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Message From The Organising Chairman

It gives me great pleasure indeed to welcome all of you to the 9th Liver Update, which is being held this year, from 13th to 17 July, at the Sunway Resort & Spa Hotel, Petaling Jaya.

The 9th Liver Update is a series of biennial regional meetings jointly organised by the Malaysian Liver Foundation and the Ministry of Health of Malaysia, to keep our doctors, specialists and allied health professionals updated in the latest advances and developments in hepatobiliary diseases. Every two years, this landmark meeting draws many Malaysians and international experts to discuss, deliberate and share their experiences in the management of challenging and complex hepatobiliary diseases.

It is our hope that through this series of international liver meetings, our health care professionals will be able keep abreast of current diagnostic tools and therapeutic strategies, including best management practices pertaining to hepatobiliary diseases.

As always, the Organising Committee of the 9th Liver Update has planned an interesting and elaborate scientific programme, which comprises three pre-congress workshops, plenary lectures, symposia, a debate, interactive case studies and a special Symposium and a Workshop for our general practitioners. The workshops include a live endoscopy workshop, a radiology workshop on TIPSS and a pathology workshop on fatty Liver. We will also be holding a Kuala Lumpur Hepatitis Day on Sunday, 17th July 2011 to create awareness on hepatitis amongst the public, conduct screening tests for hepatitis and hold counselling sessions for those who require them.

The Special MLF Lecture will take place on 14 July 2011 and this year, the award goes to Professor Aiden McCormick from Dublin, Ireland. We are also honouring Dr Richard Guan with a Special Lecture in view of his immense contributions to the success of the previous Liver Updates.

I am confident that Liver Update 2011 will continue to be an interesting and enjoyable scientific event.

Tan Sri Dato' Seri Dr. Haji Mohd. Ismail Merican
Organising Chairman
9th Liver Update
President, Malaysian Liver Foundation.

Hepatitis C Virus Abs, RNA and Genotype in Patients with Hepatocellular Carcinoma in Baghdad

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SUMMARY

BACKGROUND: Hepatitis C virus (HCV) was considered by several investigators to be a possible pathogenetic agent for hepatocellular carcinoma (HCC) in a number of countries. **AIMS:** To identify whether exposure to HCV, acts as a risk factor for HCC development. And the predominant HCV genotype among Iragi patients with HCC. **MATERIALS AND METHODS:** A case-control study was conducted consist of 65 patients with HCC compared to 82 patients having other malignant disease rather than HCC (control group). HCV Abs (anti-HCV) was tested for both groups, using subsequently third generation enzyme immunoassay (EIA-3) and immunoblot assay (Lia-Tek III) as screening and confirmation tested respectively. In addition, 26 positive anti-HCV Sera (both groups) were subjected to molecular analysis, using the most recently developed RT-PCR and DNA Enzyme immunoassay (DEIA) method (Sorin Biomedica Italy). **RESULTS:** Anti-HCV seropositivity rate significantly was higher 17(26.1%) among HCC patient compared to 9(1.1%) control group. And HCV-RNA was confirmed positively in 12 and 2 sera of HCC and control group respectively with positive anti-HCV. Moreover, anti-HCV seropositivity was found significantly acts as a risk factor for HCC development (OR=2.37, 95%CI=1.1-7). No significant association was detected between HCC and HCV genotypes. However, 7HCC patient were harboring HCV-1b (as a single or mixed pattern of infection). One HCC sera with positive HCV-RNA could not be type. While the remaining were infected by genotype 1a or 4. **CONCLUSION:** Our study detected a significantly higher rate of anti-HCV seropositively in HCC patients. And HCV infection acts as a significant risk factor of HCC. Also HCC patient harboring HCV-1b in higher rate than their counter group.

Non-operative Management of Blunt Liver Trauma in Periphery Hospital

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SUMMARY

Non-operative management of blunt liver trauma is currently being considered the treatment of choice for hemodynamically stable patients who sustained blunt liver injury. This approach was first proposed in 1970's by pediatric surgeons but it was partly ignored. It was the advancement in technology and radiological imaging especially computed tomography which changed the surgical philosophy in the management of blunt liver trauma. However, before we can even consider non-operative management of blunt liver injury, there are at least three criteria that must be fulfilled. First of all, patient must be hemodynamically stable and there is no peritoneal signs demonstrated on abdominal examination. Last but not least, there must not be any intraperitoneal or retroperitoneal injuries on computed tomography scans which require operative interventions. This study is looking into the 13 patients with blunt liver trauma who were successfully treated with non-operative approach for blunt liver trauma in surgical department of Hospital Sultan Abdul Halim from July 2008 to December 2009. We are looking into the length of stay of these patients, grading of the liver injury on CT scan, the need of blood transfusions, the need of intensive care unit admissions and any other associated injuries.

In conclusion, non-operative approach in patients with blunt liver trauma is considered the treatment of choice for the modern days as long as the patient's condition met the three criteria mentioned above. However, we must always bear in mind the possibility of missing other associated intraabdominal injury in these patients that requires surgical intervention.

Case Report – Gallstone Ileus, A Rare Presentation of Gallstone Disease

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SUMMARY

Gallstone disease is a common medical condition. Its common presentations can vary from right hypochondriac pain and vomiting to obstructive jaundice and fever. This case report involved a patient with a rare presentation of gallstone disease. She was initially presented with epigastric pain, vomiting and abdominal distension. She was afebrile and not jaundice. Her serum amylase level was slightly elevated and total white cell count was normal. Abdominal X-ray revealed slightly dilated small bowel. Diagnostic laparoscopy was done and noted a huge gallstone in the lumen of proximal ileum with proximal small bowel dilatation. Enterolithotomy was performed and the gallstone was successfully removed laparoscopically. Mechanical intestinal obstruction due to a gallstone was first described by Bartholin in 1654, with the term "gallstone ileus". The symptoms can vary depending on the site of impaction. The diagnosis is not easy to make, as up to 50% of diagnoses was made during laparoscopy or laparotomy. Only 10% of gallstones are visible on radiographs, hence plain abdominal X-rays might not be very helpful. Computed Tomography has its value in the evaluation of patients with gallstone ileus. However, it is not readily available in our hospital setting. One of the common complications that can arise from this condition is ileal perforation as the huge gallstone compresses on the bowel wall causing ischemic necrosis which leads to perforation.

In conclusion, mechanical obstruction of the small bowel by gallstone is an uncommon complication of gallstone disease. It only occurs in less than 0.5% of patients. The diagnosis can be difficult to make at the time of initial presentation due to the lack of previous history in the majority of patients and it is relatively rare as a cause of obstruction.

Fatty Liver in Obese Children: A Study of Ultrasonography and Liver Enzyme Levels

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SUMMARY

OBJECTIVES: 1. To determine the prevalence of fatty liver in obese children, as assessed by ultrasonography and liver enzyme levels. 2. To identify any correlation between the two investigatory methods. 3. To identify other co-factors affecting fatty liver in obese children. **MATERIALS AND METHODS:** This study was carried out in Hospital USM, Kelantan from December 2004 until May 2006. A total of 32 obese children were subjected to several anthropometric measurements, blood investigations and abdominal ultrasonography. The degree of fatty liver involvement was analyzed using several ultrasonographic criteria. Comparison between fatty liver on US and raised liver enzymes as well as correlations with other demographic figures were analyzed using appropriate statistical tests. **RESULTS:** Prevalence of fatty liver as assessed by ultrasound and liver enzyme levels were 65.6% and 37.5% respectively. There was 65.6% of children with hepatomegaly, and 90.5% of these children had fatty liver. Significant correlations were found between ultrasonographically detected fatty liver and liver enzyme levels ($p < 0.005$ for ALT; $p < 0.01$ for AST), and between degrees of fatty liver and raised liver enzymes ($p < 0.005$). Hepatomegaly showed significant correlations with fatty liver and liver enzyme levels ($p < 0.01$ for both), however not with degrees of fatty liver ($p > 0.05$). BMI was the only other factor which showed significant correlation with ultrasonographically detected fatty liver, hepatomegaly and raised ALT levels ($p < 0.05$). No significant correlation was found between fatty liver disease and other demographic data or fasting lipid profiles using both methods ($p > 0.05$). **CONCLUSION:** Ultrasound is a reliable, non-invasive method which correlated well with hypertransaminases and increasing BMI. It is recommended that ultrasound be included in the screening and monitoring of NAFLD in children.

Yield of Endoscopic Ultrasound (EUS) in Diagnosing Common Bile Duct (CBD) Stones in Acute Gallstone Pancreatitis after Routine Blood Tests and Transabdominal Ultrasound (TUS)

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SUMMARY

BACKGROUND: EUS can be used for identifying common bile duct stones and determining the need for ERCP in clinically ambiguous situations in gallstone pancreatitis. **OBJECTIVES:** To determine the yield of EUS in diagnosing CBD stones in acute gallstone pancreatitis and predictive factors of CBD stones in acute gallstone pancreatitis. **MATERIALS AND METHODS:** A cross-sectional study was conducted in Hepatology Department of Selayang Hospital from 1st January 2008 to 31st December 2010. All patients presented with acute pancreatitis (typical acute epigastric pain after exclusion of other causes, serum amylase > 3x upper limit of normal) and TUS revealed cholelithiasis but no choledocholithiasis were included. EUS was done on all patients and Endoscopic retrograde cholangiopancreatography (ERCP) was done if choledocholithiasis was found. The demographic data of patients, TUS, EUS and ERCP findings was analyzed. Statistical significance was defined as $p < 0.05$. **RESULTS:** Thirty one patients were recruited in this study. Sixteen patients were female and median age was 55 years. Nine patients (29%) were found to have choledocholithiasis from EUS and all of them showed CBD stones at ERCP. Male gender, Chinese ethnic group, dilated CBD size from TUS, normal alkaline phosphatase (ALP), high bilirubin and ALT were associated with higher proportion of CBD stone from EUS but all did not reach statistical significance. **CONCLUSION:** Twenty nine percents of patients with acute gallstone pancreatitis and absence of CBD stones from TUS had CBD stones detected with EUS. Size of CBD, serum bilirubin, ALP and ALT are not reliable predictor for detection of CBD stones by EUS.

Yield of Endoscopic Ultrasound (EUS) in Diagnosing Aetiology of Acute Pancreatitis (AP) After Negative Routine Blood Tests and Transabdominal Ultrasound (TUS)

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SUMMARY

OBJECTIVES: To determine the yield of EUS in aetiology of acute pancreatitis after negative routine blood tests and TUS. **MATERIALS AND METHODS:** A cross-sectional study was conducted in Hepatology Department of Selayang Hospital from 1/1/2008 to 31/12/2010. All patients presented with acute pancreatitis (typical acute epigastric pain after exclusion of other causes, serum amylase > 3x upper limit of normal) and unable to ascertain aetiology after bedside clinical evaluation, TUS, serum calcium and lipid level were included. EUS was done on all patients and Endoscopic retrograde cholangiopancreatography (ERCP) was done if common bile duct (CBD) stone and/or sludge were found. The demographic data, TUS, EUS and ERCP findings was analyzed. **RESULTS:** Thirty four patients were recruited. Twenty patients were male and median age was 56 years. Nine patients was found to have gall bladder (GB) stone or sludge missed by TUS. Twelve patients had CBD stone or sludge on EUS. Two patients had chronic pancreatitis and one had intraductal papillary mucinous neoplasm (IPMN). The other ten patients had normal EUS findings. The 21 patients (62%) who had biliary related aetiology of pancreatitis. Raised alkaline phosphate (ALP), female gender, Chinese ethnic group, dilated CBD size from TUS, normal alkaline phosphatase (ALP), high bilirubin and ALT were associated with higher proportion of biliary stone from EUS but all only high ALP ($p < 0.05$) reach statistical significance ($p < 0.05$). **CONCLUSION:** Sixty two percents ($n = 34$) were found to have biliary stones as aetiology of AP by EUS. Two cases of chronic pancreatitis and one IPMN was diagnosed by EUS. Only high ALP was significantly associated with biliary related aetiology of pancreatitis.

Pancreatic Head Carcinoma that is almost Deemed Inoperable

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SUMMARY

Pancreatic cancer is often associated with poor prognosis as patients often present late and the management remained challenging. Although perioperative morbidity and mortality has reduced over the years with proper preoperative staging and advanced surgical skills, the 5-year survival rate remained low. Early detection offers the best chance of survival with proper preoperative evaluation an important task. CT scan remained the “gold standard” in clinical staging. EUS as an adjunct to preoperative staging is a useful tool in small tumour and detecting vascular invasion although lymph node assessment is less effective. The most important prognostic factor in pancreatic resection is to achieve a complete resection margin. The role of extended lymphadenectomy and vascular resection in determining prognosis remains controversial. Recent evidence suggests that extended resection can be performed safely with perioperative morbidity and mortality similar to those without extended resection. Although arterial involvement is a known contraindication to surgery, nevertheless when there is isolated venous involvement, excision of portal vein is recommended and should not be deemed as contraindication to surgery. Extended lymphadenectomy is rarely performed as no survival benefit is reported although positive lymph node yield for malignancy may predict prognosis in patients. Here, we report a case of a 63 year old lady who had pancreatic head carcinoma with portal vein infiltration and celiac nodes on preoperative EUS and CT scan. She had a pancreatoduodenectomy with portal vein excision/reconstruction and extended lymphadenectomy done. Histopathological report revealed a well differentiated adenocarcinoma with portal vein infiltration, there was not lymph node involvement. Post-operative recovery was uneventful. In conclusion, portal vein invasion or pre-operative radiological diagnosis of lymph node involvement should not be a contraindication for pancreatoduodenectomy.

Case Report: Central Hepatectomy Post Transarterial Chemoembolization (TACE): Does it make Surgery More Difficult?

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SUMMARY

Treatment approach to Hepatocellular carcinoma (HCC) is ever evolving and challenging because of the nature of the disease. When tumour is centrally located, it presents a challenge to clinicians as resectable tumour from a centrally located lesion often involves technical complexity with regards to surgery. When the centrally located tumour is large, resection can sometimes be contraindicated and not recommended. Often times, transarterial chemoembolization (TACE) are administered when such lesion is encountered in the hope that it may make resection favorable. However, TACE has both its advantages and disadvantages. Its role today remained controversial. Recent literature have suggested that pre-operative TACE prior to central hepatectomy for centrally located HCC can be associated with perihepatic adhesions, pediculitis, chronic cholecystitis, and increase in operating time as well as increase intraoperative blood loss with rise in transfusion requirement. Here we report a case of a 62 year old man, with known Hepatitis B status, who has been diagnosed with Segment 4, 5 and 8 HCC and underwent central hepatectomy in our institution. Prior to surgery, patient underwent preoperative TACE twice. Pre-operative work up was unremarkable. Intra-operatively, the tumour was adherent to the gallbladder and removed en bloc. Dense adhesions were encountered at the hilar plate during dissection. Blood loss was about 1.5L. Post-operative recovery was otherwise uneventful. His histopathological examination (HPE) showed poorly differentiated hepatocellular carcinoma with complete resection margin and tumour size was smaller than initially reported on CT scan.

Eosinophilia in Autoimmune Hepatitis: Is There An Association?

