Diagnosis	n
Acetaminophen induced	26
Cryptogenic	14
Autoimmune	10
Hepatitis B	9
Hepatitis A	3
Wilson's Disease	2
Fatty liver of Pregnancy	1
Reyes Syndrome	1
Malignant hemangioendothelioma	1
Parvovirus B-19	1
Idiosyncratic drug reaction	1
Giant cell Hepatitis	1
Mitochondrial Disease	1

TJLB was technically successful in all patients.

Outcomes of TJLB performed in 71 patients with ALF

Technical Success	100% (71/71)
Complication rate	5.6% (4/71)
Mean Procedure Time	20 mins (range: 14-35 mins)
Adequacy of Specimen	97.1% (69/71)
Mean number of cores	3 (range: 2-5)
Mean core tissue length	1.9 cm (range: 1.7-2.2 cm)

TJLB confirmed the clinical diagnosis in 66 (92.9%) patients, identified the cause of ALF in remaining 5 patients, and determined the percentage of liver necrosis and changes of chronic liver disease in all patients.

Comparative analysis of histological findings between pretransplant TJLB and explanted liver among 31 patients who underwent LT

	Pretransplant TJLB	Explanted Liver
Liver Necrosis (%)		
< 25	-	-
25 - 50	3	1
> 50 < 75	15	11
> 75	13	19
Fibrosis	1	5

Conclusions: TJLB is a safe technique to obtain liver tissue in both adult and pediatric patients with ALF. It helps in establishing the clinical diagnosis and estimation of degree of hepatic parenchymal necrosis, thereby assisting in clinical decision-making for LT.

Abstract# O-128

Indocyanine Green Clearence as a Tool To Predict the Need of Liver Transplantation in Pediatric Acute Liver Failure. Jesus Quintero[1], Juan Ortega[2], Maria Legarda[1], Jordi Roqueta[2], Javier Bueno[1], Ramon Charco[1]. *[1]Pediatric Liver Transplant Unit, Hospital Universitario Valle de Hebron, Barcelona, Catalunya, Spain; [2]HPB Surgery and Transplants Department, Hospital Universitario de la Vall d'Hebron, Barcelona, Catalunya, Spain*

BACKGROUND:

Pediatric Acute Liver Failure (PALF) is a rare disease that results in death or the need of Liver Transplantation (LT) in nearly 50% of cases. Distinguishing the patients with PALF who require LT from those patients who will survive with medical care alone remains unclear. The scoring systems aviables for the prognosis evaluation in adults are not able to predict survival without LT of pediatric patients.

AIM

To assess the use of Indocyanine Green Plasma Disappearance Rate (ICG-PDR) as a tool to predict the evolution of patients affected of PALF and compare it with King's College (KHC) and Clichy's criteria.

PATIENTS AND METHODS

All patients were younger than 18 years without chronic liver disease, and presented Acute Liver Failure (prothrombine time (PT) > 15 sec or INR > 1.5 in the presence of Hepatic Encephalopathy (HE) or a PT >20 sec or INR >2 regardless of the HE). ICG-PDR were taken on diagnosis and repeated every 24 hours until ALF resolution, death or LT. For each measurement, 0,25 mg/Kg of ICG was given intravenously and its blood concentration was detected over time with a non-invasive method the LiMON Monitor. We calculated the Sensitivity (S), Specificity (E), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of ICG-PDR, KHC and Clychy's criteria. All the ICG-PDR measurements were performed under hemodynamic stability without splachnic vasoconstrictives drugs and intrabdominal pressure < 8 mmHg.

RESULTS

From January 2003 to July 2010 68 patients were diagnosed of PALF. The most frequent etiology was ischemic hepatitis (33%). A total of 217 ICG-PDR were performed with a median ICG-PDR of 12.6 %/min (r:6 – 26.95 %/min). The median value of ICG-PDR was significantly lower in patients who suffered an irreversible liver injury compared with those who survived without LT (4.1%/min vs 20.5 %/minrespectively) (P< 0,001). The S, PPV for ICG-PDR were higher than KHC and Clichy's criteria (S of 91.6%, 84 % and 76% and VVP of 84.6%, 55% and 71% respectively).

CONCLUSION

ICG-PDR is an easy non-invasive tool that provides an accurate estimation of the need of LT in the setting of PALF under hemodynamic stability conditions.

Abstract# O-129

The Role of Living Donor Liver Transplantation for Acute Liver Failure. Mustafa Ates[1], Abuzer Dirican[1], Burak Isik[1], Cengiz Ara[1], Volkan Ince[1], Ayse Selimoglu[2], Cuneyt Kayaalp[1], Sezai Yilmaz[1]. *[1]General Surgery, Inonu University, Medical Faculty, Malatya, Turkey; [2]Pediatrics, Inonu University, Medical Faculty, Malatya, Turkey*

Acute liver failure (ALF) is a syndrome defined by coagulopathy and hepatic encephalopathy resulting from severe liver damage in patients without pre-existing liver disease. There are no established effective treatments except for emergency liver transplantation. Since there are few cadaveric donors in our country (Turkey), living donor liver transplantation (LDLT) is an excellent option for patients with ALF. We analyzed the etiologies and outcomes of patients who underwent emergency LDLT for ALF and compared the results with those of deceased donor liver transplantation (DDLT).

Methods: We reviewed the charts of 35 transplant patients with ALF treated between 2009 and 2010.

Results: We performed 284 liver transplants at our clinic, of which 35 (12.3%) were to treat ALF. Of the 35, 25 patients underwent LDLT and ten patients underwent DDLT. The median recipient age was 18.5 (range 2–62) and 16.5 (range 1–45) years, for the LDLT and the DDLT groups, respectively. The etiologies of ALF in the LDLT patients were acute hepatitis B in six patients, hepatitis in five, fireworks intoxication in three, drug intoxication in two, Budd-Chiari syndrome and mushroom intoxication in one each, and six unknown etiologies. The etiologies of the cadaveric donor transplant patients were hepatitis A and acute hepatitis B in one patient each, and eight unknowns. The LDLT group had a higher biliary and vascular complication rate (40%, %20 respectively) than the DDLT group (%11, %0 respectively). While the LDLT group survival rate was 76%, six deaths occurred due to pulmonary (n=2), cardiac (n=2), and infective (n=1) complications. Three deaths occurred in the DDLT group due to pulmonary (n=2) and encephalopathy (n=1) complications; the survival rate was 70%. The median follow-up times were 430.32 (range 4–635) and 73.4 (range 5–273) days, for the LDLT and the LDLT, respectively.

Conclusions: Although cadaveric donor grafts are shared nation-wide and priority is given to ALF, in Turkey, there may not be a cadaveric donor available within the necessary period for ALF patients. In this context, living donor liver transplantation offers a definitive life-saving treatment for patients with ALF, an irreversible condition, and allows easier and quicker access to liver grafts, despite the shortage of cadaveric grafts.

Abstract# O-130

Appropriate Liver Support Systems as Perioperative Care in Liver Transplantation Improves Survival. Kazuaki Inoue. *Gastroenterology, Showa University Fujigaoka Hospital, Yokohama, Japan*

Introduction

The purpose of artificial liver support (ALS) is to sustain patients with fulminant hepatic failure (FHF) for long enough for the patient's liver to regenerate and regain its function. In cases where the liver cannot regenerate, ALS should support liver function until transplantation is successfully

performed. If these liver support systems had the capability to sustain patients with FHF in a favorable condition, survival rates would be improved and the criteria for liver transplantation would be simpler and more accurate.

Method

Our study group of 159 patients comprised 90 cases of FH, 16 cases of late-onset hepatic failure (LOHF), and 53 cases of severe acute hepatitis (SAH). Immediately after the onset of hepatic coma, patients were placed on ALS involving plasma exchange and hemodiafiltration using huge volumes of buffer. Treatment for underlying hepatitis consisted of immunosuppressive therapy using a methylprednisolone pulse followed by withdrawal with continuous infusion of cyclosporin A. Antiviral treatment comprising interferon beta and/or a nucleic acid analogue.

Results

Of the 90 FH cases, 3 were the hyper-acute type and progressed to an ahepatic state. They were immediately placed on ALS, which sustained them in a good condition. One of the three patients subsequently underwent LDLTx and survived. Although the ALS system sustained the remained two in a favorable condition for more than two weeks, they died because an organ donor was not found. Of the remaining FH cases, 42 were FH acute type and 36 of the 42 patients survived under ALS. The remaining 45 patients were FH subacute type and 32 of these survived. They were placed on the ALS system and underwent treatment for underlying liver disease. Four of the remaining 13 patients underwent LDLTx and 2 survived. The survival rate of LOHF patients under the same treatment as FH subacute type was 50% (8/16). Of the 53 SAH patients, 51 survived (96%). After several session of ALS, 109 of 116 (94%) patients regained consciousness and the 2-week survival rate was 107 of 116 (92.2%). Brain edema was found in a few cases and was reversible by several sessions of ALS in most cases.

Conclusions

The Japanese treatment system for FH improved the prognosis of acute liver failure. The treatment system described in this study would sustain patients in good condition until the liver recovers or an adequate donor is found, and make perioperative management including organ sharing more appropriate.

Abstract# O-131

An Artificial Liver Support System Using Huge Buffer Volumes Can Prevent Brain Edema and Is an Ideal Bridge for Liver Transplantation in Fulminant Hepatic Failure. Kazuaki Inoue, Makoto Yoshiba. *Gastroenterology, Showa University Fujigaoka Hospital, Yokohama, Japan*

Background: Fulminant hepatic failure (FHF) is a fatal and intractable disease of varying etiology. Artificial liver support (ALS) is used to control serious symptoms of fulminant hepatitis, such as brain edema, which may induce postoperative neurological deficit, hepatic coma and bleeding tendency. Standard intensive medical care for FHF has not been established and prognosis of subacute form with indeterminate etiology is very poor. Therefore ALS should have enough capability to sustain patients with severe liver damage comparable to ahepatic state.

Methods: In the present study, ALS was evaluated in seven patients with fulminant hepatitis, who had been placed on an ALS system comprising plasma exchange and online hemodiafiltration. Etiology of all patients was indeterminate. The effects of ALS were evaluated on the basis of improvements in clinical symptoms, removal of amino acids such as glutamine (Gln) and brain computed tomography.

Results: All patients regained consciousness with ALS and four of seven patients survived; three patients died despite recovering from hepatic coma. This ALS system sustained three deceased patients in a favorable condition more than two weeks. The median estimated plasma equivalent volume of Gln removed was 17.9 L (range 6.7–64.3 L). There was a significant relationship between total buffer volume and the plasma equivalent volume of Gln removed. Removal efficacy of other amino acids was as same as that of Gln.

Conclusions: Plasma exchange combined with online hemodiafiltration can sustain patients with severe liver damage in a favorable condition and it is also effective bridging method to liver transplantation.

