ribavirin. HCV genotypes and the level of serum insulin of patients were measured, fatty liver was detected by B ultrasound, and the body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Of the 90 chronic hepatitis C patients, 35 (38.9%) were genotype 1, 41 (45.6%) were genotype 2, 5 (5.6%) were genotype 3 and 9 (10.0%) were undetermined. The incidence of fatty liver in HCV genotypes 1, 2, 3 and undetermined genotype was 11.4%, 9.8%, 60.0% and 11.1%, respectively, which suggested that the distribution of fatty liver in different HCV genotypes was imbalanced ($\chi^2 = 9.95$, $P < 0.05$). In a multivariate analysis, the efficacy of combination therapy was significantly associated with BMI ($P = 0.011$), WHR ($P = 0.024$), the level of serum insulin ($P = 0.001$), and the fatty liver ($P = 0.028$). With multivariate regression analysis, the serum insulin level proved to be an independent predictor of the efficacy of antiviral therapy. The incidence of fatty liver in HCV genotype 3 was significantly higher than that of other genotypes. The BMI, WHR, the level of serum insulin, and fatty liver were associated with the sustained virologic response. The level of serum insulin was an independent factor for predicting the effect of antiviral therapy.

119

Abstract withdrawn

APASL/Poster/Abstract/120

Description function of the liver in malaria and the factors that influence it

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Introduction: There are 300–500 million malaria cases in the world with an annual death rate of 3 million. In Indonesia, 95% of malaria is caused by *Plasmodium falciparum*, *vivax* and a mixture of both. This research tried to observe the function of the liver in malarial cases and the factors that influence it.
Materials and Methods: This research used a cross-sectional method to evaluate the feature of the function of the liver, in Dr. M. Jamil General Hospital. The inclusion criteria were patients with clinical symptoms, with or without anemia, with or without liver enlargement, with or without enlargement of spleen, age exceeding 12 years, whohad *P. falciparum* in the sexual stage, and agreed to participate in the research. The exclusion criteria were age less than 12 years, damage of the function of the liver caused by other malaria, peripheral routine blood examination, SGOT, SGPT, bilirubin, and the parasitic count. For data analysis the SPSS version 11 was used with a *P*-value <0,05. **Results:** From the 172 cases of malaria, the following results were obtained: *falciparum* parasitic 168 (97%), *vivax* 3 (4%,16%), mixture 1 (0%, 58%), males were affected more than females 117:55 (68.02:31.98%), the most common age group 21–30 years old 63 (36%, 62%), the area background, middle incidence area 8 (4%,65%) and low area 164 (95%, 35%), the fever lasted up to 7 days 89 (51%, 74%) , icteric 8 (4%, 65%), anemia 21 (12%, 21%),enlargement of the liver 78 (45%,35%) and spleen 74 (43%, 02%), the increasing SGOT 39.83 ± 39, 42 U/l, SGPT 38.99 ± 33.5 U/l. The parasitic count = 120–165.000 par/μl in tropozoid form. **Conclusion:** In this research, the damage function of the liver was found with increase of SGOT, SGPT, and bilirubin. No correlation was found with the increase of SGOT, SGPT with parasitic count. There was correlation between bilirubin with parasitic count. The was no correlation between SGOT, SGPT, bilirubin with long periods of fever and no correlation between SGOT, SGPT with hemoglobin. There was negative correlation between bilirubin and hemoglobin.

APASL/Poster/Abstract/121

Influence of storage duration on sensitivity of HBV-DNA detection among samples stored in filter paper

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Hepatitis B virus (HBV) DNA detection plays an important role in ensuring a proper management of HBV infections, which is becoming a major health problem in Indonesia. However, taking the geographic condition of Indonesian territory into consideration, transportation of samples from remote areas to major cities where DNA detection is available may take a considerable amount of time. The objective of this study was to determine the sensitivity of HBV-DNA detection on samples stored in filter paper as a medium, and the influences of storage duration on detection sensitivity. A total amount of 20 HBV-DNA serum samples previously quantified using COBAS Amplicore was dripped onto filter papers. Half of the samples were stored for a week, and the other half for 2 weeks, after which the samples were analyzed for the presence of HBV-DNA by means of nested PCR. The group which was stored for 1 week was 95% positive and the groups stored for 2 weeks were 85% positive; with quantitative results 2×10^5–3.05×10^2. Detection of HBV-DNA on samples stored in filter papers should be performed before 1 week of storage, since a decline in sensitivity was observed in samples stored for more than 1 week. However, detection should still be positive on samples stored for over 2 weeks if viral load is high.

APASL/Poster/Abstract/122

Genotype determination of hepatitis B virus from dried serum on filter paper

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Background: Genotype of hepatitis B virus (HBV) is an important test in clinical epidemiology as well in the management

of patients. In our institution, we determined the HBV genotype with primer-specific method, which can reveal 100% HBV genotype from serum of chronic hepatitis patients and 80% from hepatoma patients. Filter paper can preserve HBV-DNA and this method can be used to transport the specimen from a remote area. We determined the HBV-DNA from dried serum on filter paper and use this for genotype analysis. **Method:** A volume of 100 µl sera from patients that already quantitated for HBV DNA with Amplicor HBV DNA (Roche) was dropped onto a filter paper (9 cm^2 of Whatman No. 1). After drying at room temperature, the paper was put in a plastic clip and kept in a closed cabinet with room temperatures of 25–33 °C and humidity of 90–96% for 1 week. HBV-DNA determinations were done with nested PCR. Genotypes of HBV were determined by means of specific primers in the region of Pre-S1, Pre-S2 and S for detection of genotypes A, B, C, D, E and F. **Results:** Twenty-three sera quantitated for DNA of HBV were obtained. Eighteen (78.3%) of these sera were successfully determined for genotype. Genotypes B were the most frequent (13/18%, 72.2%) and the rest were genotype C (5/18%, 27.7%). The proportions of HBV genotypes in our study were comparable to the other studies in our country that used serum and sequencing of the whole genome for genotyping of HBV. Five samples that could not be determined by this method showed positive with nested PCR and mostly had $<10^3$ copy/ml. **Conclusion:** Filter paper can be a good alternative method to transport HBV-DNA for genotype determination in most cases of HBV infection. However, a small number of HBV-DNA in serum can hamper the results and other methods of genotyping must be used.

123
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124
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APASL/Poster/Abstract/125
Endoscopic injection of *N*-butyl-2-cyanoacrylate (Histoacryl) vs transjugular intrahepatic portosystemic shunt (TIPS) for the treatment of gastric variceal bleeding: comparison of short-term results

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Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) has been widely used for the treatment of gastric variceal bleeding in many centers and, more recently, the endoscopic injection of *N*-butyl-2-cyanoacrylate (Histoacryl) was reported to be effective. This study was to compare the efficacy and safety of the two treatments as the initial treatment of gastric variceal bleeding. **Patients and Methods:** From July 2003 to January 2004, 27 patients with gastric variceal bleeding were treated with endoscopic Histoacryl injections in our institution (Histoacryl group). Twelve weeks after treatment, survival rate, rebleeding rate and complications of these patients were compared with the historical control group of 37 patients who were treated with TIPS between January 2001 and April 2004 (TIPS group). **Results:** Basal characteristics of the patients were not different between the two groups. The number of patients with hepatocellular carcinoma was significantly higher in the Histoacryl group (44.4%) than in the TIPS group (13.5%) ($P = 0.006$). Overall survival rates in 12 weeks after treatment were not different between the two groups (Histoacryl, 85.2%, TIPS, 89.2%, $P = 0.712$). The rebleeding rates were 11.1% in the Histoacryl group and 18.9% in the TIPS group and the incidences of PSE after treatment were 18.5% and 21.6%, respectively, which were not different between the two groups ($P = 0.498$, 0.761, respectively). **Conclusions:** Endoscopic Histoacryl injection was effective and the safe initial treatment modality for bleeding gastric varices comparing TIPS, although the follow-up period was not long enough. Long-term prospective study of Histoacryl injection versus TIPS on gastric variceal bleeding is warranted.

APASL/Poster/Abstract/126
The relationship of VII factor with the degree of liver functional status based on Child–Pugh criteria on liver cirrhosis

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It is predictable that haemostatic disturbances will be found in the liver cirrhosis patient. This is due to the fact that coagulation factor, inhibitor and fibrinolysis factor are produced in the liver. The VII factor will decrease progressively, and it is the most sensitive to the damage of liver parenchyme in cirrhosis. The aim of this study is to examine the VII factor concentration in liver cirrhosis, and to know whether this factor can be used to change the grade/stage/severity of liver cirrhosis. **Methods:** A cross-sectional study was conducted in 29 ambulatory and non-ambulatory liver cirrhosis patients in two hospitals, RSPM and RSHAM Medan in September 2002. It consisted of 21(72%, 4%) men and 8 (27%, 6%) women and the mean ages were 56 and 14 years. The matched age control was taken from 15 healthy subjects who had a mean age of 50.27 years. For control subjects, data were taken after the interview, physical examination, and normal laboratory tests. The examination of the VII factor is the VII-C (pro coagulant) activity, which is based on one-stage assay with the VII-depleted plasma. **Results:** Differences were observed in the VII factor value and thrombocyte count in the case and control groups. While the first decreased continually for the control group, Child–Pugh A, B, C, the second did not show significance relations to these observations. The values were $138.71 \pm 13.77\%$, $103.98 \pm 10.43\%$, $78.13 \pm 10.42\%$, and $38.97 \pm 14.77\%$, respectively for the decrease of mean concentration of factor VII. The thrombocyte concentrations were 259.80 ± 58.47, 125.40 ± 50.92, 134.38 ± 71.96, and 135.56 ± 59.30, respectively. To conclude, there is a significant decrease of the VII factor in the control group and liver cirrhosis patients regardless of the stage of Child–Pugh criteria. However, it was not shown in the prothrombin time changes by these observations. The other result is that there is no significant relationship between the thrombocyte count and the VII factor.

127
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128
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APASL/Poster/Abstract/129

Serum adiponectin correlates with viral characteristics but not histologic features in patients with chronic hepatitis C

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Introduction: Adiponectin induces insulin sensitivity and modulates inflammatory responses. We thus studied the implications of adiponectin in patients with chronic hepatitis C virus (HCV) infection inherently linked to insulin resistance. **Patients and Methods:** We analyzed the association of serum adiponectin levels with clinical, virologic and histologic findings in 95 naïve Taiwanese patients with chronic hepatitis C before and after antiviral therapy. **Results:** At baseline, 14 (15%) of the 95 patients were obese and 26 (27%) had type 2 diabetes mellitus. Fifty-seven patients were infected with HCV genotype 1 and 38 with genotype 2. Steatosis and periportal fibrosis was present in 44 (46%) and 69 (73%), respectively. In multivariate analysis, male gender, insulin resistance, high HCV load and genotype 2 were significantly associated with a lower serum adiponectin level. In contrast, intrahepatic gene expression of adiponectin receptors was higher in genotype 2 compared with genotype 1. Serum adiponectin level did not correlate with other clinical or histologic parameters. After treatment, change of steatosis also did not correlate with the change of adiponectin level ($P = 0.61$). **Conclusion:** Adiponectin correlated with hepatitis C viral factors at both serum and liver tissue levels. The interactions among adiponectin, insulin resistance and chronic HCV infection merit further studies.

130

Abstract withdrawn

APASL/Free Paper/Abstract/131

Durability of response to peginterferon α-2a (40 kDa) 1 year after the end of treatment in patients with HBeAg-negative chronic hepatitis B: results from a large multicentre trial

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Introduction: In patients with **HBHB**HBeAg-negative CHB, peginterferon α-2a (40 kDa) provides significantly higher sustained response rates 6 months after the end of treatment than lamivudine (LAM) (Marcellin, N Engl J Med 2004). The combination of peginterferon α-2a and LAM did not provide an advantage over peginterferon α-2a alone. This analysis aims to evaluate the durability of response 1 year after the end of treatment in patients treated with peginterferon α-2a alone. **Patients and Methods:** In the initial study, 177 patients with HBeAg-negative CHB received 48 weeks of peginterferon α-2a 180 μg once weekly and were assessed 6 months post-treatment. Results generated 12 months post-treatment in a roll-over long-term observational study (LT-study) are presented. **Results:** In total, 62% of the patients participating in the original study opted to participate in the LT-study. The rates of biochemical and virologic response measured 12 months after the end of treatment with peginterferon α-2a monotherapy were similar to those reported 6 months after the end of treatment: 59% vs 59% for ALT normalization; 42% vs 43% for HBV-DNA $<20\,000$ copies/ml; and 17% vs 19% for HBV-DNA <400 copies/ml. In a sub-analysis of those patients who responded to peginterferon α-2a monotherapy at the end of treatment, more than half (55%) had HBV-DNA levels $<100\,000$ copies/ml for most of the 12-month follow-up; 30% had HBV-DNA levels $<20\,000$ copies/ml, and 15% had HBV-DNA levels permanently <400 copies/ml. **Conclusion:** A finite 48-week course of peginterferon α-2a can induce high rates of biochemical and virologic response that are sustained 1 year after the end of treatment.

APASL/Free Paper/Abstract/132

HBe-antigen negative chronic hepatitis B: cost-effectiveness of peginterferon α-2a compared with lamivudine treatment in Taiwan

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Introduction: In Taiwan, the carrier rate of HBsAg is 15–20%, one of the highest in the world. Among those patients with chronic hepatitis B (CHB), HBeAg-negative disease accounts for approximately 40–50% patients. A recent study found that peginterferon α-2a (40 kDa) is more effective than lamivudine in treating HBeAg-negative CHB, but its cost-effectiveness has not been evaluated. We aimed to evaluate the incremental cost-effectiveness of 48 weeks of peginterferon α-2a compared to 48 weeks of LAM, from the perspective of the Taiwan Bureau of National Health Insurance. **Patients and Methods:** We developed a Markov model to simulate the natural history of HBeAg-negative CHB in a cohort of 40-year-old patients. Efficacy, disease progression, economic, and quality of life data were derived from the published literature and a survey of clinical experts in Taiwan. Life expectancy, quality-adjusted life expectancy, lifetime costs (NTD$), and incremental cost-effectiveness ratios (ICERs) were calculated. **Results:** The gain in quality-adjusted life years (QALYs) for 48 weeks of peginterferon α-2a compared to 48 weeks of LAM was 0.45 at an additional cost of NTD$157 000 (US$5000), resulting in an ICER of NTD$347 000 (US$11 000) per QALY gained. Despite the variation in each parameter used in the analysis, the ICER did not exceed NTD$448 000 (US$14 000) per QALY gained. **Conclusion:** In HBeAg-negative CHB, 48 weeks of treatment with peginterferon α-2a compared to 48 weeks of LAM appears to offer life expectancy and quality of life improvements at a favorable cost-effectiveness ratio.

APASL/Poster/Abstract/133

More potent on-treatment viral suppression with lamivudine ± peginterferon α-2a (40 kDa) [is not associated with increased rates of sustained response: results from two large randomised trials

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Introduction: Nucleos(t)ide analogues are associated with high on-treatment HBV-DNA suppression. However, the effect of on-therapy viral suppression on HBeAg seroconversion and off-therapy sustained response is unclear. We investigated the effect of on-treatment HBV-DNA suppression on sustained response in two large, randomised trials of patients with HBeAg-positive or HBeAg-negative CHB. **Patients and Methods:** HBeAg-positive ($n = 814$) and -negative ($n = 537$) patients received 48 weeks of peginterferon α-2a (40 kDa) (180 μg once-weekly)+placebo, peginterferon α-2a+lamivudine (LAM) (100 mg once-daily) or LAM. Patients were assessed 24 weeks post-treatment (week 72). **Results:** In the HBeAg-positive and -negative studies, viral suppression by week 48 was greater with peginterferon α-2a+LAM (-7.2 log and -5.0 log, respectively) and LAM alone (-5.8 log and -4.2 log) than with peginterferon α-2a alone (-4.5 log and -4.1 log). However, at week 72, responses with peginterferon α-2a (32% HBeAg seroconversion (HBeAg-positive) and 59% ALT normalisation (HBeAg-negative)) were similar to peginterferon α-2a+LAM (27% and 60%), but significantly superior to LAM (19% and 44%; $P \leq 0.004$). HBsAg seroconversion rates with peginterferon α-2a (3% (HBeAg-positive) and 3% (HBeAg-negative)) and peginterferon α-2a+LAM (3% and 2%) were also superior to LAM (0% and 0%; $P = 0.004$ and 0.029). More potent HBV-DNA suppression resulted in lower rates of LAM-resistant YMDD mutation development. **Conclusion:** Despite greater viral reduction with LAM ± peginterferon α-2a, off-therapy response was highest with peginterferon α-2a alone, suggesting that more potent on-treatment HBV-DNA suppression does not always translate into improved sustained response. This indicates that the immunomodulatory activity of peginterferon α-2a contributes considerably in sustaining response post-treatment.

APASL/Poster/Abstract/134

Histologic improvement and sustained response in patients with HBeAg-positive or HBeAg-negative chronic hepatitis B treated with peginterferon α-2a (40 kDa)

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Introduction: Established treatments for CHB have been shown to promote improvements in liver histology that are generally associated with virologic and biochemical response. We investigated the relationship between histologic improvement and off-therapy sustained responses in patients receiving peginterferon α-2a (40 kDa) monotherapy in two large, randomised studies. **Patients and Methods:** HBeAg-positive ($n = 271$) and HBeAg-negative ($n = 177$) patients received peginterferon α-2a (180 μg once-weekly) ± placebo for 48 weeks and were assessed 24 weeks after the end of treatment (week 72). Histologic response was defined as a reduction in the modified HAI score of at least 2 points, compared with the pre-treatment score. **Results:** Among patients with a paired biopsy, rates of histologic improvement 24 weeks after the end of treatment were 49% and 59% in the HBeAg-positive and HBeAg-negative studies, respectively. In both studies, there was a significant association between improved histologic activity and sustained virologic and biochemical responses at week 72 ($P \leq 0.001$). In the HBeAg-positive study, a histologic response occurred in 73% of patients with sustained HBeAg seroconversion vs 36% of patients without HBeAg seroconversion. In the HBeAg-negative study, a histologic response occurred in 71% of patients with sustained normal ALT vs 43% of patients without normalised ALT. **Conclusion:** A finite 48-week course of peginterferon α-2a was able to induce histologic improvements 24 weeks after the end of treatment in around a half of all patients, regardless of whether they had HBeAg-positive or HBeAg-negative CHB. In patients treated with peginterferon α-2a, there is a significant association between improved histology and sustained response.

APASL/Free Paper/Abstract/135

Cost-effectiveness of peginterferon α-2a compared with lamivudine treatment in patients with HBe-antigen positive chronic hepatitis B in Taiwan.

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Introduction: Peginterferon α-2a (40 kDa), a new treatment option for patients with chronic hepatitis B (CHB), offers improved efficacy with a defined treatment duration compared with lamivudine (LAM), but at a higher cost. We undertook an economic evaluation from the perspective of the Taiwan Bureau of National Health Insurance to assess the clinical outcomes and costs of peginterferon α-2a for the treatment of patients with HBeAg-positive CHB, compared with LAM treatment for 48 weeks. **Patients and Methods:** A cost-effectiveness analysis was carried out using a state-transition Markov model simulating the natural history of HBeAg-positive CHB. Efficacy data were obtained from a randomized clinical trial of 820 patients (87% were Oriental) comparing peginterferon α-2a to LAM. We modeled a hypothetical cohort of 32-year-old patients with HBeAg-positive CHB. Life expectancy, quality-adjusted life expectancy, lifetime costs (NTD$), and incremental cost-effectiveness ratios (ICERs) were estimated. **Results:** A 48 week treatment with peginterferon α-2a compared to LAM resulted in higher total costs, but longer quality-adjusted life expectancy, yielding an ICER of NTD$381 000 (US$12 000) per quality-adjusted life year (QALY) gained. Although there is uncertainty associated with the prognosis of HBeAg-positive CHB, the ICER did not exceed NTD$485 000 (US$15 000) per QALY

gained despite variation in each parameter used in the analysis. **Conclusion:** A 48 week treatment with peginterferon α-2a compared to 48 weeks of LAM treatment in CHB patients who are HBeAg-positive appears to offer life expectancy benefits at a favorable cost-effectiveness ratio.

APASL/Free Paper/Abstract/136

Effect of age, gender, prior anti-HBV therapy and drug exposure on sustained response in Asian patients enrolled in a large multinational study of peginterferon α-2a (40 kDa) ± lamivudine vs lamivudine for chronic hepatitis B

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Introduction: This analysis examined the effect of age, gender, prior anti-HBV therapy and drug exposure on sustained response in Asian patients enrolled in a large, randomised clinical trial. **Patients and Methods:** Asian patients ($n = 708$) HBeAg-positive CHB received 48 weeks of peginterferon α-2a (40 kDa) peginterferon α-2a([180 μg once weekly+placebo), peginterferon α-2a+lamivudine (LAM) (100mg once-daily) or LAM. Patients were assessed 24 weeks post-treatment (week 72). **Results:** Rates of HBeAg seroconversion 24 weeks post-treatment were significantly higher with peginterferon α-2a containing treatment than with LAM: 31%, 29% and 19% for peginterferon α-2a, peginterferon α-2a+LAM and LAM, respectively ($P < 0.02$) in patients receiving peginterferon α-2a monotherapy, age did not affect the rate of sustained HBeAg seroconversion , but response was slightly higher in female (35%) vs male (30%) patients; rates of HBeAg seroconversion in patients without prior anti-HBV therapy, with prior LAM or prior conventional IFN treatment were comparable to the overall rate (30%, 27%,36%, and 31%, respectively). In the peginterferon α-2a monotherapy arm, drug exposure was very high, with 79% of patients receiving >90% of the total peginterferon α-2a dose. HBeAg seroconversion rates in patients receiving <90% or >90% of the total peginterferon α-2a dose were 22% (95% CI: 9–34%) and 33% (95% CI: 26–40%). **Conclusion:** In Asian patients, peginterferon α-2a provided higher rates of HBeAg seroconversion than LAM, irrespective of prior anti-HBV therapy, age or gender. Exposure to peginterferon α-2a among Asian patients in the study was high, reflecting the good tolerability of the drug. The extent of peginterferon α-2a exposure did not significantly affect HBeAg seroconversion rates.

APASL/Plenary/Abstract/137

Sustained response in Asian patients enrolled in two large, multinational studies of peginterferon α-2a (40 kDa) ± lamivudine vs lamivudine for chronic hepatitis B

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Introduction: The influence of ethnicity on treatment response in patients with chronic hepatitis B (CHB) has been a subject of recent debate, Asian patients have traditionally been considered to have more 'difficult-to-treat' CHB. We investigated treatment response in Asian patients enrolled in two large, randomised clinical trials. **Patients and Methods:** Asian patients with HBeAg-positive ($n = 708$) or –negative ($n = 332$) CHB received 48 weeks of peginterferon α-2a (40 kDa) (180 μg once-weekly)+placebo, peginterferon α-2a+lamivudine (LAM) (100 mg once daily) or LAM. Patients were assessed 24 weeks post-treatment (week 72). **Results:** Asian patients were enrolled at centres throughout Asia, Europe and America. The predominant infecting HBV genotypes in Asian patients from both studies were C (63%) and B (35%). In the HBeAg-positive study, sustained HBeAg seroconversion rates were significantly higher with peginterferon α-2a (31%; $P = 0.005$) or peginterferon α-2a+LAM (29%; $P = 0.02$) than with LAM (19%). In the HBeAg-negative study, rates of sustained HBV-DNA <400 copies/ml were significantly higher with peginterferon α-2a (26%; $P = 0.003$) or peginterferon α-2a+LAM (24%; $P = 0.012$) than with LAM (11%). Among Asian patients treated with peginterferon α-2a (± LAM), 8 of 476 (2%) patients in the HBeAg-positive study and 5 of 220 (2%) patients in the HBeAg-negative study achieved sustained HbsAg seroconversion after only 6-month treatment-free follow-up. No patients treated with LAM alone achieved HbsAg seroconversion. **Conclusions:** In Asian patients, peginterferon α-2a provides significantly higher rates of off-therapy sustained response than LAM. The results demonstrates the possibility of sustained HbsAg response in Asian patients after a finite duration of peginterferon α-2a, an outcome that was not seen with LAM.

APASL/Poster/Abstract/138

Predicting response in a large, multinational trial of peginterferon α-2a (40 kDa ± lamivudine vs lamivudine alone for HBeAg-positive chronic hepatitis B

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Introduction: Baseline and on-treatment predictors of response are used in the treatment of hepatitis C to improve the chance of response, enhance patient motivation and avoid unnecessary treatment. We investigated predictors of response in patients with CHB receiving peginterferon α-2a (40 kDa) ± lamivudine (LAM) or LAM alone. **Patients and Methods:** HBeAg-positive patients ($n = 814$) received 48 weeks of peginterferon α-2a (180 μg once-weekly)+placebo, peginterferon α-2a+LAM (100 mg once-daily) or LAM. Response was defined as HBeAg seroconversion 24 weeks post-treatment (week 72). **Results:** Rates of HBeAg seroconversion at week 72 were significantly higher with peginterferon α-2a alone (32%; $P < 0.001$) and combination therapy (27%; $P < 0.023$) than with LAM alone(19%). In multivariate analyses, high ALT, low HBV-DNA and low HBeAg levels at baseline were significant predictors of HBeAg seroconversion ($P < 0.001$). Among patients receiving peginterferon α-2a alone, the rate of HBeAg seroconversion was 41% if baseline ALT levels

were $>5 \times$ ULN, and 53% if HBV-DNA levels were <9.1 log copies/ml. HBV genotype was not significantly predictive of response. Of note, response in genotype C patients receiving peginterferon α-2a alone (31%) was similar to genotype B patients (30%). Quantitative HBeAg was a better on-treatment predictor than HBV-DNA; HBeAg-seroconversion rates at week 72 were 14% in patients with week 12 HBeAg levels >100 IU/ml, but were 53% in patients with week 12 HBeAg levels <10 IU/ml. **Conclusions:** High ALT, low HBV-DNA and low HBeAg at baseline were independently predictive of sustained response in patients with HBeAg-positive CHB. In contrast to results with conventional IFN-α, peginterferon α-2a provides equally good response rates in patients with genotypes B and C.

139
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140
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141
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APASL/Free Paper/Abstract/142
Pitfalls in management of symptomatic simple liver cysts: report of two cases
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Management options for symptomatic non-parasitic simple liver cyst vary widely. Therapeutic options range from percutaneous cyst aspiration, aspiration and instillation of sclerosing agent, open cyst unroofing, laparoscopic cyst unroofing, cystenterostomy, and cyst excision. Despite improved imaging modality, the presence of neoplasia is still difficult to be determined before and during surgery. The management of neoplastic cyst is totally different. To achieve a satisfactory result, a good preoperative evaluation and a tailored patient approach is very important before considering any intervention. Similar to the widely and rapidly accepted laparoscopic cholecystectomy, laparoscopic wide cyst unroofing is performed with great enthusiasm for any symptomatic simple liver cyst. After a period of time, there are some unsuccessful cases with laparoscopic unroofing. A retrospective review was done for our two unsuccessful simple liver cyst cases in the hope that it can be avoided in the future.

APASL/Poster/Abstract/143
Clinical and laboratory features of non-cirrhotic portal hypertension in Cipto Mangunkusumo Hospital
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Objective: To describe clinical and laboratory features of oesophageal varices due to non-cirrhotic portal hypertension in children. **Methods:** We describe six patients of non-cirrhotic portal hypertension admitted to Cipto Mangunkusumo Hospital during 1999–2004. **Result:** Six of 25 portal hypertension patients were diagnosed as non-cirrhotic portal hypertension based on clinical manifestations, laboratory findings and Doppler ultrasound examinations. Five boys and one girl ranging from 4 to 14 years old were registered as this group during 1999–2004. Recurrent haematemesis and melaena were the main problems of all cases. Splenomegaly was found in all cases but only three cases showed hepatomegaly. Peripheral blood test revealed anaemia and thrombocytopenia. Liver function tests were within normal limits except for prolonged prothrombin time in two cases, which was not persistent. Only three patients underwent liver biopsy, which showed hydropic degeneration and mild piece necrosis. Three patients showed third to fourth grade of oesophageal varices and two patients were with first to second grade. One patient was only clinically diagnosed. We performed ligation in three cases and sclerotherapy in two cases. All patients were given isosorbide mononitrate and propanolol for long-term management. **Conclusion:** Non-cirrhotic portal hypertension showed recurrent haematemesis and melaena, normal liver function and splenomegaly. In spite of oesophageal varices in endoscopic findings, no sign of liver cirrhotic was found in liver biopsy.

APASL/Poster/Abstract/144
Prevalence of hepatitis B virus infection among children of HBV carrier or infected mothers
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Objective: Hepatitis B is endemic in several regions of the world including Indonesia with the carrier rate as much as 3–20%. This high prevalence has occurred because of vertical transmission and horizontal infection since an early age. The aim of this study was to determine the prevalence of hepatitis B virus infection among children of HBV carrier or infected mothers. **Methods:** This study was carried out descriptively cross-sectional on children of HBV carrier or infected mothers who came to the Hepatology Subdivision, Internal Medicine Department Dr. Cipto Mangunkusumo Hospital during January 2002–April 2003. Serologic tests of HBsAg, anti-HBs and anti HBc were done using ELISA method. **Results:** There were 59 children of 32 HBV carrier/infected mothers who matched the inclusion criteria with the age range of 9 months to 18 years. We found HBsAg positive in 13.6%, anti HBs positive in 62.7% and anti HBc positive in 6.8% of the children. **Conclusion:** Prevalence of hepatitis B virus infection among children of carrier/infected mothers was 13.6%.

APASL/Poster/Abstract/145
Pancreatic metastasis from breast carcinoma presenting as obstructive jaundice: serial case reports
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Metastatic pancreatic tumors from breast cancer are uncommon and rare cases. Most tumors in the breast are slow growing so it is possible to find this metastasize to other regions. Two cases of jaundice are reported that were secondary to obstruction of the common bile duct by metastatic carcinoma of the breast. Our first patient, a 43-year-old woman, was admitted with unexpected

obstructive jaundice. She also felt right breast mass and pain. Physical examination showed a mass $7 \times 7 \times 5$ cm^3 in the right breast, suggestive of breast cancer. No lymph node metastasis was observed. Laboratory findings showed that the carcinoembryonic antigen (CEA), AFP and Ca 19-9 levels were still in normal range. We diagnosed obstructive jaundice due to pancreatic tumor demonstrated on computed tomography and then performed ERCP plus endoscopic stenting. Resolution of jaundice was achieved in this patient. Chemotherapy was given to the patient using six courses of chemotherapyusing fluorouracil, adryamicin and cyclophosphamide (FAC), intravenously. The second patient, a 44-year-old woman, was hospitalized for obstructive jaundice 2 years after extended mastectomy. Laboratory findings showed that the carcinoembryonic antigen (CEA), Ca 15-3 and Ca 19-9 levels increased to 22.9 ng/ml, 76.2 U/ml and 15887 U/ml, respectively. Abdominal ultrasound found dilatation of common bile duct due to a tumor in the head of the pancreas. ERCP examination showed dilatation of common bile duct with dorsal narrowing. **Conclusion:** This clinical picture was a late manifestation and the first evidence of spread of the disease. In patients with a history of carcinoma of the breast, the possibility of extrahepatic biliary metastasis should always be considered in the differential diagnosis of jaundice before concluding that extensive hepatic involvement is the cause of jaundice.

APASL/Poster/Abstract/146

Ten year follow-up of a liver cirrhosis patient following transjugular intrahepatic portosystemic shunt (TIPS)

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The transjugular intrahepatic portosystemic shunt (TIPS) is an advance management in the complications of portal hypertension. It is most commonly used in the management of refractory variceal bleeding, where it can prevent rebleeding. TIPS usefulness is limited by two major problems: shunt dysfunction and hepatic encephalopathy. Patients who bled from gastric varices had lower mortality than those who bled from esophageal varices. Hepatic encephalopathy is a frequent event after transjugular intrahepatic portosystemic shunt (TIPS). We report a 68-year-old female with liver cirrhosis who underwent TIPS 11 years ago. She had liver cirrhosis presenting with complications of portal hypertension since 1 year before the TIPS procedure. The diagnosis of cirrhosis was confirmed by biopsy and was basedon clinical, radiological and laboratory findings. This patient was without hepatic encephalopathy history and ascites before. Pre-TIPS assessment showed that her bilirubin, creatine and albumin were within normal limits. We evaluated that this patient had Child–Pugh class A before the TIPS procedure. Her main problem before the TIPS procedure was esophageal varices and thrombocytopenia with platelet count 40 000. The indication of TIPS for this patient was recurrent variceal bleeding. Ten years follow-up found that the patient had variceal rebleeding only once during 7 years after the TIPS insertion. Esophageal band ligation had succeeded to eradicate esophageal varices. She had hepatic encephalopathy only twice in 10 years after the TIPS procedure. In this patient, this problem can be overcome with conservative treatment. At present, even after 11 years of the TIPS procedure, the condition of this patient is still good. **Conclusions:** This case report has demonstrated that TIPS has been used successfully in the management of variceal bleeding, and has a low complication rate after 10 years follow-up for a patient with Child–Pugh class A. The evaluation of prognostic factors is the key towards evaluatingclinical interventions in liver cirrhosis.

147

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148

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APASL/Poster/Abstract/149

Lower serum viral loads in young patients with hepatitis B virus-related hepatocellular carcinoma

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Introduction: Advanced age and high hepatitis B virus (HBV) DNA level are risk factors associated with the development of HBV-related hepatocellular carcinoma (HCC). However, little is known about the role of viral load in the carcinogenesis of HCC in young people. **Patients and Methods:** A total of 183 HBV-related HCC patients and 202 HBV carriers were enrolled. Serum viral loads in young ($\leq$ 40 years of age) and old ($>$40 years of age) HCC patients were compared with those in HBV carriers. Other factors associated with the development of HCC were also analyzed. **Results:** Serum alanine aminotransferase (38.7 ± 24.1 vs. 58.4 ± 65.4 IU/l, $P<0.05$) and HBV DNA levels ($\log_{10}$ titer: 4.20 ± 1.33 vs. 4.80 ± 1.39, $P=0.05$) were lower in young HCC patients than in old HCC patients. There was a positive correlation between the age and serum HBV DNA loads in HCC patients but a negative correlation in HBV carriers. Young HCC patients with HBV genotype B infection had higher viral loads than those with genotype C ($\log_{10}$titer: 4.79 ± 1.34 vs. 3.27 ± 0.60, $P<0.05$). By multivariate logistic regression analyses, high serum HBV DNA levels were associated with the development of HCC in old patients (odds ratio (OR) 1.584, 95% confidence interval (CI) 1.075–2.333) rather than in young patients (OR 0.848, 95% CI 0.645–1.116). **Conclusion:** Viral factors in association with the development of HBV-related HCC in young patients are different from their old counterparts. The complicated interplay between host and virus could be responsible for the emergence and aggressive outcome of early-onset HCC.

APASL/Poster/Abstract/150

Clinical significance of intrahepatic HCV RNA level in chronic HCV infection

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Introduction: There was a correlation between serum and intrahepatic HCV RNA levels in chronic HCV infection. However, the debate continues on whether intrahepatic HCV viral load correlates with the severity of liver disease activity. This

study was carried out to identify the clinical significance of intrahepatic HCV RNA level in chronic HCV infection. **Patients and Methods:** Thirty-eight anti-HCV positive patients were included (M:F = 24:14, mean age: 51.3 y.o.) (CH:LC = 29:9). Percutaneous liver biopsy was performed and remaining tissue was stored in liquid nitrogen. HCV RNA was extracted by QIAamp® RNA Micro Kit and quantification of serum and hepatic HCV RNA were performed using the AMPLICOR™ HCV MONITOR Kit. Seventeen of them were treated with INF-α and ribavirin for chronic hepatitis C. **Results:** (1) There was a significant correlation between intrahepatic and serum HCV RNA levels (intrahepatic HCV RNA:$1.9 \pm 3.1 \times 10^7$ copies/g vs serum HCV RNA: $3.2 \pm 3.2 \times 10^6$ copies/ml) ($R = 0.538$, $P < 0.05$). (2) Histologically, total HAI score ($R = 0.346$, $P < 0.05$) and periportal inflammation ($R = 0.398$, $P < 0.05$) were weakly correlated with intrahepatic HCV RNA level. (3) Serum ALT level was not correlated with intrahepatic HCV RNA level. (4) Intrahepatic HCV RNA level was not different according to HCV genotype. (5) Intrahepatic HCV RNA level was not different according to treatment response. **Conclusion:** Intrahepatic HCV RNA level was correlated with serum HCV RNA level and weakly correlated with periportal inflammation. However, it was not associated with serum ALT, HCV genotype or response to antiviral therapy. Therefore, it seems unlikely that measurement of intrahepatic HCV RNA level provides additional information in anti-HCV positive patients.

APASL/Poster/Abstract/151

Clinical and laboratory profile of hepatitis C in hemophiliac children

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Many hemophiliacs were infected with hepatitis C virus (HCV) in childhood after transfusions with inadequately or non-virus-inactivated clotting factor products. There is still limited information available on the clinical course of HCV infection in children. Patients registered in hemophilia society who tested anti-HCV positive at Pediatric Department Dr. Cipto Mangunkusumo Hospital were enrolled. None of them received antiviral treatment. All of the subjects were infected with HCV before the age of 18 years and after at least 6 months of acute infection clinical examination, ALT, platelets and HCV RNA test were performed. Thirty-nine subjects were enrolled. Current median age was 15 years. The median age for first time transfusion was 15 months. Twenty-two (56%) of 39 subjects showed clinical manifestations. Liver and spleen enlargement were not found in all of the subjects. Ten (26%) of the 39 subjects had elevated ALT. Platelet counts were within normal limits in all subjects. Twenty-four (61%) patients had chronic hepatitis, whereas the remaining 15 (39%) subjects spontaneously cleared HCV. In conclusion: HCV infection in pediatric patients had mild clinical manifestations and laboratory abnormality. Sixty-one percent of the subjects developed chronic hepatitis.

APASL/Poster/Abstract/152

Efficacy of low-dose peginterferon α – 2b with ribavirin in chronic hepatitis C – an Indian experience

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Introduction: The combination of peginterferon and ribavirin is the main stay of treatment in chronic hepatitis C. Peginterferon α-2b is recommended in a dose of 1.5 mcg/kg body weight weekly in combination with ribavirin. We conducted a non randomized pilot study to assess the efficacy of peginterferon α-2b in doses of 50 and 80 mcg weekly (based on body weight) plus ribavirin in HCV genotype 2 and genotype 3 chronic hepatitis C patients. **Methods:** During the study period of January 2002 to December 2003, all patients diagnosed as chronic hepatitis C or HCV-related compensated cirrhosis were treated with peginterferon α-2b 50 mcg S/C weekly (body weight < 60 kg) or 80 mcg S/C weekly (body weight > 60 kg) plus ribavirin 800 mg/day for 24 weeks. **Results:** Overall 28 patients, 14 patients in each group (based on body weight) were treated during this period. Out of 28 patients, 75% were genotype 3, 18% were genotype 2 and 7% were genotype 1. The mean doses of peginterferon α-2b were 0.91 mcg/kg in group 1 and 1.23 mcg/kg in group 2, respectively. The end of treatment (ETR) and sustained virologic response (SVR) were 82% and 78%, respectively. Serious adverse effects were seen in 3.5% patients. **Conclusion:** Low-dose peginterferon α-2b in combination with ribavirin for 24 weeks is effective in HCV genotypes 2 and 3 chronic hepatitis C patients.

APASL/Poster/Abstract/153

Liver disorders in children with malignancy in RSCM

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Liver disorders in children with malignancy can be caused by liver necrosis due to administration of cytostatic agents and other medicines, infiltration of tumor cells into the liver, infection by hepatitis virus obtained through transfusion, sepsis, and others. The aim of this study was to find out the clinical patterns of liver disorders in children with malignancy. This study used retrospective data. Data were obtained from the Pediatric Hema-Oncological Division of FKUI-RSCM from March 1 2004 until March 31 2005. Of the 39 patients, 18 patients were diagnosed as having acute lymphoblastic leukemia (ALL), eight patients had acute myeloblastic leukemia (AML), and 13 patients had solid tumors. Patients with ALL were given therapy as follows: nine patients for induction therapy, four patients for CNS-prevention therapy, one patient for maintenance therapy, and four patients had no therapy. Patients with AML were given therapy as follows: seven patients for induction therapy and one patient for consolidation therapy. Liver disorders were found in 25 patients with hepatitis, 11 patients with cholestasis, two patients with both of the diseases and one patient with hepatomegaly due to hepatoblastoma. Of the 39 patients with liver disorders, the disorders in 28 patients were caused by cytostatic agents, in seven patients due to infiltration of tumor cells, in three patients suspected of viral infection and of infiltration of tumor cells, and in one patient due to sepsis. The following medications were given for ALL: methotrexate, cytosine arabinoside, L-asparaginoside, daunorubicin, vincristine, 6-mercaptopurine, cyclophospamide, and for AML: methotrexate, cytosine arabinoside, vincristine, cyclophospamide, adryamicin. Fourteen patients on cytostatic agents had reduced doses, 10 patients had strict follow-up, and five patients had delayed treatment. These results showed that patients with malignancy should be regularly followed up to detect any liver disorders due to cytostatic agents, tumor cell infiltration, viral infection, and sepsis, or a combination of these factors. Treatment could be delayed or the doses reduced or continued under monitoring.

APASL/Poster/Abstract/154

Neonatal liver disease in Ciptomangunkusumo Hospital

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Primary liver disease in neonates is rare. Much of the liver dysfunction seen in the neonatal period is secondary to systemic illness such as sepsis or hypoxic injury. Early intervention to address the cause of dysfunction is critical to successful management of liver disease. A retrospective descriptive study has been done by evaluating the medical records of hepatic diseases in the neonatal ward, which had been consulted to the Gastroenterohepatology Division from January 2004 until February 2005 in Child Health Department, Cipto Mangunkusumo Hospital, Jakarta. Of 523 neonates in the perinatology ward, we reviewed 47 (9%) cases of neonatal liver diseases, which had been consulted to the Gastrohepatology Division. There were 42 girls and five boys, aged between 5 and 31 days old. There were 12 (25.5%) preterm infants and 35 (74.5%) term infants. The diagnosis of these patients was 35 cholestasis alone, two hepatitis, seven cholestasis and hepatitis, three others (one ascites, one unconjugated hyperbilirubinemia, one suspected neonatal hemochromatosis). Cholestasis were due to sepsis alone in 32, antifungal therapy alone in six, both sepsis and antifungal therapy in three, suspected Crigler–Najjar type-2 in one patient. Two patients underwent colostomy due to atresia ani and malrotation. Of 42 patients with cholestasis, 29 patients underwent blood culture. We found 17 *Acinetobacter calcoaceticus*, one *Enterobacter aerogenes*, one *Staphylococcus epidermidis*, one *Klebsiela pneumonia*, one *Escherichia coli*, one *Serratia marcessens*, one *Candida albicans*, yeast cell in one patient and five sterile. Of the 523 patients, 47 (9%) neonates had been consulted to the Gastroenterohepatology Division with presentation of cholestasis in 42 patients (89%). The etiology of liver disease in neonates in our department was mainly sepsis (74.5%) and mainly caused by *Acinetobacter calcoaceticus* (58.6%).

155

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APASL/Poster/Abstract/156

Significance of caput medusa in Budd–Chiari Syndrome: Our experience of 12 patients and collateral pathways as compared with post-necrotic cirrhosis

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Background/Aims: The Budd–Chiari syndrome is an unusual form of portal hypertension caused by occlusion of the hepatic venous flow and it is often frequently complicated by inferior vena caval occlusion with a potentially dismal outcome if not treated optimally. Our study is to review etiogical, clinical features and especially collateral pathways in the Budd–Chiari syndrome. **Methods:** From 1990 to 2004, 12 patients were diagnosed with the Budd–Chiari syndrome in our hospital. **Results:** Seven patients were males and five were females. Median age at presentation was 48 years (range 20–74 years). Four patients (33%) have membranous obstruction of vena cava, but the other six patients (50%) do not have any etiologic factors or associated disorders. Generalized swelling and abdominal distension were the most common symptoms. Splenomegaly and ascites were the common signs. The diagnosis of this syndrome was performed by abdominal CT scans and in six patients, vena cavography through femoral vein catheterization was confirmed. Eighty-three percent of the patients showed obstructing lesions of the hepatic portion of the inferior vena cava. Only two patients (17%) had hepatic vein obstruction without caval lesions. The collateral pathways in abdominal CT scans showed vertebrolumbar-azygous pathway and intrahepatic collaterals at seven patients (58.3%), respectively. Especially, para-umbilical collaterals of the abdominal wall (Caput Medusa) were shown in six patients (50%) and theirs occurrence rate was significantly higher in two patients among the 149 patients with post-necrotic cirrhosis from January to March 2004 in our hospital ($P = 0.00028$). **Conclusion:** The Budd–Chiari syndrome is a rare form of portal hypertension. Therefore, diagnosis of the syndrome was delayed and resulted in poor prognosis. If para-umbilical collaterals of the abdominal wall were presented, especially in the early period of cirrhosis, we should think of the Budd–Chiari syndrome as a cause of liver cirrhosis.

157

Abstract withdrawn

158

Abstract withdrawn

APASL/Poster/Abstract/159

Clinical assesment of transarterial chemoembolization using polyvinyl alcohol for management of hepatocellular carcinoma: concern about hepatic damage

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Background: Polyvinyl alcohol (PVA) has seldom been used for the embolic agents during transarterial chemoembolization (TACE). It may completely occlude the vessels and might compromise the patient's hepatic functions and distort arterial access for subsequent TACE. But, several experimental and clinical reports have shown that the occluded vessels with PVA particles also recanalize with another mechanism rather than with gelfoam. **Aim:** To assess the liver function and the initial results after arterial embolization using PVA during TACE. **Material and Methods:** The authors performed arterial embolization using PVA particles, instead of commonly using gelfoam pledgets at the end of TACE after infusion of chemotherapeutic agent and lipiodol emulsion for 28 HCCs in 27 patients. Three patients were excluded in this study because of lack of follow-up computed tomography (CT) after TACE. Eighteen patients were men. The mean age of the patients was 59.8 years.Twenty patients were in class A and 4 patients were in class B according a Child–Pugh classification. The cause of cirrhosis was hepatitis B (13), hepatitis C (four) and alcohol or unknown (seven). The inclusion criteria for embolization with PVA were viable single or lesser than three nodular HCCs having visible feeder(s) and possible segmental or subsegmental embolization. The longest diameter of nodules varied from 12.9 to 135.7 mm

(mean: 31.8 mm) and the mean amount of cisplatin and lipiodol used were 61.3 mg and 5.3 ml. Follow-up was done with contrast-enhanced spiral CT in all patients and continuing TACE in four patients. Mean follow-up period was 13.5 weeks. **Results:** Complete embolization was achieved in all patients and compact lipiodol accumulation was noted in 19 nodules, faint accumulation in four nodules and partial accumulation in two nodules on a post-TACE spot shot. Two of the faintly accumulated nodules and the other two partially accumulated nodules became compact on follow-up CT. All nodules except three were stable compact during the follow-up periods. The mean tumor reduction ratio was 17% at 2 weeks and 63.5% at last follow-up CT after TACE ($P<0.001$). The decline of the level of AFP between a baseline value and that of last follow-up was significant ($P=0.006$). The elevation of AST, ALT and total bilirubin levels between baseline and that of early follow-up period within 2 weeks after TACE was significant ($P<0.05$), but it was restored after that period. This pattern was similar regardless of the tumor size, Child–Pugh class or size of PVA particle. No severe adverse reactions or complications were noted. **Conclusion:** Adjunctive embolization with PVA particles during TACE is effective in getting stabilization of HCC. It may deteriorate hepatic functions for at least 2 weeks, but after that hepatic function is recovered.

APASL/Poster/Abstract/160
Combination of peginterferon α-2b (12 kDa) and lamivudine in HBeAg negative chronic hepatitis B – an Indian experience
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Introduction: Treatment of HBeAg negative chronic hepatitis B infection (e-CHB) is associated with poor sustained response (SR). Recently, Marcellin et al. showed SR of 44% with peginterferon (40 kDa)–lamivudine combination therapy in treatment naïve e-CHB. We undertook this open-labeled prospective study to study the response of peginterferon α-2b (12 kDa)–lamivudine combination in Indian patients of e-CHB. **Methods:** Patients of e-CHB with persistently elevated transaminases (>2 times upper limit of normal) were treated with lamivudine 100 mg PO daily and peginterferon 1.5 μg/kg SC once a week for 12 months. These patients were divided into (1) treatment naïve group and (2) treatment failure group – patients who were non-responsive to at least two treatment regimens. Patients were tested for LFT, HBeAg, antiHBe, quantitative HBVDNA and liver biopsy when possible at inclusion. During the treatment period, LFT was tested at monthly intervals and HBeAg, antiHBe and HBVDNA at 3 monthly intervals. End of treatment response (EOR) was assessed at the end of the treatment period and SR at 6-months post treatment. Treatment response was defined as normalization of enzymes and loss of detectable HBVDNA. **Results:** A total of 18 patients with e-CHB was included in this study with mean age of 34.7 ± 6.2 years (range 20–54 years) and male:female = 8:1. (1) In treatment naïve e-CHB, 8/11 patients achieved EOR (72.7%), whereas 6/11 patients (54.5%) had SR. (2) In treatment failure e-CHB, 4/7 patients had EOR (57.1%) and 3/7 patients achieved SR (42.8%). **Conclusion:** SR was achieved in 9/18 e-CHB patients (50%) with combination of peginterferon and lamivudine.

APASL/Poster/Abstract/161
Angiomyolipoma in the liver: a case report
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Angiomyolipoma is very rare in the liver. It is more frequent in the kidney than in the liver. This is the first liver case found in Indonesia. Biologic behavior is another problem. Although considered benign, we found in the literature that a renal angiomyolipoma that had extended into the liver and metastasized to the lung exhibited typical angiomyolipoma along with other foci of transformation into a high-grade spindle cell carcinoma. In the liver, the case is also similar. It is curative with adequate surgical excision. One patient whose tumor was not excised was followed for 4 years with CT examinations; the diameter of this tumor increased by 10%. One report mentioned a case of hepatic angiomyolipoma that underwent malignant change.

APASL/Poster/Abstract/162
Comparison grading and staging at chronic hepatitis C using Knodell and METAVIR system: a retrospective study
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Interpretation of liver biopsy done on chronic hepatitis with the Knodell system did not satisfy the clinician because of discontinuity of the scale/range. In this system, fibrous septa that were also used as standard therapy were not mentioned. Some experts suggest that the Metavir system has continuity of the scale to interpret chronic hepatitis C. The aim of this study is looking for a better system that can interpret histological activity and fibrosis comparing the Knodell and Metavir systems. Samples from 27 cases of chronic hepatitis C patients were taken from 2000 to 2003. The slides were stained by hematoxylin and eosin (H&E), Van Gieson (VG), Victorian Blue (VB) and Retikulin staining. Interpretation was done by two observers individually, and then interpreted again together using the Knodell and Metavir systems. If discrepancies were found, a discussion towards the most agreeable figure is tried. In conclusion, the Metavir system is better than the Knodell system in histological activity and fibrosis because the Metavir system has less variables than the Knodell system and the scale is continuous.

163
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164
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APASL/Free Paper/Abstract/165
Hepatocellular carcinoma in infant: a case report
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Hepatocellular carcinoma is one of the most common tumors in the world. The incidence of hepatocellular carcinoma generally increases with age in all populations but it has a tendency to decrease in the elderly and is very rare in children. This is a case report of hepatocellular carcinoma in a 9-month-old boy, admitted with palpable abdominal mass in the right upper quadrant. Imaging modalities by USG could not adequately demonstrate definite findings of the tumor arising from the liver and the patient was diagnosed with neuroblastoma. Intra-operatively, the tumor mass was found to arise from the surface of the posterior edge of the liver; it was a pedunculated tumor. The histopathological examination revealed a pedunculated hepatocellular carcinoma grade 3. The Victorian Blue staining and immunohistochemistry staining done afterward showed HBsAg positivity in non-tumor as well as in neoplastic liver tissue.

APASL/Free Paper/Abstract/166

Prevalence, virological and clinical characteristics of hepatitis B virus genotypes in Pakistan

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Background: Hepatitis B virus (HBV) genotypes are gaining importance in terms of epidemiology and clinical significance. Currently, eight HBV genotypes (A–H) and their serial subtypes are known and seem to be distributed along particular geographical locations globally. However, data are scanty from many parts of the world. **Aims:** To investigate the prevalence of HBV genotypes in Pakistan and their relationship to the pattern of HBV-related liver disease. **Methods:** The HBV genotype was determined in 257 HBV DNA-positive patients using PCR-RFLP. Four of these isolates were then fully sequenced and compared to isolates from other parts of the world using molecular evolutionary analysis. **Results:** Four patients had acute and 253 had chronic HBV infection. Mean age was 28 years and there were 201 (78%) males and 56 (22%) females. HBeAg was positive in 219 (85%) patients (wild type infection) and was negative in 38 (15%) patients (pre core/ core promoter mutant infection). Patients with wild type infection were younger than patients with mutant infection (95% vs 21% patients ≤ 30 years, $P<0.001$). Mean ALT level in chronic HBV patients was 103 ± 26 IU and there was no difference in the two groups. Overall, HBV genotype D was found in 247 (96.2%) cases, followed by a combined infection with HBV genotype B+D in 9 (3.3%) and one (0.5%) case of genotype A. Seven of eight patients with mixed B+D genotype had wild type infection and only one had mutant infection. Sequence and phylogenetic analysis did not show significant differences between HBV type D isolates from Pakistan and other parts of the world. **Conclusions:** Genotype D is the most common genotype in Pakistani patients with acute and chronic hepatitis B, irrespective of the presence of wild type or mutant infection. A mixed genotype (B+D) was found in some patients, mainly with wild type infection.

167

Abstract withdrawn

APASL/Poster/Abstract/168

Hepatic vein waveforms revisited

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Purpose: Changes in Doppler waveforms of hepatic veins have been studied in cirrhotic liver and it is postulated that dampening of phasic oscillations appears with worsening of liver function. We aimed to reevaluate the significance of Doppler waveforms of hepatic vein in cirrhotic patients and to correlate them with hepatic blood flow. **Patients and Method:** One hundred and twenty-six consecutive patients of liver cirrhosis and 60 non-cirrhotic controls were enrolled in this study. The diagnosis was confirmed by histopathological examinations and/or imaging diagnosis together with clinical and biochemical parameters. Doppler waveforms were obtained from the right hepatic vein. Other parameters measured were flow volume of portal trunk, right portal vein and the hepatic artery. **Result:** Waveforms of the hepatic vein were classified into triphasic, biphasic and flat patterns. Flat waveform was rare. There was no correlation between liver dysfunction and patterns of waveforms. Inflow was elevated in cases associated with non-triphasic waveforms. **Conclusion:** Flat waves, which are postulated to be diagnostic of worsening liver function, are independent of liver function and have no diagnostic value. The role of hepatic blood flow seems to be important, suggesting hemodynamic changes rather than liver dysfunction as a plausible cause of change in waveforms.

APASL/Free Paper/Abstract/169

Profile of increasing serum transaminase in adult dengue fever and dengue hemorrhagic fever

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Introduction: Dengue virus mainly infects mononuclear phagocyte cells, but it is also present in other non-hematopoietic cells including hepatocytes. Increased levels of serum transaminase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in severe dengue infection and related to liver cell damage. In this study, we will report a profile of increasing ALT and AST in primary or secondary adult dengue fever and dengue hemorrhagic fever, and its relation to other liver functions (bilirubin direct, gamma-glutamyl transferase (γGT) and alkaline phosphatase (ALP)). **Method:** A retrospective study was conducted in Dr. Cipto Mangunkusumo National General Hospital and private (Pluit) hospital, Jakarta, in 2004. Data were selected from medical records according to these criteria: age above 14 years old, primary or secondary dengue fever confirmed by positive rapid dengue immunochromatographic test, and liver function test were performed on the first day of admission. The definition of dengue fever or dengue hemorrhagic fever was determined by WHO criteria. **Results:** Eighty-four cases fulfilled the enrollment criteria; they consisted of 54 males and 30 females aged between 14 and 72 years old. Primary infection and secondary dengue infection was present in 26 and 74% cases; dengue fever was present in 62% and dengue hemorrhagic fever in 38% cases (grade I 25% and grade II 13%). ALT and AST were increased in 78 and 60% cases, respectively; most increasing of ALT and AST was below threefold of upper normal limit (63% and

75%). Bilirubin direct, γGT and ALP were also increased in 27%, 36% and 9%, respectively. There were significant correlations between increasing of ALT and AST with GI symptoms: nausea, vomiting and abdominal pain ($P<0.05$), but no significant correlation with type of infection (primary or secondary) and severity (dengue/hemorrhagic fever grade I or II). **Conclusion:** ALT and AST were increased in 78% and 60%, and related to the presence of GI symptoms in dengue fever or dengue hemorrhagic fever. Other liver function tests (bilirubin direct, γGT and ALP) also showed an increase in some cases. Further study is needed to know the correlation between dengue virus serotype and abnormalities of liver function tests in dengue infection.

APASL/Poster/Abstract/170

Liver function profile of leptospirosis in Tarakan Hospital, Jakarta, during heavy and local floods

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Introduction: Leptospirosis is a health problem which is correlated with the environment. Floods cause Leptospira to spread out to new areas and new hosts. The aim of this study was to compare liver function in leptospirosis during heavy floods (in 2002) with local floods (in 2003–2005). **Methods:** Secondary data were from Tarakan Hospital, with inclusion criteria: fever and positive serology of leptospira (leptotek/MAT), and exclusion criteria: no data available at the end of hospitalization. **Results:** In 2002, 26 samples were gained from 43 suspected cases of leptospirosis, nine had died (three positive serology). In 2003, there were 63 cases of suspected leptospirosis (no serology, all excluded). In 2004, 29 samples were gained from 31 suspected cases of leptospirosis, and there were four deaths. Recent data (2005), from 47 cases of suspected leptospirosis, were all included, and there was one death. The liver function tests were significantly different between cases in 2002 compared with cases in 2004–2005: mean AST of cured cases was 188.55 ± 240.20 (fatal: 386.67 ± 295.55), in 2004–2005: 39.57 ± 42.74 (fatal: 178.00 ± 205.59). ALT in 2002: 106.82 ± 113.85 (fatal: 256.67 ± 219.5), in 2004–2005: 56.12 ± 68.03 (fatal: 58.00 ± 33.06). Direct bilirubin 7.99 ± 8.65 (fatal: 1.45 ± 0.92), in 2004–2005: 2.29 ± 3.78 (fatal: 5.99 ± 5.74). Indirect bilirubin 4.76 ± 5.88 (fatal: 3.25), in 2004–2005: 2.46 ± 3.87 (fatal: 0.93). Platelet count: 123.000 ± 117.146 (fatal: 104.000 ± 147.254), in 2004–2005: 124.757 ± 81.248 (fatal: 46.400 ± 33.93). **Conclusions:** The elevation of AST, ALT, and indirect bilirubin and thrombocytopenia were found more severe in 2002 when leptospirosis outbreak occurred during heavy flood in Jakarta.

APASL/Free Paper/Abstract/171

Is there still a need for early virological response evaluation in anti viral therapy for chronic hepatitis C?

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The combination of interferon α and ribavirin provides sustained virological response (SVR) in approximately 40% of chronic hepatitis C naïve patients. SVR is defined as the absence of detectable HCV RNA at 24 weeks after cessation of therapy. Analysis of patients who were treated with interferon-α demonstrated that HCV RNA levels measured at week 12 of therapy (early virological response, EVR) in genotype 1 infection were extremely useful in predicting SVR. This study represented clinical experience used of peginterferon α-2a plus ribavirin for the therapy of hepatitis C, 48 weeks for genotype 1 and 24 weeks for genotype non-1. This is to report preliminary data of ongoing evaluation and observation covering viral load, HCV genotypes and subtypes, ALT, AST, GGT, hematology, and side effects. The study was conducted from March 2003 to March 2005. There were 24 patients of hepatitis C who received 180 mcg peginterferon α-2a plus 1000 mg ribavirin. At the start of therapy, 19 patients (79.17%) had genotype 1 (Subtype 1a: 14 patients, 1b: five patients) with viral load 2.71×10^5–1.85×10^6 copies/ml, three patients had genotype 2 (2a) with viral load 3.70×10^5–5.99×10^5 copies/ml, one patient had genotype 3 (3a) with viral load 8.71×10^5, and one patient of genotype 4 (4b) with viral load 1.7×10^3 copies/ml. Twenty-four patients (100%) had ALT $\geq$ 1, 5 times upper normal limit (UNL), and one patient had normal AST. Nineteen patients had GGT normal and five patients (20.83%) had $\geq$ 1, 5 times UNL. At the start of therapy, all patients had normal Hb, leucocytes, and platelets. At week 12, all patients had undetectable viral load, five patients (20.83%) had normal ALT and four patients (16.67%) had normal AST, three patients (13.40%) had neutropenia and five patients (21.74%) had thrombocytopenia. One patient with genotype 1 at week 23 discontinued therapy because of allergic reaction and 1 patient of genotype 1 discontinued therapy at week 35 because of extreme thrombocytopenia. At the end of therapy, all patients had undetectable viral load, 19 patients (86.36%) had normal ALT and AST. SVR evaluation was offered but was not done as it was expensive. EVR is a reliable predictor of therapeutic outcome, and could serve to justify avoiding unnecessary continuation of therapy. Patients with negative EVR may be advised to stop therapy as the burden of therapy may outweigh the benefits. In this study, all patients had low viral load ($<2 \times 10^6$ copies/ml) and after 12 weeks therapy all patients showed positive EVR. Therapy for hepatitis C with peginterferon α-2a plus ribavirin repaired liver function which showed normalization of ALT and AST. Hematologic side effects due to the treatment were anemia, neutropenia, and thrombocytopenia. One patient had extreme thrombocytopenia and stopped therapy. Cessation of therapy is recommended if platelet count decreases to levels $\leq 25\,000/mm^3$. The evaluation of EVR in low viral load genotype 1 hepatitis C infection is probably not cost-effective. This assumption should be clarified with additional large-scale data.

172

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173

Abstract withdrawn

APASL/Poster/Abstract/174

Endoscopic management of bleeding oesophageal varices with *N* butyl cyanoacrylate (Histoacryl) – preliminary experience in a tertiary centre

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Background: Insufficient data exist on efficacy of treating bleeding (OV) with Histoacryl. **Objectives:** To analyse the efficacy of Histoacryl in controlling bleeding OV. **Methods:** We performed a retrospective analysis of all patients who presented to the hepatology service of our hospital with bleeding OV who were treated with Histoacryl as a primary method of achieving haemostasis. Patient records from 1 January 2004 to 1 April 2005 were reviewed. All patients underwent emergency upper gastrointestinal (GI) endoscopy within 24 h of admission. All patients received the same standard of care including transfusion of blood products, pharmacologic therapy (octreotide or terlipressin) and prophylactic antibiotic therapy. Assessment of rebleeding was made using standard clinical and endoscopic parameters. **Results:** Thirteen patients were treated with Histoacryl for bleeding OV. Immediate haemostasis was achieved in all patients. Rebleeding within the first 24 h occurred in 0 patients in the Histoacryl arm. During the first 2 weeks, no patients in the Histoacryl arm had evidence of rebleeding. No patients in the Histoacryl arm showed clinical and/or radiological signs of pulmonary embolism. **Conclusion:** Histoacryl injection for the management of bleeding OV appears to be efficacious in achieving primary haemostasis and preventing rebleeding within the first 2 weeks. Thus, our data support the use of Histoacryl injection in patients with acute OV bleeding. A prospective randomised trial comparing Histoacryl to endoscopic variceal ligation is needed before this can be recommended as routine therapy.