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SUMMARY

BACKGROUND: There were several reports on eosinophilic drug-induced hepatitis. We report a case of autoimmune hepatitis (AIH) presenting with eosinophilia in whom steroid therapy induces resolution of both eosinophilia and hepatitis. **CASE REPORT:** A 57 years old lady who presented with jaundice and right hypochondriac pain associated with tender hepatomegaly and urticarial rash. Blood investigations showed high eosinophil counts persistently ranging from 800 to 1500/mm³ with highly elevated bilirubin of 380 µmol/L, alanine transaminase 750 U/L and aspartate transaminase of 1015 U/L. She has raised serum immunoglobulin IgG of 21.6 g/l. Liver biopsy showed moderate interface hepatitis and plasma cells infiltration suggesting AIH. However her antinuclear antibody was negative. She had negative serology for hepatitis A, B and C, and a normal ultrasound abdomen. Definite diagnosis of AIH was made based on Codified Diagnostic Criteria of the International Autoimmune Hepatitis Group with aggregate score 17. On starting steroid, she has a complete normalization of liver function and eosinophil count. **DISCUSSION:** Eosinophilia is a manifestation of allergic reactions characterized by IgE-mediated eosinophil production induced by compounds released by basophils and mast cells, including eosinophil chemotactic factor of anaphylaxis, leukotriene B₄, complement complex (C5-C6-C7), interleukin 5, and histamine. AIH is characterized by an inflammation of the portal tract with lymphocytes and plasma cells, hypergammaglobulinemia and presence of a variety of circulating autoantibodies. While eosinophilia is humoral (antibody-mediated), AIH is thought to be cell-mediated. Presence of both conditions in an individual is uncommon. In this case effort had been made to rule out other cases of eosinophilia such as drug-induced or helminthic infections but there were all negative. The mechanism of dual-pathology in this case remains unresolved. **CONCLUSION:** Eosinophilia is not a diagnostic feature for AIH. An association with AIH is suggested in this case.

Autoimmune Hepatitis – Clinical Features and Outcomes: Hospital Selayang Experience

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SUMMARY

OBJECTIVE: Autoimmune hepatitis (AIH) is an inflammatory condition of the liver from an unknown cause. Local data regarding the disease is not well known. **MATERIALS AND METHODS:** We reviewed all cases diagnosed to have AIH in Hospital Selayang (HS), Malaysia from 2004 until 2008. **RESULTS:** There were 51 cases of AIH diagnosed between year 2004 until 2008. Mean age at presentation was 42.4 ± 15.4 years with female preponderance (84.3%). The ethnic distributions were 68.6% malays, 27.4% chinese and 3.92% indians. Their presentations were jaundice (76.4%), decompensated cirrhosis (11.7%) and asymptomatic transaminitis (11.7%) Liver biopsy were done in 40 patients (78.4%) and consistent with AIH. Detectable antinuclear antibodies and elevated Immunoglobulin G above 1.5 upper limit normal were present in 66.6 % and 68.6 % of patients respectively. There were 4 cases of Acute liver failure (ALF) due to AIH and 2 patients recovered with medical treatment without liver transplant. Up to the last follow-up in 2011, a total of 35 patients (68.6%) remain in follow-up, 6 (11.7%) defaulters, 5 patients (9.8 %) were discharged to the referral hospital and 5 death (2 due to ALF, 3 due to non-liver related causes). Two patients (3.92%) died before discharge and another 3 patients (5.88%) died on subsequent follow-up from non liver related causes. A total of 35 patients (68.6%) remained in biochemical remission with 6 patients (11.7%) off treatment and the remaining on maintenance therapy with prednisolone \pm azathioprine. **CONCLUSION:** In our experience AIH cases presented with severe liver disease and the patients who were still under our follow-up responded to treatment and remained in remission for mean duration of 52.3 ± 19.6 months.

Autoimmune Hepatitis in A Malaysian Tertiary University Hospital

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SUMMARY

INTRODUCTION: Autoimmune hepatitis (AIH) is a rare immune mediated chronic inflammatory destruction of liver parenchyma. Without treatment, it will progress to cirrhosis and eventual liver failure. The prevalence and characteristic of AIH is not known in Malaysia. **MATERIALS AND METHODS:** We aimed to evaluate the characteristic of patients with AIH presented to a tertiary university teaching hospital. This is a retrospective study with review of patients' records from the clinical notes and computerized hospital record system. The diagnostic criteria of AIH were based on the revised International Autoimmune Hepatitis Group score. **RESULTS:** Eleven patients were diagnosed to have AIH from 2002 to 2010. Mean age of patients were 49.2 years (range 23-60). There were 5 female and 6 male patients. Racial distribution consists of 8 Malays followed by 2 Chinese and 1 Indian. Most patients complaint of jaundice (63.6%), followed by tea colored urine (45.5%). Two patients complaint of loss of appetite, pale stool and nausea. Only one patient complained of arthralgia, myalgia and loss of weight. Three patients were asymptomatic with mild deranged liver function and were referred for further investigation. Eight patients had jaundice on examination. Only one patient had stigmata of chronic liver disease when presented. Two patients have concomitant autoimmune disease, with Hashimoto thyroiditis and discoid lupus respectively. The mean alanine transferase, bilirubin, alkaline phosphatase, albumin and IgG level was 743.6 U/L, 116.5 $\mu\text{mol/L}$, 152.4 U/L, 39.5 g/L and 2613.5 mg/dL. Anti-nuclear (ANA) and anti-smooth-muscle antibody (ASMA) were found in nine and five patients respectively. Three patients were noted to have both ANA and ASMA. Liver biopsy was performed in 10 patients. Intrephase hepatitis, plasmacytic infiltration and rosetts formation were noted in 72.7%, 81.8% and 36.4% of the liver biopsy respectively. A mean duration of 169 days is required before the diagnosis is made. Three patients were given monotherapy of corticosteroid. Combination therapy of corticosteroid and azathioprine were given to 6 patients. Treatment was not initiated in two patients. Relapse of AIH only occur in two patients and responded well to reintroduction of corticosteroids. **CONCLUSION:** AIH is a disease that requires recognition. In our center, AIH commonly presented as acute hepatitis and older age group. From our review, it response well to treatment and relapse are uncommon.

KEY WORDS:

Autoimmune Hepatitis, Immunoglobulin, Anti-nuclear antibody

Clinical Usefulness of Endoscopic Ultrasound in Asymptomatic Patients with Raised Carbohydrate Antigen 19-9

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SUMMARY

INTRODUCTION: CA19-9 is a non specific tumour marker that may be raised in patients with small pancreatic lesion or biliary obstruction. EUS has been shown to be useful in detecting small pancreatic lesion which may be missed by other imaging modality. **MATERIALS AND METHODS:** We retrospectively reviewed the clinical usefulness of endoscopic ultrasound for detecting pancreatic pathology in asymptomatic patient with incidental finding of raised CA19-9 referred to our centre from 2009 to 2011. The clinical notes of patients were reviewed on the presence of symptoms, level of CA19-9, liver function test, and radiologic imaging. All the patients underwent a radial endoscopic ultrasound using an Olympus Aloka Alpha-10 system. **RESULTS:** A total of eight patients (5 females and 3 males) were identified. The mean age of patients were 55.4 ± 9.0 years (range 45-74). The serum CA19-9 ranges were 47-600 IU/ml with a mean value of 219.5 ± 206.7 IU/ml. Four patients had epigastric discomfort. The mean value of alanine transaminase were 22.9 U/L, alkaline phosphatase 67.9 U/L, albumin 38.1 g/L, and bilirubin 14.6 $\mu\text{mol/L}$ respectively. Hepatobiliary ultrasound was performed in two patients with unremarkable findings. Computer tomogram were performed in 7 patients, which showed fatty liver (n=1), gallstone disease (n=1), renal cyst (n=1), prostatomegaly (n=1), bulky head of pancreas (n=2), and unremarkable (n=1). Endoscopic ultrasounds of these patients were unremarkable of pancreatic biliary lesion in all the patients with a normal CT abdomen. Two patients with bulky head of pancreas also had a normal EUS study. One patient with gallstone disease detected on CT abdomen had EUS confirmation. **CONCLUSION:** In asymptomatic patients with raised CA19-9 and an unremarkable CT abdomen findings, does not offer additional information. However, our study is limited by the small sample size. A prospective study with a larger sample size is required to consolidate our findings.

KEY WORDS:

Carbohydrate Antigen 19-9, Endoscopic ultrasound

Sarawak General Hospital Experienced in Managing Severe Acute Pancreatitis

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SUMMARY

The clinical course of acute pancreatitis varies from a mild transitory form to a severe necrotizing disease. Severe pancreatitis is associated with organ failure and/or local complications such as necrosis, abscess formation, pseudocysts and bleeding pseudoaneurysm. The mortality rate of patients with necrotizing pancreatitis is higher than 30%, and more than 80% of fatal outcomes in acute pancreatitis are due to septic complications. With surgical treatment, the mortality rate for patients with infected pancreatic necrosis was decreased to about 10 to 20% in various specialized centers. However, recently there is general agreement that surgery in severe pancreatitis should be performed as late as possible. The rationale for late surgery is the ease of identifying well-demarcated necrotic tissue from the viable parenchyma, with the effect of limiting the extent of surgery to pure debridement. This approach decreases the risk of bleeding and minimizes the surgery-related loss of vital tissue which leads to surgery-induced endocrine and exocrine pancreatic insufficiency. This approach however increased the risk of pancreatic necrosis becoming infected and septicemia.

This is a collective data of surgical management of severe pancreatitis in Hospital Umum Sarawak dated from January 2008 to June 2010. There were 37 patients with severe pancreatitis out of 130 patients suffering from acute pancreatitis. Those with severe pancreatitis, 20 patients were treated conservatively despite having local complication of pancreatitis and 13 patients had undergone surgical from its complication. 7 patients had died due to multi-organ dysfunctions. The surgical management included open cystogastrotomy for pancreatic pseudocyst (6 cases), open necrosectomy for necrotizing pancreatitis (3 cases), open drainage for pancreatic abscess (3 cases) and ligation of bleeding splenic artery pseudoaneurysm (1 case). All patients who had undergone surgery recovered well although six of them had developed pancreatic insufficiency.

Spontaneous Regression of Hepatocellular Carcinoma. Do You Believe it Happens?

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SUMMARY

Spontaneous regression of hepatocellular carcinoma (HCC) has been defined as the disappearance of the hepatic lesions in the absence of any specific therapy. It is very uncommon condition with very limited data available in the English literature. It has incidence rate of 1 in 140, 000 cases of HCC. From 1982 to January 2007, only 62 cases of spontaneous regression of HCC had being published. Although several factors such as reduction in blood supply, inflammation and immunological factors had been suggested as the mechanism of spontaneous reduction of HCC, the true mechanism of this unusual phenomenon is still remained unknown. We are reporting a case of advanced HCC that has undergone regression without any specific intervention to the extent that the lesion is resectable. It was successfully removed surgically and the patient is currently still alive and healthy. The diagnosis of HCC was confirmed by the histopathological examination.

Hepatic Resection for Cystic Lesions of The Liver

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SUMMARY

OBJECTIVES: The purpose of this study was to report the authors' experience with hepatic resection for cystic lesions of the liver, and to identify the outcome. **MATERIALS AND METHODS:** A retrospective review of patients who had liver resection for cystic lesions between January 1, 2003, and December 31, 2010 was carried out at Selayang Hospital, a tertiary referral centre in Malaysia. **RESULTS:** 63 patients (11 male, 52 females) with a median age of 53.5 (range 25–78 years) underwent surgical treatment for nonparasitic cystic liver lesions. There was one mortality (1.6%), and morbidity developed in 8 patients (12.7%). Symptomatic relief was complete and permanent in all of the patients with benign congenital cysts and biliary cystadenomas. None of the patients developed recurrence during the follow up period. In patients with polycystic liver disease, symptomatic relief after surgery was prompt, but temporary. **CONCLUSION:** Hepatic resection is safe and effective for cystic lesions of the liver. Symptomatic relief is complete and permanent after hepatic resection, except in cases of diffuse polycystic disease of the liver where liver transplantation should be considered when symptoms are extremely severe. Further studies are required to identify the role of laparoscopic management of symptomatic single or localized multiple cysts.

Fish Bone Induced Liver and Pancreatic Abscess

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SUMMARY

OBJECTIVES: Ingestion and migration of fish bone through the gastrointestinal wall is a rare cause of abscess's affecting the liver and pancreas. We present cases of pyogenic liver and pancreatic abscess's caused by fish bone migration through the gastrointestinal wall. **CASE REPORT:** The first case is a 34 years old male patient presented with fever for five days associated with cough, epigastric pain and vomiting. Abdominal CT scan showed an abscess at segment III of the liver with a calcified foreign body pointing from the gastric pylorus to the inferior aspect of the left lobe of the liver. An open drainage was required to remove the foreign body which proved to be a fishbone, the abscess drained and the perforation site at the pylorus was sutured primarily. The second patient was a 65 years old female patient who presented to our hospital with 4 days history of constant epigastric pain radiating to the back. She also had fever, intermittent chills and rigors. CT scan showed an abscess in the head of pancreas with a calcified foreign body that have penetrated the duodenum to the head of pancreas with a localized abscess in the head of pancreas. Open drainage was also required in this patient in which the foreign body which proved to be a fishbone was removed and drain left there for few days. Both patients recovered and discharged well. **CONCLUSION:** Although fish bone ingestion is a common problem, most cases have uneventful outcome. But occasionally it can cause serious complications if the gastrointestinal tract is perforated including liver and pancreatic abscesses. It often requires surgical drainage to remove the fish bone.

Calcified Liver Nodules with Biliary Stricture in A Young Gentleman

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SUMMARY

INTRODUCTION: Tuberculous biliary stricture rarely leads to obstructive jaundice. The commonest differential diagnosis in such cases is cholangiocarcinoma. **CLINICAL PRESENTATION:** This was a 26-year old man who was referred from Queen Elizabeth Hospital, Sabah in February 2010 for management of biliary stricture. Imaging performed and revealed multiple calcified liver nodules with distal bile duct strictures. ERCP and biliary stenting was carried out. He was sent over Sultanah Bahiyah Hospital with the diagnosis of Mirizzi's syndrome or cholangiocarcinoma. He was subsequently operated with histopathological examination of regional lymph node pointing toward granulomatous lymphadenitis. **DISCUSSION:** There were few case reports of obstructive jaundice caused by TB lymphadenitis either at the porta hepatis or in the peripancreatic region. Treatment with anti-tuberculous regimen in full dose is universally effective in hepatobiliary tuberculosis. **CONCLUSION:** Imaging and histological examination are very important in establishing the diagnosis of tuberculous stricture. High index of suspicion of the disease is essential as it is a curable condition.

Port Assisted Closure of Laparoscopic Supraumbilical Wound. An Easy, Safe and Feasible Technique

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SUMMARY

BACKGROUND: There have many methods used for closure of laparoscopic wound, especially supraumbilical incision. The single most crucial aspect of interest was the prevention of incisional hernia. **MATERIALS AND METHODS:** We have performed a total of 170 cases of laparoscopic cholecystectomy from 2009 to 2010 and all wound closure technique applied was port assisted closure. Patients demographic data and outcome parameter were recorded. Prospective data from the study were analyzed retrospectively. **RESULTS:** There was no immediate significant wound complication post operatively and occurrence of incisional hernia during the follow up period was not seen. **CONCLUSION:** Port assisted closure of laparoscopic supraumbilical wound is an easy, safe, cheap and feasible technique.