Abstract# O-132

A Comparison of Baseline International Normalised Ratio (INR) and Thromboelastography (TEG) R Times, and Transfusion Requirements for Patients with Fulminant Hepatic Failure Undergoing Orthotopic Liver Transplant (OLT). Deborah J. Herriman, Susan Mallett. *Anaesthetics, Royal Free Hospital, London, United Kingdom*

Background

Patients with Fulminant Hepatic Failure often require Intra-Cranial Bolts, with an associated risk of intra-cranial haemorrhage. Traditionally INR is used to guide the use of blood products prior to bolt insertion, but does INR truly reflect coagulation and blood product requirement? It has been demonstrated in patients with cirrhosis that the INR is not a good indicator of bleeding diathesis[1].

Methods

A retrospective observational study performed using the Liver Transplant database at the Royal Free Hospital (RFH), London. We investigated 15 patients with Fulminant Hepatic Failure who underwent OLT between 2005 and 2010. We investigated if there was any correlation between:

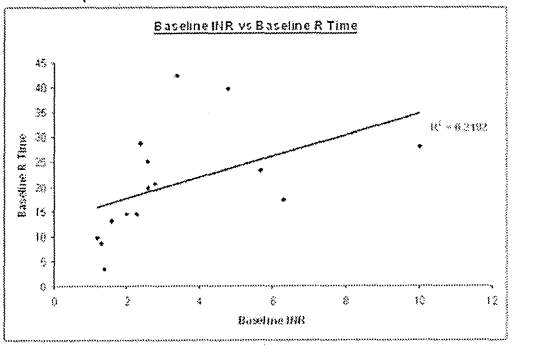
- Baseline INR and TEG
- Baseline INR and intra-operative Transfusion requirements particularly looking at Red Blood Cells and Fresh Frozen Plasma (FFP)

The INR and TEG values were taken from the first blood sample taken during line insertion in theatre. The blood samples were processed in the Point Of Care Testing (POCT) laboratory next to the Transplant Theatre at the RFH. Native and Heparinase R times were measured for each sample, as an endogenous heparin effect is sometimes observed in ALF. For this study we used the lower R time for each patient.

The blood and FFP requirements were taken as the total transfusion requirement used intra-operatively for each case.

Results

We found a poor correlation between Baseline INR and TEG:



We found no correlation between Baseline INR and both blood (R^2=0.028) and FFP (R^2=0.0339) requirements intra-operatively.

Conclusion

Although this is a limited study, we have found INR to be poorly correlated to TEG R values, and to be a poor reflection of intra-operative blood and FFP requirements. We propose INR is therefore not a reliable guide to haemostatic status prior to insertion of intra-cranial bolts in patients with Fulminant Hepatic Failure.

1: Tripodi A et al. Hepatology 2005;41: 553-8

Abstract# O-133

Clinical Analysis of Emergency Liver Transplantation in Adult. Dong Goo Kim, Young Chul Youn, Jung Hyun Park, Tae Ho Hong, Young Kyung You. *Surgery, Catholic University of Korea, Seoul, Korea*

Purpose: Organ from brain death in liver transplantation (LT) is distributed by UNOS system or MELD score to more urgent hepatic failure. Recently, surgical technique and perioperative care evolved significantly and need to re-evaluate the result of LT in UNOS I or IIA, MELD score and the role of living donor liver transplantation (LDLT), alternative to cadaver donor LT (CDLT) in emergency LT. Methods: Between Jan. 2000 and Feb. 2010, 62 patients (13.7%, 17 for Status I and 45 for Status IIA) with emergency LT out of 453 patients who underwent total LT were evaluated retrospectively. We reviewed clinical characteristics, cause of death and factors influence on survival between UNOS I and IIA, between MELD <33 and >33 scores,

PP01-38

Hypermethylation of IL-17 Promoter in the Patients with Acute-on-Chronic Liver Failure

Y.-C. Fan[1,2], J. Ge[1,2], X.-P. Fan[1,2], Z.-X. Qi[1,2], F.-L. Meng[1,2], L.-Y. Chen[1,2], F.-C. Li[1,2], K. Wang[1,2]

[1]*Department of Hepatology, Qilu Hospital of Shandong University;* [2]*Hepatology Institute of Shandong University, Jinan, China*

Background/aims: We previously reported that down-regulation of interleukin 17A (IL-17A) might contribute to the acceleration of liver failure. However, the exact mechanism with regard to the epigenetic alteration of IL-17A has not been fully understood. This present study was aimed to determine the methylated alteration of IL-17A promoter in the patients with acute-on-chronic hepatitis B liver failure (ACHBLF).

Methods: Fifteen patients with chronic hepatitis B (CHB) and twenty ACHBLF patients were included in our present study. Methylation-specific polymerase chain reaction (MSP) was used to evaluate methylation status of IL-17A promoter. The mRNA level of IL-17A was measured with quantitative real-time polymerase chain reaction (PCR). Model for End-stage Liver Disease (MELD) was performed for the evaluation of liver failure. Ten healthy volunteers were enrolled as control.

Results: The frequency of CPG island methylation in CHB patients was significantly decreased than that in ACHBLF patients (46.7 vs. 100%, $p < 0.01$). Moreover, we did not find any CPG island methylation in healthy controls. IL-17A mRNA expression was significantly decreased in ACHBLF patients than that in CHB patients. Furthermore, CPG island methylation of IL-17A promoter was negatively correlated with IL-17A mRNA expression ($r = -0.701$, $p < 0.01$). However, we did not find any significant correlations between IL-17A promoter methylation and MELD scores in ACHBLF patients.

Conclusion: The down-regulation of IL-17A due to its promoter CPG island methylation is an important event in acute-on-chronic hepatitis B liver failure.

PP01-39

Acute Liver Failure in Tertiary Care Center of Nepal

S. K.C., D. Sharma, S. Khadka

Liver Unit, National Academy of Medical Sciences, Kathmandu, Nepal

Objective: Acute liver failure (ALF) also known as fulminant hepatic failure is a multisystem illness characterized by severe and sudden liver cell dysfunction leading to hepatic encephalopathy and hepatic coagulopathy in a person without history of liver disease in past. This catastrophic illness can rapidly progress to coma and death from cerebral edema and multi organ dysfunction. The natural history of this illness is variable and survival without transplantation ranges from 10% to 90%. So far, there is no published data on ALF in Nepal. This retrospective study aims to analyze the cases of acute liver failure in Nepal where conservative treatment only is available till date.

Materials and methods: Registry of the admitted patient admitted between April 2004 to March 2010 were searched and all cases of acute liver failure were included. Different factors were analyzed and significant findings were included in the result.

Results: A total of 92 (male, 72; female 20, age 38 ± 9 years) patients who fulfilled the criteria of ALF were analyzed. Hepatitis E was the main etiological agent. The mortality rate was high among pregnant women, specially presenting during third trimester. Injudicious use of herbal medicines was noted in 62% patients. Secondary bacterial infection, hypoglycaemia and hyponatremia were the non-hepatic factor that was associated with increased mortality. Overall survival was 59%. If pregnant cases were excluded, survival rate was 75%. Use of SNMC (Stronger neominophagen compound) increased the survival and lessened the hospital stay.

Conclusions: Acute liver failure is not uncommon in Nepal. It is the number one killer in pregnant women who suffered from HEV hepatitis during third trimester of pregnancy. Prevention of infection and education regarding indiscrete use of herbal medicines may decrease the mortality.

PP01-40

Etiology and Outcome of Fulminating Hepatic Failure in Rural and Urban Population of Sindh, Pakistan

S. Ali, S. Memon, M. Zaki, N. Lal, P. Kumar, P. Abbasi, F. Naz, I. Saba, S. Gill, K. Ansari, S. Laghari

Medicine, Isra University Hospital, Hyderabad, Pakistan

Background and aim: The aim of this study was to identify the etiology for fulminating hepatic failure and to asses the outcome of fulminating hepatic failure in urban and rural population of sindh, Pakistan.

Methods: Descriptive type of study was conducted in isra university hospital over a period of 1 year belongs to all over sindh except Karachi. Patients were divided into urban and rural groups. Patients having both clinical and labortical markers suggestive of fulminating hepatic failure were included in this study and their outcome was also noted as expiry and recovery during hospitalization.

Results: Out of 65 patients, 52.3% were HBV positive. In rural 82.4 and 17.6% in urban patients with P value of 0.63. Non-B etiology including (hepatitis C, E and toxinemia of pregnancy) was about 47.7 with P value of 0.2. Hepatitis B was significantly more prevalent in rural male (70.6%) compared to urban male (29.4%) then the females. Etiology was not possible in 8 patients. Mortility rate was also high about 72.5% in rural as compared to urban population 57.11%. Poor outcome was associated with high level of PT > 50, bilirubin > 3, INR > 5 and development of grade 4 encephalopathy.

Conclusion: Hepatitis B is more common cause of fulminating hepatic failure in rural population (82.4%) of sindh province. Deteoriating clinical condition like hepatic encephalopathy and raised level of bilirubin, PT, INR indicates the poor prognosis and high mortility without liver transplantation.

PP01-41

Change in MELD Score Is a Useful Tool of Liver Transplantation for Patients with Fulminant Hepatic Failure under ALS

K. Inoue[1], M. Yoshiba[2]

[1]*Gastroenterology, Showa University Fujigaoka Hospital, Yokohama;* [2]*Internal Medicine, Sempo Tokyo Takanawa Hospital, Tokyo, Japan*

Background/aim: We have already established the effective artificial liver support system comprising of plasma exchange and hemodiafiltration using huge volume of buffer. Over 90% of patients with fulminant hepatic failure (FHF) regain consciousness under the treatment of this system. After induction of this system, we can easily discriminate the patients who recover spontaneously. Therefore, we also developed the treatment for underlying disease of FHF. The advent of emergency liver transplantation has highlighted the need for prognosis indicators. In the present study, we verify usefulness of change in MELD score as prognosis indicator under these intensive medical care.

Methods: Subject of the study were 47 patients with FHF referred to the Emergency Center at Showa University Fujigaoka Hospital. 22 patients were acute form and 25 patients were sub-acute form. These patients had presented within 8 weeks of disease onset without apparent pre-existing liver disease. These patients were placed on the artificial liver support system immediately after admission. We also did treatment corresponding to underlying disease. We calculated MELD score at admission, day 3, day 7 and day 14 and also analyzed change in MELD score and prognosis.

Results: 44 of 47 patients (93%) regained their consciousness. 31 patients (15 of acute form and 16 of subacute form) survived and 16

patients (7 of acute form and 9 of subacute form) deceased. MELD score on admission, day3, day7 and day14 were 20.1, 10.1, 7.5 and 7 in survived patients and 22.8, 18.9, 18.1 and 18.1 in deceased patients.
Conclusion: Assessment of the prognosis of FHF is essential when making decisions on the requirement for and timing of liver transplantation. Under the treatment of the artificial liver support system, we can have sufficient time to obtain a liver graft. Change in MELD is a helpful indicator for making decisions.