APASL/Poster/Abstract/175

Unusual low prevalence of hepatitis B infection in Tahuna, Sangihe island, the northern part of Indonesia – a preliminary report

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Indonesia consists of thousands of islands inhabited by hundreds of ethnic groups. The prevalence of HBV infection varies widely from one part to the other, ranging from moderate to high prevalence. The most frequent HBsAg carrier rate reported from each area was 5–10%. Tahuna is the capital of Sangihe island in a relatively isolated archipelago located 150 km north of Manado, Sulawesi with a population of 35 000. There is no previous report on the prevalence of hepatitis B infection in the population. Hepatitis B universal immunization program in Tahuna was started 3 years ago. The HBsAg carrier rate reported in the blood donors in Manado is 4.7%. This study was done to measure HBsAg carrier rate and HBsAg subtype in Tahuna. The population of the study was elementary, secondary, and high school students in Tahuna city, inhabitants of a small village inside Tahuna, and a group of adults gathered in the hepatitis presentation given by our team. Venous blood sample was taken, and then HBsAg was assayed using RPHA and IC method. Blood samples were collected from a total of 836 persons (658 students, 6–18 years, 117 villagers and 61 other persons gathered in the presentation). The oldest was 76 years old. HBsAg was positive in 8 persons (0.96%). Of the 658 school children, HBsAg was positive in 2 (0.24%). HBsAg was positive in adults excepting school children in 6 (0.72%). HBsAg subtypes found in Tahuna were adw (37.5%), ayw (12.5%), and adyw (25%). The subtype pattern was different from a previous study in Menado that showed adr (50.0%), adw (35.0%), ayw (5.0%), and ayr (10.0%). The HBsAg carrier rate of 0.92% in Tahuna is much lower than the carrier rate reported from the other parts of Indonesia. The low prevalence of HBsAg in Tahuna is unusual. The HBsAg carrier rate was even lower than the Anti-HCV rate in the same population (1.2%). Study in the other islands of Indonesia showed a higher HBsAg carrier rate in the inhabitants of small islands than in those of the main island. The higher HBsAg carrier rate in the small islands was thought to be caused by the relatively closed environment in the small islands. The different pattern of HBsAg subtype in Tahuna, especially the absence of sub determinant "r", may reflect the different ancestors of the population of Manado and Tahuna. The low prevalence of Hepatitis B infection in the Tahuna population should be explored by further more detailed study.

176

Abstract withdrawn

APASL/Poster/Abstract/177

HBsAg carrier rate in pediatric patients in Mataram General Hospital (12 years after universal vaccination program)

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In 1988, before hepatitis B universal vaccination performed in Mataram, a study in pediatric patients admitted to the pediatric ward of Mataram General Hospital showed 4.3% of the children were HBsAg positive using reversed passive hemagglutination (RPHA). Universal hepatitis B immunization program had been performed in the whole of Lombok Island including Mataram since 1991. The study was done to determine HBsAg carrier rate in pediatric patients of Mataram General Hospital 12 years after hepatitis B universal vaccination program. In the present study, blood samples were taken from all the new patients admitted to the pediatric ward and were assayed for HBsAg using the same method (RPHA) in Biomedical Research Unit, Mataram General Hospital. Data on sex, age, diagnosis, and vaccination status were recorded. Of 436 patients consisting of 185 (42.4%) female and 251 (57.6%) male, aged from 1 month to 14 years old, 23 (5.3%) were HBsAg positive. The carrier rate among female patients was 10 (5.4%) and carrier rate among male patients was 13 (5.2%). The carrier rate child from the urban area was 7/175 (4%) and from the rural area was 16/261 (6%). The carrier rate of 5.3% in the pediatric patients in the current study was not lower than the carrier rate in a similar population reported in 1988 before universal vaccination program was performed in Mataram. The ineffectiveness of universal hepatitis B vaccination in this population is unusual, and the reason for this should be investigated cautiously.

APASL/Poster/Abstract/178

HBsAg antigenemia in male applicants for a job in a foreign country: the HBeAg and ALT status

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The prevalence of HBsAg antigenemia in adults from several locations in Lombok Island ranges from 8.5% to 20.3%. Mass neonatal HBV vaccinations in Lombok Island have been conducted since 1991 and this project was successful because within 4 years the project lowered the HBsAg carrier rate in vaccinated childrenby as much as 70% of the carrier rate of the same age group before the vaccination program. At the time of the study, the oldest individual who received mass neonatal immunization was 15 years old. Most of the job applicants are 19–40 years old and one of the important health qualifications of the applicants is negative HBsAg. The objective of the study was to determine the rate of HBsAg antigenemia, the HBeAg and the ALT status in male job applicants for a foreign country in Mataram. In this study, blood samples were taken from 1586 male job applicants for a foreign country in Mataram General Hospital Laboratory, assayed for HBsAg (ELISA), HBeAg (ELISA) and ALT (spectrophotometric). The results of this study showed that of 1586 male applicants aged 19–40 years, 167 (10.53%) were HBsAg positive and (33.53%) of the HBsAg-positive applicants were also HBeAg positive. The ALT of $>2\times$ normal upper limit was found in 1.8% of HBeAg-positive individuals. More than 10% of male job applicants lost the opportunity for getting a job in the foreign country due to positive HBsAg. More than a third of them were very infectious and have a possibility of getting chronic liver disease in the future. However, most of the HBsAg-positive individuals showed normal ALT.

APASL/Poster/Abstract/179

The factor associated with liver abscess recurrence

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We studied retrospectively 57 patients who were admitted to DanKook hospital. Liver abscess recurred in six of 57 patients. The male:female ratio was 1.3:1 in the nonrecurred group but in the recurred group all were male. The mean average age was 58.6 years in both groups. The duration of symptoms was 12.8 days in the nonrecurred group and 21 days in the recurred group. The right lobe was the most frequent site in both groups. The mean size of abscess was 6.3 cm in the nonrecurred group and 3.5 cm in the recurred group. PCD insertion rate was lower, with decreased abscess size and a statistical significance of $P<0.01$. PCD insertion duration was 12.2 days in the nonrecurred group and 8.75 days in the recurred group, but there was no statistical significance. *Klebesiella pneumoniae* (50%) was the most frequent bacteria in the nonrecurred group followed by *Streptococcus*, *Escherichia coli*. *E. coli* (60%) was most frequent in the recurred group followed by *K. pneumoniae*. *E. coli* was more often seen in the recurred group. Admission period was 22.8 days in the nonrecurred group and 19.8 days in the recurred group. The nonrecurred group showed a higher PCD insertion rate and longer duration than the recurred group. The larger the abscess, the higher the PCD insertion rate was, leading to a lower recurrence rate. *E. coli* was isolated in the recurred group more often than in the nonrecurred group. Aggressive PCD insertion and thorough drainage seemed to be helpful to prevent abscess recurrence. When *E. coli* is isolated, careful follow-up is necessary.

180

Abstract withdrawn

APASL/Free Paper/Abstract/181

Effect of interferon-β on the regulatory mechanism in activation of hepatic stellate cells

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Objective: To investigate the regulatory effect of interferon-beta (IFN-β) on the activation of hepatic stellate cells (HSC) through transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) pathways. **Materials and Methods:** HSC (rHSC-99 cell lines and LX-2 cell lines) were cultured in DMEM supplemented with 10% fetal bovine serum. HSC were incubated with 1000 IU/ml IFN-β for 24, 48 and 72 h in groups 1–3; HSC were incubated with 2000 IU/ml IFN-β for 24, 48 and 72 h in groups 4–6; HSC were incubated with 4000 IU/ml IFN-β for 24, 48 and 72 h in groups 7–9. Western blots were used to detect the protein expression of collagen type I, desmin, TGF-β1, TβR-I, Smad7, Smad4, PDGF-BB, PDGFR-β and β-actin in HSC. **Results:** Compared with the control group, expression of collagen type I, desmin, TGF-β1, Smad4 and PDGF-BB of groups 1–9 in rHSC-99 was significantly lower (F values were 26.235, 15.456, 27.312, 10.576 and 28.179 respectively, $P<0.01$), expression of Smad7 of groups 1–9 in rHSC-99 was significantly higher (F values were 2.492, $P=0.033$). Compared with the control group, expression of collagen type I, desmin, TGF-β1, Smad4 and PDGF-BB of groups 1–9 in LX-2 was significantly lower (F values were 35.346, 21.237, 5.526, 120.740 and 24.125 respectively, $P<0.05$), expression of Smad7 of groups 1–9 in LX-2 was significantly higher (F values were 39.988, $P<0.001$). **Conclusion:** IFN-β inhibits the fibrosis of the liver and inhibits the activation of HSC through the TGF-β and PDGF pathway.

APASL/Free Paper/Abstract/182

The function of G-CSF mobilized hematopoietic stem cells on 50% orthotopic partial liver transplantation

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Background: On the basis of the recently recognized potential of hematopoietic stem cells (HSC) to give rise to hepatocytes, we investigated the possibility that HSC and granulocyte colony-stimulating factor (G-CSF)-mobilized HSC could home to the injured liver and promote tissue repair. We also examined the origin of cells (endogenous or HSC) reconstituting liver after damage. **Materials and Methods:** Fifty percent orthotopic partial liver transplantation (PLTx) was established. Female SD rats were used as donors and male SD rats as recipients. The recipients were repeatedly administered human recombinant G-CSF for 5 consecutive days before and after 50% PLTx. Orthotopic whole liver transplantation (WLTx) and 50% partial hepatectomy (PHx) groups were used as control groups. Blood and liver samples were collected on days 1, 3, 5, 7 and 14 postoperatively (each $n=6$). The quantitative variations of the peripheral white blood cells with stem cell markers, including 02m − /Thy-1.1+, CD45+/CD34+, flt2/3+ and c-kit+ markers, were detected by flow cytometry. The expressions of CD34, c-kit and Thy-1.1 in liver grafts were detected by immunohistochemistry technique. AST and ALT in serum, mitosis index, PCNA and BrdU index were employed to evaluate liver injury and regeneration. Sry gene, a sex-determining region for Y chromosome, was detected to confirm the origin of proliferating cells reconstituting liver after injury by *in situ* hybridization

in liver sections. **Results:** Compared with the WLTx groups, 02m − /Thy-1.1+, CD45+/CD34+ cells in blood in the 50% PLTx groups and 50% PHx increased on the first day postoperatively and decreased on the following days and returned to the normal level on the seventh day postoperatively. In 50% PLTx, the CD34, c-kit and Thy-1.1 positive cells detected in portal tract areas peaked during 3–5 days postoperatively. CD45+/CD34+ positive cells could be detected. Compared with WLTx and 50% PHx groups, the survival rate was low ($P<0.05$) and liver injury was serious in the 50% PLTx groups. Compared with the 50% PHx groups, on 3 days postoperatively, mitosis index and the expression of PCNA and BrdU were low in the 50% PLTx groups, after G-CSF administration, compared with the 50% PLTx and G-CSF+50% PLTx groups, there was a high survival rate in the 50% PLTx+G-CSF groups ($P<0.05$). Compared with the 50% PLTx groups, on the third day postoperatively, the level of AST and ALT were low, and mitosis index and the expression of PCNA and BrdU were high ($P<0.05$) in the 50% PLTx+G-CSF groups and these parameters showed no obvious difference from the G-CSF+50% PLTx groups. Compared with the 50% PLTx groups, the expression of CD34+ around the portal tract region increased on the third day post-transplantation in the G-CSF+50% PLTx groups and on the fifth day post-transplantation in the 50% PLTx+G-CSF groups. Sry+cells were detected in the G-CSF mobilized groups, and increased during 3–5 days after transplantation. **Conclusions:** P2m/Thy 1.1+ and CD45+/CD34+ HSC were mobilized on the first day after 50% PLTx. G CSF treatment after 50% PLTx significantly improved survival rate and liver histology of partial graft, predominantly by promoting endogenous repair mechanisms. Therefore, mobilization with G CSF might offer a novel therapeutic approach for the increased survival of patients of partial liver graft.

183
Abstract withdrawn

APASL/Free Paper/Abstract/184
Upregulation of toll-like receptor 7 is essential for serological clearance of hepatitis B surface antigen in chronic hepatitis B virus (HBV) infection

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Background/Objective: Toll-like receptors (TLRs) play an essential role in innate defence as well as in shaping the adaptive immune response. We studied the role of TLRs in HBsAg clearance in chronic HBV patients. **Method:** We compared the expression of TLR1-9, by real-time PCR, in PBMCs collected from chronic HBV patients (HBeAg ± ; $n = 30/30$) and patients with resolved HBV infection (anti-HBs+ and anti-HBc+, $n = 20$). We further studied the TLR7 expression in serial PBMCs collected from 16 patients treated with pegylated interferon (IFN)-α2a at baseline, during the 48-week treatment period and 24 weeks after the end of therapy. HBV-specific CD4 and CD8+ T-cells were enumerated by IFN-γ producing CD4+ELISPOT assays and tetramer staining for CD8+ T-cells. **Signaling Pathway of TLR7 using *Ex Vivo* Co-culture Model:** PBMCs of patients with and without HBsAg clearance were infected with live HBV virus and TLR7 expression, HBV RNA and cccDNA in the PBMCs quantified by real-time PCR. SiRNA was then used to inhibit TLR7 expression on the PBMCs of patients with spontaneous HBsAg clearance. MyD88-dependent pathway was studied with Western blotting and real-time PCR. **Results:** TLR7 expression in PBMCs was higher in resolved HBV patients (mean ± SD 1.4 ± 0.7) than in chronic HBV patients (0.9 ± 0.4, $P = 0.03$). The expression of TLR7 was higher in chronic HBV patients with HBsAg clearance ($n = 4$) after pegylated IFN-α2a than those who remained HBsAg+ at weeks 24 (3.2 ± 1.1 vs. 1.2 ± 0.9, $P = 0.02$) and 48 (3.0 ± 1.2 vs. 1.8 ± 0.8, $P = 0.04$) of therapy and 24 weeks after the end of therapy (2.0 ± 0.7 vs. 0.8 ± 0.2, $P = 0.03$). In the *ex vivo* model, the higher TLR7 expression in PBMCs from patients with HBsAg clearance is accompanied by up-regulation of MyD-88, TRAF6 and NFκβ expression. HBV-specific CD8+ activity against surface and core peptide was higher in patients with HBsAg clearance on Day 8 of co-culture. HBV-specific CD8+ activity was reduced in patients with HBsAg clearance after SiRNA inhibition of TLR7. **Conclusion:** Up-regulation of TLR-7 plays an essential role in HBsAg clearance in patients with chronic HBV infection.

APASL/Poster/Abstract/185
The incidence and risk factors of renal dysfunction after spontaneous bacterial peritonitis in cirrhosis

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The deterioration of renal function in patients with cirrhosis and spontaneous bacterial peritonitis (SBP) is the most sensitive predictor of in-hospital mortality. A previous randomized, controlled study has shown that for patients with SBP, treatment with high-dose intravenous albumin in addition to antibiotics reduces the incidence of renal impairment and improves hospital survival. But, it would be important to know which patients with SBP may benefit from albumin infusion or if this treatment should be used to treat all patients with SBP. Therefore, we conducted a retrospective study to elucidate the incidence and risk factors of renal dysfunction in cirrhotic patients with SBP. All medical records of 136 consecutive episodes of SBP in 100 patients were analyzed. Renal dysfunction was considered present if any of the following criteria were met: admission serum creatinine $\geq$ 1.5 mg/dl, admission blood urea nitrogen (BUN) $\geq$ 30 mg/dl or a doubling of serum creatinine or BUN to levels $\geq$ 1.5 and $\geq$ 30 mg/dl, respectively during admission. Of the 136 episodes of SBP, renal dysfunction was present in 64 (47.1%). Age, serum sodium, Child class, previous use of antibiotics and previous history of large volume paracentesis were significant risk factors on univariate analysis. Of these, only age was an independent risk factor on the logistic regression model. These data show that renal dysfunction occurs frequently in patients with SBP and only age is an independent risk factor. Considering the poor prognosis, close monitoring of renal function is warranted and albumin infusion with antibiotics should be used in all these SBP patients.

APASL/Free Paper/Abstract/186
Molecular background of HBeAg-negative chronic hepatitis B in Indonesia (preliminary report)

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Introduction: HBeAg-negative chronic hepatitis B (CHB) is associated with mutations in pre-core and core promoter regions of hepatitis B virus (HBV) DNA, and tends to have severe necroinflammatory changes. It was initially reported to prevail in certain parts of the world (the Mediterranean, the Middle East and Fareast Asia), but recent studies suggest a much wider geographical distribution with increasing frequency. Since geographically HBV has a genetic diversity, the viral characteristics responsible for this form of disease might vary in different parts of the world. This is a preliminary study to investigate the characteristics of HBV DNA in HBeAg-negative CHB patients in Indonesia and the relationship with the clinical pattern. **Patients and Methods:** Sixteen untreated CHB patients and four patients previously treated with lamivudine who HBeAg seroconverted were included; all were HBsAg positive for >6 months, HBeAg negative, anti-HBe positive, and serum HBV-DNA $>100\,000$ copies/ml. Clinical and laboratory data were periodically evaluated. HBV-DNA was sequenced for the core promoter and pre-core regions and analyzed. **Results:** Of the 16 untreated patients, four displayed previously reported pre-core stop mutation, G1896A, and two also showed core promoter mutations, A1762T and G1764A. Of four treated patients, three had mutations A1762T and G1764A, and one showed *wt* HBV sequence. All patients with core promoter mutations developed more severe inflammation, unresolved by retreatment with lamivudine. **Conclusion:** Our study represents one of the first analyses of core promoter and pre-core mutations in HBeAg-negative CHB patients in Indonesia, revealing the presence of core promoter and pre-core mutations previously reported in other geographical regions. Core promoter mutations could contribute to the severity of the disease.

187
Abstract withdrawn

APASL/Free Paper/Abstract/188
A study of serum cytokine levels, polymorphisms in interferon-γ promoter and their correlation with treatment outcome of chronic hepatitis C virus-infected patients
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A balance between Th1 and Th2 cytokine response to hepatitis C virus (HCV) may be important in persistence of infection and response to treatment with antiviral agents. The maximal capacity of cytokine production varies among individuals and correlates with the presence of polymorphisms in the cytokine genes. In particular, interferon gamma (IFN-γ) plays an important role in the elimination of hepatocytes infected with HCV. **Aims:** (1) To determine whether the Th1- and Th2-related cytokine profile of chronic HCV patients is associated with response to interferon therapy. (2) To correlate the frequency and association of the single nucleotide polymorphism (SNP) in the IFN-γ promoter region at -179 bp between patients with different treatment outcomes and controls. **Methods:** We studied 100 HCV+ subjects and 100 normal controls. Patients received interferon α 3 MIU thrice weekly+ribavirin 800–1200 mg/day for 6 months. Serum levels of IL-4, IL-6, IL-10, IL-12, IFN-γ and TNF-α were determined by ELISA. The IFN-γ promoter region was amplified by PCR using genotyping primers from genomic DNA extracted from peripheral blood lymphocytes. The polymorphic site was identified by digestion of PCR product using *Ava*II restriction endonucleases. **Results:** Mean IFN-γ levels were significantly elevated in patients compared to controls (78.0 ± 14.9 pg/ml vs 24.7 ± 6.9 pg/ml, $P<0.05$), and in responders to therapy compared to non-responders (89.3 ± 17.6 pg/ml vs 35.4 ± 10.4 pg/ml, $P<0.05$). Polymorphic analysis of IFN-γ promoter showed that the G allele was highly dominant in both patients and controls. In addition, an extra band of 50 bp was found in 22% controls and 25% patients, indicating the presence of a new *Ava*II restriction site. Linkage association showed no correlation between this polymorphic site and therapy outcome of patients. **Conclusions:** High levels of IFN-γ were present in chronic HCV patients, despite the presence of the G allele, which has been reported as less responsive to pathogens as compared to the T allele. These findings suggest that the SNP -179 G polymorphic site does not have a direct effect on IFN-γ upregulation.

189
Abstract withdrawn

APASL/Free Paper/Abstract/190
Efficacy and safety of oral *N*-Acetylcysteine in non-acetaminophen-induced acute liver failure
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Efficacy of *N*-Acetylcysteine (NAC), although well established in acetaminophen-induced acute liver failure (ALF), is not yet clear in non-acetaminophen-induced ALF. **Aims:** To evaluate the efficacy and safety of oral NAC in non-acetaminophen-induced ALF. **Methods:** A total of 91 adult patients admitted with non-acetaminophen-related ALF at our hospital from January 2002 to March 2005 were randomized to receive NAC ($n=47$) or no intervention ($n=44$). NAC was started immediately on admission in an initial dose of 140 mg/kg, followed by 70 mg/kg for a total of 17 doses, 4 h apart. In the absence of a liver transplant facility in our country, all patients were treated according to a standard medical protocol. Baseline characteristics were compared in the two groups and mortality was used as the primary end point. **Results:** Most baseline characteristics were comparable in the two groups except for mean age (27.7 ± 11.8 years in NAC vs 37.5 ± 18.8 in the no intervention group, $P=0.004$), serum bilirubin >17.6 mg/dl (24 patients in NAC vs 11 in the no intervention group, $P=0.01$) and a viral etiology (35 cases in NAC vs 20 in the no intervention group ($P=0.005$). Of the 34 patients who survived, 22 patients received NAC and 12 no intervention ($P=0.054$). Multiple logistic regression analysis showed that use of NAC, age ≤ 40 years, PT ≤ 50 s and hyper acute liver failure were independent predictors of survival. No untoward side effects were observed with the use of NAC. **Conclusions:** The use of NAC is safe and may improve survival in patients with non-acetaminophen-induced ALF.

APASL/Free Paper/Abstract/191
Hepatitis B and C: prevalence and social factors associated with sero-positivity among children in Karachi, Pakistan
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This cross-sectional study estimated the prevalence and identified risk factors associated with HCV and HBsAg sero-positivity among children 1–15 years. It targeted low to middle socio-economic population comprising 80–85% of the population. Parents consented for questionnaire and blood sample for anti-HCV and HBsAg. A total of 3533 children were screened. Of them, 1862 (52%) were males. Sixty five (1.8%) were positive for HBV, mean age 104 years. Fifty five (1.6%) were positive for HCV, 32 (58%) boys; mean age 94 years. Four (0.11%) boys were positive for both HBV and HCV. Sixty (92%) HBV and 51 (93%) HCV-positive children's parents ($P = 0.830$) have not heard of hepatitis viruses ($P = 0.815$). Forty-five (69%) HBV-positive individuals ($P < 0.04$) received therapeutic injections compared to 28 HCV (51%). Twenty-nine (45%) HBV and 17 (31%) HCV received injections from the local doctor. Forty-five (68%) HBV and 28 (51%) HCV patients claimed the use of a new syringe every time (OR 2.0 CI 1.0–4.2 $P = 0.05$). Forty-six (71%) HBV and 33 (60%) HCV patients received vaccination in the government hospital (OR 4.6 CI 2.6–10.7 $P < 0.001$). A new syringe was used in 49% (32) HBV and in 82% (45) HCV patients (OR 1.6 CI 0.08–3.5 $P = 0.21$). The prevalence of HBV in the east of the city was 6% (24) (OR 4.8 CI 2.7–8.7 $P < 0.001$) and in the south 2% (18) (OR 1.8 CI 0.3–3.3 $P = 0.08$). The odds of HBV were 2.2 times higher than HCV, with 95% CI 1.1–4.6. There is a need to educate the lower socio-economic population regarding HBV and HCV infection and the dangers associated with unsterilized therapeutic injections.

APASL/Free Paper/Abstract/192

A randomized, open-label, multi-center study comparing the efficacy and safety of peginterferon α-2a (40 kDa) (PEGASYS®) with conventional interferon α-2a (ROFERON®-A) in patients with chronic hepatitis C (CHC) in China

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Introduction: The prevalence of hepatitis C virus (HCV) infection in China is 3.2%. In large trials, peginterferon α-2a (40 kDa) (PEGASYS®) was significantly more effective than conventional interferon α-2a (Roferon®-A) in Western patients. We compared the efficacy and safety of peginterferon α-2a (40 kDa) and interferon α-2a in Chinese CHC patients. **Methods:** Patients were randomized to peginterferon α-2a (40 kDa) 180 μg/week or interferon α-2a 3 MU 3 × /week for 24 weeks, with 24 weeks follow-up. HCV RNA was monitored by COBAS AMPLICOR HCV Monitor® Test, v2.0 (limit of quantification = 600 IU/ml). **Results:** In all, 208 adults were enrolled. The characteristics of the two groups were similar. By intent to treat, the overall sustained virological response (SVR) rates at the end-of-follow-up (week 48) were 41.5% with peginterferon α-2a (40 kDa) and 16.7% with interferon α-2a ($P < 0.0001$). The proportion of genotype 1 (35.4% vs 14.5%, $P = 0.003$) and non-genotype 1 (66.7% vs 21.7%, $P = 0.003$) patients with SVRs was significantly higher in the peginterferon α-2a (40 kDa) than in the interferon α-2a groups. SVR rates in patients with baseline HCV RNA $\geq 8 \times 10^5$ IU/ml were significantly higher in the peginterferon α-2a (40 kDa) than in the interferon α-2a group (41.1% vs 13.1%, $P < 0.001$), but not in patients with low baseline HCV RNA (42.4% vs 22.0%, respectively, $P = 0.059$). No significant serious adverse events (AE) were reported. The frequency and severity of AE were similar in the two groups, although insomnia was more common in recipients of peginterferon α-2a (40 kDa) than in recipients of interferon α-2a (33.0% vs 15.7%, $P = 0.004$). **Conclusion:** In Chinese patients, peginterferon α-2a (40 kDa) (PEGASYS®) was significantly more effective than interferon α-2a and was well tolerated.

APASL/Free Paper/Abstract/193

Hepatitis B reactivation after withdrawal of preemptive lamivudine in patients with hematological malignancy upon completion of cytotoxic chemotherapy

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Background: The hepatic outcome of HBsAg+ patients undergoing chemotherapy after withdrawal of preemptive lamivudine is unknown. **Aim:** To examine the occurrence of HBV reactivation after withdrawal of preemptive lamivudine upon immune recovery post-chemotherapy. **Methods:** Preemptive lamivudine was started 1 week before initiation of chemotherapy in 46 consecutive HBsAg(+) patients and continued for the entire duration of chemotherapy. Preemptive lamivudine was stopped at a median 3.1 (range 3.0–3.4) months post-chemotherapy. Patients were longitudinally followed up for a median 25.7 (range 5.7–75.7) months after withdrawal of preemptive lamivudine. Serum HBV DNA was monitored with in-house real-time PCR assay. **Results:** Eleven (23.9%) patients developed HBV reactivation after withdrawal of preemptive lamivudine. The cumulative probability of HBV reactivation after lamivudine withdrawal at 6, 12, 24 and 36 months were 2%, 5%, 16% and 33%, respectively. Patients with a high prechemotherapy HBV DNA ($>10^4$ copies/ml) were more likely to develop HBV reactivation (8/16 (50%) vs. 3/30 (10%), $P < 0.001$ on log-rank). HBeAg(+) patients were also more likely to develop HBV reactivation (5 of 11 (45.5%) vs. 6 of 35 (17.1%), $P = 0.041$ on log-rank). A high prechemotherapy HBV DNA ($>10^4$ copies/ml) was the most important risk factor for HBV reactivation after withdrawal of preemptive lamivudine on Cox proportional hazards analysis (RR 16.13, 95%CI 2.99–87.01, $P = 0.001$). **Conclusions:** HBV reactivation is more likely to occur in patients with high prechemotherapy HBV DNA after withdrawal of preemptive lamivudine. A more prolonged course of antiviral therapy may be necessary in these patients after completion of chemotherapy in order to reduce post-chemotherapy HBV reactivation.

194

Abstract withdrawn

APASL/Poster/Abstract/195

Mucormycosis in patients with cirrhosis

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Introduction: Oculo-rhino-cerebral mucormycosis occurs in diabetics and immunocompromised patients and is associated with poor prognosis. Antifungal therapy with surgical debridement is the standard of care. Patients with cirrhosis of liver are more prone to develop infection. Treatment is difficult due to underlying coagulopathy and hepatic dysfunction in patients with cirrhosis. Little is known about the clinical presentation and outcome of mucor infection in cirrhosis. **Methods:** Medical records of the past 5 years were searched for patients of cirrhosis with associated diagnosis of mucor or fungal infection. Six patients with mucor infection were identified. **Results:** Out of six patients, five were male. The age range was 15–55 years. The cause of cirrhosis was hepatitis C in four, hepatitis B in one and autoimmune in one. One patient also had hepatocellular carcinoma. Four patients were diabetic; of these four, one patient was also on steroids for autoimmune liver disease. Three patients had spontaneous bacterial peritonitis. All six patients presented with rhino-ocular-cerebral mucormycosis with nasal discharge and upper motor neuron signs. Diagnosis of mucormycosis was made by culture of biopsy and scrapings taken from the palate and nasal sinuses. All patients received amphotericin as standard therapy. Four patients expired in the hospital, while one left against medical advice. One patient expired 10 days after his discharge. **Conclusion:** Mucormycosis in cirrhosis is rare and has poor prognosis. Patients with advanced cirrhosis and diabetes mellitus are at risk of developing the infection.

APASL/Free Paper/Abstract/196

Study of seroprevalence of Hbs Ag positive on medical doctors who underwent medical tests as nominees of Specialist Education in Dr. Kariadi Hospital Semarang

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Background: Hepatitis B virus (HBV) infection is one of the major diseases of mankind and is a serious global public health problem. Health care personnel are at increased risk of occupational acquisition of hepatitis B virus infection. Medical doctors are one of the high-risk groups for HBV infection byblood contact. **Objective:** The aim of this study is to determine the prevalence of HbsAg and the role of duration of time working as a doctor on exposure to Hbs Ag on medical doctors who underwent medical tests as nominees of specialist education at Dr. Kariadi Hospital Semarang. **Methods:** This study was done retrospectively from 1145 medical doctors who underwent medical tests as nominees of specialist education in Dr. Kariadi Hospital Semarang from April 2000 to October 2004.The HbsAg used as marker of hepatitis B was measured by the enzyme immunoassay (EIA) method. **Results:** Of 1145 medical doctors (422 women and 723 men), aged 25–35 years, mean age 29.34 $\pm$ 3.04 nominees of specialist education, more than 3 years as a doctor: 64% (733/1145) persons, less than 3 years as a doctor: 36% (412/1145) persons. The prevalence of HBsAg positive among the population was 3.9% (45/1145). The seropositivity among those more 3 years as a doctor vs those less than 3 years as a doctor was 5.1% (38/733) vs 1.6% (7/412), $P<0,05$ consecutively. **Conclusion:** Prevalence of HBsAg positive among medical doctors who underwent medical tests as nominees of specialist education in Dr. Kariadi hospital is 3.9%. HbsAg positive is more prevalent among doctors who have been working more 3 years.

APASL/Poster/Abstract/197

Co-infection of HIV with HCV and/or HBV in healthy persons screened for blood donors in Bandung, West Java

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Over the past few years, concomitant infection (co-infection) with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) has emerged as a major public health concern. Co-infection of HIV with HCV may have a synergistic effect on the progression of HCV-related liver diseases. Chronic liver disease from HCV has been recognized as an HIV-associated opportunistic infection. Of additional concern is the rising incidence of acute hepatitis B in high-risk groups because of poor compliance with hepatitis B vaccination; thus, HIV-HBV co-infection may become a growing problem. Co-infection behaves differently and requires different approaches to screening, diagnosis, management, and therapy. According to data from national CITBT (Contagious Infection through Blood Transfusion) Indonesian Red Cross, there were 0.06% with anti HIV positive, 0.44% HCV positive and 1.37% was HbsAg positive among all donors in Indonesia. The purpose of this study is to examine the prevalence of co-infection HIV with HCV and/or HBV in healthy persons screening for blood donors. Data were obtained and analyzed from all anti-HCV, HbsAg, and anti-HIV reactive from January to April 2005. The study was conducted in retrospect to serological data of donor's blood with the screening of CITBT reactive in the Blood Transfusion Unit, Indonesian Red Cross, Bandung, West Java. In this time period, 23 512 donors were tested for their HbsAg, anti-HCV, and anti-HIV. HbsAg was tested using Enzyme Immunoassay Murex HbsAg (version 3), anti-HIV by Enzyme Immunoassay Murex HIV-1.2.0, and anti-HCV by Enzyme Immunoassay Murex anti-HCV (version 4.0). All are from ABBOT. The results showed 645 (2.74%) donors were least reactive to one of these infections. There were 539 (83.8%) males and 104 (16.2%) females. The most common age group was 20–29 years, 194 (33.7%) persons. The prevalence of anti-HCV was 294 (1.25%), HBsAg was 250 (1.06%), and anti-HIV was 128 (0.54%). One donor was infected with all three (HbsAg, anti-HCV, and anti-HIV tests) ($P_{EF} = 0.203$). A total of 12 donors (4.4%) were reactive to anti-HCV and anti-HIV tests ($\chi^2 = 84.395$; $P<0.001$); 11 donors (4.4%) were reactive to HbsAg and anti-HCV tests ($\chi^2 = 279.106$; $P<0.001$); and five donors (2%) were reactive to HbsAg and anti-HIV tests ($\chi^2 = 81{,}724$; $P<0.001$). The prevalence of co-infection of HCV, HBV, and HIV was 0.04%, co-infection of HCV and HIV was 0.05%, while co-infectionof HBV and HIV was 0.02% ,and co-infectionof HBV and HCV was 0.05%. **Conclusion:** We have to be extra cautious since this study shows that there are an increasing number of co-infections of HIV and HCV and/or HBV in blood donors.

APASL/Poster/Abstract/198

Systemic combination chemotherapy (epirubicin, cisplatin, UFT, leucovorin) in patients with advanced hepatocellular carcinoma

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Background: Treatment of advanced hepatocellular carcinoma consists of radiation therapy and chemotherapy. However, results of these treatments have been disappointing. We administered a combination of four chemotherapeutic agents (epirubicin, cisplatin, UFT, and leucovorin) with different mechanisms to see whether response rate could be improved through the synergistic effects of each drug. **Methods:** We performed a retrospective study by reviewing the data of patients with advanced hepatocellular carcinoma who were treated with EPUL regimen from January 1995 to December 2004. A total 27 patients were enrolled. The regimen consisted of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 delivered as an intravenous infusion over 5 min and over 2 h on day 1, respectively, followed by UFT and leucovorin administered orally on days 1–21. The chemotherapy was repeated every 4 weeks. Response to chemotherapy was evaluated after every two cycles and toxicities were assessed after each cycle. **Results:** Among the total of 27 patients, 15 patients completed more than two cycles of chemotherapy. Twelve patients only completed one cycle of chemotherapy due to poor general conditions (11 patients) and cancer progression (one patient). The treatment response rate of 15 patients was 20% (95% CI 0–41%) with no complete response and three partial responses. Median progression-free survival was 4 months. The most common toxicity was leucopenia (18.5%), which improved within 1 week. Other toxicities were minimal. **Conclusion:** Although the toxicities of combination chemotherapy with EPUL regimen in advanced HCC patients were tolerable, response rate was not so high. Thus, this regimen can be considered as a palliative therapeutic modality.

APASL/Free Paper/Abstract/199

Sustained response off-treatment to entecavir and lamivudine after 48 weeks of treatment in nucleoside-naïve, HBeAg(+) patients: 24-week follow-up results of Phase 3 Study-022

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Background: Entecavir (ETV) is a potent and selective HBV antiviral that demonstrated superior efficacy to lamivudine (LVD) through 48 weeks of treatment in a Phase 3 trial in 709 HBeAg(+), nucleoside-naïve patients with chronic hepatitis B. **Methods:** Patients who achieved protocol-defined response (<0.7 MEq/ml by bDNA assay and HBeAg loss) to ETV (0.5 mg QD) and LVD (100 mg QD) by week 48 discontinued therapy and were evaluated off-treatment for an additional 24 weeks according to three sustained response endpoints. **Results:** At week 48, more patients in the ETV group than in the LVD group had serum HBV DNA levels of <0.7 MEq/ml (bDNA: 91% vs 65%, $P<0.0001$) or <300 copies/ml (PCR: 67% vs 36%, $P<0.0001$). HBeAg loss rates were similar (ETV 22%, LVD 20%). 21% of ETV patients vs 19% of LVD patients achieved response and discontinued study medication. The table below shows the proportion of patients achieving sustained response endpoints at 24 weeks off treatment. Kaplan–Meier estimates of the proportion of patients with sustained responses up to 24 weeks showed a separation among the three endpoints in favor of ETV that began between weeks 8 and 12 of the follow-up period. **Conclusions:** Over 70% of patients with response after 48 weeks of ETV therapy sustained their response when off treatment. By suppressing HBV DNA, causing loss of HBeAg, and reducing ALT levels with 1 year of treatment, ETV has the potential to sustain response when therapy is discontinued.

Outcomes at 24 weeks off-treatment		
Sustained response endpoints	ETV 0.5 mg – *n* (%)	LVD 100 mg – *n* (%)
HBV DNA <0.7 Meq/ml+loss HbeAg	61 (82)	49 (73)
HBV DNA <0.7 Meq/ml+loss HBeAg+ALT <1.25 × ULN	54 (73)	38 (57)
ALT <1.25 × ULN	56 (76)	39 (58)

APASL/Free Paper/Abstract/200

Sustained response off treatment to entecavir and lamivudine in nucleoside-naïve, HBeAg(–) patients: 24-week follow-up results of Phase 3 Study-027

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Background: Entecavir (ETV) is a potent and selective HBV antiviral which was superior to lamivudine (LVD) through 48 weeks of treatment in a Phase 3 trial in 648 HBeAg(–), nucleoside-naïve patients with chronic hepatitis B. **Methods:** Patients who achieved a protocol-defined response (HBV DNA <0.7 MEq/ml by bDNA assay and ALT <1.25 × ULN) to ETV (0.5 mg QD) or LVD (100 mg QD) by week 48, discontinued therapy and were evaluated for sustained response for an additional 24 weeks. **Results:** At week 48, 85% (275/325) of ETV patients vs 78% (245/313) of LVD patients achieved a protocol-defined response ($P=0.04$). Also, more patients in the ETV than the LVD group achieved serum HBV DNA levels of <0.7 MEq/ml (bDNA: 95% vs 89%, $P=0.0053$) or <300 copies/ml (PCR: 90% vs 72%, $P<0.0001$). Of the protocol-defined responders, 259 ETV patients and 220 LVD patients were evaluated for sustained response. A higher proportion of ETV-treated compared to LVD-treated patients sustained their response; these data are presented below. Kaplan–Meier estimates of proportions of patients with sustained responses up to 24 weeks showed a separation in favor of ETV for all three endpoints that began around week 8 during the follow-up period. **Conclusions:** Of the 85% of nucleoside-naïve, HBeAg-negative ETV-treated patients who achieved a protocol-defined response, 48% sustained that response through 24 weeks off treatment. By suppressing HBV DNA and reducing ALT levels, ETV can maintain response when therapy is discontinued.

Sustained response at 24 weeks off-treatment		
	ETV 0.5 mg ($n = 259$)	LVD 100 mg ($n = 220$)
HBV DNA <0.7 MEq/ml (bDNA), %	59	46
ALT $<1.25 \times$ ULN, %	55	37
HBV DNA <0.7 MEq/ml+ALT $<1.25 \times$ ULN, %	48	35

APASL Bali/Free Paper/Abstract/201

Entecavir (ETV) demonstrates consistent responses throughout baseline demographic subgroups for the treatment of nucleoside-naïve, HBeAG(+) and HBeAG(–) patients with chronic hepatitis B

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Background: ETV was superior to lamivudine (LVD) in Phase 3 studies of nucleoside-naïve, HBeAg(+) (ETV – 022) and HBeAg(-) (ETV-027) patients. This analysis assessed the effect of baseline demographic subgroups on efficacy outcomes.
Methods: The predictive value of potential prognostic subgroups was examined in logistic regression models for the efficacy endpoints of Histological Improvement [$\geq$ 2-point decrease in Knodell necroinflammatory score and no worsening of fibrosis ($\geq$ 1-point increase in Knodell fibrosis score)] and HBV DNA <400 copies/mL. The baseline distribution of subgroups was balanced across patient groups but not between studies (ETV-022 had a higher proportion of Asian patients).
Results: Subset analyses supported the principal analysis about superiority of ETV over LVD for both endpoints. Across subgroups, response to ETV was consistent. **Conclusions:** For endpoints of Histological Improvement and viral load reduction, ETV was comparable or superior to LVD across demographic subgroups. Gender, ethnicity and prior IFN-treatment did not affect ETV treatment outcome.

Histological improvement				
	ETV-022 HBeAg(+)		ETV-027 HBeAg(–)	
Baseline variables	ETV (%) $n = 314$*	LVD (%) $n = 314$*	ETV (%) $n = 296$*	LVD (%) $n = 287$*
IFN-naïve	71	62	70	61
IFN-pretreated†‡	78	62	71	61
Male	71	61	72	59
Female†	74	65	65	66
Asian	71	64	68	64
Non-Asian	73	60	72	58

*Histologically evaluable.
†Subgroup <100 patients ETV-022.
‡Subgroup <100 patients ETV-027.

HBV DNA <400 copies/ml				
	ETV-022 HBeAg(+)		ETV-027 HBeAg(–)	
Baseline variables	ETV (%) $n = 354$	LVD (%) $n = 355$	ETV (%) $n = 325$	LVD (%) $n = 313$
IFN-naïve	69	36	90	73
IFN-pretreated*,†	72	49	98	74
Male	67	36	92	74
Female	78	45	91	73
Asian	72	43	93	78
Non-Asian	67	32	90	71

*Subgroup <100 patients ETV-022.
†Subgroup <100 patients ETV-027.

APASL/Poster/Abstract/202

The efficacy of entecavir (ETV) is similar regardless of disease-related baseline subgroups in treatment of nucleoside-naïve, HBeAg(+) (Study-022) and HBeAg(–) (Study-027) patients with chronic hepatitis B

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Background: ETV was superior to lamivudine (LVD) in Phase 3 studies of nucleoside-naïve, HBeAg(+) and HBeAg(–) patients. This analysis assessed the effect of baseline subgroups on efficacy outcomes. **Methods:** Baseline ALT levels and HBV genotype were chosen as determinants of outcome. The predictive value of potential prognostic subgroups was examined in logistic regression models for the efficacy endpoints of Histological Improvement ($\geq$ 2-point decrease in Knodell necroinflammatory score and no worsening of fibrosis ($\geq$ 1-point increase in Knodell fibrosis score)) and HBV DNA <400 copies/ml. Baseline ALT levels were similar across treatment groups and between studies. HBV genotypes were balanced across treatment groups but differed between studies. **Results:** Subset analyses supported the principal analysis for superiority of ETV over LVD for both endpoints. **Conclusions:** For both endpoints, responses to treatment with ETV were consistent across ALT strata and HBV genotype subgroups. Efficacy of ETV was comparable or superior to LVD across subgroups in these populations.

APASL/Poster/Abstract/203

Alanine aminotransferase (ALT) flares are uncommon both on and post-treatment in entecavir (ETV)-treated HBeAg(+) patients

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Background: ETV is a potent and selective HBV antiviral. ALT flares are a concern both on and post-treatment of chronic hepatitis B. **Methods:** Flares were analysed in two Phase 3 trials in HBeAg(+) patients: Study-022 ($n = 709$ nucleoside naïve): ETV 0.5 mg QD or LVD 100 mg QD for up to 96 weeks; Study-026 ($n = 286$ LVD-refractory): ETV 1.0 mg or LVD 100 mg for up to 96 weeks. Patients with HBV DNA <0.7 MEq/ml and HBeAg loss at week 48 discontinued therapy and were followed for 24 weeks post-treatment. On and post-treatment flares were defined as ALT $>2 \times$ baseline and $>10 \times$ ULN, and ALT $>2 \times$ minimum of baseline and end of dosing and $>10 \times$ ULN, respectively. **Results:** On-treatment flares were observed for 12 (3%) ETV and 23 (6%) LVD patients in Study-022, and 1 (<1%) ETV and 16 (11%) LVD patients in Study-026. All ETV flares were associated with a $\geq 2 \log_{10}$ reduction in HBV DNA that was maintained during treatment. 12/13 ETV flares resolved on treatment. One patient discontinued ETV due to flare. 12/23 flares on LVD in Study-022 and all 16 in Study-026 were associated with rising or stable HBV DNA. Nine patients discontinued LVD due to flare. Of Study-022 patients with on-treatment flares, 1/12 ETV and 5/23 LVD patients had a clinical or laboratory abnormality consistent with hepatic dysfunction and 1 LVD patient died of hepatic failure. Flares post-treatment were observed in 3 (2%) ETV and 9 (6%) LVD patients and in 9/12 cases were associated with a return of serum HBV DNA toward baseline. No post-treatment ETV flares resulted in hepatic decompensation. **Conclusion:** ALT flares on ETV are uncommon and generally associated with declines in serum HBV DNA and a benign clinical course.

APASL/Poster/Abstract/204

Decline in serum HBV DNA and ALT normalisation is associated with histological improvement among nucleoside-naïve patients in entecavir Phase 3 trials

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Background: Improvement in liver histology is a principal endpoint in the evaluation of HBV antiviral agents. **Methods:** This report investigates if non-invasive measures of response to entecavir (ETV) could be surrogate markers of histological improvement (HI): $\geq$ 2-point decrease in Knodell necroinflammatory score and no worsening of fibrosis ($\geq$ 1-point increase in the Knodell fibrosis score). Data from two Phase 3 studies comparing ETV to lamivudine (LVD) in nucleoside-naïve HBeAg(+) (Study-022, $n = 709$) and HBeAg(−) (Study-027, $n = 638$) patients were analysed. **Results:** More ETV than LVD patients achieved HBV DNA <400 copies/ml by PCR (Study-022: ETV 69%, LVD 38%; Study-027: ETV 91%, LVD 73%). In Study-022, a higher rate of HI (80%) was observed for ETV patients with HBV DNA <400 copies/ml compared to those in higher HBV DNA strata. In Study-027, 95% (252/265) of ETV patients with HI and PCR data at week 48 achieved HBV DNA <400 copies/ml, limiting comparison with higher HBV DNA strata. ETV patients achieving ALT $<1 \times$ ULN had higher rates of HI. **Conclusions:** ETV achieved high proportions of patients with HBV DNA <400 copies/ml and serum ALT $<1 \times$ ULN. Patients achieving these endpoints had higher rates of HI than those in higher HBV DNA and ALT strata.

APASL/Poster/Abstract/205

Entecavir is well tolerated for the treatment of nucleoside-naïve and lamivudine-refractory chronic hepatitis B: Phase 2/3 safety results

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Background: Entecavir (ETV), a potent and selective inhibitor of HBV polymerase, was well tolerated in Phase 2 trials with a safety profile similar to lamivudine (LVD). **Methods:** This report summarizes data from four studies in which patients received ETV (nucleoside-naïve: 0.5 mg QD; LVD-refractory: 1.0 mg QD) or LVD (100 mg QD). Nucleoside-naïve patients (ETV $n = 679$, LVD $n = 668$) were from Phase 3 trials Study-022 (HBeAg(+)) and Study-027 (HBeAg(−)), and LVD-refractory patients (ETV $n = 183$; LVD $n = 190$) were from Phase 3 trial Study-026 and Phase 2 trial Study-014. **Results:** Proportions of patients experiencing any adverse event (AE) on treatment were similar for ETV and LVD for both datasets (nucleoside-naïve: ETV 81%, LVD 82%; LVD-refractory: ETV 85%, LVD 82%). Incidence of serious AEs was similar between ETV and LVD (nucleoside-naïve: ETV 7%, LVD 8%; LVD-refractory: ETV 10%, LVD 7%). There were fewer discontinuations due to AEs in ETV-treated patients (nucleoside-naïve: ETV 1%, LVD 3%; LVD-refractory: ETV 2%, LVD 7%). On-treatment ALT flares were less frequent in ETV-treated patients (nucleoside-naïve: ETV 2%, LVD 4%; LVD-refractory: ETV 2%, LVD 11%). While on treatment and during the 24-week follow-up, there were few malignant neoplasms for ETV and LVD (nucleoside-naïve: ETV 1%, LVD 1%; LVD-refractory: ETV 2%, LVD 1%). Few deaths were reported for ETV and LVD (nucleoside-naïve: ETV $n = 2$, LVD $n = 4$; LVD-refractory: ETV $n = 1$; LVD $n = 2$). **Conclusions:** ETV has a similar safety profile to LVD in both nucleoside-naïve and LVD-refractory patients. Discontinuations due to AEs and on-treatment ALT flares occur less frequently with ETV than with LVD.

APASL/Free Paper/Abstract/206

Entecavir resistance is absent in nucleoside-naïve patients and observed infrequently by week 48 in lamivudine-refractory patients with chronic HBV infection treated with entecavir

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Background: Entecavir (ETV) exhibits potent efficacy in all HBV patient populations. High-level ETV resistance (ETVr) requires lamivudine-resistant (LVDr) substitutions (rtM204 with or without rtL180) plus changes at rtT184, rtS202 and/or rtM250. **Methods:** Baseline and week 48 genotypes for >700 ETV-treated patients were obtained. All emerging substitutions identified, plus samples from all patients experiencing virologic rebounds (≥ 1 log increase from nadir by Roche Cobas Amplicor PCR assay), were phenotyped. **Results:** No virologic rebounds due to ETVr were observed and no ETVr-associated substitutions at residues rtI169, rtT184, rtS202 or rtM250 emerged among 430 ETV-treated nucleoside-naïve patients examined. Virologic rebounds due to ETVr were observed in 1% of ETV-treated LVD-refractory patients. ETVr-associated substitutions emerged in 6% of ETV-treated LVD-refractory patients by week 48 and only appeared when pre-existing LVDr changes were present. ETVr substitutions were noted in a fraction of LVD-refractory subjects at baseline, indicating that LVD could select for these changes. Despite the presence of ETVr substitutions at baseline, ETV treatment did not lead to rapid virologic rebound or lack of virologic response. Molecular modeling studies predicted two distinct mechanisms for ETVr. **Conclusions:** An extensive genotypic analysis of ETV-treated patients showed no evidence of ETVr by week 48 in previously nucleoside naïve subjects. Only 1% of ETV-treated LVD-refractory subjects exhibited virologic rebounds due to resistance. Clinically relevant ETVr requires the pre-existence of LVDr substitutions, and at least one additional change at residues rtT184, rtS202 and/or rtM250.

APASL/Plenary/Abstract/207

Elevated serum level of hepatitis B virus (HBV) DNA is an independent risk factor for hepatocellular carcinoma: the risk evaluation of viral load elevation and associated liver disease/cancer (The R.E.V.E.A.L.–HBV study)

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Introduction: HBV DNA is a marker of efficacy for antiviral treatment of chronic hepatitis B. We examined the independent effect of HBV DNA on the incidence of HCC in a long-term study. **Methods:** A cohort of 3851 asymptomatic HBsAg-positive subjects was recruited from seven townships in Taiwan between 1991 and 1992. Serum samples obtained at enrolment and follow-up examinations were tested for HBsAg, HBeAg, HBV DNA by PCR (LOQ 300 copies/ml), and ALT. The diagnosis of HCC was made through data linkage with profiles of the National Cancer Registry and Death Certification System and confirmed by chart review. Multivariable-adjusted relative risks (RR_{adj}) were derived using Cox proportional hazard models. **Results:** During 43 993 person-years of follow-up, 176 subjects were newly diagnosed with HCC. Removing all HCV co-infected subjects, there were 164 HCC cases among 3653 subjects. In these subjects, the incidence of HCC was strongly linked with increasing HBV DNA level in a dose–response manner (test of trend; $P<0.001$); incidence of HCC was highest (11.52/1000 PYFU) in subjects with HBV DNA $\geq 10^6$ copies/ml. In a Cox regression model, the RR_{adj} (95% CI) was 7.8 (3.7–16.2) for HBV DNA levels $\geq 10^6$ copies/ml (reference: HBV DNA < LOQ); in HBeAg negative subjects with normal serum ALT ($N=2966$), the RR_{adj} (95% CI) was 18.6 (8.2–42.2) for HBV DNA levels $\geq 10^6$ copies/ml. **Conclusion:** Serum HBV DNA can reliably predict the risk of HCC independent of HBeAg status and serum ALT level. Persistent elevation of HBV DNA over time carries the strongest risk of HCC.

APASL/Poster/Abstract/208

Viral load is a strong predictor of hepatocellular carcinoma (HCC) risk in people chronically infected with hepatitis B virus (HBV) and with normal serum alanine aminotransaminase level (ALT): the risk evaluation of viral load elevation and associated liver disease/cancer (the R.E.V.E.A.L.–HBV study)

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Background: Treatment guidelines generally recommend therapy for chronic hepatitis B patients with serum alanine aminotransferase (ALT) ≥ 2 × ULN. This study was carried out to examine the risk of hepatocellular carcinoma (HCC) in this population with emphasis on the role of serum hepatitis B virus (HBV) DNA level relative to the role of serum ALT. **Methods:** A cohort of 3851 participants with chronic HBV infection was recruited from seven townships in Taiwan between 1991 and 1992. Cohort entry serum samples were tested for HBsAg, HBeAg, HBV DNA by PCR (LOQ 300 copies/ml), and serum ALT. The diagnosis of HCC was ascertained through data linkage with computerized profiles of the National Cancer Registry and Death Certification System in Taiwan. Multivariable adjusted relative risks (RR_{adj}) were derived using Cox proportional hazard models. **Results:** Overall, during 43 993 person-years of follow-up, 176 of the 3851 participants were newly diagnosed with HCC. Of the 3851 participants, 3601 (93%) had a serum ALT level < 1 × ULN. Of these, 42% had a serum HBV DNA level $\geq 10^4$ copies/ml. Of the 7% with elevated serum ALT level, 65% had serum HBV DNA $\geq 10^4$ copies/ml at cohort entry. Compared with subjects with undetectable HBV DNA, subjects with HBV DNA $\geq 10^6$ copies/ml had the highest incidence of HCC; RR_{adj} (95% CI) 12.3 (6.7–22.6). There was a dose-dependent relationship between HBV DNA and HCC risk in people with normal serum ALT variably defined as either < 1 × ULN or < 2 × ULN. **Conclusion:** Elevated serum HBV DNA is a strong predictor of HCC in chronically infected HBV patients regardless of serum ALT.

APASL/Poster/Abstract/209

Serum hepatitis B virus (HBV) DNA level predicts the incidence of liver cirrhosis in persons chronically infected with HBV: the risk evaluation of viral load elevation and associated liver disease/cancer (TheR.E.V.E.A.L.–HBV study)

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Introduction: Cirrhosis develops as a result of hepatic inflammation and subsequent fibrosis. Chronic hepatitis B (CHB) subjects are at increased risk of developing liver cirrhosis, as ongoing viral replication is associated with hepatic inflammatory activity. This study examines if increasing levels of HBV DNA are associated with increasing risk of cirrhosis. **Methods:** A cohort of 3851 HBsAg-positive subjects was established from seven townships in Taiwan between 1991 and 1992. Serum samples were tested for HBV DNA by PCR. Cirrhosis was diagnosed by ultrasonography. Cirrhosis incidence rate per person-year of follow-up (PYFU) for each HBV DNA strata was calculated. The multivariable-adjusted relative risk (RR_{adj}) was derived from Cox proportional hazard models. **Results:** Seventy-seven subjects were excluded (two died within 6 months of enrolment, 75 were diagnosed with cirrhosis) leaving 3774 subjects. During 42 115 PYFU, 395 cirrhosis cases were newly diagnosed. Cirrhosis incidence rate ranged from 386.1/100 000 PYFU with HBV DNA <300 copies/ml to 2575.7/100 000 PYFU with HBV DNA $\geq 10^6$ copies/ml ($P<0.0001$) in a dose-dependent manner. With <300 copies/ml as reference, and adjusting for gender, age, habits of cigarette smoking and alcohol consumption, and hepatitis C virus antibodies, the risk of cirrhosis began increasing at an HBV DNA level of 10^4 copies/ml with a RR_{adj} of 2.2 (95% CI 1.5–3.3) and was 8.7 (95% CI 6.2–12.3) for those who had HBV DNA $\geq 10^6$ copies/ml. **Conclusion:** HBV DNA level is a strong predictor of cirrhosis risk. The incidence of cirrhosis increases with HBV DNA level in a dose-dependent manner. Conversely, reducing HBV DNA level is likely to decrease cirrhosis risk in CHB patients.

APASL/Free Paper/Abstract/210

Viral load is a strong predictor of cirrhosis in CHB infection regardless of serum ALT and HBeAg status: the risk evaluation of viral load elevation and associated liver disease/cancer (The R.E.V.E.A.L.–HBV study)

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Background: HBeAg status and serum ALT are considered, respectively, to be markers of active replication and disease progression. This study examined the impact of HBV DNA level on the risk of progression to cirrhosis stratified by HBeAg status and ALT level. **Methods:** A cohort of chronic hepatitis B (CHB)-infected subjects was recruited from seven townships in Taiwan between 1991 and 1992. Entry serum samples were tested for HBV DNA by PCR. Subjects were prospectively followed by clinical examination through 30 June 2004, and diagnosis of cirrhosis was made by ultrasonography. All cirrhosis cases diagnosed within 6 months of enrolment were excluded from analyses. Multivariable-adjusted relative risks (RR_{adj}) were derived using Cox proportional hazard models. **Results:** Of 3774 subjects, contributing 42 115 person-years of follow-up data, 3542 (94%) had normal ALT and 3214 (85%) were HBeAg($-$); 395 new cases of cirrhosis were diagnosed. Increasing HBV DNA was associated with increasing risk of cirrhosis within each ALT and HBeAg strata after adjusting for other variables (test of trend $P<0.001$). With normal ALT and HBV DNA $<10^4$ copies/ml as reference, the RR_{adj} (95% CI) for subjects with normal ALT and HBV DNA $\geq 10^5$ copies/ml was 6.1 (4.8–7.8), and the RR_{adj} (95% CI) for subjects with elevated ALT and HBV DNA $\geq 10^5$ copies/ml was 10.1 (7.0–14.5). Stratifying by HBeAg status, for subjects with HBV DNA $\geq 10^5$ copies/ml , the RR_{adj} (95% CI) for HBeAg($-$) subjects was 4.9 (3.7–6.4) and for HBeAg(+) subjects was 8.6 (6.6–11.2) (HBeAg($-$) and HBV DNA $<10^4$ copies/ml as reference). **Conclusion:** Elevated serum HBV DNA is a strong predictor of cirrhosis in HBV-infected subjects regardless of serum ALT level and HBeAg status.

APASL/Poster/Abstract/211

Excess mortality associated with chronic hepatitis B virus infection: the R.E.V.E.A.L.–HBV study

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Background: The long-term hepatic sequelae of chronic hepatitis B (CHB) infection have been well documented. We evaluated the mortality risk associated with CHB infection in a large prospective cohort study. **Method:** A community-based prospective cohort study was established from seven townships in Taiwan between 1991 and 1992. Mortality causes were identified through computerized data linkage to the Taiwanese National Cancer Registry, National Death Certificate Registry and National Health Insurance profiles through December 31 2002. Incidence rates were calculated and multivariable-adjusted relative risks (RR_{adj}) derived from Cox proportional hazard models. **Results:** Of the 23 820 subjects, 1545 (6.4%) died. Malignant neoplasms (37%), circulatory system diseases (20%), injury and poisoning (13%), GI disorders (8%), and diabetes mellitus (6%) were the five leading causes of death. Of the enrolled subjects, 4155 (17.4%) were HbsAg positive; the RR_{adj} (95% CI) for all cause mortality for the HBsAg-positive group was 1.7 (1.5–1.9) compared with the HBsAg-negative group. The RR_{adj} (95% CI) was 10.8 (7.7–15.2) and 5.4 (3.4–8.6) for liver cancer and chronic liver disease deaths, respectively. The RR_{adj} (95% CI) for all other causes of mortality was 1.1 (0.9–1.3). **Conclusions:** CHB-infected subjects had a significant risk of excess mortality compared to non-infected subjects. Increases in liver-related mortality account for the mortality differences. Early intervention with appropriate antiviral therapies may decrease liver-related complications and prolong survival in these individuals.

APASL/Poster/Abstract/212

Valuing health states using utility weights to capture the impact of disease progression in chronic hepatitis B (CHB)

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Background: In mainland China, approximately 9.75% of the population has chronic hepatitis B (CHB) and, there are an estimated 280 000 related deaths each year. Without effective

treatment, patients usually progress through increasingly severe disease states pre-death. Utility weights are used to estimate the impact of morbidity and mortality, the quality-adjusted life years in cost-effective analyses, and for allocation of resources. We sought to elicit utility weights for six CHB-related health states. **Methods:** Utility weights were elicited, by the standard gamble method and visual analog scale, for six CHB-related health states (defined by a panel of hepatologists) in patients (100 CHB subjects) and laypersons (100 uninfected subjects). Probability wheels with two-color pie charts for the relative probabilities of perfect health (1) and death (0) were used for the standard gamble and a 'feeling' thermometer was used for the visual analog scale. **Results:** For the patient group, mean age was 42 years (SD: 12.4, range: 20–68 years) and 93.1% were male. Mean utility weights were 0.41 (95% confidence interval (CI): 0.35–0.46) for CHB; 0.58 (CI: 0.52–0.64) for compensated cirrhosis; 0.57 (CI: 0.51–0.63) for subsequent years post liver transplant; 0.51 (CI: 0.45–0.57) for first year post-liver transplant; 0.31 (CI: 0.26–0.36) for hepatocellular carcinoma and 0.26 (CI: 0.22–0.31) for decompensated cirrhosis. Mean utility weights elicited in laypersons followed a similar pattern. **Conclusion:** For patients in this population, the health-related quality of life decreased with progression of disease. In addition, the utility weights elicited in patients were consistently lower than those of laypersons.

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APASL/Free Paper/Abstract/213

A randomized, placebo-controlled study (etv-056) in China of the efficacy and safety of entecavir (ETV) in chronic hepatitis B (CHB) patients who have failed lamivudine (LVD) therapy

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Background: ETV has potent antiviral activity against wild type and LVD-resistant HBV. **Objective:** ETV vs. placebo (PBO) for 12 weeks was evaluated in Chinese patients who had failed LVD; long-term safety and efficacy were assessed in the subsequent 36 weeks open-label phase. **Methods:** Eligible patients had documented LVD failure, stopped LVD for at least 12 weeks, HBV DNA $\geq 10^5$ copies/ml by PCR, and ALT $\leq 10 \times$ ULN. In the double-blind phase, patients were randomized (4:1) to ETV 1.0 mg QD or PBO for 12 weeks. In the open-label phase, patients received ETV 1.0 mg QD for 36 weeks. The primary endpoint was the change from baseline in HBV DNA by PCR at week 12. **Results:** At baseline for treated patients ($N = 145$), mean HBV DNA was 8.79 log copies/ml, mean ALT was 88.9 U/l, and 90% were HBeAg-positive. The mean change in HBV DNA at W12 was -4.30 log copies/ml and -0.15 log copies/ml for ETV and PBO, respectively ($P < 0.0001$). In patients with abnormal baseline ALT, 68% ETV vs. 6% PBO achieved ALT normalization (ALT $\leq 1 \times$ ULN) ($P < 0.0001$). The incidence of adverse events (AEs) was comparable: 33% ETV and 28% PBO patients reported AEs. All patients treated in the double-blind phase entered open-label dosing. Among patients initially treated with ETV in the double-blind phase, the mean change in HBV DNA was -5.08 log copies/ml, 28% had HBV DNA levels <400 copies/ml and 85% achieved ALT normalization after 48 weeks ETV. HBeAg loss was achieved in 12 patients (9%) treated with ETV. No mutations associated with resistance to ETV were detected. ETV 1.0 mg for 48 weeks was generally well tolerated. **Conclusions:** The findings from this study demonstrate the antiviral activity and safety of ETV in adults with CHB who have failed LVD.