Complications Related to Endoscopic Treatment for Pancreatic Ascites

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SUMMARY

INTRODUCTION: Pancreatic ascites is a rare complication of acute and chronic pancreatitis. Treatment mainly medical therapy. We present a patient with abdominal pain and ascites with a history of chronic alcoholism. **CLINICAL PRESENTATION:** A 33 years old Indian man with long history of alcohol intake presented to Sultanah Bahiyah Hospital on 18/6/2010 with complaint of progressive abdominal distension and sudden severe abdominal pain. He was malnourished and having generalized abdominal tenderness. CT abdomen showed cirrhotic liver with gross ascites and presence of pancreatic head pseudocyst. A diagnostic and therapeutic peritoneal paracentesis was done which showed peritoneal fluid amylase was 25698 U/L and total protein was 37.2 g/l. **DISCUSSION:** Pancreatic ascites is defined as exudative ascites with high amylase concentration in ascitic fluid, usually more than 1000 IU/L and protein concentration over 3 g/dl which differentiates if from ascites due to cirrhosis, tuberculosis or carcinomatosis. Medical and surgical therapy has met with limited success. Endoscopic intervention has gained momentum for the past few decades. Studies have reported an excellent endoscopic therapeutic alternative in patients with pancreatic ascites and effusion over a 10-year period. They have suggested the use of pancreatic stenting with sphincterotomy which offered a simple, effective and safe first line therapy. Despite its usefulness, there were complications associated with the treatment. **CONCLUSION:** More and more evidence from the literature has suggested endoscopic pancreatic stenting with sphincterotomy as the first line therapy of pancreatic ascites and pancreatic pleural effusion. Despite its usefulness, there were complications associated with the procedure.

Revolutionized Two-Incision Three Ports Laparoscopic Cholecystectomy (RTILC). A Case Series. Experience of Department of Hepato-Pancreatic-Biliary Surgery, Division of Surgery, Sultanah Bahiyah Hospital, Malaysia

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SUMMARY

BACKGROUND: Techniques of laparoscopic cholecystectomy (LC) have changed dramatically over the years. Single method LCs has gained much momentum with considerable disadvantages in terms of financial and technical aspects. Hence, we have explored into two-incision three ports (TILC) LC and further revolutionized (rTILC) its technique to enhance intraoperative ergonomics. **MATERIALS AND METHODS:** We have had 4 female patients with symptomatic gallstone disease, aged between 30 to 45 years operated with rTILC. All patients consented for the rTILC. Important parameters such as operative time, post operative complication, length of hospital stay, post operative analgesia requirement and cosmetic aspect were looked into. **RESULTS:** All four patients were successfully completed the rTILC. The operative time taken was acceptable, no postoperative complication noted, short hospital stay, usage of simple analgesia and good cosmetic effect. **CONCLUSION:** This case series reviewed that rTILC can be an alternative, feasible and safe method in the treatment of gallstone disease.

Successful Percutaneous Selective Transarterial Embolization of Bleeding Huge Pseudoaneurysm of Gastroduodenal Artery Secondary to Chronic Pancreatitis

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SUMMARY

INTRODUCTION: A bleeding pseudoaneurysm of peripancreatic artery can present with massive upper gastrointestinal hemorrhage. A history of pancreatitis and urgent imaging is crucial in making the diagnosis. Selective embolisation of the bleeding artery has gained much attention as first line of treatment. Here, we report a patient with alcoholic chronic pancreatitis presented with a ruptured pseudoaneurysm of gastroduodenal artery. He was successfully treated with percutaneous angiographic embolization. **CLINICAL PRESENTATION:** This was a 54-year old Indian man who had a long history of daily alcohol intake. He had multiple admissions to the private hospitals for pancreatitis. One afternoon, he was rushed to hospital after experiencing sudden epigastric pain and hematemesis. Upper GI endoscopy could not detect the source of bleeding. Urgent CT scan reviewed a huge bleeding pseudoaneurysm of the gastroduodenal artery. Transcatheter arterial embolization was performed. Hemostasis was secured. **DISCUSSION:** Pseudoaneurysms can bleed into the gastrointestinal tract, peritoneal cavity, retroperitoneum, biliopancreatic ducts or pseudocysts. Prompt localization of a pseudoaneurysm via imaging studies is critical. The reported success rate of embolization was 79-100% and the reported mortality rate after embolization was 12-33% in patients with acute or chronic pancreatitis. **CONCLUSION:** Transcatheter selective arterial embolization is a highly effective treatment for acute bleeding from a ruptured pseudoaneurysm secondary to pancreatitis. However, early diagnosis and effective resuscitation is an essential prerequisite factor for urgent referral to center with interventional radiology.

A Unique Aetiology of Liver Cirrhosis in a Young Gentleman

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SUMMARY

Ketamine, is a substance which is increasingly being abused by the youth. It is widely known for its relatively safe profile making it a preferred substance to abuse. Little is known about the side effects of ketamine on the human liver. We present a 26 years old Chinese gentleman, with a history of ketamine abuse for 10 years who presented recurrent urosepsis due to bladder atony with bilateral hydronephrosis. Physical examination noted a malnourished gentleman with stigmata of chronic liver disease, jaundice and presence of hepatosplenomegaly. Radiological imaging revealed early liver cirrhosis with a mildly dilated hepatic duct. Liver function test showed predominantly cholestatic picture with peak bilirubin 565 $\mu\text{mol/L}$ (direct bilirubin 415 $\mu\text{mol/L}$), alkaline phosphatase (ALP) 4985 U/L, alanine transaminase (ALT) 67 U/L and gamma glutamyltransferase (γGT) 3453 U/L. Autoimmune serological markers for autoimmune hepatitis were undetectable. Serum immunoglobulins were marginally raised with normal Alpha Fetoprotein (αFP) levels. Iron and copper studies were unremarkable. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) did not show any filling defects or evidence of primary sclerosing cholangitis. Liver biopsy showed portal and lobular hepatitis with cholestasis, hepatocyte damage and focal porto-portal bridging. Pathologically it was concluded as toxic hepatic injury secondary to exogenous substance. Gastroscopy showed portal gastropathy. He was diagnosed to have Child C liver cirrhosis secondary to Ketamine abuse. This case is unique in its presentation in that serum ALP is markedly raised and leading to liver cirrhosis which has not been reported previously. Previously documented cases have presented as biliary tree dilatation presenting as a choledochal cyst and mildly raised ALP. In conclusion, this is the first reported case of ketamine induced liver cirrhosis. Drugs of abuse should be considered as a differential diagnosis in a young individual presenting as liver impairment.

Targeted Hepatic Venous Pressure Gradient Measurements in Secondary Prophylaxis of Variceal Bleed: Selayang Hospital Preliminary Experience

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SUMMARY

BACKGROUND/AIM: Recurrent variceal bleeds (VB) occurring in patients with portal hypertension (PH) from liver cirrhosis (LC) while on secondary prophylaxis (SP) consisting of endoscopic variceal ligation (EVL) and beta blockers (BB) is a recognised problem. Hepatic venous pressure gradient (HVPG) measurement is useful in identifying patients who do not respond (NR) to BB but its applicability is limited by cost and expertise. We explored a strategy whereby HVPG measurements were performed in selected patients who have difficult varices to eradicate in order to optimize SP. **MATERIALS AND METHODS:** Records of patients with previous VB on SP between January and July 2010 were reviewed. HVPG measurements were performed on patients who have persistent varices despite having undergone more than 4 sessions of EVL. **RESULTS:** Eighty two patients (73% male) with mean age of 52 + 10 years and Child's Pugh score of 8 + 2 on SP were identified. Underlying aetiologies for the LC were viral (46%), probable non-alcoholic steatohepatitis (NASH) (20%), alcohol (18%), primary biliary cirrhosis (5%), autoimmune hepatitis (3%), Wilson's disease (1%) and cryptogenic (6%). Propranolol doses were 61 + 23mg daily. Persistent varices were found in 19(23%) patients despite having undergone more than 4 sessions of EVL. Seventy four (14 out of 19) percent of patients had diabetes mellitus (DM). HVPG measurements were successfully measured in 2 out of 3 patients. Both patients had HVPG of >12mmHg indicating high risk for recurrent VB. **CONCLUSION:** Performing HVPG measurement on selected patients whose varices are difficult to eradicate may select NR to BB who need further optimization of existing SP. Interestingly, DM is prevalent in this group of patients. Further studies are needed to confirm the usefulness of this strategy and establish the impact of DM in this group of patients.

Daycare Ascites Service

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SUMMARY

BACKGROUND/AIM: Patients with refractory ascites (RA) require repeated large volume abdominal paracentesis (LVAP) approximately once every 2 weeks for the control of ascites. In the past, these patients needed hospitalisation for the procedure. We recently established a Daycare Ascites Service (DAS) for patients with RA. The aim of this study was to observe the safety of LVAP in the DAS. **MATERIALS AND METHODS:** Data on patients attending the DAS for LVAP from December 2010 to May 2011 were reviewed. Complications from LVAP namely bleeding, leaking and bowel perforation were studied. **RESULTS:** Seventeen patients (65%, male) with mean age of 58 + 11 years were managed in the DAS during this period. A total of 96 LVAP (6-8 litres of ascitic fluid) were performed. Twenty seven of these LVAP were carried out by a paramedic. One case resulted in blood stained ascites which was not clinically significant and resolved spontaneously. No complications were observed in the 27 LVAP performed by the paramedic. **CONCLUSION:** Provision of LVAP service in the DAS for patients with RA is a practical approach to help improve the delivery of care for these patients. With proper training the procedure can be carried out safely by paramedic. We suggest setting up DAS in hospitals with high number of patients with RA.

SIRT Therapy for Metastatic Liver Secondary from Primary Breast Cancer

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SUMMARY

INTRODUCTION: SIR-Spheres with Yttrium-90 was first used in liver secondaries from colon cancer. The indication for its use was then extended to primary liver cancers. Currently more and more indications have been established. We would like to report a case of carcinoma of the breast with liver secondaries who has been heavily treated with SIRT or SIR-Spheres microspheres. **Phase I:** The hepatic artery is cannulated via the trans-femoral approach. The distribution of the blood vessels to the liver and the tumour is recorded. Particular attention is paid to the vessels supplying the gall bladder, stomach and normal variations of the blood supply. Five mCi of ^{99m}Tc macro-aggregated albumin is then injected to assess the liver to tumour uptake and the shunting of technetium into the lungs. **Phase II:** Suitable candidates will proceed with the treatment usually within 2 weeks of the above. The Yttrium-90 microspheres are injected into the specifically selected hepatic artery. **CLINICAL PRESENTATION:** A 64 years old lady presented with Carcinoma of the Right Breast Stage 2b on June 2006. She underwent primary therapy and relapsed in the liver and bone on March 2010. She subsequently underwent palliative chemotherapy with Taxotere and Xeloda followed by carboplatin and gemcitabine and finally on Vinorelbine and 5FU before she came to see us in NCI Hospital. She was advised to under go SIRT or SIR-Spheres microspheres for the liver. She did not have any acute side effects. **CONCLUSION:** Yttrium-90 SIRT or SIR-Spheres microspheres therapy should be offered for patients with liver metastasis from breast cancer.

SIRT Therapy for Metastatic Liver Secondary from Primary Colo-rectal Cancer: A Malaysian Experience

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SUMMARY

INTRODUCTION: SIRT or SIR-Spheres microspheres with Yttrium-90 is currently recommended for the treatment of colorectal liver secondary. We would like to report a series of 4 patients treated with it. **Phase I:** The hepatic artery is cannulated via the trans-femoral approach. The distribution of the blood vessels to the liver and the tumour is recorded. Particular attention is paid to the vessels supplying the gall bladder, stomach and normal variations of the blood supply. Five mCi of 99m-Tc macro-aggregated albumin is then injected to assess the liver to tumour uptake and the shunting of technetium into the lungs. **Phase II:** Suitable candidates will proceed with the treatment usually within 2 weeks of the above. The Yttrium-90 microspheres are injected into the specifically selected hepatic artery. **CLINICAL PRESENTATION:** A total of 4 cases were seen between January 2005 and December 2010 at NCI hospital. One male and 3 females. Their age ranged from 39 years to 69 years. These patients had advanced colon cancer at presentation and one patient presented with Stage III disease. All had adenocarcinoma on histology. All patients had been heavily pretreated prior to SIRT therapy. All 4 patients had treatment successfully done. Only one patient had severe epigastric pain 2 weeks post therapy but all 4 patients had liver enzyme elevation. The overall survival ranged from 19 months to 41 months. **CONCLUSION:** Yttrium-90 SIRT or SIR-Spheres microspheres should be offered for patients with liver metastasis from colon cancer. The best results are seen in patients treated with SIRT or SIR-Spheres microspheres up front and not as a last option. The success of the therapy is heavily dependent on the interventional radiologist.

Lung Metastatic of Pancreaticobiliary Tumours: A Report of 2 Cases

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SUMMARY

INTRODUCTION: Development of metastasis to the lung from a pancreatico-biliary tumour is known to mimic bronchioloalveolarcarcinoma growth. We present 2 cases of pancreatico-biliary tumour with some morphologic variation of the metastatic lesions. **CASE PRESENTATION:** Two cases; **Case 1:** A 56-year-old lady with previous diagnosis of intrahepatic cholangiocarcinoma presented with persistent consolidation of right lung on CXR and surveillance CT. **Case 2:** 72-year old man, referred to chest clinic for haemoptysis associated with on and off fever for 4 months. He stopped smoking more than 50 years ago. He was diagnosed to have an ampullary adenocarcinoma 5 years prior to the current presentation, where transduodenal ampulectomy was performed. Report from radiological examination indicates no evidence of local recurrence, but there was lung consolidation of the right lower lobe, most likely infective in origin. **In both cases** CT-guided lung biopsy were done and the morphological changes in the metastatic sites were reviewed. Histopathological examination of the initial lung biopsy of case 2 showed extensive organizing pneumonia tissue reaction with masson plug which can easily masked the typical lepidic growth of the metastatic tumour, while lung biopsy of case 1 shows typical BAC-like growth pattern. **CONCLUSION:** Thorough morphologic assessment together with good clinical input is important for a definitive and an accurate interpretation.

Do Chronic Hepatitis B (CHB) Patients with Coarse Echotexture (CE) and/or Nodularity/Irregularity (NO/IO) Outlines on Ultrasound (US) Have Liver Cirrhosis (Lc) Based on Transient Elastography (TE)?

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SUMMARY

BACKGROUND: US information like CE, NO/IO and cirrhosis (C) and/or platelet counts below $100 \times 10^3/\text{ul}$ (PC) are regularly used by clinicians as indications of LC to initiate surveillance for complications of cirrhosis and treatment. TE is a relatively new tool to assess for liver fibrosis with high specificity in LC. **AIMS:** To assess if these clinical parameters correlate with liver stiffness measurements (LSM) by TE. LSM indicative of LC for CHB are >12 kPa for normal ALT and >13.4 kPa for elevated ALT (specificity 95% and 93%; Chan *et al*). **MATERIALS AND METHODS:** Consecutive CHB patients with TE, US and PC done within 6 months of each other were recruited. TE was performed by trained operators and only valid LSM (IQR $< 30\%$, success rate $> 60\%$) were used. Data are presented in means, standard deviations (SD) and percentages. **RESULTS:** A total of 159 CHB with mean age of 47.7 (11.7) years, 57.9% male gender and mean ALT of 34.9(30.6) u/l was studied. **CONCLUSION:** US findings of CE or NO/IO in CHB are equally poor in diagnosing LC unless PC was present. Those without PC require further investigations before diagnosing LC and escalating treatment or investigations.