PP01-42

Comparison of Predictive Value of Serum Thymosin β4 in Acute-on-Chronic Liver Failure Patients with the Child-pugh and MELD Scores

Y. Liu, T. Han
Department of Hepatology, The Third Central Clinical College of Tianjin Medical University, Tianjin Third Central Hospital, Tianjin, China

Aim: To investigate whether decreased serum thymosin β4 levels are associated with mortality of acute-on-chronic liver failure (ACLF) patients and decide whether the serum thymosin β4 levels can be used in predicting the prognosis of ACLF patients by compared the predictive values with the Child–Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores.
Methods: Serum thymosin β4 levels were measured by enzyme-linked immunosorbent assay (ELISA) and CTP and MELD score were calculated for each patient on admission.
Results: Compared to survivors, higher baseline values of TBIL ($P < 0.001$), INR ($P = 0.014$), Cr ($P = 0.017$), CTP scores ($P < 0.001$), MELD scores ($P < 0.001$) and lower serum thymosin β4 concentrations ($P < 0.001$) were observed in deceased patients. Serum thymosin β4 levels negatively correlated with TBIL, Cr, CTP scores and MELD scores ($P < 0.05$). On ROC curve analysis the area under curve (AUR) of serum thymosin β4 values (0.823) exceeded that of the CTP (0.708) score ($P < 0.05$), but there was no statistically significant difference compared with the AUR of the MELD score (0.797) ($P > 0.05$). Patients with thymosin β4 value < 0.3840 μg/mL had the highest relative risk of the poor prognosis. At last, the Kaplan–Meyer test showed a strong difference between survivals of patients with initial thymosin β4 values < 0.3840 μg/mL (mean survived time 46.5 ± 4.5 days, 95% CI: 37.6–55.4) and ≥0.3840 μg/mL (mean survived time 74.7 ± 3.7 days, 95% CI: 67.4–82.1) ($P < 0.001$).
Conclusion: Serum thymosin β4 concentration is a reliable indicator of short-term mortality in patients with ACLF.

PP01-43

The Case of the Death from Acute Hepatitis C (AHCV) of Patient after Bone Marrow Transplantation (BMT)

S. Lepkov, K.N. Melkova, G.I. Storogacov, I.N. Subortceva, A.A. Gettueva, N.V. Gorbunova, Z.T. Chernyvscay, A.N. Vorobev, S.N. Abdusalamov, A.M. Kovrigina, S.D. Kosura
The Moscow Medical University of N.N. Pirogov, Moscow, Russia

BMT is an important method in treatment hematology malignansy. Among after transplantation complications, hepatic insufficiency takes an important place. Cases of death after of AHCV described only 3 cases. Patient 48 years, in first remission of acute myeloid leucosis (AML) was made BMT from HLA-identical donor. Before BMT was examined the function of a liver, nephroses, vascular and respiratory systems it has not been revealed. Donor and recipient blood analyses on a cytomegalovirus, HCV, HBV, HGV was negative. BMT was made after standard air-conditioning. At 35 day method PSR was revealed full donor bone marrow. After 120 days of BMT growth of level of hepatic ferments has been noted. (ALT – 1,100 U/L, progressing level of bilirubin (to 389.3 mkmol/l). Method PSR reveals presence RNA HCV-genotype 1b, level HCV 2×10^8 copy/ml. Antibodies to HCV is not revealed. For the purpose of reduction of hepatic and renal toxicity medicinal therapy has been reduced, made symptomatic therapy. Decrease in the immune status—CD4 absolute number 10kl/mkl. To 180 days after BMT at the patient 100% a donor hemopoiesis are conserved. Made therapy has led to moderate decrease in a cytolytic syndrome. Under vital indications it is appointed alfer-interferon in a dose of 3 million Ed 3 times a week, ribaverin on 0.4 g/sut taking into account kreatinine level. Has occurred an anaemia, thrombocytopenia, leucopenia, neutropenia and has demanded appointment SCF. Despite carrying out of intensive therapy, signs of hepatic insufficiency and an encephalopathy progressed, there were bradycardia episodes, appearance of spontaneous hematomas was marked. The patient has died for 225 days after carrying out BMT. At dissecting at the patient it has been revealed total destruction of hepatocytes invoked by HCV. In bone marrow cells were absent destruction. HCV can possesses a direct cytopathic effect on hepatocytes and bone marrow cells were.

PP01-44

Etiology and Disease Characteristics of Patients with Acute on Chronic Liver Failure in Karachi, Pakistan

A.S. Butt[1], S. Hamid[2], W. Jafri[2]
[1]*Section of Gastroenterology, Department of Medicine;* [2]*Aga Khan University Hospital, Karachi, Pakistan*

Background and aim: Acute on Chronic liver failure (ACLF) is associated with high morbidity and mortality. Hepatitis E virus (HEV) superinfection is common in patients with underlying chronic liver disease (CLD) and can lead to ACLF. Scanty data is available from Pakistan which is a hyper-endemic region for HEV virus. The aim of present study was to investigate the etiology and disease characteristics of patients presenting with Acute on Chronic Liver Failure.
Methods: Consecutive patients ≥18 years of age admitted with acute liver failure in Gastroenterology wards of The Aga Khan University hospital, Karachi, Pakistan during 2008–2009 were evaluated. Those who were diagnosed to have ACLF were included. The diagnosis of ACLF was made if the patient has

1. Acute onset jaundice within last 4 weeks.
2. Serum bilirubin ≥2 mg/dl.
3. Coagulopathy (INR ≥ 1.5).
4. Clinical/histological/ radiological or serological evidence of underlying chronic liver disease.
5. Known compensated CLD and now presented with acute decompensation.

Results: Out of 200 patients 34 patients were diagnosed to have ACLF. Mean age was 40.88 ± 12.96 years and 25 (73.5%) were males. The etiology of underlying CLD was HBV (32.4%), HCV (17.6%) concomitant HBV, HDV with or without HCV (23.3%), alcohol (5.9%), Wilson's disease (2.9%) and cryptogenic cirrhosis (17.6%). The etiology for acute decompensation was acute hepatitis E (44.1%), hepatitis A (2.9%), acute HBV (14.7%), HDV superinfection (5.9%), hepatotoxic drugs (2.9%) and unknown (29.4%). Common presentations were fever (78%), jaundice (100%), ascites (58.8%) and encephalopathy (61.8%). Mean CTP and MELD scores were 11.55 ± 2.06 and 28.38 ± 9.85, respectively. Laboratory parameters at presentation were Hb 11.9 ± 2.3 mg/dl, creatinine 1.8 ± 1.2 mg/dl, bilirubin 20.1 ± 10.4 mg/dl, albumin 2.2 ± 0.6 mg/dl, ALT 539.2 ± 396 IU/ml, PT 24.4 ± 12.4 s. Overall in hospital mortality was 55.9%. On multivariate analysis, ascites, hepatic encephalopathy, renal failure, GI bleeding, total bilirubin and coagulopathy were the significant predictors of mortality.
Conclusion: HEV was the most common cause of ACLF. ACLF is associated with significant in hospital mortality. Preventive measures against HEV could prevent severe acute hepatic decompensation and mortality.

791
MODIFIED PCR-BASED IN SITU HYBRIDIZATION REVEALS ACCURATE DISTRIBUTION OF HEPATITIS B AND C VIRUSES

K. Inoue[1], H. Nuriya[2], M. Kohara[2]. [1]*Gastroenterology, Showa University Fujigaoka Hospital, Yokohama,* [2]*Department of Microbiology and Cell Biology, The Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*
E-mail: kazuakiinoue59@gmail.com

Background and Aims: Although PCR-based in situ hybridization (PCR-ISH) can be used to determine the distribution and localization of pathogens in tissues, this approach is hampered by its low specificity. Therefore, we used a highly specific and sensitive PCR-ISH method to reveal the lobular distribution and intracellular localization of hepatitis B virus (HBV) and HCV in chronic liver disease and to clarify the state of persistent HBV and HCV infection in the liver.
Methods: Subjects were twenty-nine patients with hepatic tumors. Of these patients, 14 were considered to have chronic HCV infection, 8 were diagnosed with chronic hepatitis B and 7 showed negative results for both viral markers but had metastatic liver tumor. All 29 patients underwent hepatic resection and liver samples were obtained from all 29 patients.
We originally developed highly sensitive and specific PCR-based in situ hybridization method to detect the specific distribution of HCV RNA, HBV DNA and HBV RNA. HBV proteins were detected by immunohistochemical staining.
The Institutional Review Board approved the present study and written informed consent was obtained from all the subjects.
Results: HBV genomic DNA was detected in almost all hepatocytes, whereas HBV RNA or protein was differentially distributed only in a subset of the HBV DNA-positive region. Further, HCV genomic RNA was detected in almost all hepatocytes and was localized to the cytoplasm. HCV RNA was also detected in the epithelium of the large bile duct but not in endothelial cells, portal tracts, or sinusoidal lymphocytes. In patients with HBV and HCV coinfection, HCV RNA was localized to the noncancerous tissue, whereas HBV DNA was found only in the cancerous tissue. Using this novel PCR-ISH method, we could visualize the staining pattern of HBV and HCV in liver sections, and we obtained results consistent with quantitative results of real-time detection (RTD)-PCR analysis.
Conclusions: Almost all hepatocytes are infected with HBV or HCV in chronic liver disease; this finding implies that the viruses spread throughout the liver in the chronic stage.

792
LIPOPROTEIN SECRETION PROFILES AND VLDL PRODUCTION IN HEPATOCYTE CELL LINES

B. Jammart[1,2], F. Zoulim[1,2,3], D. Durantel[1,2,3]. [1]*INSERM U871,* [2]*Université de Lyon, UCBL and IFR62,* [3]*Hôtel Dieu (Liver Unit), Hospices Civils de Lyon (HCL), Lyon, France*
E-mail: baptiste.jammart@inserm.fr

Background and Aims: Hepatitis C virus (HCV) is highly associated to apolipoprotein-B containing lipoproteins (LDL and VLDL) in infected patient sera, as most viral RNA is co-immunoprecipitated with anti-ApoB antibodies, but this association is barely seen *in vitro* (e.g. Huh7.5 cells infected with the HCV JFH-1 strain). Recent data suggested that these cells may be deficient for mature VLDL production. Thus, our aim was to:

i. characterize lipoprotein secretion in Huh7.5 cells;
ii. compare this secretion to natural VLDL production by primary human hepatocytes (PHH);
iii. find other hepatocyte cell lines competent for VLDL production.