APASL/Free Paper/Abstract/214

Entecavir is superior to lamivudine for the treatment of chronic hepatitis B: results of the Phase 3 study ETV-023 in nucleoside-naïve patients

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Background: Entecavir (ETV) is a potent and selective antiviral with activity against wild type and lamivudine (LVD)-resistant hepatitis B virus (HBV). **Objective:** This study evaluated the safety and efficacy of ETV 0.5 mg QD vs. LVD 100 mg QD for 48 weeks in nucleoside-naïve, adult Chinese patients. **Methods:** Patients were randomized 1:1 to receive ETV or LVD. Eligible patients had HBV DNA ≥ 3 MEq/ml by bDNA, ALT levels 1.3 to $10 \times$ ULN, compensated liver function, and had received no more than 12 weeks of prior nucleoside therapy. The primary efficacy endpoint was a composite endpoint of HBV DNA <0.7 MEq/ml by bDNA assay and ALT $<1.25 \times$ ULN at week 48. **Results:** Baseline characteristics were well balanced between treatment groups; of treated patients ($N = 519$), 86% were HbeAg positive at baseline, mean HBV DNA by PCR was 8.56 log copies/ml, and mean ALT was 197 U/L. **Conclusions:** ETV achieves superior virological and biochemical improvements in nucleoside-naïve patients with chronic hepatitis B with a safety profile comparable to LVD.

APASL/Poster/Abstract/215

Entecavir vs lamivudune and pegylated interferon vs lamivudine: insights for treating chronic hepatitis B

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Introduction: Entecavir (ETV) and pegylated interferon α-2a (pIFN α-2a) are approved treatments for chronic hepatitis B (CHB): ETV is a nucleoside analog antiviral; pIFN is an immunomodulator. Phase III trials for ETV, pIFN α-2a and pIFN α-2b included lamivudine (LVD) as control or part of combination treatment. **Methods:** This is a descriptive comparison of five randomized studies. Among the ETV, pIFN α-2a, and pIFN α-2b studies of HBeAg(+) patients, baseline HBV DNA and ALT were comparable, while race and genotype distributions varied. In the ETV and pIFN α-2a studies of HBeAg(−) patients, baseline HBV DNA levels were comparable, while mean baseline ALT in the ETV trial was higher than in the pIFN trial. The pIFN trial had more Asian and more cirrhotic patients.

Results:

HBeAg(+)

	Chang (2004)		Fried (2005)/ Lau (2004)			Janssen (2005)	
Endpoint week 48–52	ETV ($n = 354$)	LVD ($n = 355$)	pIFN α-2a ($n = 271$)	LVD ($n = 272$)	pIFN α-2a +LVD ($n = 271$)	pIFN α-2b ($n = 136$)	pIFN α-2b +LVD ($n = 130$)
HBV DNA <400 copies/ml (%)	69	38	25	40	68	10	33
HBeAg seroconversion (%)	21	18	27	20	24	22	25
ALT <1.0 × ULN (%)	68*	60*	ND	ND	ND	34	51

HBeAg(−)

Endpoint Week 48	Shouval (2004)		Marcellin (2004)		
	ETV ($n = 325$)	LVD ($n = 313$)	pIFN α-2a ($n = 177$)	LVD ($n = 181$)	pIFN α-2a+LVD (n = 179)
HBV DNA <400 copies/ml (%)	91	73	63	73	87
ALT <1.0 × ULN (%)	78*	71*	38	73	49

*BMS data on file. In HBeAg(+) and HBeAg(–) patients, histological improvement favored ETV over LVD and pIFN.

Conclusions: For virologic endpoints and seroconversion, ETV was comparable to pIFN α-2a+LVD, and ETV had a higher proportion of patients with normalized ALT levels and histological response. LVD performed consistently among trials. ETV monotherapy and pIFN α-2a+LVD had similar profiles for treatment for CHB.

216
Abstract withdrawn

APASL/Poster/Abstract/217
Adefovir Dipivoxil for treatment of breakthrough hepatitis caused by lamivudine-resistant mutants of hepatitis B virus
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Background/Aims: Adefovir dipivoxil (ADV) is a nucleoside analogue that inhibits wild-type hepatitis B virus (HBV) and lamivudine-resistant HBV mutants *in vitro* and *in vivo*. The aim of this study was to evaluate the efficacy of ADV against lamivudine-resistant mutants. **Patients and Methods:** Twenty-three patients with breakthrough hepatitis due to lamivudine-resistant mutants were treated with ADV 10 mg daily. We regularly checked serum HBV DNA, HBeAgand liver function tests including ALTand serum creatinine every 1–3 months to evaluate the efficacy and safety of ADV. **Results:** For 3 to 21 months, the rate of serum HBV DNA loss was 73.3%, 83%, 83% and 100% at 12, 24, 36 and 48 weeks, respectively. The median serum HBV DNA level was decreased to 0.5 pg/ml from baseline 247 pg/ml at 12 weeks. The rate of HBe Ag loss was 22.2% at 12 weeks. The rate of serum ALT normalization was improved, extending the treatment duration by 30.7%, 67.6%, 80.0% and 87.5% at 4, 12, 24 and 36 weeks, respectively. The median serum ALT level was decreased to 100, 43, 30, 31and 26 IU/l at 4, 12, 24, 36and 48 weeks, respectively, compared to baseline 148 IU/l. **Conclusions:** Administration of ADV has become an effective option for the treatment of patients with lamivudine-resistant HBV infection.

218
Abstract withdrawn

APASL/Poster/Abstract/219
Clinical expression of C282Y homozygous HFE haemochromatosis at age 14 years
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Clinical symptoms of C282Y homozygous HFE-related haemochromatosis usually manifest in the third to sixth decades of life. If the onset of symptoms occurs before age twenty years, the clinical course is typically more severe and is usually due to mutations genetically distinct from HFE-related haemochromatosis. Juvenile haemochromatosis, a much rarer disease than HFE haemochromatosis, is characterised by endocrine and cardiac dysfunction and has been associated with mutations in either the hepcidin (HAMP) or hemojuvelin (HJV) genes. Recent reports have also documented that co-inheritance of mutations in either HAMP or HJV genes causes exacerbation of phenotypic expression of HFE-related haemochromatosis. We describe a case of C282Y homozygous HFE-related haemochromatosis in whom clinical symptoms manifested at age 14 and who underwent screening for possible mutations in four non-HFE haemochromatosis genes. The 14-year-old male presented with debilitating lethargy. Iron overload was demonstrated by an elevated liver iron concentration of 59 mmol/g

(paediatric reference range <14) measured non-invasively using proton transverse relaxation rate imaging. The early phenotypic expression was further investigated by screening genomic DNA for the presence of co-inherited mutations in genes responsible for non-HFE haemochromatosis. Previously described mutations in genes encoding hepcidin, hemojuvelin, ferroportin and transferrin receptor were absent and we conclude that early expression in this case was possibly controlled by novel mutations or genes.

APASL/Poster/Abstract/220

Chronic hepatitis C (CHC) in patients with end-stage renal disease on haemodialysis

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Introduction: Hepatitis C infection is common in haemodialysis (HD) patients. **Methods:** Medical records were reviewed. Data are reported as mean, range and percentage. **Results:** Forty-five patients (F:M = 15:30) with a mean age of 37.2 years and 55.6% <40 years (18–59 years). The duration of HD to positive anti-HCV was 4.6 years (0–18). HBsAg is negative in all of the 36 patients tested. The viral load was >200 000 IU/ml in 43.6% and <200 000 IU/ml in 56.4%. Patients with low viral load had a mean of 40 011 IU/ml (643–19 100). The remaining six patients had only HCVRNA qualitative tests, which were positive. Genotyping was done on 25 patients, 76% genotype 1 and 24% genotype 3. ALT was persistently normal in 31.8% and raised in 68.1% (ALT >1 ULN = 50%, >2 ULN = 13.6%, >3 ULN = 4.5%). Forty had liver biopsy. The fibrosis stage (modified HAI) was 0 = 25%, 1 = 50%, 2 = 10%, 3 = 5%, 4 = 5%, 6 = 2.5% and not staged = 2.5%. The inflammatory grade was grade 1 = 2.5%, 2 = 7.5%, 3 = 32.5%, 4 = 22.5%, 5 = 17.5%, 6 = 10%, 8 = 2.5%, 9 = 2.5% and not graded = 2.5%. Steatosis was absent in 45%, mild in 37.5%, moderate in 5%, severe in 2.5% and not reported in 10%. Iron stain was reported in 32 biopsies, 10% had increased or minimal load and 70% had none. **Conclusions:** This subgroup of CHC was infected after 4.6 years of HD. HBV co-infection is uncommon. The main genotype is 1 and 43.6% have high viral load. Mildly raised ALT and high inflammatory grade are common. Thepatients are young, 75% had fibrosis less than 2 and steatosis or iron overload is not common.

APASL/Poster/Abstract/221

Hepatocellular carcinoma (HCC) in Malaysia: demography, clinical features, outcome, and a comparison between the Malay and Chinese

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Introduction: HCC is one of the top 10 cancers in Malaysian males. **Methods:** We reviewed HCC cases admitted from April 2003 to December 2004. Sixty-seven of 75 patients have complete data. **Results:** HCC was diagnosed by imaging with AFP >1000 ng/ml in 42% and two highly suspicious imaging in 58%. The mean age was 55.4 years (16–81), male to female ratio was 3.16:1 and 58% were Chinese, 33% Malay, 4% Indian and 4% others. The primary liver disease was 63% CHB, 15% CHC, 3% anti-HBcore+, 4% co-infection, 6% alcohol and 9% non-B/C/alcohol. The CPS were 39% A, 33% B and 28% C. The radiological findings ($n = 60$) were 31.3% right lobe single lesion, 16.4% right lobe multiple lesions, 2.9% left lobe single lesion and 49.3% bilobar. 18.3% had main portal vein thrombosis. 19.4% were alive with mean follow-up 9.65 months (0.25–23). 28.4% died in hospital at 5.5 months (0.35–18) and 52.2% defaulted after 4.98 months (0.07–39). 8.9% had resection, 13.4% TACE, 4.5% PEI, 3% chemoinfusion, 1.5% microwave, 1.5% systemic chemotherapy and 67.2% palliative. Comparing Chinese and Malay, the mean ages were 56.3 years and 55.8 years, respectively ($P > 0.05$) There were more male patients, 79.5% in Chinese and 63.6% in Malay ($P < 0.05$). The etiology in Chinese compared to Malay was 69.2%: 59.1% CHB, 10.3%: 27.3% CHC, 5.2%: none anti-HBcore+, 2.6%: 9% co-infection, 5.2%: none alcohol and 7.7%: 4.5% non B/C/alcohol. The CPS for Chinese and Malay were 48.7%: 27.3% A, 28.2%: 45.5% B and 23.1%: 27.3% C ($P = 0.003$). 54.5% Malay and 43.6% Chinese have bilobar disease. **Conclusions:** HCC in Malaysia is mostly associated with males, Chinese and CHB. Disease at presentation was severe. Although the prevalence of HCC is higher in Chinese and similar mean age, the Malay have more severe disease. These differences warrant further study.

APASL/Free Paper/Abstract/222

Antifibrotic effects of thalidomide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats

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Tumor necrosis factor alpha (TNFα) plays a central role in cellular necrosis, apoptosis, organ failure, tissue damage, inflammation and fibrosis. These processes, occurring in liver injury, may lead to cirrhosis. Thalidomide, α-*N*-phthalidoglutarimide $(C_{13}H_{10}N_2)_4$, has been shown to have immunomodulatory and anti-inflammatory properties, which are possibly mediated through its anti-TNFα effect. In this study, we investigated the in vitro and in vivo effects of thalidomide on hepatic fibrosis. A cell line of rat hepatic stellate cells (HSC-T6) was stimulated with transforming growth factor β1 (TGF β1) or TNFα. The inhibitory effects of thalidomide (100–800 nM) on the NFκB-signaling cascade and fibrosis markers including α-smooth muscle actin (α-SMA) and collagen, were assessed. *In vivo* therapeutic study was conducted in DMN-treated rats, which were randomly assigned to 1 of 4 groups : vehicle (0.7% carboxyl methyl cellulose, CMC), thalidomide (40 mg/kg), thalidomide (200 mg/kg), or silymarin (50 mg/kg), each given by gavages twice daily for 3 weeks starting after 1 week of DMN administration. Thalidomide (100–800 nM) concentration-dependently inhibited NFκB transcriptional activity induced by TNFα, including IKKα expression and IκBá phosphorylation in HSC-T6 cells. In addition, thalidomide also suppressed TGF-β1-induced α-SMA secretion and collagen deposition in HSC-T6 cells. Fibrosis scores of livers from DMN-treated rats receiving high doses of thalidomide (0.89+0.20) were significantly reduced in comparison with DMN-treated rats receiving vehicle (1.56+0.18). Hepatic collagen contents of DMN rats were also significantly reduced by either thalidomide or silymarin treatment. Immunohistochemical double staining results showed that α-SMA and NFκB-positive cells were decreased in the livers from DMN rats receiving either thalidomide or silymarin treatment. In

addition, real-time PCR analysis indicated that mRNA expressions of TGF β1, α-SMA, collagen 1α2 and iNOS genes were attenuated by thalidomide treatment. In conclusion, our results showed that thalidomide exerted anti-fibrotic effects in both HSC-T6 cells and in DMN-intoxicated rats.

APASL/Poster/Abstract/223

Primary hepatocellular carcinoma detected far behind tumor markers and lymph node metastases – beyond our vision?

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The diverse manifestations of hepatocellular carcinoma (HCC) often present difficulty in early diagnosis due to variability seen by tumor markers, imaging modalities and clinical presentations. An asymptomatic 75-year-old man presented with elevated alpha-fetoprotein (AFP) levels in spite of no evidence of HCC in the liver on ultrasonography, helical CT, MR imaging and CT angiography (CTA and CTAP). During an 18-month follow-up, AFP and des-gamma-carboxy prothrombin levels gradually increased and abdominal lymph nodes were detected on dynamic CT. Surgical resection was performed and histopathology revealed poorly differentiated HCC with lymph node metastases (LM). Abrupt decrease of tumor markers was recognized after surgery. However, postoperative recurrence of LM, as well as repeat increase of tumor markers was recognized 7 months later. A tumor measuring 1 cm was finally detected within the liver on CT one year after surgery. Overall, the times from abnormal AFP level and LM to HCC detection were 38 and 22 months, respectively. We report the first case of identification of primary HCC that emerged after LM. Additionally, this reports the longest lag time between the appearance of tumor markers and that of primary HCC. It suggests the limitation of diagnostic modalities as well as the rare and/or diverse presentations of HCC.

APASL/Free Paper/Abstract/224

Molecular analysis of lamivudine-resistant hepatitis B virus: a report from Indonesia

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Introduction: Lamivudine (LMV) is a potent antivirus against hepatitis B virus (HBV). It inhibits reverse transcription and causes termination of DNA synthesis. Extended treatment is needed to maintain low viral load and results in higher HBeAg seroconversion; but is also associated with increased rate of LMV-resistant-HBV. rtM204 mutation in the YMDD motif, a conserved region of the C domain in the P gene, is responsible for LMV resistance. Here, we report the molecular characteristics of the P gene of HBV DNA in Indonesian LMV non-responders. **Methods:** Forty patients positive for HBsAg and HBeAg with ALT >2 ULN were treated with LMV 100 mg/day. Treatment was terminated at week 24 for patients showing HBeAg seroconversion and normal ALT (group I), and extended 24 weeks for the others (group II). At week 48, patients without HBeAg seroconversion and with ALT >2ULN from group II and those from group I who relapsed were studied. The P gene of HBV isolated from baseline and end-of-treatment sera was sequenced and analyzed. **Results:** At week 48, rtM204V (YVDD) mutant developed in 4 (10%), with rtL180M and rtY141F mutations in three cases. One sample had YVDD mutant at baseline. Other samples showed *wt* YMDD. Mutations in other parts of the P gene and S gene also occurred in some samples. **Conclusion:** rtM204V (YVDD) mutation occurred in our LMV-resistant patients, some accompanied by rtL180M and a novel rtY141F. This study confirmed that YMDD mutant may appear independent of LMV treatment, and LMV resistance is not only due to YMDD mutation.

APASL/Young Investigator/Abstract/225

Genotype B of hepatitis B virus as a marker for Austronesian population

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Background: Genotypes of hepatitis B virus (HBV) have been suggested as markers of population migration. In this study, we have examined the distribution of subgenotypes of HBV genotypes B and C (HBV/B and HBV/C) in the various populations of the ethnically diverse Southeast Asian archipelago. We report here the population association of certain subgenotypes, indicating their ancient migration affinity. **Material and Method:** A total of 138 HBAg-positive samples were collected from asymptomatic carriers of eight ethnic populations (Batak-Karo, Dayak Benuaq, Kajang, Makasar, Mandar, Toraja, Alor and Sumba) and from chronic hepatitis patients from Java and Chinese ethnic populations of Indonesia. Phylogenetic trees based on S and Pre-S2 sequences were constructed for genotyping. Genotype distribution was obtained also from the serotype–genotype conversion of published Indonesian serotype data (from 27 cities), and from sequence data obtained from the Genebank for populations of mainland East Asia. **Result:** Genotype B was dominant in Indonesia (73.9%), followed by C (24.6%) and D (1.5%). The existence of subgenotypes of HBV/B and their population association was confirmed: Bei (East Indonesia), Bwi (West Indonesia) and Bc (Chinese Indonesian). Their distribution was consistent with the human ancient migration pattern in the peopling of the Indonesian archipelago. HBV/B was dominant in most regions of Indonesia inhabited by populations speaking Austronesian languages. Dominance of HBV/C was observed only in Papua, and the neighbouring Austramelanosid populations. **Conclusion:** Results of this study indicate that HBV/B is a marker for Austronesian population migration, and the population distribution of subgenotypes Bwi and Bei reflects the ancient migration pattern.

APASL/Poster/Abstract/226

The relationship between serotype and genotype of HBV: study of the East Asian genotypes B and C

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Introduction: HBV is classified into four serological subtypes (serotypes; *adw*, *adr*, *ayw* and *ayr)* based on antigenic determinants of surface protein (HBsAg), and into eight genotypes (A–H). Accumulating evidence suggests the clinical importance of HBV genotypes and serotypes. The relationship between genotypes and serotypes has been suggested, but controversies exist. This study examined the genotype–serotype relationship of the most common Asian genotypes, B and C. **Material and Method:** A total of 110 HBsAg positive samples from various populations of Indonesia were studied. HBV serotypes were detected by ELISA, and DNA was sequenced for the PreS2 and S regions. Genotypes were determined from sequence polymorphisms in these regions. **Result:** We discovered subgenotypes of HBV genotype B (HBV/B), which are population associated: Bei (East Indonesia), Bwi (West Indonesia) and Bc (Chinese Indonesian). Strong correlations between serotypes and genotypes were observed: serotypes *adw* to genotypes Bwi and Bc, *ayw1* to Bei, *adr* and *ayr* to genotype C, and *ayw2* to D. Certain anomalies were noted (e.g. HBV/B with *adr* [*adr*-B] and HBV/C with *adw* [*adw*-C]) and the molecular basis was determined. *adr-B* was a result of mixed infection of HBV/B (*adw*) and HBV/C (*adr*); cloning experiment detected more colonies of HBV/B, but *adr* was dominant in serological assay. In the second case, *adw-C* appeared due to alteration of aminoacid 160 changing *r* to *w*, and mutations P127 T and C139W in the vicinity of the *a* determinant of HBsAg. **Conclusion:** Strong correlation between serotype and genotype/subgenotype was discovered for HBV/B and HBV/C. The ability to convert serotype data to genotype information would be useful for further scientific and clinical studies.

APASL/Poster/Abstract/227

Serological profile and hepatitis B infection in kindergarten children previously vaccinated in a mass neonatal vaccination in Mataram, Lombok Island

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Introduction: Following a WHO mass neonatal vaccination in Lombok Island in 1987–1992, a nationwide hepatitis B vaccination has been implemented and incorporated into the existing expanded program of immunization (EPI). The vaccination in Lombok Island was given to babies at months 0, 1 and 2, irrespective of the maternal HBsAg status. This study was performed to evaluate the serological profile and HBV infection among the kindergarten students previously vaccinated in Mataram, Lombok Island. **Materials and methods:** A total of 374 serum samples of kindergarten students aged 4–8 years from Mataram were assayed for HBsAg, anti-HBs and anti-HBc. Anti-HBc positive sera were tested for the presence of HBV DNA by Qiaquick method. The S-region of HBV DNA was amplified by nested-PCR, and sequenced and analyzed by Bioedit and DNAstar softwares. Sera from several corresponding mothers were also investigated. **Result:** Of 374 samples, three were HBsAg positive, 280 were anti-HBs positive, and eight were anti-HBc positive. Children with completed vaccination had a higher rate of anti-HBs and lower rate of anti-HBc. All anti-HBc-positive samples were HBV DNA positive, some with sequences identical to those of the mothers. DNA analysis of one sample positive for both anti-HBs and anti-HBc revealed mutations T126I and T143S in the S-gene, both with altered Jameson–Wolf antigenicity index. **Conclusion:** HBsAg prevalence decreased after a mass vaccination under the EPI program. Children with completed vaccination had better protection and less HBV infection. HBV infection still happened despite the vaccination; some resulted from vertical transmission, and one was due to escape mutation with altered antigenicity.

APASL/Free Paper/Abstract/228

Viral factors determining ultra good response to 5-year lamivudine treatment

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We aimed to determine factors associated with ultra good response (UGR), defined as HBV DNA of <2000 copies/ml, after 5-year lamivudine treatment. The HBV DNA levels at baseline and various time points over 5 years were measured by VERSANT® HBV DNA 3.0 assay (Bayer HealthCare LLC, NY). Part of the nucleotide sequence of reverse transcriptase (RT) and surface (S) genes were determined by TRUGENE® HBV Genotyping Kit (Bayer HealthCare LLC). This is an interim report for 28 out of 50 recruited patients (genotype B:C 4:24). Eleven patients had UGR. Fifteen patients had YMDD mutations at year 5 (one had no HBV DNA reduction at any time point). There were no differences in the baseline HBV DNA levels (median 8 log copies/ml) between patients with and without UGR. The patient without HBV DNA reduction had a baseline S256C mutation at the RT gene (Ciancio et al, Hepatology 2004). Of the 11 patients with UGR, two had transient development of YMDD mutations. Both patients had concurrent mutations at the S gene (L229 V and L229S). The HBV DNA levels of one of them did not drop below 3×105 copies/ml even with wild-type HBV but decreased to 5482 copies/mL when the YMDD mutants disappeared. The number of patients with HBV DNA levels 104 copies/ml at different time points are as follows:

	Week						
	2	4	8	12	16	24	48
Patients with UGR ($n = 11$)	0	3	3	4	5	5	9
Patients without UGR ($n = 17$)	0	0	0	0	2	3	1

S256C mutation might be associated with poor primary response. Patients achieving HBV DNA104 copies/ml at week 12 will have UGR. This prediction could be generalized to the majority of patients at week 48. Development of YMDD mutations did not preclude subsequent UGR.

APASL/Poster/Abstract/229

Was the hepatic venous pressure gradient (HVPG) really increased in acute variceal bleeding patients with cirrhosis?

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March 2004 to March 2005, in order to ascertain whether portal pressure is really increased in acute variceal bleeding patients, we measured the HVPG in cirrhotic patients who were admitted to our hospital because of variceal bleeding and other causes of cirrhotic complications. With the variceal bleeders, HVPG was measured after stabilization of vital signs and proper medical treatment and after resolution of the main cause of admission with non-variceal bleeders. Of all the 50 patients (M/F:44/6, mean age 55.3 ± 25.1 years), the causes of cirrhosis were alcohol, HBV, HCV, alcohol and HBV, and cryptogenic in 29, 8, 3, 5, and 5 patients, respectively. 17 of them were variceal bleeders, and remained 33 were non-variceal bleeders, in whom the causes of admission were ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, ulcer bleeding, worsening of liver function, and nonspecific GI symptoms. Between both groups, there was no statistically significant difference in vital signs, serum hemoglobin concentration, Child–Pugh score, and MELD score. In the endoscopic workup, F3 varices were more common in variceal bleeders than in non-variceal bleeders (64.7% vs 33.3%, $P = 0.019$). Despite the HVPG being correlated with the Child–Pugh score ($r = 0.552$, $P = 0.000$) and MELD score ($r = 0.489$, $P = 0.000$), there was no statistically significant difference in the HVPG between variceal and non-variceal bleeders (14.53 ± 7.29 vs 14.88 ± 6.74, $P = 0.867$). This study suggests that other causes of variceal bleeding, except increased portal pressure, may be present. But because this study might not reflect the accurate HVPG just before the bleeding, a prospective, large randomized controlled cohort study is needed.

APASL/Poster/Abstract/230

Budd–Chiari syndrome: a tertiary care hospital experience from Pakistan

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Introduction: Budd–Chiari syndrome (BCS) is a rare disorder that is characterized by hepatic venous outflow obstruction. Patients with BCS carry poor prognosis without definitive treatment such as portal decompressive surgery, TIPS or liver transplantation. There is no data regarding its presentation and outcome from Pakistan. **Methods:** We retrospectively studied the clinical presentation and outcome of patients with the BCS admitted to our hospital between 1994 and 2004. Diagnosis was made on the basis of clinical presentation and imaging studies, revealing occlusion of the hepatic veins. RESULTS: Only 19 patients, eight (42%) males with a mean age 28.9 ± 9.0 years were found. Presentation was acute in six (31.5%), sub acute in seven (37%) and chronic in six (31.5%). Pedal edema in 17 (90%), ascites in 16(84%), right upper quadrant pain and discomfort in 16 (84%), jaundice in 11 (58%), encephalopathy in four (21%) and upper GI bleeding in three (16%) were the main presentations. Imaging studies demonstrated hepatomegaly in 17 (90%), caudate lobe hypertrophy in 17 (90%), ascites in 17 (90%) splenomegaly in 11 (58%), intra-abdominal collaterals in nine (47%) and portal vein thrombosis in three (16%) cases. Three patients received anti-coagulation therapy; three were subjected to angiography, stenting and TIPS while thirteen patients were managed conservatively. Two patients are alive while 17 patients are dead, with a median survival of 8 weeks (mean = 52.5 ± 97.4 weeks). One-month survival was only 34% with acute presentation compared to 71.5% with sub-acute presentation and 67% with chronic presentation. Univariate analysis showed that encephalopathy ($P = 0.04$) and hypo-albuminemia ($P = 0.02$) were bad prognostic factors. **Conclusion:** The Budd–Chiari syndrome is uncommon in our part of the world with poor prognosis in the absence of definitive therapeutic options. Encephalopathy and hypo-albuminemia at presentation are poor prognostic factors.

APASL Bali/Poster/Abstract/231

Detection of hepatitis B virus precore mutant in chronic hepatitis B patients in pekanbaru (*preliminary report*)

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Background: Chronic hepatitis B infection is still one of the serious public health problem in Indonesia. Chronic hepatitis B patients have an increased risk for the development of liver cirrhosis and hepatocellular carcinoma. Hepatitis B e antigen (HBe Ag) is a marker of hepatitis B virus (HBV) replication in the liver cells and seroconversion to antibodies to HBeAg (anti-HBe) usually accompanied by cessation of HBV replication and remission of liver disease. However in some patients with chronic hepatitis B infection were reported to have Hbe-negative but still have HBV replication due to HBV precore mutants. **Objective:** The aim of this study was to assess the prevalence of HBV precore mutants in chronic hepatitis B patients and its association with chronic hepatitis B clinical manifestation. **Methods:** Thirty-four subjects with chronic active hepatitis B infection and 21subjects with asympthomatic hepatitis B infection were studied. The study consisted of isolation DNA HBV from sera and amplification of precore region by nested polymerase chain reaction (nested-PCR) method. Determination of precore HBV mutants were carried out by RFLP method. **Result:** This study is still in progress. Temporary results show that HBV DNA was found in 82% of chronic active hepatitis B patients and 57% of asympthomatic hepatitis B patients. HBV precore mutants were detected in 96% of chronic active hepatitis B patients and 67% of asympthomatic hepatitis B patients. **Conclusion:** The prevalence of HBV precore mutants in chronic hepatitis B infection in Pekanbaru was 64%. Further studies and more samples are needed to determine the association between HBV precore mutants and chronic hepatitis B clinical manifestation.

APASL/Young Investigator/Abstract/232

Primary biliary cirrhosis: study of a Singaporean population – demographics, prognosis and factors involving progression

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Introduction: Primary biliary cirrhosis (PBC) is a rare disease. Most natural history studies were performed in Caucasians and studies among Asians are rare. We aimed to evaluate the natural history of PBC among Asian patients at our tertiary liver center.

Methods: All patients with PBC followed at our institution from 1990 till 2005 were reviewed. Their demographics, biochemical, histology data, and natural history were analyzed. Factors including demographics, baseline and change of laboratory markers were evaluated for their association with hepatic decompensation. Multivariate analysis was not performed due to the small number of subjects and multicollinearity amongst the clinical predictors. **Results:** Thirty-two patients with PBC, mean ± SD (range) age of 55.1 ± 10.7 (26.7–79.8) years were identified, of whom 31 (97%) were female and 29 (91%) Chinese. Sixteen (50%) were asymptomatic at diagnosis, 14 had bone mineral densitometry performed with a mean T-score of −1.79 (spine) and −1.99 (hip), and AMA was positive in 26 (81%). Duration of follow-up was 5.3 ± 4.4 (0.02–5.1) years, and five (15.6%) had an event of hepatic decompensation within 5 years and at the end, a total of 10 (31%) within 10 years. Kaplan–Meier analysis showed a mean 9.94 (95% CI, 7.6–12.3) with median 8.7 years to hepatic decompensation. Significant predictors upon univariate analysis were initial s.bilirubin (14.8 vs.77.6 μmol/l, $P<0.001$), prothrombin time (11.7 vs.14 s, $P=0.008$), s.albumin (38.3 vs. 31.8 g/l, $P<0.001$), s.ALP (271.7 vs. 571.8 U/l, $P=0.005$) and HDL levels (1.73 vs.0.66 mmol/l, $P=0.01$) between stable patients and those with decompensation. Interestingly, rate of change of laboratory indices was not a significant predictor. **Conclusions:** The demographics of PBC in Singapore mirrored the populace's ethnic make-up, with a preponderence for females of middle-age and the rate of decompensation at 5 and 10 years being 15.6% and 31%. Initial bilirubin, prothrombin time, albumin, ALP and HDL levels at time of diagnosis have promise as prognostic indicators for an adverse outcome.

APASL/Poster/Abstract/233

New prognosis prediction system for liver transplantation in patients with fulminant hepatic failure

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Many patients with fulminant hepatic failure die before receiving liver transplantation because of the difficulty of pinpointing suitable timing for liver transplantation. The aim of this study was to establish a new prognostic scoring system useful for predicting the timing of liver transplantation. The first sample group consisted of 80 patients. We examined 2-week poor prognostic parameters at the diagnosis of fulminant hepatic failure (day 1) and on days 4, 8, and 15, and a 2-week prognostic scoring system was constructed. In order to confirm the accuracy of this scoring system, validation was performed in a second sample group consisting of 26 patients. By using a stepwise multiple linear regression analysis, the cause of FHF (hepatitis B virus or indeterminate), hepatic coma grade (III or IV), systemic inflammatory response syndrome (yes) and ratio of total to direct bilirubin (>2.0) were found to be associated with a 2-week fatal outcome during days 1 to 15. These four parameters were elicited and scored as+1 in this model. The 2-week survival rate in patients with scores<3 was 80% in contrast to less than 30% in patients with scores 3. When this scoring model was applied to the second sample group, the sensitivity, specificity, and positive and negative predictive values were 87.5%, 90.0%, 93.3%, and 81.8%, respectively. This 2-week prognostic scoring system may be useful for predicting a 2-week outcome and determining suitable timing for liver transplantation.

APASL/Poster/Abstract/234

Regulation of hepatitis B virus X protein expression using doxycycline-inducible gene expression system

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Background: Hepatitis B virus X protein (HBx) is a multifunctional protein, which may play an important role in HBV-associated pathogenesis, especially hepatocarcinogenesis. The functions of HBx have been shown to be related to its location and level of expression. **Objective:** To establish *in vitro* cell line with stable, effective and regulatable HBx expression using a doxycycline (Dox)-inducible gene expression system. **Methods:** A doxycycline-inducible retroviral plasmid (pBPSTR3-FlagX) was constructed by replacing the tetracycline-controlled transcriptional activator (tTA) gene in pBPSTR1 with the reverse tTA (rtTA) gene and inserting of the HBV X gene. Doxycycline-regulated expression of Flag-HBx in transient transfected HepG2 and Hep3B cells were analyzed by Western blot. Doxycycline-regulated transactivation function of HBx was also measured with luciferase reporter gene assay. Stable HBx expression HepaG2 cell clones were established through screening with puromycin. **Results:** The doxycycline-inducible recombinant plasmid (pBPSTR3-FlagX) containing the full-length HBV X gene and all the components of the tetracycline-on (Tet-on) gene expression system was developed successfully. Expression studies with this vector showed a Dox dose-dependent induction of Flag-HBx protein expression in HepG2 and Hep3B cells. The transactivation function of HBx was also achieved in HepG2 cells in a Dox dose-dependent manner. After transfecting HepG2 cells with pBPSTR3-FlagX plasmid, five puromycin-resistant cell clones with stable HBx expression were obtained, and two clones showed stable and tight control of HBx expression by doxycycline.
Conclusion: The doxycycline-inducible HBx expression system was developed and a stable cell line with effective and regulatable HBx protein expression was established in this study. The quantitative regulatory property of this system ensures its great potential in the functional studies of the HBV X gene. This work was supported by the National Science Fund for Distinguished Young Scholars from the National Natural Science Foundation of China, No. 30325036

APASL/Plenary/Abstract/235

Study on the role of liver-enriched transcription factors in regulating HBV transcription and replication

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Background: Hepatitis B virus (HBV) replicates by reverse transcription of the 3.5-kb viral pregenomic RNA. Therefore, the regulation of the transcription of the pregenomic RNA is a critical step in the viral life cycle. **Objective:** To investigate the

effects of various liver-enriched transcription factors in regulating HBV transcription and replication, and explore their potential roles in HBV hepatotrophism. **Methods:** The replication-competent HBV recombinant plasmid pHBV4.1 plus different liver-enriched transcription factor (HNF1, HNF3, HNF4, HNF6, C/EBP and RXRα/PPARα) expression plasmids were transfected into nonhepatic cell lines (NIH3T3, HeLa, 293T, SW1353, CV-1 and COS1). The transcription levels of 3.5-kb, 2.4/2.1-kb, 0.7-kb HBV RNA and HBV replication intermediate DNA were analyzed by Northern and Southern blot hybridization. **Results:** In the absence of cotransfected liver-enriched transcription factor expression vectors, the 3.5-kb HBV RNA is not transcribed and HBV DNA replication is not detected after transfecting of NIH 3T3 cells with pHBV4.1. Expression of the liver-enriched transcription factor HNF4 or RXRα/PPARα stimulates transcription of the 3.5-kb HBV RNA and replication of the HBV DNA. In contrast, expression of HNF1, HNF3, HNF6 and C/EBP does not stimulate transcription of the 3.5-kb HBV RNA and therefore does not activate viral replication. HNF4 and RXRα/PPARα were also shown to activate transcription of the 3.5-kb HBV RNA and viral replication in diverse cell types including HeLa, 293T, SW1353, CV-1 and COS1 cells. Mutation of the proximal nucleocapsid HNF4-binding site results in a greatly decreased level of HNF4 or RXRα/PPARα-dependent HBV replication. **Conclusion:** This study demonstrated that the liver-enriched transcription factors HNF4 and RXRα/PPARα can support HBV transcription and replication in nonhepatic cells, indicating liver-specific gene transcription is one of the determinants of HBV hepatotropism. This work was supported by the National Science Fund for Distinguished Young Scholars from the National Natural Science Foundation of China, No. 30325036

236
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237
Abstract withdrawn

APASL/Poster/Abstract/238
Screening of oesophageal varices with platelet count/spleen diameter ratio in patients with liver cirrhosis
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Background and Aim: Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of oesophageal varices (OV) is one of the major complications of portal hypertension The prevalence of OV in patients with liver cirrhosis may range from 24% to 80%, and the reported mortality from variceal bleeding ranges from 17% to 57%; therefore, endoscopic screening of OV is recommended in patients with liver cirrhosis. As endoscopy units and endoscopists are not well distributed in hospitals in our country, platelet count/spleen diameter ratio might be a non-endoscopic tool to predict the presence of OV in patients with liver cirrhosis. **Methods:** We evaluated all the 75 liver cirrhosis patients with complete biochemical work-up, upper digestive endoscopy, ultrasonographic measurement of spleen bipolar diameter. Platelet count/spleen diameter ratio was calculated for all patients. **Result:** The prevalence rates of OV were 88%. A platelet count/spleen diameter ratio with a cut off value of 967 had 98.5 % sensitivity, 88.9% specificity, 98.5% positive predictive value, 88.9% negative predictive value and had 8.9 in positive likelihood ratio and 0.02 in negative likelihood ratio. **Conclusion:** Platelet count/spleen diameter ratio could be a non-endoscopic tool to predict the presence of OV in patients with liver cirrhosis.

APASL/Poster/Abstract/239
The correlation of anemia parametric with the severity of liver cirrhosis
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Background: Anemia is a lower than normal hemoglobin in the blood and is frequently found in liver cirrhosis. The causes of anemia in liver cirrhosis patients were of multifactorial character such as suppression of erythropoiesis by alcohol as well as folate deficiency, hemolysis, hypersplenism, and insidious or overt blood loss from the gastrointestinal tract. **Aim of the Study:** To study anemia in liver cirrhosis patients and the correlation of anemia, including iron deficiency anemia and hemolytic anemia, with the severity of liver cirrhosis patients. **Material and Method:** The study was done cross-sectional in 37 liver cirrhosis patients during June 2003–April 2004. Child–Pugh score was calculated and we studied anemia parametrics such as hemoglobin, hematocrit, MCV, MCH and MCHC. Iron deficiency anemia examination by transferrin, feritin serum and hemolytic anemia examination was done with reticulocyte count. **Result:** Anemia was found in 28 (76%) patients, 10 (27%) patients with transferrin $<16\%$, three (8.1%) patients with feritin serum $<12\%$ and two (5.4%) patients with reticulocyte count $>1.5\%$. There was no correlation between degree of anemia, MCV, MCH, MCHC and hemolytic anemia with the severity of liver cirrhosis. There was correlation only between iron deficiency anemia with the severity of liver cirrhosis patients ($P = 0.0001$). **Conclusion:** Anemia occurred in about 76% cirrhosis hepatic patients and was not correlated with severity of liver cirrhosis. There was correlation of iron deficiency anemia with the severity of liver cirrhosis. There was no correlation of hemolytic anemia with the severity of liver cirrhosis

APASL/Poster/Abstract/240
The level of thrombopoietin serum in liver cirrhosis patients and correlation with the severity liver cirrhosis
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Background: Thrombopoietin is a thrombopoietic factor mainly synthesized in the liver. Its production will be decreased related to the severity of liver disease. Impaired production thrombopoietin may be responsible for thrombocytopenia in

liver cirrhosis patients. **Aims:** To measure serum thrombopoietin levels and to examine the relationship between serum thrombopoietin concentration and clinical stage of the disease in patients with liver cirrhosis (Child–Pugh criteria). **Method:** A prospective cross-sectional analytic study was conducted involving 35 liver cirrhosis patients and 39 healthy volunteers. Serum thrombopoietin levels were measured by enzyme-linked immunosorbent assay. **Results:** Mean serum thrombopoietin level was (84 229 ± 44 857) pg/ml in the cirrhotic patients group and (116 269 ± 75 978) pg/ml in the healthy group ($P = 0.033$). In patients with liver cirrhosis serum thrombopoietin levels were found to be decreased as the disease progressed: (101 ± 44 455) pg/ml in patients at Child–Pugh stage A, (98 638 ± 53 058) pg/ml in patients at Child–Pugh stage B and (57 785 ± 18 957) pg/ml in patients at stage C with $P = 0.868$ compared thrombopoietin level Child-Pugh stages A and B, $P = 0.019$ compared thrombopoietin level Child–Pugh stages A and C and $P = 0.016$ compared thrombopoietin level Child–Pugh stages B and C. **Conclusion:** The findings revealed that serum TPO levels were decreased as degree of cirrhosis progressed. The impaired production of thrombopoietin may contribute to the development of thrombocytopenia in advanced liver disease.

APASL/Poster/Abstract/241

Plasma prothrombin time as a diagnostic tool of esophageal varices due to liver cirrhosis

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Background: To diagnose esophageal varices (EV) among liver cirrhosis (LC) patients we usually used endoscopy, but it is not practical if only the diagnosis of EV serial endoscopy has to be performed. This study investigated the accuracy of plasma prothrombin time (PPT) as a tool for VE detection among LC **Methods:** In all, 93 patients with LC were allocated to the VE-positive group (47) and VE-negative group. (46). The diagnosis of LC was based on clinical, laboratory and ultrasonography examination. EV was diagnosed by endoscopy and done on the same day that the liver function test was performed. Diagnostic test and χ^2 test were used for statistical analysis. **Result:** Abnormal PPT defined as gradient in patients and controls 4 s or longer were found in 37 out of 47 patients of the VE-positive group compared with only seven out of 46 patients of the VE-negative group ($P < 0.005$). The sensitivity was 78.7% and specificity 84.7%. If we use abnormal PPT of 7 s or longer as the cut off point, the specificity will be more than 95%. **Conclusion:** PPT is a good diagnostic tool for esophageal varices due to LC.

242
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243
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244
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245
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APASL/Poster/Abstract/246

Factors to affect serum levels of adipokines in Korean male patients with nonalcoholic fatty liver disease

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Adipokines is known to be associated with metabolic disorders such as insulin resistance, obesity, and dyslipidemia. The metabolic disorders were also reported to be related with nonalcoholic fatty liver disease (NAFLD). We aimed to find the relationship between serum adipokine levels and the degrees of hepatic fat infiltration in NAFLD. We also tried to determine independent factors to influence the serum adipokine levels in NAFLD. 65 Korean male patients were classified into three groups: Group I: normal liver, Group II: mild fatty liver and Group III: moderate to severe fatty liver. All subjects were measured for anthropometric parameters, fasting serum adipokine levels including leptin, adiponectin and resistin. Insulin resistance was estimated by HOMA-IR. Serum leptin levels increased with the degree of fatty infiltration with significance (mean ± SD: Group I; 2.052 ± 1.071, Group II; 2.879 ± 1.016, Group III; 4.457 ± 1.965 ng/ml, $P < 0.001$), whereas serum adiponectin and resistin levels were not significantly different. BMI and HOMA-IR were independent factors only for changes in serum leptin levels ($P = 0.029$, $P = 0.001$, respectively), but not for serum adiponectin and resistin levels. Our study supports an indirect role for leptin in the pathogenesis of NAFLD, but not for adiponectin or resistin. BMI and HOMA-IR were the only independent factors influencing the serum leptin concentrations.

APASL/Poster/Abstract/247

Relations between coagulation parameters and portal vein thrombosis in hepatocellular carcinoma

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Portal vein thrombosis (PVT) is an important complication and a prognostic factor in cirrhosis and HCC. Although PVT is mostly associated with portal vein invasion by HCC, the development of PVT has been reported in association with the imbalance between clotting activators and inhibitors. The purpose of this study was to evaluate the correlation between coagulation parameters and PVT in HCC. We divided the cirrhotic patients (≥ Child–Pugh Class, B) into three groups: only cirrhosis (Group A, $n = 17$), HCC without PVT (Group B, $n = 14$) and HCC with PVT (Group C, $n = 8$). Demographic information and coagulation parameters (platelet, prothrombin time, fibrinogen, prothrombin, factor V, VII, IX, X, protein C/S antigen/activity, lupus anticoagulant, antithrombin III, plasminogen, tissue type plasminogen activator (tPA), D-dimer, plasminogen activator inhibitor type-1 (PAI-1) were compared between the three groups. Age and αFP level were significantly

higher in HCC with PVT. But, coagulation parameters did not show any significant difference among the groups. The prognosis of HCC is highly dependent on the extent of tumor invasion and residual liver function. In addition, this study showed that age and αFP level were highly associated with the prognosis of HCC with PVT. But the relation between coagulation parameters and PVT did not show any statistical association because of the limitation of sample size.

APASL/Free Paper/Abstract/248

Grafts from older donors are associated with decreased recipient survival after liver transplantation for hepatitis B-related liver disease

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Introduction: It remains unclear whether donor age influences recipient survival in liver transplantation (LT) for hepatitis B virus (HBV)-related liver diseases. We assessed the effect of donor age on post-LT outcomes and recipient survival in patients with HBV infection. **Patients and Methods:** A total of 217 patients underwent LT for HBV-related liver diseases from January 1996 to April 2004. Recipients were divided into two groups according to donor age: older donor group (donor age 40 years, $n = 67$, median age = 45) and younger donor group (donor age < 40 years, $n = 150$, median age = 27). Post-LT outcomes and patient survival were compared. **Results:** Baseline characteristics of recipients (sex, age, MELD score, presence of HCC, HBeAg positivity, HBV DNA level) and transplantation factors (graft type, cold/warm ischemia time and graft volume) were similar in the two groups. Acute rejection occurred in 17.9% of the older donor group and in 14.7% of the younger donor group ($P = 0.55$). The mean ALT at 4 months after LT was similar (63 IU/l vs. 49 IU/l, $P = 0.32$). Recurrent HBV infection was observed in 13.4% of the older donor group and in 6.7% of the younger donor group ($P = 0.12$). One- and 5-year survival rates of the older donor group (76% and 56%) were significantly lower than those of the younger donor group (88% and 80%, $P = 0.02$). Hepatic failure was the more common cause of death in the older donor group, than in the younger donor group (9.0% vs. 2.0%, $P = 0.03$). **Conclusions:** These findings suggest that grafts from older donors can be associated with decreased recipient survival after LT for HBV-related liver diseases.

APASL/Poster/Abstract/249

Usefulness of Milan and UCSF criteria to predict outcomes of liver transplantation in hepatocellular carcinoma patients receiving prior transarterial chemoembolization

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Introduction: It remains unclear whether the Milan and/or UCSF criteria are still valid in hepatocellular carcinoma (HCC) patients who have received transarterial chemoembolization (TACE) before liver transplantation (LT). Hence, we assessed the usefulness of Milan and UCSF criteria in HCC patients receiving prior TACE, compared with those without any treatment for HCC before LT. **Patients and Methods:** From September 1996 to April 2004, LT was done in 40 HCC patients who had received prior TACE (TACE-LT group) and in 40 without any previous treatment for HCC (LT group). The numbers of patients fulfilling Milan and UCSF criteria were 36 and 34 in the TACE-LT group, and 33 and 30 in the LT group. Post-LT outcomes and survival rate were compared between the patients within the criteria from the two groups. **Results:** Baseline characteristics, such as age, sex, etiology of liver diseases, α-fetoprotein level, MELD score, and graft type were similar in the two groups. The tumor profiles of patients fulfilling Milan and UCSF criteria in each group were also similar. No significant differences were found in post-LT 60-day mortality (5.6% vs. 12.1%, $P = 0.42$) and in HCC recurrence rate (5.6% vs. 6.1%, $P = 0.93$). Five-year survival rate of patients fulfilling Milan criteria in each group was 65% and 71%, respectively ($P = 0.54$). Five-year survival rate of patients fulfilling UCSF criteria in each group was 65% and 72%, respectively ($P = 0.73$). **Conclusion:** The Milan and UCSF criteria are useful criteria to predict favorable post-LT outcomes in HCC patients receiving prior TACE as well as those without previous anti-cancer treatment.

250

Abstract withdrawn

APASL/Free Paper/Abstract/251

DNA-based immunization increased the survival rate of mice loaded with HBV preS2S antigen expressing myeloma cells

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Background: DNA vaccine can induce cell-mediated immunity, especially CTL responses. It may be a potential therapy for chronic hepatitis B virus (HBV) infection. We established a mouse model here, which loaded a myeloma stably expressing HBV preS2S antigen. This model mimics the status of liver when it infects HBV chronically. The cells of the myeloma were used as the targets of the CTL *in vivo*. **Objectives:** The goal of this study was to investigate if the DNA vaccine could increase the survival rate of the mice model and to observe its probably therapeutic effects for chronic HBV infection. **Methods:** The SP2/O-S2S cell line with stably expressed HBV preS2S was obtained by transfecting pCMV-S2S into SP2/O cells. BALB/c mice were subcutaneously inoculated with SP2/O-S2S cells into the bilateral flanks. One week after loading of the cells, the mice were divided into four subgroups, and pCMV-S2S, HB_SAg, pCMV or normal saline was injected into the tibial anterior muscle of each group, respectively; another group was inoculated with SP2/O cells and was injected with pCMV-S2S at the same time. Two mice of each group were sacrificed one week after injection. HBV preS2S expressing was detected by immunohistochemistry. *In vitro* CTL activity was detected by the Cytotoxicity Detection kit. The life span and survival rate were analyzed by Log-Rank statistics, and Kaplan–Meier Survival Curve separately. **Results:** HBV preS2S expression was demonstrated in muscles injected with pCMV-S2S and SP2/O-S2S cells formed myelomas. The experimental group got much higher *in vitro* preS2S-specific CTL activity, prolonged life span ($P < 0.05$) and significantly increased survival rate ($P < 0.05$) than all control groups. **Conclusion:** This study demonstrates that HBV preS2S expression construct can generate substantial HBV preS2S specifically CTL response and significantly increase the survival rate only of mice loaded with a HBV preS2S-

expressing myeloma; thus, it may be a potential immunotherapy for chronic HBV infection.

APASL/Poster/Abstract/252

HCV core protein may play an important role in the inhibition of HCV on HBV replication

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Background: Both chronic hepatitis B and C virus (HBV, HCV) infection are major causes of cirrhosis and hepatocellular carcinoma. It has been shown that HCV may inhibit HBV replication at superinfection or coinfection status. However, the mechanism of this phenomenon is still unclear. **Objectives:** The aim of this study was to investigate the possible role of HCV core gene product on the inhibition effect of HCV on HBV replication. **Methods:** A series of plasmids were constructed, which contain HCV full genome, CE2, core, E1, E2, NS2, NS3, NS4 and NS5 gene, respectively. All of these plasmids and the empty control vector were transiently transfected into HepG2 2.2.15 cells by calcium phosphate method, separately. About 72 h posttransfection, HBV surface antigen (HBsAg) and e antigen (HBeAg) in supernatants of the cultured cells were detected by ELISA, HBV DNA was detected by quantitative PCR analysis. The replication intermediates of HBV and the total RNA were extracted from the cells, and they were analyzed by Southern and Northern hybridization, respectively. **Results:** The secretion of HBVviral particles, as well as HBsAg and HBeAg in the supernatant, was obviously reduced by thepresence of the HCV full genome, CE2and core genes, but not by thepresence of other genes. Analysis of the intracellular HBV replication intermediates and RNA were also shown obviously declined by thepresence of the same genes and not by thepresence of other genes. **Conclusion:** These data suggest that HCV can inhibit the replication of HBV, and the HCV core gene may play a critical role on this inhibition effect. This work was supported by the National Science Fund for Distinguished Young Scholars from the National Natural Science Foundation of China, No. 30325036, and the Application Fundamental Research Program of Sichuan Province, China, No. 04JY029-002-7.

APASL/Free Paper/Abstract/253

Comparison of hepatitis B Virus (HBV) genotyping assays between TRUGENE™ HBV genotyping and RFMP™ HBV YMDD genotyping

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Introduction: Many assays for detection of mutations leading to lamivudine resistance, which were developed by long-term lamivudine therapy in chronic hepatitis B patients, have been introduced. However, it is difficult to select one to apply among these assays. **Materials and Methods:** HBV DNA was extracted from the sera of 50 patients with chronic hepatitis B who have received lamivudine therapy during more than 3 months, and were analyzed by the TRUGENE™ HBV Genotyping (TRUGENE), DNA sequencing-based assay, and RFMP™ HBV YMDD Genotyping (RFMP), MALDI-TOF MS-based assay. We investigated the pattern of mutations in YMDD motif of HBV polymerase by the TRUGENE and the RFMP. **Results:** Among 50 patients, HBV genotypes were all C (100%). Detection rate of mutation by the RFMP was 74% and that by the TRUGENE was 68%. The site of mutation detected by the TRUGENE was V517L, L528 M, M552I, and V555I. The RFMP found mutation in L528 M and M552I. The concordance rate between the TRUGENE and the RFMP was 88% in L528 M and 90% in M552I. **Conclusion:** The TRUGENE analyzed mutations in more variable sites than the RFMP. However, the detection rate of mutation by the RFMPwas 6% higher than that of the TRUGENE. Moreover, high concordance rate between two assays was observed. Therefore, the RFMP method was thought to be a cost-effective method for detection of lamivudine resistance.

APASL/Poster/Abstract/254

Comparative analysis of the tolerability of interferon α-2α and pegylated interferon in the treatment of CHC

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Objective: To compare the tolerability of interferon α-2a and pegylated interferon α-2a (40 kDa) in combination with ribavirin in the treatment of chronic hepatitis C. **Methods:** Sixty patients with chronic hepatitis C were included with standard combined therapy: interferon α-2a, 3 million IU every day – eight patients (first group), high dose ascertained therapy – 10 patients (second group) and pegylated interferon α-2a(40 kDa) in standard dosage 180 mg once a week – 42 patients (third group) with ribavirin in doses according to body weight and genotype of HCV. **Results:** Flu-like symptoms were recorded in all patients in the first group and second group and in 32 patients (76%) in the third group, hyperthermia was marked in the first group – after 2.8 injections, in the second group – 3.5 injections. In the third group – in 10 patients rise of temperature was not recorded, in eight cases hyperthermia was recorded during 52.8 h after every one of three injections, in five cases – during 60 h after each of two first injections, in nine patients – during 48 h after the first injection, in 10 patients – during 24 h after the first injection. Depression was recorded in 90%, 77.7%, and 64.4% in the corresponding groups. The most evidence of leukopenia was recorded in the second group, the least in the – first group. Skin eruption and hyperemia on the injection site were recorded in six patients – first group and second group and 10 patients taking pegisis. Cancellation of therapy was required in five cases. Causes of cancellation: vasculitis – after 34 weeks of treatment (first group), expressed thrombocytopenia and leukopenia – after the first injection (third group), anaphylactoid reaction – after the second injection (third group), thromboembolism of small branches of the pulmonary artery (second group). Devotion for treatment was highest in those taking pegisis. **Conclusion:** In that way, pegisis type of interferon A-2α is different by the best portability and devotion for treatment, than interferon A-2α in high dosage ascertained therapy. Portability of therapy by pegisis type of interferon A-2α commensurable with portability of standard dosage 3 million IU/day, devotion for treatment is higher with pegisis type.

APASL/Poster/Abstract/255

The efficacy and tolerability of the combination therapy of CHC with pegylated interferon α-2a and ribavirin

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Objective: To evaluate the efficacy and tolerability of the antiviral treatment of chronic hepatitis C (CHC) according to HCV genotype and viral load. **Methods:** Among 47 HCV RNA-positive patients were 24 patients with genotype 1b, 11 with genotype 2 and 10 with genotype 3a, while in two patients genotype was not determined. The efficacy of the treatment was analyzed by standard protocol. Side effects and tolerability were evaluated by general condition, monitoring blood tests every 2 weeks, serum iron, coagulogramma and blood proteins every month. **Results:** Normalization of transaminase activity level was noted after a 4-week therapy in 38 patients, and in eight patients, transient rising of ALT was seen during the period of observation. Decreasing of HCV RNA was recorded in all patients. Currently, 32 patients have finished their therapy. Sustained virological response was achieved in 30 patients, two recurrences were noted (genotypes 1b and 2), the observation period of 12 patients did not finish and three patients left the study. Therapy was cancelled for one patient after the first injection because of a decreasing level of platelets and leucocytes' lower critical magnitude, in the second case because of thromboembolism of small branches of pulmonary artery after 28 weeks of treatment. One patient stopped therapy after 30 weeks forpersonal reasons. Positive biochemical and virological response was noted in two cases. Observation is continuing. **Conclusion:** By our observations, a combined therapy of CHC allowed us to achieve a sustained virological and biochemical response in 93.7% cases. Side effects led to canceling of therapy in 4.2% of the observations.

APASL/Free Paper/Abstract/256

Prevalence of viral hepatitis in different population address groups of Republic of Kazakhstan

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Objective: To study the prevalence of viral hepatitis B and C in different population groups in the Republic of Kazakhstan. There were no prevalence data in Kazakhstan before. **Materials and Methods:** Investigated population groups were as follows: first group – random sampled patients (3336), consulted for the first time for viral hepatitis, second group – asymptomatic patients (654) with different kind of biliary and liver diseases in anamnesis, third group – 134 healthy persons, fourth group – children with leucosis (69), fifth group adult leucosis patients, sixth group – intravenous drug users (1434), seventh group – medical staff of hematological center (94), eighth group – blood donors (1440). Exploration realized by analyzer close-ended type – Vitros Eci, with test system ''Orto-Clinical Diagnostic''. **Results:** In the first group percentage positive markers of viral hepatitis B was 38.4, and at the same time revealed HBsAg – 11.6%, HBsAb – 35.6%, HBcorAb total – 34.5%, HBcor IGM – 2.5%, HBeAg – 24.9% and HBeGb – 28.9%. In this group, anti-HCV total was revealed in 18.6%. The second group was characterized with high levels of positive markers of HCV and HBV infection (87.3%), with co-infection in 78.9%. In the third group, 21.5% was revealed with viral hepatitis B and 13.6% with anti-HCV. Morbidity rate of viral hepatitis in the fourth group in 1998 was 54.6% with a decrease to 37.7% in 3 years, mostly by CHB. Among children, co-infection of HBV and HCV was observed in 73%, HBV – in 21% and HCV – 6%. In the fifth group HBV infection was revealed in 55.8% with acute leukemia and 70.8% with chronic leucosis. Among them, 11.5% and 8.3% were HbsAg positive,respectively. In patients with chronic leucosis, 1.2% cases of HDV were revealed. In HIV positive i.v. drug users, antiHCV was found in 97.5%; among them, 84% were HCV RNA positive –. In HIV negative i.v. drug users, 77.1% observations showed antiHCV, and 82% were HCV RNA positive. The seventh group was different by heterogeneous frequency of markers of HCV and HBV infection. The most liable to infection were patient's mothers, medical and laboratory staff. The prevalence of antiHCV positive donors come to 2.5%; among them, 89.1% were HCV RNA positive. **Conclusion:** A high level of prevalence in HBV and HCV infection in all groups was accepted to start the screening program for viral hepatitis in the country.

APASL/Poster/Abstract/257

Hematopoietic stem cell mobilization contributes to liver graft regeneration after partial orthotopic liver transplantation

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Background: On the basis of the recently recognized potential of hematopoietic stem cells to give rise to hepatocytes, we investigated the possibility that auto HSC and granulocyte colony-stimulating factor (G-CSF)-mobilized HSC could home to partial liver graft and promote liver repair. **Materials and Methods:** Fifty percent sex-mismatched rat partial orthotopic liver transplantation (PLTx) was established. Female SD rats were used as donors and male SD as recipients. The recipients were repeatedly administrated human recombinant G-CSF (rG-CSF) for five consecutive days before and after 50% PLTx. Serum biochemical parameters, mitosis index, PCNA and BrdU incorporation were employed to estimate liver regeneration and liver injury. CD34 and c-kit were detected by immunohistochemistry to confirm stem cell migrating to the liver. The SRY (sex-determining region for Y chromosome) gene was detected to confirm the origin of cells by *in situ* hybridization in liver sections. **Results:** In 50% PLTx+G-CSF group, G-CSF administration ameliorated the histological damage and accelerated the regeneration process. Compared with the 50%PLTx and G-CSF+50%PLTx groups, there was a high survival rate in the 50%PLTx+G-CSF groups ($P<0.05$). On the third day post-operatively, the levels of AST and ALT were lower, and mitosis index, PCNA and BrdU incorporation were higher ($P<0.05$) in the 50%PLTx+G-CSF groups, and these parameters showed no obvious difference between the 50%PLTx and G-CSF+50%PLTx groups. Compared with 50%PLTx groups, CD34+cells around the portal tract region increased on the third day post-transplantation in the G-CSF+50%PLTx groups and on the fifth day post-transplantation in the 50%PLTx+G-CSF groups, respectively. SRY, a Y chromosome marker, could be detected in the G-CSF mobilized groups by in situ hybridization, and increased during the 7–14 days after transplantation. **Conclusions:** G-CSF treatment after 50%PLTx significantly improved survival rate and liver histology of partial graft, predominantly by promoting endogenous repair mechanisms. Therefore, mobilization with G-CSF might offer a novel therapeutic approach for the treatment of liver diseases in humans.

APASL/Free Paper/Abstract/258

Interferon-induced protein – ISG20 partially mediating the inhibitory action of IFN-α on HCV replicon

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One important biological function of interferons (IFNs) is its antiviral activity. This function is thought to be mediated by the products of specific and functionally overlapped cellular genes induced by interferon in the target cells. Interferon-α has been used to treat hepatitis C virus infection for more than ten years. But the mechanisms of its antiviral action are not fully understood. ISG20 is a newly found interferon stimulated gene and encodes an exonuclease, which can degrade single-stranded RNA and inhibit some RNA viruses. In this report, we investigated the effect of ISG20 on HCV replicon replication by transient and stable overexpression of ISG20 in HCV replicon cells. The results showed that overexpression of wild type ISG20 led to the reduction of HCV RNA and NS5A protein levels, whereas overexpression of mutated ISG20 did not have an inhibitory effect on HCV replicon and seemed to play a dominant negative function. Our research findings suggested that ISG20 partially mediated the inhibitory effect of interferon-α on HCV.

APASL/Free Paper/Abstract/259

ISGF3, a critical factor of the IFN-α pathway in the antiviral action of HBV

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Objective: To study the mechanism of signal transduction in anti-HBV with IFN-α. **Methods:** The HBV DNA in HepG 2.2.15 cell line supernatant with/without IFNα-2b was monitored by fluorescence real-time quantitive PCR. Southern blot analysis was performed on HBV replicative intermediate DNA extracted from core particles. Detected STAT1, STAT2, ISGF3γ, PKR 2′5′-OAS mRNA levels from HepG 2 and HepG 2.2.15 cell lines were treated with/without IFNα-2b at different times by semi-quantitive RT-PCR. Also, the STAT1, P-STAT2, ISGF3γ and PKR proteins were measured by means of Western blot. The same measurements were performed in cells treated with genistein, which can block the JAK-STAT pathway. **Results:** The HBV DNA in HepG 2.2.15 supernatant that were treated by IFNα-2b for 8 h decreased by 2.07×10^5 copies/ml. However, similar decreases did not occur in cells pretreated with genistein. IFN-α2b upregulated the STAT1, STAT2, ISGF3γ 2′5′-OAS PKR mRNA levels as well as the STAT1, P-STAT2, ISGF3γ and PKR proteins. In cases of genistein pretreating before IFN, the STAT1, STAT2 and ISGF3γ levels remained unchanged but the 2′5′-OAS and PKR mRNA levels decreased. The expressions of the STAT1, P-STAT2, ISGF3γ and PKR protein were also augmented by IFNα-2b treatment, which was blocked by genistein. **Conclusion:** These observations suggested to us that the JAK-STAT pathway plays a major role in IFNα-2b against HBV, with ISGF3 being a 'key factor'.