US and platelet	Cirrhotic by TE	Non cirrhotic by TE	Total
CE without PC			
n (%)	2 (11.1)	16(88.9)	18 (100)
mean age (SD)	48.5(3.5)	46.1(11.0)	
mean platelet $\times 10^3/\text{ul}$ (SD)	243.5(50.2)	237.9(36.7)	
mean ALT (SD)	24(8.5)	33(11.4)	
mean LSM (SD)	45.8(35.1)	6.0(1.7)	
CE with PC			
n (%)	1(100)	0(0)	1(100)
mean age (SD)	65		
mean platelet $\times 10^3/\text{ul}$ (SD)	83		
mean ALT (SD)	36		
mean LSM (SD)	35.8		
NO/IO without PC			
n (%)	5(20)	20(80)	25(100)
mean age (SD)	56.8(8.7)	44.2(12.7)	
mean platelet $\times 10^3/\text{ul}$ (SD)	134.4(38.7)	234.9(92.9)	
mean ALT (SD)	33.4(17.5)	30.5(12.5)	
mean LSM (SD)	27.3(18.6)	6.7(2.5)	
NO/IO with PC			
n (%)	5(100)	0(0)	5(100)
mean age (SD)	54(13)		
mean platelet $\times 10^3/\text{ul}$ (SD)	84.4(10.5)		
mean ALT (SD)	53.6(53.2)		
mean LSM (SD)	25.2(7.5)		
C without PC			
n (%)	1(50)	1(50)	2(100)
mean age (SD)	44	41	
mean platelet $\times 10^3/\text{ul}$ (SD)	161	156	
mean ALT (SD)	93	43	
mean LSM (SD)	30.8	7.3	

C with PC n (%) mean age (SD) mean platelet x10 ³ /ul (SD) mean ALT (SD) mean LSM (SD)	1(100) 51 73 16 12.4	0(0)	1(100)
Normal without PC n (%) mean age (SD) mean platelet x10 ³ /ul (SD) mean ALT (SD) mean LSM (SD)	0(0)	71(100) 46.6(12.6) 249.2(57.8) 31.5(33.1) 5.4(1.7)	71(100)
Normal with PC n (%)	0(0)	0(0)	0(0)
Fatty liver without PC n (%) mean age (SD) mean platelet x10 ³ /ul (SD) mean ALT (SD) mean LSM (SD)	3(8.3) 48(13.1) 215.3(106.0) 50(34.6) 19.7(8.3)	33(91.7) 49.9(9.0) 274.3(82.0) 41.1(36.3) 6.2(2.2)	36(100)
Fatty liver with PC n (%)	0(0)	0(0)	0(0)

SUMMARY: In CHB patients without PC, 88.9% of CE and 80% of NO/IO on US had LSM below the LC cut-off. If PC was present 100% of both CE and NO/IO had LSM above LC cut-off. CHB with normal US and mean ALT 31.5(33.1) u/l have low LSM at 5.4(1.7)kPa. CHB with fatty liver found in 22.6% in this series, had higher LSM compared to the normal US group and in a small proportion the LSM were above the LC cut-off despite absence of PC.

The Demography and Risk Profiles for Chronic Hepatitis B and C from the Malaysian Liver Registry

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SUMMARY

BACKGROUND: Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) are two common liver diseases in Malaysia. We aim to identify the demographic and risk characteristics of these adult patients who presented to the hospitals in the Malaysian Liver Registry group between 2001 and 2010. **MATERIALS AND METHODS:** Retrospective data collection and entry into the Liver Registry were carried out by research assistants. **RESULTS:** A total of 2134 CHB and 460 CHC were registered during the study period. **CONCLUSION:** CHB and CHC are mainly diseases affecting the male gender. The age distribution of patients who attended our hospitals is in the productive age group. The predominant ethnic group in CHB is the Chinese. There is a higher proportion of Indian in CHC compared to CHB. The main potential risk factor in CHB is a positive family history especially in the Chinese ethnic while previous transfusion of blood products is important in CHC. Intravenous drug use is the second important risk for CHC. There are also differences in the risk factor profiles between genders. These data may help our local health care providers in formulating disease prevention, management and public education strategies.

	CHB (n=2134)	CHC (n=460)
Male Gender	67.1%	69.3%
Age Distributions in Years	<31 (22%) 31-40 (18.8%) 41-50 (23.3%) 51-60 (22.1%) 61-70 (11.0%) ≥71 (2.6%)	<31 (15.4%) 31-40 (22.1%) 41-50 (30.6%) 51-60 (23.7%) 61-70 (6.3%) ≥71 (1.3%)
Ethnic Distributions	Malay (33.8%) Chinese (55.8%) Indian (2.2%)	Malay (44.1%) Chinese (41.4%) Indian (12.7%)
Potential Risk Factors- self reported	Positive family history=34.4% Previous transfusion of blood products=8.5% Needle Stick Injury=0.7% Intravenous Drug Use=2.1% Tattooing=1.3% Body Piercing=0.4% Hemodialysis=0.5% No known risks=41.5% Others=10.6%	Previous transfusion of blood products=31.6% Needle Stick Injury=0.9% Intravenous Drug Use=23.5% Tattooing=7.4% Body Piercing=0.9% Hemodialysis=9 % No known risks=10.6% Others=16.2%
Top 3 Potential risk Factors according to - Ethnic - Gender	Malay- no known risks, positive family history and previous transfusion of blood products. Chinese- positive family history, no known risks and others. Indian- no known risks, others and previous transfusion of blood products. Male- no known risks, positive family history and others Female- positive family history, no known risks and previous transfusion of blood products.	Malay- previous transfusion of blood products, intravenous drug use and others. Chinese- previous transfusion of blood products, intravenous drug use and others. Indian- previous transfusion of blood products, hemodialysis and no known risks. Male- intravenous drug use, previous transfusion of blood products and others Female- previous transfusion of blood products, hemodialysis and no known risks.

Biomarkers to Predict Risk of Subsequent Hepatocellular Cancer in Patients with Chronic Hepatitis B

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SUMMARY

BACKGROUND: Chronic hepatitis B (CHB) is a major cause of hepatocellular carcinoma (HCC), a disease with poor prognosis and high mortality. This study identifies a blood-based gene expression biomarker signature prognostic for later development of HCC in patients with CHB. **MATERIALS & METHODS:** PaxGene™ blood RNA isolation system was used to isolate RNA from blood samples taken from over 1,000 Malaysian individuals representing matched HCC patients, CHB patients and healthy controls. Complementary DNA (cDNA) was generated from the isolated RNA via reverse transcription and quantitatively analyzed using Affymetrix U133Plus 2.0 array using MAS 5.0 normalization. To minimize bias, we developed a novel algorithm based on analysis of gene pairs for identification of biomarker panels. A Monte Carlo search identified different combinations of pairs which could differentiate between cancer and controls. Genes with the best ROC AUC values were selected for verification via qRT-PCR analysis. **RESULTS:** Quantitative microarray analysis of cDNA samples from HCC patients (n=47) and healthy controls (n=50) was used to select three sets of 500 probeset pairs with high, medium or low capacity, respectively, for discriminating between HCC patients and healthy controls, and these three sets were analyzed to identify combinations of 3 probeset pairs achieving a high level of discrimination (ROC AUC up to 0.94) between samples from HCC patients and controls. Samples from CHB patients (n=50) were evaluated using models based on these 3 probeset pairs to identify those models achieving an HCC vs healthy positive prediction rate consistent with the observation that 12% of CHB patients develop HCC. Additionally, a subset of 43 individual microarray probesets differentially expressed ≥ 1.2 -fold (p-value < 0.05) between HCC patients and controls was identified from the 3 probeset pair models. **CONCLUSION:** These studies identified gene expression biomarker models based on 6-gene and 1-gene panels which can be used for preclinical detection of HCC, and potentially improve prognosis of this disease. Functional analysis indicates that the biomarker genes identified are involved in transcription, apoptosis, signal transduction, cell cycle, as well as inflammation and angiogenesis.

Case Report on Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Induced by Allopurinol

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SUMMARY

BACKGROUND: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe acute drug induced hypersensitivity reaction defined by the presence of fever, skin eruption and systemic findings. Systemic involvement includes enlarged lymph nodes, abnormal liver function, renal impairment, pulmonary or cardiac infiltrates and haematological abnormalities. Numerous drugs have been reported to cause this syndrome and we report a case of allopurinol induced DRESS.

CASE REPORT: A 35 year old Malay gentleman with renal calculi, renal impairment and hyperuricaemia was commenced on allopurinol 200mg od after his percutaneous nephrolithotomy. He was noted to have developed a macular rash over his upper limbs 3 weeks later associated with fever. He visited the doctor who prescribed him symptomatic treatment for his fever and continued his allopurinol. His symptoms persisted and was noted to be jaundice a week later. He was then admitted to a District General Hospital where the following blood investigations were done : Hb 10.6g/dl, WCC 17.0×10^3 /ul, platelet 170×10^3 /ul, total protein 48g/l, albumin 24g/l, bilirubin 220micromol/L, ALP 119 u/L, ALT 3696 micromol/L, AST 2661 micromol/L, PT 30.4sec. The patient was subsequently transferred to our centre and our blood results were as follows : Hb 11.4g/dl, WCC 20.1×10^3 /ul, eosinophil 18.9 % platelet 180×10^3 /ul, total protein 48g/l, albumin 24g/l, bilirubin 345 micromol/L ,ALP 152u/L, ALT 3677 micromol/L, AST 2068 micromol/L, PT 40.9, Creat 214 micromol/L. A diagnosis of DRESS was made and allopurinol was discontinued. The patient was commenced with meropenem and hydrocortisone. He however progressed to grade 3 hepatic encephalopathy requiring ventilation for cerebral protection and died 4 days later with multi organ failure. **CONCLUSION:** DRESS has been reported in 0.4 % of patients receiving allopurinol. It is vital that there is a clear indication for the use of allopurinol with appropriate dosage for the renal function. Doctors should recognise drug hypersensitivity and the importance of prompt withdrawal of the drug.

An Automated Computer Aided Diagnosis System (CAL) for Delineating and Visualizing Liver and Liver Tumor from Computer Tomography (CT) Images

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SUMMARY

We report an automated Computer Aided Diagnosis system (CAD) for delineating and visualizing liver and liver tumor from Computer Tomography (CT) images. Liver related diseases have been leading causes of death worldwide. Several applications such as hepatic volumetry, hepatic transplantation, evaluation and planning for resection liver surgery, liver cirrhosis assessment, liver tumour diagnosis, monitoring of liver metastases, etc., require accurate delineation and visualisation of liver, as well as liver tumour. Manual delineation is a highly skilled, subjective and a laborious task especially when it involves hundreds of images per patient. Therefore, automated liver delineation is a vital preliminary step in analyzing medical data for liver pathologies with the aim of increasing the productivity of radiologists and assist them in not only delineating but also in quantifying the pathologies such as tumour. Automated liver and tumour delineation has many challenges due to low contrast between structures of interest and their neighbouring structures and their varying pathologies. In addition, variation in size and shape of the tumour further complicate this task. As a result, it become a major topic of interest. Even though there have been several research as well as commercial efforts, each with a varying degree of automation, accuracy and generic nature of the algorithms, there is much room for further research and improvement. Our approach is focusing on increasing the level of automation and accuracy. In this work, the liver is delineated using anatomical and expert knowledge combined with multiview information which minimizes manual intervention in the delineation process. Further processing is using machine learning algorithms combined with fuzzy theory to delineate the tumour. Finally the delineated liver and liver tumours are quantified and visualized in 3-Dimension to provide an intuitive visualization to the radiologist or clinicians. These methodologies are on our in-house rapid prototyping platform ENDEAVOR to produce a complete system that analyzes liver tumor.

Clinico-Epidemiology of Liver Cirrhosis Patients Treated at Hospital Tengku Ampuan Rahimah Klang

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SUMMARY

INTRODUCTION AND OBJECTIVE: Liver cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The prevalence rate of liver cirrhosis in Malaysia is 15 in every 10,000 population. The distribution of underlying etiology vary regionally, with viral hepatitis being much higher compare to the European countries. The aim of this study was to evaluate the clinico-epidemiology data of liver cirrhosis, including the etiology, complication and treatment among patients in HTAR, an 864 bedded government tertiary hospital in the state of Selangor. **MATERIALS AND METHODS:** Retrospective analysis was performed on both inpatient and outpatient attending gastroenterology clinic with a diagnosis of liver cirrhosis from June 2010 to March 2011. A comprehensive data collection form and database with details of patients' demography, etiology, disease monitoring and treatment was used to in this study. **RESULTS:** A total of 129 patients with liver cirrhosis were treated during this period. 4 patients were excluded due to insufficient data for analysis. There were 94 (75.2%) males and 31 (24.8%) females in this study. 55 (44.0%) patients were Indians, followed by 46 (36.8%) were Malays, 22 (17.6%) Chinese and 2 (1.6%) others. Severity of liver cirrhosis is classified according to Child's-Pugh classification with 40 patients (32.0%) have Child's A, 32 patients (25.6%) Child's B and 53 patients (42.4%) have Child's C. The commonest etiology of liver cirrhosis was alcoholic liver disease, 60 patients (48.0%) was diagnosed to have liver cirrhosis due to alcohol overuse. 31 patients(24.8%) has viral hepatitis, of which 15 patients(12.0%) has hepatitis B, 10 patients(8.0%) has hepatitis C and 6 patients(4.8%) has co-infection of hepatitis B and C. Other etiology of liver disease include autoimmune hepatitis, 5 patients (4.0%), drug induced hepatitis, 1 patient (0.8%). 28 patients (22.4%) have unknown etiology (include those patients still under investigation). Most of the patients have developed decompensated liver cirrhosis. Ascites being the commonest complication were noted in 72 patients (57.6%), follow by esophageal varices, 57 patients (45.6%), history of spontaneous bacteria peritonitis in 26 patients (20.8%) and hepatic encephalopathy in 14 patients (11.2%). UGIB is not uncommon among these patients, with non-variceal UGIB in 10 patients (8.0%) and variceal UGIB in 7 patients (5.6%) . Out of the 125 patients, 5 patients (4.0%) had developed hepatoma (3 patients in Child's C cirrhosis, 1 patient in Child's B and 1 patient in Child's A cirrhosis. **DISCUSSION AND CONCLUSION:** Clinico-epidemiology data has show alcohol as the commonest etiology of liver cirrhosis in HTAR. This could be due to the higher percentage of Indian population with local cultural and social-economy variety in this region. Most of the liver cirrhosis patients presented late to our care with almost half of them in Child's C cirrhosis. Furthermore, most of these patients had developed decompensated liver cirrhosis like ascites, esophageal varices, spontaneous bacteria peritonitis and hepatic encephalopathy.