Methods: Cell culture supernatants were harvested, concentrated using an Amicon centrifugal filter unit with a cut-off of 100 kDa (Millipore™) and ultracentrifuged over an iodixanol-sucrose gradient. Density distributions of apolipoproteins were determined using ELISA or western blot. The production of mature VLDL was further assessed by co-immunoprecipitation of different apolipoproteins.
Results: We found that Huh7.5 cells secrete a large amount of ApoB as compared to PHH. However, ApoB was detected at a density corresponding to LDL or IDL (sup. than 1.01 g/mL), but not VLDL, and was not associated with ApoE, as neither co-segregation nor co-immunoprecipitation were observed. Importantly, HCV infection increased ApoB secretion but did not affect the density of secreted particles. In contrast, secretion of ApoB/ApoE-containing lipoproteins with a density and composition comparable to that of PHH was observed in differentiated HepaRG cells, although the amount of secreted particles was lower. Finally, the hepatoblastoma cell line HepG2 was also able to secrete very-low-density particles containing ApoB and ApoE upon treatment with oleic acid (to stimulate lipoprotein production) and MEK/ERK inhibitors (to reduce the over-activation of MEK1 kinase in these cells).
Conclusion: We have characterized lipoprotein secretion profiles in 3 different cell lines (Huh7.5, HepG2 and HepaRG) as well as in PHH. Huh7.5 cell line, which is commonly used to study HCV replication, does not seem to produce mature VLDL and is therefore a poor model to study HCV particle secretion and its association to lipoproteins as observed *in vivo*. The other hepatocyte cell lines may therefore be more relevant study models of HCV morphogenesis.

793
HEPATITIS C VIRUS INDUCES ULTRASTRUCTURAL MODIFICATIONS IN DIFFERENTIATED HUH7.5 CELLS

B. Jammart[1,2], E.I. Pécheur[3], P. Roingeard[4], F. Zoulim[1,2,5], D. Durantel[1,2,5]. [1]*INSERM, U871, Molecular Physiopathology and New Treatments for Viral Hepatitis,* [2]*Université de Lyon, UCBL and IFR62,* [3]*IBCP, UMR 5086, Lyon,* [4]*INSERM, U966, Morphogenèse et Antigénicité du VIH et des Virus des Hépatites, Tours,* [5]*Hôtel Dieu (Liver Unit), Hospices Civils de Lyon (HCL), Lyon, France*
E-mail: baptiste.jammart@inserm.fr

Background and Aims: Upon Hepatitis C virus (HCV) infection of undifferentiated Huh7 (or derived) cells or overexpression of individual viral proteins in various cell types, ultrastructural modifications were observed, including for instance core-induced lipid droplets accumulation and clustering, NS4B-induced "membranous web", and autophagic structures. However little is known about ultrastructural modifications induced by chronic HCV infection in differentiated cells. As Huh7 and derived cell lines can be functionally re-differentiated by DMSO treatment, we analyzed ultrastructural changes in differentiated HCV infected Huh7.5 cells.
Methods: Huh7.5 cells were cultivated in the presence of DMSO to induce partial cell re-differentiation featuring growth-inhibition, polarization, and albumin-secretion. We initiated HCV replication in these cells after infection with cell-culture-optimized JFH-1 viral strain and looked at the evolution of subcellular ultrastructures in chronically infected, as well as, in control cells using light and electron microscopy.
Results: We found that Huh7.5 cell differentiation itself did not affect subcellular ultrastructures apart from an initial increase in lipid droplet (LD) accumulation followed by a progressive clearance of neutral lipid storage in the differentiated cells. However viral infection clearly increased autophagy *(as shown by arrows on the right panel)*, LD gathering *(arrowheads)* in peculiar structures containing double-membrane vesicles and LD persistence overtime. Similar ultrastructures were obtained in Huh7.5 and in HepG2 cells stably replicating a blasticidin-tagged JFH-1 virus. We did not observe any differential association of LD with the endoplasmic reticulum.
Conclusion: We have characterized HCV-induced ultrastructural modifications in differentiated Huh7.5, highlighting the critical role

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2011, p. 4420 Vol. 49, No. 12
0095-1137/11/$12.00 doi:10.1128/JCM.05516-11

Reply to "Significance of a Single-Nucleotide Primer Mismatch in Hepatitis B Virus Real-Time PCR Diagnostic Assays"†

We established a hepatitis B virus (HBV) DNA quantification system based on *Taq* Man chemistry, and it has been used not only in our laboratory but also in a commercial laboratory in Japan. This system has been working very well (2). In every assay, we use copy control of HBV DNA as described in our paper and can detect low copy numbers of HBV DNA without any problems.

We know empirically that the sensitivity of a real-time PCR depends on several factors. First, extraction of nucleic acid influences the sensitivity of the assay and crude extraction of nucleic acid sometimes reduces the sensitivity about 1/100. Second, the quality of the TaqMan probe greatly affects the sensitivity of the PCR (1, 2). We know also that the quality of the primers used greatly affects the sensitivity of the PCR (1, 2); however, the precise mechanism is unknown. Third, the quality of the reaction mixture, especially the quality of the enzyme and copy control, has a grave impact on the PCR. Fourth, we have changed the reverse primer for detection of all HBV genotypes in the world (2). A real-time detection PCR was performed using PCR primers and a probe complementary to sequences located in the hepatitis B surface region. This set was universally conserved among all known sequences. Primers and probes located in the S gene comprised forward primer HB-166-S21 (nucleotides [nt] 166 to 186; 5′-CACATCAGGA TTCCTAGGACC-3′), reverse primer HB-344-R20 (nt 344 to 325; 5′-AGGTTGGTGAGTGATTGGAG-3′), and TaqMan probe HB-242-S26FT (nt 242 to 267; 5′-CAGAGTCTAGAC TCGTGGTGGACTTC-3′).

We have no problem in operating our quantification system. Therefore, we ask you to check the above-mentioned four items in your experimental system.

REFERENCES

1. **Nuriya, H., et al.** 2010. Detection of hepatitis B and C viruses in almost all hepatocytes by modified PCR-based *in situ* hybridization. J. Clin. Microbiol. **48**:3843–3851.
2. **Tanaka, T., et al.** 2004. Virological significance of low-level hepatitis B virus infection in patients with hepatitis C virus associated liver disease. J. Med. Virol. **72**:223–229.

Kazuaki Inoue*
Department of Medicine
Division of Gastroenterology
Showa University Fujigaoka Hospital
1-30 Fujigaoka, Aoba-ku
Yokohama 227-8501, Japan

Michinori Kohara†
Department of Microbiology and Cell Biology
The Tokyo Metropolitan Institute of Medical Science
1-6 Kamikitazawa 2-chome, Setagaya-ku
Tokyo 156-8505, Japan

*Phone: 81 45 974 6249
Fax: 81 45 973 8394
E-mail: kazuakiinoue59@gmail.com

†Phone: 81 3 5316 3232
Fax: 81 3 5316 3137
E-mail: kohara-mc@igakuken.or.jp

† This is a response to a letter by Chow et al. (doi:10.1128/JCM.05224-11).

1557
SOPHISTICATED IN SITU PCR AND IMMUNOHISTOCHEMISTRY IS HELPFUL TO UNDERSTAND PATHOGENESIS OF CHRONIC HEPATITIS AND FULMINANT HEPATITIS

Kazuaki Inoue[1,2], Makoto Yoshiba[1], Michinori Kohara[2]; [1]Gastroenterology, Showa University Fujigaoka Hospital, Yokohama, Japan; [2]Microbiology and cell biology, Tokyo metropolitan institute of medical science, Tokyo, Japan

Introduction Although PCR-based in situ hybridization (PCR-ISH) can be used to determine the distribution and localization of pathogens in tissues, this approach is hampered by its low specificity. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the primary causative agents of chronic liver disease. Therefore, to reveal the distribution and localization of genomes and proteins of HBV and HCV is helpful to understand the pathogenesis of the disease. Patients and method Thirty-five patients were enrolled in the present study. Of these patients, 14 were considered to have chronic HCV infection, 8 were diagnosed with chronic hepatitis B, 6 were diagnosed with fulminat hepatitis B (five are due to acute infection and one is due to acute exacerbation) and 7 showed negative results for both viral markers but had metastatic liver cancer (6 with colonic cancer and 1 with gastric cancer). We used a highly specific and sensitive PCR-ISH and RT-PCR-ISH method to reveal the lobular distribution and intracellular localization of hepatitis B virus genome and HCV genome and to clarify the state of HBV and HCV infection in the liver. We also used specific antibodies against hepatitis B surface and core antigens to reveal the lobular distribution and intracellular localization. Results In patients with persistent infection, HBV genomic DNA was detected in almost all hepatocytes, whereas HBV RNA or protein was differentially distributed only in a subset of the HBV DNA-positive region. Further, HCV genomic RNA was detected in almost all hepatocytes and was localized to the cytoplasm. HCV RNA was also detected in theepithelium of the large bile duct but not in endothelial cells, portal tracts, or sinusoidal lymphocytes. In patients with HBV fulminat hepatitis developed from HBV carrier, HBV genomic DNA was detected almost all hepatocytes and HBcAg and HBsAg were detected in cytoplasm of almost all hepatocyte three weeks before the onset of fulminant hepatitis. Conclusion Almost all hepatocytes are infected with HBV or HCV in chronic liver disease; this finding implies that the viruses spreads throughout the liver in the chronic stage. Before onset of fulminant hepatitis B, HBsAg and HBcAg were strongly positive in almost all hepatocytes and HBV DNA was also positive as same way and they might induce fulminant hepatitisB.

Disclosures:

The following people have nothing to disclose: Kazuaki Inoue, Makoto Yoshiba, Michinori Kohara

1558
INNATE IMMUNE RESPONSES INVOLVING NK AND NKT CELLS PROMOTE LIVER REGENERATION AFTER PARTIAL HEPATECTOMY

Satoko Hosoya[1], Kenichi Ikejima[1], Kumiko Arai[1], Kazuyoshi Kon[1], Shunhei Yamashina[1], Kazuyoshi Takeda[2], Sumio Watanabe[1]; [1]Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan; [2]Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan

Background: Innate immunity has been proposed to play a pivotal role in the mechanisms of liver regeneration. Notably, it has been reported that hepatic NK cells suppress regenerative response through production of IFNγ; however, the role of NKT cells, which preferentially localize in the liver, in hepatic regeneration is poorly understood. In this study, therefore, we investigated the role of NK and NKT cells in hepatic regeneration after partial hepatectomy (PH) using mice selectively depleted NK and/or NKT cells. **Methods:** Male, 12 week-old CD1d-knockout (KO) mice, which lack NKT cells systemically, and wild type (WT; C57Bl/6) mice were used. Some mice were pretreated with asialo-GM1 or NK1.1 antibody (Ab) 24 hr prior to experiments to deplete NK cells alone or both NK/NKT cells, respectively. Mice underwent the 2/3 PH, and the uptake of BrdU and the expression of PCNA in hepatocyte nuclei were detected by immunohistochemistry. Hepatic expression levels of cyclin D1 and IFNγ mRNA were analyzed quantitatively by Western blotting and real time RT-PCR, respectively. HGF levels in liver homogenates were determined by ELISA. **Results:** In CD1d-KO mice, BrdU uptake and PCNA expression were almost similar to those in WT mice 48 hr after PH, the labeling indices being nearly 20% and 30%, respectively. Pretreatment with an asialo-GM1Ab had minimal impact on these parameters following PH in WT mice. In sharp contrast, CD1d-KO mice given an asialo-GM1Ab demonstrated poor regenerative responses, the BrdU and PCNA indices reaching only 4.0% and 11.1%, respectively. Further, impaired regeneration was also observed in WT mice pretreated with NK1.1Ab, the values being only 1.7% and 11.9%, respectively. Moreover, expression of cyclin D1 in the liver 48 hr after PH was nearly normal in CD1d-KO mice, but the levels were blunted almost completely both in CD1d-KO/asialo-GM1Ab and in WT/NK1.1Ab groups. Hepatic IFNγ mRNA levels were elevated nearly 5-fold in WT mice 6 hr after PH, which were not affected by pretreatment with an NK1.1Ab. On the other hand, induction levels of HGF in the liver following PH were blunted significantly both in CD1d-KO/asialo-GM1Ab and in WT/NK1.1Ab mice. **Conclusions:** These observations clearly indicated that depletion of both NKT and NK cells by two different ways results in impaired liver regeneration. The role of NK cells in hepatic regeneration appears to be paradoxical in the presence or absence of NKT cells, and this phenomenon cannot be explained simply by the secretion of IFNγ. Rather, these two innate immune cells most likely up-regulate HGF in a coordinate fashion, thus promoting normal regenerative responses in the liver.