260

Abstract withdrawn

APASL/Free Paper/Abstract/261

Chronic exposure of Mengkudu (*Morinda citrifolia*) Juice in Balb C Mice

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Mengkudu (*Morinda citrifolia*) juice was very popular as a food supplement in the world, but there is little known about side effects, especially in chronic exposure. This research was conducted in order to prove the influence of mengkudu (*M. citrifolia*) juice to the percentage of mice liver cells that suffer necrosis. The research design was The Post Test Only Control Group Design. Animals being used in this research were 36 2-month male mice of Balb C, whose average weight was 20–25 g. The mice were randomly divided into four groups. The first group (P_0) was the control group which was given aquadest. The second group (P_1) was given mengkudu juice A. The third group (P_2) was given mengkudu juice B. Finally, the fourth group (P3) was given mengkudu juice C. All four groups were orally given an equal dose of 0.8 cm^3 once a day for 28 days. On the 29th day, the mice livers were taken and made into histopathology blood smears. LSD test were conducted to find out the difference of liver cells suffering necrosis between all of the treatment groups. The results of this research show that there are significant differences between the giving of mengkudu juice A, B, C and the changing (necrosis) of histopathology of mice livers. The changing is considered significant if the significant value is less than 0.05. The result of LSD test shows that treatment P_0 is significantly different to treatment P_1 and P_3 with the value of $P = 0.000$. However, the treatment P_0 is insignificantly different from treatment P2 ($P = 0.057$). Treatment P_1 is significantly different from treatment P_2 ($P = 0.013$), but insignificantly different from treatment P_3 ($P = 0.069$). Treatment P_2 is significantly different from treatment P3 ($P = 0.000$). From these results, it can be concluded that the giving of mengkudu A, B and C has different effects on the necrosis of mice liver cells.

262

Abstract withdrawn

APASL/Poster/Abstract/263

Choledochal cysts – presentation, symptoms and related complications

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Background/Purpose: The study aims to compare the presentation, diagnostic evaluation and complications in patients with choledochal cysts in a tertiary hospital. **Methods:** A retrospective review of case records of 41 patients, between June 1987 and May 2005, with known preoperative diagnosis of choledochal cysts was performed. These patients were operated by and under the care of the same surgeon. **Results:** The median age at presentation was 36 months (range 19 weeks of gestation to 44 years). Of them, 29.3% were male. Six (14.6%) patients were diagnosed antenatally, three of whom were asymptomatic at the time of operation. The remaining 38 (92.7%) patients had at least one presenting symptom; recurrent abdominal pain in 28 (68.3%) and jaundice in 21 (51.2%) patients. In patients with jaundice, the median age of presentation (30 months) was less than that of those without jaundice (64 months) ($P = 0.09$).

Correspondingly, in those with pain as the main complaint, the median age at presentation was significantly higher (40 months vs 8.5 months) ($P = 0.01$). ALP was raised significantly as with any obstructive jaundice. Interestingly, in those without jaundice, the serum median ALP was 194.5 and mean 256.8, all above the normal range. Amylase was more likely to be raised in those with abdominal pain (median 151 vs 25) ($P = 0.01$) Ultrasound was the most common form of imaging modality and was performed in 27 (93.1%) patients. CT scan was used as part of the diagnostic workup in 38 patients (92.7%) and MRCP in eight patients (19.5%). Excision of the extrahepatic cyst was performed in 36 (87.8%) patients. There were no cases of cholangiocarcinoma found at frozen section at the time of operation or at follow up. Todani Type 1c (51.2%) was type of choledochal cyst seen most often. The mean duration of follow-up was 6.4 years, with a median of 5.8 years. Of the 37 patients who already underwent an operation, 33 (89.2%) underwent an uneventful recovery. Of the four (10.8%) complicated cases, two had postoperative wound infection; one had postoperative ileus and rising amylase and the last had a viral fever. **Conclusions:** Obstruction of the biliary system by the choledochal cyst resulting in jaundice allows an earlier age of presentation and diagnosis, unlike those who present with pain alone. Ultrasound is the main modality for diagnosis, and with advances in antenatal ultrasound, patients can now be diagnosed antenatally. Isolated extrahepatic choledochal cysts make up the majority of cases and are amenable to early resection with little postoperative morbidity.

APASL/Free Paper/Abstract/264

The correlation between cyclooxygenase-2 and p53 expression in hepatocellular carcinoma and the effects of recurrence after surgery

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Introduction: Overexpression of cyclooxygenase-2 (COX-2) has been well documented in variable malignancies that develop in the gastrointestinal tract, breast, cervix, lung, prostate, and hepatocellular carcinoma (HCC). The p53 tumor suppressor gene has a critical role for regulation of cell cycle, cellular growth, and maintenance of genomic integrity. However, the exact correlation of COX-2 and p53 expression in HCC is still unclear. We investigated the expression of COX-2 or p53 and their relationships to clinicopathological variables in patients with HCC and feasiblity of chemoprevention of hepatocellular carcinoma by COX-2 inhibitors. **Materials and Methods:** Formalin-fixed, paraffin-embedded, archival surgical specimens that had been obtained from 50 patients who had received a diagnosis of primary HCC were studied. The expression of COX-2 and p53 in tissue were assessed immunohistochemically. We studied the correlation between COX-2 or p53 expression and various clinicopathological variables. **Results:** The COX-2 overexpression was not significantly associated with p53 positivity. High COX-2 expression was associated with well-differentiated HCC ($P = 0.049$). Disease-free survival rates of high COX-2 expressor in peritumoral liver tissue are significantly lower than those of patients with low COX-2 expressor. **Conclusion:** Our results suggest that the COX-2 may play a role in the early stage of hepatocarcinogenesis and it provides preliminary evidence for testing whether COX-2 inhibitors can prevent development of HCC.

265
Abstract withdrawn

266
Abstract withdrawn

APASL/Free Paper/Abstract/267

Basal core promoter, precore region mutations of hepatitis B virus and their association with genotype, e antigen status and severity of liver disease in chronic hepatitis B patients in India

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Background and Aim: Spontaneous mutations of hepatitis B virus (HBV) could influence the severity of HBV-related liver disease. We analyzed the basal core promoter (BCP) and precore (PC) regions of HBV and correlated these with HBV genotype, e antigen status and severity of liver disease. **Patients and Methods:** In 82 patients (mean age 31 ± 17 years, M:F: 66:16) with histologically proven chronic hepatitis B (CHB), the BCP and PC regions were sequenced and aligned with known wild type sequences. Sequence-based HBV genotyping was done and HBV DNA was quantified. **Results:** Thirty-three (40%) patients had decompensated chronic liver disease (CLD) and the remaining had CHB. Forty-six (56%) patients were HBeAg positive. HBV Genotype A was seen in 28%, D in 65 % and B/C in 7.3 %. The PC G1896A mutation was more common in HbeAg-negative (33% vs. 2%, $P<0.01$) patients, and was genotype D specific. The PC G1862T mutation was more often detected in HBeAg positive than HbeAg-negative (37% vs. 11%, $P<0.01$) patients and was genotype A specific ($P<0.01$). BCP mutations at 1762/64 nucleotide positions were more common in HBeAg negative than in HbeAg-positive patients (36% vs. 13%, $P<0.05$) and were equally common in different genotypes. TA 1–3 region mutations of BCP were more commonly detected in HBeAg negative than in HbeAg-positive patients (72% vs. 33%, $P<0.01$). Patients with BCP 1762, 64 and precore stop codon mutations showed significantly higher histological activity in the liver than the wild type ($P<0.05$). HBV DNA levels were significantly higher in 1762, 64 and TA1-3 mutations than in the wild type. **Conclusions:** PC G1862T is genotype A specific but not always confined to e antigen positive status. TA 1–3 rich mutations of the BCP region are also associated with e antigen negativity in Indian patients. PC stop codon and BCP 1762, 64 mutations are associated with severity of liver disease.

APASL/Poster/Abstract/268

The safety and efficacy of prophylactic endoscopic histoacryl injection for non-bleeding gastric varices with high risks of bleeding

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Backgrounds: Gastric varices (GVs) are not uncommon in patients with portal hypertension. Endoscopic histoacryl injection (EHI) is reported to be effective treatment for bleeding GVs but controversial as a prophylactic treatment because efficacy and safety are undetermined yet. The aim of this study was to evaluate safety and short-term outcomes of prophylactic EHI for non-bleeding GVs with high risks of bleeding.

Methods: Twenty-nine patients (18 males/11 females, mean age 56.9 years) with high risks of gastric variceal bleeding (large tumorous (22), red color sign (12) or rapidly growing in size (4)) underwent EHI. Five patients had IGV1 type, 17 GOV2, and 7 GOV1, respectively. EHI was performed in a standard method and repeated injection was done as needed within 3 days. Follow-up endoscopic examination was performed 1, 3, and 6 months after the procedure and every 6 months thereafter. **Results:** Obliteration of GVs was achieved in all of the treated patients. Twenty-two patients required one session and seven patients more than two sessions to obliterate GVs. A mean of 1.7 ml of histoacryl was used. As a procedure-related complication, oozing at the injection site developed in two patients and infection in one patient. The mean duration of follow-up was 6.3 months and eradication of GVs was achieved in 16 patients (55.2%). There was no recurrence of treated GVs but an additional session was required to obliterate other GVs in two patients. **Conclusions:** Prophylactic EHI for non-bleeding GVs with high risks of bleeding was a feasible, safe and effective procedure for eradication.

APASL/Poster/Abstract/269

The clinical characteristics of patients with chronic hepatitis B who persistently have detectable serum HBV DNA during lamivudine therapy

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Some patients persistently have detectable serum HBV DNA by hybridization method despite lamivudine (LAM) therapy. The aims of this study were to investigate the prevalence and clinical outcome of patients who persistently have detectable serum HBV DNA during LAM therapy. Serum HBV DNA, HBeAg/anti-HBe, and ALT levels were serially monitored. Persistently detectable HBV DNA was defined as positive serum HBV DNA by Digene Hybrid Capture II assay until 6 months LAM therapy. The incidence of patients with persistently detectable HBV DNA was 7.7% (17/221 cases). In the first year of LMV therapy, viral breakthrough (BT) rate was 21% in group I (undetectable HBV DNA, $n = 204$) and 63% in group II (persistently detectable HBV DNA, $n = 17$) ($P < 0.001$); HBeAg loss rate was 38% in group I and 0% in group II ($P < 0.001$); serum ALT normalization rate was 71% in group I and 28% in group II ($P < 0.001$). The log10 reduction of serum HBV DNA after 6 months of LAM therapy was -4.58 log10 in group I and -1.97 log10 in group II ($P < 0.001$, bDNA assay). There were no known pretreatment-resistant HBV DNA mutations in the domains B and C. The chronic hepatitis B patients who persistently have detectable serum HBV DNA despite 6 months therapy with LAM have little effect on serum HBV DNA suppression, higher incidence of viral BT, and low possibility of HBeAg loss and ALT normalization. Early termination of LAM therapy in these patients could be advocated.

APASL/Poster/Abstract/270

Ketosis in liver cirrhosis: as biochemical marker for severity of hepatic dysfunction

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Background: Ketone bodies are produced by oxidation of fatty acids especially in the liver, and this process occurs in the mitochondria as the source of fuel energy in the catabolic state. In liver cirrhosis (LC) patients, it has been reported to be associated with insulin resistance and decrease of metabolic function. The role and mechanism of ketosis in LC is not known. In the present study, blood ketone bodies (BKB) level was measured to know the hepatic reserve in LC with Child-A, B and -C. **Methods:** Blood concentration of beta-hydroxybutyrate (B-OHB) in 48 patients with liver cirrhosis (LC) and 26 healthy volunteers was measured by MediSense Optium Blood Beta-Ketone Test Strips. Hepatic dysfunctions were classified according to Child–Pugh score. Ketone level between two groups and child class were analyzed by *t*-test and one-way ANOVA, respectively. **Results:** Blood ketone bodies concentration is significantly higher in LC (0.429 ± 0.916 mmol/l) than in healthy volunteers (0.054 ± 0.076 mmol/l) with $P < 0.05$). In 48 patients of LC, 13.5% (10) was Child-A, 23.0% (17) Child-B and 28.4%(21) Child-C. B-OHB level in LC with Child-A (0.100 ± 0.221 mmol/l), Child-B (0.282 ± 0.354 mmol/l) and Child-C (0.705 ± 1.302 mmol/l) is significantly increased with the progression of LC. **Conclusions:** We concluded that blood ketone bodies in LC patients was higher than in the normal population and tended to increase with the progression of LC. Upregulation of fatty acids oxidation is required to fulfill energy requirement in LC. It is suggested that BKB may contribute as a biochemical marker of severity of hepatic dysfunction.

APASL/Poster/Abstract/271

The effect of pretransplantation treatment on the recurrence of HCC after liver transplantation

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Some hepatocellular carcinoma (HCC) patients exceed meeting the selection criteria (solitary lesion < 5 cm, three lesions < 3 cm) for liver transplantation (LT). In addition, about 20% of patients were dropped from the candidate list because of tumor progression while waiting for a donor. From May 1997 to December 2003, 71 consecutive LT patients for HCC in our transplantation center were enrolled in this analysis to explore the effect of pretransplantation treatment (TACE or local therapy) on HCC recurrence. A total of 49 patients were eligible for pretransplantation treatment for HCC. Twenty-two patients received living-donor liver transplantation without preoperative treatment because they already had living donor from relatives. Twenty-one patients (group 1) met the selection criteria, while twenty-eight patients (group 2) exceeded the selection criteria. The mean frequency of pretransplantation treatment was 5.6 cycles (range, 2–15). At the time of LT in group 1, there was no tumor progression during the median waiting time of 8.1 months. Among group 2 patients, there were 11 cases in progressive diseases of HCC, six cases in stationary diseases, and 11 cases down-staging below selection criteria. Among group 2, during the median follow-up of 26 months (12–89), the HCC recurrence rates after OLT were 66% (6/9), 33%(2/6), and 9%(1/11), respectively ($P < 0.05$). There were no HCC recurrence in the 21 group 1 patients. Pretransplantation treatment in HCC is effective in preventing the progression of HCC meeting the selection criteria, and downstage HCC exceeding the selection limit in about one-third. Progressive diseases after repeated treatment mean a high recurrence of HCC after transplantation.

272
Abstract withdrawn

APASL/Poster/Abstract/273
Short-term efficacy of human lymphoblastoid interferon in the treatment of chronic hepatitis C
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Introduction: Currently, the treatment of chronic hepatitis C is based on the combination of interferon α with ribavirin. Human lymphoblastoid interferon is produced from human lymphoblast cells (BALL-1). A favorable antiviral activity is expected because it has characteristic composition and makes fewer neutralizing anti-interferon antibodies. The aim of this study was to assess the antiviral activity of human lymphoblastoid interferon in chronic hepatitis C. **Methods:** Twenty-three patients with chronic hepatitis C were enrolled. Patients received 5 million U human lymphoblastoid interferon three times weekly for 24 weeks. Eighteen patients received 800–1000 mg/day ribavirin based on body weight. The primary end point was end of treatment response (ETR), defined as undetectable HCV RNA level at the end of treatment. **Results:** Three patients were excluded due to side effects. Overall, 70% (14/20) of subjects achieved ETR. In the interferon only patients (4/23), one with genotype 2a/c showed ETR and three with genotype 1b showed nonresponse. In the genotype non-1b group, HCV RNA was successfully eradicated compared with the genotype 1b group (100% vs. 50%, $P = 0.007$). There is no statistical difference between groups classifying as initial viral load (High vs. low, 88% vs. 58%; $P = 0.15$), past treatment history (treatment-naïve vs. relapse, 85% vs. 43%; $P = 0.09$) and initial ALT level (<2 times vs. 2–5 times vs. >5 times; 75% vs. 73% vs. 60%, $P = 0.87$). **Conclusion:** This study demonstrated that human lymphoblastoid interferon seem to have a favorable antiviral response. Further follow-up study is needed to confirm the sustained virological response.

APASL/Poster/Abstract/274
Clinical course of hepatocellular carcinoma in patients after seroclearance of HBsAg – a cause for concern
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Background: Despite HBsAg seroclearance, patients are still at risk of developing hepatocellular carcinoma (HCC). Whether they differ from those arising in HBsAg-positive patients remains unclear. **Aim:** To examine differences in clinical characteristics between HCCs in post-HBsAg seroclearance and HBsAg-positive patients. **Materials and Methods:** The study population comprised 638 HCC patients seen in our department from 1988 to 1997. Of these, there were 97 patients negative for HBsAg but with serological evidence of prior hepatitis B infection, i.e., post-HBsAg seroclearance (group A), and 344 HBsAg-positive patients (group B). Clinical and tumor characteristics at presentation and survival were compared between the two groups. **Results:** In group A, 93.8% of patients were ≥ 45 years old compared to 82.0% in group B ($P = 0.004$). In both groups, the majority was male. There was no significant difference in ethnicity. Child–Pugh score at diagnosis was comparable in both groups. In group A, 14.6% had normal AFP levels ($\leq 10\,\mu g/l$) compared to 9.9% in group B ($P = 0.198$) and median serum AFP was similar. There were no significant differences in TNM stage, portal vein invasion and presence of extrahepatic spread. Kaplan–Meier survival analysis showed no significant difference in survival ($P = 0.75$). **Conclusions:** Patients who develop HCC after HBsAg seroconversion present at a later age compared to HBsAg-positive carriers. However, the severity of underlying liver disease, extent of HCC and survival do not differ significantly from HBsAg-positive patients. Hence, patients with chronic hepatitis B infection who achieved seroclearance with loss of HBsAg should remain in a surveillance program for HCC similar to their HBsAg-positive counterparts.

APASL/Poster/Abstract/275
Serum glypican-3 as a predictive biomarker of postoperative recurrence of hepatocellular carcinoma
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Hepatocellular carcinoma (HCC) is an end-result of chronic infection with hepatitis virus. Although remarkable advances in treatment have improved the prognosis, high incidence of intrahepatic recurrence remains a major problem. We have reported that serum glypican-3 is a potent biomarker especially for detection of well-to-moderately differentiated HCC (Cancer Res 2004). The aim of this study is to evaluate usefulness of glypican-3 as a biomarker of recurrent HCC after curative surgery. This study includes a total of 99 patients with HCC treated with curative hepatectomy. Serum glypican-3 was measured by sandwich ELISA. Patient characteristics, tumor stage, pathological grade and serum tumor markers were screened for their prognostic significance by univariate analysis, and a Cox proportional hazard model was used to identify independent predictors of recurrence. In 99 patients, 44 cases experienced recurrence in the follow-up period (mean; 18.4 months). Recurrence-free survival rates at 6 months and 1 year after surgery were 78.8% and 65.6%, respectively. In multivariate analysis, pathological diagnosis of microvascular invasion (HR 2.11, $P = 0.024$) and microsatellite lesion (HR 3.09, $P = 0.008$) and serum glypican-3 measured after 2 weeks to 2 months postoperatively (HR 2.45, $P = 0.004$) and AFP $>$ 100ng/ml postoperatively (HR 3.19, $P = 0.01$) were significant factors associated with recurrence. Patients with postoperative serum glypican-3 below 0.3 ng/ml of value was a significantly higher recurrence-free rate than patients with glypican-3 $\geq$ 0.3 ng/ml (86% vs 52% at 6 months, 74% vs 35% at one year, $P < 0.001$). Serum glypican-3 can be a predictive marker of recurrence after surgical treatment of HCC.

APASL/Free Paper/Abstract/276
Long-term outcomes of transcatheter arterial chemoembolization using autologous blood clot for unresectable hepatocellular carcinoma less than 5 cm in diameter: comparison between autologous blood clot and gelfoam as embolizing material
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Transcatheter arterial chemoembolization (TACE) has been performed for unresectable hepatocellular carcinoma (HCC). Permanent ischemic occlusion and liver damage by arterial injury with gelatin particles was a problem, especially for patients with advanced cirrhosis. We have performed TACE with mild ischemic effect by using an autologous blood clot as embolizing material from 1988. The aim of this study is to compare the long-term survival benefit of short occlusion time TACE (S-TACE) with the conventional model TACE (C-TACE). Two hundred and thirty-six patients with unresectable HCC less than 5 cm in diameter treated with TACE (Child–Pugh A: 112, B: 118, C: 12) were retrospectively analyzed. One hundred and twenty-three patients received autoclot and 113 received gelfoam as embolizing material. Repeated session was undertaken unless hepatic insufficiency was suspected. Long-term survival and factors associated with survival were analyzed. Median follow-up period was 29.3 months. 3 and 5-year survival rates were 56% vs 57% and 31% vs 39%, respectively. Child–Pugh score of the patient who received S-TAE was significantly defective. Hazard ratio was 0.99 ($P = 0.94$) for long-term prognosis, which treated S-TACE compared to C-TACE. Low serum albumin, multicentricity, and AFP were significantly associated with poor prognosis by multivariate analysis. 13 cases (10%) experienced adverse effects and improved gradually. Overall sessions of treatment were 4.3 (maximum 13) and 2.6 for S-TACE and C-TACE. TACE with an autologous blood clot can be effective treatment for patients with HCC under 5 cm. By short duration of occlusion, mild ischemia and reperfusion can show anticancer effect for carcinoma, and minimum harmful effect for surrounding cirrhotic liver.

APASL/Poster/Abstract/277

Comparison of the efficacy and safety of peginterferon α plus ribavirin and standard interferon α plus ribavirin in Thai patients with chronic hepatitis C

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Objectives: To compare efficacy and safety of peginterferon alfa (PEG-IFNα) plus ribavirin (RBV) and interferon alfa (IFNα)+RBV for treatment of Thai patients with chronic hepatitis C (CHC). **Methods:** The data were collected from medical records of CHC patients who were under care at Phramongkutklao hospital, Siriraj hospital, and Ramathibodi hospital from January 2000 to February 2005. **Results:** There were 261 CHC patients (139 males, 122 females; mean age = 47.69 ± 10.55 years; genotype 1 = 91 patients, genotype non-I = 170 patients); 131 patients received PEG-IFNα+RBV and 130 patients received IFNα+RBV. Sustained virological response (SVR) rates for each group were not significantly different (61.1% and 60.8%, respectively) ($P = 0.60$). According to HCV genotype, in patients infected with HCV genotype 1, SVR rates were higher in the PEG-IFNα+RBV group than in the IFNα+RBV group. (58.2% and 38.9%, respectively) ($P = 0.04$). There is no statistical significance in other genotypes. Adverse effects from PEG-IFNα+RBV and IFNα+RBV were the same except for hematological effects. In the PEG-IFNα+RBV group, anemia, neutropenia and thrombocytopenia were found in 84.7%, 61.1% and 43.5%, and in 69.2%, 21.5% and 19.1% in the IFNα+RBV group. Mean maximal hemoglobin levels decreased were 3.61 ± 1.32 and 3.24 ± 1.36 g/dl, mean maximal platelet levels decreased were $62\,206 \pm 35\,755$ and $40\,903 \pm 38\,102$ cell/mm^3 in the PEG-IFNα+RBV group and the IFNα+RBV group, respectively. ($P = 0.03$ and $P < 0.001$). **Conclusions:** PEG-IFNα+RBV is more effective than conventional IFNα+RBV in Thai patients infected with the HCV genotype 1. Hematological side effects are more common in the PEG-IFNα treatment group. CHC genotype non-I treated with conventional IFNα+RBV is as effective as PEG-IFNα+RBV.

APASL/Poster/Abstract/278

Evaluation of band ligation in portal hypertensive patients

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From September 2001 to May 2005 (44 months), a prospective study was conducted on the role of band ligation for esophageal varices. Four hundred and five patients were enrolled in the study population either attending OPD or admitted in the ward of Department of Gastroentreology Government Medical College & Super Speciality Hospital, Nagpur, irrespective of disease etiology. All patients had grade 3–4 varices, except for one who had grade 2 varices. Of the 405 cases, 233 cases (57.5 %) had cirrhosis, 162 cases (40 %) had extra hepatic portal vein obstruction and there were 20 cases of non-cirrhotic portal fibrosis. Band ligation was successfully done, without any complications. The age group of patients varied from 10 to 60 years, mean age was 54.5 years. Male to female ratio was 2:1.Successful band ligation criterion was taken as decrease in the grade of varices by at least one grade, i.e., from grade 4 to 3 or grade 3 to 2. Repeat endoscopy was performed at one month. At the 1-month follow-up of the 405 cases, 168 cases (41.5 %) had grade 2 varices, 207 cases (51%) had a very good response developing grade 1 varices, and in 30 cases (7.5%) no significant response was noted. Overall response to band ligation was observed in 375 cases (92.5%). Only one patient had massive upper GI bleed following the band ligation due to an ulcer over the band ligation site. **Conclusion:** Band ligation is easier and is effective for early eradication of varices in portal hypertensive patients.

APASL/Free Paper/Abstract/279

Clinical applications of various tumor staging systems to predict long-term survival in hepatocellular carcinoma patients treated with transcatheter arterial chemoembolization

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Backgrounds: A clinical tumor staging system to predict long-term survival is important to provide guidance for patient assessment and to make therapeutic decisions. The long-term survival of HCC is related to tumor stage, liver function, and treatment modality. Currently, there is no consensus as to which staging system is practically useful in predicting the survival of patients with HCC. **Aims:** We investigate which staging system

is practically useful in predicting the survival of patients with HCC undergoing the same initial treatment of TACE, to exclude the confounding effect of the treatment modality. **Patients and Methods:** A total of 460 patients with HCC who had been diagnosed and initially treated with TACE in Severance hospital between January 1997 and December 2001 were retrospectively studied. The male to female ratio was 4:1. The median age of the patients was 55.3 years. HbsAg-positive patients were 75.7% and anti-HCV-positive patients were 12.0%. **Results:** The median survival was 20.5 months and cumulative 1-, 3-, and 5-year survival rates were 66.2%, 33.5%, and 22.1%, respectively. Child–Pugh Class A and B showed significant survival difference, whereas it was not observed between Class B and C ($P = 0.06$). TNM stage, CLIP score and JIS score could generally predict the survival of HCC patients treated with TACE according to their scoring. In high scoring groups, such as JIS score 4 and 5, or CLIP score 5 and 6, they did not show significant survival differences; therefore, some other treatment modality (including conservative care) should be considered. **Conclusion:** Both CLIP score and JIS score could predict the survival of HCC patients treated with TACE. Because JIS score is quite easily calculated, we propose its use as a prognostic staging system for HCC in clinical practice.

APASL/Poster/Abstract/280

Clinical outcome of resected hepatocellular carcinoma in relation to preoperative AFP and PIVKA-II levels

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Backgrounds: Alpha-fetoprotein (AFP) and prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) are widely used for diagnosis of hepatocellular carcinoma (HCC). But, the clinical difference of AFP and PIVKA-II-producing HCC is not yet established. **Aims:** This study was to evaluate the clinical prognosis of surgically resected HCC in relation to preoperative AFP and PIVKA-II levels. **Patients and Methods:** A total of 109 patients who underwent curative hepatic resection for primary HCC in Severance hospital between April 2001 and March 2004 were studied. As cut-off values of AFP and PIVKA-II, two different combinations were used for analysis: 20 ng/ml and 40 mAU/ml, or 50 ng/ml and 100 mAU/ml (Shimada et al. Cancer 1996; 78:2094–2100). Patients were classified into four groups according to positivity for AFP and/or PIVKA-II: Group 1, positive AFP and negative PIVKA-II levels; Group 2, negative AFP and positive PIVKA-II levels; Group 3, positive levels of both AFP and PIVKA-II; Group 4, negative levels of both AFP and PIVKA-II. Disease-free survival was calculated by the Kaplan–Meier method and compared among four groups using the log-rank test. The predictable value of tumor marker for recurrence was also calculated with receiver operating characteristic (ROC) curve. The Cox proportional hazards model was used for multivariate analysis of prognostic factors. **Results:** The median age of the patients was 53 years, and 81 of 109 patients (74%) were male. Under cut-off values of AFP and PIVKA-II as 20 ng/ml and 40 mAU/ml, the prognosis was not significantly different, but disease-free survival of group 2 was poorer than any other groups using cut-off values as 50 ng/ml and 100 mAU/ml. The negative AFP and positive PIVKA-II status, Edmonson IV histology, poor UICC TNM stage, and tumor diameter over 5cm were independent factors of poor prognosis for disease-free survival. The predictable value of PIVKA-II for recurrence after operation was 150 mAU/ml, using the ROC curve. **Conclusions:** The negative AFP and positive PIVKA-II status and cut-off value of PIVKA-II over 150 mAU can be prognostic predictors for patients with HCC after hepatic resection.

APASL/Poster/Abstract/281

Peginterferon α-2a (40 kDa) plus ribavirin (800 or 400 mg/day in patients with hepatitis C virus (HCV) genotype 2 or 3 infection: interim results of a prospective randomised multicentre study

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Objective: We aimed to determine whether the dose of ribavirin (RBV) could be reduced from 800 to 400 mg/day in genotype 2 or 3 patients treated with peginterferon α-2a (40 kDa) plus RBV. Interim results of this prospective, randomised study are reported herein. **Methods:** Patients with chronic hepatitis C genotype 2 or 3 infection were randomised to 24 weeks of treatment with RBV 400 or 800 mg/day combined with peginterferon α-2a (40 kDa) 180 μg/week. Sustained virological response (SVR) was defined as undetectable HCV RNA (<50 IU/ml) at the end of a 24 week untreated follow-up period (week 48).

Results:

	Peginterferon α-2a (40 kDa) 180 μg/week plus	
	RBV 400 mg/day (n = 80)	RBV 800 mg/day (n = 80)
Baseline characteristics		
Male, *n* (%)	49 (61)	45 (56)
Mean age (year)	35	38
HCV genotype 2; 3, *n* (%)	10 (12); 70 (88)	14 (17); 66 (83)
Virological response at EOT in pts completing treatment (%)		
Overall	66/66 (100)	64/69 (93)
SVR in pts who have completed treatment and follow-up (%)		
Overall	38/47 (81)	37/45 (82)
Genotype 2; 3	3/3 (100); 35/44 (79)	7/7 (100); 30/38 (79)

To date, 207 patients have been randomised and interim data are available for the first 160 patients. SVR rates are similar in those who have completed follow-up after treatment with RBV 400 (83%) or 800 mg/day (79%). During treatment, mean haemoglobin concentrations were consistently higher in patients treated with the lower RBV dose. **Conclusion:** Our interim analysis suggests that SVR rates are similar in HCV genotype 2 or 3 patients treated for 24 weeks with peginterferon α-2a (40 kDa) plus RBV 400 or 800 mg/day but that mean haemoglobin levels are higher in those treated with the lower RBV dose. Final results are awaited with great interest.

APASL/Poster/Abstract/282

Impact of new legislation on the number of liver transplants in Singapore

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Introduction: Liver transplant is the definitive treatment of choice for patients with end-stage liver disease. However, the number of liver transplants performed in many Asian countries is low. Singapore has implemented the Human Organ Transplant Act (HOTA) since 1 July 2004, which allows for removal of the kidneys, liver, heart, and cornea, in the event of death, for transplantation. **Aim:** To evaluate the impact of HOTA on the number of liver transplants performed in Singapore. **Methods:** All cases of potential liver organ donors referred to the Liver Transplant Program from 1 July 2002 to 30 May 2005 were reviewed. The number of referrals, liver retrievals, and liver transplants were compared between the 24-month pre-HOTA and the 11-month post-HOTA periods. **Results:** 240 potential cadaveric donors were referred over the 35-month period, i.e. 6.86 cases/month: 7.46 vs 5.54 cases/month pre- and post-HOTA, respectively. Characteristics of donors: age 46 ± 1 years, 168 (70%) male. The commonest causes of death were intracranial bleeding or stroke 155 (65%), non-traffic accident trauma 34 (14%), traffic accident trauma 29 (12%). Liver donation was deemed unsuitable in 175 (73%) of the referrals, with commonest reasons being disapproval from family 66 (38%) and medical unsuitability 55 (31%). 7 and 4 liver grafts were eventually transplanted in the pre- and post-HOTA periods ($P = 0.48$). **Conclusion:** The number of cadaveric liver graft referrals and actual cadaveric liver transplants did not differ in the pre- and post-HOTA periods.

APASL/Poster/Abstract/283

HBeAg loss and seroconversion treated with adefovir dipivoxil in HbeAg-positive chronic hepatitis B disease with lamivudine resistance

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Introduction: Adefovir dipivoxil, a nucleoside analogue, inhibits both wild-type hepatitis B virus and lamivudine-resistant mutants. The aim of this study was to evaluate clinical outcome achieved by adefovir rescue in HBeAg-positive chronic hepatitis B (CHB) patients with lamivudine-resistant YMDD mutants. **Patients and Methods:** From March 2003 to March 2004, adefovir was administered in 56 patients with HBeAg-positive CHB who developed breakthrough hepatitis (increased alanine aminotransferase (ALT) level over the upper limit of normal (ULN)) due to lamivudine-resistant YMDD mutant virus. We assessed virological response and biochemical response at 12 months. HBeAg responses and their determinant factors were also evaluated. **Results:** The duration of adefovir administration ranged from 6 to 24 months with a median of 15 months. The mean age was 41.3 years (range, 19–67 years) and male to female ratio was 4:1. At 12 months of therapy, 42 (75.0%) of patients had a virological response (< 105 copies/ml). Biochemical response at the corresponding time point was also 66.6%. The cumulative HBeAg response rates at 6, 12, and 18 months were 11.6%, 26.2%, and 42.9% for HBeAg loss, and 10%, 21.9%, and 30.2% for HBeAg seroconversion, respectively. Baseline ALT level of $> 10 \times$ ULN and 3 log10 decrease in serum HBV DNA level at 3 months of initiating adefovir were independent predictors of adefovir-induced HBeAg seroconversion ($P = 0.041$ and 0.031, respectively). For all patients, the treatment was well tolerated. **Conclusions:** Administration of adefovir for patients with lamivudine resistance showed relatively good virological and biochemical responses. High ALT and early virological suppression predict better outcome in patients with lamivudine resistance.

APASL/Poster/Abstract/284

Comparison of viral dynamics between peginterferon α-2b and interferon α-2b treatment in Chinese patients with HBeAg-positive chronic hepatitis B virus

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Introduction: Few data are available on peginterferon α treatment for patients with chronic hepatitis B virus (HBV). We compared the change in serum HBV-DNA levels of Chinese patients with HBeAg-positive chronic HBV, treated with peginterferon α-2b (PEG-IFN α-2b) or interferon α-2b (IFN α-2b). **Patients and methods:** Patients with HBeAg-positive (Abbott KIT) chronic HBV, serum HBV-DNA ≥ 105 copies/ml (by real time PCR, LLQ < 103 copies/ml) and ALT levels $\geq 2 \times$ ULN were included in this study. Following randomization, patients received PEG-IFN α-2b 1.0 μg/kg/week, or three-times-weekly IFN α-2b 3 MIU for 24 weeks (EOT), with 24 weeks of follow-up. **Results:** Two hundred and thirty patients were included. At baseline, the mean serum HBV-DNA load was 8.06 and 7.99 log10 copies/ml for PEG-IFN α-2b and IFN α-2b, respectively, and mean ALT was 4.17 × ULN and 3.77 × ULN, respectively. Both treatments reduced serum HBV-DNA levels during therapy; however, the reduction was greater with PEG-IFN α-2b at all timepoints. Mean reduction at EOT was significantly higher in the PEG-IFN α-2b group (see table). In patients whose serum HBV-DNA was > 8 log10 copies/ml at baseline (PEG-IFN α-2b: $n = 60$; IFN α-2b: $n = 59$), the proportion of patients whose serum HBV-DNA levels decreased by > 2 log 10 copies/ml was greater in PEG-IFN α-2b than in IFN α-2b recipients at EOT (12% vs 7%) and follow-up (15% vs 7%), but did not reach statistical significance. **Conclusions:** PEG-IFN α-2b was associated with a significantly greater decrease in serum HBV-DNA levels at EOT compared with IFN α-2b. The decrease remained greater with PEG-IFN α-2b after 24 weeks of follow-up.

Timepoint	Mean (SD) decrease in HBV-DNA from baseline (log10 copies/ml)		*P*-value
	PEG-IFN α-2b ($n = 115$)	IFN α-2b ($n = 115$)	
12 weeks	1.62 (1.85)	1.27 (1.53)	0.1207
EOT	2.22 (1.91)	1.68 (1.78)	0.0283
Follow-up	1.26 (2.11)	1.19 (2.05)	0.8020

APASL/Poster/Abstract/285

Prevalence of hepatitis B in individuals screened during a country-wide campaign in Pakistan

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Introduction: Pakistan is in the area of intermediate endemicity for hepatitis B. The aim of the present study was to find out the prevalence of hepatitis B in individuals who visited designated vaccination centers during a countrywide vaccination campaign. **Methods:** During October 2003, a vaccination campaign was initiated. Centers were identified in the provincial and federal capital cities (Lahore, Karachi, Peshawer, Quetta, Islamabad) and Multan, a city in the area known for higher prevalence of chronic hepatitis in Pakistan. All visitors were screened for HBsAg and HBeAg using ICT kit (HBsAg/eAg Test by GSK). **Result:** The total number of persons screened was 11372 (males = 7575). Prevalence of HBsAg positivity was Karachi 3.1%, Islamabad 3.1%, Lahore 3.9%, Quetta 3.9%, Peshawer 5.2%, and Multan 6.7%. Overall prevalence was 4.3% (males 4.4%, females 3.9%). Most of the HbsAg-positive individuals were young with a median age of 24 years (range 12–66). HBeAg was positive in 97 persons (20% of HbsAg-positive individuals). **Conclusion:** Overall prevalence of Hepatitis B in apparently healthy persons visiting vaccination centres is 3–4% in most cities. However higher prevalence in Peshawer may be due to settled Afghan refugees, and in Multan due to known higher endemicity in the "hepatitis belt" involving southern Punjab and upper Sindh provinces.

APASL/Poster/Abstract/286

Chronic hepatitis B (CHB) patients treated with lamivudine – the experience of a tertiary referral centre in Malaysia

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Introduction: Lamivudine is one of the available treatments for CHB in Malaysia. However, prolonged therapy increases the risk YMDD mutation and the relapse rate is high after stopping treatment. **Methods:** We reviewed all CHB patients on lamivudine from August 2001 to January 2005 in our unit. **Results:** 123 CHB patients were treated with lamivudine; mean age of 40.8 years (21–73 years), 78% males, 53.6% Chinese, 43% Malays and 2.4% Indians. At baseline, 65% of patients were eAg+. In the eAg–CHB group, 72% of patients had HBV DNA level $>/=10\,000$ copies/ml. 31.7% patients completed lamivudine treatment after a mean of 19.9 months while 59.3% required continued treatment with a mean duration of more than 22.2 months. 8.9% either defaulted or died while on treatment. In the eAg+CHB group with a defined period of therapy, 40.7% achieved e-seroconversion and 29.6% achieved eAg loss. In the eAg- CHB group, 75% achieved HBV DNA loss. Of those who responded and stopped treatment, 56.4% relapsed after a mean of 6.9 months (2–17). Viral breakthrough occurred in 9.8% after a mean of 24.2 months of therapy. Drug resistance testing was done on 66.7% of these patients and we found L180M/M204I/M204V (50%), L180M/M204I (25%), M204I (12.5%), and L180M, M204V (12.5%). 75% were rescued with adefovir and 25% were continued on lamivudine therapy. **Conclusions:** In our experience, the majority of our patients responded to treatment with lamivudine. However, relapse rate is observed in more than half of them and majority required long-term therapy. The risk of viral breakthrough is low.

APASL/Plenary/Abstract/287

Prevalence and risk factors of gallstone disease in general health screening people

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Gallstone is the most common disease of the biliary system, of which prevalence, composition, and location have different demographic characteristics. Recently, the prevalence rate for gallstones goes on increasing in Korea. Most patients with gallstones are asymptomatic and are often found incidentally in a community health survey. Our study was designed to obtain the prevalence and risk factors for gallstones in people undergoing health screening. A total 36 469 persons, who visited health promotion center in Kyungpook National University Hospital from 1998 to 2004, were enrolled in this study. They were examined using ultrasonography and biochemical tests such as liver function tests, lipid profiles and fasting blood glucose. Gallstone disease was defined as the presence of posterior shadowing, and echogenic and movable structures within the gallbladder, as determined by ultrasonography. All subjects were divided into several groups according to the characteristics, and the particular prevalence of gallstone disease of each group was calculated. Among 36 469 persons, comprising 19 429 males (53.3%) and 17 040 females (46.7%), gallstones were found in 735 persons (2.1%). The male group showed a prevalence of 2.0% (387/19 429) and the female a prevalence of 2.1% (348/17 040). The annual prevalence for gallstone disease was 1.9% in 1998, 1.5% in 1999, 1.4% in 2000, 1.7% in 2001, 1.6% in 2002, 2.8% in 2003, and 2.7% in 2004. In a univariate analysis, the risk factors for gallstone disease were older age ($P = 0.001$), body mass index ($P = 0.001$), fasting blood sugar ($P = 0.001$), total cholesterol ($P = 0.001$), LDL-cholesterol ($P = 0.018$), triglyceride ($P = 0.001$), and serum aspartate transferase ($P = 0.005$). In a multivariate logistic regression analysis, the risk factors were older age (OR = 1.54 per age decade), high body mass index (OR = 1.55), and high fasting blood sugar (OR = 1.19) in health screening people. The major risk factors for gallstone disease are older age, high body mass index, high fasting blood sugar in health screening people. Further studies will be needed about the prevalence of gallstone disease in the general population according to the composition of gallstones.

APASL/Poster/Abstract/288

Death related to variceal bleeding and long-term outcome after balloon-occluded retrograde transvenous obliteration in the patients with gastric variceal bleeding

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Background and Aims: Balloon-occluded retrograde transvenous obliteration (BRTO) has been introduced for the treatment of gastric variceal bleeding (GVB) in cirrhotic patients with gastrorenal shunts but its effect remains unclear. Hence, we evaluated the effectiveness and long-term outcomes of BRTO for treatment of GVB. **Methods:** In our institution, from October 2002 to March 2005, BRTO was performed to control GVB in 46 cirrhotic patients with documented gastrorenal shunt. Rates of successful hemostasis and rebleeding, death related to variceal bleeding (DRVB; death within 6 weeks) and risk factors, long-term outcome, and complications of BRTO were analyzed. **Results:** GVB was successfully controlled in 42 patients (91.3%). Within 6 weeks, seven patients (15.2%) died of failure to control bleeding ($n = 1$), bleeding from esophageal varix ($n = 2$), and hepatic failure without rebleeding ($n = 4$). Multivariate analysis showed that Child–Pugh class C and impaired renal function were independent risk factors for

DRVB (relative risk = 7.44, 95% CI = 1.10–99.08; relative risk = 9.07, 95% CI = 1.77–46.47, respectively). Overall survival rates were 86.5%, 80.8%, and 71.8% at 6 weeks, 12 months, and 24 months. After BRTO, hemoglobinuria (27.3%), fever (59.0%), worsening of ascites (43.2%) and pleural effusion (52.3%) developed but they were mild and transient. Follow-up endoscopy showed worsening of esophageal varices in 11 (52.0%) of 21 patients but recurrence of gastric varix was not seen in any patients. **Conclusions:** Our results suggested that BRTO can be an effective and safe treatment to control GVB but rate of DRVB can be high in patients with Child–Pugh class C and impaired renal function.

APASL/Free Paper/Abstract/289

Expressional diversity and antiapoptotic role of survivin in hepatocellular carcinoma

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Survivin, a unique member of inhibitor of apoptosis protein, is known to be expressed in most human cancers. Because deregulation of apoptosis results in destruction of cellular homeostasis including tumor development and growth, we investigated the survivin expression in hepatocellular carcinoma (HCC), and analyzed the association of expression pattern of survivin with NF-κB and caspase-3 expression. Two HCC cell lines, HepG2 and Hep3B, and four human HCCs revealed the expression of 439 bp survivin mRNA by reverse transcription-polymerase chain reaction. Two to three splicing variants of survivin transcript identified previously, survivin-deltaEx3 (321 bp), survivin-2B (508 bp), or survivin-3B (604 bp), were co-expressed with wild type transcript of survivin in two HCC cell lines and some human HCCs. Adjacent nontumor cirrhotic livers and two normal livers showed no or little expression of any survivin transcript. Western blotting analysis was used for expression of NF-κB (65 kDa) and caspase-3 (35 kDa). The expression of NF-κB was higher in HCC cell lines and human HCCs than in adjacent nontumor tissues and normal livers, but most expressed NF-κB was cytosolic but not nucleic. The expression of caspase-3 was variable except for two HCCs which showed lower expression than in the surrounding cirrhotic liver. These results suggest the anti-apoptotic role of survivin in development of HCC. Significance of splice variants and key regulator of survivin expression should be investigated for the therapeutic target of hepatocellular carcinoma in the future.

290

Abstract withdrawn

APASL/Poster/Abstract/291

Hepatitis D virus genotypes: clinical implications and correlation with hepatitis B virus genotypes

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Different genotypes of the hepatitis viruses may influence the clinical outcome of the disease. The aim of this study was to evaluate the clinical implications of HDV genotypes IIa and IIb, and their correlation with HBV genotypes B and C in patients with chronic hepatitis in Taiwan. Genotyping was performed for 153 patients with chronic hepatitis B and serum anti-HDV positive antibody. Of them, 40 were asymptomatic carriers, 70 chronic hepatitis, 29 liver cirrhosis, and 14 hepatocelluar carcinoma. HBV genotyping was performed by PCR–RFLP methods. HDV genotyping was performed by RT-PCR, autosequencing, and phylogenetic analysis. HDV genotype distribution was as follows: 9 (5.9%) genotype I, 39 (25.2%) genotype IIa, and 54 (33.4%) genotype IIb in 102 patients with positive HDV-RNA. HBV genotypes also were as follows: 17(11.5%) patients were genotype A, 87 (56.9%) genotype B, 30 (19.6%) genotype C, and 1 (0.7%) genotype D in 135 patients with HBV DNA positive. The Kaplan-Meier method showed that chronic dual infection of HDV genotype II and HBV genotype C patients more frequently progressed to advanced liver disease (cirrhosis and/or HCC) than those with chronic HDV genotype II and HBV genotype B dual infection ($P = 0.03$). No particular HDV genotype IIa or IIb are linked to specific HBV genotype B or C infection. Chronic HDV genotype II-infected patients coinfected with HBV genotype C more frequently progressed to advanced liver disease than those coinfected with HBV genotype B.

APASL/Young Investigator/Abstract/292

Insulin resistance, TNF-α, and adiponectin levels in subjects with non-alcoholic steatohepatitis (NASH) in Jakarta, Indonesia

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Background: Non-alcoholic steatohepatitis (NASH) is considered to be the liver component of the metabolic syndrome and is frequently associated with obesity, abnormal lipid profile, and type II diabetes mellitus. There is evidence that insulin resistance (IR) is a major part of a mechanism that has been consistently associated with NASH. Study about the occurrence of insulin resistance and adipocytokine level in subjects with NASH in Indonesia has not been reported. **Aim:** To investigate the insulin resistance, TNF-α, and adiponectin in addition to components of metabolic syndrome in Indonesian subjects with NASH. **Subjects and methods:** Seventeen subjects (seven females and 10 males), mean age 45 (14.6) years, with a diagnosis of fatty liver (ultrasound examination) underwent examination of blood pressure, anthropometric measurement, and tests for fasting glucose and insulin levels to define the insulin resistance by HOMA-R (homeostasis model assessment) method, lipid profile, serum TNF-α (ELISA), and adiponectin. Subjects with a history of excessive alcohol intake, drug abuser, HBsAg positive, anti HCV positive, and ANA positive were excluded. A liver biopsy diagnosis was confirmed from every subject, which has been examined by two experienced pathologists. Fasting insulin levels and HOMA-IR in eight of 17 subjects with NASH were compared with 8 matched controls (people with normal BMI, normal liver function test, normal blood glucose level, and normal ultrasound). The mean level of adiponectin of nine subjects with NASH was compared with nine matched controls. All analyses were performed with SPSS for Windows version 12. A significance level of 5% was used. **Results:** Of the 17 subjects studied, all biopsies showed features compatible with NASH,

mean (SD) HOMA-R was 6.43 (7.5), TNF-α 1.74 (1.14) pg/ml, adiponectin 4883.5 (4573.2) ng/ml, SGPT level 64.53 (41.15), and BMI 26.5519 (4.0340). Furthermore, obesity was found in 12 (70%) subjects, hypercholesterolemia in 10 (58.8%) subjects, diabetes in six (35%) subjects, hypertension in six (35%) subjects, and hypertriglyceridemia in four (23.5%) subjects. Of the eight subjects with NASH comparing with controls, we found statistical significance ($P = 0.012$ for the fasting insulin levels and $P = 0.035$ for the HOMA-IR). Of the nine subjects with NASH comparing with controls, we also found statistical significance for adiponectin levels ($P = 0.007$). **Conclusion:** Most subjects with NASH have at least one component of the metabolic syndrome. Insulin resistance and adiponectin might have a role in subjects with NASH. Further study is needed to obtain normal values for TNF-α, and values from subjects with fatty liver. We also need a larger sample to support this study.

APASL/Plenary/Abstract/293

A randomized placebo-controlled trial of thymosin α-1 and lymphoblastoid interferon for HBeAg+chronic hepatitis B

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Combination therapy between two immunomodulators used for treatment of chronic hepatitis B was explored based on the reported therapeutic efficacy of interferon α, and thymosin α-1 as monotherapeutic agents, to determine if combination therapy was superior to interferon alone. This double–blind, randomized placebo controlled trial of lymphoblastoid interferon (5 MIU three times per week compares the addition of thymosin α-1, 1.6 μg three times per week for 24 weeks (Combination) with thymosin placebo (Monotherapy) for the same period. Entry criteria included positive HBeAg, ALT $\geq 1.510 \times$ ULN, positive HBV DNA, absence of cirrhosis, treatment naivety and no co-morbid factors. A total of 98 HBeAg-positive patients were recruited, of whom 48 were randomized to Combination and 50 to Monotherapy. The primary endpoint was loss of HBeAg at 72 weeks and secondary endpoints HBeAg seroconversion, normalization of ALT, loss of HBV DNA and improvement in histology. The HBeAg loss was 45.8% and 28.0% for Combination and Monotherapy, respectively (difference, 17.8%; 95% CI, −1.2% −35.3%, *P*-value = 0.067). There was no statistically significant advantage to Combination with respect to time to HBeAg loss. There were also no statistically significant differences with respect to the secondary endpoints of HBeAg seroconversion, changes in histology, normalization of ALT or loss of HBV DNA. In conclusion, this trial showed a 17.8% improvement in HBeAg loss rates with Combination over interferon Monotherapy that could indicate a potential clinically important difference that would need confirmation in subsequent trials.

APASL/Free Paper/Abstract/294

Relationship between cumulative exposure to ribavirin (RBV) and sustained virological response (SVR) rates in patients with genotype 1 chronic hepatitis C receiving peginterferon alfa-2a (40kd) plus RBV

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Background: Genotype 1 patients who receive 48 wks of full-dose peginterferon alfa-2a (40KD) (PEGASYS) plus RBV (COPEGUS) have higher SVR rates than patients who undergo dose reductions. **Objective:** Assess cumulative drug exposure to RBV and SVR rates. **Methods:** Data from two trials in which patients received peginterferon alfa-2a (40KD) 180μg/wk/RBV 1000/1200 mg/d × 48 wks were combined. SVR = undetectable HCV RNA (<50IU/mL) at end of untreated follow-up (wk72). Cumulative drug exposure was expressed as a proportion of the planned dose. Exposure categories were determined using clinic records and patient diaries. **Results:** 427/569 randomised patients (75%) completed treatment. Reductions to <97% of the planned RBV and peginterferon alfa-2a (40KD) doses occurred in 182 patients (43%) and 114 patients (27%), respectively. 62 patients (15%) received <97% of the planned dose of both drugs. Cumulative RBV exposure during treatment wk1-12 and wk1-48 was significantly and positively correlated with SVR. 325 patients received ≥ 97% of the planned RBV dose during wk1-12 and reductions during wks13–48 were associated with decreasing SVR rates in patients receiving <80% of the planned RBV dose. **Conclusion:** RBV exposure during wks1–12 of is significantly correlated with the SVR rate in genotype 1 patients receiving 48wks of peginterferon alfa-2a (40KD) (PEGASYS) plus RBV (COPEGUS) therapy. Dose reductions to <80% during wks13–48 in those who received full doses during wk1–12 compromised SVR rates. Minimizing RBV dose reductions at any point in therapy is likely to improve SVR rates in genotype 1 patients.

295

Abstract withdrawn

APASL/Free Paper/Abstract/296

Detection and genotyping of human TT virus in different types of liver disease from Delhi

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Introduction: In 1997, a novel virus was detected, among the three Japanese cases with post-transfusional hepatitis by T. Nishizawa, in patients with fulminant hepatitis and chronic liver disease of unknown etiology. To look further into the prevalence of TTV in different types of liver disease and their prevalent genotypes in Delhi, the present study was designed. **Materials and Methods:** A total of 262 serum samples were collected from patients with different liver diseases. TTV DNA was detected by semi-nested polymerase chain reaction followed by direct sequencing and phylogenetic analysis to characterize

the TTV isolates. **Results:** TTV DNA was detected in 5 (18.5%) of the 27 patients with chronic liver disease (CLD) associated with HBV and HCV, which was significantly higher than the 5.4% (2/37) prevalence in non A-G CLD patients. 28.5% (2/7) TTV prevalence was observed in acute viral hepatitis (AVH) patients associated with other hepatotrophic viruses, which is also higher than the 8% (2/25) in non A-G AVH cases. None of the 23 cases showed TTV DNA in non A-G fulminant hepatic failure (FHF) cases whereas 8.3% (1/12) TTV prevalence observed in FHF was associated with HBV, HCV and HEV. The majority of the cases with TTV DNA positivity showed no significant evidence of biochemical or histological damage of the liver. Direct sequencing of 25 TTV isolates showed genotype 1a, which was similar to genotypes found in western India. **Conclusion:** TTV prevalence was higher among the CLD patients, followed by acute and fulminant hepatitis. All the groups showed genotype 1a. Hence, it is the most prevalent genotype among patients seen in Delhi.

APASL/Free Paper/Abstract/297

Outcome of paediatric liver transplant – 14 years of experience at the Children's Medical Institute, Singapore

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Background/Objectives: This study summarizes the experience of a single centre on 47 paediatric liver transplantations from living and cadaveric donors performed on 44 paediatric patients. The outcome of transplant surgery, and recipient, immunosuppression, rejection, and survival rates were reviewed. **Methods:** A retrospective case note review of all paediatric patients who received liver transplantation between March 1991 and January 2005 was carried out. **Results:** Forty-four cases were reviewed, of which 21 were boys (47.7%) and 23 were girls (52.3%). Patients were between 11 months and 14 years of age. The mean age of the recipients at transplant was 35 months, and the median age 21 months. Biliary atresia (72.3%), Alagille syndrome (6.4%) and metabolic liver disease (6.4%) were the most common indications for liver transplant. Biliary atresia was significantly associated with a good post-transplant outcome. ($P = 0.04$). The allografts were distributed as 29 (61.7%) living related and 18 (38.3%) cadaveric. The retransplant rate was 6.3% and solely due to hepatic vessel thrombosis. Tacrolimus (FK-506) was the immunosuppressive agent used in 37 (78.7%) patients. The other immunosuppressives utilized were corticosteroids (8.5%) and cyclosporine (8.5%). After transplantation, 37 (78.7%) of the patients, including three retransplants, were well. There were eight deaths, and the current survival rate of our series is 83.0%. **Conclusions:** Liver transplantation is an established form of intervention for end-stage liver disease and a variety of extrahepatic metabolic diseases. Good long-term survival rates comparable to most tertiary centres can be expected. Future advances in immunosuppression and organ availability are likely to lead to greater improvements in survival rates.

APASL/Free Paper/Abstract/298

The influence of HBV-specific cytotoxic T-lymphocyte stimulated by dendritic cell *in vitro*

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Objectives: To observe the enhancement of cytotoxic T lymphocyte responses in patients with chronic hepatitis B following vaccination with a dendritic cell stimulated by poly I:C *in vitro*. **Methods:** Peripheral blood mononuclear cells (PBMC) were isolated from whole blood by density gradient centrifugation on Ficoll–Hypaque; the non-adherent cells were cultured in the medium AIM-V containing recombinant human IL-4 and recombinant human GM-CSF. On day 7, one part of wells were added with poly I:C. On day 9, mature DC (mDC) were harvested and used for phenotype analysis. Both of the immature DCs and mature DCs were cocultured with the auto-T cell for another 2–3 days. Detection of the function and frequency of HBV-specific CTL was carried out by enzyme-linked immunospot assay (Elispot) and tetramer staining. **Results:** The dendritic cell was stimulated by poly I:C in vitro, whose CD83 and CD80 expression increased and became more mature. The average of percentages of HBV-specific CD8+cells of total CD8+cells was 0.72% (0.43–1.74%) in 12 chronic hepatitis B patients and the average of the spots of antigen-specific IFN-γ-releasing effector cells was 17(9–28); stimulated by the the dendritic cell, the percentages of HBV-specific CD8+cells of total CD8+cells rise to 1.86% (0.78–2.65%) and the average of the spots of antigen-specific IFN-γ-releasing effector cells was 49 (36–66); while stimulated by the dendritic cell added with poly I:C, the percentages of HBV-specific CD8+cells of total CD8+cells rise to 3.10% (1.16–4.60%) and the average of the spots was 106 (68–130). There was statistical difference of conclusion of Elispot and tetramer in the three groups ($P < 0.001$). **Conclusion:** The T lymphocyte of patients with chronic hepatitis B stimulated by the self-dendritic cell may result in obtaining high percentage and functional antigen-specific T lymphocyte. The addition of poly (I:C), which was used as maturation-promoting factor in DC culture can enhance the function of DC significantly and can get even higher percentage antigen-specific T lymphocyte with enhanced function.

APASL/Free Paper/Abstract/299

Study of phenotype and function of cord blood dendritic cells whose mothers are patients with chronic hepatitis B

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Objectives: To investigate the phenotype and function of cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B, compared to the dendritic cells of healthy cord blood, healthy adult peripheral blood and adult peripheral blood with chronic hepatitis B. **Methods:** Peripheral blood and cord blood mononuclear cells (PBMC) were isolated from whole blood by density gradient centrifugation on Ficoll–Hypaque, and the non-adherent cells were cultured in the medium AIM-V containing recombinant human IL-4, TNF-α and GM-CSF. On day 9, mature DC (mDC) were harvested and used in phenotype analysis; the amounts of IL-12 that dendritic cells produced were measured; dendritic cells from human cord blood or adult peripheral blood, which support a mixed leukocyte reaction in cord blood, and adult T cells have been compared. **Results:** The expression rates of CD80 and CD83 on cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B were decreased compared with healthy cord blood, healthy adult peripheral blood and adult peripheral blood with chronic hepatitis B, $P < 0.05$; The amounts of IL-12 produced by cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B were lower than the amounts of IL-12 produced by healthy cord blood, healthy adult peripheral blood and adult peripheral blood with chronic hepatitis B, $P < 0.05$;

and the comparison of the ability of dendritic cells inducing T lymphocyte proliferation was described as the ability of healthy adult peripheral blood dendritic cells inducing cord blood T lymphocyte proliferation > the ability of healthy adult peripheral blood dendritic cells inducing adult T lymphocyte proliferation > the ability of healthy cord blood dendritic cells inducing cord blood T lymphocyte proliferation > the ability of healthy cord blood dendritic cells inducing adult T lymphocyte proliferation > the ability of healthy cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B inducing cord blood T lymphocyte proliferation > the ability of cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B inducing adult T lymphocyte proliferation. **Conclusion:** The maturation and function of cord blood dendritic cells in those whose mothers are patients with chronic hepatitis B were lower than dendritic cells of healthy cord blood, healthy adult peripheral blood and adult peripheral blood with chronic hepatitis B.

300
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APASL/Poster/Abstract/301
Pathological and clinical analysis of 40 liver failure cases of hepatitis B
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China

In order to study the pathological characteristics of the acute on chronic liver failure (AoCLF) and the decompensated liver cirrhosis (DCLC) caused by hepatitis B, and the differences between the AoCLF and the DCLC in the clinical characters, a pathological analysis of 40 liver failure cases of hepatitis B was carried out. Thirty-five males and five females aged 27–75 years old from the center of liver transplantation of Zhongshan University 2003–2005 were the subjects.Orthotopic liver transplantation (OLT) was performed in all 40 cases. Seventeen cases were diagnosed as AoCLF, and 23 cases as DCLC. Three pieces of the liver tissue were collected from the left and right lobes of the liver parenchyma , made into slices stained with hematoxylin–eosin and reticular fiber, and read by two pathologists independently. The SPSS 11.0 statistical software was used for statistical analysis. The measurement data and the enumerations data were analyzed by Fisher method and T test, respectively. Probabilities of $P<0.05$ were recognized as statistically significant. Twenty-one of the 40 cases were observed with unaided eyes and can be divided into three groups: nine cases were nodular liver cirrhosis, eight cases postnecrosis cirrhosis and four cases non-cirrhosis. Through microscope examination, chronic injury and, recently, a big lesion were observed in 17 AoCLF cases; the 23 DCLC cases could be divided into two groups: one was nodular cirrhosis (four cases) and the other was postnecrosis cirrhosis (19 cases). The liver lesions were distributed in the whole liver, but not evenly in all the spots. The two groups' clinical data (ALT, TBIL, PTA, etc.) were compared; no statistical significance was found. In summary, the clinical features of AoCLF were similar to those of decompensated cirrhosis; the approach to patients with liver failure should be guided principally on clinical backgrounds, and further classification should be based on pathological and etiologic considerations. However, histological classification and prognosis based on percutaneous biopsy specimens alone may be misleading.

302
Abstract withdrawn

APASL/Plenary/Abstract/303
Association of vitamin D receptor, CCR5, TNF-α and TNF-β gene polymorphisms and HBV infection and severity of liver disease
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Background and Aims: The role of host factors in persistence of HBV infection and progression of liver disease is not clear. 1,25-dihydroxy vitamin D is involved in immune regulation, local control of cellular growth and differentiation. Expression of vitamin D receptors in hepatocytes suggests its importance in the pathophysiology of the liver. We studied the association of single nucleotide polymorphisms (SNPs) in the genes involved in immunoregulatory functions of vitamin D with susceptibility and severity of chronic hepatitis B (CHB). **Methods:** Five polymorphisms in vitamin D receptor (intron 8 and exon 9), CCR5 (32 bp deletion), TNF-α (-308) and TNF-β (intron 1) were studied in 214 histologically proven CHB patients and 408 healthy subjects. Genotype frequencies were compared between patients and controls. Clinical parameters were compared between patients with a fibrosis score of ≤ 2 (mild) or >2 (severe) and histological activity index (HAI) of ≤ 5 (mild) or >5 (severe). **Results:** The frequency of heterozygosity of CCR5Δ32 was greater in patients with chronic hepatitis B than in controls (4.2% vs 0.73%, $P=0.005$). Frequency of VDR a/a and TNF-β A/A was higher in severe than in mild liver disease based on HAI (19.3% vs 5.4%, $P=0.003$ and 18.1% vs 3.8%, $P=0.001$, respectively) and fibrosis score (23.7% vs 3.6%, $P<0.001$ and 18.1% vs 4.4%, $P=0.002$, respectively). **Conclusion:** CCR5Δ32 heterozygosity was associated with susceptibility to HBV infection and VDR a/a, and TNF-β A/A with severity of liver disease in CHB patients. These results affirm a role for the immunogenetic factors in chronic hepatitis B.