Obesity and the Liver

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SUMMARY

The prevalence of obesity is increasing unabated and with it a spectrum of liver abnormalities known as nonalcoholic fatty liver disease (NAFLD) generally characterized by an increase in intrahepatic triglyceride (IHTG) content (i.e., steatosis) with or without inflammation and fibrosis (i.e., steatohepatitis). NAFLD is a major public health problem due to increasing prevalence and strong association with serious cardiometabolic risk factors which are the antecedents to T2D and cardiovascular disease. Consideration will be given to the strong association between various obesity phenotypes and NAFLD and will highlight the singular importance of NAFLD as an independent predictor of morbidity, with or without obesity. The presentation will also address current knowledge supporting a role for nonpharmacological, lifestyle-based interventions that lead to increased physical activity combined with a healthful diet as part of the management and treatment of NAFLD.

Live Donor Liver Transplant - A Glimpse into the Past

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SUMMARY

Live Donor Liver transplantation (LDLT) was first successfully performed between a Japanese mother and her son in Brisbane in July 1989, following unsuccessful attempts at the technique in Brazil by Raia the same year. The procedure evolved from descriptions of deceased donor reduced size segmental engraftment published by Ringe in Germany and Strong in Brisbane virtually simultaneously the year before. The rationale for development of these skills in liver partition and implantation was to address the issue of unacceptable paediatric waiting list mortality on a background of scarcity of deceased child donors. LDLT was then pioneered in Asia in Shimane Japan and subsequently in the USA by Broelsch in Chicago in October 1989. During the following decade programmes of LDLT proliferated throughout Europe, Asia and the Americas with intense activity in regions where access to deceased donation was limited or nonexistent leading to large single centre experiences particularly in Kyoto and Seoul. The paediatric focus of LDLT broadened along the way to encompass adult to adult transplantation and the implantation of right lobes with considerable contribution by the groups in Hong Kong and Denver. Inevitably donor deaths emerged and the enthusiasm for LDLT was tempered by these rare but nevertheless tragic and devastating occurrences. In the USA results in terms of recipient and graft survival out to 3 years post transplant (corrected for recipient age, gender, race, diagnosis and MELD/PELD score) appeared comparable to those obtained from deceased donation although recipient benefit requires balance against donor risk and donor morbidity.

Live Donor Liver Transplants: What The Future Holds

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SUMMARY

Adult-to-adult living donor liver transplantation (LDLT) has emerged as a partial solution to the current shortage of allografts for those awaiting liver transplantation. However, a number of important clinical and ethical concerns necessitated careful evaluation before advocating widespread use. Partitioning a liver in two parts, with one portion used to rescue a dying recipient and the other to maintain a previously healthy donor, requires considerable surgical expertise. In 2002, the NIDDK organized a national consortium, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), to examine the overall outcomes of ALDLT donors and recipients, using deceased donor liver transplantation (DDLT) as controls. In addition, refinements coming from the LDLT community at large also contributed to improved outcomes, including provisions for generous hepatic venous drainage, the application of three-dimensional CT reconstruction of the liver to map surgical approaches to LDLT and the avoidance of portal hyperperfusion by surgical decompression, splenic artery ligation/embolization or splenectomy.

There are limitations on the smallest amount of liver [generally considered to be <30% of the ideal recipient liver mass] that can be effectively transplanted in the face of a hostile recipient physiology with hyperdynamic cardiac output and markedly increased mesenteric blood flow (*Miller C et al: Ann Surg, 2001;234:301-12*). Consequently, physiologic and anatomic considerations dictate that ALDLT operations use a larger donor liver mass, usually the right lobe, which also increases the risk of donor complication (*Fan ST et al: Arch Surg, 2000;135:336-40*). In addition, any other factors that negatively influence liver regeneration, such as older age and steatosis can negatively influence the outcome for both the donor and recipient. In essence, a better understanding of the underlying biology can minimize both the risk of failure for the recipient and complications in the donor and thus lessen or eliminate some of the ethical concerns.

Cirrhosis causes a state of hyperdynamic portal circulation with resultant increased portal vein flow. Marcos et al (*Liver Transpl 2000;6:296-301*) documented this by measuring portal vein and hepatic artery resistance and blood flow in the donor before resection and in the recipient after transplantation. They showed that portal vein flow into the LDLT allograft was greatly enhanced and that hepatic artery flow was diminished in the early post-transplant period, such that the ratio of hepatic artery to portal vein flow was greatly diminished. This is also manifested by higher HA resistance in the recipient of ALDLT grafts compared to their respective donors. These findings are certainly of importance, but until recently, the clinical manifestations in LDLT have not been appreciated. In one A2ALL study, the classification of 3.1% of graft loss as “primary non-function”, characterized by coagulopathy, encephalopathy, cholestasis requiring retransplantation within 7 days likely represents a phenomenon of small-for-size syndrome (SFSS), in which portal hyperperfusion coupled with decreased hepatic artery flow and relative hepatic venous congestion leads to early graft failure or prolonged cholestasis. In fact, there is still significant unawareness and lack of understanding of SFSS. While the portal venous hyperperfusion is recognized by many as a contributing factor, the functional dearterialization is not commonly recognized. Thus, animal models have been developed in attempts to study the pathophysiology seen in transplanted partial liver grafts, since the failure to understand the pathophysiology of dysfunctional LDLT grafts will only prolong the learning curve and inhibit greater application of this technique.

The adoption of dual-LDLT grafts has been advanced as one method of increasing sufficient liver mass to prevent SFSS. The pioneering work by Sung-Gyu Lee and his colleagues (*Lee SG et al. Surgery. 2001;129-647-50*) has demonstrated the practicality of this approach, and for which application using combined split and LDLT grafts has been advocated in the United States. This technical feat requires spatial orientation, which depends greatly on individual fit of the donor grafts within the recipient. The recipient and two donor operations are started simultaneously. The bigger left-lobe liver graft is orthotopically implanted at the original left position in the recipient. Then the second left-lobe liver graft is heterotopically positioned at the right upper quadrant fossa with 180° rotation to accommodate anastomosis of the hepatic vein and the hilar glissonian structures. The rotation of the heterotopic second left-lobe liver graft brings the hilar structures into a reversed position. Therefore, the bile duct comes to lie behind the portal vein and the hepatic artery. This will make the hepaticojejunostomy of the second liver graft difficult in a hidden area once the portal vein anastomosis is made. Therefore, the bile duct is reconstructed by duct-duct anastomosis before portal vein anastomosis. When the second liver graft is small enough to cause undue pressure on the hilar anastomosis, the tissue expander filled with saline solution may be placed underneath the liver graft to relieve the pressure.

Other approaches to improving donor safety and improving recipient outcomes, as well as to understand the underlying processes of liver regeneration and the potential impact on other phenomenon, e.g. HCC and HCV recurrence, are still being studied. Advances in these areas will assist in the adoption of LDLT for the future.

Management of Hep C – A Cocktail of Antivirals

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SUMMARY

An estimated million people have chronic hepatitis C virus (HCV) infection. With current treatment success rates, by 2030, more than 40% will be cirrhotic and the number of cases with end-stage liver disease is projected to treble. Current standard-of-care (SOC) is combination of pegylated interferon (PEG) plus ribavirin (RBV) for 24-48 weeks. Unfortunately this is associated with poor efficacy (45% in HCV GT1; 75% in GT2 and 65% in GT 3) and tolerability. In addition, many patients decline current treatment infection because of the significant side-effects, including those with decompensated cirrhosis or severe psychiatric illness.

The introduction of direct acting antiviral agents (DAAs) will hopefully address this huge unmet medical need. More than 60 DAAs are currently in clinical development, including 20 protease inhibitors, of which 5 are in Phase III trials and 2 (Boceprevir and Telaprevir) have been recently approved by the US FDA for combination with PEG/RBV. This triple therapy is associated with increase in efficacy and shortened duration of therapy in both treatment-naïve and treatment-experienced patients with HCV Gt1 infection. In treatment-naïve patients, the addition of telaprevir (TVR) to PEG/RBV has shortened duration of treatment from 48 weeks to 24 weeks but increased sustained virologic response (SVR) rates from 45% to 75% (Jacobson I, et al. *N Engl J Med* 2011; 364: 2405-16). The addition of boceprevir (BCV) to PEG/RBV increased SVR rates from 40% to 68% (Poordad F, et al. *AASLD 2010*).

In treatment-experienced patients, the addition of TVR has increased SVR rates from 17% to 66%, with best responses in previous relapsers (from 24% to 88%). The poorest efficacy of triple therapy was observed in patients who were previous null responders to PEG/RBV (defined as less than 2 log reduction from pretreatment HCV RNA levels after 12 weeks of full-dose PEG/RBV), in whom the SVR rates increased from 5% to 29% (Zeuzem S, et al. *N Engl J Med* 2011; 364: 2417-28). Similar results have been reported with the addition of boceprevir to PEG/RBV in treatment experienced patients, although null-responders were not included in these trials. Incremental benefits of triple therapy are greatest in the most-difficult-to-treat patients, including those >50years, males, cirrhotics and those with high baseline viral loads (Everson GT, et al. *AASLD 2009*).

A recently discovered inherited polymorphism on chromosome 19 at rs12979860, close to the IL28B gene, is strongly associated with SVR in patients infected with HCV Genotype 1. The non-CC genotype explains most cases of null response to PEG/RBV. IL-28B genotype also determines SVR rate to triple therapy, with highest SVR achieved in those patients with the CC genotype (Jacobsen I, et al, *EASL 2011*; Poordad F, et al. *EASL 2011*). There is emerging evidence that more potent DAAs such as the new protease inhibitor TMC-435 (Fried M, et al. *AASLD 2010*) or the nucleoside polymerase inhibitor PSI-7977 (McHutchison, J et al. *AASLD 2010*) may overcome the impact of IL28B genotype on SVR.

However, triple therapy with protease inhibitors will have limited efficacy in patients infected with HCV GT non-1, previous null-responders and those with contraindications to interferon. It is hoped that the combination of multiple DAAs which target different steps of HCV replication should provide interferon-free treatment regimen. In the first proof-of-concept study of IFN-free combination DAA therapy (INFORM-1), 87 patients with HCV genotype 1 infection receive 14 days of mericitabine, a nucleoside polymerase inhibitor, and danaprevir, an NS3/4A protease inhibitor (Gane E, et al. *Lancet* 2010). This combination achieved profound synergistic antiviral suppression and prevented the emergence of resistance to either compound. Viral kinetic data derived from this study suggested that 8-10 weeks DAA therapy should eradicate HCV infection. In the first study of curative intent, 11 patients received 24 weeks of combination of NS3/4A protease inhibitor (BMS-650032) and NS5A inhibitor (BMS-795002) (Lok A, et al *EASL 2011*). Although 7 patients had virologic breakthrough within 2 months, with dual resistance, the remaining 4 patients were cured. Current and planned studies of Interferon-free combination DAA will determine the number of different DAAs, the need for RBV and duration of therapy needed to maximise cure whilst minimising the risk of emergence of multi-resistance, which would jeopardise future retreatment options.

In conclusion, the addition of a protease inhibitor to PEG/RBV increases efficacy in both treatment-naïve and treatment-experienced patients with HCV GT1. Future combinations of DAAs will improve the tolerability and efficacy of antiviral therapy on patients affected with all HCV genotypes.

Cirrhosis as a Haemodynamic Disease

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SUMMARY

Many of the complications of cirrhosis are due to alterations in the splanchnic or systemic circulations. Understanding of these haemodynamic changes is important in designing rational treatment strategies. In the 1950's it was recognised that cirrhotic patients had vasodilated peripheries, low systemic blood pressure, tachycardia and vascular spiders. Investigations confirmed that cardiac output was increased and systemic vascular resistance increased. Subsequent investigations have shown that circulatory abnormalities are of major prognostic significance in patients with decompensated cirrhosis or acute on chronic liver failure. One of the most obvious haemodynamic changes in cirrhosis is the development of portal hypertension. For many years this was believed to be due to passive congestion as a result of increased intra-hepatic resistance to portal venous blood flow. In a seminal series of investigations published in the early 1980's Prof Roberto Groszmann and colleagues showed that splanchnic arterial inflow was increased in portal hypertension, and not decreased as predicted. It appears that the increase in splanchnic blood flow can contribute up to 40% to the increase in portal venous pressure. The importance of this increased blood flow is that it is dynamic rather than anatomic and is thus potentially amenable to pharmacological intervention. Portal hypertension is believed to be responsible for many of the complications of chronic liver disease including ascites, hepatorenal syndrome, hepatic encephalopathy and hypersplenism. It is also associated with the pulmonary vascular complications, hepatopulmonary syndrome and portopulmonary hypertension. Treatment of hepatorenal syndrome relies on haemodynamic principles. Hepatorenal syndrome is due to severe renal vasoconstriction due to peripheral arterial vasodilation and decreased effective central blood volume. Treatment with vasoconstrictor drugs along with increasing central blood volume with albumin may reverse or ameliorate hepatorenal syndrome and improve prognosis. This is particularly important in patients awaiting liver transplantation as a high serum creatinine is one of the main adverse prognostic markers for survival following liver transplantation.

Liver Cancer Prevention: Myth or Fact

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SUMMARY

INTRODUCTION: Liver cancer is the 5th most common cancer in man and 8th most common cancer in woman worldwide. Mortality figures suggest that liver cancer is a difficult malignancy to treat. Most cases present late and at presentation only a third are resectable. Chronic hepatitis B and C infections account for about 80% of liver cancer while alcohol abuse account for most of the rest. Nonalcoholic fatty liver disease (NAFLD) is an up and coming cause. The relative contributions to the various causes differ in different parts of the world, with chronic hepatitis B infection being the most common cause in the Asia pacific region. Chronic hepatitis C infection, alcohol and obesity are predominant causes in Europe and North America. The importance of viral causes of liver cancer is reflected by the fact that this malignancy is highest in areas with the highest prevalence of hepatitis B virus (HBV). In some parts of the world where exposure to aflatoxins produced by molds infecting decaying grains and groundnuts are high, the incidence of liver cancer is also increased. Liver cancer prevention is a realistic option for reducing liver cancer related mortality worldwide, as the major risk factors are known.

LIVER CANCER PREVENTION: Primary prevention of liver cancer involves both public health measures to reduce the population's exposure to the known etiologic agents and the use of medications or dietary interventions. Different strategies are necessary in different geographic regions. In Africa and Asia, interruption of HBV transmission and improvement of food storage (to avoid contamination of food by aflatoxin producing molds), are primary options, whereas in the West and Japan, preventing liver cancer primarily requires interruption of hepatitis C transmission. Lifestyle and dietary habits (alcohol, tobacco and obesity) education can contribute substantially to the efforts to prevent liver cancer worldwide.

HEPATITIS B VACCINATION: In HBV hyper endemic regions where infection by HBV in early childhood is the main cause of chronic liver disease including cancer, universal vaccination of all infants has been found to be the most effective way to prevent liver cancer. Adult hepatitis B vaccination does not prevent HBV related liver cancer as HBV infection in this age group rarely becomes persistent. Investigators in Taiwan have confirmed a significant reduction in HBV related liver cancers in children and young adults since the introduction of the universal HB vaccination program¹. Subjects who received 4 vaccine doses have the lowest incidence of liver cancer amongst this once hyper endemic HBV population. Similar findings were noted by investigators in Alaska and Thailand^{2,3}. The incidence of adult HBV related liver cancers in these countries have not fallen yet and is expected to do so in the next three decades, when vaccinated cohorts reach the age when liver cancer usually occurs.