Disclosures:

The following people have nothing to disclose: Satoko Hosoya, Kenichi Ikejima, Kumiko Arai, Kazuyoshi Kon, Shunhei Yamashina, Kazuyoshi Takeda, Sumio Watanabe

1559
ADENOSINE AND ADENOSINE SIGNALING CONTRIBUTE TO THE ANTI-INFLAMMATORY EFFECT OF GLOBULAR ADIPONECTIN IN MACROPHAGES

Michele Pritchard[1,2], Palash Mandal[1], Dian J. Chiang[1], Ogechukwu Ndum[1], Laura E. Nagy[1,3]; [1]Pathobiology, Cleveland Clinic, Cleveland, OH; [2]Gastroenterology and Liver Disease, Case Western Reserve University, Cleveland, OH; [3]Molecular Medicine, Case Western Reserve University, Cleveland, OH

Alcohol-induced liver injury is associated with exacerbated inflammatory responses in the liver. Identification of effective anti-inflammatory pathways in the liver is critical for the development of therapeutic strategies for preventing or treating alcoholic liver disease. Globular adiponectin (gAcrp) has potent anti-inflammatory effects that are mediated, at least in part, via an IL-10 and heme oxygenase (HO)-1-dependent pathway in Kupffer cells and macrophages. Adenosine, an endogenous purine nucleoside, acting via the adenosine 2a receptor (A2AR) also suppresses inflammatory cytokine expression. HO-1-dependent CO production has been associated with increased

apoptosis of the infected host cell. The aims of this study were to examine the pathogenicity of these variants.

METHODS: Huh7 cells were transfected with infectious HBV encoding surface stop codons rtM204I/sW196*, rtA181T/sW172*, rtV191I/sW182*, or full-length surface proteins rtA181T/sW172L, rtA181V/sL173F, rtM204V/s195M, rtM204I/sW196S. Secretion and expression of altered HBsAg were measured by Western blotting and quantitative serology (Abbott Architect). Proliferation, apoptosis, and intracellular HBsAg levels of transfected Huh7 cells were measured using flow cytometry.

RESULTS: The three stop codon variants were completely defective in HBsAg secretion, which could be partially rescued by co-expression with wt HBV. HBV encoding rtA181T/s172L and rtM204I/sW196S had slight secretion defects, whereas rtA181V/sW173F and rtM204V/sI195M had wt secretion levels. Flow cytometry was used to show that the truncated surface proteins also accumulated to higher intracellular levels than full-length controls. Cells transfected with these variants were less proliferative and had higher levels of apoptosis than full-length HBV. A consistent decline in the number of HBsAg positive cells over 5 days was also observed. The most cytopathic variant was rtM204I/sW196*, followed by rtV191I/sW182* and rtA181T/sW172* which were approximately equal. HBV encoding full-length surface proteins had wt levels of apoptosis and proliferation.

CONCLUSIONS: Some drug-resistant HBV variants selected during NA therapy are directly cytopathic to the host cell, promoting apoptosis. Apoptosis and chronic liver injury are strongly associated with disease progression and the development of HCC. Hence, although low genetic-barrier drugs may decrease viral load and increase survival in the short term, we predict that there may be long term detrimental effect in patients who have selected these variants. Supporting clinical data comes from a recent study where the rtM204I variant, which can result in the sW196* variation, was shown to be a significant risk factor for the development of HCC, whilst the rtM204V variant, which does not result in a truncated HBsAg, was not (Hosaka *et al.*. *Hepatol Res* 2010; 40:145).

ABSTRACT 99

Localization and distribution of viral genomes and proteins are helpful to understand pathogenesis of hepatitis

K Inoue[1,2], *M Yoshiba*[1], *and M Kohara*[2]

1 Gastroenterology, Showa University Fujigaoka Hospital, Yokohama, Japan; 2 Microbiology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

INTRODUCTION: Although PCR-based *in situ* hybridization (PCR-ISH) can be used to determine the distribution and localization of pathogens in tissues, this approach is hampered by its low specificity. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the primary causative agents of chronic liver disease. Therefore, to reveal the distribution and localization of genomes and proteins of HBV and HCV is helpful to understand the pathogenesis of the disease.

PATIENTS AND METHOD: Thirty-five patients were enrolled in the present study. Of these patients, 14 were considered to have chronic HCV infection, 8 were diagnosed with chronic hepatitis B, 6 were diagnosed with fulminat hepatitis B (five are due to acute infection and one is due to acute exacerbation) and 7 showed negative results for both viral markers but had metastatic liver cancer (6 with colonic cancer and 1 with gastric cancer). We used a highly specific and sensitive PCR-ISH and RT-PCR-ISH method to reveal the lobular distribution and intracellular localization of hepatitis B virus genome and HCV genome and to clarify the state of HBV and HCV infection in the liver. We also used specific antibodies against hepatitis B surface and core antigens to reveal the lobular distribution and intracellular localization.

RESULTS: In patients with persistent infection, HBV genomic DNA was detected in almost all hepatocytes, whereas HBV RNA or protein was differentially distributed only in a subset of the HBV DNA-positive region. Further, HCV genomic RNA was detected in almost all hepatocytes and was localized to the cytoplasm. HCV RNA was also detected in theepithelium of the large bile duct but not in endothelial cells, portal tracts, or sinusoidal lymphocytes. In patients with HBV fulminat hepatitis developed from HBV carrier, HBV genomic DNA was detected almost all hepatocytes and HBcAg and HBsAg

Laboratory Practice

移植医療

移植医療と検査⑤

肝臓移植における血小板動態

菅原寧彦*・田村純人*・國土典宏*

*東京大学医学部人工臓器移植外科
〒113-8655 東京都文京区本郷7-3-1

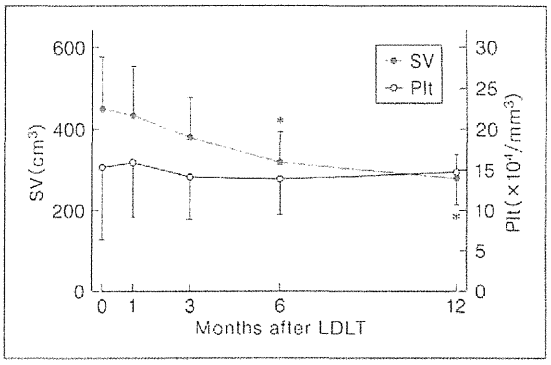


図1 術後血小板数(Plt)と脾臓(SV)の大きさの変化
脾臓は徐々に縮小する傾向があるが，血小板数は術前と比較して有意差はない．
LDLT：living donor liver transplantation.

はじめに

肝移植は，脳死患者より全肝を移植する全肝移植と，血縁者の部分肝を移植する生体部分肝移植に分類される．わが国では，いまだ全肝移植が一般的医療としては定着していないが，生体部分肝移植は盛んに施行されている[1]．生体部分肝移植はその導入期には脳死肝移植実施までの緊急避難的手段と位置付けられていた．しかしながら，その後の実績の積み重ねにより，疾患や年齢に制限が付け加えられていた保険適用範囲は2004年1月から大幅に拡大し，現在では一般的な治療法として認められるようになった．肝移植は末期肝硬変に対する根本的治療として確立している．

移植後の血小板数の変化

1．脾臓の大きさ

肝移植によって，門脈系の鬱血状態は劇的に改善されると考えられる．しかし，術前あった門脈圧亢進症の結果生じた脾腫や門脈側副血行路は容易に改善されない．例えば，脾腫に関しては，脾容積は移植後，縮小傾向はあるものの，著明な縮小をみることはない．脳死肝移植後8例の分析[2]では，平均23%の縮小を認めたものの，脾臓容積はいずれも400 ml以上であった．やはり脳死肝移植後の18例の分析[3]では，脾臓容積は94%の患者で縮小したが，56%の患者で脾腫は残存していた．筆者らの成人生体肝移植後19例の分析[4](図1)では，脾腫は術後経過中改善されるが，1年後の平均値で370 mlと脾腫は残存していた．ただし，筆者らの分析では，小児例[5]ではおおむね5年で正常の大きさに復することがわかっている．

2．門脈側副血行路

移植後に脾腫が直ちに改善されないことと同様に，移植しても門脈側副血行路が短期に自然閉鎖することはない．再還流した後に，遠肝性の門脈血流しか得られない場合は，グラフトに流入する門脈血を維持するために，移植手術中にシャント閉鎖を行う必要がある[6]．門脈側副血行路の発達の程度や場所は症例により多彩であり，技術的に高度な対応が必要となることも少なくない．発達した食道静脈瘤を合併している症例では術前の内視鏡的食道静脈瘤結紮術の積極的な施行，内視鏡的にアプローチの困難な胃静脈瘤ではHassab術(血行郭清術ならびに脾摘術)の施行が検討される必要がある．最近では，発達した脾腎門脈側副血行路に対して直接のアプローチをせずに左腎静脈根部をステイプラー式器械による処理を行う方法や，脾摘に際して超音波振動メス(超音波凝固切

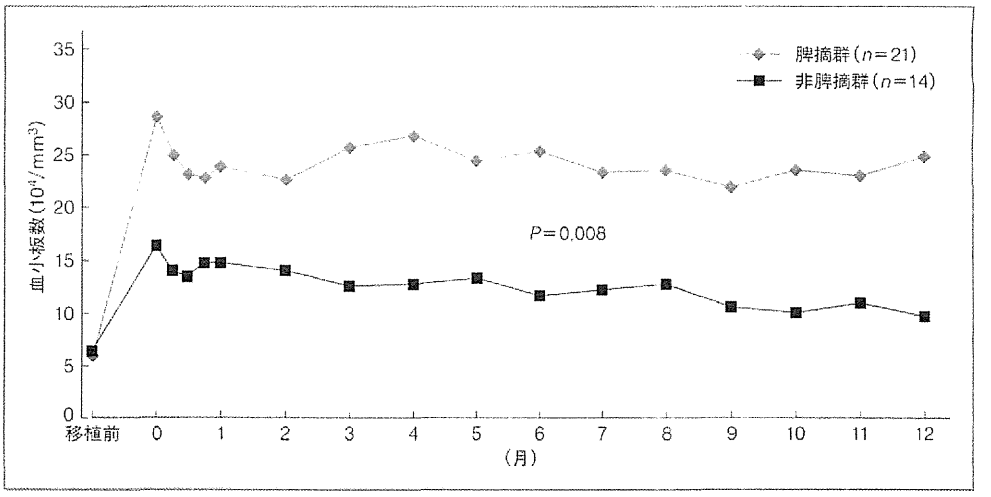


図2　脾摘の術後血小板数に対する影響　(文献7から改変して転載)
脾摘を行うと術後血小板数が高いレベルで長期間維持される.