304
Abstract withdrawn

APASL/Poster/Abstract/305
Drug-induced acute liver failure in a tertiary liver centre in Malaysia
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Background: Drug-induced acute liver failure is uncommon and may be fatal. **Objective:** To examine the characteristics and the outcome of patients who are thought to have developed acute liver failure secondary to drugs. **Method:** Retrospective analysis of patients with acute liver failure, as diagnosed according to King's College criteria over a 3-year period. Patients are included if they had used drugs known to be hepatotoxic near to the time of liver injury. Patients' demography, category of liver injury, clinical presentation, liver biopsy results and the outcome are documented. The patients are scored according to the Causality-Assessment-of-Adverse-Reaction-To-Drugs, which categorizes them into highly probable, probable, possible and unlikely to be drug-induced liver injury (DILI). **Results:** In

all, 17 patients were identified (M:F is 2:15). Mean age is 33.1years(13–66 years). Nine patients were categorized as probable and 8 patients were categorized as possible DILI. Anti-HBcore (total) was positive in three out of eight patients tested. Anti-HCV was positive in one out of all 17 patients. ANA was reactive in one patient but IgG was not significantly raised. Anti-tuberculous drugs were implicated in seven cases. The other drugs implicated include amoxicillin ($n = 2$), propylthiouracil ($n = 2$), Chinese/traditional medication ($n = 2$) lamotrigine ($n = 1$), diclofenac ($n = 1$), paroxetine ($n = 1$), and ticlopidine ($n = 1$). Hepatocellular injury pattern is more common in the antiTB group (72%) whereas the non anti-TB group has more cholestatic/mixed injury pattern (60%). Rash and eosinophilia tend to co-exist and occurred more frequently in the anti-TB group than the non anti-TB group (86% vs 30%). Mortality rate is almost equal in both groups (anti-TB = 86%, non anti-TB = 70%). The mean survival is 0.97 month (0.23–2.5) for those who died, and the mean follow-up for those who survived is 7.64 months (3.6–22). Post-mortem liver biopsy in five patients showed extensive fibrosis, extensive necrosis or both. **Conclusion:** Acute liver failure secondary to drugs has a high mortality. Careful monitoring of patients started on medications known to cause liver injury is vital. This is particularly true for women who seem to be more susceptible.

APASL/Poster/Abstract/306

Acute severe hepatitis B, outlook at two urban centers

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Design: Retrospective clinical, serological, biological and follow-up study of 124 patients with severe forms of acute viral hepatitis B (AVHB). **Setting:** In-patient service at Aga Khan University and Hamdard University Hospitals, Karachi, Pakistan. **Measurements:** A total of 124 patients with HepB core IgM Ab were selected who had follow-up greater than 6 months and their 70 different parameters, HBsAg conversion rate, Hep delta co-infections and outcomes were recorded. These parameters were compared in seroconverted and in those who became chronic carriers in a univariate analysis. All significant factors on univariate analysis were entered into a stepwise logistic regression analysis to identify independent variables of prognosis. The sensitivity and specificity of significant prognostic factors were then assessed. **Results:** Out of 168 patients with acute hepatitis with Hep B core IgM Ab, 41 patients had follow-up less than 6 months or they could not be approached by electronic medium. Those with Hep D co-infection and fulminant course were excluded. In all, 61/124 patients had HepBeAg positive. Mean follow-up was 6 to 48 months. Ninety-two patients seroconverted out of the remaining 32 and eight went on to develop CAH. Four variables differed significantly between seroconverted and chronic carriers on univariate analysis, includingage less than 20 years and HepBeAg negative; falling titers of hepatitis BsAg predicted the outcome on multivariate analysis. **Conclusion:** Acute severe hepatitis patients are affected more by Hep BeAg-negative variants and overall spontaneous seroconversion was 74%, emphasizing the need to look for therapeutic options for acute severe hepatitis B.

APASL/Poster/Abstract/307

Anti-tuberculous therapy and fulminant hepatic failure: experience at tertiary care center, non-transplant scenario

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Background: The incidence of tuberculosis is not decreasing in this part of the world. On the other hand, there have been increasing prescriptions of anti tuberculosis medications and at times empirically, which is exposing a greater number of patients to the risks of three potentially hepatotoxic drugs: isoniazid, rifampicin, and pyrazinamide? Thorough awareness of potentially severe drug hepatotoxic reactions of these medicines is essential because fulminant hepatic failure is a devastating and often fatal condition without liver transplantation. **Methods:** This is a description of 17 cases of fulminant hepatic failure caused by rifampicin, isoniazid, pyrazinamide or all. They were admitted to Aga Khan University hospital. **Results:** Patients were adults from Karachi, of whom 13 were females. Nine had pulmonary, four intestinal, two glandular, one genitourinary and one PUO. Twelve were on three drugs. One had underlying CLD. Most of the patients were on correct doses. Eight patients had baseline LFTs and only three had follow-up LFTs. Only eight had jaundice at the time of presentation. Most of the patients were of ATT for more than 8 weeks. Fifteen patients died. Six patients died within 48 h of admission. These cases highlight the dismal outcomes of this potentially avoidable menace and also elaborate on the lack of acceptance of current guidelines on liver function tests after starting anti-tuberculosis therapies.

APASL/Free Paper/Abstract/308

Clustering of poor prognostic factors in heavier patients with chronic hepatitis C (CHC): baseline characteristics and outcomes with peginterferon α-2a (40 kDa) (PEGASYS®) plus ribavirin (RBV, COPEGUS®) in randomized, international, Phase III trials

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Introduction: SVR rates decrease as weight increases. This is apparent in a retrospective subanalysis of a Phase III trial of pegylated-interferon α-2b (12 kDa)/RBV: the overall SVR of 54% increased to 61% when patients weighing $\geq$ 75.5 kg were excluded (Lancet 2001; 358:958). Therefore, in this study, we assessed the complex relationship between body weight and baseline factors in patients in two Phase III randomized studies, and between weight and outcomes in patients treated with peginterferon α-2a (40KD) (PEGASYS®)/RBV (COPEGUS®). **Methods:** Data from two studies were combined (N Engl J Med 2002; 347:975; Ann Intern Med 2004; 140:346). Patients were classified by weight ($\leq$ 75.5 or $>$ 75.5 kg) and baseline characteristics of all patients were compared. Outcomes in patients who were treated for 48weeks with peginterferon alfa-2a (40 kDa)/RBV 1000/1200 mg/day were also compared. **Results:** Significantly more patients in the $>$75.5 kg group were male, black, had cirrhosis, genotype 1 or had acquired HCV through intravenous drug use (IVDU). Heavier patients had significantly higher HCV RNA levels. SVR rates were significantly higher in the lighter patients (odds ratio 1.9, 95%CI, 1.4–2.5). When those weighing $>$ 75.5 kg were excluded, the SVR rate was 67% (59% in genotype 1). Serious adverse events (SAEs) were more common in lighter patients, although there was no difference in withdrawal

rates for AEs. **Conclusion:** Body weight has a complex relationship with a range of patient characteristics and outcomes in patients with CHC. This clustering of poor prognostic characteristics in heavier patients may explain the lower SVR rates observed in heavier patients with all interferon-based regimens.

309
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310
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APASL/Poster/Abstract/311
Effectiveness of pegylated interferon and ribavirin combination therapy in patients with chronic hepatitis C: an Indian experience
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Background: Chronic hepatitis C (CHC) is an important form of liver disease in India. Treatment with pegylated-interferon (PEG-IFN) and ribavirin combination is highly effective in CHC patients. There is a paucity of data from the Indian subcontinent. **Aim**: To study the efficacy of PEG-IFN and ribavirin combination therapy in patients with CHC. **Patients and Methods:** In 124 liver biopsy-proven CHC patients with ALTlevels $> 1.2 \times$ ULN and positive HCV RNA at baseline were included in the study. All were treated with a combination of PEG-IFN 1.5 μg/kg/week and ribavirin 10 mg/kg/day. Patients with genotypes 1 and 4 were treated for 52 weeks and other genotypes for 24 weeks and subsequently followed up for 24 weeks. Both end of treatment response (ETR) and sustained viral response (SVR) were assessed at the end of treatment and 24 weeks after therapy, respectively. Biochemical response was defined as normalization of ALT (i.e., ≤ 40 IU/L) and viral response was defined as negativity of HCV RNA. **Results:** Of the 124 patients (mean age 41.75 ± 11.75 years and male:female 104:20), 14 (11.3%) were genotype 1, 103 were genotype 3, 5 (4%) were genotype 4 and 2 (1.6%) were of mixed genotypes (more than one genotype). Two patients were withdrawn due to severe side effects and four patients dropped out during the study. End therapy and sustained ALT response was found in 68/124 (54.8%) and 67/124 (54%) patients, respectively. Overall virological ETR was found in 113/124 (91.1%) and SVR in 101/124 (81.5%). SVR with respect to genotypes 1, 3, 4 and mixed genotype was 71.4% (10/14), 82.5% (85/103), 80% (4/5), and 100% (2/2), respectively. **Conclusion:** Combination therapy with PEG-IFN and ribavirin is effective in achieving SVR in more than three quarters of patients with CHC and the virological response is similar in all the genotypes.

APASL/Poster/Abstract/312
Effectiveness of mandatory immunization in Mongolian children
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Background: Mongolia is placed on high priority on universal immunization. However, there has been no systematic investigation on effectiveness and coverage of vaccination by the titer against the associated immunization. **Objective:** To determine the effectiveness and coverage of HBV vaccination in rural and urban populations and to compare this with another vaccine included with mandatory immunization in Mongolia. **Methods and Materials:** The design of this study was cross-sectional. There were 160 children randomly selected, from Ulaanbaatar (urban) and 433 children from 13 somons of rural 12 aimaks (province) from 21. All serum samples were tested for HBsAg, anti-HBs and anti-HBc. In addition, there was tested for pertussis, tetanus and diphtheria antitoxin antibody. **Results:** HBsAg detected was 0–2.5% in urban children and 3.9–8.7% in rural children of vaccinated groups and 10.0–19.7% in non-vaccinated groups. Tests for anti-HBs were positive in 34.0–77.0% in urban and 23.0–31.0% in rural children of the vaccinated groups, depending on age. Anti-HBc was detected in 6.4% urban children of vaccinated ages and 35.8% in the same age group in rural settings. Pertussis, tetanus and diphtheria antitoxin antibody was detected in 84.2–96.1% of all subjects. There was no significant difference between rural and urban subjects studied for these antitoxin antibodies. **Conclusion:** 1. Seroconversion to HBV vaccination is significantly lackingcompared to that found in other countries. Also, the vaccination immunity achieved in rural areas is significantly lower than that of urban areas. 2. Seroconversion to vaccines for pertussis, tetanus and diphtheria is 86.2–96.1%. Unlike for HBV, there was no significant difference in immunity achieved between urban and rural areas.

APASL/Poster/Abstract/313
Relationship between HBV DNA levels and presence of PC/BCP mutation
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HbeAg/anti-HBe seroconversion often coincides with loss of serum HBV DNA and normalization of liver enzyme, butthe relationship between HBV DNA levels and precore or basal core promoter mutation is not clear. We hypothesized that the mutant group had higher DNA levels than the no mutant group and then analyzed DNA levels according to the presence of mutation at the precore and corepromoter regions. We analyzed 67 sera of eAg-negative chronic hepatitis B patients; male: female, 53:14, lamivudine treatment: naïve, 46:21, and 30 patients had achieved eAg loss after lamivudine treatment. DNA levels were measured by hybridization capture and bDNA method. Mutant analysis was done by INNO-LiPA method for 39 patients; it is designed for detection of G1896A at the precore region, A1762T, and of G1764A at the core promoter region. Twenty-eight patients were analyzed by the AFLP method, which is designed for detection of the precore region mutation. Six cases were PCR negative. At the core promoter region, wild types were two (5.1%), mutants were 36 (92.3%) and mixture was one (2.6%) in 39 samples. At the precore region, wild types were 17 (27.9%), mutants were 35 (57.3%) and mixtures were nine (14.8%) in 61 samples. Mean HBV DNA levels of wild types, mutants, mixtures of the precore region are 223.4 ± 426.7, 332.3 ± 789.6, and 31.4 ± 45.9 pg/ml, respectively. But there are no statistically significant relationships among DNA levels, presence of mutant, and lamivudine treatment. Single serum HBV DNA test does not determine precore mutation or wild type in patients with HBeAg/anti-HBe seroconversion; therefore, genetic analysis is needed in HbeAg-negative patients to differentiate the precore mutants from wild types.

APASL/Poster/Abstract/314

The impact of steatosis on treatment response and histological evolution in chronic hepatitis C patients treated with interferon α-2b plus ribavirin

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Background/Aims: We evaluated the impact of steatosis on the response to antiviral therapy and histological outcome in patients with chronic hepatitis C. **Methods:** One hundred and sixty-one consecutive patients (genotype 1, $n = 76$; genotype 2, $n = 73$) receiving interferon α-2b (3 or 5 million U thrice weekly) and oral ribavirin (1000–1200 mg/day) for 24 or 48 weeks were included. Ninety patients had paired biopsies obtained a mean of 29.1 ± 7.1 months apart. **Results:** Variables associated with baseline steatosis in logistical regression were higher in body mass index (≥ 25) (odds ratio (OR): 4.832, $P = 0.002$) and higher fibrosis stage (≥ 2) (OR: 3.131, $P = 0.019$). Neither the presence nor the severity of steatosis was associated with the sustained virological response (SVR). Evaluation of paired biopsies demonstrated that the distribution of steatosis evolution was not different between patients with and without SVR ($P = 0.374$). Among patients achieving SVR, there was a significant difference in the fibrosis changes between those with nil or grade 1 steatosis and with grade 2 or 3 steatosis at posttreatment biopsy (-0.6 ± 1.2 vs. 0.3 ± 1.3, $P = 0.032$). Stepwise logistic regression analysis showed that SVR (OR: 16.33, $P = 0.004$), nil or grade 1 steatosis at posttreatment biopsy (OR: 12.82, $P = 0.018$), and age <50 years (OR: 6.757, $P = 0.053$) were independently associated with fibrosis regression. **Conclusion:** Although steatosis is not associated with SVR in our patients, however, it not only correlates with advanced fibrosis at baseline but also may affect fibrosis regression after therapy with interferon and ribavirin.

APASL/Poster/Abstract/315

Risk assessment of hepatocellular carcinoma by transient elastography apparatus

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The prognosis and clinical management of chronic hepatitis C highly depend on the degree of liver fibrosis. Chronic hepatitis C with cirrhosis is a major risk factor for hepatocellular carcinoma (HCC). Until recently, liver biopsy was the only way of assessing liver fibrosis. However, liver biopsy is an invasive procedure that is not well accepted by patients. Fibroscan (FS) is a novel, rapid, non-invasive and reproducible method for measuring liver stiffness. The aim of this study was to identify the efficacy of FS as a predictor of HCC development. Consecutive patients with hepatitis C with or without HCC seen in our institution between September 2004 and February 2005 were included. FS was performed on the right lobe of the liver through an intercostal space. Ten validated measurements were performed on each patient. Conditional logistic regression analysis was used to determine risk factors of HCC. Age, total bilirubin, platelet cell counts, liver stiffness obtained by FS, AST to ALT ratio, albumin, and age were significant factors in the univariate analysis, and liver stiffness obtained by FS ($P = 0.0002$) and age ($P = 0.0318$) were significant factors in the multivariate analysis. The risk increased by a factor of 13.5 when the FS value doubled. A prospective study is being conducted to confirm these results further.

316

Abstract withdrawn

APASL/Poster/Abstract/317

Manifestation and factors associated with YMDD mutant development in lamivudine treatment

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Backgrounds: Lamivudine administration can achieve potent suppression of HBV replication, normalization of ALT and improvement in liver histology. However, the emergence of lamivudine-resistant HBV strains has been reported in long-term lamivudine therapy. Though factors associated with the frequency of appearance of YMDD mutant have been much reported, those with the time of emergence have not been. We sought to examine the factors associated with the time of appearance of the YMDD mutant, mutant type and each one's characteristics. **Patients and Methods:** This study included 56 patients with chronic hepatitis B who tested positive for HBsAg, received long-term lamivudine monotherapy and the YMDD mutant confirmed by CLIP sequencing method. We investigated liver function tests and HBV DNA copy at baseline, 3 months and 6 months after treatment, the appearance of mutant and the type of mutant, genotype. **Results:** The mean age of patients was 41 ± 11 and the male:female ratio was 41:15. All cases were genotype C. The mean time of viral and chemical breakthrough for the appearance of the YMDD mutant was 21 ± 12 months. Age, sex, ALT and HBV DNA at baseline, 3 months and 6 months after treatment did not influence the time of appearance of the YMDD mutant. But the higher the HBV DNA ($\log_{10}$ copies/ml) at 6 months after treatment, the earlier the mutant appeared. YIDD type was 34/56 (60%), YVDD type 22/56 (40%) and there was no difference about ALT, HBV DNA at the appearance of the mutant between the two. L528M accompanied in 43/56 (77%). **Conclusion:** HBV DNA ($\log_{10}$ copies/ml) at 6 months after lamivudine treatment was associated with a more rapid selection of the YMDD mutant. L528M usually accompanied it. We must study not only clinical manifestation and prognosis about the emergence of YMDD and L528M variants, but also investigate the presence of other mutant variants.

APASL/Poster/Abstract/318

The factor associated with liver abscess recurrence

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We studied retrospectively 57 patients who were admitted at DanKook hospital. Liver abscess recurred in six of 57 patients. The male:female ratio was 1.3:1 in the nonrecurred group but

the recurred group consisted of all males. The mean average age was 58.6 years in both groups. The duration of symptoms was 12.8 days in the nonrecurred group and 21 days in the recurred group. The right lobe was the most frequent site in both groups. The mean size of abscess was 6.3 cm in the nonrecurred group and 3.5 cm in the recurred group. PCD insertion rate was lower with decreased abscess size, with a statistical significance of $P<0.01$. PCD insertion duration was 12.2 days in the nonrecurred group and 8.75 days in the recurred group but there was no statistical significance. *Klebesiella pneumoniae* (50%) was the most frequent bacteria in the nonrecurred group followed by *Streptococcus* and *Escherichia coli*. *E. coli* (60%) was most frequent in the recurred group followed by *K. pneumoniae*. *E. coli* was more often seen in the recurred group. Admission period was 22.8 days in the nonrecurred group and 19.8 days in the recurred group. The nonrecurred group showed a higher PCD insertion rate and longer duration than the recurred group. The larger the abscess, the higher was the PCD insertion rate, leading to a lower recurrence rate. *E. coli* was isolated in the recurred group more often than in the nonrecurred group. Aggressive PCD insertion and thorough drainage seemed to be helpful to prevent abscess recurrence. When *E. coli* is isolated, careful follow-up is necessary.

APASL/Plenary/Abstract/319

Vascular response to vasoconstrictor is increased in rabbit model of non-cirrhotic portal hypertension (NCPH) at one month

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Background: Pathophysiology of non-cirrhotic portal hypertension (NCPH), a common cause of portal hypertension (PHT) in Asia, is obscure. Most studies report a decreased responsiveness to vasoconstrictors in aortic tissue from partial portal vein-ligated or cirrhotic rats. **Aim:** To evaluate the responsiveness of aorta to vasoconstrictors, phenylephrine, PE (α_1 adrenergic receptor agonist) and potassium chloride (KCl) (a classical membrane depolarizing agent) in an NCPH model at 1 month. **Animals and Methods:** PHT was induced by gastrosplenic vein (GSV) cannulation and repeated *Escherichia coli* injection. New Zealand white rabbits were randomly grouped into experimental animals ($n=6$) receiving 4 mg/ml of lipopolysaccharide (LPS) (from heat-killed *E. coli*) into the portal circulation through an indwelling cannula placed in GSV; and sham-operated animals ($n=5$) receiving equivalent amount of saline in similar fashion at 0, 1, 7, 14 and 28 days. Portal pressure (PP) and splenic weight were recorded in both the groups of animals. The reactivity of isolated thoracic aortic rings from NCPH and sham-operated rabbits at 1 month was evaluated by PE (10^{-12}–10^{-4}) and KCl (15–75 mM). **Results:** At 1 month, the experimental group rabbits showed a significant increase in PP (14.29 ± 1.32 vs 5.94 ± 0.39 mmHg, $P<0.001$) and splenic weight (0.91 ± 0.17 vs 0.61 ± 0.16 gm, $P<0.01$) compared with the sham-operated rabbits. *In vitro* tension preparation showed maximum contractile response to PE in intact (3.36 ± 1.15 vs 1.97 ± 0.91 g; 10^{-4} M, $P<0.001$) and denuded (2.47 ± 0.97 vs 1.87 ± 0.75; 10^{-4} M, $P=$ NS) aortic rings from NCPH rabbits as compared to the sham-operated group. Contractile response to KCl was similarly increased (3.07 ± 1.04 vs 1.46 ± 0.17 g; 75 mM, $P<0.001$) in NCPH rabbits as compared to sham-operated rabbits. **Conclusion:** These results demonstrate that in NCPH animals, there is a paradoxical increase in the contractile response to vasoconstrictors. This hyperresponsiveness may be due to up-regulation of α-adrenergic receptor or an increase in intracellular calcium $[Ca^{2+}]_i$ at the initial stage of portal hypertension.

APASL/Poster/Abstract/320

The clinical role of hepatitis B virus genotype in hepatocellular carcinoma type B

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Background: Hepatitis B virus (HBV) is one of the major causative agents associated with hepatocellular carcinoma (HCC) in Southeast Asia where the HBV genotype B (HBV/B) and genotype C (HBV/C) are prevalent. The role of hepatitis B virus genotypes on the clinical features and prognosis of patients with hepatocellular carcinoma is currently uncertain. The aim of the present study was to evaluate the distribution of HBV genotypes in HCC patients and their clinical relevance. **Methods:** A total of 21 patients with HCC were enrolled. HCC was diagnosed by a combination of α fetoprotein (AFP) and CT scanning. HBV genotypes were determined by nested polymerase chain reaction (nPCR) using genotype-specific primers. The clinical data were analyzed in relation to the HBV genotype including age, sex, liver function test, Okuda stage, and survival. **Result:** HBV genotypes B and C were predominant in this study, accounting for 16 (76.2%) and 5 (23.8%), respectively. Genotype B with Okuda criteria 1 or 2 was 4 (25%) and 12 (75%), respectively, whereas Genotype C with Okuda criteria 1 or 2 was 1 (20%) and 4 (80%), respectively. Regardless of Okuda criteria, median survival rate for genotype B was 166 days and for genotype C was 60 days. However, there were no statistical differences between those genotypes regarding tumor staging by Okuda criteria and the overall median survival. **Conclusion:** This study could not exhibit the association between genotypes and other parameters including group of age, sex, liver function test, AFP, and Okuda criteria. The prognostic of HCC patients with genotype C may be less than that of genotype B.

APASL/Plenary/Abstract/321

Viral hepatitis in pregnancy; etiology, clinical course and outcome: a study of 144 patients

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Background: Severity of viral hepatitis in pregnancy and its influence on the mother and the fetus are areas of continued investigation. There is paucity of data on the etiology, clinical course and outcome of viral hepatitis in pregnancy. **Patients and Methods:** Consecutive pregnant women with viral hepatitis were included in the study. The etiology, clinical course and feto-maternal outcome were prospectively assessed. **Results:** In all, 144 pregnant women (mean age 22.3 ± 3.1 years) in gestational ages between 13 and 38 weeks (median gestational age 32.3 weeks), 69% third trimester and 31% in second trimester were included. The etiology of viral hepatitis was hepatitis E (HEV) in 58.2%, HBV in 32.6%, hepatitis A (HAV) in 0.6%,

HCV in 7.6% and co-infection in 1.3%. The maternal complications were coagulation defect 56%, postpartum hemorrhage 20%, acute renal failure 18%, gastrointestinal bleeding 12.5% and ascites 17.3%. Of the 144 women, 61 (42.3%) had fulminant hepatic failure (FHF) (HEV 77%, HBV 23%). Of the 61 FHF women, 41 (67%) died (HEV 90% and HBV 9.8%, $P<0.05$). Maternal mortality was two times higher in the third compared to the second trimester (28.2% vs 13.1%) ($P<0.01$). The causes of death were cerebral edema 48.7%, hepato-renal failure 29.2%, postpartum hemorrhage 21% and multiorgan failure 7%. The perinatal mortality rate was 56.2%. There were 37 (25.6%) live births, 59 (40.9%) stillbirths and 22 (15%) neonatal deaths. Perinatal mortality was 56% in acute viral hepatitis and 100% in FHF ($P<0.01$). Perinatal mortality was higher in women with HEV than in those with HBV (65.4% vs.30.8%, $P<0.01$). **Conclusion:** Based on the results of this very large prospective study, hepatitis E is found to be the commonest cause of viral hepatitis and FHF in pregnancy in India. This is associated with a very high maternal–perinatal morbidity and mortality, which increases as the gestation advances.

APASL/Poster/Abstract/322

Prompt diagnosis of spontaneous bacterial peritonitis and analysis of ascitic fluid protein content by reagent strip

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Introduction: Ascitic fluid PMN count remains a crucial tool in diagnosing spontaneous bacterial peritonitis (SBP), but may not be done promptly in some situations. A few studies have shown the accuracy of reagent strip test for diagnosing SBP. The objective of this study is to evaluate the use of reagent strip in Thailand, Combur[10]Test®M, which is different from that used in previous studies, for diagnosing SBP and detection of ascitic fluid with low protein content. **Patients and Methods:** One hundred and seventeen ascitic fluid samples of 72 cirrhotic patients were analyzed by PMN count and 113 samples for protein measurement. Granulocyte esterase strip results for diagnosis of SBP, and protein strip results for detection of ascitic fluid with low protein content (<1 g/dl) were compared to the corresponding routine measurement. **Results:** Of the 12 samples with ascitic fluid, PMN >250 cells/mm^3, seven samples were diagnosed as SBP by reagent strip. No samples were diagnosed as SBP by reagent strip in the samples with PMN <250 cells/mm^3. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for diagnosis of SBP by reagent strip were 58%, 100%, 100% and 95%, respectively. Of the 13 samples with ascitic fluid protein <1 g/dl, 18 samples were diagnosed correctly by reagent strip. Of the remaining 80 samples with ascitic fluid protein >1 g/dl, 57 samples were diagnosed correctly by reagent strip. The sensitivity, specificity, PPV and NPV for detecting ascitic fluid with protein <1 g/dl by reagent strip were 55%, 71%, 44% and 79%, respectively. **Conclusion:** The reagent strip test can be used for prompt diagnosis of SBP with specificity and PPV of 100%. The clinical application for protein measurement is not as reliable as conventional laboratory because of low PPV and NPV.

APASL/Poster/Abstract/323

Comparison of prevalence and clinical features of autoimmune liver diseases in Japan and other countries

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The prevalence of primary biliary cirrhosis (PBC) and other autoimmune liver disease (AILD) reportedly varies widely among countries. The aim of this study is to compare the prevalence and clinical presentations of AILD between Japan and other countries by analyzing cases seen during the same period using the same diagnostic criteria. The design is a prospective case series of consecutive patients referred to institutes. Patients with AILD who visited physicians during four months were enrolled. The number of patients with HBV- or HCV-chronic liver diseases seen during the same period were used as a reference. Totally, 24 135 cases were enrolled from 72 institutes in Japan, of which 1960 cases (8.1%) were AILD, while in total 3501 cases were from outside Japan, of which 58cases (1.6%) were AILD. The prevalence and the features of AILD were quite different among countries. The prevalence of AILD was extremely low in Korea and India. The prevalence of PBC was higher than AIH in Japan but it was inverted in Korea, India and Egypt. Less symptomatic cases of AIH and PBC are more frequent in Japan than in other countries. Though some bias should exist, the AILD is unevenly distributed in the world.

APASL/Poster/Abstract/324

PBMC is the home of HBV, or just the hotel?

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It is known that covalently closed circular DNA (cccDNA) persists throughout the natural history of chronic hepatitis B, even in patients with serologic evidence of viral clearance. Long-term antiviral therapy significantly decreased cccDNA levels by a primarily noncytolytic mechanism. At present, the method of monitoring of HBV cccDNA levels only focuses on infected human liver biopsies. We presumed that, if the cccDNA persisted in PBMCs, its levels could be used for monitoring long-term anti-HBV therapy. Based on this hypothesis, the present study aims at (i) whether or not there are cccDNA in PBMCs of HBV DNA positive serum and (ii) and the cccDNA mainly inhabited CD4+T cells, CD8+T cells, or other PBMCs. **Methods:** A fluorescence quantitative polymerase chain reaction (PCR) for detection of HBV cccDNA in serum was established using two pairs of primers designed according to the relatively conservative sequences between the gap upstream and downstream of HBV DNA plus and minus strands. A positive reference panel was developed from a HBV recombinant plasmid for the quality control of the assay. PBMCs were isolated by Ficoll–Hypaque density-gradient centrifugation. BD FACSCalibur was used to isolate CD4+, CD8+, T, and other T cells. **Results:** The linear correlation equation between threshold cycle value (C_t) and the logarithm of cccDNA initial copies is as follows: $Y = -3.588X+55.228$; the correlation coefficient is 0.999, and efficiency of PCRIS 90.0. The minimum detection level of the assay is 6×10^3 copies/ml of cccDNA. The linear range of the assay is 5×10^4–5×10^9 copies/ml of cccDNA. The range of total HBV DNA/cccDNA ratio detected in serum of patients with hepatitis B is 66.3 ± 15.2 (2.62–341.98), with a median of 24.7. HBV cccDNA was detected in CD4+ T cells but not in CD8+ T cells. **Conclusion:** The fluorescence quantitative

polymerase chain reaction for detection of HBV cccDNA in serum is simple and highly sensitive, specific and reproducible. It can be used for detection of HBV cccDNA in serum to evaluate the efficacy of antiviral treatment for patients with chronic hepatitis B. HBV cccDNA in CD4+ T cells may be related to persistence of HBV infection.

325
Abstract withdrawn

APASL/Free Paper/Abstract/326
Genotypes of hepatitis B virus infection in the Philippines
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Background/Aims: In Asia, the predominant hepatitis B virus (HBV) genotypes are A, B and C. In Southeast Asia, the most common genotypes are B and C. There has been no large population study on hepatitis B virus (HBV) genotypes in the Philippines to date; thus, the objective of this study is to determine the predominant HBV genotypes in Filipino patients with chronic hepatitis B (CHB), liver cirrhosis (LC) and hepatocellular carcinoma (HCC). **Patients and Methods:** Between January 2001 and January 2005, sera from patients with HBV-associated chronic hepatitis ($n = 31$), liver cirrhosis ($n = 37$) and liver cancer ($n = 40$) seen in the Liver Clinic of the UST Hospital were collected and stored in our -80C deep freeze facility. To determine the genotypes, they were subjected to restriction fragment length polymorphism (RFLP) described earlier by Mizokami et al. (FEBS Lett 1999; 450:66–71). **Results:** The most common genotypes in all disease forms of HBV are A, B and C. In chronic hepatitis, the most common genotypes are A (77%), B (13%) and C (10%). In liver cirrhosis, the common genotypes are A (41%), C (41%) and B (18%). Likewise, in hepatocellular carcinoma, the predominant genotypes are A (38%), B (38%) and C (24%). HBeAg (+) disease is noted in 82% of genotype A, 85% of genotype B and 79% of genotype C. **Conclusion:** Among the Filipino patients, genotype A is the most predominant HBV genotype. The most common genotypes noted are genotype A in CHB, genotypes A and C in liver cirrhosis and genotypes A and B in hepatocellular carcinoma.

APASL/Free Paper/Abstract/327
cccDNA levels and histologic response in Filipino chronic hepatitis B patients treated with nucleoside analogues
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Background: Hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) is a replicative intermediate responsible for viral persistence and reactivation after treatment withdrawal. Recently, studies involving nucleoside analogue therapy reveal substantial reduction of cccDNA and serum HBVDNA post treatment. **Objective:** We aim to describe the relationship of intrahepatic cccDNA concentration with histopathologic changes in chronic hepatitis B (CHB) before and after nucleoside analogue treatment. **Methods:** Liver biopsy was done on 17 consecutive HbeAg (+) Filipino CHB patients with elevated serum alanine transaminase (ALT) $> 2 \times$ ULN. Intrahepatic cccDNA, total hepatic and serum hepatitis B virus DNA (HBVDNA) were determined and correlated with Knodell and Ishak histologic scores using Pearson's correlation. Serum and hepatic HBVDNA, including ALT, were likewise correlated with cccDNA levels by linear regression. **Results:** Mean cccDNA pre-treatment level was 5.7 ± 7.3 HGEq as compared to 1.1 ± 1.7 HGEq post treatment ($P = 0.025$). Mean total hepatic HBVDNA pre-treatment levels of 453.5 ± 558.0 HGEq decreased significantly to 40.4 HGEq post treatment ($P = 0.009$). Mean pre-treatment serum HBVDNA reduced from 4 115 800+6956 cpm to 1 507 335 $\pm$ 4264cpm after treatment ($P = 0.165$). Baseline mean Knodell scores were 4.4 ± 3.4 and 2.5 ± 2.1 pre- and post-treatment, respectively ($P = 0.07$). Mean Ishak scores pre- and post-treatment were 4.5 ± 3.2 and 3.0 ± 2.4, respectively ($P = 0.18$). Reduction of hepatic cccDNA after treatment correlates significantly with lower Knodell and Ishak scores ($P = .003$ and 0.024, respectively). cccDNA levels correlate directly with serum and total hepatic HBVDNA ($P = < 0.001$). Most patients with pre-treatment cccDNA levels above 4.38 HGEq were found to have higher Knodell and Ishak scores. **Conclusion:** Low levels of post-treatment cccDNA are noted in patients with lower serum and total hepatic HBVDNA, as well as in those with improvement in liver histology.

APASL/Free Paper/Abstract/328
Baseline factors affecting disease progression in chronic hepatitis B (CHB) patients with advanced fibrosis or cirrhosis
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Introduction: Lamivudine reduces disease progression in patients with advanced CHB (Liaw New Engl J Med 2004). Additional factors affecting disease progression were investigated. **Methods:** A total of 651 CHB patients with histologically confirmed cirrhosis or advanced fibrosis were randomised 2:1 (double-blind) to lamivudine 100 mg/day or placebo for ≤ 5 years. The primary endpoint was time to disease progression, defined by ≥ 2 points increase in Child–Pugh score or occurrence of hepatocellular carcinoma (HCC). The study was stopped after the second interim analysis showed a clear benefit for lamivudine. Results were analysed by covariate modelling of time to disease progression using a Cox's proportional hazard model to identify factors which had significant impact on outcome. **Results:** Endpoints occurred in 34/436 (8%) of patients on lamivudine and 38/215 (18%) on placebo (hazard ratio (HR) 0.45, 95%CI 0.28–0.73, $P = 0.001$). Other factors with a significant impact on outcome included Child–Pugh score 6 vs 5 ($P < 0.001$), Child–Pugh score 7—9 vs 5 ($P < 0.001$), age per 10-year increase ($P = 0.003$), fibrosis score 6 vs ≤ 4 ($P = 0.036$). In another analysis of patients with known HBV genotypes, 68% had genotype C, 28% B and 4% others. Among patients with genotype C, endpoints occurred in 5% (15/275) receiving lamivudine and in 19% (26/137) receiving placebo. Increase in Child–Pugh score occurred in 4% (10/275) and 9% (12/137),

respectively, and occurrence of HCC in 2% (5/275) and 8% (11/137), respectively. For the smaller group with genotype B, there was no apparent difference in treatment responses. **Conclusions:** Along with therapy, baseline Child–Pugh score, age and fibrosis score significantly impacted on disease progression.

APASL/Poster/Abstract/329

The accuracy of clinical diagnosis criteria of Korea Liver Cancer Study Group-National Cancer Center practice guidelines for hepatocellular carcinoma

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Background: Pathologic studies are the confirmative diagnosis of hepatocellular carcinoma (HCC) but have shown that many small nodules do not correspond to HCC, and tumor seeding after biopsy is significant. Non-pathological (clinical) criteria of HCC have therefore been suggested by the Barcelona-EASL conference and Korean guidelines. However, there are no data to support the usefulness of the clinical criteria of HCC. In this study, our aim was to validate the accuracy of clinical diagnosis of the KLCSG-NCC guidelines for HCC in the cohort of patients admitted to NCC Korea. **Method:** The database of 232 patients who were examined completely for clinical diagnosis criteria and underwent surgical resection or liver biopsy for hepatic mass in the NCC from 2001 to 2004 were reviewed retrospectively. **Result:** One hundred and eighty-six cases of HCC were confirmed by pathologic examination and 189 cases of HCC were diagnosed with clinical diagnosis criteria. The sensitivity, specificity and positive predictive value of clinical diagnosis criteria of HCC were 95.1%, 73.9% and 93.7% , respectively. There was no statistical difference of sensitivity and positive predictive value of the criteria for HCC according to tumor size, stage and the presence of cirrhosis. The sensitivity in the HBV positive and negative groups was 97.3% and 86.8%, respectively ($P<.001$) and the specificity was 56.5% and 91.3%, respectively ($P<.001$). **Conclusion:** The clinical diagnosis criteria of KLCSG-NCC for HCC had high sensitivity and positive predictive value irrespective of the presence of cirrhosis, tumor size and stage.

APASL/Poster/Abstract/330

Characteristics of HBV genotypes among chronic liver diseases in the Philippines

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Background/Aim: Hepatitis B virus (HBV) is classified into eight genotypes. In Asia, HBV genotype B (HBV/B) and C predominate, however HBV/A is also found in the Philippines. Recently, several subtypes, HBV/Aa, Ae, Baand Bj, were reported and clinical differences between the patients infected with these subtypes are coming to the fore. In this study, we investigated HBV genotype distribution among patients with chronic liver diseases (CLD) in the Philippines. **Methods:** A total of 100 sera were obtained from CLD patients, consisting of 32 chronic hepatitis (CH), 37 cirrhosis and 31 hepatocellular carcinoma (HCC). HBV genotypes and subtypes were mainly determined by sequencing and molecular evolutionary analyses. ALT and HBeAg were examined by Integra (Roche) and Elecsys (Roche), respectively. **Results:** In the CH patients, mean age was significantly lower and HBeAg positivity was higher. A phylogenetic analysis showed that 32 HBV/Aa, 37 HBV/Ba and 31 HBV/C strains were found in this study. Interestingly, the HBV/C strains in the Philippines had the specific cluster distinct from previous HBV/C strains from the database. Comparing age, sex, HBeAg and HBV genotypes among the CLD patients, only the HBV genotype was associated with disease progression; HBV/Ba or C was significantly highly prevalent in cirrhosis or HCC compared to HBV/Aa ($P<0.003$). In the HCC patients with the three genotypes (Aa ,. Ba and C), there were no significant differences of age, sex and HBeAg positivity. **Conclusion:** In the Philippines, three HBV genotypes, HBV/Aa, Ba and C, were prevalent, and a possible novel subtype of HBV/C was found. HBV/Ba or C would be associated with disease progression.

APASL/Poster/Abstract/331

Hepatocellular carcinoma with hypoglycemia (case series)

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Introduction: Hypoglycemia is the most frequent endocrine emergency, which mostly occurred in diabetic patients as the consequence of treatment and hypoglycemic medication. Hypoglycemia that happens in non-diabetic patients needs attention because it could be serious depending on its cause. Fasting hypoglycemia is most frequently due to insulinomia, which is an islet cell tumor that secretes insulin and is rarely caused by a non-islet tumor, which originates from hematopeotic. Big mesenchimal tumors that grow in the abdominal retro peritoneum or chest were involved in half of all cases. Hepatocellular carcinoma, gastrointestinal carcinoma, carcinoid and carcinoma adrenocortical frequencies were 25% and of the rest 25% were other carcinoma. Hypoglycemia frequently occurs in patients with big hepatocellular carcinoma. A national study in Japan found 20 cases from 2599 patients with a frequency of 0.8%. Other authors reported hypoglycemia frequency in hepatocellular carcinoma $<0.1\%$. **Method:** Case series. Time-line: January 2004to April 2005. **Result:** We found five hypoglycemia cases out of the 57 in the hepatocellular carcinoma cases, with a frequency of 8.77%. The diagnosis of hepatocellular carcinoma was established based on biopsy and fine needle aspiration in four cases and based on USG examination in one case. The causes of hepatocellular carcinoma were hepatitis B in three cases, hepatitis C in one case, and unknown in one case . The blood glucose level varies between 34 and 44 mg/dl. Generally, the patient comes with the most frequent complaint of fatigue and sweating as hypoglycemic management is by bolous 40% glucose and maintenance using D 10% infusion. Out of the five cases, two of them died due to septic shock and two of them had repeated hypoglycemic episodes.

APASL/Young Investigator/Abstract/332

Hepatic venous pressure gradient and disease severity in acute-on-chronic liver disease

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Introduction: Hepatic venous pressure gradient (HVPG) is an important factor in the prediction of variceal hemorrhage. Due to the paucity of data on portal hemodynamics and disease severity, indices in acute-on-chronic liver disease (ACLD), we evaluated the HVPG and disease severity in patients with acute on chronic liver disease. **Patients and Methods:** Ninety-nine patients were recruited, which included compensated chronic liver disease (CLD) ($n = 25$), decompensated CLD ($n = 48$) and ACLD ($n = 26$). ACLD was defined as acute deterioration in liver function in a pre-existing patient of chronic liver disease, over a period of 2–4 weeks, leading to severe deterioration in clinical status in the form of ascites, high jaundice and/or complications of CLD such as hepatic encephalopathy and/or hepatorenal syndrome (HRS). HVPG was measured by the standard technique. Liver disease severity was calculated using the Child–Pugh–Turcot (CPT) score and MELD score. **Results:** Of the 99 patients, etiology of CLD was hepatitis B ($n = 31$), alcoholic liver disease ($n = 24$), hepatitis C ($n = 7$), Wilson disease ($n = 2$), autoimmune hepatitis ($n = 1$) and cryptogenic CLD ($n = 33$). **Conclusion:** HVPG in acute-on chronic liver disease is similar to compensated CLD but lower than decompensated CLD. MELD score is significantly higher in acute-on chronic liver disease than in compensated and decompensated CLD.

333
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334
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335
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APASL/Poster/Abstract/337
Prevalence of hepatitis B virus genotypes among patients with chronic liver disease in Jakarta
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Background/Aims: Differences in clinical features and in response to antiviral treatments were known among patients infected with different hepatitis B virus (HBV) genotypes. Serological HBV-genotyping assays were conducted to observe the prevalence of HBV genotypes among patients with chronic liver diseases in Jakarta. **Methods:** Sera from patients with chronic hepatitis (CH), liver cirrhosis (LC), and hepatocellular carcinoma (HCC) were selected at random, and HBV genotypes were tested by ELISA at The Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Science, Nagoya, Japan. (under Professor Mizokami). **Results:** One hundred sera collected from 57 patients (46 males, 11 females) with CH, 32 patients (18 males, 14 females) with LC, and 11 patients (8 males, 3 females) with HCC, were tested for HBsAg, anti-HBs, anti-HBc, and HBV genotypes, as well as anti-HCV. The mean age and age range of CH, LC, and HCC patients were 39.6 years (19–75 years), 53.4 years (22–71 years) and 53.2 years (26–74 years), respectively. HBsAg was detected in 36 (36%) sera, while 35 (35%) sera were positive for anti-HCV, of which 1 (1%) serum was positive for both markers. It was interesting to note that 89 (89%) of the sera were anti-HBc-positive. There were 30 (30%) sera that showed negative results for HBsAg and anti-HCV as well, although most (26 sera or 87%) of them were anti-HBc-positive, which meant that there was the possibility that they were suffering from occult HBV infection. Among the 36 HbsAg-positive sera, HBV genotype B was detected in 31 (86%), genotype C in 2 (6%), genotype D in 1 (3%), and the other 2 (6%) were untypeable. All genotype B infections were of the Ba (Asia) type; none were of the Bj (Japan) type. **Conclusion:** Infection with HBV is common among patients with chronic liver diseases in Jakarta, and is comparable with HCV infection. The most prevalent HBV genotype is genotype B (Ba), while the minor genotypes are genotypes C and D.

APASL/Free Paper/Abstract/338
Co-infection of HBV, HCV and HIV in Cipto Mangunkusumo Hospital, Jakarta
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Background: Patients with co-infection of hepatitis C virus (HCV) and human immunodeficient virus (HIV) tended to be increased in recent years due to an increased number of injection drug users (IDU). Co-infection of these viruses has been reported to worsen the natural history of each other. This has drawn more attention to explore this condition further. Until now, there have been few published reports about co-infection of HIV and hepatitis viruses, especially from developing countries around Asia–Pacific where hepatitis B viruses (HBV) and HCV were prevalent. **Method:** This is a retrospective analysis of medical records from patients who were treated in our institution, and tertiary centers in Indonesia, for 1 year (January 2004–December 2004). **Aim:** To reveale patients' profiles and clinical conditions of HCV–HIV co-infected patients and compare it to non-co-infection patients. **Results:** In all, 313 patients who are HIV positive have been examined for HCV infection by means of anti-HCV. Co-infection of HCV–HIV was detected in 253 (80.8%) cases. Male:female sex ratio in HIV patients was 4:1, whereas in HCV–HIV co-infection patients it was 27.1:1 ($P = 0.0001$). Modes of transmission in HIV patients were mostly through sexual relationships (28/60, 46.7%) and in HCV-HIV co-infection were mostly through injection drug users (218/253, 86.2%). Hepatitis B virus infection was detected in 6 (10%) patients of the HIV group and 17 (6.7%) patients in the HCV–HIV co-infection group, but the difference were not significant. ALT level in patients with HCV–HIV co-infection was significantly higher than in patients with HIV, which was 68.8 ± 170.6 U/l vs. 44.4 ± 50.7 U/l ($P = 0.004$). Mean CD4 level in HIV patients was 193.4 ± 230.5 cells/ml, compared to 182.1 ± 221.4 cells/ml in HCV-HIV patients that was not significantly different. Hepatotoxicity of anti-retroviral therapy was found in 2/26 patients (7.7%) without HBV or HCV infections, 1/3 (33.3%) in patients with co-infection with HBV, 51/127 (40.2%) in patients with co-infection of HCV and 3/6 (50%) in patients with co-infection of HBV–HCV ($P = 0.014$). **Conclusion:** There is a tendency of more aggressive HIV prognosis in patients with HCV–HIV co-infection. Co-infection of hepatitis viruses in HIV patients may worsen the prognosis because of higher hepatocellular damage and increase the likelihood of hepatotoxicity in treatment with ART.

APASL/Free Paper/Abstract/339

Genotype of hepatitis B virus in patients with chronic hepatitis B and hepatocellular carcinoma in RSCM-Jakarta

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Eight genotypes of hepatitis B virus (HBV), A–H, have been described on the basis of the similarity of the complete genome sequence. Information on HBV genotypes is important, since many studies reported the relationship between the HBV genotype and its clinical manifestation, natural course, and also the response to antiviral treatment. The aim of this study is to find the pattern of genotype in HBV infection in patients with chronic hepatitis B and hepatocellular carcinoma. A total of 20 chronic hepatitis B and 29 hepatocellular carcinoma (HCC) serum samples obtained from patients came to RSCM, Jakarta. The HBV genotypes were determined in their sera by a genotyping system based on polymerase chain reaction (PCR) using type-specific primers. Only genotypes B and C HBV were identified in chronic hepatitis B patients. Eighteen (90%) patients were infected by genotype B HBV and only 2 (10%) patients with genotype C. Nineteen (65%) genotype B and 5 (17%) genotype C were found in HCC serum samples. These results indicate that genotype B is predominant in our chronic hepatitis B patients; this is similar to previous studies, which reported that genotypes B and C were confined to populations with origins in eastern Asia. Genotype C was higher in HCC than in chronic hepatitis B patients, suggesting that the natural history of HBV infection with genotype C may be worse than that with genotype B.

APASL/Poster/Abstract/340

Protective effect of soybean on hepatotoxicity of acetaminophen induction

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Objective: Soybeans containing lecithin have a protective effect. Acetaminophen, widely used as a nonprescription analgesic and antipyretic, causes hepatic necrosis. **Method:** As many as 40 *Rattus norvegicus* were used. Twenty rats were given only three times acetaminophen 50 mg/body weight for as long as 10 days, while the 20 remaining rats were given three times 1 ml soybean extract followed by acetaminophen, which was given at a dose similar to the treated group. After 10 days of observation, the two groups were mechanically scarified, and the livers were processed for histopathogic examinations. Microscopic findings from the two groups were compared with each other. **Result:** Both groups showed zonal necrotic hepatic, which visually gave no difference in microscopic findings. **Conclusion:** From this observation it could be concluded that soybean extract, which contains lecithin, has no function in protection against the hepatotoxic effect of acetaminophen.

APASL/Free Paper/Abstract/341

Knowledge of hepatitis C among primary care doctors working in allied hospitals of Rawalpindi Medical College, Rawalpindi

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This cross-sectional study was conducted to assess the 'knowledge of hepatitis C virus among primary care doctors', of allied teaching hospitals of Rawalpindi Medical College Rawalpindi, in December 2004. A self-administered proforma was designed and pre-tested to conduct the survey. Three trained interviewers conducted the survey. The response rate was 98%. Simple frequencies, associations by Pearson χ^2 test and independent sample test for continuous variables were analyzed using SPSS version 10.0. Out of 100 interviewed doctors, 41 (41%) had completed 1 year after graduation, 29 (29%) 2 years, 26 (26%) 3 years, one (1%) 4 years, and three (3%) 5 years. Twenty-nine (29%) have seen fewer than 10 patients, 37 (37%) have seen 11–20 patients, and 34 (34%) have seen more than 20 patients in the past year. Eighty-six (86%) have graduated from Pakistan, while only 14 (14%) graduated from other countries. When asked about testing of HCV, 56% recommended HCV testing of those with raised ALT level, 64% those with history of drug abuse, 55% those with a history of blood transfusion, 42% those with multiple tattooing and 8% recommended HCV testing all the people. Regarding routine vaccination for HAV (negative for antibodies) and HBV (negative for antibodies) in HCV-positive patients, 44% and 78% would vaccinate these patients. In all, 41% recommended vaccination for HCV (negative for antibodies) persons, while 70% would treat the patients with recommended combination therapy of α-interferon and ribavarin. Of them, 43% said that information regarding HCV is not enough. Most of the primary care residents lack knowledge of recommended guidelines for the management of HCV infected patients and many do not test when required and many test in inappropriate situations. Many do not have an idea of combination treatment. Regular educational programmes are needed to control the spread, early diagnosis and proper treatment of the disease.

APASL/Free Paper/Abstract/342

Improved survival with screening for hepatocellular carcinoma in cirrhosis and chronic hepatitis B

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Background: Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide with the major risk factor being liver cirrhosis. Survival for patients who present with symptomatic HCC is poor. We report our experience with HCC screening in chronic hepatitis B and liver cirrhosis in conjunction with our National Hepatitis B Screening programme. **Methods:** All patients referred for management of HCC have been followed by the New Zealand Liver Transplant Unit, including all cases detected through the national hepatitis B screening programme (since 1999). Demographic, laboratory, treatment and outcome data were collected in all patients. Screening was performed with 6-month serum alpha-fetoprotein (AFP) measurements $\pm$ ultrasound or CT imaging. The impact of screening on tumour stage, suitability for treatment, and survival was determined. **Results:** A total of 421 cases were reviewed, of which 339 were included in this study. Patients were excluded if there was incomplete data or if the tumour was detected following transplant. Of the screen-detected HCC cases, 72% had a single HCC, 81% had HCC restricted to a single lobe and 74% had tumour size less than 5 cm. Of the nonscreen-detected HCC patients, 46% had a single HCC, 56% had HCC restricted to a single lobe and 19% had tumour size less than 5 cm ($P<0.001$, χ^2 test). In total, 73% in the screened patients received treatment for their HCC (transplantation in 40%, resection in 22%, radiofrequency ablation/transarterial chemoembolisation in 16%) compared to 10% in the non-screened patients (transplantation in 1%, resection in 6% and radiofrequency ablation/transarterial chemoem-

bolisation in 3%) ($P<0.001$). Advance tumour stage (CLIP score ≥ 2) was seen in 90% of the nonscreened HCCs compared with 29% of the screened HCCs ($P<0.001$). In all, 46% of the nonscreened tumours had serum AFP of greater than 1000 ng/ml compared with 16% in the screened tumours ($P<0.001$). Median survival from diagnosis was 1313 days in screened cases and 83 days in nonscreened cases. One- and 5-year cumulative survival was 79% and 49% in the screened cases, compared to 17% and 2% in non-screened cases ($P<0.0001$; Logrank Test). **Summary:** These results suggest that screening for HCC in high-risk populations (chronic hepatitis B or cirrhosis of any cause) may improve survival, provided liver transplantation is available.

343
Abstract withdrawn

APASL/Poster/Abstract/344
Hepatic arterial infusion chemotherapy by using reservoir for the treatment of advanced HCC
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Introduction: Hepatic resection, percutaneous ethanol injection (PEI), local ablation, and transcatheter arterial chemo-embolization (TACE) are considered as an effective treatment for localized HCC. Because HCCs are chemotherapy-resistant tumors, in order to increase the concentration of drug achieved at HCC, hepatic arterial infusion chemotherapy (HAI) is usually used for the treatment of multifocal bilobar tumors of the liver or HCCs combined with tumor thrombi, not amenable to TACE. Recently, reservoir has been used for HAI in Japan. In this presentation, we describe the current situation and therapeutic efficacy of HAI by using reservoir for the treatment of far advanced HCC. **Patients and Methods:** Between December 1987 and December 2004, 319 patients with far advanced HCCs were treated by repeated HAI. All patients were percutaneously implanted with an infusion catheter connected with a reservoir in the hepatic artery via the femoral artery or the axillary artery. Epirubicin, pirarubicin, or carboplatin was administered as a single bolus injection through the reservoir, and repeated every 4 weeks on an outpatient basis, until the appearance of disease progression. **Results:** The mean number of arterial infusions given during the follow-up period was 10.8. An objective response rate was 35.4% (95% CI 30.1–40.7%). The mean survival time was 20.7 months (95% CI: 18.4–23.0%). The cumulative survival rates were 60.9% and 30.1% for the periods of 12 and 24 months, respectively. **Conclusion:** Hepatic arterial infusion chemotherapy using reservoir is active and well tolerated in patients with far advanced HCC, and may improve their quality of life.

345
Abstract withdrawn

346
Abstract withdrawn

347
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APASL/Free Paper/Abstract/348
Single-dose and steady-state pharmacokinetics and safety of telbivudine following oral administration in healthy Chinese subjects
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Background: Telbivudine (LdT, β-L-2′-deoxythymidine), an L-nucleoside with potent anti-HBV activity, is being evaluated in phase III clinical trials in patients with chronic hepatitis B. This study assesses the pharmacokinetics (PK) of telbivudine in healthy Chinese subjects. **Patients and Methods: -** Forty-two healthy male and female Chinese subjects were randomized to receive a single oral dose of telbivudine 200, 400 or 800 mg (10 subjects/dose), or multiple doses of 600 mg/day (12 subjects). Single-dose (D1) and steady-state (SS) PK results are reported. **Results:** Telbivudine was absorbed rapidly and exhibited dose-related plasma exposure. PK parameters including AUC, C_{max}, T_{max}, $T_{1/2}$ and renal clearance (CLR) are summarized below (600 mg dose), and compared to results from previous phase I studies in non-Chinese subjects.

	AUC 24 h (μg/ml/h)		C_{max} (μg/ml)				
	D1	SS	D1	SS	T_{max} (h) D1	$T_{1/2}$ (h) D1	CLR D1
Chinese ($N=12$)	21.9 (7.7)	26.1 (7.2)	3.7 (1.2)	3.7 (1.2)	2.0 (0.5-3.0)	39.4 (12.1)	6.5 (1.5)
Non-Chinese	20.5 (6.2, 64)	28.0 (6.2, 64)	3.0 (0.8, 64)	3.4 (0.8, 64)	3.0 (1.0–6.0, 64)	45.6 (23.2, 6)	8.5 (2.5, 14))

Data indicate mean (SD) for Chinese and mean (SD, *N*) for non-Chinese, except T_{max} where median and range are shown.

Telbivudine was well tolerated, with 15 mild AEs in 8 subjects and no serious AEs. The nature and frequency of AEs in study subjects were comparable to those reported in previous telbivudine phase I studies. **Conclusions:** Telbivudine was well tolerated in healthy Chinese subjects with an overall safety and PK profile similar to that observed in non-Chinese subjects.

APASL/Poster/Abstract/349
Final results of a phase I/II dose escalation trial of valtorcitabine in patients with chronic hepatitis B
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Introduction: L-deoxycytidine (LdC) and L-thymidine (telbivudine; LdT) are potent inhibitors of hepatitis B virus (HBV) replication *in vitro*. Valtorcitabine, a well-absorbed prodrug of LdC, is synergistic with telbivudine for inhibiting HBV replication *in vitro* and in the woodchuck hepadnavirus model. We evaluated valtorcitabine in chronic hepatitis B (CHB) patients in

preparation for potential development in combination with telbivudine. **Methods:** Antiviral efficacy, safety, and pharmacokinetics of two valyl ester prodrugs of LdC were evaluated in a phase I/II dose escalation trial. 3′,5′-divalyl (50, 100, 200, and 400 mg/day cohorts) and 3′-monovalyl (300, 600, 900, and 1200 mg/day cohorts) prodrug forms of valtorcitabine were investigated. Each cohort comprised seven HBeAg+CHB patients, randomized 6:1 (drug vs placebo). Serum HBV DNA levels and safety were evaluated weekly during treatment (28 days), with 12 weeks' follow-up. E_{max} modeling assessed the quantitative relationship between dose and antiviral response (week 4). **Results:** Consistent, dose-related HBV DNA reductions were observed. At day 28, decreases from baseline ranged from 1.63 $\log_{10}$ (50 mg/day) to 3.04 $\log_{10}$ (900 mg/day) copies/ml. E_{max} modeling confirmed a progressive increase in HBV DNA suppression toward the theoretical maximum at doses up to 900 mg/day, with a diminished effect thereafter. Safety appeared comparable to placebo, with no treatment-related pattern of adverse events or laboratory abnormalities. **Conclusions:** Valtorcitabine demonstrated substantial suppression of serum HBV DNA and was well tolerated in patients with CHB. A dose of 900 mg/day maximized viral suppression and was selected for ongoing clinical evaluation of valtorcitabine in combination with telbivudine.

APASL/Poster/Abstract/350

Reactivation of hepatitis B carrier state during cytotoxic chemotherapy cases: a report

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Hepatitis B virus (HBV) reactivation has been described in cancer patients who received cytotoxic/immunosuppressive therapy and may result in liver damage of varying degrees of severity. Now lamivudine, a nucleoside analogue, has been known as an effective drug to suppress HBV replication and to improve histology in chronic carriers of hepatitis B virus. The outcome of lamivudine therapy (at doses 100 or 150 mg/day) in patients who developed HBV reactivation while receiving cytotoxic chemotherapy resulted in clinical improvement. In the present report, six cancer patients received cytotoxic chemotherapy treatment. Four of the six patients is a Hepatitis B carrier. Three patients received 100 mg lamivudine for hepatitis B reactivation treatment and one patient for preemptive lamivudine therapy. Three patients, consisting of 2 male and one female, had lamivudine treatment, and preemptive treatment was given in the female patient. Normalizations of ALT and total bilirubin were achieved in all treated patients, and suppression of HBV-DNA for preemptive treatment. The patient who had preemptive treatment discontinued lamivudine treatment after HBV DNA seroconversion was done. Six months after discontinuing lamivudine, she had fulminant hepatic failure after she had cytotoxic drugs. Two patients who had fulminant hepatic failure after cytotoxic chemotherapy treatments were dead. In these laboratory tests we found HBsAg seropositive. They were not those given lamivudine treatment. It is concluded that early commencement, i.e. at the onset of HBV reactivation before severe hepatic decompensation, of lamivudine may be effective in the control of HBV reactivation during chemotherapy. We suggest screening all cancer patients for hepatitis B surface antigen before immunosuppressive/cytotoxic therapy, and closely monitoring liver function of those who are found to be HBsAg seropositive.

APASL/Poster/Abstract/351

Long-term efficacy of intra-variceal n-butyl-2-cyanoacrylate for bleeding gastric varices

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Introduction: Endoscopic intra-variceal injection of *N*-butyl-2-cyanoacrylate (NBC) has been shown to be an effective haemostatic technique for the treatment of bleeding gastric varices. However, minimal data is available with regard to its long-term efficacy. In this study, we evaluated the long-term efficacy of endoscopic intra-variceal NBC injection as treatment for gastric varices.
Patients and methods: Patients who presented with actively bleeding gastric varices from January 1996 to December 2003 and were treated with endoscopic intra-variceal injections of NBC were included in the study. NBC was injected intra-variceally as a 1:1 mixture with lipiodol. Patients with concomitant oesophageal varices also underwent band ligation if there was evidence of stigmata of recent haemorrhage or Grade IV varices. All patients were treated with intravenous somatostatin in addition to endoscopic therapy. Demographic data, Child–Pugh score, presence or absence of hepatocellular carcinoma (HCC), 1-year survival and long-term follow-up data were collated.
Results: Eighteen patients were included in the study. In all cases, the actively bleeding gastric varices were located in the fundus. Initial haemostasis (no bleeding occurred for 48 h after intra-variceal NBC injection) was achieved in all 18 patients (100%). Of these, three patients had HCC, without evidence of portal vein thrombosis. Five patients (33%) (all three patients with HCC and a further two patients with Child's C cirrhosis) died within the first year. There was no mortality due to variceal bleeding. Three patients were lost to follow-up. The remaining 10 patients who are still on follow-up have a mean survival time of 39.8 months (range 14–90 months). **Conclusion:** Endoscopic intra-variceal NBC injection is highly effective in achieving haemostasis in actively bleeding gastric varices. Variceal obliteration by intra-variceal NBC injection reduces the risk of further variceal haemorrhage, thus improving long-term survival. Mortality is mainly due to malignancy or poor liver function.

352

Abstract withdrawn

APASL/Poster/Abstract/353

Hepatocellular carcinoma in ectopic liver

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Suspected as an ovarian carcinoma, hysterectomy, bilateral salphingopherectomy and biopsy from omentum were done. Small nodules were found almost everywhere and bilateral malignant ovarian tumor was suspected. Microscopically, sections from endometrium, mesoappendix and omentum showed hepatocellular carcinoma. No pedicles were seen from those masses to the main liver. There is no written data at all about the liver condition, but the clinician said the liver was normal. We concluded that this

case is one of hepatocellular carcinoma in ectopic liver tissue at the female genital tract, mesoappendix and omentum.