TREATMENT OF VIRAL HEPATITIS: An estimated 350 million people have chronic HBV infection and about 200 million people have chronic hepatitis C infection. The annual incidence of liver cancer reaches 3% in cirrhotic patients infected with HBV and 7% in cirrhotic patients infected with HCV. A recent long term observational study from Taiwan highlighted the importance of hepatitis B viral load (HBVDNA) as a risk factor in the development of liver cancer, presumably by causing liver damage. Subjects with high viral loads were more prone to develop liver cancers and the risk is reduced with (spontaneous) reduction in viral loads during the course of the study⁴. Effective suppression of HBV with interferons and oral nucleos(t)ide analogues (NA) have been shown to reduce the risk of liver cancer development in these patients⁵. The efficacy of NA in preventing liver cancer in patients with advanced cirrhosis was first demonstrated in a randomized controlled multicentre Asian study involving patients with biopsy-proven advanced fibrosis and cirrhosis and high levels of HBV DNA. The results conclusively showed that lamivudine was able to arrest disease progression in patients with chronic hepatitis B cirrhosis, including the complication of liver cancer. The role of HBV DNA in the pathogenesis of liver cancer was confirmed when patients who developed viral resistance during the study had the advantages of treatment blunted⁶. Several other studies have since confirmed the role of lamivudine and other oral anti-viral agents in the chemoprevention of liver cancer in patients infected with the hepatitis B virus. The situation with HCV infection is rather similar. Sustained response with the present standard of care therapy has resulted in lower risk of liver cancer development if cirrhosis has not developed⁷. It is a known fact that abstinence from alcohol will reduce the risk of liver cancer in an alcoholic cirrhotic.

OTHER CHEMOPREVENTIVE MEASURES: Effective cancer chemoprevention in high-risk individuals with cirrhosis of unknown cause is still wanting. Many compounds exhibiting anti-cancer effects have been tested in animal models of liver cancer, but only a handful have been studied in patients at risk for this malignancy. Cancer chemopreventive agents work through various mechanisms and sometimes a combination of some of these. These include blocking the activation of carcinogens, inducing carcinogen metabolism, altering intracellular signaling pathways to prevent progression of an initiated cell to a malignant cell, inhibiting angiogenesis, inducing apoptosis selectively in malignant cells, and inhibiting pathways linked to inflammation. Chlorophyllin (a food additive) and oltiporaz (a drug used to treat schistosomiasis) increase aflatoxin breakdown to non-carcinogenic compounds thereby decreasing the effective exposure of this mold toxin to liver cells. These compounds are being investigated in regions where the aflatoxin contamination is high. Because the liver cancer risk in patients with chronic hepatitis C and alcohol strictly correlates with the degree of liver inflammation, treatments aimed at attenuating liver inflammation might also have a beneficial impact on liver cancer risk. Glycyrrhizin, an aqueous extract of licorice root is widely prescribed in Japan as therapy for viral hepatitis. A 2-month treatment was shown to improve liver function and histological markers of liver inflammation, whereas long-term administration for more than several years led to a significant reduction in both cirrhosis and liver cancer risk in hepatitis C patients⁸. The natural forms of vitamin K1 and K2 and the synthetic K3 inhibits cell growth and may have a role in liver cancer prevention. A subgroup analysis of a prospective randomized controlled study in women with viral cirrhosis receiving 45 mg/day of vitamin K2 to prevent osteoporosis showed a significant reduction in liver cancer risk in patients receiving active treatment (2 versus 9, p=0.02)⁹. Other chemicals including Gefitinib (Iressa) tamoxifen and S-Adenosylmethionine (SAME) all showed anti-liver cancer properties in rat models of liver cancer. Large, well-designed, randomized, double-blind, controlled trials, with well defined endpoints, different dosages, and proven biomarkers that correlate well with clinical outcome is needed to assess the role of the above agents in the prevention of liver cancers.

DIETARY FACTORS: The observation that diets rich in antioxidants and other micronutrients protect against liver cancer requires further validation. Antioxidant-rich dietary supplements such as selenium, vitamin A, vitamin C, and vitamin E have been used in controlled trials, but without showing prophylactic activity against liver cancer. Epidemiological studies have shown an inverse relationship between coffee drinking and liver cancer risk. This apparent beneficial role of coffee consumption was found both in areas of high and low coffee consumption. The inverse relation of coffee is independent of major established risk factors for liver cancer¹⁰. It remains difficult, however, to translate the inverse relation between coffee drinking and liver cancer risk observed into potential implications for prevention of liver cancer by increasing coffee consumption.

CONCLUSION: It is possible to prevent liver cancer as the risks factors for malignancy are known. The screening of blood donors and universal vaccination against HBV of all new-borns has been significant steps in preventing liver disease including liver cancer. Substantial progress in the treatment of chronic hepatitis B and C, have also contributed to the drop in incidence of liver cancer. The potential efficacy of chemoprevention in altering the susceptibility of these people to the action of carcinogens and the effect of dietary factors on liver cancer prevention needs further investigation.

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Fatty Liver and Beyond

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SUMMARY

Nonalcoholic fatty liver disease (NAFLD) is emerging as a global epidemic. It is recognized as the most common cause of chronic liver disease in the West with a reported prevalence of 20–30% in the adult population. NAFLD is also becoming a problem in children related to increasing rates of childhood obesity. NAFLD is aetiologically associated with systemic and hepatic insulin resistance and is considered as the hepatic manifestation of the metabolic syndrome which encompasses obesity, diabetes mellitus or insulin resistance, hyperlipidaemia and hypertension. The diagnosis of NAFLD is based on clinicopathological criteria. The minimal histological change is steatosis in a patient without excessive alcohol consumption. NAFLD has a wide histological spectrum ranging from steatosis, which generally has a benign course, to nonalcoholic steatohepatitis (NASH), which is the progressive form of the disease. Progressive fibrosis occurs in 10–15% of patients with NASH. In total, 3–5% of patients with NAFLD may end up with cirrhosis. Hepatocellular carcinoma may occur in NASH-related cirrhosis and cryptogenic cirrhosis. Currently available noninvasive methods for the diagnosis of NASH lack high sensitivity and specificity. Liver biopsy still remains the 'gold standard' for confirming or excluding the diagnosis of NASH, grading and staging, and exclusion of other conditions in patients with chronically-elevated liver enzymes, image-detected steatosis, and the metabolic syndrome. Liver biopsy is performed selectively in patients with NAFLD because: (i) the course of the disease is benign in most cases, (ii) liver biopsy is costly and is related to rare but serious complications, (iii) clinical algorithms guide the decision for biopsy, and (iv) currently, there is no effective treatment for NASH. Steatohepatitis can be due to diverse aetiologies apart from the metabolic syndrome, such as, disorders of lipid metabolism, total parenteral nutrition, severe weight loss following gastro-intestinal bypass surgery for morbid obesity, drugs (amiodarone, tamoxifen, steroids, methotrexate, etc), refeeding syndrome, and toxic exposure. Histological interpretation of a liver biopsy with steatohepatitis without clinicopathological correlation is generally not considered sufficient to differentiate between the various aetiologies. About 2.6% of liver biopsies show concurrence of NASH with another liver disease, most common being chronic hepatitis C. Minimal criteria for histological diagnosis of NASH include steatosis, lobular inflammation and hepatocellular ballooning with zone 3 predominance. The characteristic perisinusoidal (chicken-wire type) fibrosis in zone 3 is not required for diagnosis. Other lesions include Mallory-Denk bodies, apoptosis and necrosis, megamitochondria, glycogenated nuclei and iron deposition. Immunohistochemistry can be helpful - K8/K18 to exhibit hepatocyte loss; and ubiquitin to demonstrate cytoskeleton damage and Mallory-Denk bodies. Histological scoring systems for grading and staging NAFLD are mainly used in treatment trials and natural history studies. Brunt's grading and staging system for NASH has been modified by the NASH Clinical Research Network (CRN). The NAFLD activity score (NAS 0 - 8) should not be used as an absolute severity scale. The numbers generated by the NASH CRN scoring system are not meant to replace morphological diagnosis and are to be applied only after this important process is completed.

Liver Fibrosis and Cirrhosis: Paradigm Shift with Clinical Significance

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SUMMARY

Cirrhosis is the end-stage of many liver diseases characterized by fibrosis, nodular regeneration and disturbed vascular architecture throughout the liver. There has been a paradigm shift in the thinking of liver fibrosis and cirrhosis. Fibrosis is now considered reversible whilst regression of cirrhosis is still controversial. Observations by Wanless et al have led to the concept of the “hepatic repair complex” to support the regression theory. This complex comprises histological evidence of three regenerative phenomena, namely (i) Fragmentation and regression of scar; (ii) Evidence of prior, now resolving, vascular derangements; and (iii) Parenchymal regeneration in the form of hepatocyte “buds”. Scarring during chronic liver disease represents a balance between synthesis of matrix and its resorption. This is a dynamic process of extracellular matrix remodeling. Regression of fibrosis requires breaking up of collagen and elastin fibres by metalloproteinases. As long as the disease persists, the balance favours deposition and scar formation. If the disease is inhibited or eliminated, then fibrosis and even cirrhosis can regress. Hepatic stellate cell activation plays a central role in liver fibrogenesis.

There are important therapeutic implications with the advent of antiviral, fibrinolytic and antifibrogenic therapies for chronic hepatitis C and B patients. As such, there is a need for accurate, and more frequent, monitoring of the dynamic nature of fibrosis progression or regression in order to evaluate the efficacy of treatment. So is the liver biopsy still the gold standard? It is a semiquantitative assessment of fibrosis using several scoring systems, namely, Knodell, modified Knodell (Ishak), Batts and Ludwig, and METAVIR scoring systems. The current practice has several drawbacks – sampling error, sample size, intra- and inter-observer variability, and application of inappropriate statistical techniques for stage scores. The use of computer-assisted image analysis of histochemically stained sections of liver biopsies provides a quantitative morphological method. A new tool in the assessment of liver fibrosis is second harmonic microscopy for fibrillar collagen scoring. However, it still does not obviate the need for a biopsy; hence, the development of noninvasive methods, such as, assessment of serum biomarkers and imaging modalities comprising transient (ultrasound) elastography [Fibroscan] and magnetic resonance elastography. In this interim period, liver biopsy is still considered the gold standard for validation of such noninvasive methods for assessing liver fibrosis.

Recent studies have supported the regression of cirrhosis, especially in hepatitis C cirrhosis after interferon treatment with sustained virological response. Bedossa et al reported that 61% of such patients had a downgrading of F4 stage to lower stages of fibrosis. The diagnostic utility of immunohistochemistry is illustrated. CK7 is used for (i) highlighting ductular reaction often seen at the periphery of cirrhotic nodules after interface damage; and for (ii) labeling hepatic progenitor cells and intermediate hepatocytes; and it correlated with F stage before and after treatment. Glutamine synthetase, labeling centrilobular hepatocytes, showed decreased and more focal positivity after treatment. CD34 to highlight arterialization of sinusoids (“sinusoidal capillarization”), and anti-smooth muscle actin to label activated hepatic stellate cells, showed no significant change. The biological implications and clinical significance of F stage downgrading in previously histologically-confirmed cases of cirrhosis; and the dilemma of recognizing and labeling “regressed” cirrhosis in a first-time biopsy are discussed.

Frozen Section Assessment of Donor Liver

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SUMMARY

The variables associated with patient and graft outcome after liver transplant include donor factors, procurement logistics, recipient factors and operative factors. The Donor Risk Index was developed based on 7 donor and 2 procurement factors, namely, donor age (>40 yr), race (African-American), height, donor after cardiac death status, donor after cerebrovascular accident, donor after brain death, donor liver macrovesicular steatosis (>30%), cold ischaemia time (>11 hr), and split/partial grafts. The pathologist has an important role to play in determining the suitability of the donor liver. The histological quality assessment of donated livers is a key factor for extending the limited cadaveric donor pool for liver transplant. The main reason for performing a frozen section (FS) is to uncover any potential abnormal donor or graft characteristics, in particular, steatosis. Protocol liver biopsies for FS are not routinely performed; instead, it is targeted at the high-risk donor group with marginal livers. Steatosis leads to decreased capability of ATP production and storage; increased lipid peroxidation; and increased release of tumour necrosis factor- α , believed to be partly responsible for lung damage after transplant. In macrovesicular steatosis, enlarged hepatocytes cause mechanical obstruction to blood flow during reperfusion leading to ischaemia. Microvesicular steatosis does not pose such a problem and is not a contraindication for transplant.

The histological features that need to be evaluated at FS analysis are as follows: macrosteatosis, microsteatosis, total steatosis, portal inflammation (+/++/+++), lobular necrosis, myointimal thickening (mild/severe), cholestasis (+/++/+++), hepatocellular polymorphism, lipofuscin storage, and fibrous septa. Some of the pitfalls encountered in FS assessment of donor livers include: (i) sampling errors – type of specimen (core or wedge biopsy); sampling of one/both lobes; focal steatosis, hypersteatosis and hepatic fatty sparing; (ii) tissue fixatives can induce fusion/collapse of lipid droplets; (iii) visualization of lipid droplets influenced by staining method (H&E, Oil Red O); (iv) under-estimation of macrosteatosis; (v) over-estimation of microsteatosis due to water droplets entrapped in hepatocytes at time of freezing; (vi) freezing artefacts; (vii) inter-/intraobserver variability; and (viii) junior faculty. It is important to develop accurate, unbiased and reproducible predictive indicators of possible primary graft nonfunction, delayed graft nonfunction, early graft loss, and retransplant. Steatosis is categorized into <10%, 10-30%, and >30%. Livers with increasing fat content are associated with increasing risk of graft failure/loss, e.g. livers with >30% fat have >60% risk. The degree of macrosteatosis is typically evaluated in liver biopsies by visual estimation on H&E and Oil Red O-stained slides, which is subject to intra- and interobserver variations. Computer morphometry (digital pathology) and biochemical measurement may provide more accurate results. Visual estimation has been shown to have a systematic bias, giving results nearly 4-fold higher than other methods. This may be because visual estimation denotes rather crudely the fraction of hepatocytes containing fat droplets, instead of the true fraction of fat.

Although some series document strong correlations between different methods of fat assessment, suggesting that all are valid methods for measuring steatosis; there are authors who report otherwise. One study revealed significant variation in quantitative and qualitative assessment of histological features of steatosis (macro-, microsteatosis, total fat) and steatohepatitis (lobular and portal inflammation, ballooning, Mallory-Denk bodies). There were obvious inconsistencies and disagreements amongst the blinded international expert liver pathologists involved in the study. Quantitation of fat in histological sections was strongly observer-dependent, not reproducible, and did not correlate with computer estimation. Current standards of histological assessment, conclusions of clinical studies on graft outcomes, and selection/rejection criteria of potential donors must be challenged. Their conclusion was that this is the end of FS evaluation of liver biopsy as a gold standard. The evaluation of hepatic fat in liver grafts currently remains histological examination. New more objective techniques of assessment of steatosis are needed. Computer morphometry is easy to implement and not affected by the bias seen in visual estimation. It may serve as a potential supplemental or alternative method. The only effective and available strategy for an optimal allocation of steatotic (marginal) liver grafts is an appropriate balance between donor age, graft macrosteatosis, graft cold ischaemia time and recipient MELD score.