開装置)を採用するなど，機器の発展に伴うさまざまな工夫がなされており，今後の評価が待たれるところである.

3．血小板数の変化

脾摘を移植時に併施した場合では，術後血小板数が高いレベルで長期間維持されるが，そうでない場合，長期でも10～15万/mm³程度にしか増加しない[7](図2)．C型肝炎陽性症例では移植後，インターフェロン治療を要することが多い．血球減少が，インターフェロン治療の中断，中止原因になることが多いことから，C型肝炎陽性症例では脾摘を全例で行うようにしている．欧米では一般的ではないが極めて有効であり，筆者らの教室では血小板減少を原因としてC型肝炎陽性例でのインターフェロン治療を中断した例は経験していない.

血栓性微小血管障害症(TMA)と血小板

1．ADAMTS 13とTMA

血栓性微小血管障害症(thrombotic microangiomiopathy，TMA)は，肝移植のみならず腎移植，小腸移植など，種々の臓器移植後の合併症として注目されている．感染や手術侵襲を契機に発症する溶血反応が顕在化し，問題となる播種性血管内凝固症候群(disseminated intravascular coagulation，DIC)様の病態である．一般的によく知られている溶血性尿毒症症候群(hemolytic uremic syndrome，HUS)や血栓性血小板減少性紫斑病(thrombotic thrombocytopenic purpura，TTP)を含む概念である．肝移植後のTMAはBonserらによる報告[8]が最初である．その後，筆者らは肝移植後のTMAの頻度は3.4%と報告[9]した．脳死臓器移植に比べ，臨床的には生体肝移植において顕在化し重篤な状態となる報告が多いものの，その直接の原因や詳細なメカニズムは今もって明らかではない．A disintegrin-like and metalloprotease with thrombospondin type-1 motis 13(ADAMTS 13)活性の低下によるものと考える報告もあるが，背景の一部であることが示されることがあるものの，今後のさらなる検討が必要である．ADAMTS 13活性の低下の原因として，グラフト機能回復の遅れやカルシニューリン阻害剤による副作用などが提唱されているものの，これらは生体移植後の一般的な状態であり，決定的とまではいえない.

TMAの原因を虚血再還流後のグラフト内血流の問題という意見もある[10]．血管内では静脈のような低ずり応力部位と動脈内のような高ずり応力部位が存在し，両者では血小板活性化の機序が異なっている．移植で問題になるような高ずり応力下では，肝類洞内皮細胞に発現するvon Willebrand因子(vWF)は立体構造をなし，活性型となる．また肝臓のように，血流が豊富で類洞構造

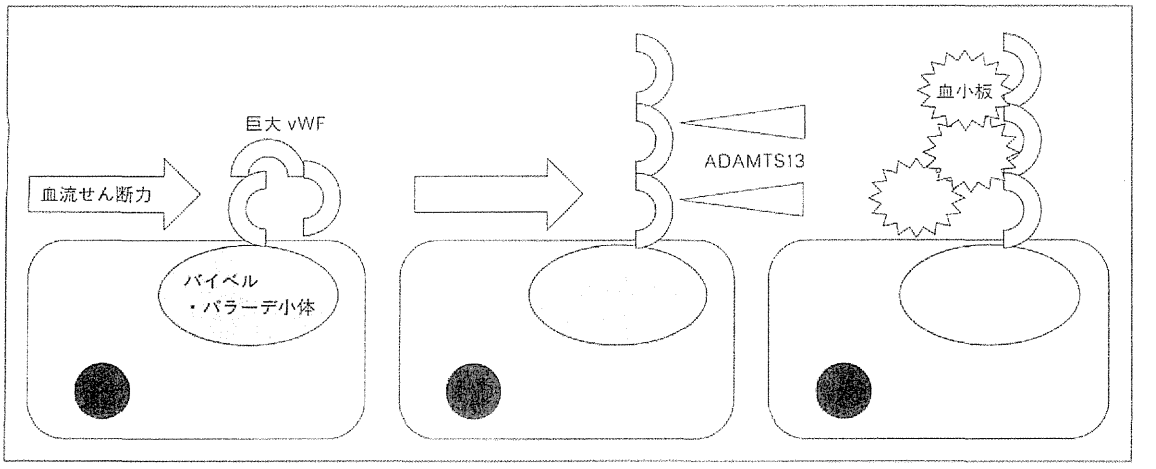


図3　TMA のメカニズム
vWF：von Willebrand 因子，ADAMSTS 13：A disintegrin-like and metalloprotease with thrombospondin type-1 motis 13(ADAMTS 13)．

を有する臓器では，血管内皮の表面積が大変広くなり，内皮障害の影響が顕著になると思われる．内皮障害は，血小板の凝集や活性化を惹起し，活性型 vWF はその構造変化により血小板凝集や ADAMTS 13 の作用を受けやすくなるため，ADAMTS 13 が消費され，結果として活性が低下する(図3)．

2．治　療

TMA の治療にあたっては，まず早期診断が重要である[9](表)．可及的な原因の除去と血漿交換が必要であることが臨床経験から明らかとなっている．具体的には，まずカルシニューリン阻害剤の変更(多くはタクロリムスからシクロスポリンへ)や中止を試みる．また，重症の場合は，血漿交換を行う．これは，巨大 vWF などの血小板凝集に関連する因子の除去や，血小板凝集抑制因子の補充を目的としている．このほかに，γグロブリンの投与を考慮することがある．C 型肝炎症例では，C 型肝炎再燃の制御が困難である症例において発症することがあり，対応がより困難となる場合がある．

表　肝移植における TMA の診断基準

進行する血小板減少＜50,000 mm³/ml
溶血性貧血の所見
　LDH 上昇(＞500 U/l)
　破砕赤血球
DIC を除外できる

おわりに

肝移植における血小板動態について概説した．移植後は脾腫や門脈側副血行路は容易に改善されない．血小板も長期でも 10～15 万/mm³ 程度にしか増加しない．肝移植後の TMA はそれほど頻度は高くないものの，免疫抑制剤や感染症が原因で起こる．微小血管内における血小板活性化や凝固線溶系の異常が原因である．

文　献

1) 日本肝移植研究会：肝移植症例登録報告．移植 45：621-632，2009
2) Yanaga K, Tzakis AG, Shimada M, et al : Reversal of hypersplenism following orthotopic liver transplantation. Ann Surg 210：180-183，1989
3) Chezmar JL, Redvanly RD, Nelson RC, et al : Persistence of portosystemic collaterals and splenomegaly on CT after orthotopic liver transplantation. AJR Am J Roentgenol 159：317-320，1992
4) Kaneko J, Sugawara Y, Akamatsu N, et al : Spleen volume and platelet number changes after living donor liver transplantation in adults. Hepatogastroenterology 51：262-263，2004
5) Egami S, Sugawara Y, Mizuta K, et al : Effect of pediatric living-donor liver transplantation on splenomegaly. Transplantation 74：1639-1642，2002
6) Kita Y, Harihara Y, Sano K, et al : Reversible hepatofugal portal flow after liver transplantation using a small-for-size graft from a living donor. Transpl Int 14：217-222，2001
7) Kishi Y, Sugawara Y, Akamatsu N, et al : Splenectomy and preemptive interferon therapy

for hepatitis C patients after living-donor liver transplantation. Clin Transplant 19：769-772, 2005
8）Bonser RS, Adu D, Franklin I, et al：Cyclosporin-induced haemolytic uraemic syndrome in liver allograft recipient. Lancet 2(8415)：1337, 1984
9）Tamura S, Sugawara Y, Matsui Y, et al：Thrombotic microangiopathy in living-donor liver transplantation. Transplantation 80：169-175, 2005
10）坂田洋一：移植と血栓．移植 39：415-424，2004

3．移植内科医の役割*

山敷宣代　菅原寧彦　小池和彦　國土典宏**

〔要旨〕臓器移植法改正に伴い，国内での脳死臓器移植件数の増加が期待される．治療手段としての移植手術を患者にオプション提示するなど，内科医にも移植医療が身近なものとなりつつあるが，移植医療にかかわる移植内科医の認知度は低い．移植内科医は，移植手術適応の評価や術前のマネジメント，そして術後の診療にいたるまで長期にわたり継続診療を行う，移植チームの主要なメンバーである．本稿では主に移植肝臓内科医について例をあげながら，移植内科医の役割を述べる．

はじめに

臓器移植を実施する場合，その執刀医となる外科医だけではなく，幅広い専門分野からなるアプローチ（multidisciplinary approach）が必要となる（図1）[1]．その中で，移植内科医（transplant physician）は臓器不全状態に陥った患者のケア，移植手術適応の評価や術前のマネジメント，そして術後の診療にいたるまで長期にわたり継続診療を行う主力メンバーである．生体臓器移植に依存してきた日本において，術前・術後の管理は長らく外科医主導で行われてきた．特に筆者のかかわる肝臓移植においては，生体ドナーの医学的適応判断にも高度な外科専門知識を必要とする．術前・術後の難題を一つひとつ乗り越えて築いた移植成績を，外科医の手で守り抜き長期生存へとつなげたいとの意気込みが感じられる分野といえる．しかし，2004年生体肝移植適応疾患が成人のほとんどの末期肝障害をカバーするようになり，生体肝移植実施件数が飛躍的に増加してからは，消化器内科医が患者に肝移植をオプション提示する機会も増加し，内科医にとって身近な治療となりつつある．

2010年の臓器移植法改正に伴い国内での脳死臓器移植が増加した．このことにより臓器不全例において診療にあたっている主治医が治療オプションとしての脳死臓器移植を検討する時代へと前進した．そのため，各臓器の移植適応基準について各疾患分野の専門医に周知するとともに，移植医療の専門的経験をもつ内科医の増員が望まれる．筆者は肝臓移植にかかわる内科的診療を行っているため，本稿では主に移植肝臓内科医について例をあげながら，移植内科医の役割を述べる．