APASL/Poster/Abstract/354
Efficacy of additional intravenous isosorbid dinitrate in acute bleeding of oesophageal varices in cirrhotic patients
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Background: Upper gastrointestinal bleeding occurs in 33% of hepatic cirrhotic patients, 40% of whom die in each episode of bleeding. Death rate within 2 years reached up to 60%. Seventy-five to 93% of upper gastrointestinal bleeding is due to rupture of oesophageal varices. Isosorbid dinitrate (ISDN), which is an organic nitrate is a venodilator frequently used as anti-angina medicine. Recent studies showed that ISDN given orally, sublingual, transdermal or intravenous is proven to lower portal venous pressure in hepatic cirrhosis patients with portal hypertension. This effect is equivalent to the effect with vasopressin and somatostatin. **Aim of Study:** To investigate the efficacy of intravenous ISDN per drip in addition to conventional therapy to stop acute bleeding of oesophageal varices in hepatic cirrhotic patients. **Method:** Prospective, controlled open trial. **Place and Time of Study:** Internal Medicine Ward, Dr. Sardjito Hospital. Period of study: January 1–December 31, 2004. **Subjects of Study:** Hepatic cirrhotic patients admitted to hospital due to acute oesophageal bleeding, age above 18 years old, with systolic pressure >90 mmHg, in the absence of shock, encephalopathy and renal function impairment were enrolled. Subjects were assigned to Group A (receiving conventional therapy and intravenous ISDN per drip 20 mg with the rate of 2 mg/h) or Group B (receiving only conventional therapy). **Results:** There were 16 patients assigned to each group. Fourteen (87.5%) patients in Group A stopped bleeding in under 24 h, compared to eight (50%) in Group B ($P = 0.0225$). The average time to stopping of bleeding was 5.42 ± 2.8 h (interval 2–11 h) in Group A, whereas in Group B it was 15.12 ± 6.08 h (interval 6–20 hours) ($P < 0.01$). Re-bleeding within 24 h occurred in one out of 14 (7.1%) patients in Group A and none in Group B ($P = 0.7721$). No death occurred in Group A and two (12.5%) occurred in Group B. **Conclusion:** Addition of ISDN per drip with 2 mg/h to conventional therapy is more effective in stopping acute oesophageal bleeding within 24 h in hepatic cirrhotic patients compared to conventional therapy alone.

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APASL/Poster/Abstract/359
Microsatellite instability and methylation pattern of DNA repair genes in hepatocellular carcinoma
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Background: Epigenetic silencing of DNA repair genes, *O6-methylguanine-DNA methyltransferase (MGMT), hMLH1,* and *hMSH3*, by promoter hypermethylation have been observed in various cancers. However, the relationship between microsatellite instability (MSI) and hypermethylation of DNA mismatch repair genes has not been studied in hepatocellular carcinoma (HCC). Therefore, MSI and the methylation pattern of CpG islands of three genes by using methylation-specific PCR (MSP) were investigated in 40 paired hepatocellular carcinoma and associated cirrhosis. **Method:** MSI status was determined by fluorescent PCR to amplify loci D2S123, D5S346, D17S250, BAT 25 and BAT 26. *hMSH3* and *MGMT* were the most methylated genes both in cirrhosis (70% and 68% respectively) and in HCC (75% and 73% respectively). **Results:** The methylation of *hMLH1* was rarely found both in cirrhosis (three of 40 cases, 8%) and in HCC (two of 40 cases, 5%). Gene promoters methylated in cirrhosis were methylated also in HCC, with the exception of nine cases found to be methylated either in cirrhosis or in HCC (four for *hMSH3*, three for *hMLH1*, and two for *MGMT*). Of 40 HCC associated with cirrhosis, three had MSI-positive phenotype in which two were MSI-low and one was MSI-high. Immunohistochemically, expression of hMLH1, MGMT, and hMSH3 protein was 16 (40%), 6 (15%), and 11 (28%) of 40 cases of HCC. **Conclusions:** These data suggest that the promoter methylation of *MGMT* and *hMSH3* play an important role in the pathogenesis of liver cirrhosis and hepatocellular carcinomas as an early event. Therefore, detection of *MGMT* and *hMSH3* methylation may be useful for screening patients who may be at risk of developing hepatocellular carcinoma.

APASL Bali/Abstract/360
Predictors of gastric variceal bleed and results of sclerotherapy with n-butyl 2 cyanoacrylate
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Introduction: Various modalities of treatment have been tried for bleeding GV but sclerotherapy with *N*-butyl 2 cyanoacrylate (NBC) glue injection seems to be the most promising. **Aim:** To study the incidence, predictors of bleed and outcome following NBC sclerotherapy of GV bleed. **Methods:** Retrospective analysis of case records of 1436 patients who underwent endoscopy for portal hypertension (PHTN) in the last 5 years. GV were classified according to Sarin's classification. Outcomes with respect to primary hemostasis i.e., bleeding control within the first 24 h of endoscopy, rebleed i.e., bleed after the first 24 h of endoscopy and 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. The main etiology of PHTN in bleeders was hepatitis C in 34 (68%), followed by HBV and NBNC in 6 (12%) patients; 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 PHTNn 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%.

APASL Bali/Abstract/361
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APASL Bali/Poster/Abstract/362
Peptic ulcer and helicobacter pylori infection in liver cirrhosis
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An increased frequency of peptic ulcer is noted in patients with cirrhosis, but the role of *Helicobacter pylori* in this condition remains to be determined. The aim of this study is to know the prevalence of peptic ulcer in liver cirrhosis and also the role of *H. pylori* infection in this condition. We explored medical records of liver cirrhosis patients who underwent endoscopic examination in the year 2004. The diagnosis of liver cirrhosis was confirmed by a combination of clinical, biochemical, radiology and endoscopic examination. Diagnosis of peptic ulcer was confirmed by endoscopic procedures. *H. pylori* status was assessed by serology test from some available stored serum of these patients. In all, 128 patients was evaluated; there were 103 (80.4%) males and 25 (19.6%) females. We found patients with peptic ulcer 27/128 (prevalence was 21.1%), of which 13/128 (10.2%) was gastric and 10/128 (7.8%) was duodenal ulcer. The Helicobacter pylori test was positive in 23/52 (44.2%) in all cases, 5/15 (33.3%) in gastric ulcer and 3/12 (25%) in duodenal ulcer patients and the difference was not significant ($P=0.7$). In conclusion, the prevalence of peptic ulcer in liver cirrhosis patients is 21.1% and the role of *H. pylori* infection in peptic ulcer disease in liver cirrhosis is weak.

APASL Bali/Poster/Abstract/363
Cost-effective use of antibiotics for the management of spontaneous bacterial peritonitis in patients with chronic liver disease
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Introduction/aim: In a third world country like Pakistan, where the burden of chronic liver disease (CLD) is enormous with scarce resources available to patients, there is need for cost effective management of SBP. Therefore we aimed to assess the cost effective use of antibiotics in SBP. **Methodology:** This is a cross sectional study involving consecutive adult patients. We compared the efficacy and cost effectiveness of third generation cephalosporin, Ceftriaxone with the fourth generation cephalosporin, Cefipime in patients with SBP. **Results:** In all, 137 patients records were reviewed from 1 August 2003 to 31 December 2004. Cefipime was used in 69 (group A) and ceftriaxone used in 68 (group B); 35 (51%) patients underwent repeat paracentesis in group A and 34 (50%) in group B. Clinical parameters are shown in Table 1. **Conclusion:** Efficacy of both fourth generation cephalosporin, cefepime vs third generation cephalosporin, Ceftriaxone is almost equal. We endorse that the cost constraints should be addressed before selecting the antibiotic.

APASL Bali/Poster/Abstract/364
Chronic hepatitis B virus infection (CHBVI) in pregnant females
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Introduction: Many Asians acquire CHBVI perinatally or during early chilhood. Hence, it is important to understand the natural history of CHBVI in the peripartum period as many patients may be affected when they reach child-bearing age. Hence, the aim is to study the clinical outcome of CHBVI in peripartum females. **Method:** Clinical and laboratory data of pregnant female patients, as well as randomly selected (in ratio 1:4) age- and HBe status-matched, non-pregnant, female controls, who were seen in the department for CHBVI between the years 2000 and 2004, who were studied retrospectively. Clinical progress of pregnant patients and female controls were observed up to 6 months postpartum and over a 1-year period, respectively. **Results:** Nineteen patients and 76 controls, aged (mean) 31.1 ± 4.3 years, were studied. Majority of the patients (68%) presented during pregnancy, mostly in the second trimester. 12/19 (63%) were positive for HBeAg at the time of presentation. 13/19 (68%) patients had a clinical event (ie., s.ALT elevation or loss of HBeAg) vs. 28% among controls ($P=0.001$). There was no significant difference in frequency of clinical events between the HBeAg positive and negative patients. More patients (27%) than controls (2%) had HBeAg loss by end of the follow-up ($P=0.003$). Among HBeAg negative subjects, more patients (5/7; 71%) than controls (2/28; 7%) had s.ALT elevation ($P<0.001$). None of the clinical event had resulted in hepatic decompensation clinically. **Conclusion:** Pregnancy is associated with s. ALT elevation, and increased HBeAg loss compared to age-matched female controls, in patients with CHBVI during the peri-partum period.

APASL Bali/Poster/Abstract/365
Acute exacerbation of chronic hepatitis B (AECHB) post-hepatic resection for hepatocellular carcinoma (HCC)
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Liver resection for HCC often involves patients with chronic hepatitis B virus infection. To better understand the incidence, outcomes and risk factors of AECHB post hepatic resection, a retrospective review of consecutive HepBsAg-positive patients who underwent liver resection ($n=77$) for hepatocellular carcinoma in our centre between January 2002 to December 2004, was carried out. The following data were systematically collected: (i) baseline demographic, biochemical, virological and surgical characteristics, (ii) incidence of postoperative hepatitis (i.e. ALT $>2\times$ baseline or ALT >200 IU/l between 2 and 24 weeks post-resection) and HBV flares (i.e. postoperative hepa-

titis associated with detectable HBV DNA), (iii) mortality and tumour recurrence rate. All results are expressed as median unless otherwise stated. **Results:** Seventy-seven patients (87% male), aged (mean) 58.0 + 12.1 years, underwent 82 liver resections (70% segmentectomy, 30% hemi-hepatectomy). Twenty one (26%) and seven (9%) had postoperative hepatitis and HBV flares, with peak ALTs of 231.0 & 312 IU/l observed at day 85 & 84 post-resection, respectively. Hepatic decompensation was more frequent in HBV flare (88% vs 39%, $P = 0.03$). Overall mortality rate was significantly higher among those with HBV flare compared with those without postoperative hepatitis (67% vs 21%, $P = 0.03$). Neither postoperative hepatitis nor HBV flare resulted in higher HCC recurrence. Preoperative ALT >100 IU/l was the only risk factor for postoperative hepatitis but not for HBV flare. **Conclusion:** HBV flare, or AECHB, occurred in 9% of HBsAg-positve patients who underwent liver resection and was associated poorer outcome.

APASL Bali/Poster/Abstract/366

Hepatitis B vaccine with a novel adjuvant, immunostimulatory phosphorothioate oligonucleotide (1018 ISS), achieves protective antibody levels more quickly in 40–70-year-old subjects

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Worldwide use of hepatitis B (HB) vaccine has dramatically decreased cirrhosis and hepatocellular carcinoma due to persistent HB virus infection. However, difficult-to- immunize populations, including older persons, patients with diabetes, renal failure, HCV and HIV infection, do not rapidly or completely develop seroprotective antibody levels when given currently available vaccines. A new oligonucleotide adjuvant, 1018 ISS, which mimics microbial DNA patterns recognized as foreign by the host has shown promise of improving HB vaccine response in younger individuals. Unmethylated CpG motifs signal through a Toll-like receptor 9, evoking an innate immune response and training the adaptive immune response toward a Th1 path. In this Phase 2 study, 88 healthy, seronegative subjects aged 40–70 were randomized to receive recombinant HB surface antigen (rHBsAg) + 1018 ISS (0, 2, 6 months) or Engerix-B®, a licensed HB vaccine with an equivalent dose of rHBsAg (0, 1, 6 months). Anti-HbsAg antibody concentrations were assessed 4 weeks after the second immunization. By intent-to-treat analysis, 91% of the rHBsAg/1018ISS recipients had a protective antibody response ($\geq$ 10 mIU/ml anti-HBsAg) compared with 38% of the Engerix-B® treated subjects. Median concentrations of anti-HBsAg antibodies four weeks after the second immunization were 539 mIU/ml for the rHBsAg/1018 ISS group and 1.5 mIU/ml for the Engerix-B® group. In conclusion, higher antibody levels and greater seroprotection were achieved after two injections of rHBsAg + 1018 ISS than of Engerix-B® in the 40–70-year-old population. More than 90% of individuals immunized with the experimental vaccine were protected after the second immunization.

APASL Bali/Poster/Abstract/367

The clinical and histopathology features differences between NSAID-induced gastropathy patient with positive CLO test and NSAID-induced gastropathy patient with negative CLO test

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Background: Nowadays NSAIDs are widely used and often caused side effects, like dyspepsia, peptic ulcers, bleeding/perforation, and malignancy of the stomach. *Helicobacter pylori*-infected gastric mucosa or duodenum, especially with previous NSAIDs-induced mucosal injury, were found in almost 100% of chronic gastritis and peptic ulcers, and caused further mucosal damages. *H. pylori* produces urease enzyme that converts urea into ammonia, which makes the microorganism could live in the gastric acidity. *H. pylori* infection can be detected by serologic test, Urea Breath Test, *H. pylori* stool antigen test, macroscopic endoscopy, Rapid Urea Test, histopathology, and culture from biopsy specimen. **Objective:** To determine whether there are differences in the clinical and histopathology features of NSAIDs-induced gastropathy patient with and without *H. pylori* infection. **Methods:** This descriptive analytic study with *cross sectional* approach was held in Dr. Saiful Anwar General Hospital Malang. The samples were collected *consecutively* during 6 months (November 2003–April 2004) at Rheumatology and Gastroenterohepatology outpatient department, and inpatient of Internal Medicine Department of Dr. Saiful Anwar General Hospital Malang. **Results:** There were 39 patients with chronic dyspepsia who fulfilled the criteria, ages with ranging from 21 to 78 years old, among whom there were 20 male (46.69 $\pm$ 18.10 years) and 19 female patients (47.91 $\pm$ 14.74 years). From CLO test, there were 16 cases with CLO (+) and 23 cases CLO (–). Gastroscopy revealed 39 cases, as 25 cases of erosive gastritis without gastric ulcer consisted of six cases CLO positive (three male, three female) and 19 cases CLO negative (11 male, eight female); and 14 cases of erosive gastritis with anthral gastric ulcer consisted of nine cases CLO positive (four male and five female) and 5 cases CLO negative (two male and three female). From 16 cases with CLO (+), nine cases female and 7 cases male, with clinical symptoms gradation as four mild, three moderate, and nine severe cases, while the gastric mucosal damages showed one case grade I, two cases grade II, seven cases grade III, and six cases grade IV. From 23 cases with CLO (–), 13 cases were males and 10 cases females, with clinical symptoms gradation as 2 mild, 9 moderate, and 12 severe cases, while the gastric mucosal damages showed 7 cases grade I, 11 cases grade II, five cases grade III, without grade IV cases. **Conclusion:** This study showed that the gastric mucosal damages and the gastric ulcers in NSAIDs-induced gastropathy patients with positive CLO test were more severe than that in NSAIDs-induced gastropathy patients with negative CLO test; while the clinical symptoms were not significantly different.

APASL Bali/Poster/Abstract/368

EEG pattern in chronic liver disease patients in Saiful Anwar General Hospital Malang

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Background and Objective: There was high incidence > 50% subclinical hepatic encephalopathy (SHE) in Western countries, according to Reitan Trailmakery test (Zeegen et al. 1970). But this incidence is not well known in Indonesia. Many tools and methods are available for SHE, e.g EEG examination. Early screening and treatment of SHE will be useful in preventing Hepatic Encephalopathy in the coming days. **Methods:** Descriptive study, data obtainied from outpatients and inpatients with chronic liver diseases without any disturbance of consciousness, from January–March 2005. Chronic Liver diseases are confirmed by history taking, laboratory test and USG. EEG is performed by Neurofox (EEG 9200 J/K) and read by a neurologist. The abnormality of EEG if the wave was less

than 8 cps (Hz). **Result:** Sixteen patients (61.5%) were diagnosed with SHE of 26 patients in study. Ten patients (38.46%) mild diffuse of hepatic encephalopathy with EEG result of general intermittent slow acting (frequency 5–8 Hz) and 6 patients (23.07%) moderately diffuse of hepatic encephalopathy with EEG result of general intermittent slow acting (frequency 3–5 Hz). EEG pattern patients with Hepatic Encephalopathy were treated by lactulose. **Conclusion:** SHE incidence in RSSA within 3 months of study with EEG examination in Chronic Liver Diseases Patients is 61.5%. From the preliminary study was methods that event though there are no sign/symptom of HE but by EEG SHE could be detected early.

APASL Bali/Poster/Abstract/370

Prospective evaluation of hepatic small nodules: radiographic findings and probability of hepatocellular carcinoma

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Introduction: Owing to recent progress in imaging techniques, many small nodules are detected in advanced liver diseases, including in cirrhosis. But such small nodules are difficult to distinguish from macrogenerative nodules or other mimicking lesions. We aimed to determine whether such small nodules are truly hepatocellular carcinoma (HCC) or not. **Patients and methods:** From August 2001 to November 2002, Dynamic-enhanced CT (CT) and the combination of CT during arterial portography and CT hepatic arteriography (CTAP/HA) were performed on 387 consecutive patients suspected of having HCC. Among them, we enrolled 23 consecutive patients having small hepatic nodules less than 2 cm detected by CT or CTAP/HA but not depicted as typical hepatocellular carcinoma by ultrasonography. The 23 patients had a total of 41 such nodules. All the patients underwent clinical, biochemical, and ultrasonographic evaluation periodically. **Results:** The mean follow up was 12 ± 5 months (range, 4–20 months). Of the 41 nodules, neoplastic transformation occurred in eight nodules (19.5%) after 12 months (range, 4–20 months). Edmondson I-II HCC was confirmed histopathologically by percutaneous needle biopsy. We compared parameters of transformed and non-transformed nodules. Baseline size of the nodules was not related to the transformation. Hypervascularity on CT was significant. **Conclusions:** Some hepatic small nodules less than 2 cm were transformed to overt HCC. Hypervascularity of the nodules should be recognized to be a high risk for transformation to HCC.

Asia Hep

APASL/Abstract/Asia Hep 1

Benefits and hazards of long-term lamivudine therapy

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The ideal goall of CHB therapy is to eradicate HBV infection and, in doing so, arrest or even revert necroinflammation and fibrosis and restore normal healthy life. Lamivudine is the first available nucleoside analogue shown to bring therapy nearer to this goal. However, eradication of HBV under long-term lamivudine therapy is not achieved in majority of CHB patients who harbor high viral load with serum HBV DNA level around 8–12 $\log_{10}$ copies/ml. Among Asian CHB patients, persistent viral suppression may be maintainable in a proportion of the patients, but HBsAg seroconversion is rare. So is there any benefit in maintaining CHB patients on long-term lamivudine therapy? What are the hazards during long-term lamivudine therapy?

To answer the first question, there are benefits certain patients can derive from maintenance of long-term lamivudine therapy. Data from clinical trials and experience in clinical setting showed a proportion of patients remaining HBV DNA negative as measured by sensitive real time PCR assays. Serum ALT is normalized and remains in low level. Liver histology showed significant improvement not only in necroinflammatory grade, but also reversion in fibrosis stage. Patients with cirrhosis have occasionally been reported to have histologic reversion of cirrhosis. The benefit of 3 years of therapy with lamivudine among patients with advanced fibrosis and cirrhosis has demonstrated significant reduction in disease progression and has prevented the development of hepatocellular carcinoma when viral suppression was maintained. Patients with acute exacerbation have also been shown to have reduced mortality when rescued with long-term lamivudine therapy. Post liver transplant CHB patients also derived benefits.

The answer to the second question regarding hazards in long-term lamivudine therapy mainly centered on the continued emergence of lamivudine resistant mutants that result in viral breakthrough and relapse of hepatitis. Hepatic flare developed in a significant proportion of these patients and a percentage suffered from fatal decompensation. The risk of transmission of this mutated HBV species and the global spread of HBV with resistance to lamivudine that exhibit cross resistance to other nucleoside analogues is a real threat to the overall control and prevention of HBV infection and related liver diseases.

In order to maximize the benefit and minimize the risk of long-term lamivudine therapy, patient selection for therapy need to be carefully scrutinized and considered. Patients with mild liver disease and high viral load are unlikely to responsed well and stand a high risk of developing resistance. Careful monitoring of patients undergoing therapy, including serum HBV DNA measurement at regular intervals, will detect early emergence of resistance and timely rescue therapy with adefovir or enticavir.

APASL/Abstract/Asia Hep 2

Current status of adefovir in the treatment of chronic hepatitis B

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Adefovir dipivoxil has been a welcome addition to the armamentarium of medications for the treatment of chronic hepatitis B (CHB) since its availability in 2002. Treatment for 36 months resulted in higher HBeAg seroconversion in HBeAg positive CHB patients taking adefovir (43%) than in those taking lamivudine (33%). Drug resistance was observed in 3.1% of 309 with HBeAg positive CHB patients treated for 144 weeks with continued inhibition of viral replication and normalization of liver enzymes. Significant and continued reductions of HBVDNA levels were also documented in HBeAg negative individuals treated for 144 weeks, HBV DNA became undetected in 71% patients at 96 weeks and 79% at 144 weeks. The on-therapy response for patients on lamivudine for 36 months was 40–50%. This difference can be attributed to the low frequency of drug resistant variants in patients on adefovir

(5.6%) at three years compared with 55% of patients taking lamivudine for 3 years. The cumulative probability for developing adefovir resistance by week 192 was calculated to be 15%. This compares favorably to the incidence of 67% of patients on lamivudine for the same period of time. Adefovir is mainly used for rescue therapy in patients who developed lamivudine resistance. Normalisation of liver enzymes was achieved in 31 to 53% patients with lamivudine resistance after one year of combination therapy using lamivudine and adefovir. A recent study showed that adefovir plus lamivudine suppressed HBVDNA better than adefovir alone in HBeAg negative CHB patients. No major side effects of adefovir therapy have been reported to date and the initial concern on renal toxicity appeared to be unfounded with the 10 mg dose.

AsiaHep 3

Pegylated interferon for chronic hepatitis B

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Conventional interferon alpha (IFN-α) has been used for the treatment of chronic hepatitis B (CHB) for more than 20 years, with the antiviral and immunomodulatory mechanism. Pegylated interferon alpha (PegIFN-α) is now approved for the treatment of CHB. The use of conventional IFN-α in the dose of 5 MIU daily or 5–10 MIU three times weekly for 4–6 months can achieve HBeAg loss in approximately 33% comparing with 12% of control. In a phase II Asian study, a 24-week course of PegIFN-α 2a (40 KD) give a e-seroconversion rate of 33% (assessed 24 weeks after cessation of the treatment) compared with conventional IFN-α 2a (25%, $P > 0.05$). In the phase III study, PegIFN-α 2a (40 KD) monotherapy 180 μg once weekly for 48 weeks can achieved HBeAg seroconversion in 32% and HBsAg seroclearance in 3% when assessed 6 months after end of therapy. The sustained HBeAg seroconversion rate is quite similar to that after 6 months therapy even though there is no head to head comparison between the 6 and 12 months therapy. A 52-week course of the other PegIFN-α 2b (12 KD) trial (100 μg once weekly for 32 week followed by 50 μg weekly for 20 weeks) was well tolerate and gave a 6 month e-seroconversion in 29% of patients. Conventional IFN-α can achieved biological and virological response in up to 90% on the patients treatment but sustained response is low to 10–15% with 4–6 months of treatment, 22% with 12 months of treatment and 30% with 24 months of treatment. Twelve months of PegIFN-α 2a (180 μg) monotherapy in 564 HBeAg negative and HBeAb positive CHB patients showed HBV-DNA level less than 20,000 copies/ml in 43% and HBV-DNA less than 400 copies/ml in 19% with HBsAg loss in 3% when assessed 6 months after end of the therapy. However when assessed at the 48 weeks after the end of therapy, the HBV-DNA less than 20,000 copies/ml is 42%, HBV-DNA less than 400 copies/ml is 17% with about 30–50% dropped out rate. **Conclusion:** Even pharmacological industrial trying to persuade using of PegIFN-α in CHB patients, new PegIFN-α cannot achieve dramatically response in patients with CHB but higher cost of the treatment. Fortunately, the toxicity is the same with more convenience once a week administration.

APASL/Abstract/Asia Hep 4

Hepatitis B antiviral drug resistance–problems and prevention

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For the management of hepatitis B virus (HBV) infection, in addition to interferon treatment a large number of nucleotide and nucleoside analogues are available, though currently, and Lamivudine, Adefovir, Entecavir are licensed. Other drugs like Tenofovir, Emtricitabine, Telbivudine, Claudine and many others are in clinical trials.[1] Although all these drugs have potent antiviral activity, successful cure of infection at the end of 1 year of therapy does not go beyond 20%.[1] As we have learned from Lamivudine treatment long-term use beyond 1 year may improve success rate of cure of HBV infection; but this is frequently associated with the development of resistance mutation that affects YMDD motif of HBV polymerase gene.[2] The mutation occurs at the rate of 20% at the end of 1 year which increases beyond 60% at the end of 4 years.[3] Appearance of resistance can result in return to pretherapy viral replication levels, and most importantly, ongoing disease progression in both hepatitis B e antigen (HbeAg)-positive and HbeAg-negative patients.[4]

The molecular target for currently available antiviral drugs like Lamivudine and Adefovir is the HBV polymerase/reverse transcriptase (POL/RT).[5] POL/RT can be divided into seven functional subdomains A–G. Mutations in the region of A–D has been described with various antiviral drugs. Common YMDD mutation to Lamivudine resistance resides in the domain C (M204V/I/S). An other mutation that co-exists with M204V/I have been found predominantly in the B domain and also in the A domain. Two mutations with Adefovir resistance have been described, one in the B domain and the other in the D domain.[6]

For determining the antiviral treatment efficacy, the following definitions are used [7] (1) antiviral treatment effect is defined as a sustained ≥ 1 $\log_{10}$ IU/ml reduction of HBV DNA from baseline levels during therapy and within 3 months of starting therapy. A decreased of ≥ 1 $\log_{10}$ IU/ml can be used to assess the early virological response. (2) Primary antiviral treatment failure is defined as failure of a drug, initially reduced HBVDNA level by ≥ 1 $\log_{10}$ IU/ml within 3 months. (3) Secondary antiviral treatment failure is defined by rebound of HBV replication of ≥ 1 $\log_{10}$ IU/ml in patients with an initial antiviral treatment effect who continued to take the drug, as confirmed by two consecutive laboratory assessment at a 1-month interval. HBV resistance can be defined as (1) primary or secondary antiviral treatment failure (as defined previously) resulting in increase in serum ALT level and development of symptoms after elimination of non- HBV related causes, (2) genotypic assay of known mutant and (3) phenotypic assay.

Clinical consequences of resistance can be (1) decreased rate of HBeAg seroconversion, (2) reversal of histological improvement, (3) increased rate of disease progression, (4) severe exacerbation in patients with cirrhosis, (5) risk of graft loss and death in liver transplant patient, (6) transmission of drug resistant strains and (7) HBsAg mutations leading to vaccine failure.[8]

Now, there are several options to monitor HBV drug resistance.[9] They can be divided into (A) genotypic assays e.g.: (1) direct DNA sequences, (2) clonal analysis, (3) RFLP, (4) DNA hybridization, and (5) Microchip based assays; (B) Indirect methods like (1) determination of ALT and (2) quantification of HBV DNA; (C) Phenotypic methods. As drug resistance is a serious clinical problem, predicting drug resistance and monitoring for drug resistance becomes mandatory. It has been suggested that antiviral drug-resistant HBV mutants emerge as a function of at least six factors: (1) viral mutation frequency, (2) intrinsic mutability of antiviral target site, (3) selection pressures exerted by drugs, (4) magnitude and rate of viral replication, (5) overall replication fitness of mutant, and (6) availability of replication space (as determined by the number of uninfected hepatocytes available). HBV is highly mutagenic, and there are enough nucleotide substitutions occurring daily to allow for a broad range of quasi-species. Predictors of resistance

to Lamivudine therapy are high baseline HBV DNA, elevated serum ALT, serum HBV DNA $> 10^2$–10^3 IU/ml after 6 months therapy, duration of Lamivudine therapy, high body weight and BMI and male sex[10]. In a recently published study, HBe status, HBV DNA, ALT levels and treatment duration were shown to be major determinant's of YMDD mutation.[11] As development of resistance is clinically detrimental, monitoring the patients on antiviral treatment is recommended. Drug resistance monitoring is done by assessment of HBV DNA and ALT at baseline and 3 months after the therapy in all patients. Subsequently, in patients with mild liver diseases assessment is to be repeated for every 6 months for the first 2 years and every 3 months thereafter and at any change of therapy. In patients with advanced liver disease or cirrhosis, three monthly assessments along with clinical evaluations are recommended.[7] Preventing resistance is the best policy. With currently available nucleotide analogues, there is a modest first phase decline in viral DNA followed by a prolonged second phase of viral clearance. And hence, there is adequate time for drug resistant mutants to emerge when monotherapy is used.[1] Combination therapy can be used to decrease the risk of drug resistance with monotherapy. To prevent resistance in (1) compensated liver disease if HBV DNA increases by $\geq 1 \log_{10}$ IU/ml on Lamivudine addition or switching to Adefovir is recommended. Adefovir is preferred for long-term therapy (2) cirrhosis and liver transplantation. Adefovir is preferred because of a less resistance rate, or combination of Adefovir and Lamivudine is used as there is less likelihood of resistance to either drug. For management of drug resistance (1) in compensated liver disease a second drug is added to continued therapy with first drug, or switching to a second drug with 1–2 month over-lap is recommended. Stopping the therapy may be considered if it appears that the original therapy would not have been started, e.g. patients with mild disease. (2) In cirrhosis, HIV/HBV co-infection and liver transplantation, a second drug is added with the continued use of the first drug. The second drug should be without cross-resistance to the first drug and should be started early, preferably before ALT flare.[7]

Results of the randomized-controlled trial can prove the efficacy of the drug; to know the effectiveness of the drug in real life, one needs to analyse the outcome of research. We analysed real-life data on our patients receiving long-term Lamivudine treatment, and development of Lamivudine resistance is the clinical impact and outcome after adding Adefovir in patients who developed Lamuvidine resistance. Our study included 82 patients (males 66, age range 5–85 years). Of the 82 patients, 50 patients were HBeAg positive (chronic hepatitis 35, compensated cirrhosis 7, decompensated cirrhosis 8). These patients received a mean duration of Lamivudine treatment of 32.44 months. Seventeen out of 50 (34%) developed resistance to Lamivudine, 32 patients were HBeAg negative (chronic hepatitis 14, compensated cirrhosis 9, decompensated cirrhosis 9), mean duration of treatment with Lamivudine was 28 months. Eight out of 32 (25%) developed Lamuvidine resistance. Total of 25 out of 82 patients (30.48%) developed Lamivudine resistance. The presentation of Lamivudine resistance was clinical decompensation 3, sero-reversion 7, flare of liver enzymes 8, and increased viral load 5. All the patients who developed resistance were treated with Adefovir in addition to Lamivudine. Mean period of follow up was 8.5 months; two patients died because of to decompensation, the remaining patients are stable with normalized liver function.

APASL/Abstract/AsiaHep 5
New drugs in the pipeline: will promises be fulfilled?
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Over the last 10 years, the management of chronic hepatitis B has evolved with better understanding of the virus, changing disease patterns, new molecular testing techniques like HBV genotyping and development of novel nucleoside/nucleotide analogues. Several host and virological factors are associated with poor response rates to current therapies. Some of these include insufficient or incompetent host immune responses, persistence of HBV covalently closed circular (ccc) DNA and hepatitis B surface antigen in the blood. Trials have been primarily with monotherapy using interferon alpha or nucleoside/nucleotide therapy. Combination therapy of an immune based therapy with an antiviral agent has shown no added benefit. This review will focus on some new drugs in the 'pipeline', with early efficacy and trial data on these agents.

APASL/Abstract/AsiaHep 7
Management of hepatitis B with normal ALT
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ALT measurement is important in the management of Hepatitis B. It is an assessment of liver disease and determines the need for therapy and response to therapy. Pre-treatment ALT level is helpful but a normal ALT level does not always correlate with the extent of liver injury. The normal ALT should be interpreted with specific reference range in the report. Persistently normal ALT is considered predictive of histological quiescence and milder inflammation on liver biopsy. Treatment is not warranted in this group as the response to antiviral treatment is poor. In patients with minimally elevated ALT, treatment not recommended unless liver biopsy shows moderate to severe necro-inflammation. In gray areas whereby ALT level alone is unable to determine the decision for treatment liver biopsy should be considered.

How I do it

APASL/Abstract/How I do it 1
What you should not do in laparoscopic cholecystectomy
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The lecture starts off with a video recording showing laparoscopic cholecystecomy. The operation apparently went on smoothly but suddenly the common bile duct was transected and the right hepatic artery was also divided. Why did these injuries happen? The second part of the lecture is a power point presentation emphasizing on the proper techniques in laparoscopic cholecystectomy.

- Technique of dissection
  - – Stay close to gallbladder;
  - – Conclusive identification of cystic duct structures:- critical view of safety as advocated by Strasberg et al.
- Retraction of gallbladder

– Proper retraction should be with one grasper on the fundus retracting the gallbladder superiorly and one grasper on Hartmann's porch retracting it laterally. Wrong direction of gallbladder retraction can lead to the CBD being mistaken as the cystic duct.

- Use of diathermy: Injudicious use is hazardous

  - – Prolonged application of energy can led to direct injury to the CBD or indirect by damaging its blood supply;
  - – Insulation defects in instruments lead to thermal injury;
  - – Capacitative coupling leading to discharge of current to adjacent tissues;
  - – Arcing;
  - – Residual heat.

- Operative cholangiogram

  - – It is controversial as whether it is able to decrease the incidence of bile duct injuries. The advantages are early recognition and limit the damage.

The lecture ends by showing the video recording once again but stopping at points where mistakes were made that led to the injuries.

APASL/Abstract/How I do it 2
An aggressive hepatic resection for advanced intrahepatic cholagiocarcinoma after pre-operative PTBD and portal vein embolization
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The development of surgical technique and preoperative management including PTBD and PTPE has made it possible to apply aggressive surgical approaches for intrahepaic cholangiocarcinoma, improving the resectability rate. (Case) A 59 year-old woman was admitted due to abdominal discomfort and jaundice. Laboratory studies revealed that total bilirubin 5.4 mg/dL, albumin 3.4 g/dL and prothrombin time 10.9 second. In addition, the retention of indocyanine green at 15 min was 2.8%. CEA was 2.8 ng/mL and CA19–9 was 3,032 U/mL. Preoperative imaging study revealed malignant appearing huge mass located left medial section and causing both side intrahepatic duct dilatation. The celiac angiography showed encasement of right main portal vein and hepatic artery. We performed PTBD through the both dilated IHD and preoperative portal vein embolization(PVE) for hypertrophy of the future remnant liver (FRL). Two weeks after PVE, preoperative volumetry showed hypertrophy of the FRL accounts for 25% of the whole liver. At operation, there were encasement of right portal vein and hepatic artery and hardness of confluence of common hepatic duct. We performed extended right trisectionectomy (including segment 1, 4, 5, 6, 7, and 8), portal vein segmental resection and end to end anastomosis, bile duct resection with Roux-en Y left hepaticojejunostomy and dissection of lymph nodes. The pathologic diagnosis was intrhepatic cholangiocarcinoma with 7 cm sized tumor, invasion of portal vein and hepatic duct, and involvement of regional lymph nodes. There was no evidence of recurrence 5 months after operation.

APASL/Abstract/How I do It 3
Laparoscopic common bile duct exploration
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In the era of minimal invasive surgery, the management of cholecystolithiasis and choledocholithiasis (CBD stone) must involve not only the techniques themselves but also patient safety, efficiency and cost effectiveness.

Three major options for management of cholelithiasis with CBD stone are (1) open cholecystectomy+CBD exploration, (2) endoscopic sphincterotomy and stone extraction+laparoscopic cholecystectomy (two Stages), and (3) laparoscopic cholecystectomy+laparoscopic CBD exploration (one Stage).

Techniques of laparoscopic CBD exploration: (1) transcystic approach (transystic laparoscopic CBD exploration), (2) anterior choledochotomy (transcholedochal laparoscopic CBD exploration).

Laparo scopic common bile duct exploration (LCBDE) will become an important alternative in treatment of CBD Stone in the near future, especially in case of failure of ERCP/endoscopic stone extraction. LCBDE as a minimally invasive procedure has the advantages of high success rate, low morbidity and mortality rate and faster postoperative period recovery. LCBDE need more proper training and longer learning curve.

Breakfast Session

APASL/Abstract/BS I.1
Mechanism of coagulopathy in liver disease
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Hepatic disease, particularly advanced hepatic disease is characterized by a severe coagulopathy after confounded by a prominent fibrinolytic process and the laboratory manifestations of a disseminated intravascular coagulation (1–2). The coexistence of these combined abnormalities of blood clotting and dissolution create considerable problems for the physicians caring for, evaluating and treating patients with advanced liver disease. The phenomenon of blood clotting and dissolution in individuals with liver disease is only understandable if one is knowledgeable about the processes of coagulation and fibrinolysis as they occur in normal individuals. Liver failure is characterized by multiple alterations in the hemostatic system that can range from a clinical problem consisting of a bleeding disorder to a thrombotic disorder as a consequence of advanced liver disease, therapeutic interventions, and/or the development of new complications (varix rupture, spontaneous bacterial peritonitis, endotoxemia and others). The thrombocytopenia occurring in advanced liver disease has a multifactorial origin (5–7). This consists of a combination of reduced synthesis of TPO, the megakaryocyte growth factor produced exclusively by the liver, increased splenic sequestration as a consequence of portal hypertension and the resultant splenomegaly; a reduced half life of platelets as a result of splenic sequestration and in certain liver diseases having an autoimmune pathogenic mechanism; reduced platelet production as a result of folic acid deficiency which is common in liver disease especially alcoholic liver disease and those requiring continuous diuretic therapy; reduced platelet production as a direct consequence of exposure to a toxin or drug such as ethanol, various H2 antagonists, proton pump inhibitors and antibiotics used to treat hepatic encephalopathy and prevent spontaneous bacterial peritonitis and other infections common to debilitated individuals with advanced liver disease and finally a low grade DIC process that is a remarkably common occurrence in individuals with cirrhosis. An additional abnormality seen in cirrhotics is hypofibrinogenemia occurring as a result of reduced hepatic synthesis as fibrinogen is synthesized solely in the liver. Reduced fibrinogen levels are common in very advanced chronic liver disease and in

cases of acute hepatic failure. A third situation in which fibrinogen levels may become critical is in the presence of decompensated DIC. In this later case, it is not reduced fibrinogen synthesis but rather increased fibrinogen consumption that is responsible for the reduced fibrinogen level. Dysfibrinogenemia occurs also in individuals with cirrhosis and is a consequence of excessive sialic acid residues on the fibrinogen molecule as a result of an abnormal processing of the fibrinogen molecule prior to hepatic secretion possibly as a result of intrahepatocyte enhanced glucosyltransferase activity. The DIC syndrome can occur in both a compensated and decompensated state. In the former, markers of DIC such as d-dimers and fibrin split products are increased in the plasma but the majority of the plasma coagulation factors remain in the normal range or just outside and below the normal range. Moreover, the platelet count is usually normal but can be reduced in very far-advanced cirrhotic liver disease. In contrast, in decompensated DIC, the platelet count is always reduced. Both the PT and aPTT are abnormal (prolonged) as is the thrombin time. The plasma levels of factors II, V and VII are reduced and plasma levels of fibrin split products and d-dimers are increased markedly. The balance of the coagulation and fibrinolytic systems in individuals with advanced liver disease is frequently abnormal. These abnormalities vary as a function of disease severity, type of liver disease and the presence or absence of the more common complications of advanced liver disease such as bleeding, infection, encephalopathy and endotoxemia.The recognition of these abnormalities and their correction are essential for a normalization of the balance between hemostasis and bleeding.

APASL/Abstract/BS I.3
Hypercoagulation in NASH and metabolic syndrome
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The metabolic syndrome is characterized by a combination of obesity, chronic inflammation and insulin resistance (1, 2). Nonalcoholic steatohepatitis (NASH) is a liver disease characterized by steatosis, periportal and lobular inflammation. It is considered to be the liver component in the metabolic syndrome (3–6). An association of NASH with hyperinsulinemia as well as with the clinical features of insulin resistance has been frequently reported (3, 7–8). Patients with both clinical and histological diagnosis of NASH develop metabolic problems only a few years from diagnosis (9). This metabolic syndrome also has features of a hypercoagulable state, consisting of increased levels of clotting factors (tissue factor, factor VII and fibrinogen) (10–12) as well as inhibition of the fibrinolytic pathway (increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator activity) (13–15). Simultaneously, the presence of endothelial dysfunction and dyslipidemia triggers platelet aggregability, thus further increasing the risk of thrombotic events both in the arterial and venous system (16, 17). Although mechanisms of coagulation activation are well described for other diseases, the precise etiology is not well known in metabolic syndrome and NASH. So far, only obesity has been shown to be a modest risk factor for venous thromboembolic events whereas accurate data for metabolic syndrome and NASH patients are lacking. Hence, routine interventions for prevention of venous thromboembolism are not yet warranted. However, as dyslipidemia is associated with procoagulant change, this could be a possible target for therapeutic intervention. In view of the rising incidence of metabolic syndrome even at a young age, both the incidence of venous thromboembolism and the effect of intervention markers of hypercoagulability in metabolic syndrome and NASH need further studies.

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APASL/Abstract/BS II.2
Managing sepsis in liver disease
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Bacterial infections are present or develop in a third of cirrhotics admitted to a hospital. In half of the patients admitted with variceal haemorrhage, bacterial infection is associated, and contributes adversely towards morbidity and mortality. The most commonly encountered infection (25%) in cirrhotics is spontaneous bacterial peritonitis (SBP) followed in frequency by urinary tract infection (20%), pneumonia (15%), and bacteremia (12%). Gram-negative bacteremia predominate in SBP and UTI while Gram-positive bacteria predominate in pneumonia and bacteremias associated with invasive procedures. The appropriate and prompt use of antibiotics is the key to successful management. Early recognition and prompt treatment of SBP has reduced its mortality from 90% to 30%. Regarding the choice of antibiotics for patients who develop SBP, and are not on chronic quinolone prophylaxis, patients have shown a very good response with cefotaxime; equally good results are seen with ceftriaxone. Ciprofloxacin and ofloxacin have shown good results as well. Patients who develop SBP and have been on quinolone prophylaxis usually have *E. Coli* infection resistant to quinolone; they seem to be equally well treated by cefotaxime. However, if gram-positive organisms are detected, especially MRSA, then addition of Vancomycin should be considered. In case of community acquired pneumonia, the newer quinolones like levofloxacin, moxifloxacin and gatifloxacin have shown good results in cirrhotic patients. Equally effective however in such circumstances are cefotaxime and ceftriaxone. It is recommended that after starting empirical therapy with the above, necessary modifications be made according to culture and sensitivity results. Aminoglycosides, though effective, have a high propensity of causing renal disease or developing during the course of treatment, do very well with intravenous albumin transfusions in the range of 1.0 to 1.5 g/kg body weight. Lastly, good nursing care, prevention of bedsores, prevention of infection introduced via IV lines catheters go long way overall control of bacterial sepsis in cirrhotic patients.

APASL/Abstract/BS IV.1
Abnormality of energy metabolism in the skeletal muscle of patients with liver cirrhosis and change under administration of glucose and branched-chain amino acid
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Changes in energy metabolism in the skeletal muscle under exercise loading in healthy volunteers and patients with liver cirrhosis were assessed based on the measurement of creatine phosphate (PCr), inorganic phosphorus (Pi) and changes in intracellular pH associated with the production of lactic acid using 31P-magnetic resonance spectroscopy (31P-MRS). Concurrently, the oxygenation kinetics of intramuscular hemoglobin/myoglobin were determined using near-infrared spectroscopy (NIR) to examine the condition of the oxygen supply to the muscle under the influence of blood flow in order to assess the cause of abnormality of muscular energy metabolism. Furthermore, causes of intracellular metabolic impairment were assessed, based on the changes in the parameters under the administration of glucose and branched-chain amino acid (BCAA).

As a result, patients with liver cirrhosis had a reduction in intracellular pH and PCr index (PCr/PCr+Pi) by a markedly increased variation (ΔpH, ΔPCr index) ($P<0.05$), and aerobic metabolic impairment in the skeletal muscle after exercise loading under fasting, compared with healthy volunteers. The tissue oxygen level, concurrently determined using NIR, substantiated the absence of difference in the oxygen supply to the muscle. The findings indicate declined efficacy of oxygen use by the muscle, or in other words, ineffective operation of the TCA cycle in the patients with liver cirrhosis. Under the condition, glucose-only administration resulted in the insufficient production of ATP from the TCA cycle, which increases the percentage of anaerobic metabolism and the production of lactic acid, and ineffectively reduces ΔpH. Meanwhile, it is suggested that the co-administration of BCAA, which directly acts on the TCA cycle, markedly reduces ΔpH compared with the preloading level ($P<0.05$) and alleviates the abnormality of energy metabolism in the skeletal muscle. Based on these findings, it is suggested that the co-administration of BCAA rather than glucose-only administration is the key to alleviate abnormality of the energy metabolism, particularly aerobic metabolic abnormality, in patients with liver cirrhosis.

APASL/Abstract/BS V.2
Thymosin alpha 1 in chronic hepatitis B infection
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Thymosin alpha 1(Tα1) is a synthetically produced 28-amino acid polypeptide similar to a molecule found in bovine thymus extract. This polypeptide molecule increases T cell production and maturation, stimulates production of Th 1 cytokines like interferon gamma and interleukin-2, and activates natural killer cell-mediated cytotoxic activity. Several randomized controlled studies using Tα1 monotherapy showed that a six month treatment with this agent (1.6 mg twice weekly) resulted in significantly higher sustained response rate than untreated controls. A recent study from Japan involving 316 patients with chronic hepatitis B infection and comparing 0.8 mg Tα1 twice weekly with 1.6 mg twice weekly showed no difference in efficacy between these two doses except in patients with advanced fibrosis when the 1.6 mg twice weekly dose fare better. The effect of Tα1 therapy is usually not immediately apparent during therapy, unlike those of interferon or the oral anti-viral agents. Complete virological response usually occurs up to 12 months after the end of therapy. The drug is extremely safe with virtually no clinical side effects. No incidence of liver toxicity has been reported to date. Two small open labelled studies using Tα1 and interferon combination showed promising results. Tα1 –interferon combination was also found to be more effective than interferon monotherapy in the treatment of chronic hepatitis B. Thymosin α1 and famcyclovir combination significantly reduced median HBVDNA levels in immune tolerant patients with normal ALTs when compared to famcyclovir monotherapy. A study using Tα1 and lamivudine in combination is ongoing.

APASL/Abstract/BS VI.1
Overview of antiviral resistance in chronic hepatitis B: An update
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The recent development of safe and effective nucleotide and nucleoside analogues has been an important advance in the treatment of chronic hepatitis B. These drugs specifically inhibit the hepatitis B virus (HBV) polymerase and result in a substantial decease in viral load, however, their long-term use is confounded by the development of resistance. Lamivudine, adefovir dipivoxil and entecavir have been approved for clinical use and in vivo resistance to each has been reported. As demonstrated by sequence analysis, resistance is associated with nucleotide mutations which produce structurally and functionally altered polymerases. Interestingly, resistance to each respective inhibitor requires different mutations in the polymerase gene. Sequence information, together with results of in vitro assays and computer modelling, have provided some insights into the mechanism of action of each drug. To optimize treatment regimes it will be important to characterize the patterns of resistance as well as cross-resistance associated with the various HBV mutants.

APASL/Abstract/BS VI.2

Molecular diagnosis of antiviral resistance in hepatitis B

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Advances in antiviral therapy such as lamivudine have brought about an increasing need for sensitive and early detection of emerging drug-resistant mutants to monitor drug resistance as it develops and aids early intervention. The identification of such mutations is of increasing importance, especially as alternative antivirals such as adefovir and entecavir, which are effective against lamivudine-resistant HBV, have become available.

The detection of HBV variants is largely performed by sequencing analysis, RFLP and hybridization-based assays. Sequencing can give information on the majority species present in the viral populations, but generally cannot detect species comprising fewer than 15–50% of a viral population. Thus it is necessary to analyze multiple clones representing viral quasispecies for determining the heterogeneity of a population. For example, an rtM204V/rtM204I variant mixture could be incorrectly scored as rtM204V variant/wild type mixture by direct sequencing even after visual inspection. This is due to the inability of the sequencing software to determine the correct variants present in the sample when the nucleotide mixture at position 1 (R = A or G) and position 3 (K = T or G) of codon 204 are present. Assays based on RFLP and hybridization have been contributing to the understanding of the occurrence of the mutant HBV strains. However, such assays are time consuming, labor intensive, and are not suitable for a high throughput screening of large number of samples, as they require multiple DNA amplifications and enzyme digestions or complex hybridization steps. Recently we have developed a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)-based genotyping assay, termed restriction fragment mass polymorphism (RFMP), which exploits differences between wild-type and variant sequences. This assay can represent an improvement over gel-based assays because it relies upon precise information about the molecular mass of the analyte; both DNA strands can be analyzed in parallel and it can be fully automated.

For clinical application, we established a RFMP assay for detecting rtL180M and rtM204I/V variants to monitor lamivudine resistance, and also developed a RFMP assay for interrogating rtA181T/V and rtN236T mutations to characterize the genotypic and phenotypic mutation profiles to adefovir in patients who were treated with adefovir. By comparing the results from RFMP assays with those of the INNO-LiPA HBV DR line probe assay, RFLP, and sequencing, the concordance and ability to identify mixed wild type and mutant viral populations of different methods were assessed among the methods. The results showed that the RFMP technology is very useful for the detection of viral quasispecies and subtle genetic variations, due to the intrinsic sensitivity of MALDI-TOF MS. The improved sensitivity and specificity of the RPMP assays can help monitor drug resistance as it develops, enabling early intervention and prevention.

APASL/Abstract/BS VI.3

Clinical impact of early detection for YMDD mutant on the outcomes of long-term lamivudine therapy in patients with chronic hepatitis B

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In patients with HBeAg postitive CHB, HBeAg seroconversion rate increases with increasing duration of lamivudine (LMV) therapy. However, long-term monotherapy with lamivudine are often complicated by emergence of drug-resistant YMDD mutants. Viral breakthrough that is the reappearance of HBV DNA has been reported to occur usually after 6–9 months of LMV therapy. However, early emergence of LMV mutant can be detected very early during or even before lamivudine therapy. We previously reported that YMDD mutants were detected within a few weeks during LMV therapy in Korea. However, it has been unclear whether early detected YMDD mutant may affect the long-term prognosis of LMV monotherapy in patients with CHB. We investigated the impact of early detected YMDD mutation at 3 month on the outcomes of long-term LMV therapy in HBeAg positive CHB patients. We prospectively investigated the emergence of YMDD mutation by the nested PCR at 3 month of LMV therapy in patients with HBeAg positive CHB. Long-term outcome of LMV therapy was compared between the patients having the early emergence of YMDD mutation at 3 month and who didn't. YMDD mutation was detected in 58% patients at 3 month and only the type of mutation found was YIDD. Cumulative HBeAg loss rate at 1, 2, and 3 year was 7%, 14% and 14%, respectively in patients who had YIDD mutant at 3 month, and 20%, 50% and 60%, respectively in patients who had only wild type at 3 month ($p = 0.017$). Cumulative viral breakthrough rate at 1, 2 and 3 year was 43%, 71% and 71%, respectively in patients who had YIDD mutant at 3 month, and 0%, 20% and 20%, respectively in patients who had only wild type at 3 month ($p = 0.024$). **Conclusions:** Our data suggest that early detection for HBV YMDD mutation at 3 month may be useful to predict the long-term outcome of LMV therapy in patients with HBeAg positive CHB. And appropriate treatment strategy such as combination anti-viral therapy or changing antiviral agent may be needed for those patients who showed early detection of YMDD mutant.

APASL/Abstract/BS IX.1

HBV genetic diversity and its impact on diagnostic assays

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HBV circulates in blood as closely related, but genetically diverse molecules called quasispecies. During replication, HBV production may approach 10^{11} molecules/day, although during peak activity this rate may increase 100–1000 times. Ordinarily, DNA polymerases have excellent fidelity in reading DNA templates because they are associated with an exonuclease which removes incorrectly added nucleotides. However, the HBV DNA polymerase lacks fidelity and proofreading function partly because exonuclease activity is either absent or deficient. Thus, the HBV genome, and especially the envelope gene, is mutated with unusually high frequency. These mutations can affect more than one ORF because of overlapping genes. HBsAg preparations consist of three polypeptides: S, M and L. These are not distributed uniformly among the various circulating particles. The more numerous 20-nm particles (by a factor of 10^4–10^6) are composed primarily of the S protein and essentially no L chains. Conversely, the virion contains relatively large amounts of the L chains that contain the recognition site for binding to hepatocytes and are important for viral assembly and infectivity. The S gene contains an exposed major hydrophilic region (residues 110–155) which encompasses the *a* determinant that is important for inducing immunity. Nucleotide substitutions in this region are common and result in reduced binding or failure to detect HBsAg in diagnostic assays with polyclonal and/or monoclonal antibodies. Adaptive immunity also depends on the recognition of HBsAg by specific antibody, and variants pose a threat if they interfere with binding to antibody. Finally, genomic hypervariability allows HBV to escape selection pressures imposed by antiviral therapies, vaccines and the host immune system and is responsible for creating genotypes, subgenotypes and subtypes.

APASL/Abstract/BS IX.2
The role of hepatic stellate cells in hepatic fibrosis
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Hepatic fibrosis occurs in chronic liver diseases (CLD) due to various etiologies such as viral hepatitis, autoimmune hepatitis, alcoholic liver diseases, nonalcoholic fatty liver diseases and primary biliary cirrhosis, and develops according to mechanisms characteristic of the its underlying disease. The most prevalent mechanisms of hepatic fibrosis in different CLD are chronic inflammation, oxidative stress, direct cytotoxicity, hypoxia and so on. Hepatic stellate cells (HSC), which are located in the Disse spaces, are stimulated and activated by various inflammatory cytokines or soluble factors containing platelet-derived endothelial cell growth factor (PDGF), transforming growth factor (TGF)-β and endothelin (ET)-1. The activated HSC exhibit the migration, apoptosis, chemoattraction and contraction. Activated HSC can undergo transformation into proliferative and fibrogenic myofibroblast-like cells during liver injury. In addition, specific lymphocytes and Kupffer cells stimulate fibrogenesis. Hepatic fibrosis also forms a part of tissue repair, and it proceeds under condition when fibrogenesis surpasses fibrolysis. Tissue repair is the recruitment of inflammatory cells in order to remove necrotic space. In this stage of the process, HSC are recruited at the site of injury in order to synthesize and secrete extracellular matrix (ECM) components. HSC secrete several chemokines such as monocyte chemotactic protein (MCP)-1, which is the most prominent chemotactic factor, and it induces the proliferation of leukocytes and activated T cells. A cascade of signaling and transcriptional events in HSC underlies the fibrogenic response to liver injury, with each step in the cascade being a potential target for antifibrotic therapy.

APASL/Abstract/BS IX.3
Mitochondrial involvement in hepatitis
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A mitochondrion is an organelle found in the cells of most eukaryotes. Mitochondria are cellular 'power plants' because their primary function is to manufacture adenosine triphosphate (ATP), which is an essential substance for the life of a cell. Impaired function of ATP production will cause dysfunction or death of the cell. The production of ATP is achieved by the Krebs cycle, electron transport and oxidative phosphorylation. Depending on energy demands, the amounts of mitochondria vary from cells to cells. Fat storage cells, which require little energy, have very few mitochondria, but energy-demanding muscle cells tend to have many. Human liver cells have around 2000 each.

Two things certain in a cell are cellular life and death. Mitochondria are not only essential in energy generation and as key regulators for cellular survival, but also in regulating physiological cell death. One important function of mitochondria is apoptosis, or programmed cell death, which is a normal physiological process occurring in senescent or damaged cells, when specific cells need to be removed during development or during normal tissue turnover.

In liver disorders, mitochondrial involvements can be directly because of intrinsic mitochondrial defects or caused by systemic disorders that impair its function. Several disorders of different mechanisms involving mitochondria are alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune diseases, drug-induced hepatopathy, and hepatitis because of infectious agents, such as hepatitis B and hepatitis C viruses (HBV and HCV).

HBV, through the function of its proteins (HBxAg and large surface protein), induces hepatocyte apoptosis by decreasing the mitochondrial membrane potential. However, HBx stimulation of NF-κB protects hepatocytes against apoptosis, as a possible mechanism to maintain persistent infection. HCV infection is directly correlated with increased apoptotic activity. The pathogenesis can be through the direct effect of HCV proteins on hepatocytes, or through the oxidative stress primarily induced by the HCV core protein. The apoptosis in hepatitis C may progress even without the increase of transaminase. Steatosis is also recognized as a cofactor influencing the progression of fibrosis in chronic hepatitis C, while hepatocyte apoptosis itself contributes to the advancement of fatty liver disease. In the treatment of hepatitis C, the antiviral effect of interferon may be mediated through induction of apoptosis. The administration of antiapoptotics, such as vitamin E, ursodeoxycholic acid, could ameliorate hepatitis C.

APASL/Abstract/BS X.1
Anemia associated with chronic hepatitis C and its treatments
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HCV infection itself can induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia. The most effective treatment for HCV infection is combination therapy with (PE-G)IFN- and ribavirin(RBV). Anemia, neutropenia, leukopenia, and thrombocytopenia are among the numerous hematologic disorders frequently observed during HCV treatments. THESE side effects can influence HCV treatment and adherence, which is the most important factor in successful eradication of HCV. Major hematologic side effect of IFN-α and PEG-IFN-α is bone marrow suppression leading to anemia and neutropenia; IFN-α-induced anemia can also occur by activation of apoptosis in erythroid progenitor cells, provocation of

immune hemolysis, and impairment of renal function. Anemia tends to occur less frequently with PEG-IFN-α than with non-pegylated IFN-α. The major side effect of treatment with RBV is dose-dependent hemolytic anemia. At RBV doses of $\geq$ 800 mg/day, RBV-induced hemolytic anemia causes a dramatic decrease in hemoglobin levels (of 2–3 g/dL), usually within 4 weeks of initiation of treatment. In addition to hemolysis, RBV induces anemia by suppression of erythropoiesis, possibly as a result of down-regulation of erythropoietin(EPO) receptors. Accordingly, anemia has been found to be more pronounced with combination therapy with IFN-α/RBV than with IFN-α monotherapy; hemoglobin levels $<$11 g/dL occur in 25%–30% of patients. Actually, the incidence of dose reductions due to anemia increased from 1% with PEG-IFN-α monotherapy to 22% with PEG-IFN-α/RBV therapy. IFN-α/RBV treatment–induced anemia has been called a "mixed" anemia, because patients treated with combination therapy are subject to RBV-related hemolytic anemia as well as IFN-related bone marrow suppression, which may impair the compensatory reticulocytosis that is an expected response to most hemolytic processes. HCV-infected patients treated with PEG-IFN/RBV appeared to have inappropriately low levels of endogenous EPO for their degree of anemia. Although serum EPO levels increased, the Hb level did not return to normal, suggesting that the increase in serum was not sufficient to fully compensate for the degree of anemia. A recent randomized, double-blind, placebo-controlled trial suggests that EPO can increase Hb levels, maintain RBV dosage in a substantial proportion of patients, and improve patient quality of life significantly in this setting. In summary, currently available HCV treatments induce hematologic disorders that may exacerbate an already fragile hematologic state in the HCV-infected individual and may compromise treatment adherence. Reported risks of developing anemia were higher among Asian studies. Therefore, close monitoring of haemoglobin levels and judicious adjustment of the RBV dosage are currently the widely accepted clinical practice to avoid discontinuation of HCV treatment and to achieve consequent eradication of HCV infection. Many clinical questions still exist concerning the adjunctive use of EPO to ameliorate the anemia associated with standard combination therapy. There are also economic issues relating to the long-term costs of therapy. These two clinical issues will be discussed separately at this BREAKFAST SESSION.

APASL/Abstract/BS XII.1

Laparoscopic pancreatic resection : preliminary results of a multicenter european study (127 patients)

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Objective: The role of laparoscopy in resection of pancreatic tumors remain controversial despite an increasing number of publications reporting laparoscopic pancreatic resections (LPR). The objective of this study is to assess the feasibility, safety, and outcome of LPR in a multicenter setting. **Methods:** A retrospective study (from 1995 to 2002) was conducted in 25 European surgical centers, collecting a series of 127 patients operated on an (intent-to-treat) basis of LPR. **Results:** Final diagnosis included benign pancreatic diseases in 111 patients (87%) (insulinoma: 22, neuroendocrine tumor: 20, mucinous cystadenoma: 26, serous cystadenoma: 21, chronic pancreatitis: 11, others: 11) while 16 patients suffered from malignant pancreatic diseases (13%) (insulinoma: 3, neuroendocrine tumor: 5, ductal adenocarcinoma: 4, cystadenocarcinoma: 2, renal metastases: 2). Five patients with presumed benign pancreatic diseases had malignancy at final pathology. The median tumour size was 30 mm (range: 5–120 mm). The tumours were located in the left part of the pancreas in 89%. Laparoscopically successful procedures included 21 enucleations, 24 distal spleno-pancreatectomies, 58 distal pancreatectomies with splenic preservation, and 3 pancreato-duodenectomies. The overall conversion rate was 14%. There was no postoperative death. The rate of overall postoperative pancreatic-related complications was 31%, but including only 17% of clinical pancreatic fistula. The surgical reoperation rate was 6.3%. In laparoscopically successful operations, the median postoperative hospital stay was 7 days (range: 3–67 days), significantly reduced in comparison to converted patients. During a median follow-up of 15 months (range: 3–47 months), 23% of the patients with pancreatic malignancies had tumour recurrence. No port-site metastases were observed. Late outcome was satisfactory in all patients with benign diseases. **Conclusions:** LPR is feasible and might be safe in selected patients with presumed benign and distal pancreatic tumours. The best indication for a laparoscopic approach appears to be the resection of benign and endocrine tumors without a need for pancreato-enteric reconstruction (i.e enucleation or distal pancreatectomy). As in open surgery, the successful management of the pancreatic stump remains the challenge of this procedure. The role of LPR for pancreatic malignancies remains controversial.

APASL/Abstract/BS XII.2

Laparoscopy for liver and biliary disease at the Cipto Mangunkusumo Hospital

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Nowdays laparoscopies was performed on more wider indication in the field of liver and biliary surgery. In the past, cholecystectomy, appendectomy, diagnostic biopsy and adhesiolisis were the common indications.

We report laparoscopic procedures out of the routine indications, which were performed at our centre in the last 2 years.

There were more than 15 procedures done beside the routinely laparoscopic indication. Most of the cases were women with an average age at 20–60 years.

Shortage of facilities and learning curve period made these procedures growth slow.

Five liver cyst cases, five common bile duct stones, one case of choledochal cyst and a few liver abcessess were operated laparoscopically.