An Algorithmic Approach to Assessment of Liver Biopsies

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SUMMARY

Pathological lesions occur in the liver in primary hepatic disorders as well as in systemic diseases with hepatic manifestations. Clinical categories of hepatic disorders include: acute liver disease; cholestasis; fulminant hepatic failure; chronic hepatitis; cirrhosis; extrinsic systemic diseases with hepatic involvement; and focal lesions. A single aetiology can give rise to several morphological hepatic lesions. A single morphological pattern can be attributed to different aetiologies. A practical algorithmic approach to reporting of liver biopsies is presented. To avoid bias, biopsies are analyzed blind initially to arrive at a **morphological diagnosis** based solely on descriptive histological findings. **Differential clinical diagnoses** are then considered in order of likelihood. The **final diagnosis** is made after close clinicopathological correlation. A morphological diagnosis, although not specific, serves as a useful interim "working diagnosis". The **morphological categories** are: Portal hepatitis; Periportal (Interface) hepatitis; Lobular hepatitis; Cholestatic hepatitis; Cholestasis; Steatosis/Steatohepatitis; Granulomas/Granulomatous hepatitis; Necrosis; Fibrosis; and Cirrhosis. **Helpful features** are abnormal hepatocytes, including inclusions; pigments; abnormal cellular infiltrates; abnormal bile ducts, including bile duct loss; abnormal blood vessels, vascular lesions and haemorrhages. Optimal specimens and the diagnostic utility of special stains and immunohistochemistry are emphasized. The 'blind' unbiased approach is highly recommended. It is felt that the proper time to evaluate clinical information is after the histology has been assessed. Diagnostic possibilities that might have been overlooked may present themselves; thus, decreasing the risk of compounding errors in clinical judgement. Close rapport with the hepatology team is crucial for the rendering of useful and accurate histopathology reports.

Clinical Aspects Of Non-Alcoholic Fatty Liver Disease

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SUMMARY

Non-alcoholic fatty liver disease (NAFLD) is a major health problem and rapidly becoming the commonest liver disease worldwide. It is estimated that one in three adults in Western countries has NAFLD. The incidence of NAFLD is increasing in both adults and children due to rising rates of Type 2 diabetes and obesity which are approaching epidemic proportions worldwide. The spectrum of NAFLD ranges from simple steatosis (fatty liver), to non-alcoholic steatohepatitis (NASH) and to cirrhosis. Cirrhosis can potentially progress to liver decompensation and hepatocellular carcinoma. Simple steatosis is common and only a minority will progress to steatohepatitis. Individuals with NASH, however, have a poorer outcome with a significant proportion progressing to advanced fibrosis. Liver histology remains the gold standard to diagnose and stage NASH. The management of patients with NAFLD continues to evolve and focuses on improving weight loss, insulin resistance and oxidative stress to prevent or reduce disease progression. There is a high incidence of cardiovascular morbidity and mortality in patients with NAFLD associated with a very high prevalence of cardiovascular risk factors and coronary artery disease. Therefore, there is also need to focus on improving the cardiovascular risk profile in patients with NAFLD

Portal Hypertension and the Utility of Hepatic Venous Pressure Gradient Measurements in the Management of Chronic Liver Diseases

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SUMMARY

Portal hypertension, defined as pathological increase in the portal venous pressure, is the end result of chronic liver diseases. Many of the complications of liver cirrhosis are direct manifestations of portal hypertension. These complications are consequent to the portal venous pressure elevation. Over the years, researchers have developed a technique to indirectly measure the pressure within the portal vein using the wedge hepatic venous pressure (WHVP) technique.

Hepatic venous pressure gradient (HVPG) measurement has gained its way into the management of patients with chronic liver disease. HVPG measurement provides comparable and in some aspects more information in the assessment of patients for liver cirrhosis as compared to liver biopsy. It is also able to classify portal hypertension into the prehepatic, hepatic and posthepatic causes. Furthermore, HVPG allows clinicians to predict disease progression. An HVPG value above 10mmHg is a strong predictor for variceal development while an HVPG value of ≥ 12 mmHg signifies a risk for re-bleeding. In contrast, in patients with decompensated cirrhosis, an HVPG value of ≤ 12 mmHg or reduction $\geq 20\%$ from baseline reduces the risk of developing ascites, hepatic encephalopathy and spontaneous bacterial peritonitis.

HVPG is useful in monitoring of therapeutic response to pharmacological treatment. In patients with previous variceal bleed, achieving HVPG value of ≤ 12 mmHg or $\geq 20\%$ reduction from baseline protects these patients from recurrent bleed. In addition, HVPG allows prognostication of patients with Child's A liver cirrhosis, undergoing hepatic resection. Risk of death was also found to be associated with baseline HVPG (<16 mmHg best cut off to predict survival) for those patients on primary prophylaxis against variceal bleed. For those patients on beta blockers as part of secondary prophylaxis, responders (HVPG <12 mmHg) have a higher survival.

Many complications from portal hypertension is a serious and direct consequence of portal pressure elevation. HVPG is an important tool in the management of patients with chronic liver disease, compensated and decompensated liver cirrhosis as it provides diagnostic, monitoring and prognostic information.

Key To Success: Portal Venous Access

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SUMMARY

The transjugular intrahepatic portosystemic shunt is considered one of the most complex procedures in Interventional Radiology. It involves multiple steps that sequentially include: (1) puncture of the jugular vein, (2) cannulation of the hepatic vein, (3) passage of needle through the liver parenchyma into the portal vein, (4) dilatation of the tract created by the needle and, (5) stent deployment to ensure long term patency of the tract.

The most crucial and difficult step in TIPS creation is a safe and successful access of the portal vein. This step is often the longest and, at times, most frustrating part of the procedure. Whilst various methods have been described to aid portal venous access, the most fundamental is an understanding of the hepatic vascular anatomy. The relative position between the hepatic and portal veins can be quite variable, and it is imperative to recognise these with an US, CT, and/or MR prior to starting the TIPS. Pre-TIPS imaging can additionally detect anatomic variants, and rule out any anatomic contraindications for the TIPS procedure. If there are any doubts about the anatomy, an invasive arteriogram or even a percutaneous portal venogram may be considered.

The commonest method used for guiding portal venous access is a "blind" one, using just fluoroscopic landmarks during needle advancement. In 90% individuals, the right portal vein is expected to lie in a zone bounded supero-inferiorly by the right 10th and 12th ribs, and medio-laterally about 0.5 to 1.5 times the vertebral body width from the right vertebral margin. A needle targeted to this area would have a high chance of a successful portal vein access.

When this method fails, or if the anatomy forebodes a challenging puncture, other guiding methods can be used, which include:

- a. US guidance : External US can be used to estimate the needle direction and trajectory, but would however require an additional operator to perform the US. The tip of the needle used for portal venous access is not very echogenic and may not be recognisable in small echogenic livers. However, they do have good utility in determining the hepatic vein being used when portal venous access is constantly failing.
- b. Intravascular US: IVUS has been used by some centres where available. The expense of the equipment and the requirement of an additional operator precludes its use in routine practice.
- c. Wedged hepatic venography: Some operators prefer to obtain a wedged hepatic venogram with either iodinated contrast or CO₂ prior to or during needle puncture. With this, contrast is forced retrograde through the hepatic sinusoids to fill the portal vein. This provides information about the relationship between the hepatic vein and the portal vein. Care should be taken with this manoeuvre as liver laceration and capsular hematoma are known complications.
- d. Radio-opaque landmark in or around the portal vein: Some investigators prefer to use a radio-opaque marker within or adjacent to the portal vein, either in form of an embolization coil deposited near the portal vein, or a catheter or a guidewire inserted percutaneously within the portal vein. These landmarks would be visible throughout the procedure, and would provide an accurate target for the needle. However, it would potentially increase the procedural time and risk.
- e. Use of newer technology like 3D-US, cone-beam CT or rotational digital fluoroscopy: These new techniques are promising and are likely to improve the efficiency and success rate of a successful TIPS procedure.

The Role of HVPG Measurement

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SUMMARY

Portal hypertension causes many of the complications commonly associated with chronic liver disease including variceal haemorrhage, ascites, hepatorenal syndrome and hepatic encephalopathy. Portal venous pressure is determined by the combination of portal venous inflow, intrahepatic portal venous resistance and collateral out-flow. Because of these variables portal venous pressure cannot be reliably estimated using non-invasive investigations such as ultrasound. It can be measured directly by cannulation of the portal vein or indirectly by measurement of hepatic venous wedged pressures. It is also possible to measure variceal pressure directly using the varipress. Wedged hepatic venous pressure measurement requires cannulation of the hepatic veins with an occlusion balloon via the femoral or transjugular routes. It is a reliable and reproducible measurement but requires some expertise. It is of no value in patients with portal vein thrombosis and may underestimate portal venous pressure in patients with non-cirrhotic portal hypertension. Measurement of portal venous pressure is of value in guiding pharmacological therapy of portal hypertension both for prevention of variceal bleeding or in preventing re-bleeding. It is also useful in the emergency situation to determine which patients may benefit from urgent TIPS shunt. Patients with potentially resectable hepatocellular carcinoma may also benefit from portal venous pressure measurement to determine whether it is safe to proceed to surgical resection. Measurement of wedged hepatic venous pressure is a robust, reliable technique which is probably under-utilised in current clinical practice.

Surgery in Portal Hypertension

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SUMMARY

Abdominal surgery (non shunt, non transplant) in patients with portal hypertension is associated with higher morbidity and mortality. Patients with cirrhosis and portal hypertension are prone to develop complications because of altered liver function, hyperkinetic circulatory status, impaired renal function, compromised ventilatory capacity, disordered coagulation, existent malnutrition and increased chances of infection. Surgical intervention can cause liver failure, variceal bleeding and ascites. In patients with Child A disease, risks of surgery are acceptable but patients with Child C disease have uniformly poor outcome after abdominal surgery. Selection of patients with Child B disease and need for abdominal surgery requires judicious assessment. Presence of ascites, serum albumin <30g/l, raised transaminase levels (>3 times the normal values) and need for emergency surgery have been found to be associated with high morbidity and possible mortality. Procedures like cholecystectomy and hernia repair can safely be performed laparoscopically in good risk patients. Major surgical procedures like pancreatic resection, esophagectomy and colorectal resections should be carefully planned in selected patients. Surgical intervention in patients with Child C disease should be avoided as far possible.

Imaging in HCC – Latest Updates

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SUMMARY

The primary objective of imaging in liver cirrhosis is to detect HCCs at an early stage when curative treatment is available. The imaging modalities routinely used in HCC imaging include, 1) grey scale non-contrast enhanced US, 2) dynamic contrast enhanced CT (CECT) using iodinated contrast media and 3) dynamic contrast enhanced MRI (CEMRI) using extracellular Gadolinium chelates. US is used in screening. Following detection on the preliminary US, dynamic CECT and/ or dynamic CEMRI would then be done for definitive diagnosis.

The AASLD and APASL guidelines state that a diagnosis of HCC can be made if a mass larger than 2 cm shows typical features of HCC (hypervascularity in the arterial phase and washout in the venous phase) at dynamic CECT or dynamic CEMRI or if a mass measuring 1-2 cm shows these features at both modalities. The HCCs that conform to these typical or classical imaging features are mostly the larger lesions of more than 2cm, and of the moderately and poorly differentiated types. The lesions that do not conform to the classical imaging features of HCC, are these which are well differentiated and smaller than 2cm in size. It is shown that 87% of well-differentiated HCCs and 41–62% of lesions smaller than 2 cm do not exhibit classical imaging features of HCC. Importantly, these are the lesions that should be the target of surveillance and diagnoses, since they can be ablated with high likelihood of cure.

The sensitivities of dynamic CECT and dynamic CEMRI for HCC lesions 1-2cm are generally poor; at 40% and 47% respectively. To improve lesion detection and characterisation, keen interest has been given to exploring the potential of MRI, particularly in the use of hepatocyte-specific contrast agents namely, 1) superparamagnetic iron oxides [SPIO], manganese chelates and gadolinium based hepatocyte agents; and incorporation of diffusion weighted imaging.

At present SPIO and manganese agents are on the decline due to decreased clinical usage. Studies on Gadolinium based hepatocyte-specific MRI contrast agents have shown great promise to improve current methods of imaging diagnosis. They are increasingly used in the United States, Europe and parts of Asia. The gadolinium-based agents have hepatocyte and perfusion imaging properties and are called dual or bimodal contrast agents. This is because they behave as both an extracellular and a hepatocyte-specific agent as it undergoes both renal and biliary excretion. This allows for dynamic contrast enhanced imaging due to its extracellular function and delayed static hepatobiliary imaging due to its hepatocyte specific function. The contrast agents that demonstrate these dual functions are Gadobenate dimeglumine (MultiHance, Bracco, Milan, Italy; formerly known as Gd-BOPTA) and gadoxetate (Primovist, Bayer-Schering, Berlin, Germany; formerly known as Gd-EOB-DTPA). Between the two agents, Gd EOB DTPA was found to be more sensitive than Gd BOPTA (86% vs 64%). This is because up to 50% of the injected dose is taken up into normal hepatocytes, compared to 5% in Gd BOPTA. Current evidence and experience suggest that Gadoxetic acid-enhanced MRI will improve the accuracy of HCC imaging diagnosis by allowing better characterization of hypovascular lesions and better differentiation of small arterial enhancing lesions as well as by providing improved preoperative staging accuracy. Therefore, with the aid of Gadoxetic acid-enhanced MRI, very early HCC will be more commonly diagnosed, with patient treatment occurring in earlier stages of the disease. The sensitivity and accuracy were significantly superior to MDCT for the diagnosis of lesions less than 1.5 cm. One study compared Gadoxetic acid enhanced MRI, at 1.5T and 3.0T, and showed similar diagnostic performances for detection of small HCCs. Advantage of 3T are a) better SNR b) liver lesion CNR allows higher sensitivity and accuracy in the detection and characterisation of hepatocellular nodules.

The values of diffusion weighted imaging (DWI) have also been explored, with encouraging results. Addition of DWI to dynamic CE MRI showed improved MR detection of HCCs, particularly in lesions smaller than 2cm, with sensitivities of 84–98% compared to 76–85% for dynamic MRI alone. Potentially, objective measurement of the apparent diffusion coefficient (ADC) may allow for distinction between the different tumour grade.

Current evidence and experience suggest that Gadoxetic acid –enhanced MRI will improve the accuracy of HCC imaging diagnosis by allowing better characterisation of hypovascular lesions and better differentiation of small arterial enhancing lesions as well as providing improved preoperative staging accuracy.

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Managing HCC – Are We Making Progress?