Ⅰ．術前評価および移植待機中の管理

肝疾患の各病期において，医師がどのようにかかわるかを図示した（図2）．内科医や救急医から移植適応について相談を受けるが，特に消化器・肝臓専門医からの紹介が多い[2]．末期肝不全例の移植適応について紹介がある場合に，その病名お

キーワード：移植認定医，専門医制度

* The role of transplant physician in Japan.
** N. Yamashiki〈臓器移植医療部／消化器内科〉，Y. Sugawara〈准教授〉〈人工臓器・移植外科〉，K. Koike〈教授〉〈消化器内科〉，N. Kokudo〈教授〉〈人工臓器・移植外科〉：東京大学．

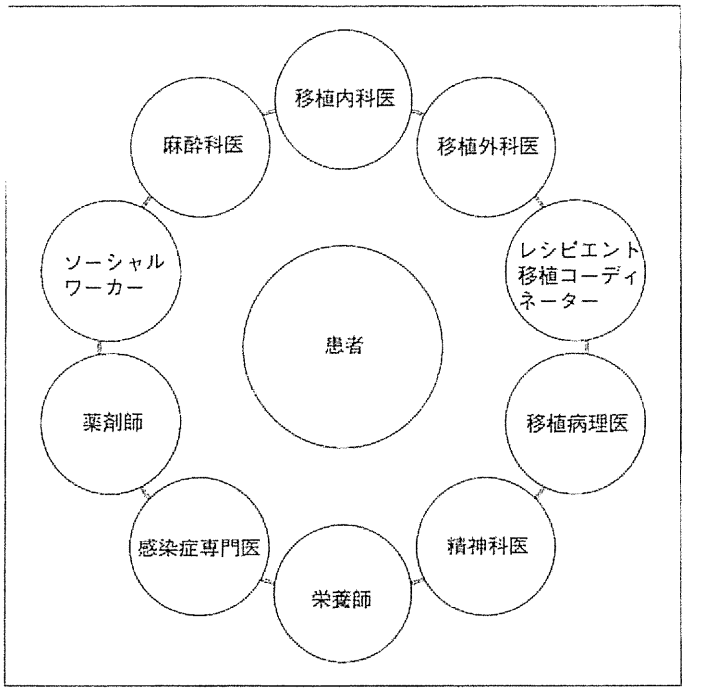


図1. 移植医療にかかわる multidisciplinary team
各専門家による集学的アプローチにより複雑な医療を成功に導く．示した以外にも多くの職種がかかわる．

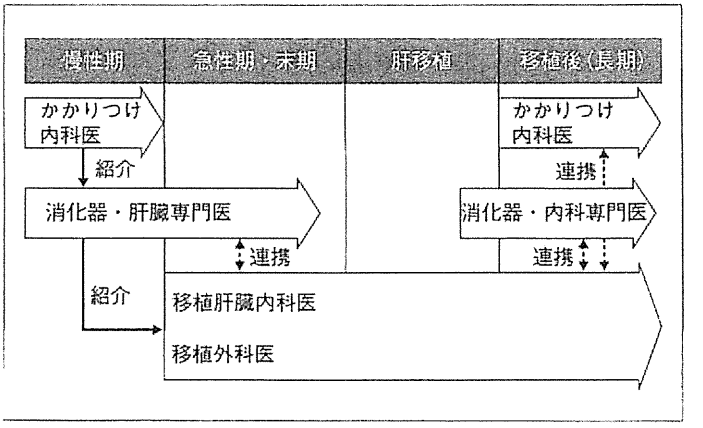


図2. 移植医療の流れと各専門家の役割
肝臓移植手術を例にとり，疾患のステージと医師のかかわりを示す．

[illegible][3]．内科的治療[illegible]移植以[illegible]ないかどうか，移植以[illegible]ないかどうかについても検[illegible]また，[illegible]となる併存疾患の有無[illegible]．末期肝硬変で移植適応があると紹介されても，真菌感染症や重度呼吸不全，悪性腫瘍合併などにより移植適応外となるケースもある．

移植適応と考えられる場合，移植治療の緊急性についても評価する．急性肝不全例などで緊急性

の高い場合には，数日以内に移植手術を実施する必要があり，チームで協力して迅速な対応をする．

脳死肝移植を希望する症例の場合には，このような術前評価を行った後，施設で適応判断をし，そのうえで移植適応評価委員会により適応判断，医学的緊急度の判断がなされる[4]．臓器提供件数が増加したとはいえ，実際に移植を必要とする症例数との差は大きく，脳死登録後も長期間の待機を余儀なくされる．なるべく良好な状態で待機するためには，自宅近くの消化器・肝臓専門医と連携しながら内科的管理を行っていく必要がある．

Ⅱ．生体ドナーの評価

脳死ドナーの限られる日本において，生体ドナーからの臓器移植が可能な腎移植，肝移植などの領域では，しばしば生体臓器移植を積極的に検討せざるをえない．生体ドナーへの説明，評価，選択についても医学的評価のみならず倫理的，社会的な配慮を要する．生体ドナーの倫理指針については移植学会から示されているが，各臓器および移植施設でより具体的な倫理規定を定めている[5]．移植内科医もこれらの事項について十分習熟する[6]．

Ⅲ．術直後の管理

移植手術および術後の管理については外科医が行うが，拒絶反応，動脈塞栓症，胆管狭窄，感染症などさまざまな合併症を認めるためきめ細かい周術期管理を要する．内科医が周術期管理にかかわることは少ないが，免疫抑制薬の選択，合併症などについて理解しておく必要がある[7]．肝臓移植領域ではカルシニューリン阻害薬（ciclosporin，tacrolimus hydrate）とステロイドで導入し，同剤またはmicophenolate mofetilといった代謝拮抗薬を併用して維持療法が行われることが多い．近年は，IL-2受容体抗体に特異的なbasiliximabなどの抗体製剤を導入期に用いることで，導入時のステロイドおよびカルシニューリン阻害薬の使用量を最小限とし，急性拒絶反応の頻度を増加させずに腎機能障害や代謝性疾患などの合併症のリスクを減らせるとして海外でしばしば用いられる．またrapamycinなどのmTOR阻害薬を使用することにより移植後長期の腎障害発生頻度を低下させ，また抗腫瘍効果も期待できるなどという報告もある．本邦では移植臓器別に保険収載されている免疫抑制薬が限定されているため，海外の報告どおりの免疫抑制療法が実施しづらい状況である．

Ⅳ．術後の長期管理

移植後長期的には，原病の再発，拒絶反応，胆管合併症などによる肝臓機能障害などが生じる可能性がある．移植医は，それらについて評価し治療方針を決定する．術後の肝機能異常は血液検査所見や画像所見だけでは原因を鑑別できないことも多く，しばしば肝生検が必要となる．また，移植後5年，10年と長期経過した後の原病の再発頻度や重症度についてはいまだ不明なことも多く，プロトコル生検（手術後1年ごとなど，スケジュールを決めた生検で，肝機能異常を認めない場合にも適応とする）を実施する施設が多い．移植後の抗ウイルス療法や自己免疫性肝疾患の治療，肝臓癌再発のサーベイランスなど，肝臓内科医としての専門性を発揮できる分野である．また，原則生涯免疫抑制薬を服用するため，生活習慣病，悪性腫瘍，感染症などの内科的治療を行うことも重要である．これらについては，患者の自宅近くのかかりつけ医と連携をとりながら，診療にあたる必要がある[8]．

Ⅴ．日本と欧米における認定医制度の動向

これまで述べたように，移植内科としてかかわる病態は肝臓移植だけをみても幅広い．臓器別の専門性と移植内科医としての知識や経験をもつ医師を育て移植医療の水準を向上させるために，この分野における認定医制度が望まれるところである．日本では，腎移植に関して日本臨床腎移植学会による認定医制度が2007年9月付で設立された[9]．他臓器を含め，今後正式に日本移植学会移植認定医制度が発足することも決定した[10]．

一方，米国では2002年には移植肝臓内科専門医制度のカリキュラムが発表された[11]．2006年にAmerican Board of Internal Medicine（ABIM）の認定する移植肝臓内科医（transplant hepatology）としての専門医制度が確立した[12]．制度の発足にいたる背景として肝移植実施件数の飛躍的な増加と抗ウイルス療法の発展が貢献している．現在は

表1. 米国，欧州における移植肝臓内科医研修内容の抜粋

項　目	米　国[11,15]	欧　州[14]
要　件	消化器内科専門医	消化器・肝臓専門医
移植内科医としての一般的事項		・移植医療の歴史 ・倫理的事項 ・移植にかかわる組織 ・免疫学 ・免疫抑制薬と拒絶反応 ・感染症の知識 ・移植と妊娠
移植肝臓内科としてのプログラム	・末期肝疾患およびその合併症の治療と移植適応 ・肝細胞癌・胆管癌の診断と治療 ・レシピエント・ドナーの適応評価 ・(脳死移植および生体肝移植) ・倫理的事項 ・外科手技についての理解 ・免疫抑制療法についての知識と使用経験 ・グラフト機能障害の評価	・肝疾患の自然予後 ・末期肝疾患の治療選択 ・肝移植の適応と禁忌 ・病理学的評価 ・移植待機中の診療 ・脳死・生体ドナーの評価 ・周術期の内科的治療 ・術後長期合併症の診断と治療
目　標	・移植適応評価20例 ・周術期の治療20例 ・術後1年以上の症例30例 ・経皮肝生検30例 ・組織についての理解(コーディネーター，ソーシャルワーカー，OPO，UNOS) ・ドナー摘出および移植手術それぞれ3例以上の見学 ・脳死ドナーの適応について理解 ・生体肝移植5例 ・小児移植，人工肝補助，リサーチなどについての知識	・術前の診療50例 ・周術期の治療20例 ・術後の治療50例 ・腹部超音波検査50例 ・自己肝および移植肝の肝生検40例 ・非侵襲的な肝機能検査20例 ・上部・下部内視鏡検査の判断各20例 ・ERCP実施の助手20例

OPO：organ procurement organization，UNOS：United Network for Organ Sharing，ERCP：内視鏡的逆行性膵胆管造影

術前評価や長期管理の大部分を移植肝臓内科医が行うことにより，周術期管理や臓器の摘出などに外科医が専念できる環境になっているとうかがえる．ただし，最近の報告ではむしろ内科医に過重負荷がかかるようにすらなっているようである[13]．その他のABIMの制度として，2010年から移植心臓内科医に対するAdvanced Heart Failure and Transplant Cardiologyの認定医制度も発足している．また2011年9月には，欧州における移植内科医の専門医試験も開始されるようである[14]．米国・欧州における移植肝臓内科医認定制度の研修内容や目標について，表1に抜粋した．数値目標などは異なるものの，おおむね同様の研修目標をかかげているように見受けられる．また，チームの一員としてコーディネーターなどほかの専門職を理解したり，臓器あっせん組織や臓器搬送について理解したり，コミュニケーション能力があることなども目標にかかげられている．