In the liver cyst, the unroofing procedure and omentalpexy were successfully done, in one case, with pathologic result *in situ*, cholangiocarcinoma was suggested for wide cyst excision. The common bile duct stones were first explored laparoscopically in two cases then were converted to open for definitive treatment. In the other cases, stone extraction and t-tube were successfully performed.

Laparoscopic preparations to free the fusiforme cyst and the gallbladder was performed on the type I choledochal cyst, and then continued on to laparotomy for total excision and Roux & Y biliodigestive reconstruction.

In the liver abcess cases, most were amoebic. Aspiration and tube drainage were performed, the tube itself being removed 7 days later in out patient clinics.

There was no operative death; length of stay wad less than 3 days and the patient returned routine activity faster. **Conclusions:** Indication of laparoscopic procedures should be widened in liver and biliary cases in our institution.

APASL/Abstract/BS XIII.1
Hepatitis B genotypes in South Asia
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Viral hepatitis caused by hepatitis B virus (HBV) infection is a worldwide disease. The clinical outcome, progression of the disease and response to the antiviral therapy may depend on HBV genotypes. HBV isolates even of the same genotype can differ in virological and clinical characteristics. While genotype B and C are common in Southeast Asia, this may not be the case in South Asia. In Karachi, Pakistan, the predominant genotype is D and about one fourth of the patients have chronic hepatitis due to HBeAg negative mutants. As most of the patients from different clinical categories are infected with the same genotype D, it is difficult to conclude any influence of the genotype on the outcome of HBV infection. Genotype D is also the predominant genotype circulating in the western India (92%), in primitive tribes of the Andaman and Nicobar Islands, and Calcutta. In India, this genotype is associated with more severe liver disease than genotype A and may predict occurrence of HCC in young patients. Genotypes A and D are the commonest in northern India and Delhi. Genotype A is more often associated with ALT elevation, HBeAg positivity, and among those aged 25 years and above, cirrhosis of liver, than is genotype D. In southern India, genotype D is detected in 57.3%, genotype A in 18%, and genotype C in 11.5%. Patients with chronic hepatitis B genotype C have higher alanine transaminase (ALT) levels than those who had genotype A or D. Genotype C has a greater potential for causing disease than other genotypes. Patients with genotype C have a higher HBeAg-positive rate and a faster progression to liver fibrosis and hepatocellular carcinoma (HCC) than those infected by genotype A or B. Subgenotype C1 is common in Bangladesh. Within the genotype A, the double mutation (T1762/A1764) in the core promoter is significantly more frequent in Asian isolates (HBV/Aa) than in Eupopean (HBV/Ae) isolates.There is rational evidence that the duration of the hepatitis B e antigen (HBeAg) positive replicative phase varies for the different genotypes, being shorter for A and D which dominate in South Asia, than for B and C which dominate in Southeast and East Asia. This may be the reason for vertical transmission being less common in this region.

Satelite Symposium

APASL/Abstract/SS 1.1
Hepatic encephalopathy
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Hepatic encephalopathy (HE) is a neuropsychiatric syndrome during the course of acute or chronic liver disease. It is functional in nature, potentially reversible and precipitated by rather heterogeneous factors. At the neurophysiological level HE is characterized by a low-frequent cortico-cortical electrical coupling, which may explain the cognitive deficits and a low frequent cortico-muscular coupling, which may explain the fine motor deficits. Current evidence suggests that HE is the clinical consequence of a low grade chronic glial edema with subsequent alterations of astrocyte function, which finally results in disturbances of glioneuronal communication. Modern in vivo brain imaging techniques have demonstrated this low grade cerebral edema, whose extent parallels the severity of clinical symptoms. Different factors, such as ammonia, benzodiazepines, inflammatory cytokines can induce or aggravate astrocyte swelling, which results in oxidative stress, the activation of osmosignaling cascades, protein modifications, alterations in gene expression and neurotransmission. Among the protein modifications nitration of critical tyrosine residues in glial proteins may play an important role. Several proteins, which are nitrated in response to ammonia, benzodiazepines, hypoosmotic astrocyte swelling or inflammatory cytokines have been identified, inluding glutamine synthetase and the peripheral type benzodiazepine receptor. These findings not only explain why HE is precipitated in clinical settings by a variety of factors such as gastrointestinal bleeding, trauma, protein ingestion, sepsis, diuretics, and sedatives, but also offer novel potential sites of treatment.

APASL/Abstract/SS 1.3
Inter organ metabolism of ammonia: clues to how LOLA works
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In 1893 members of Pavlov's group in St. Petersburg described 'The Meat Intoxication Syndrome'. They described a causal relationship whereby the shunting of blood from the portal vein into the vena cava (bypassing the liver), resulted in the liver not being able to metabolise ammonia into urea leading to ammonia accumulation in the blood. Within this historical paradigm, ammonia was thought to be produced in the intestine and metabolized in the liver. Since then numerous studies have confirmed a central role for ammonia in the pathogenesis of Hepatic Encephalopathy. Recent studies in both animals and also in humans have started to change this historical paradigm suggesting that when the liver is diseased, the muscle becomes one of the most important organs involved in the detoxification of ammonia. In keeping with this hypothesis, data accumulated over the past 30 years have failed to show in a metanalysis a role for the current 'gold standard', i.e Lactulose in the treatment of Hepatic Encephalopathy. Indeed the metanalysis concluded that there was insufficient evidence for Lactulose in the treatment of Hepatic Encephalopathy. From the pathophysiological perspective, LOLA enhances the body's ability to detoxify ammonia in the muscle. Clinical and laboratory data have confirmed that its administration can reduce ammonia concentration. Data in animal models show that administration of LOLA can reduce ammonia induced brain swelling. Relatively large clinical trials have shown that compared with standard medical therapy, LOLA is effective in the treatment of Hepatic Encephalopathy and a preliminary metaanalysis has also confirmed its efficacy. Large scale clinical trials are underway to explore the full potential of LOLA for the therapy of hepatic encephalopathy.

APASL/Abstract/SS 11.3
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APASL/Abstract/SS 12.3
Abstract withdrawn

Guest Lecture

APASL/Abstract/GL 1
Clinical application of recombinant human hepatocyte growth factor for fulminant hepatic failure
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We first purified hepatocyte growth factor (HGF) from patients with fulminant hepatic failure (FHF) as a hepatotrophic factor in 1998 (J Clin Invest 88:xxx–xxx, 1998) and succeeded in cloning HGF cDNA in 1999. The molecular weight of HGF is approximately 92 kDa, consisting of a heavy chain (62 KDa) and a light chain (34 KDa). Measurement of serum HGF levels is useful in predicting the progress from acute hepatitis to FHF and the outcome of patients with FHF. HGF treatment stimulates liver regeneration in pigs after partial hepatectomy and increases the survival rate of rats treated with Jo2 (agonistic antibody against Fas), in which the mortality is quite high (>90%). HGF treatment also improved demethynitrosamine (DMN)-induced liver fibrosis in rats. In addition, we recently found that HGF facilitates the repair of large intestine in detxran sulfate sodium (DSS) or 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats. Many reports of in vivo experiments indicate that HGF is an extremely important tissue repair factor for various organs. We have finished pre-clinical trials for the clinical application of HGF. The half-life of intravenously administered HGF in the blood of rats is quite short - even as short as a few minutes; however, HGF accumulates in the liver, particularly of rats. The phosphorylation of HGF receptor (c-Met) in the liver of mini-pig with intravenous treatment of HGF was confirmed. A harmful side effect of HGF is proteinuria; however, it is reversible, and pathological findings of renal tissues at 2 weeks after the cessation of HGF administration revealed that tissues had fully recovered. We are going to start phase I and II clinical trials for patients with FHF using recombinant human HGF.

APASL/Abstract/GL 2
Does hepatic steatosis affect sustained virological response in chronic hepatitis C genotype 3 infected patients?
S. Rasool, S. Hamid, M. Zubair, K. Mumtaz, H. Shah and W. Jafri

Hepatic steatosis can be a prominent feature of chronic hepatitis C virus (HCV) infection, especially in genotype 3 patients, and is considered to be an independent factor for treatment failure. However, the association of this observation with different genotypes is not clear. Prevalence of genotype 3 is very high among chronic HCV patients in our community (in the range of 85–90%). **Objectives:** The purpose of this study was to define the role of steatosis in sustained virological response (SVR) to antiviral therapy in chronic hepatitis C genotype 3 patients. **Methods:** We analyzed all naïve chronic HCV patients treated in our department during the last 4 years. Patients were included in the study only if a pretreatment liver histopathology was available, were infected with HCV genotype 3 patients, completed 6 months of therapy with interferon-α and ribavirin and had follow up available of at least 6 months. Liver biopsies were graded according to HAI and steatosis according to Brunt et al. **Results:** A total of 98 eligible patients were studied. Mean age was 38.09 $\pm$ 9.02 years and 60 (61%) were males. Steatosis was present in 67/98 (68.3 %) of patients. It was mild in 35/98 (35.7%) and moderate to severe in 32/98 (32.6%) of patients. End treatment response was achieved in 65/98 (66.3%) and SVR in 62/98 (63.3%) patients. SVR was associated with stage of fibrosis ($P = 0.02$) and pre-treatment platelet count ($P = 0.05$) but was not associated with age ($P = 0.92$), gender ($P = 0.39$), BMI ($P = 0.74$), grade of inflammation (0.53) and grade of steatosis (0.28). **Conclusion:** Hepatic steatosis is present in a significant number of patients with chronic hepatitis C genotype 3 infection but does not affect sustained virological response.

APASL/Abstract/GL 3
Evidence-based medicine in the treatment of (hepatic encephalopathy)
Peter Ferenci
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A large spectrum of clinical conditions are summarized under the term (HE) 'HE' and include a variety of neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function, overt psychiatric and/or neurological symptoms to deep coma. Accordingly, the methods to measure treatment effects and treatment endpoints are highly variable. Another variable is the treatment of control groups. Most studies compare a new drug to 'standard treatment' (which by itself maybe highly effective) or to lactulose (whose efficacy was never demonstrated by a proper placebo controlled trial) as 'gold standard'. However, in view of the natural history of HE the inclusion of a placebo group is mandatory. In studies comparing a combination of a test drug with 'standard treatment' to 'standard treatment alone', an additional effect of the test drug can be detected only if the sample size is sufficiently large.

Author (Ref)	Test drug	HE grade	*N*	Observation time	Exclusion criteria	Survival % (on placebo)	HE better %
Barbaro* (1)	Flumazenil	III#	265	6 days	HR, RF,	97.3	>90
		IV#	262		acidosis	91.3	>90
Kircheis (2)	Ornithin-aspartate	MHE=	27	7 days	GI-bleed,	100	0
		I=	19			100	22
					HR, RF		
		II#	27			100	44
Strauch (3)	Ornithin-aspartate	MHE=		14 days	Unstable pts.	100	0
		I+II#	20			100	40
Marchesini (4)	BCAA oral	I#	34	3 mo	Unstable pts.	100	38
Michel (5)	L-DOPA	I-III=	38	7 days	none	61	37
Michel (6)	BCAA iv.	I-III=	24	5 days	Unstable pts.	74	26
Wahren (7)	BCAA iv.	II-IV=	25	5 days	None	80	48
Blanc(8)	Neomycin+ lactulose	II-IV=	40	5 days	?	85	70
Strauss (9)	Neomycin	II-IV=	19	5 days	MOF	89.5	89.5
Gentile (10)	Acarbose	MHE-II	107	2 mo		?	?
		MHE	55	30 days		100	13
Liu (11)	Synbiotics						

HR, hepatorenal syndrome; RF, respiratory failure; MOF, multiorgan failure; BCAA, branched chain amino acids; MHE, minimal HE. *All patients on neomycin. #Test drug better than placebo. =Test drug equal to placebo.

To identify all randomized controlled trials (RCT) in HE, a MEDLINE search (1966–2005) was conducted using several terms. A total of 2690 papers, written in English dealt with treatment of HE; less than 100 were some forms of controlled

trials. From these, 40 randomized studies had the endpoint 'improvement of HE' and included more than 10 patients per study group. Only 11 placebo RCTs were performed (table below shows survival rates and improvement of HE in placebo-treated patients in randomized controlled trials). Only ornithin-aspartate and synbiotics were superior to placebo in improving HE. Depending on the stage of HE, spontaneous recovery rates ranged between 0% in minimal HE (in the absence of clinical symptoms, a clinical benefit may not be detected) to over 90% when patients with grades III and IV are studied. By excluding unstable patients, the short-term mortality was low. Thus, patient selection is the most powerful predictor of outcome. In patients with minimal HE, it is impossible to detect a clinical benefit of a drug. In contrast, in patients with overt HE, the high spontaneous recovery rate on standard care will make every new treatment very attractive if no controls are included.

APASL/Abstract/GL 4
Minimally invasive surgery for HPB disease: the present and the future
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Surgery is a form of trauma, and trauma induces local and systemic responses in a person. If the responses are too excessive, harm can result. In recent years, the avoidance of harmful responses by a lesser degree of surgical trauma has been the subject of intensive research, thus the evolution of the concept of minimally invasive surgery (MIS). MIS has been around for many years, but the first successful laparoscopic cholecystectomy in 1987 by Mouret brought a sudden and dramatic development of MIS. Within a decade, many new MIS procedures were invented and the medical literature on this subject increased exponentially. The rapid and wide acceptance of MIS by the patients and the surgeons is due to the benefits of the MIS: rapid patient recovery, less pain, short hospital stay and good cosmetics. However, MIS brought the new problems of loss of three-dimensional visual field, loss of tactile sensation and operating by looking into the monitor instead of the patients. These initial problems were solved by good training, accumulation of experience and technical development in instruments. The high costs involved in MIS are partially balanced by the more rapid recovery of the patients, the shorter hospital stay and the earlier return to work. As the initial problems of MIS were solved, more complicated MIS procedures were carried out. New problems arise such as limited working space in the peritoneal cavity, poor retraction and exposure, removal of larger specimens through small wounds and the potential benefit of the use of MIS in procedures in which the access trauma forms an insignificant proportion of the total trauma of the whole operation. There is no doubt that technological development will help to develop MIS further in HPB surgery in the future. At present, there are a number of HPB MIS procedures which are adopted as a 'routine' procedure in selected centers.

Symposium

APASL/Abstract/S1.2
Clinical relevance of hepatitis B virus genotypes
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Hepatitis B virus (HBV) exhibits genetic variability. Based on an inter-group divergence of 8% or more in the complete genome nucleotide sequence, HBV has been classified into at least 8 genotypes. Each genotype has its distinct geographical and ethnic distribution. Genotypes A and D occur frequently in Africa, Europe and India, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and F is found in Central and South America. Genotype G was reported in France, Germany and the United States. Recently, the eighth genotype H has been described in Central America. Even within the Asian-Pacific region, HBV genotype distribution varies. In addition, subgenotypes are identified within some genotypes; however, their clinical significance remains to be examined. The clinical relevance of HBV genotypes has become increasingly recognized. Because of the preponderance of genotypes B and C in Asian countries, several studies have clearly shown that compared to genotype C, genotype B is associated with spontaneous HBeAg seroconversion at a younger age, less active liver disease, slower progression to cirrhosis, and less frequent development of HCC. These data indicate that a shorter duration of high levels of HBV replication and less active necroinflammation may contribute to a more favorable clinical outcome among genotype B patients. A study from India indicated that genotype D is associated with more severe diseases and may predict the occurrence of HCC in young patients. HBV genotype has also been shown to correlate with response to conventional interferon (IFN) therapy in patients with HBeAg-positive chronic hepatitis B. Two studies found that genotype B patients have a higher HBeAg seroconversion rate than genotype C patients. These findings were confirmed by recent studies of pegylated interferon, where HBeAg seroconversion occurred more often in patients with genotypes B ($33 \sim 44\%$) than in those with genotypes C ($21 \sim 28\%$). Regarding the correlation between HBV genotype and response to lamivudine therapy in patients with HBeAg-positive chronic hepatitis B, several studies showed that the rates of HBeAg seroconversion rate and drug resistant YMDD mutation occur in similar proportions of patients with genotypes B and C. However, genotype B patients may be more likely to have sustained response when treatment is discontinued. A clinical trial of adefovir dipivoxil found that all HBV genotypes ($A \sim G$) resulted in a similar reduction in serum HBV DNA levels, but a correlation with HBeAg seroconversion or durability of sustained response has not been determined. The influence of HBV genotypes on the response to antiviral treatment among patients with HBeAg-negative chronic hepatitis B remains less clear. In summary, there is increasing evidence that HBV genotype affects clinical outcomes of chronic HBV infection and response to antiviral therapy. The evidence for the clinical difference is stronger between genotype B and C, and in response to conventional or pegylated IFN but not lamivudine or adefovir dipivoxil. Whether HBV genotype guides the choice or duration of therapy, as is the case of HCV genotype awaits the coming results of several large randomized controlled studies.

APASL/Abstract/S2.1
Dual liver grafts in living-donor adult liver transplantation
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In Asian countries, the majority of organs for liver transplantation come from live donations. Because many live liver donors death has been reported from many centers, the risk is

not eliminated and remains a major consideration in the potential donor's decision. In adult recipients, if a left-lobe graft is selected, the liver graft volume (GV) is often less than 40% of the standard liver volume (SLV) of the recipient or 0.8% of the graft-recipient-weight-ratio (GRWR); therefore, right-lobe liver transplantation was introduced, and this trend has been spreaded widely. However, the risk to the donor of the right-lobe graft is higher than the risk of the left-lobe graft. Recently, dual left-lobe grafts from two living donors for 1 recipient were obtained to make up the insufficient graft size and to ensure donor safety, although it is technically complex and requires long operation time. Furthermore, if a larger recipient needs a bigger GV than the sum of dual left-lobes, and the right-lobe hepatectomy from one potential donor is safe, the combination of a right and a left-lobe from two donors can be applicable to avoid a small-for-size graft problem. From March 21, 2000 to December 31, 2004, 150 dual adult living donor liver transplantations (ALDLT) were performed at the Asan Medical Center. Indications of DLDLT were the same as the single liver graft LDLT. Dual liver grafts consisted of 62 two left lobes, 51 a left lobe and a lateral segment, 21 a right lobe and a left lobe, 10 two lateral segments, 3 a left lobe and a posterior segment, and 2 a lateral segment and a posterior segment. There was neither mortality nor morbidity in donors. In-hospital mortality occurred in 8 patients. Our results suggest that dual ALDLT can be a viable option to alleviate a small-for-size graft problem and secure donor safety.

APASL/Abstract/S2.4
Right lateral sector graft for living donor liver transplantation
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The major limitation of living donor liver transplantation (LDLT) for adult recipients is the size of the graft that can be procured from a living donor, because a small-for-size graft might not meet the metabolic demands of an adult recipient. This problem has been overcome by the use of a right liver graft. Right hepatectomy, however, imposes an increased surgical risk on the donor due to the reduced residual liver volume. Our group was the first to design the right lateral sector (RLS) graft, consisting of segments VI and VII. The indication for harvesting this type of graft includes a right liver of over 70% of the estimated total donor liver volume, and an estimated volume of the two right lateral segments that is greater than that of the left liver. In addition, this graft needs to be more than 40% of the recipient's standard liver volume. The postoperative course in all donors was uneventful. By the end of 2004, 21 patients received RLS grafts and 19 patients are still alive with normal graft function. Clearly RLS graft harvesting techniques will be of use for expanding the donor pool and minimizing the donor morbidity rate.

APASL/Abstract/S 3.1
Imaging of choice for difficult biliary stricture
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Biliary stricture is caused by various kinds of diseases. We have to differentiate between biliary cancers, pancreatic cancers, ampularly tumors, cholangitis including Mirrizi syndrome, primary sclerosing cholangitis, autoimmune pancreatitis and so on. Patients with jaundice should first undergo transabdominal ultrasonography, computed tomography or MRCP in order to know whether the cause for jaundice is biliary obstruction. After confirming the biliary stricture, endoscopic ultrasonography (EUS) and endoscopic retrograde cholangio-pancreatography (ERCP) provide further information for its final diagnosis. Cytology of bile obtained by ERCP- and EUS-guided fine-needle aspiration cytology are useful for biliary and panctratic tumors, respectively.

APASL/Abstract/S 4.2
Management of obstetrical cholestasis
Sibitul Hasnain
Pakistan

Obstetrical cholestasis is intrahepatic interference with bile flow or formation encountered during the third trimester of pregnancy but can also occur in the first trimester. Obstetrical cholestasis is often familial. It is particularly common in Scandinavia, Northern Europe, Chile, Bolivia and China. Prevalence is increasing worldwide. Management aims to ease symptoms e.g. pruritus, and to reduce complication during pregnancy. Pruritus is the main symptom of this disease. General measures include reassuring the patient and advising her to avoid hot humid environment and wear loose cotton clothes. Choletyramine is a frequently used medicine in this condition. Other drug options, including Ursodeoxycholic acid, Phenobarbitone, Nalmefene, S-adenosyl-L-methionine, are being evaluated. Steroids have been used for both maternal pruritus and for helping in fetal lung maturation. An early delivery from 35 to 38 weeks of gestation has been recommended to eliminate the risk of still birth. Mothers with obstetric cholestasis are at increased risk of bleeding after birth because of vitamin K malabsorption. Therefore, vitamin K is prescribed in this condition. There is a 60–80% chance that future pregnancy will be affected. Patients are advised to avoid contraceptive pills in future.

APASL/Abstract/S 5.1
New evidence: primary sclerosing cholangitis
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The introduction of magnetic resonance cholangiography has markedly enhanced our ability to make a confident diagnosis of sclerosing cholangitis without the need to perform ERC with all its attendant complications. Thus the diagnosis of sclerosing cholangitis is made with increasing frequency but it is hard to tell whether this is a true increase in incidence. There is documentation that the incidence of primary bile duct cancer is increasing. The pattern of stricturing and dilatation of the intrahepatic and/or extrahepatic biliary system typical of primary sclerosing cholangitis (PSC) is most commonly seen in association with colonic inflammatory bowel disease, although frequently both conditions are not simultaneous. More recently a number of other conditions of the extra and sometimes intrahepatic biliary system which resemble PSC have been observed in other clinical situations. In children given a diagnosis of autoimmune hepatitis 50% show radiographic evidence of a sclerosing cholangitis. Overlap of PSC with autoimmune hepatitis may also occur, although less frequently, in adults. Sometimes the two diseases are simultaneous and at other times they occur consecutively. Another form of sclerosing cholangitis is seen in association with autoimmune pancreatitis. Both respond well to corticosteroid therapy in contrast to the two previously described forms of cholangitis. Similarly the hyper-

eosinophilic syndrome may be associated with a sclerosing cholangitis (and pseudotumors) and responds to treatment with anti-inflammatory agents. Mostly in countries where portal vein thrombosis (PVT) is not a rarity, a simultaneous portal biliopathy is described in individuals with PVT. Such individuals may present with cholangitis and a markedly abnormal biliary tree can be visualized on MRC. Under these circumstances, it is assumed but not proven that damage to the biliary tree is secondary to ischemia. This may also occur in patients who have a hepatic artery thrombosis following liver transplantation. There is no evidence that ischemic duct injury is the etiology of primary sclerosing cholangitis associated with IBD – to date the cause(s) remain unknown. As many years may separate the two diagnoses, it is unlikely a "local" effect. Infections of the biliary tract that may give rise to a radiologic picture similar to that of PSC. This has been reported with bacterial sepsis of the liver and in individuals with AIDS and infection with cryptosporidia or other parasites. However effective therapy leads to resolution of these biliary changes which simulate PSC.

APASL/Abstract/S5.4

Autoimmune hepatitis and primary biliary cirrhosis: experience from China

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Autoimmune liver diseases including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are increasingly reported in world medical literature, but generally believed, at least in China as "western diseases" involving predominantly Caucasian peoples. However, as the awareness and understanding of this group of diseases has being steadily improved among Chinese hepatologists, more and more such cases has been diagnosed and a number of large series published in Chinese literature. For example, as one of the major centers with special interest in autoimmune liver diseases in China we diagnosed and managed more than hundred cases of PBC and more 20 cases of AIH and some cases of PSC in the last 5 years. To observe the clinical manifestation and biochemical response to immunosuppressive therapy in Chinese patients of AIH, we followed 21cases (20 female, 1 male; age ranged from 32 to 78 years, with a mean of 55 years) of probable or definite cases of autoimmune hepatitis assessed by IAIHG scoring system. We treated them with immunosuppressive therapy. The liver function tests were checked at baseline and 2 weeks, 1 months, 3 months, 6 months of treatment. Nineteen patients were classified as type 1 AIH, one as type 2 AIH, one as type 3 AIH. Three patients had concurrent diseases, including 1 patient each with sicca syndrome, hypothyroidism, and hemochromatosis. Two patients have AIH-PBC overlap syndrome. Fatigue (65%), anorexia (47%) and icterus (35%) are the dominant symptoms and signs. Laboratory investigations showed elevated serum aminotransferase activities (ALT median 179U/L, AST median 132.5U/L), elevated serum globulin (median 4.6 mg/dl), and positivity of autoantibodies (ANA 88.2%, SMA 29%, anti-LKM1 6%, anti-SLA/LP 17.6%, pANCA 17.6%, ds-DNA11.8%). Eighteen received immunosuppressive therapy (prednisone and/or azathioprine). Compared with baseline, after 2 weeks of treatment, serum ALT, AST and GLO decreased remarkably, reaching statistical significance ($P<0.05$). After 3 months of treatment, serum ALP, GGT also decreased, reaching statistical significance ($P<0.05$). At the time point of 3 months after treatment, serum levels of TBIL decreased compared with baseline, reaching statistical significance ($P<0.05$). Most patients developed mild cosmetic changes during induction period of the therapy, but usually resolved upon dose reduction. **Conclusion:** 1) Autoimmune hepatitis occurred mainly in women, characterized by elevated serum aminotransferase, hypergammglobulinemia, and circulating autoantibodies. 2) Prednisone alone or combined with azathioprine can relieve symptoms and improve laboratory abnormalities very effectively. PBC has been recognized as a chronic intrahepatic cholestatic liver disease in Western countries for a half century. For decades, in China and other Asian countries, PBC had been less well recognized and less reported. In recent years, however, more than 600 hundred cases of PBC have been reported in the mainland China. As in western countries, in China PBC is predominantly affects women, with a peak age of about 50 years. The earlier series was consisted of mainly older late stage cases which had not been correctly diagnosed until very late stage of the disease. Recent series comprised of more earlier and even asymptomatic cases who has been accidently identified at routine health check or workup for other medical reasons. In our institutel more than 100 cases of PBC have been diagnosed in the last 5 to 10 years. All 112 patients were either hospitalized or out-patients at Beijing Friendship Hospital from January, 1991 to August, 2004. The diagnosis of PBC was made according to the 2000 Practice Guidelines of AASLD. Ninety-eight were females (98/112) and mean age at diagnosis was (52.2 ± 9.7) years. The time interval from initial symptom or preliminary diagnosis to final diagnosis was 21.0 ± 27.6 months. The most frequent symptom was fatigue (59.8%, 67/112), then was pruritus (52.7%, 59/112) and jaundice (50%, 56/112). Forty-five patients (40.2%) were asymptomatic when they were diagnosed with PBC. Thirty-three patients (29.5%) were associated with other auto-immune diseases such as Sjogren's syndrome and/ or rheumatoid arthritis. Serum alkaline phosphatase and glutamyl transpeptidase levels were markedly elevated [449.1 ± 378.4 IU/L and 591.0 ± 537.2 IU/L, respectively), whereas alanine aminotransferase and aspartate aminotransferase levels were mildly to modestly elevated [(91.5 ± 93.9)IU/L and 103.2 ± 90.2 IU/L, respectively]. Half patients (50%) had a total bilirubin level $\geqslant 34.2$ μmol/L. Eighty-one patients (72.3%) had elevated serum immunoglobin M and 79.5% of the patients (89/112) were anti-mitochondrial antibody (AMA)/AMA-M2 positive. 38.4% of the patients (43/112) were serum anti-nuclear antibodies and/or anti-smooth-muscle antibodies positive. Most patients were treated with oral ursodeoxycholic acid and the liver function test findings were improved. During a median follow-up of 38 months, there were 13 patients died from liver failure and/or gastroentestinal bleeding. Five patients accepted orthotopic liver transplantation and recovered well. **Conclusion:** PBC in China is probably much more common than we thought before, and the clinical characteristics as well as the biochemical response to UDCA are similar to that reported in western literature.

APASL/Abstract/S6.3

Management of drug induced hepatotoxicity due to ART

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Antiretroviral therapy has improved survival in HIV affected individuals. However simultaneously there has also been an increased morbidity as a result of ART induced hepatotoxicity. All the three classes of ART are known to have varying degrees of hepatotoxicity. AIDS Clinical Trial Groups criteria have classified the grades of hepatotoxicity (1–4: 4-being severe with ALT $>$ $10 \times$ ULN). Severe hepatotoxicity occurs in 5–10% within the first

one year but in the vast majority, it is not associated with symptomatic hepatitis or adverse outcome and resolves within a few months. ART will need to be discontinued in grade 4 hepatotoxicity or symptomatic hepatitis, lactic acidosis or drug hypersensitivity. Amongst the risk factors for severe hepatotoxicity are co-infection with B and C viruses, Nevirapine and high dose Ritonavir based therapy and abnormal baseline levels of transaminases. Mechanisms of liver injury include mitochondrial toxicity and steatosis with NRTI (D4 T, DDI, and AZT) hypersensitivity with Nevirapine and Abacavir, immune reconstitution illness after treatment with nucleoside analogues in HBV co-infection and virus induced flares due to abrupt withdrawal of drugs or following drug resistance. Management includes assessment of the severity, exclusion of other causes of acute and chronic hepatitis and cessation of ART if deemed necessary. Recommencement of ART is done when ALT/AST decline to 2–3 $\times$ ULN and symptoms subside with careful monitoring of LFT in case of rechallenge with implicated agents.

APASL/Abstract/S 7.2
Nonalcoholic steatohepatities in Korea
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Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized, especially in patients with risk factors such as obesity, diabetes, hypertriglyceridemia or severe weight loss. As one spectrum of NAFLD, nonalcoholic steatohepatitis (NASH) is characterized by macrovesicular hepatic steatosis and parenchymal inflammation in liver biopsy and may ultimately result in cirrhosis or even hepatocellular carcinoma. Until now no population-based prospective study has been performed in Korea partly because of the limited concern of physicians and the lack of accurate, noninvasive diagnostic measures for screening. With the increment of obesity and diabetes in general population, the prevalence and clinical importance of NASH is expected to increase in Korea. In a cohort study of 1192 factory workers, the prevalence of ultrasonographic fatty liver was 10.7%, and 51.1% of them had abnormality in liver function. Among those with abnormal ALT, 21% did not have history of alcohol or viral hepatitis, which suggested possible NAFLD. Another recent study including 8379 health screening subjects who had neither hepatitis virus nor significant alcohol consumption showed moderate-to-severe fatty liver on ultrasonography in 19%. Men between 20 and 40 years of age, with high BMI, high triglyceride and ultrasonographic fatty change more than moderate degree were significantly associated with elevated ALT. A small case–control study of biopsy-confirmed NAFLD (39 patients) revealed a strong relationship of high body mass index and NASH. These cases had relatively progressive fibrosis in comparison with studies from Western countries and less prominent aminotransferase abnormalities. Korean physicians are now getting more interested in NASH and efforts to elucidate the prevalence, natural course and possible therapeutic modalities of NASH are under way.

APASL/Abstract S 7.5
Non-alcoholic steatohepatitis
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Pakistan

Non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD) is fatty inflammation of the liver when it is not because of excessive use of alcohol. It is the major cause of cirrhosis of liver. It differs from the simple accumulation of fat in the liver (fatty liver or hepatic steatosis) in that the inflammation of NASH causes damage to the liver cells while simple fat does not. Recent studies indicate that NASH can result in the development of liver fibrosis in upto 40% of patients, or cirrhosis in upto 5–10% of the patients. NASH accounts for about 10% of newly diagnosed chronic liver disease in USA. Studies report that the progression to fibrosis or cirrhosis for NASH is variable but can occasionally occur in less than 20 years, but progresses more so in diabetic and hyper lipidemic patients above the age of 45 years. NASH occurs worldwide in both sexes. It has been estimated to affect about 50% morbidly obese, about 20% of obese and 3% of lean persons. It may occur in about 2% of children but in 20–50% of obese children. Diabetes mellitus, insulin resistance, obesity and hyper lipoproteinemia are associated with increased risk of NASH. Studies have shown that in type 2 diabetes mellitus, 90% have fatty liver, 20% have NASH and 10% have cirrhosis. Currently, there is no specific therapy for NASH; however, weight loss if over weight and correcting elevated cholesterol, triglycerides and blood sugar are beneficial. Antioxidant drugs and antidiabetics, which lower insulin resistance, may be advantageous.

APASL/Abstract/S 7.8
Prevalence of metabolic syndrome, severity and treatment of NASH in Thailand
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Non-alcoholic fatty liver disease (NAFLD) is associated with dyslipidemia, obesity, and insulin resistance, which are the main features of metabolic syndrome. The prevalence of overweight (BMI $>25\,kg/m^2$) and obesity (BMI $>30\,kg/m^2$) among 18 389 Thai population, between 2000 and 2004, were 11–28% and 2.4–10.5%, respectively. The prevalence of metabolic syndrome (NCEP-ATP III criteria) by the population-based cross-sectional survey in 5305 Thai adults aged $\geq$ 35 years was 19% in men and 27% in women. The most important risk factors in the Thai populations were central adiposity, high triglyceride and low HDL cholesterol (InterASIA study). The true prevalence of NASH in the Thai population and in metabolic syndrome remains unknown. Liver biopsy from 70 patients with ALT >1.5 UNL and without other causes of hepatitis, was taken in the Ramathibodi Hospital, with mean age 45.5 (range 28–68) years, and of whom 50 (71.4%) were male. Forty-six (65.7%) patients had features of metabolic syndrome. Liver histological was graded by Brunt's classification were mild 20 (28.6%), moderate 46 (65.7%) and severe 4 (5.7%). The degree of fibrosis in stage 1, 2 and 3 were 44 (62.5%), 24 (34.3%) and 2 (2.9%), respectively. Obesity, increased abdominal and visceral fat, insulin resistance, DM, metabolic syndrome, Homar IR >3.5 and high triglyceride levels were significantly higher in NASH than healthy control ($P = 0.01$). Treatment of NASH in Thailand mainly focused on the management of associated conditions i.e. obesity, DM and hyperlipidemia; life-style changes and alcohol abstinence are implemented before pharmacotherapy included antioxidants, UDCA, silymarin, and insulin insensitizers.

APASL/Abstract/S8.1
Contrast harmonic ultrasound is a useful technology in the diagnosis and treatment of hepatic tumors.
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Recently developing, contrast-enhanced harmonic ultrasonography (US) using contrast agent is a new technique that has been developed to overcome some of the drawbacks of conventional color Doppler imaging. A dramatic improvement of contrast-enhanced US brought us the new strategy in the diagnosis and treatment of hepatic tumors. In this lecture, I would like to talk about that the present status of US technology and US contrast agent for hepatic tumors. ***More accurate diagnosis than conventional color Doppler imaging:*** Contrast-enhanced harmonic US using Levovist has proven to be significantly more accurate than color Doppler US in assessing the vascularity of hepatic tumors. ***Evaluation of treatment responses after TAE and RFA:*** We prospectively analyzed the relationship between detection of contrast-enhanced Doppler signals in HCC after TAE and histological confirmation of viable tumor cells in order to quantify a possible beneficial use of contrast-enhanced harmonic US. We concluded that tumor blood flow detected by contrast-enhanced harmonic US indicates the presence of residual viable tumor cells by biopsy specimens after TAE. Contrast-enhanced harmonic US is useful in evaluating the effect of TAE. However, regarding after RFA, It was difficult to evaluate viability because of unclear the tumor marginal zone to ablate. ***Distinguishing Benign and Malignant Focal Liver Lesions by Kupffer Imaging:*** We evaluated the differentiability of the late-phase harmonic sonography (Kupffer imaging) with the contrast agent Levovist between benign and malignant hepatic tumors. We concluded that Kupffer imaging is a promising non-invasive technique to differentiate between benign and malignant hepatic tumors, the use of which may obviate invasive and expensive further diagnostics. ***Three–Dimensional Power Doppler Ultrasonography:*** We assessed clinical usefulness of recently developed three-dimensional power Doppler US for the diagnosis of HCC. We concluded that three-dimensional power Doppler US provides definite diagnosis of HCC in a real-time, non-invasive manner under certain conditions.

APASL/Abstract/S 8.2
MRI vs CT in detecting small HCC
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There are many pitfalls in the imaging of small hepatocellular carcinoma (HCC). This talk attempts to confront these issues frustrating the diagnosis of small HCC. The current imaging criteria of hypervascularity in the hepatic arterial phase with wash-out in the portal venous phase, the presence of a multinodular or mosaic pattern, the portal venous enhancement of pseudocapsule and internal sepate; are based on the gross pathology findings and the increased vascularity of HCC. They are more commonly seen in larger HCC. Step-wise evolution of regenerating nodules into low grade and subsequently high grade dysplastic nodule and HCC is recognized. Radiologic-pathologic studies of these nodules have revealed a gradual decrease and degeneration of native hepatic arterial supply and an increase in angiogenesis. In high grade dysplastic nodules and well differentiated HCC, the increase in angiogenesis may balance the normal normal degeneration of hepatic arterial supply and thus no increase or decrease in vascularity is noted in the hepatic arterial phase. This makes diagnosis of these nodules difficult. Arterio-portal shunts or perfusion anomalies are increasingly recognized as common imaging findings which may mimic a small HCC. MRI provides the best differentiation between a pseudolesion due to shunts and a small HCC. The modality of choice for imaging small HCC remains MRI though CT is currently still the workhouse in many institutions. Recent evidence has shown that Lipiodol-CT is associated with a high false positive rate. Angiography is less sensitive compared with dynamic MRI and CT. New MR contrast agents and FDG PET also have limited success. The diagnosis of small HCC (1 to 2 cm) still rests on histology. Presumptive diagnosis of HCC can be made if a hypervascular lesion (confirmed by 2 modalities and >2 cm) is seen in a cirrhotic liver according to the EASL criteria.

APASL/Abstract/S 8.3
Prognostic scoring in hepatocellular carcinoma
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As most patients with hepatocellular carcinoma (HCC) present at an advanced stage, it is useful to be able to predict their probability of surviving the next few months. Thus prognostic scoring is valuable in the management of HCC. Besides estimating the survival time, prognostic scoring is also useful in identifying patients suitable for clinical trials. The prognostic of a patient with HCC is not just dependent on the disease extent alone. The underlying liver function is of equal, if not greater, importance as well. Hence a prognostic scoring system should incorporate liver function in addition to tumour characteristics. Many prognostic models and scoring systems have been proposed and validated. These models usually require a large number of data input. Some of these data can only be obtained by advanced imaging techniques or from a multitude of blood tests. Our department in the Singapore General Hospital has developed and validated a simple bedside prognostic model in contradistinction to the existing models. With so many prognostic models and scoring systems available in the literature, it is important to select the appropriate one for our patients and to understand the shortfalls of that particular model. Only then can we utilize it in a useful manner.

APASL/Abstract/S 9.1
Iron overload with particular reference to the Asian Pacific area
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Our understanding of the mechanisms by which the body regulates iron absorption and iron homeostasis has improved greatly in recent years with the identification of key molecules such as HFE, ferroportin, transferrin receptor 2, hepcidin and haemojuvelin. Hereditary haemochromatosis, a primary inherited disorder of iron metabolism leading to progressive iron loading of parenchymal cells of the liver and other organs, can result from mutations in any of these genes. However, HFE-associated hereditary haemochromatosis accounts for over 90% of cases in Caucasian populations. Penetrance is incomplete with variable clinical expression. The majority of cases demonstrate biochemical expression but a lower proportion develop advanced disease. Clinical disease, especially hepatic fibrosis, is related to the level of body iron stores which is reflected primarily in the liver. The available evidence indicates that adequate screening and diagnostic strategies can ensure that early case detection and treatment occur prior to the development of irreversible end-organ damage. The most cost-effective methods of early case detection are family (cascade) screening and evaluation of poten-

tial cases by primary care physicians with a high index of clinical suspicion. Clearly, HFE-associated haemochromatosis is uncommon in Asian populations. However, inherited iron overload with similar manifestations can be seen resulting from mutations in the other key molecules mentioned above as well as secondarily to iron-loading anaemias.

APASL/Abstract/S 9.2
Neonatal metabolic liver disease
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Metabolic and genetic liver diseases lead to considerable morbidity and account for 30% of liver transplantations performed in children. It is important for paediatricians and neonatologists to keep in mind inborn errors of metabolism as a cause of illness in the neonatal period many disorders are treatable and, in most cases, successful outcome is dependent on a rapid diagnosis and early instigation of therapy. Even with untreatable disorders, it is important to establish the diagnosis in the index case in order to allow prenatal diagnosis in subsequent pregnancies. Most babies with an inborn error are born in good condition and of normal birth weight but a high index of suspicion of metabolic disease is essential in approaching any sick neonate.

Patterns of Presentation:

- Liver dysfunction
- CNS – encephalopathy & /- seizures
- Metabolic acidosis
- Hypoglycemia
- Cardiac disease
- Dysmorphic features
- Body odour is abnormal or unusual as in Maple Syrup Urine Disease
- Non immune hydrops fetalis

Timely investigation and where possible intervention is essential in the management of any of these conditions. When considered a battery of screening tests should be performed and could include the following:

- Plasma lactate persistently $>$ 2.5 mmol/l
- plasma lactate : pyruvate $>$ 20:1
- arterial β-OH butyrate : acetoacetate $>$ 2:1
- amino acids

  –elevatedalanine and proline

- urine organic acids
- plasma acylcarnitine profile

  –totaland free carnitine
  –FattyAcid Oxidation Defects

- CSF

  –Lactateto pyruvate ratio and amino acids measurement

Specific diagnostic tests are more difficult and are the realm of a limited number of more specialized centres. Recently, attempts at developing a regional reference laboratory have been made with some success using the neonatal dry blood Guthrie card as a vehicle for providing a sample for analysis via tandem mass spectroscopy. Using this technique the rapid analysis for amino acid disorders, urea cycle defects, fatty acid oxidation defects, organic aciduria's, peroxisomal defects and possibly congenital disorders of glycosylation are all possible. This will allow for rapid assessment and also rapid (within days) reporting of results which will allow for appropriate therapy where possible.

APASL/Abstract/S 9.3
What does fat do to the children liver: is non-alcoholic steatohepatitis a clinical problem?
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Non-alcoholic steatohepatitis (NASH) is an entity in the spectrum of non-alcoholic fatty liver disease. It is associated with obesity, diabetes, insulin resistance, and hyperlipidemia. The prevalence of NASH in children is not known. Generally, children with NASH presented in the prepubertal age group. A two-hit hypothesis has been proposed in the pathogenesis of NASH. The first hit is insulin resistance resulting in steatosis. The second appears to be oxidative stress, which produces lipid peroxidation and activates inflammatory cytokines like TNF – resulting in NASH. The role of fatty acid oxidation is complex. Appropriate fatty acid oxidation is essential in order to prevent accumulation of fat in the liver. On the other hand, excessive fatty acid oxidation is probably responsible for the generation of oxidative stress. There is evidence that intact mitochondrial fat oxidation is required for progression to inflammation and fibrosis.

APASL/Abstract/S 11.3
Long-term problems associated with paediatric liver transplantation
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Liver transplantation in children has now reached a level of sophistication and success that it is now timely to consider any comorbidities that may now be apparent. It is now normal to consider that in excess of 70% of paediatric liver recipients will be alive 10 or more years following their transplant. As growth is the cornerstone of childhood, it is imperative to examine not only physical, but also psychological growth in these long-term survivors. It is becoming apparent from many studies and reports that the catch up linear growth is suboptimal in children following liver transplant. Our group and others have shown that there is continuing disparity between height and weight when compared with age-matched controls. This is at odds with what is seen with the long-term growth characteristics of children who have undergone successful Kasai procedures for extra hepatic biliary atresia which would suggest that there are some inherent factors arising from the liver transplant itself. It has been suggested that the use of corticosteroids as part of the immunosuppressive regime play a large part of this growth effect but recent studies have suggested that this is not the only actor at play. Recently, it has been suggested that the degree of malnutrition prior to transplant and the episodes of rejection also have some bearing on the outcomes. Psychological outcomes are also now being examined. Several groups have suggested that there are subtle abnormalities in psychomotor development and also cognitive functioning is being seen in long-term survivors. These outcomes are also being suggested to having been influenced by preoperative factors, including nutrition, although, a recent single centre experience from Paris has shown no effects upon cognitive function and school performance. The latest challenges now appear to involve the advent of increasing incidence of underlying hepatic histological issues. Increasing fibrosis is being reported in otherwise asymptomatic

patients but the implications of these findings are only now being considered.

APASL/Abstract/S 12.1

HEV replicase: Subcellular localization and interaction with HEV 3'UTR by Fluoresence Resonance Energy Transfer (FRET)

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The replication complex of an animal virus consists of a complex of viral RNA template, replicating strands, viral RNA polymerase along with cellular proteins and structures. We investigated the site of replication of HEV by coloclisation studies using EGFP tagged HEV replicase and organell specific fluoroprobes/phores. Further we used the earlier identified cis-acting elements at the 3'end of HEV plus strand RNA, which interacts with the viral replicase (RdRp), in vitro, labeled with alexa 546-UTP for Fluorescence resonance energy transfer (FRET) Sensitized Emission *in-vivo*, using confocal inverted microscope in living HepG2 cells, permanently transfected with and expressing replicase-EGFP fusion protein. We observed, that the HEV replicase localizes to the membranes of endoplasmic reticulum. FRET Sensitized emission was performed within 12 hours of RNA transfection. FRET image was generated and over 50 region of interest (ROIs) were used for calculating FRET efficiency for every cell analysed. Significant FRET efficiency values were obtained. We could demonstrate in carefully controlled system interaction between the HEV replicase and the 3'end of HEV genome at the subcellular level on endoplasmic reticulum.

APASL/Abstract/S 12.3

Hepatitis E virus infection in patients with cirrhosis causes rapid decompensation and death

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Background: In healthy individuals, hepatitis E virus (HEV) causes self-limiting acute hepatitis with negligible mortality. Few case series indicate that HEV infection in cirrhosis of liver may cause rapid decompensation and death. Prospective study evaluating cirrhotics as high-risk to contract HEV infection and natural course of HEV infected cirrhotics have not been studied. **Methods:** Consecutive patients with cirrhosis liver, and age/sex-matched healthy blood donors as controls were included in study. Cirrhotics were categorised into three groups (Group I – with rapid decompensation, Group II- chronically decompensated, Group III – stable cirrhotics without decompensation). Sera from cirrhotics and controls were tested for HEV-RNA by reverse transcriptase polymerase chain reaction. Presence of HEV-RNA was considered as evidence for HEV infection. Frequency of HEV-RNA positivity among cirrhotics and controls was compared. Similar comparison was made between the three groups of cirrhotics. Natural course, mortality and complication frequencies between HEV-infected cirrhotics and cirrhotics without HEV infection were assessed. All cirrhotics were followed up for 12 months. **Results:** One hundred and seven consecutive patients with cirrhosis and 200 controls were included. Thirty (28%) cirrhotics and nine (4.5%) controls had detectable HEV-RNA ($P<0.001$). HEV-RNA positivity among Group I ($n=42$), II ($n=32$), and III ($n=33$) cirrhotics was 21 (50%), six (19%) and three (10%), respectively ($P=0.002$). Four-week mortality among these three groups were 21 (50%), six (19%) and 0 (0%), respectively ($P=0.001$). Child–Pugh's score among HEV-infected cirrhotics ($n=30$) was significantly worser (at inclusion and 4 weeks) than cirrhotics without HEV infection ($n=77$) ($P=0.0001$). Seventy percent (21/30) with HEV infection and 27% (21/77) without it had rapid decompensation ($P=0.001$). The former 21 HEV-infected cirrhotics were asymptomatic before presenting with rapid decompensation; 13 (64%) of them died within 4 weeks and all died within 12 months. Mortality among HEV-infected and non-infected cirrhotics at 4 weeks (43% vs 22%, $P=0.001$) and 12 month (70% vs 30%, $P=0.001$) was significantly different. Multivariate analysis identified HEV infection, Child-Pugh's score, renal failure and sepsis as independent factors for mortality. **Conclusion:** Patients with cirrhosis were prone to HEV infection, which caused rapid decompensation and death. Prevention of HEV infection inpatients with cirrhosis may improve their survival.

APASL/Abstract/S 12.4

The unique riverine ecology of hepatitis E virus transmission in Southeast Asia

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AbstractThe ecology of hepatitis E virus (HEV) transmission in South-East Asia was assessed from a review of six published and three unpublished NAMRU-2 reports of hepatitis outbreak investigations, cross-sectional prevalence studies, and hospital-based case–control studies. Findings from Indonesia and Vietnam show epidemic foci centered in jungle, riverine environments. In contrast, few cases of acute, clinical hepatitis from cities in Indonesia, Vietnam and Laos could be attributed to HEV. When communities in Indonesia were grouped into areas of low (<40%), medium (40–60%), and high (>60%), prevalence of anti-HEV antibodies, use of river water for drinking and cooking, personal washing, and human excreta disposal were all significantly associated with high prevalence of infection. Conversely, boiling of river drinking water was negatively associated with higher prevalence ($P<0.01$). The protective value of boiling river water was also shown in sporadic HEV transmission in Indonesia and in epidemic and sporadic spread in Vietnam. Evidence from Indonesia indicated that the decreased dilution of HEV in river water because of unusually dry weather contributed to the risk of epidemic HEV transmission. But river flooding conditions and contamination added to the risk of HEV infection in Vietnam. These findings attest to a unique combination of ecological and environmental conditions in predisposing epidemic HEV spread in South-East Asia.

APASL/Abstract/S 13.1
Pregnancy and the liver
Nurdan Tozun and Hakan Akin

The liver is the site of many important metabolic and synthetic functions and two types of liver diseases which may occur at this phase of life are either directly related to pregnancy or to common liver disorders which may also affect the liver of a pregnant woman. In the first group of disorders, hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets syndrome are pregnancy specific and may either affect the quality of life of the pregnant woman and/or cause serious complications in the course of pregnancy.

APASL/Abstract/S14.1
Imaging options in cholangiocarcinoma
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Tumors of the biliary tract are uncommon but serious problems. The spectrum of lesions ranges from benign tumor, such as adenoma, to malignant lesions, such as adenocarcinoma. Most patients with such lesions present with jaundice due to the obstruction of the biliary tree by the tumor. The tumors generally are small and difficult to visualize with the standard imaging studies such as ultrasonography and computed tomography scanning, but these techniques may provide a clue to the level of the obstruction and help exclude metastatic disease.

Cholangiocarcinoma is the most important primary tumor of the bile ducts and may involve either the intrahepatic or the extrahepatic biliary ducts. This tumor variety is the second most common primary hepatic malignancy after hepatocellular carcinoma.

There are several imaging modalities (ultrasonography, CT scan, MRI and PET), and their diagnostics values for detection will be discussed. Ultrasonography has been widely accepted as an initial screening procedure for bile duct dilatation in patients with jaundice. MRI, MRCP, Contrast Enhanced Computed Tomography with optimal acquisition timing permits improved lesion detection and will improve characterizations of lesions.

The role of PET in the diagnostic work up of Cholangio Carcinoma still remains unclear. PTC and ERCP are helpful in the unresectable disease based on the palliative procedures to improve the quality of live.

APASL/Abstract/S 15.2
Booster for hepatitis B vaccination: how long is forever?
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Hepatitis B vaccination in infancy has been proved to be effective in preventing acute and chronic hepatitis B virus (HBV) infection, and its complication, e.g. fulminant hepatitis, and hepatocellular carcinoma. The first hepatitis B vaccination program has been launched since July 1984 in Taiwan. According to the report of World Health Organization (WHO), 147 of the 192 countries in the world have integrated the HBV vaccination program in to the infant immunization program up to the end of 2003. After long term follow-up, the levels of hepatitis B surface antibody have waned gradually with time. Yet anamnestic antibody responses to a booster dose were demonstrated before 15 years of age in previous studies after primary HBV vaccination in infancy. It is generally accepted that for immune competent individuals, routine boostering is not needed before 15 years of age. However, for immune compromised hosts, regular annual testing for anti-HBs and a booster dose should be considered when the anti-HBs titer falls below 10 mIU/mL. For immune competent high risk subjects, e.g. those with house hold contacts and sex partners of HBV carriers, and persons with occupational risk, etc. should also be considered for boostering if the anti-HBs levels fall below 10 mIU/mL. As the vaccinees are getting older than 15 years of age, both the humoral and the cellular immunity to HBV may decay further. At the mean time, they may become more sexually active, and expose to more risk of HBV infection. Theoretically, a booster dose may be considered to be given to those whose anti-HBs levels fall below 10 mIU/mL. On the other hand, those who are infected by HBV during adulthood hve a lower risk of becoming chronic carriers ($<5\%$) than those infected in infancy and earl childhood. In addition, low infection rates were demonstrated by low anti-HBc rates in vaccines after long term follow-up. In Taiwan, 4% of anti-HBc was observed in adolescents 15 to 17 years of age born after the universal HBV vaccination program in Taiwan. The necessity and the best timing of boostering therefore need to be analyzed further.

APASL/Abstract/S 17.1
Specific issues of hepatitis C virus infection in the Asia Pacific
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Hepatitis C viral infection in the Asia Pacific region is characterized by diversity in epidemiology, socio-economic issues affecting the strategy in identifying and treating infected patients, and the resources allocated by the government health organizations to manage the disease burden and health impact. HCV genotype profile varies in different regions. Genotype 1b predominates, with 2, 3, 4 and 6 genotypes making up the entire population. The clinical outcome among these genotypes and its responsiveness to therapeutic strategy are slowly being recognized. These will contribute to the overall management plan and design of cost-effective treatment plans. The routes of transmission of HCV infection in Asia Pacific region are similar to that in other parts of the world. However, effective preventive measures are implemented to different degrees of success. For example, donors of blood, blood products and organs are still not properly counseled and screened, resulting in new infection occurring in situations that can be readily prevented. Paid donors are strongly discouraged but is still practiced in many regions. Intravenous drug users and substance abusers are well known to be difficult to control. Health authorities have limited resources to counsel these individuals, to provide detoxification programs or non-reusable syringe exchange programs. Similarly, sex workers also contribute in spreading the infection and, in line with the prevention of HIV infection, education of these sex worker, their client and public as a whole is important. In many regions, the spread of HCV infection can be traced to unsafe medical and paramedical practices. Surgical, dental and medical equipment may not be properly disinfected before being reused. Reusable syringes or lancet have been found to contribute to major HCV transmission in some health programs for vaccination or therapy. It is also the practice of some Asian population to undergo paramedical treatment such as acupuncture, cupping, scarring and rubbing. Tattoo and body piercing are also popular among the general population. These activities involve breach of intact skin and HCVs transmitted if universal precaution is not practiced. Treatment for hepatitis C is ex-

pensive. Only a small proportion of CHC patients in Asia Pacific region can afford therapy. The distribution of health dollars is not even in many regions. The management strategy for these patients needs to be carefully designed to achieve meaningful cost-effective results. The same argument applies in the surveillance for hepatocellular carcinoma. Without a robust program in oncology and liver transplantation, such exercise becomes futile. The lack of resource and coordinated effort to manage hepatitis C infection, high disease burden, morbidity, and early mortality will be inevitable. The end results are human misery and indirect negative impact on the countries' economy.

APASL/Abstract/S17.2
Management of hepatitis C in end-stage renal disease
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In chronic hepatitis C patients with end-stage renal disease, hepatic necroinflammation and liver fibrosis deteriorate more rapidly after renal transplantation (1, 2). This is presumably attributed to extensive use of immunosuppressants. Increased risk of glomeruonephritis, fibrosing cholestatic hepatitis, and possibly diabetes mellitus has been reported (3, 4, 5). Despite these disadvantages, overall survival is still better for patients receiving renal transplantation comparing with those receiving continuous hemodialysis (6, 7). After renal transplantation, interferon therapy for chronic hepatitis C is associated with a high risk of rejection and graft loss (8, 9). Management of chronic hepatitis C in such patients becomes a major challenge for medical doctors. Pre-transplantation antiviral therapy has been reported to be beneficial for the patients, although the viral clearance rate is very low. This is supposedly owing to poor tolerance of the patients to full dose interferon as well as occurrence of severe hemolysis when ribavirin is used (10, 11). In patients who achieved sustained virological response, serum viral RNA remained negative after renal transplantation in some studies, arguing for the strategy of pre-transplantation therapy (12, 13). However, a high recurrence rate post renal transplantation has been reported in at least one study (14, 15). An appropriate therapeutic strategy remains to be established. In conclusion, antiviral therapy is an important issue in chronic hepatitis C patients with end-stage renal disease. Current therapeutic regimens are far from satisfactory. New antiviral agents are needed imperatively.

APASL/Abstract/S 17.3
Treatment of difficult to treat hepatitis C infection
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The standard of care for chronic hepatitis C is Pegylated Interferon alpha + Ribavirin (Peg IFN + RBV). Newer targeted treatments with enzyme inhibitors are still only in phase 1 and phase 2 trials and thus Peg IFN + RBV will likely remain the standard of care for at least another five years. Hence the need to optimize current therapy to enhance the likelihood of achieving a sustained virologic response (SVR) and improve the cost effectiveness of therapy. Over a lifetime less than 15% of individuals chronically infected with hepatitis C will die of their liver disease. Thus there are many individuals infected who do not require therapy and the current recommendation is that therapy should be offered to those who on liver biopsy have some evidence of progressive disease, i.e. fibrosis score of ≥ 2 in those infected with genotype 1 or 4. But for those infected with genotype 2 or 3 pretreatment liver biopsy is not currently recommended because their response to antiviral therapy is so good, and thus it is recommended that all receive treatment. In those infected with genotype 1 and to a lesser extent genotype 4, the chance of a sustained virological response (SVR) depends on a number of intumsic and extrimsic influences. Factors that markedly influence the likelihood of achieving an SVR are adherence to full dose therapy given for the appropriate duration of time, viral factors (genotype, viral load, co-infection with HIV or HBV and quasispecies development) and host factors (age, gender, degree of fibrosis and steatosis, BMI and alcohol intake). Thus in order to optimize therapy, many issues need to be addressed on an individual basis. Overall approximately 50% of individuals given Peg IFN + RBV fail to respond to antiviral therapy. Likelihood of non-response may be predicted by the degree of fall in viral titre upon the introduction of antiviral therapy. It is generally recommended that in those who fail to have a ≥ 2 log drop in HCV RNA after the first 12 weeks of therapy stop treatment as they have only a 2–3% chance of achieving an SVR should they persist with therapy. Recent data from examining gene expression in liver tissue pre-treatment would suggest that non-responders may be predicted by a specific 8 gene molecular signature. This needs to be validated by further studies.

APASL/Abstract/S18.1
Emerging of NASH in the Asia Pacific Region
Diana Payawal

The concept of steatohepatitis as the consequence of two hit theory was first projected by Day and James in 1998. Steatosis is the recognized first and usually reversible hit. The development of inflammation, ultimately leading to cell death and fibrosis is the less well-defined second hit. NASH is strongly related with the one or more of the conditions that characterize the metabolic syndrome, including obesity, insulin resistance, hypertriglyceridemia, low levels of high density cholesterol and hypertension. Moreover, there is growing evidence that the metabolic syndrome is caused by an unbalanced production of hormones, and cytokines that leads to a chronic inflammatory state that promotes degenerative diseases and cancer in various tissues including the liver. The Asia-Pacific Region has exposed itself to an increasing trend of NASH due to the high fat/energy-excessive diet, apparent urbanization, increasing affluence and behavioral changes of physical inactivity and, type 2 diabetes. The rates range from 7–40%, which in countries like Japan represents a 3–20-fold increase (depending on age) over the last 20 years. The role of obesity in generating the inflammatory process results from events that occur in adipocytes throughout the body particular within the omental and mesenteric adipose depots (central obesity). The oxidative process results in lipid peroxidation resulting in organelle dysfunction, necrotic and apoptotic cell death. After cancer, cirrhosis from NASH is now the second most common age-related cause of death in type 2 diabetes. Resolution of histopathologic evidence of steatosis including regression of fibrosis, inflammation remains to be the ultimate goal of therapy. Unfortunately there are limited large randomized placebo controlled clinical trials demonstrating efficacy in achieving all of these aims.

APASL/Abstract/S 18.4
Crucial problems of histopathologic diagnosis in nonalcoholic steatohepatitis
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Nonalcoholic steatohepatitis (NASH) is a chronic liver disease, with a low risk of progressive fibrosis, cirrhosis and end-stage liver disease. Another complication is hepatocellular carcinoma (HCC).

The diagnosis of NASH is a clinicopathologic correlation but histopathologic evaluation is required because the parenchymal injury and fibrosis cannot be detected by imaging studies or laboratory test.

This histopathologic study was based on 18 cases, including steatosis, ballooning degeneration, lobular inflammation (polymorphonuclear leukocytes), fibrosis and Mallory bodies.

Our problems are:

1. Statingmild ballooning degeneration is very difficult.
2. Perinuclearfibrosis is difficult to evaluate because the histochemistry laboratory in our Department is not constant.
3. Wewere not very aware in recognizing Mallory bodies (maybe in Indonesia alcoholic hepatitis is very very low).
4. Notevery center has the benefit of seeing miscellaneous liver pathology because liver biopsy is difficult to motivate in patient.
5. Weused to diagnose NASH using previous Brunt classification.

And using Kleiner et al., we think, for the time being, adding simple steatosis and simple steatosis with nonspecific reaction took a longer time to adjust to.

APASL/Abstract/S 19.2

Liver transplant for hepatitis C virus cirrhosis

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Natural history: The hepatitis C virus reinfects the liver allograft as early as the reperfusion phase during surgery. This is associated with the return to pre-transplant viral levels, sometimes within 48 hours following transplantation. Virological replication then reaches a steady state of approximately 1_{log} higher than in the pre-transplant situation. An additional peak of viral replication is seen at the time of acute hepatitis in the allograft at approximately 2–5 months post transplantation. Progression from acute viral hepatitis to chronic hepatitis over the next 12 months is associated with a gradual decline back to levels of virus approximately 1_{log} greater than in the pre-transplant situation. There is unusual variant of acute hepatitis that is cholestatic hepatitis C infection. This occurs in 5–10% of patients, is associated with a cytopathic injury to the allograft due to extremely high levels of virus and may result in early allograft loss. Patients with chronic hepatitis C in the allograft have an increased rate of progression to cirrhosis with cirrhosis rates of approximately 30% at 5 years and up to 50% at 10 years following liver transplantation. Predisposing factors to more severe fibrotic progression in the allograft have been identified. These include:

- high levels of virus pre-transplant and at the 4 month period post-transplant
- donor age
- episode of CMV disease
- pulse corticosteroid therapy
- OKT3 therapy
- There is debate about the role of genotype 1b and genotype 4 and the role of the calcineurin inhibitors (Cyclosporin versus Tacrolimus) and the continuing use of low-dose Prednisone.

Therapy for HCV in the setting of liver transplantation: There have been some studies trying to eradicate HCV from the cirrhotic liver before transplantation. This is associated with the introduction of low-dose Interferon + Ribavirin with increasing doses depending on tolerability. Patients up to Childs Pugh 7 category can be treated, although the sustained virological response rates for genotype 1 (<15%) and genotypes 3 (30%) are low on an intention to treat basis. However, it should be noted that if sustained virological response rate can be obtained in this situation, then viral recurrence in the allograft does not occur. Following liver transplantation, there have been various approaches to treat with Interferon therapy before the episode of acute hepatitis or once chronic HCV has been established. Unfortunately, results of treating early are associated with poor tolerability and sustained virological response rates have only been achieved in some 10–15% of patients for genotype 1. It has been claimed from one group that treatment of genotype 3 infection in the early phase is quite successful but the numbers studied are small. The treatment of established chronic hepatitis C with Pegylated Interferon + Ribavirin are associated with significant reduction in SVRs compared to the non-transplant situation. SVRs are obtained in approximately 40% of patients with genotype 3, but only 20% of patients with genotype 1. They are also associated with significant side effects particularly anaemia, leucopoenia and many centres use Granulocyte Stimulating Factors and Erythropoietin to enable them to continue therapy. **Conclusion:** HCV infection in the setting of liver transplantation arguably is the greatest challenge to liver transplant units throughout the world, improved treatments in the cirrhotic state and under immunosuppression are certainly needed. Furthermore, an understanding of the deleterious effects of immunosuppression itself on the virus need to be further studied.

APASL/Abstract/S 19.3

Liver transplantation and nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease is an increasingly common cause of chronic liver disease. There is a concern that this increased prevalence will translate into an increased demand for liver transplantation. At present, accurate data on the proportion of patients undergoing liver transplantation for non-alcoholic fatty liver disease is not available. However, the number and proportion of patients who have been transplanted with a diagnosis of non-alcoholic fatty liver disease or cryptogenic cirrhosis has not increased in recent years at our centre. Steatohepatitis causes an increased rate of disease expression in hepatitis C virus infection and other chronic liver diseases. As such, the present contribution of steatosis to demand for liver transplant may be more as a cofactor in disease progression of other liver diseases rather than as a primary diagnosis. As well as recipient issues, there are major donor problems related to the presence of hepatic steatosis. The use of grafts with macrovescicular steatosis is associated with increased rates of primary non-function and poorer outcome. The mechanisms by which steatotic livers develop primary non-function are multifactorial, and include impaired hepatocyte metabolism, physical effects of lipid and increased sensitivity to oxidative stress. Strategies to improve the outcomes of patients receiving steatotic grafts are under investigation and may help redress the balance between supply and demand for donor livers. Fatty liver disease may develop following liver transplantation. Patients using standard immunosuppressive agents are at increased risk of developing

hypercholesterolaemia, diabetes mellitus hypertension and obesity, and these are recognised risk factors for insulin resistance syndrome/fatty liver disease. These issues are very important aspects of care in the postliver transplant patient to reduce the risk of vascular disease and postliver transplant steatohepatitis.

APASL/Abstract/S 20.2
Chronic hepatitis B; current and future management
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The primary goal of treatment for chronic hepatitis B is to eliminate or permanently suppress hepatitis B virus (HBV) replication before irreversible liver damage develops. Treatment is indicated for patients in the immune clearance and reactivation phases. During the last decades, major breakthroughs have been achieved in treatment of chronic hepatitis B. Currently, three antiviral agents are approved globally for the treatment of chronic hepatitis B: interferon-alpha, lamivudine and adefovir dipivoxil. Interferon-alpha has a limited duration of treatment and leads to a more durable response but side effects are frequent and potentially serious. Lamivudine is effective and well tolerated, but its efficacy is limited by the high incidence of resistance during long-term therapy and the low durability of response after HBeAg seroconversion. Adefovir has a comparable efficacy with a very low frequency of resistance in nucleoside-naïve patients. Adefovir is also effective against lamivudine-resistant strains, but the emergence rate of resistance seems to be relatively high in these patients. Recently, new immunomodulatory therapies and nucleoside analogues have been evaluated for the treatment of chronic hepatitis B. This review will summarize the results obtained with current available treatments and knowledge on the newer antiviral agents such as pegylated IFNs, entecavir, emtricitabine, tenofovir, telbivudine and clevudine.

APASL/Abstract/S 21.3
Obesity and statins in liver disease
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Baclground: At least in developed countries, obesity is reaching epidemic proportions, being present in about 30% of young adults. One of the many sequelae of obesity is hepatic steatosis, which can be present as the only symptom of this metabolic syndrome or occur together with other conditions like type 2 diabetes mellitus or coronary heart disease. In obese subjects, hypercholesterolemia is frequently treated with statins. Currently, six statins are available for clinical use, all with an excellent safety profile. As asymptomatic elevations in liver enzymes are common in patients who are placed on statins, the issue of using them in patients with fatty liver disease is relevant. **Statin hepatotoxicity:** Although some observations in animals suggested that statins may cause liver disease, no predictable hepatocellular necrosis occurred in humans. Statins have no signature pattern of hepatotoxicity as all common patterns of liver injury (hepatocellular, cholestatic or mixed) have been reported with all available statins. The most common clinical hepatic manifestation is asymptomatic elevation in aminotransferases and this appears to be a class effect of statins. The incidence is less than 3% and with a minor dose-related increase. In a meta-analysis evaluating of 49 275 patients who participated in 13 large, placebo-controlled trials, therapy with statins at low-to-moderate doses was not associated with a significant increase in liver enzyme elevations compared with placebo. Very rarely, after initiating statins, liver enzymes can rise without evidence of liver dysfunction and decrease upon stopping or reducing the dose. Irreversible liver damage leading to death or liver transplantation appears to be extremely uncommon. The estimated risk of fulminant liver failure attributable to lovastatin is two in one million patients. Liver transplantation was performed for presumably statin induced acute liver failure in three patients. **Statins in patients with nonalcoholic fatty liver disease:** NAFLD is common in patients with hyperlipidemia and type 2 diabetes (primary targets for long-term statins) but the presence of fatty liver disease may itself portray higher cardiovascular risk, necessitating statin therapy. Furthermore, fatty liver is frequently present in conjunction with an other liver disease i.e. chronic hepatitis C. The studies examining the safety of statins in patients with NAFLD are limited, but the existing data provide some evidence that they can be used safely. Hyperlipidemic patients with elevated baseline ALT are at not higher risk for hepatotoxicity than patients with normal ALT. Some individuals with elevated baseline liver enzymes have increases in their liver biochemistries, whether or not they receive statins. No worsening of hepatic histology by statins was found in a few patients with biopsy-proven NASH treated for about 2 years. Some patients exhibited an improvement. **Unresolved issues:** The natural history of elevated aminotransferases on statins, continued at the same doses for many years, is unknown. As statins have been shown to cause various in rodents, concerns about the potential carcinogenicity of long-term use of statins have been raised. A meta-analysis of five large clinical trials demonstrated no association between statin use over a 5-year period and the risk of fatal and nonfatal cancers. **Conclusion:** Unquestionably, statins are extremely valuable drugs with no evidence to cause significant liver disease.

APASL/Abstract/S22.1
Predictive value of arterial ammonia for clinical outcome and complications in acute liver failure
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Background: In acute liver failure (ALF), brain is exposed to increased amount of ammonia. However, human studies defining the clinical significance of ammonia in ALF are lacking. The aim of this prospective study was to evaluate the relation of arterial ammonia levels at admission with survival and complications among patients with ALF. **Methods:** 80 consecutive ALF patients admitted from March 2001 to December 2003 were followed up till death or complete recovery. All had arterial ammonia estimation at admission (Enzymatic method, Randox lab, UK). Logistic regression analysis was performed to identify the independent predictors of mortality. **Results:** 42 (52.5%) patients died. Non-survivors had significantly higher ammonia levels than the survivors at admission (212 ± 148 vs. 123 ± 128μmol/L, $p = 0.005$). An arterial ammonia level of $\geqslant$ 123.9 μmol/L was found to predict mortality with 81% sensitivity and 79% specificity. Patients with higher ammonia levels also developed more complications like deeper encephalopathy ($p = 0.055$) cerebral edema ($p = 0.020$), need for ventilation ($p = < 0.001$), and seizures ($p = 0.006$). Logistic regression analysis showed age, presence of cerebral edema at admission and arterial ammonia to be independent predictors of mortality (RR: 1.059, 15.164, 1.008 respectively). Incorporating these three variables, a risk score for mortality was derived: –3.578 + 0.057 age + 2.719 edema + 0.008 ammonia. **Conclusion:** Ar-

terial ammonia levels at presentation are predictive of outcome and can be used for risk stratification. Therefore trials evaluating ammonia lowering therapies are warranted in patients with ALF.

APASL/Abstract/S22.3
MARS therapy acute-on-chronic liver failure
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The vast majority of patients that are referred to a specialist hepatological centre suffer from acute deterioration of their chronic liver disease. Yet, this entity of acute-on chronic liver failure remains poorly defined. With the emergence of newer liver support strategies, it has become necessary to define this entity, its pathophysiology and the short and long term prognosis. Current research focusses upon how a precipitant such as an episode of gastrointestinal bleeding or sepsis may start a cascade of events that culminate in end-organ dysfunction and liver failure. Our current strategy for the management of liver failure involves supportive therapy for the end-organs with the hope that the liver function would recover if sufficient time for such a recovery is allowed. Because, liver failure, whether of the acute or acute-on-chronic variety, is potentially reversible, the stage is set for the application of newer liver support strategies to enhance the recovery process. The molecular adsorbents recirculating system (MARS), which is based upon the principle of albumin dialysis may provide an opportunity to create an environment in which further liver injury can be prevented and enhanced liver regeneration may occur.

Post Graduate Course

APASL/Abstract/PGC I.1.1
Abstract withdrawn

APASL/Abstract/PGC I.1.2
Hepatitis C virus and malignancy
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Hepatitis C virus (HCV) is a hepatotropic virus that causes chronic hepatitis, fibrosis and cirrhosis. HCV is associated with the development of primary liver tumors, i.e. hepatocellular carcinoma, cholangiocarcinoma and lymphoma. This article reviewed HCV-related malignancies, their prevalence and probable oncogenesis.

APASL/Abstract/PGC I.1.3
Early detection in patients with hepatitis C virus infection
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Epidemiology of hepatocellular carcinoma (HCC) in Japan

Eighty percent of HCCs found in Japanese hospitals are suffering from hepatitis virus infectious diseases. 70% of HCC patients are suffering from hepatitis C virus (HCV) cirrhosis.

The age is the most important factor when we are dealing with HCC patients with HCV. The average age of HCV–HCC patients in Japan is the later half of 60s. This advanced age tendency is increasing because the of the aging of Japanese society, in which the average life expectancy is 80 years old. Therefore, we have to consider their age and the remaining expectancy after treatment of HCCs, and at the same time, the higher quality of their lives (QOL).

At the same time we have to remember the existence and increase of non-B and non-C HCCs. The ratio of non-B and non-C HCCs between whole HCCs was less than 5% ten years ago. This ratio has increased up to 30% in the present time especially in the city area. It is suggested that a part of this increase is caused by an increase in non-alcoholic steatohepatitis (NASH). Increase in NASH patients could be explained by the changes of life style habits in recent Japanese population such as motorization, computerization and food habits involving calories and high fat.

Early detection program of HCCs in Japan

Blood test for α-feto-protein (AFP), its lectin fractioning (L3) and PIVKA2 should be checked every 1 or 2 months.

Imaging diagnosis is the most important method for detection of HCCs in the high risk group patients. The diagnostic imaging modalities used in the detection of HCCs are ultrasound (US), contrast CT and MRI. PET has been used for detection of malignancy in the whole body. However, it is a pessimistic view that FDG–PET can detect HCCs in the liver because glucose is metabolized actively in the normal liver.

Recently several contrast agents have been developed for ultrasound of the liver imaging. SonoVue has been launched in European countries and China. Contrast US has been used for characterization of the known liver lesions with B-mode US and/or dynamic CT. Accuracy of HCC diagnosis of contrast ultrasound is the same between contrast US and CT. Contrast US is superior to contrast CT in diagnosis of histological differentiation such as well, moderately and poorly differentiated HCCs. Rapid spreading of contrast US is disturbed by the necessity of doctors' skills to make an accurate diagnosis using contrast study comparing contrast CT.

Next generation contrast agent, Sonazoid is expected to perform both detection and characterization of HCCs because of their ability to make a Kupffer imaging. This microbubble agent could be phagocytosed by the macrophages in the reticuloendothelial system such as the liver and spleen. By using these characteristics we could make more precise diagnosis of liver lesions.

Multi row detector CT (MDCT) has spread rapidly because of higher spatial resolution and higher throughput. MDCT has made it possible to detect slight increases in arterial blood flow and a slight decrease in portal blood flow in the liver lesions seen in the cirrhosis liver. At the same time, X-ray exposure has been increased in accordance with a wide use of MDCT.

MRI is useful when the patient has an iodine allergy, and to avoid further X-ray exposure when the patients are checked frequently for many years. At the same time, SPIO-MRI is used for Kupffer imaging, like Sonazoid and Levovist contrast ultrasound.

Treatment of HCCs

It is important that effective and safe therapeutic methods be developed when the program for early detection of HCCs in high risk patients for HCCs works well. Surgical treatment including liver transplantation has been established. However, we have to consider that the recurrence ratio in patients with HCV positive HCCs, after first nodule is treated, is very high; 25% per year. It might be right that a curative ratio less than 10% is enough when we take a very high aberrant recurrence ratio into consideration.

We have several modalities of local ablation therapy: TAE, PEI, PMCT, RFA and freezing ablation therapy. Recently, high

intensity focus ultrasound (HIFU) has also been coming up because it does not need a needle puncture.

Local ablation therapy can display its greatest force when the HCC lesion is detected in an early stage. Therefore, early diagnosis is the most important factor governing their prognosis.

Prevention of HCC carcinogenesis

Prevention of HCC carcinogenesis would be the most important role for hepatologists after early detection and early treatment of HCCs. Interferon and other chemoprevention methods should be developed and widely used in Asian countries.

APASL/Abstract/PGC I.1.4
Carcinogenesis of hepatocellular carcinoma with hepatitis B virus infection
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Hepatitis B virus (HBV) remains the most important risk factor for hepatocellular carcinoma (HCC) worldwide. An estimated 300 million individuals worldwide are chronically infected with HBV. Several risk factors increase the risk of HCC in HBV carriers, including host factors (older ages, male gender, severity of underlying liver disease, Asian or African ethnicity, family history of HCC), viral factors (HBV replication, HBV genotype/mutant, HCV coinfection), and external factors (exposure to aflatoxin, alcohol, and cigarette). HBV vaccination, antiviral therapy with sustained suppression of viral replication, and reduction of exposure to aflatoxin are important preventive measures.

APASL/Abstract/PGC I.2.1
Hepatocellular carcinoma not associated with either hepatitis C or hepatitis B
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Cirrhosis from any cause predisposes to hepatocellular carcinoma (HCC). It is quite uncommon to find HCC in the absence of cirrhosis. Cirrhosis related to either hepatitis C virus (HCV) or hepatitis B virus (HBV) infections represent the major known risk factors for HCC. Persistent HBV or HCV infection account for over 80% of HCC cases worldwide.

Although the regenerative activity inherent in cirrhosis is attributed to predispose to HCC, malignant transformation is also attributed to a specific disease state that leads to cirrhosis. In the absence of cirrhosis, studies have found that HCC almost always occurs in a histologically abnormal liver and the mere existence of chronic liver disease represents a potential risk for HCC development.

APASL/Abstract/PGC I.2.3
Recent progress in imaging of hepatocellular carcinoma from Ultrasound to PET Scan
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With the recent progress in imaging modalities, detection of small hepatic nodular lesions has become much easier, but differential diagnosis still remains difficult. However, a combination of tomographic imaging techniques and angiography such as US angiography, CT arteriography (CTA), and CT during arterial portography (CTAP) has contributed considerably to the differentiation of overt (advanced) hepatocellular carcinoma (HCC) from benign or premalignant/borderline lesions. With such techniques, estimation of the grade of malignancy is also possible.

Recently, non-invasive ultrasonographic vascular imaging techniques have been developed, such as color Doppler, power Doppler, and enhanced Doppler imaging. In particular, gray-scale contrast harmonic imaging proves useful in the management of HCC and recently replaced some of the roles of MRI and CT; ultrasonographic visualization of the vascularity of viable cancer cells is essential for the US-guided interventional therapy of HCC.

APASL/Abstract/PGC I.2.4
Pathology of hepatocellualar carcinoma: up-to-date
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According to the establishment of follow-up system of the high-risk populations and the remarkable advance in diagnostic imagings, increasing number of small hepatocellular carcinoma (HCC) of the early-stage has been detected and successfully treated. Extensive studies on small HCC of the early stage have explored that the majority of early stage HCC is indistinctly nodular and well differentiated, and it is frequently difficult to differentiate early-stage HCC from dysplastic nodules. Many of the early-stage HCCs proliferate with a stepwise process of dedifferentiation, and a 'nodule-in-nodule' appearance morphologically reflects the progression of dedifferentiation, process. However, many of the HCCs are still detected in advanced stage, and it is also important to understand that HCC sometimes presents unusual morphological features such as sarcomatous change, intrabile duct or intraatrial tumor growths in daily practice.

APASL/Abstract/PGC I.2.6
Portal vein tumor thrombosis in HCC: is it really the end of the road?
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In a previous study by angiograms, the portal vein was shown to be often used as an outflow tract of arterial blood, supplied to cancer nodules by hepatic artery. This may explain, in part, the high frequency of portal vein tumor thrombus (PVTT) in hepatocellular carcinoma. The average life span of patients with PVTT is only 6 months. Every effort including surgical removal and liver transplantation failed to reveal that these are significant treatment modalities to prolong patients' lives. However, we have recently experienced the success of treating these patients by the combination of 5FU+Interferon treatment. We have treated more than 150 cases with PVTT in either the major trunk or the first branch of the portal vein. Among these, more than 15% of the patients showed complete response (CR) after the treatment. This is unprecedented, at least for us. In a previous study, we have revealed that the cases with DCP positive hepatocellular carcinoma tend to show higher frequency of portal vein tumor invasions (1). In this publication, those without DCP positivity only developed PVTT in the range of 1–2%/year, whereas with DCP positivity the range was 20% (1). DCP is a tumor marker that is produced by tumor cells on

the condition that Vitamin K is deficient inside hepatocytes. Therefore, we decided to conduct a study to reveal whether Vitamin K can prevent the PVTT development in DCP-positive HCC. We have also attempted to reveal the function of Vitamin K on tumor growth (2). Among the many signaling systems inside hepatocytes, we revealed that PKA plays a critical role in suppression of the tumor gross *in vitro*. Because of its possible tumor suppressive effect and ability to prevent portal vein tumor thrombus, now phase 3 study of the function of Vitamin K in the prevention of tumor recurrence is ongoing nationwide in Japan. We also thought of the possibility of pharmacogenomic measures to predict the treatment effect (3). In this study, we analyzed hepatocellular cell lines to see whether there is any gene expression profiles which are associated with this treatment effect (3). In this study, we identified the genes which may predict treatment outcome prior to the initiation of chemotherapy (3). In clinical settings, patients are urgently seeking remedies for of immediately life threatening disorders and we should continue to make every effort to treat this condition.

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APASL/Abstract/PGC I.3.1
Liver resection in HCC

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Introduction: The aim was to define the evidence-based guideline for the surgical treatment in hepatocellular carcinoma (HCC). **Materials and Methods:** We searched the papers by using Medline Dialog System with 4 keywords: HCC, surgery, English papers, and in the recent 20 years. The clinical evidence was categorized into 5 levels: level-1 (randomized controlled trial), level-2 (prospective concurrent cohort study), level-3 (retrospective historical cohort study), level-4 (pre-post study), and level-5 (case series). Based on the evidence level, we made the guidelines on 5 surgical issues: surgical indication, procedure, care, prognosis, and adjuvants. **Results:** We identified and reviewed 915 papers, 100 of which were selected as the source of the guideline. The evidence level comprised level-1 (13%), level-2 (11%), level-3 (52%), and level-4 (24%). 1) For surgical indication, Makuuchi's criteria and ICG clearance test would be recommended to use. 2) In operative procedure, systematic segmentectomy would be the most favorable option of choice. 3) In perioperative care, the nutrition support and hemihepatic vascular occusion were recommended to use. 4) On prognostic factor, 3 factors (vascular invasion, HCC stage, and liver function) were the most powerful prognostic factors. 5) As postoperative adjuvants, 3 interventions (retinoid, iodine-lipiodol, and immunotherapy) had positive effect to reduce HCC recurrence. **Conclusion:** We have made a Japanese guideline, showing that surgery is the primary option of choice for HCC.

APASL/Abstract/PGC I.3.2
Living donor liver transplantation for hepatocellular carcinoma

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One million new cases of hepatocellular carcinoma(HCC) occur each year worldwide, accounting for approximately 1 million deaths annually. Hepatectomy has been the mainstay of therapy for these tumor, although 41% of these tumors are nonresectable due to tumor inaccessibility or extensive cirrhosis with poor hepatic functional reserve. In recent years, however, progress has been achieved in the treatment of HCC, and an increasing number of patients can survive with mwny therapeutic modalities including transcatheter arterial chemoembolization, percutaneous alcohol injection, radiofrequency cytoablation, and liver transplantation. Liver transplantation is theoretically an excellent treatment modality for HCC because this procedure can cure not only the tumor but also the underlying cirrhosis. Through most of the 1980s, however, results of liver transplantation for extensive unresectable HCC were discouraging, with high recurrence rates and patients survival of only 30% at 3 years. Because of the limited supply of cadaveric donor organs and the better organ allocation, the Milan criteria is widely accepted as patients selection criteria of liver transplantation for HCC. According to these criteria, liver transplantation for HCC is limited to patients with solitary tumor up to 5 cm in diameter or with no more than 3 nodules, each 3 cm or less in diameter. Patients with extrahepatic spread and/or macrovascular invasion is ineligible. When the Milan criteria is instituted, the 5-year survival rates have reached 70%. Since living donor liver transplantation has been a successful and fully accepted treatment for adult patients with end-stage liver disease, interest in this mpdality as the treatment for HCC has arisen. The Milan criteria are based on deceased organ allocation. The situation is quite different from living donor liver transplantation, where the donor comes from self-giving and dedication. Additionally, many recently published data demonstrate that the guidelines of the Milan criteria may be too restrictive, potentially excluding some patients who might benefit from liver transplantation. The increasing incidence of HCC worldwide ensures that HCC will continue to be an important and growing indication especially for living donor liver transplantation. Therefore, it becomes crucial to establish new patient selection criteria for living donor liver transplantation

APASL/Abstract/PGC I.3.3
Intraoperative Ultrasound

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Intraoperative ultrasound (IOUS) is now considered to be indispensable in the diagnosis and the surgical treatment for liver tumors. In this session we described the basic and novel techniques of IOUS in liver surgery. The simplest use of IOUS is detection and diagnosis of the invisible and nonpalpable tumors. However, especially in patients with chronic viral hepatitis, the differentiation of classical hepatocellular carcinoma (HCC) from other precancerous lesions is sometimes difficult in

IOUS. It is possible that the development of enhanced materials for ultrasound enables us to make their differential diagnosis. By injecting contrast materials systemically or via portal vein, the undetectable tumors by conventional IOUS can be demonstrated clearly. HCC invades the portal venous branch and cancer cells detach from the tumor into the portal blood flow, which would induce intrahepatic metastases in the distal part of the portal perfusion area. Therefore, systematic resection has been theoretically considered to be preferable in the resection of HCC. And it has already been proved clinically that patients with anatomical resection have significantly better prognosis than those with non-anatomical resection. The technique of staining portal branches for systematic segmentectomy is demonstrated precisely. As for the interventional usage of IOUS, open biliary drainage for patients with Klatskin tumor should be introduced. Less involved and less dilated bile duct should be punctured before resection of the hemiliver which has more involved and more dilated bile duct. Using this technique we can puncture 2-mm intrahepatic bile ducts. Doppler ultrasonography is another new technique in ultrasound. Doppler ultrasonography is not only necessary in confirming the flow after anastomoses but also available in diagnosing hepatic venous congestion. Just after the dissection of hepatic vein, venous anastomoses can be detected by Doppler IOUS in only approximately 20% of the cases. In the other cases, venous anastomoses cannot be found and the portal branches in the veno-occlusive area are regurgitated. Doppler IOUS enables us to diagnose the hepatic congestion and to decide whether or not we reconstruct the dissected hepatic veins. In summary, the development of ultrasound has extended the possibility of IOUS in hepatobiliary surgery and transplantation surgery.

APASL/Abstract/PGC I.3.4
Local ablation therapy: from ethanol injection to radiofrequency ablation
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Japan

Backgrounds & aims: In hepatocellular carcinoma, surgical resection plays a limited role as underlying cirrhosis or multiple lesions often contraindicates surgery. Furthermore, this cancer frequently recurs even after apparently curative resection. Consequently, various non-surgical therapies have been developed. Among them, percutaneous ethanol injection therapy (PEIT) has been widely used as a standard therapy for small hepatocellular carcinoma. On the other hand, percutaneous radiofrequency ablation (RFA) has recently been introduced in the treatment of hepatocellular carcinoma. We conducted a randomized controlled trial to compare their survival and recurrence. **Methods:** Two hundred and thirty-two patients with hepatocellular carcinoma who had three or fewer lesions, each 3 cm or less in diameter, and liver function of Child–Pugh class A or B were entered into a randomized controlled trial. We performed RFA percutaneously with a cooled-tip electrode. We used the multiple-needle insertion method in PEIT. As a general rule, we ablated not only the tumor but also some amount of surrounding tissue. Two or three days after the treatments, CT was performed to determine the efficacy. If there were any possible undestroyed portions, RFA or PEIT was repeated until the entire tumor necrosis. All patients had CT and US every 4 months to find any recurrence. The primary endpoint was survival, and the secondary endpoints were overall recurrence and local tumor progression. **Results:** One hundred and eighteen patients were assigned to RFA and 114 to PEIT. The number of treatment sessions was smaller (2.1 vs 6.4 times, $P<0.0001$) and the length of hospitalization was shorter (10.8 vs 26.1 days, $P<0.0001$) in RFA than in PEIT. Four-year survival rate was 74% (95% CI, 65–84%) in RFA and 57% (95% CI, 45–71%) in PEIT. RFA had a 46% smaller risk of death (adjusted relative risk 0.54 (95% CI, 0.33–0.89), $P=0.02$), a 43% smaller risk of overall recurrence (adjusted relative risk 0.57 (95% CI, 0.41–0.80), $P=0.0009$) and an 88% smaller risk of local tumor progression (relative risk 0.12 (95% CI, 0.03–0.55), $P=0.006$) than PEIT. The incidence of adverse events was not different between the two therapies. **Discussion:** RFA improves survival of patients with small hepatocellular carcinoma compared with PEIT. This result can probably be explained by the fact that RFA reduces overall recurrence and local tumor progression through its more reliable local antitumor effect. Actually, there was no statistical difference in the recurrence rates away from the original lesion between the two therapy groups ($P=0.560$), and thus, the difference in overall recurrence was mainly because of the difference in the local control of the primary tumor. We have put no restrictions on lesion location. We have successfully used RFA or PEIT on more than 99% of patients, some of whom had lesions near the heart, gallbladder, diaphragm, or on the surface of the liver. In this study, we did not have any case in which we had to give up treatment because of tumor location. We have not restricted the number of treatment sessions. We have repeated RFA or PEIT until CT demonstrates entire tumor necrosis. As a result, we have successfully ablated tumors in more than 99% of cases. In this study, we did not have any case in which the final CT demonstrated incomplete tumor ablation. The incidence of adverse events was not significantly different between the two treatments, although previous comparison studies have suggested that RFA would have higher complication rates than PEIT. Reported mortality rates are 0.3–0.5% and morbidity rates are 2.2–8.9% in RFA,while they are 0.1% and 3.2%, respectively, in PEIT. Common complications are bleeding, biliary injury, and seeding of malignant cells in both procedures. This study was restricted to tumors 3 cm or less in diameter, although larger tumors have also been treated with these procedures. We speculate that the superiority of RFA to PEIT would be more significant in middle-size or large tumors because of its more reliable local effect. This study was also restricted to patients with relatively good liver function, although some patients in Child–Pugh class C have been treated with these procedures. We are not sure that RFA could achieve better outcomes in patients with poor liver function, because preserving liver function might be more important than achieving curative treatment. **Conclusion:** Judging from the higher survival but similar adverse events, RFA is superior to PEIT in the treatment of small hepatocellular carcinoma.

APASL/Abstract/PGC I.3.5
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APASL/Abstract/PGC I.3.6
Emergent chemoembolization for spontaneous rupture of hepatocellular carcinoma
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Objective: The purpose of this study was to analyze the clinicoroentogenologic findings and the prognostic factor of emergent embolotherapy (E-TAE) for 107 patients with ruptured hepatocellular carcinoma (R-HCC). **Materials and Methods:** From 1983 to 2003, 107 patients with R-HCC underwent E-TAE. We evaluate the prognostic factor of E-TAE in these patients. The patients were divided into two groups. (group A ($n=88$):

hypobilirubinemia less than 3.0 mg/dl, group B ($n = 19$): hyperbilirubinemia). Forty-six patients (43%) had portal vein tumor thrombus (PVTT). Among 61 patients without PVTT, six had hepatectomy following E-TAE. Chemoembolization with lipiodol emulsion and gelatin sponge particles was preferred for patients without hyperbilirubinemia, while embolization with particles of gelatin sponge was selected for patients with extensive tumors or hyperbilirubinemia. **Results:** Hemorrhage was stopped immediately after embolization. Progressive jaundice developed in 16 patients who died of hepatic failure and repeated bleeding within 10 days after E-TAE. Twelve patients (13.6%) in group A (12/88), and 17 (89.5%) in group B (17/19) died within 1 month after E-TAE. Fourteen patients (15.9%) in group A and no patient in group B survived more than 2 years after E-TAE. Nineteen (41.3%) of 46 patients with PVTT and 10 (16.4%) of 61 patients without PVTT died within 1 month. Thirteen patients without PVTT (21.3%) and only one patient with PVTT (2.2%) survived more than 2 years after E-TAE. Eight patients in group A, including four patients treated by hepatectomy following E-TAE, survived more than 5 years after E-TAE. **Conclusion:** Hyperbilirubinemia is a main factor in influencing the risk and prognosis of E-TAE for these patients, whether PVTT is present or not.

APASL/Abstract/PGC I.3.7
Chemotherapy of advanced stage of hepatocellular carcinoma
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Hepatocellular carcinoma (HCC) is a major cause of death among the malignancies in Asia. Early detection of HCC because of advanced imaging diagnostic technique has contributed to improving its 5-years survival. However, patients in early stage of HCC who are the subjects not only of local therapy such as PEI and RFA, but also of surgical resection, are so limited. That is, we have to take the huge number of patients with advanced HCC seriously. In Japan, arterial infusion of low dose FP(5-FU and CDDP) via hepatic artery and combination of 5-FU and interferon are performed in 29 of such advanced patients. Efficacy rate over PR was 48%, while survival rate was 48% in 1-year survival and 15% in 3-year survival.

In this postgraduate course, chemotherapy in advanced stage of HCC at present will be summarized.

APASL/Abstract/PGC I.4.3
Abstract withdrawn

APASL/Abstract/PGC II.3.1
Abstract withdrawn

APASL/Abstract/PGC III.1.5
Transient elastography: a new non-invasive method for assessment of hepatic fibrosis
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Background & Aims: The degree of liver fibrosis in chronic liver disease is classified into fibrosis stages from F0 (no fibrosis) to F4 (cirrhosis), which has been found to be well correlated with the risk of hepatocellular carcinoma. (1–3). However, the determination of fibrosis stage requires histologic examination of liver biopsy specimen. Recently developed transient elastography apparatus (Fibroscan) provides completely non-invasive measurement of liver stiffness, and the correlation between the stiffness thus measured and liver fibrosis stage has been validated (4–6). **Patients & Methods:** A total of 137 patients, 127 with chronic liver disease and 10 with normal liver, were enrolled (Table 1). The stiffness of the liver measured by the elastography, presented in kPa, was compared with laboratory tests, etiology of liver disease, liver fibrosis stage, and other characteristics of patients. Liver biopsy was obtained in 54 patients with hepatitis C, and the correlation was examined. An ultrasonic transducer (3.5 MHz) is mounted on the axis of a vibrator. The vibrator generates an elastic wave which propagates through the subcutaneous tissues and the liver. During the propagation of the shear wave, pulse echo ultrasonic signals are acquired and allow to measure the shear wave velocity. Measurements are totally non-invasive and performed on the right lobe of the liver through intercostal space between 25 and 45 mm from the skin surface. For each patient, several measurements (usually 10) were taken. The whole examination duration is around 5 min. Box plots were used to study the liver stiffness and other laboratory tests distribution according to the fibrosis stages. The correlation coefficient of Spearman estimated a trend between liver stiffness, albumin concentration, bilirubin concentration, platelet cell count, and the fibrosis stages. We plotted liver stiffness measured by Fibroscan against bilirubin, albumin concentration, and platelet cell count. Regression curves were plotted using spline regression. **Results:** Liver stiffness was well correlated with fibrosis stage ($R = 0.688$) using the Spearman rank correlation (Table 2). The stiffness, after logarithmic transformation, was correlated with laboratory tests including serum total bilirubin concentration , albumin concentration, and platelet count (Fig. 2). Linear correlation with total bilirubin or albumin was higher in the range over 10 kPa, which is suggestive of cirrhosis, than in the range below ($r = 0.354$ vs. 0.014, 0.25 vs. 0.053). In contrast, the correlation with platelet count was higher in the range below 20 kPa ($r = 0.517$ vs. 0.085) (Fig. 3). **Conclusions:** As compared with laboratory tests, transient elastography showed wide dynamic range in differentiating liver stiffness covering both cirrhotic and non-cirrhotic patients. Sequential determination of liver stiffness may be useful in assessing progression of chronic liver disease.

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APASL/Abstract/PGC III.1.4
Comparison of Contrast Enhanced US and Histopathologic Finding in Hepatocellular Carcinoma
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Distinguishing Benign and Malignant Focal Liver Lesions by Kupffer Imaging with Sonographic Contrast Agent, Levovist **Purpose:** To evaluate the differentiability of the late-phase harmonic sonography (Kupffer imaging) with the contrast agent Levovist between benign and malignant liver lesions. **Methods:** 150 consecutive patients (102 men and 48 women; mean age 65 years, range 45–80) with a focal liver lesion suspected of hepatocellular carcinoma on conventional sonography were examined with contrast-enhanced harmonic sonography with Levovist. The Kupffer imaging was generated by stimulated acoustic emission 5 min after intravenous injection of 7 ml Levovist (250 mg/dl). The 'defective' Kupffer imaging was defined as no enhancement inside the tumor and the 'non-defective' imaging as otherwise. Ultrasound-guided needle tumor biopsy was performed in each case and histopathology was evaluated with hematoxylin and eosin staining. **Results:** 82 (55%) lesions showed 'defective' Kupffer imaging while 68 (45%) showed 'non-defective' one. On histopathologic examination, 82/90 (91%) in the former group were either poorly or moderately differentiated hepatocellular carcinoma, while 57 (95%) out of 60 tumors in the latter group were diagnosed as dysplasia or well differentiated hepatocellular carcinoma. Except 5 cases who chose to receive ablation because of being well differentiated hepatocellular carcinoma, 52 cases were followed up with no treatment group. During three years of observation, only 7 patients of them developed turned out to be classical hepatocellular carcinoma. **Conclusions:** Kupffer imaging is a promising non-invasive technique to differentiate between benign and malignant liver tumors, the use of which may obviate invasive and expensive further diagnostics.

Using Contrast-Enhanced US to assess the effectiveness of TAE for HCC: Histological confirmation **Objective:** The present study was prospectively performed to elucidate the relationship between the contrast-enhanced Doppler signals of hepatocellular carcinoma (HCC) after TAE (transarterial embolization) and histological confirmation of viable tumor cells. **Subjects and Methods:** Between Sep. 2001 and Sep. 2002, 74 nodules in 74 patients were examined. HCC-related Doppler signals were examined after TAE, and its correlation with tumor viability, US-guided biopsy specimens was analyzed. We scanned lesions using contrast-enhanced wideband harmonic US after injection of a garactose-palmitic acid contrast agent (Levovist). Lesions were considered to have residual viable tumor if presenting perfusion images or residual Doppler signals in tumor. Ultrasonographic examination was performed with an Advanced Dynamic Flow system (Toshiba, Japan) with a 3.5 MHz convex probe. **Results:** After TAE, 50 of the 74 lesions(67%) showed residual Doppler signals on Contrast-enhanced US. Viable tumor cells were histologically proven in 43 of 50 nodules(83%) that presented Doppler signals, while only 3 of the 24 nodules(13%) negative for Doppler signals showed viable tumor cells ($P < 0.001$). **Conclusion:** Tumor blood flow detected by contrast-enhanced harmonic US indicates the presence of residual viable tumor cells after TAE. Contrast-enhanced harmonic US is useful in evaluating the effect of TAE for HCC.

APASL/Abstract/PGC III.2.1
Ultrasound-guided liver biopsy
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Diagnostic value: In our department, most liver biopsy is performed to check for inflammatory activity and fibrosis grade before interferon therapy for chronic hepatitis C. Liver biopsy should be performed to diagnose the patient with jaundice or liver injury whose etiology is unknown. Liver biopsy can reveal the following liver diseases: steatosis or steatohepatitis, autoimmuno-hepatitis, primary biliary cirrhosis and sclerosing cholangitis, idiopathic portal hypertension, congestive liver, and so on. Biopsy for nodular lesion of the liver can reveal histological diagnosis or differentiation degree of malignant tumors. **Prerequisite:** Adequate coagulation is required, for example, thrombocyte count must be more than 50 000/μl; prothrombin time more than 50%. Also there must be no massive ascites. Mastery of the technique is needed for safe tumor biopsy. As it is difficult to direct the biopsy needle to the nodule target of 1 cm or less, the target nodule must be sonographically visualizable and it is preferable if the size is more than 1 cm. Although liver biopsy has a low rate of complication, patient's cooperativeness is still required. The patients must be informed of the potential risks. Written, informed consent should be obtained. **Preparation:** Ultrasound equipment which is able to use color Doppler imaging and tissue harmonic imaging is better for liver biopsy. Color Doppler can visualize vascular images including vessels to be avoided. As tissue harmonic imaging can reduce side lobe artifacts and reverberation, tumor and vessels are visualized more clearly. A sterile probe sheath or sterilized probe must be prepared. An exclusive puncture attachment for the probe is necessary. If the attachment is capable of altering the puncture angle, tumor biopsy becomes easier. I encourage the use of the mechanical biopsy needle because of its reliability. Other preparations include intravenous access, premedication, local anesthesia and sample preparation. **Methods:** The ultrasound equipment we use in our department for liver biopsy or radio frequency ablation (RFA) is the Hitachi EUB6500 (Hitachi Medical Corp.). This is a high performance and compact ultrasound machine, and includes wide band convex probe and pulse inversion harmonic imaging for both tissue and contrast. We have newly developed exclusive variable-angle puncture attachment for this probe. This attachment is fitted with a needle guide replacement kit (Ultra-Pro II™; Civco Medical Instruments Co., Inc.). This kit contains needle sleeves from 20 to 14 G, plastic needle guide and sterile probe sheath. The probe with a puncture metal attachment is covered with a sterile sheath and the plastic needle guide is attached outside the sheath (Figure 1). Numbers 15, 22, 30 and 45 are carved on the metal attachment in the back view. These numbers indicate the puncture angle. The puncture angle can be varied according to the depth of the lesion. Needle sleeves can be exchanged without changing of the puncture angle (Figure 2). The mechanical biopsy needle that we use in our department is the Monopty™ (C. R. Bird, Inc.). Biopsy performed using this needle is speedy and reliable. This needle is sterilized and disposable and its weight is so light (only 65 g) that needle biopsy can be performed one-handed while holding probe in the other hand (Figure 3). Sixteen gauge needle for liver histology and 18 G needle for liver tumor is selected. After skin

disinfection, local anesthesia must be administrated, in a quantity enough to reduce pain from the skin to the liver capsule. A skin incision of around 3 mm is necessary. For a safe biopsy, the tip of the needle must be constantly monitored. Making a preliminary inspection to select a safe puncture line is very important. The selected puncture line must avoid the bowel, lung, gallbladder, spleen, large vessels and the bile duct. It is best to approach the target nodule when it appears clearly and shallowly to achieve this without taking a deep breath, optimal posture and intercostal plane factors should be taken into account. For example, sitting position for lateral segment, or left lateral position for posterior segment is better. When the biopsy needle runs off from the expected puncture line in cirrhotic liver or deep lesion, you can tilt the probe to the right or the left, monitoring the tip of the needle to revise the direction of the needle (Figure 4). **Complication:** Bleeding is the most problematic complication in liver biopsy. Possible bleeding sites include the intraperitoneal space, under the liver capsule (Figure 4), the intrathoracic space, and/or the bile duct (Figure 5). Hemobilia causes abdominal pain and obstructive jaundice. Pneumothorax seldom occurs under ultrasound-guided liver biopsy. **Monitoring after biopsy:** In principle, we let the patients take complete bed rest for at least 4 h. After biopsy, monitoring of vital signs is needed at least once every 30 min. Attention should be paid to any pain or discomfort because these signs may indicate bleeding. If these signs are observed, subsequent ultrasound, CT or blood examination must be requested. Antibiotics are administrated for 1 day to prevent infection. In our department, patients must be in hospital for at least 24 h after biopsy.

APASL/Abstract/PGC III.2.2
Local ablation therapy: from ethanol injection to radiofrequency ablation
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Background & Aims: In hepatocellular carcinoma, surgical resection plays a limited role because underlying cirrhosis or multiple lesions often contraindicates surgery. Furthermore, this cancer frequently recurs even after apparently curative resection. Consequently, various nonsurgical therapies have been developed. Among them, percutaneous ethanol injection therapy (PEIT) has been widely used as a standard therapy for small hepatocellular carcinoma. On the other hand, percutaneous radiofrequency ablation (RFA) has recently been introduced in the treatment of hepatocellular carcinoma. We conducted a randomized-controlled trial to compare their survival and recurrence. **Methods:** Two hundred and thirty-two patients with hepatocellular carcinoma who had three or fewer lesions, each 3 cm or less in diameter, and liver function of Child–Pugh class A or B were entered into a randomized-controlled trial. We performed RFA percutaneously with a cooled-tip electrode. We used the multiple-needle insertion method in PEIT. As a general rule, we ablated not only the tumor but also some amount of the surrounding tissue. Two or three days after the treatments, computed tomography (CT) was performed to determine the efficacy. If there were any possible undestroyed portions, RFA or PEIT was repeated until the entire tumor necrosis. All patients had CT and ultra sonography (US) every 4 months to find any recurrence. The primary endpoint was survival, and the secondary endpoints were overall recurrence and local tumor progression. **Results:** One hundred and eighteen patients were assigned to RFA and 114 to PEIT. The number of treatment sessions was smaller (2.1 vs. 6.4 times, $P<0.0001$) and the length of hospitalization was shorter (10.8 vs. 26.1 days, $P<0.0001$) in RFA than in PEIT. Four-year survival rate was 74% (95% confidence interval (CI) 65–84%) in RFA and 57% (95% CI 45–71%) in PEIT. RFA had a 46% smaller risk of death (adjusted relative risk 0.54 (95% CI 0.33–0.89), $P=0.02$), a 43% smaller risk of overall recurrence (adjusted relative risk 0.57 (95% CI 0.41–0.80), $P=0.0009$) and an 88% smaller risk of local tumor progression (relative risk 0.12 (95% CI 0.03–0.55), $P=0.006$) than PEIT. The incidence of adverse events was not different between the two therapies. **Discussion:** RFA improves survival of patients with small hepatocellular carcinoma compared to PEIT. This result can probably be explained by the fact that RFA reduces overall recurrence and local tumor progression through its more reliable local antitumor effect. Actually, there was no statistical difference in the recurrence rates away from the original lesion between the two therapy groups ($P=0.560$), and thus the difference in overall recurrence was mainly because of the difference in the local control of the primary tumor. We have put no restrictions on lesion location. We have successfully carried out RFA or PEIT on more than 99% of the patients, some of whom had lesions near the heart, gallbladder, diaphragm, or on the surface of the liver. In this study, we did not have any case in which we had to give up treatment because of tumor location. We have not restricted the number of treatment sessions. We have repeated RFA or PEIT until CT demonstrates entire tumor necrosis. As a result, we have successfully ablated tumors in more than 99% of the cases. In this study, we did not have any case in which the final CT demonstrated incomplete tumor ablation. The incidence of adverse events was not significantly different between the two treatments, although previous comparison studies have suggested that RFA would have higher complication rates than PEIT. Reported mortality rates are 0.3–0.5% and morbidity rates are 2.2–8.9% in RFA, while they are 0.1% and 3.2%, respectively, in PEIT. Common complications are bleeding, biliary injury, and seeding of malignant cells in both procedures. This study was restricted to tumors 3 cm or less in diameter, although larger tumors have also been treated with these procedures. We speculate that superiority of RFA to PEIT would be more significant in middle-size or large tumors because of its more reliable local effect. This study was also restricted to patients with relatively good liver function, although some patients in Child–Pugh class C have been treated with these procedures. We are not sure that RFA could achieve better outcomes in patients with poor liver function, because preserving liver function might be more important than achieving curative treatment. **Conclusion:** Judging from higher survival but similar adverse events, RFA is superior to PEIT in the treatment of small hepatocellular carcinoma.

APASL/Abstract/PGC III.2.3
Artificial pleural effusion technique
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Definition: Artificial pleural effusion is the infusion of 5% glucose or saline into the thoracic cavity. This method is done under ultrasound with no special tools. This method is easy and safe when used. If you can make an artificial pleural effusion, the dead space of ultrasound will disappear and the lesion under the diaphragm dome can be visualized and ablated (Fig. 1). In addition, safe puncture lines to tumors in posterior segment of the liver will be available (Fig. 2). **Preparation:** For making artificial pleural effusion, the same preparation used for ultrasound guided liver biopsy is needed, that is, ultrasound equipment, a sterile probe sheath or sterilized probe, a puncture attachment, intravenous access and local anesthesia. In addition, a bed with a raisable backrest must be prepared, because radiofrequency ablation (RFA) under artificial pleural effusion is performed in the sitting position. We use an exclusive made-

to-order bed for RFA (Fig. 3). Any position can be maintained using this bed. The right back of this bed is open for puncture of the right back. A saturation monitor and oxygen by nasal cannula are needed for the reason that saturation of oxygen may fall during instillation of artificial pleural effusion. The dosage is 500–1000 ml of 5% glucose or saline. A 16 gauges intravenous cannula (Surflo; Terumo, Tokyo, Japan) is used for instillation of artificial pleural effusion into the thoracic cavity, in our department. Two sterile extension tubes to connect the cannula and the route of the drip are required (Fig. 4). **Process:** First, the injection site of the artificial pleural effusion must be selected. The intercostal plane where a part of the lung seems to move in time to the breath on the left side of the ultrasound image, is best for the injection site (Fig. 5). However, the same plane as the target tumor should be avoided because some air may enter the diaphragm. The entered air may prevent the observation of the tumor. Second, Local anesthesia is administrated from the skin to the diaphragm. Third, 20 ml of 5% glucose or saline is injected into the diaphragm to make a space of 1 cm in thickness, to insert an intravenous cannula (Fig. 6). Fourth, an intravenous cannula is inserted into the widened diaphragm and is connected to the route of the drip immediately. The speed of the drops changes in time with the breath. When the instillation of artificial pleural effusion is not effective, the tip of the cannula should be adjusted delicately or a reinsertion of the cannula should be tried. After instillation of 500 ml of 5% glucose or saline, seated position must be maintained for observation using ultrasound. If an artificial pleural effusion of 500 ml is not enough for observation, instillation of another 500 ml is necessary. It is not necessary to drain artificial pleural effusion because it will be absorbed in 2–3 days. **Complication:** Complications such as bleeding, pnemothorax and pleuritis are considered possible, but these complications have never been experienced in around 150 instances of the artificial pleural effusion method being employed in our department. However, after RFA for large tumors under the diaphragm, artificial pleural effusion tends to remain unabsorbed for around 1 month.

State of the Art Lecture

APASL/Abstract/STAL 1
Hepatitis B in 2005

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Key issues on hepatitis B before 2005 have been reviewed in the APASL consensus update and the European consensus on chronic hepatitis B and C in HIV co-infected patients, both published in 2005 (Liver Int. 2005;25:472–89 and J Hepatol 2005;42:615–24, respectively). Existing and emerging data on hepatitis B in 2005 include: (1) Basic studies including molecular biology, HBV mutants, RNA interference and immunology, especially regulatory T cells; (2) HBsAg seroclearance and occult hepatitis B virus infection; (3) Association of serum HBV-DNA level and HBV genotype with the development of liver cirrhosis and hepatocellular carcinoma; (4) Therapy of chronic hepatitis B with currently available or new drug(s), including viral kinetic, long-term outcomes, the role of HBV genotype, the problems and management of drug resistance. In addition to new findings, a cost-effectiveness analysis using a third-party payer perspective has appeared. The analysis has shown that interferon monotherapy is preferred in health care system with limited resources, especially in populations with a high prevalence of HBeAg-negative HBV, and that salvage strategy reserving adefovir only for lamivuidne resistance my be highly cost-effective across most health care settings. With the new approval of entecavir and pegylated interferon 2a for the treatment of hepatitis B, further studies on cost-effectiveness are needed. In light of these new developments, the landscape of chronic hepatitis B may change, including patient selection and drug of choice for initial therapy, toward better control of chronic HBV infection.

APASL/Abstract/STAL 2
Current status of liver transplantation for hepatocellular carcinoma from living donor

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It has been generally accepted that the patients with early stage hepatocellular carcinoma (HCC) and Child C liver cirrhosis are the best candidate for liver transplantation. HCC develops from hepatitis B or C (HBV and HCV) cirrhosis, it is important to control hepatitis virus before and after liver transplantation. Fortunately, using lamivudine (adephovir) and hepatitis B immunoglobulin, we can control HBV almost completely. On the other hand, HCV is difficult to be controlled by interferon and ribavirin. HCV infection recurs in all patients and it is the cause of fibrosing cholestatic hepatitis resulted in graft loss. From the extension of HCC in the liver, indication of liver transplantation should be limited to Milan criteria. In our institution, indication of liver transplant is restricted by the size of the tumor no more than 5 cm and number of nodules no more than 5. Vascular invasion of the tumor and extrahepatic metastatic lesion are the contraindication. We have to consider the lower limit of survival in the liver transplant both in the living and decreased donors. Three-year survival of the LDLT patients for HCC was 82% (n = 67) in our institution and 3-year survival was 65% in Japan (n = 316). Even in advanced HCC, there are patients who can obtain complete cure. We have to find out new indication criteria for HCC.

APASL/Abstract/STAL 5
Recent progress: cholestatic liver injury

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Major progress has been made since the mid 1990's in our understanding of the control of bile flow as many of the transporters of the components of bile namely bile acids, inorganic anions and phospholipids as well as cholesterol have now been cloned. Thus the pattern of disease in children with progressive familial cholestasis can be subcategorized into types 1, 2 and 3 according to the particular canalicular transporter defect. It is also possible that in some women who suffer intrahepatic cholestasis of pregnancy that they too may have a mutation in the MDR3 transporter responsible for PFIC-3. Other genetic mutations of transporters have been found in association with benign recurrent intrahepatic cholestasis and Dubin Johnson syndrome. Immunohistochemistry studies indicate that compensatory mechanisms may take place once cholestasis is established, in that relocation of non-specific transporters e.g. MDR3,4 to the basolateral membranes of hepatocytes occurs thus promoting the transport of bile back into the sinusoid. Similarly a number of compensatory mechanisms which enhance bile flow in the presence of cholestasis occur via the nuclear receptor FXR leading to down regulation of NTCP, CYP7A1, and CYP8B1 (essential for bile acid synthesis) and up regulation of BSEP, MDR3 and MRP2 – which enhance bile acid clearance. Our improved understanding of the mechanisms that control bile flow will allow for the development of new targeted therapies. From a clinical standpoint the reversibility of biliary cirrhosis following relief of extrahepatic biliary strictures is well described. It remains to be seen whether new drugs may reverse the hepatic

fibrosis that complicates long term intrahepatic cholestasis which is associated with inflammation in the portal tracts. The hydrophilic, dihydroxy bile acid ursodeoxycholic acid if given early in the course of chronic cholestatic liver diseases markedly delays progression of fibrosis, but has not been shown to be associated with regression of fibrosis. Again, in those patients with inflammatory diseases of the bile ducts, namely primary biliary cirrhosis, Prednisolone and Budesonide have both been shown to delay progression to cirrhosis in this chronic disease.

Okuda Memorial

APASL/Abstract/Okuda 4

Transjugular intrahepatic portosystemic shunts – the auckland experience

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The New Zealand Liver Transplant Unit provides tertiary management for the complications of portal hypertension, including transjugular intrahepatic portosystemic shunts (TIPS). A retrospective analysis of TIPS efficacy and clinical outcome at our centre was undertaken. The clinical records on all patients who underwent TIPS at Auckland Hospital between September 1998 and May 2005 were reviewed. Clinical indices including aetiology of liver disease, TIPS indication, Child-Pugh and MELD scores, pre- and post-procedure serum creatinine and imaging were documented. Recurrence of gastrointestinal (GI) bleeding, ascites and hydrothorax, stent patency rates, procedural complication and mortality rates were analysed. Forty two TIPS procedures were attempted in 40 patients. Indications were ascites 17 (43%), variceal bleeding 10 (25%), portal hypertensive bleeding 5 (13%), hydrothorax 2 (5%), hepatopulmonary syndrome 2 (5%), acute Budd Chiari syndrome 1 (2.6%) and severe hypersplenism 2 (to allow antiviral treatment for Hepatitis C). Half the cases were as a bridge to transplantation. Technical success was achieved in 38 patients (95%). Primary patency was 73%, 50% and 44% at 3, 6 and 12months respectively. Secondary assisted patency was 100% at 3, 6 and 12months. Refractory ascites responded in 16 of 17 patients and control of gastrointestinal bleeding was provided in 13 of 15 patients. Mean serum creatinine improved following TIPS (from 0.10 to 0.08 mmol/l; $p = 0.02$). Cumulative mortality was 7.7% at 1 year, and 12.8% at 6 years. No procedure-related mortality occurred. Four patients (10.2%) developed hepatic encephalopathy, 2 were transient and 2 were intractable (one of whom required listing for liver transplantation). All TIPS patients awaiting transplantation survived to transplant. Mean time to transplantation after TIPS was 123days. Expanded polytetrafluoroethylene covered stents were used in 11 patients, of whom 3 had transient hepatic decompensation, attributed to partial hepatic venous infarction. Successful TIPS improves all complications of portal hypertension and may facilitate management of patients on the waiting list for transplantation. Hepatic encephalopathy in uncommon and usually responds to lactulose.

Debate

APASL/Abstract/Deb 1

Entecavir as first-line treatment for CHB: Pros and Cons

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The traditional and pegylated α interferons give the same rate of hepatitis B e antigen (HbeAg) seroconversion – 32–33% in 1 year, are associated with a lot of side effects, and are probably less useful in people who acquire the infection early in life, i.e., the majority of the Asian hepatitis B carriers. Lamivudine has a high resistance rate of up to 67–68% after 4 years of therapy. Adefovir, though associated only with 18% of resistance up to 3 years of therapy, has potential renal toxicity (3% in 3 years) and is slower acting than lamivudine. Entecavir is a guanosine nucleoside analogue. It can inhibit the priming of hepatitis B virus (HBV) DNA polymerase which involves guanosine triphosphate. Its EC50 is much lower than those of lamivudine, adefovir, Telbivudine and tenofovir. In large pivotal phase 3 trials involving HBeAg+ and HBeAg− subjects, 81% of patients had <300 copies/ml of HBV DNA after 48 weeks of treatment, compared with 57% with lamivudine. For lamivudine-refractory patients, 22% had <300 copies/ml of HBV DNA at week 48. For treatment-naïve subjects, there are no genotypic substitutions with resistance to entecavir after 48 weeks of therapy. For lamivudine-refractory subjects with YMDD mutations, 7% of patients develop entecavir resistance with 1% showing HBV DNA rebound. Entecavir has safety comparable to that to lamivudine. With its potency, lack of resistance and side effects, entecavir can be recommended as a first-line agent.

Lunch Symposium

APASL/Abstract/LS 1.3

Appropriate use of interferons in the treatment of hepatitis B patients

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Safe and effective treatment strategies for chronic hepatitis B in order to prevent disease progression into end-stage liver diseases and hepatocellular carcinoma (HCC) are still needed. Currently, five drugs have been approved for the treatment of chronic hepatitis B: conventional interferon α (IFN-α), lamivudine, adefovir dipivoxil, pegylated IFN-α and entecavir. The responses to antiviral therapy are invariably influenced by both host and viral factors. Therefore, an understanding of these factors is important for practicing hepatologists and this may help design individualized medicine for the treatment of chronic hepatitis B. Recently, Hepatitis B virus (HBV) genotypes have attracted increasing attention because they may affect the disease progression and outcomes of HBV-related chronic liver disease, as well as the response to antiviral therapies. Although clinical and pathogenic differences exist among HBV genotypes, the influence of HBV genotype on the response to current antiviral treatments is only partly clarified. Existing data indicate a better sustained response to conventional IFN-α in genotype B patients than in genotype C patients, and in genotype A patients than in genotype D patients. Nevertheless, conflicting results exist regarding the response to peginterferon-α, and more studies are needed. As to HBV genetic polymorphisms, our recent data showed that HBV nucleotide consensus sequence is identical between IFN-α responders and non-responders. The distribution of nucleotide variations along the whole HBV genomes is also not different between two groups of patients. Thus, IFN-α sensitivity-determining region (ISDR) may not exist within the genome of HBV genotype B, and host factors as well as virus-host interactions seem more important than viral factors alone in determining the treatment outcomes with IFN-α. In fact, our previous study already demonstrated that certain host genetic background, such as single nucleotide polymorphisms (SNP) within eukaryotic translation initiation factor 2, subunit 1 and MxA promoter regions,

are associated with the responsiveness to IFN-α treatment in patients with HBeAg-positive chronic hepatitis B. However, the value of these host genetic polymorphisms in predicting responsiveness to peginterferon α-based therapy requires further examinations. In the foreseeable future, we may need to establish individualized chronic hepatitis B treatment algorithm tailored to host (immune status and genomic polymorphisms), virus (HBeAg status, HBV DNA level, genotype, and precore/basal core promoter mutants) as well as liver disease status (hepatitis activity and fibrosis stage).

APASL/Abstract/LS 3.2

What are the goals of therapy that can be achieved?

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Chronic hepatitis B (CHB) virus infection continues to be an important cause of morbidity, mortality and a source of potential new infections in many parts of the world. The World Health Organization (WHO) estimates 400 million individuals being chronically infected with HBV. HBV is the 10th leading cause of death worldwide. In China, Southeast Asia, and sub–Saharan Africa, as many as 10–15% of the population are chronically infected. Epidemiology is changing as a result of universal HBV vaccination of newborn being enhanced in Asian countries, aiming to prevent mother-to-child transmission. Improved socioeconomic situation will also promote better prevention programs. However, population movement with migrants from high endemicity regions may introduce infection among those in low endemicity regions. Therapeutic advances have been shown to have significant impact on the incidence of liver-related morbidity and mortality.

It is clear that sustained viral suppression is the key to the reduction or prevention of hepatic injury and disease progression. The ultimate goal of therapy is to prevent hepatic decompensation, to reduce or prevent progression to cirrhosis and/or HCC, and to prolong survival (durable response). Therefore, the primary goal of treatment for chronic hepatitis B is to eliminate or permanently suppress HBV. This will decrease pathogenicity and infectivity, and thereby stop or reduce hepatic necroinflammation. In clinical terms, the short-term goal of treatment is to ensure HBV DNA sustained suppression, ALT normalization and prevent the development of decompensation (initial response), to reduce hepatic necroimflammation and fibrosis during and after therapy (maintained and substained response).

The first goal of therapy for patients with compensated hepatitis Be antigen (HBeAg) positive CHB is HBeAg loss, or better still, HBeAg seroconversion, together with, persistent undetectable serum HBV DNA as measured with sensitive real time PCR assays. For patients with HBeAg-negative CHB, persistent undetectable serum HBV DNA is the main goal. Biochemical and histological response will follow. The long- term serious sequelae of CHB such as cirrhosis and hepatocellular carcinoma can be prevented. Durability of viral responses off therapy is another goal that we should aim for along with health and economic considerations. However, without hepatitis B surface antigen (HBsAg) loss or HBsAg seroconversion, the durability rate is not guaranteed. Similarly, patients with cirrhosis undergoing antiviral therapy should aim for these goals; however, the complications from cirrhosis require additional management programs. The risk of hepatocellular carcinoma might be lowered but not eliminated. It has become recognized that are HBsAg-positive patient in immune compromised state or when undergoing immune suppression will experience viral rebound. Prophylactic antiviral therapy will prevent hepatitis flare and decompensation because of viral rebound and enable patient to undergo these therapy uneventfully.

Advances in therapy for CHB have abled the goal of therapy being achieved in higher proportion of the patients. The eradication of the virus and its deep- seated hold in the hepatocytes as cccDNA is a goal that may be realized if there are more potent antiviral therapies that have low rate of emergence resistant mutants. Combination therapy with immune modulator is an area that requires further investigation.

IASL Symposium

APASL/Abstract/IASL 2

Management of ascites and bacterial infections in patients with cirrhosis

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ASCITES Ascites is the most common major complication in cirrhosis of the liver. It is associated with increased morbidity from complicating spontaneous bacterial peritonitis and hepatorenal syndrome. The median survival of patients with ascites is 2–5 years; patients with refractory ascites have a median survival rate of 6 months, and those with type 1 hepatorenal syndrome have survival a rate of approximately 2 weeks.

Management of cirrhotic ascites Ascites results from renal retention of sodium and water. Therefore, treatment is aimed at achieving a negative sodium balance. This may be achieved as follows:

1. Low sodium diet.
2. Fluid restriction.
3. Diuretics.
4. Therapeutic paracentesis.

Complications of large volume paracentesis are unusual and include abdominal wall hematomas, hemoperitoneum and bowel perforation. These, however, occur in fewer than 1 in 1000 paracentesis.

Management of Refractory Ascites and Hepatorenal Syndrome

1. Large volume paracentesis.
2. Transjugular intrahepatic portosystemic shunts.
3. Systemic vasoconstrictors.
4. Orthotopic liver transplantation.

Management of Spontaneous Bacterial Peritonitis

Antibiotic therapy is recommended with cefotaxime 2 g intravenously every 12 h for a period of at least 5 days. Forty-eight hours after initiation of cefotaxime therapy, a repeat paracentesis should be carried out. If there is a $>25\%$ decrease in neutrophil count, then the patient is responding to treatment and antibiotics are continued for a total of 5 days. On the other hand, if the neutrophil count has not decreased, one should suspect secondary bacterial peritonitis and carry out a CT scan with oral contrast.

In addition to antibiotics, albumin is administered and this is associated with improved survival. Albumin is initially administered in a dose of 1.5 g/kg body weight on day 1 and repeated in a dose of 1 g/kg body weight on day 3.

Patients who have had SBP should be kept on antibiotic prophylaxis long term or until liver transplantation. The usual antibiotic recommended is norfloxacin in a dose of 400 mg/day. The only other indication for antibiotic prophylaxis against SBP is in a patient with cirrhosis and gastrointestinal bleeding. In these patients, norfloxacin 400 mg is given once daily for a period of 7 days. Intravenous antibiotics such as ceftriaxone may be preferable in this group.