おわりに

移植内科医の役割について，肝臓内科医の立場から述べた．今後移植にかかわる各専門分野の内科医が増加することにより，日本における移植医療がより洗練されたものになり，また移植医療の

知見をもとに内科専門分野が発展することが期待される．

◆ ◆ ◆ 文献 ◆ ◆ ◆

1) Busuttil RW, Memsic LD, Quinones-Baldrich W et al：Liver transplantation at UCLA：program development, organization, initiation, and early results. Am J Surg **152**：75-80, 1986
2) 山敷宣代，菅原寧彦，田村純人ほか：日本の肝移植医療における移植肝臓内科医の役割と展望．肝臓**49**：28-38，2008
3) O'Leary JG, Lepe R, Davis GL：Indications for liver transplantation. Gastroenterology **134**：1764-1776, 2008
4) 山敷宣代，菅原寧彦，田村純人ほか：日本の脳死肝移植医療における適応，評価，待機の現状と問題点―東大移植チームの経験から．肝臓**50**：634-643，2009
5) 生体肝提供（ドナー）手術に関する指針．日本肝移植研究会．＜http：//jlts.umin.ac.jp/donor.html＞[Accessed August 12 2011]
6) Yamashiki N, Sugawara Y, Tamura S et al：Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. Liver Transpl **12**：1077-1083, 2006
7) Geissler EK, Schlitt HJ：Immunosuppression for liver transplantation. Gut **58**：452-463, 2009
8) McGuire BM, Rosenthal P, Brown CC et al：Long-term management of the liver transplant patient：recommendations for the primary care doctor. Am J Transplant **9**：1988-2003, 2009
9) 日本臨床腎移植学会―腎移植認定医制度について．＜http：//www.jscrt.jp/html_doc/recognition/index.html＞[Accessed August 12 2011]
10) 寺岡　慧：移植認定医制度―日本移植学会移植認定医制度発足に至る経緯．移植**46**：1-7，2011
11) Rosen HR, Fontana RJ, Brown RS et al：Curricular guidelines for training in transplant hepatology. Liver Transpl **8**：85-87, 2002
12) Bacon BR：Certificate of added qualification in transplant hepatology. Liver Transpl **11**：4-6, 2005
13) Heller JC, Prochazka AV, Everson GT et al：Long-term management after liver transplantation：primary care physician versus hepatologist. Liver Transpl **15**：1330-1335, 2009
14) European Board of Transplant Medicine：Applicants for EBSQ Transplantation Medicine.＜http：//www.uemssurg.org/index.jsp＞[Accessed August 12 2011]
15) American Board of Internal Medicine：Transplant Hepatology Policies.＜http：//www.abim.org/certification/policies/imss/thep.aspx#tpr＞[Accessed August 12 2011]

*　　*　　*

PBCとその類縁疾患に対する肝移植

山敷宣代* 菅原寧彦** 國土典宏*,**

索引用語：生体肝移植，脳死肝移植，移植適応，PBC再発，診断基準

1 はじめに

原発性胆汁性肝硬変(PBC; primary biliary cirrhosis)は，成人肝移植症例のうち最も頻度の高い疾患の一つである．本邦における2009年までの報告では，18歳以上の初回生体肝移植3,504例中503例(14.3％)がPBC患者に対し施行された(図1)．生体肝移植後の5年，10年累積生存率はそれぞれ76.2％，72.2％と良好である[1]．欧米における脳死肝移植においても同様に，PBCは移植の対象となる主要な疾患のひとつであり，その1年，5年，10年生存率は83％，77％，69％と報告されている[2]．PBCは，その他の自己免疫性肝疾患と同様，グラフトに再発することが知られている[3]．現在では20％～30％の症例で再発を認めると考えられているが，長期予後にはさほど影響はないと考えられていた[4,5]．近年肝移植後の予後が向上し，移植後長期生存が期待できる時代となり，原疾患の再発が持つ意味合いは大きくなってきた．

2 PBCに対する肝移植の適応時期

PBCの肝移植適応については，他の原因による肝硬変と同様である．つまり，胆汁うっ滞性肝硬変により非代償性肝硬変となり，食道静脈瘤からの出血，難治性腹水，薬物治療に不応性の掻痒感などを認め内科的治療に限界をきたした場合，肝移植の適応時期と考えられる．PBCの自然予後についてはいくつかの観察研究が報告されている．Mahlらは1955年から1979年にYale Liver Study Unitに紹介された北米のPBC患者のコホートを解析し，PBCと診断された症例の平均余命は症候性PBCで7.5年，無症候性PBCで16年と報告した[6]．難治性の肝疾患に関する調査研究班平成21年度総括・分担研究報告書によると，本邦における1980年以降に登録した症候性PBC4,389例および無症候性PBC1,772例の5年生存率はそれぞれ97.7％，79.5％，10年生存率はそれぞれ93.3％，65.5％であった[7]．観察研究にもとづき，予後予測因子が

Noriyo YAMASHIKI et al: Liver transplantation for primary biliary cirrhosis and overlap syndrome
*東京大学医学部附属病院臓器移植医療部［〒113-8655 東京都文京区本郷7-3-1］
**同 人工臓器・移植外科

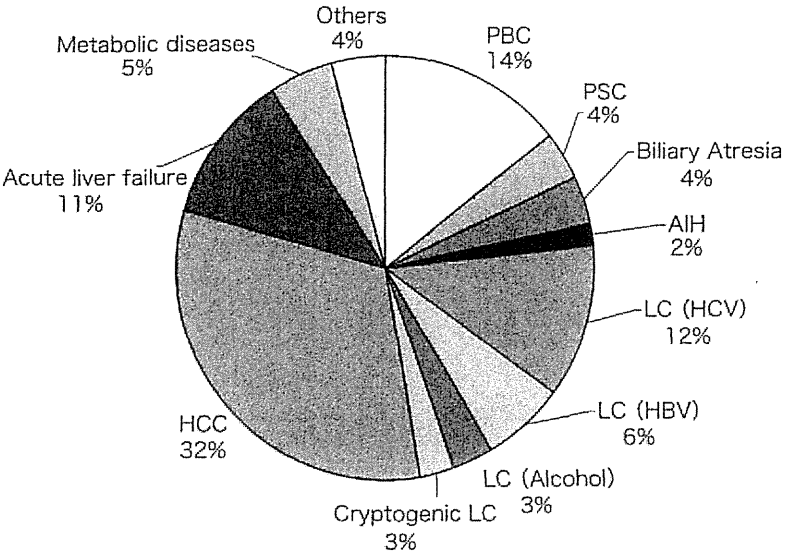


図1　疾患頻度
18歳以上の初回生体肝移植3,504例中503例(14.3%)がPBC患者に対し施行された[1].

報告されている．Mayo clinicのグループは，患者の年齢，血清ビリルビン値，アルブミン，プロトロンビン時間，浮腫の有無という5つの因子を用いた生存予測モデル(Mayo natural history model)を報告している[8]．同グループは2年以内の生存率についてより正確に予測できるupdated natural history modelを報告しており，これらの予後予測モデルを用いたリスクスコアはWebベースで簡単に計算することが可能である(http://www.mayoclinic.org/gi-rst/mayomodel2.html)[9]．

同グループはさらに末期PBC症例の移植後生存率とMayo natural history modelを比較し，肝移植によって2年生存率で43%(31%から74%)の改善を認め，末期PBCに対する肝移植によりSurvival Benefitが得られると報告した[10]．術前のMayoリスクスコアが7.8までの症例ではリスクスコアの変化は肝移植後の短期予後に影響はないが，7.8を超え，値が増加するにつれ移植後の死亡リスクは増加する．また，リスクスコア7.8以上の症例ではICU滞在日数，入院期間が長く，術中輸血量が多い．それらの結果をもってKimらはリスクスコア7.8程度が肝移植の至適時期だと報告している[11]．当院にて生体肝移植を受けたPBC50例の検討においても，術後在院日数に寄与する因子としてupdated modelによるMayoリスクスコア<10が有意な危険因子であった[12]．

3　PBCの再発

NeubergerらBirminghamのグループは1982年，肝移植後約4年でグラフト肝にPBCの再発をきたした3症例を報告した[13]．その後再発の有無について論争が繰り広げられた[14]．しかし，プロトコール肝生検の病理学的検討などが複数の施設から報告され，現在は9%～35%の症例で再発を認めると考えられる[2,15]．

PBCの再発の診断には病理学的な診断が必要であり，臨床所見・生化学所見などの

表1　PBCの再発についての報告

著者/年	地域	症例数	プロトコール肝生検	再発(%)	再発診断の時期(肝移植後)
脳死肝移植					
Hubscher/1993 [16]	Birmingham, UK	83	+	13 (16%)	NA
Slapak/1997 [29]	London, UK	33	+	8 (24%)	5年以降
Sebagh/1998 [17]	Villejuif Cedex, France	69	+	6 (9%)	1～8年
Sanchez/ 2003 [23]	Dallas, USA	156	+	17 (10.9%)	49.6カ月
Guy/2005 [30]	St.Louis, USA	48	+	4 (8% ; definite)	40カ月
Charatcharoenwitthaya/2007 [19]	Rochester, USA	154	+	52 (34%)	3.5年
Hytiroglou/2009 [26]	New York, USA	84	-	7/44 (15.9%)	2.8年
Montano-Losa/2010 [21]	Alberta, Canada	108	-	28 (26%)	NA
生体肝移植					
Hasegawa /2005 [12]	Tokyo, Japan	50	-	0	NA
Morioka/2007 [24]	Kyoto, Japan	50	-	10/35 (29%)	2.4年

有用性は劣る．肝機能検査(AST; aspartate aminotransferase, ALP; alkaline phosphatase, T-Bil; total bilirubin)は多くの再発症例において正常範囲内を示す．Hubscherらの報告では，病理学的にPBCの再発を83症例中13例(16%)に認めたと報告しているが，臨床症状として掻痒感を認めたのは1例にとどまる．また病理学的なPBC再発を認めた13例のうちASTの上昇は3例，T-Bil上昇は3例，またALPの上昇は6例に認めるのみであった[16]．Sebaghらの検討においても，6例のPBC再発症例のうち臨床症状を認めたのは2例，ALP上昇は4例，AST上昇は2例に認めるのみで，T-Bilは全例において正常範囲であった[17]．抗ミトコンドリア抗体は術後もほとんどの症例で陽性が持続するため，PBC再発の診断にはあまり有用ではない．したがって，PBC再発の診断は，病理学的所見に基づく必要がある[15,16,18]．再発の診断基準として報告される項目はおおむね次のようなものである．1)肝移植術前にPBCが診断されていること，2)胆管障害をきたすその他の疾患を除外すること，さらに，3)病理組織所見にてPBCに合致する所見を認めること，であろう．再発PBCの病理所見は通常のPBCの病理診断とほぼ同様である[15]．すなわち，感染