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SUMMARY

Hepatocellular carcinoma (HCC) is one of the most difficult malignancies since it has several unfavorable characteristics such as frequent vascular invasion/distant metastasis, multiple occurrence, bilobar disease, and accompanying liver cirrhosis. Moreover, unlike other cancers including ovarian or breast cancer, traditional systemic chemotherapy is not so effective in HCC, both for adjuvant and palliative setting. Sorafenib, a multikinase inhibitor, has opened the window for challenging this dismal disease. Actually, since the successful result of clinical trial using sorafenib, other new targeted agents for HCC is being tested in several phase II or III clinical trials. According to SHARP trial or Asia-Pacific trial, which has revealed significant survival benefit of sorafenib in HCC patients with advanced stage (BCLC stage C) compared to placebo, sorafenib has been the standard of care in the management of advanced HCC with vascular invasion or extrahepatic spread in patients with preserved liver function. In addition, patients with progressive HCC in spite of other therapies are also candidates of sorafenib therapy as a second-line treatment. The advancement of targeted therapy for HCC essentially requires the molecular pathogenic mechanism. In HCC, there are so complex intracellular pathways involved in carcinogenesis including Raf/MAPK, Akt/mTOR, Jat/Stat, and Wnt pathway. Among these, tyrosine kinase receptor (TKR) activation through TKR overexpression, ligand overexpression, or mutation of TKR is the first event followed by activation of intracellular proteins. Many efforts have been made to develop novel targeted agent to block this network of signal pathways. Molecular targeted therapy can be divided into monoclonal antibody and small-molecule tyrosine kinase inhibitor such as sorafenib. Monoclonal antibody binds directly to ligand or extracellular domain of receptor tyrosine kinase, and so blocks propagation of extracellular signal. Whereas, small-molecule binds to catalytic domain of intracellular tyrosine kinase to block protein phosphorylation and activation of downstream pathway. Escape phenomenon is unavoidable in case of single targeting. Thus, combination of single-targeted agents or development of multi-targeted single agents is necessary to overcome this limitation. Moreover, the role of targeted agent in the setting of post-operative adjuvant therapy and combination with transarterial chemoembolization (TACE) or other therapies remains to be elucidated in the near future. In this session, the mechanism of hepatocarcinogenesis, development of targeted agent, and new challenges in the era of targeted therapy as well as recent clinical outcome with sorafenib will be presented.

Transplantation For HCC: To What Extent?

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SUMMARY

Hepatocellular carcinoma (HCC) is increasingly diagnosed, in part due to an increasing prevalence of liver disease throughout the world, but also due to enhanced monitoring and improved diagnostics. The majority (70-90%) of HCC is associated with cirrhosis and under this circumstance, poor hepatic reserve in the cirrhotic liver limits the ability to resect the lesion(s). In addition, the multifocality of HCC (HCC < 5cm: 39% multifocal - HCC > 5cm: 79% multifocal) limits the success of resection with a high rate of recurrence (50-90%) after resection high by 5 years. As the underlying condition of cirrhosis is considered a pre-malignant condition, liver transplantation (LTX) treats both the cirrhosis and the cancer.

In the early development of LTX, HCC was a frequent indication, as LTX still felt to be experimental. For example, from European Liver Transplant Registry - 46% of liver transplants between 1972 and 1982 were for malignant disease. However, this led to poor selection of candidates with many early survivors succumbing to subsequent HCC recurrence. Yet it was noted that some patients with smaller HCC tended to do better. In 1995, two independent studies survival after liver transplantation for Stage I and II HCC is comparable to those patients without HCC. The recurrence rate was less than 10% and the recurrence-free survival was better than 70% at 4-5 years after LTX (Selby et al, *World J Surg*, 1995, 19:53; Mazzafero et al, *N Engl J Med* 1996;334:693).

Because of the uncertainty in the ability to reliably predict the survival of an individual patient on the liver waiting list, an objectified scoring system, the Model of End Stage Liver Disease (MELD) was adopted from a study examining the mortality after TIPS (Kamath et al: *Hepatology* 2001;33:464-470). The predictive accuracy of MELD based on its three elements (serum creatinine, serum bilirubin and INR) is only 77%, in part because it does not take into consideration other potentially important clinical events. In addition, MELD is recognized to be subject to other non-laboratory factors, such as development of HCC. In 2002, the United Network of Organ Sharing (UNOS) implemented the use of MELD for allocation of livers for transplantation. Candidates with Stage I and II HCC in accordance with the modified Tumor-Node-Metastasis (TNM) Staging Classification were able to receive extra priority on the waiting list. Initially, when MELD points were being assigned for HCC, patients fulfilling Milan Criteria: Stage I - single lesion less than 5 cm or Stage II - three lesions less than 3 cm each were eligible for additional MELD points. At that time, patients with Stage I HCC were registered at a MELD score equivalent to a 15% probability of candidate death within 3 months, whereas patients with Stage II HCC were registered at a MELD score equivalent to a 30% probability of candidate death within 3 months. This was associated with a large increase in the percentage of patients being transplanted with HCC, with an 88% probability of a HCC patient undergoing LTX by 8.5 months from listing (Yao F et al: *Liver Transpl*, 2004; 10:621). This led to several changes in UNOS policy, which removed priority for Stage I HCC and reduced the number of MELD points for Stage II. The impact of these changes did not appear to increase waitlist mortality or worsen post-LTX outcomes (Sharma P et al: *Am J Transpl*, 2006;6:1957).

The current UNOS policies require that the candidate undergo a thorough assessment to evaluate the number and size of tumors and to rule out any extrahepatic spread and/or macrovascular involvement. A pre-listing biopsy is not mandatory but the lesion must meet defined imaging criteria. The assessment of the candidate should include ultrasound of the candidate's liver, a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen that documents the tumors and a CT of the chest that rules out metastatic disease. In addition, the candidate must have at least one of the following: a vascular blush corresponding to the area of suspicion seen on the above imaging studies, an alpha-fetoprotein level of >200 ng/mL an arteriogram confirming a tumor, a biopsy confirming HCC. MELD assignment allows a candidate with an HCC tumor that is greater than or equal to 2 cm and less than 5cm or no more than 3 lesions, the largest being less than 3 cm in size (Stage T2 tumors) may be registered at a MELD score equivalent to a 15% probability of candidate death within 3 months. Candidates will receive additional MELD points equivalent to a 10% increase in candidate mortality to be assigned every 3 months until these

candidates receive a transplant or are determined to be unsuitable for transplantation based on progression of their HCC. To receive the additional points at 3-month intervals, the transplant program must re-submit an HCC MELD score exception application with an updated narrative every three months. Continued documentation of the tumor via repeat CT or MRI or those meeting criteria based on an alpha-fetoprotein level of ≥ 500 ng/mL, is required every three months for the candidate to receive the additional 10% mortality points while waiting.

Several groups have strived to include a larger number of HCC patients for LTX by expanding the tumor characteristics suitable for LTX or by downstaging patients with Stage III HCC (Yao FY: *Am J Transplant*, 2008;8:1982). While the incrementally larger number of patients served is associated with an incrementally lower survival rate and increased recurrence rates, the adoption of these strategies into allocation policies in the United States, is still being debated. All currently utilized candidacy selection schema for transplantation are based on such tumor characteristics as size, number, bilaterality, and vascular invasion. Unfortunately, the T stage component of the TNM classification system totally ignores the possibility of independent de novo tumor formation, classifying all HCC nodules as monoclonal neoplasms. Thus multinodular tumor formation is considered intrahepatic spread (i.e., metastatic disease) with a corresponding increase in T stage classification. Consequently, all bilobar tumors are classified as T4 (as opposed to two T1 or T2) tumors, and these patients are routinely denied transplantation in most centers. The methods described herein clearly distinguish between de novo cancer formation and metastatic, intrahepatic spread. These findings mandate revisions to the TNM classification to reflect these changes, as treatment options and prognosis vary greatly between T1/T2 and T4. Clearly, assignment of a patient to a T4 classification so limits the options available to that patient that it is tantamount to a sentence of death.

A search for additional tumor characteristics, which could improve upon previously developed HCC outcomes prediction models, will allow for selection based on biomarkers based on tumor biological behavioral characteristics. To that end, investigations of molecular alterations of HCC and their influence on tumor aggressiveness and recurrence-free patient survival represents a step forward.

HBV Reactivation - Who Needs Prophylaxis

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SUMMARY

INTRODUCTION: The interaction between the hepatitis B virus (HBV) and the host immune system is complex. The host innate immune response to HBV, represented by natural killer (NK) cells, natural killer T-cells, the production of type 1 interferon and TNF α , can control and resolve acute hepatitis B infection. In chronic hepatitis B infection, elimination of HBV from the host requires strong CD4 and CD8 T cell response. CD8 T cells, in particular, are the main effector cells for HBV clearance and disease pathogenesis. By inducing strong CD8+ T cells against different epitopes of HBsAg, HBcAg and polymerase, HBV infection can achieve clearance with long-term control. Additional B cell-derived antibodies against HBs, HBc, and HBe antigens mediate protection at various levels of the immune cascade. However, Individuals recovered from hepatitis B infection still harbor HBV cccDNA in the nucleus of the hepatocytes. Reactivation of HBV can occur when the immune system is severely impaired either by disease or immunosuppressive drugs. HBV reactivation is defined by reappearance of HBsAg and/or HBV DNA in the serum, thereby exposing the individual to relapse of hepatitis. This occurs in many clinical situations, be it spontaneously or precipitated by diseases or therapeutic agents that compromise cellular and/or humoral cytokine immunity.

CLINICAL SITUATIONS ASSOCIATED WITH HBV REACTIVATION

1. Organ Or Tissue Transplantation

Organ and tissue transplantation is becoming an increasingly common mode of therapy for endstage diseases. Strong immunosuppressants is required to prevent rejection of transplanted organ or tissue. The recipients and donors are carefully assessed for infective diseases that can jeopardize the clinical outcome. The risk of HBV reactivation depends on their HBV serologic status. Recipients should be treated for active chronic hepatitis B infection before the transplantation. Donors with positive HBsAg serology are generally not accepted. Much attention has been drawn to the HBV reactivation risk when anti-HBc positive organs and tissues are used. Past experience indicates that the risk is low for kidneys and heart, but higher for lung transplantations, relating to the quantity of lymphoid tissue in these organs. The use of such organs is increasing owing to the worldwide organ shortage. Data from Europe showed 15%-20% incidence of anti-HBc-positive donors, with a 3% seroconversion rate to HBsAg. Cohort data suggest that the use of such donors is safe if recipients with no evidence of HBsAb receive prophylaxis with either lamivudine or HB immunoglobulin¹. This was also demonstrated in patients undergoing allogeneic stem cell transplantation for various hematologic malignancies given lamivudine prophylaxis². In liver transplantation, long-term lamivudine monotherapy was found to be effective in preventing development of HBV infection in HBsAg-negative liver transplant recipients from HBcAb-positive donors. Some centres preferred a more safe approach of using HBIG and lamivudine combination therapy to prevent de novo HBV infection in anti-HBs and HBsAg negative recipients of hepatic allografts from anti-HBc positive donor³⁻⁵. Systematic review on 39 studies including 903 recipients of anti-HBc positive liver grafts over the past 15 years showed recurrent HBV infection 11% of HBsAg-positive liver transplant recipients. Their survival was similar (67-100%) to HBsAg-positive recipients of anti-HBc negative grafts. De novo HBV infection developed in 19% of HBsAg-negative recipients, and was less frequent in anti-HBc/anti-HBs positive than HBV naive cases without prophylaxis (15% vs 48%, $p < 0.001$). Anti-HBV prophylaxis reduced de novo infection rates in both anti-HBc/anti-HBs positive (3%) and HBV naive recipients (12%). De novo infection rates were 19%, 2.6% and 2.8% in HBsAg-negative recipients under HBIG, lamivudine and their combination, respectively⁵. Similar findings was reported in another review of 36 articles on 552 liver transplants, multiple strategies as preventive interventions were used including lamivudine, HBIG, revaccination, and combined therapies. Currently, liver grafts from anti-HBc positive donors are regarded as safe and preferentially used in HBsAg-positive or anti-HBc/anti-HBs positive recipients. HBsAg-negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis⁶. Follow-up and preventive therapies should be maintained for five year or preferably throughout the recipients' life span⁷. The prevention of HBV reactivation may be further reduced with more potent nucleos(t)ide analogs and awaits updated data from studies. HBsAg-positive recipients should be treated with potent nucleos(t)ide analogs to render them non-viraemic prior transplantation, and continue therapy with additional low-dose HBIG.

2. Chemotherapy for Malignancy

Chronic HBV infection is endemic in the Asian-Pacific region, and reactivation of HBV post-cancer chemotherapy is an emerging clinical challenge [8]. Patients may respond well to chemotherapy but succumbed to HBV reactivation and liver failure. Viraemic patients and those receiving intensive chemotherapy are particularly at a risk. Report from Hong Kong showed 67% of chronic hepatitis B patients developed hepatitis complications on chemotherapy in the era when no prophylaxis was available. 22% developed icteric liver failure, 4% fulminate liver failure, and 4% died⁸. Hepatitis can be caused by direct hepatotoxicity of chemotherapeutic agents or other blood borne disease from blood product transfusion. HBV serological tests and sensitive serum HBV DNA monitoring are essential to diagnose HBV reactivation and initiate appropriate therapy. Prophylactic antiviral therapy with nucleos(t)ide analogue for HBsAg positive patients is now a standard of care in many countries. The prophylactic use of nucleos(t)ide analogs before chemotherapy and its continuation until reconstitution of host immunity remain the mainstay of effective prevention of HBV reactivation⁹. Patients with past HBV exposure and are HBsAg negative but anti-HBc positivity may experience reactivation spontaneously or induced by potent chemotherapy. One can adopt a pre-emptive strategy by close monitoring of serum alanine aminotransferase, HBsAg, and HBV DNA, initiate antiviral therapy when HBV reactivation evident.

Special attention should be paid to lymphoma patients. They have a higher prevalence of seropositive for HBsAg at the time of diagnosis compared with the general population, indicating disease induced HBV reactivation among those with past HBV exposure. Antiviral prophylaxis should be administered before chemotherapy. For lymphoma patients with resolved hepatitis B, the more potent chemotherapeutic regimen of CHOP+rituximab was shown to increase the risk of HBV reactivation and could be fatal. Prophylactic antiviral therapy should be administered in this situation¹⁰⁻¹².

3. Immunosuppression Therapy for Rheumatologic Diseases

TNF- α inhibitors have emerged as a potent therapeutic agent for many immunologic diseases including rheumatoid arthritis. However, they are not without significant side-effects. Limited data suggest that TNF- α inhibitors may facilitate uncontrolled hepatitis B viral replication. 13 patients with chronic hepatitis B infection treated with TNF- α inhibitors showed clinically apparent HBV reactivation. Typically, this occurred one month after the third dose of infliximab. Recent systematic literature review (1996 to January 2010) identified 35 HBsAg positive patients of 17 were treated with Infliximab, 12 with etanercept, and 6 with adalimumab. All six cases of clinically symptomatic hepatitis were associated with infliximab therapy. So, it seems that HBV reactivation during therapy with TNF- α inhibitor is not a class effect, but attributable to infliximab only. Six of nine cases had greater than 2-fold increase in alanine aminotransferase, and three of four had greater than 1,000-fold increase in HBV DNA level. Two deaths occurred. While such reactivation may be due to a variety of reasons, clinicians prescribing TNF- α inhibitors to HBsAg-positive patients should consider prophylactic antiviral therapy and close monitoring for any clinical or serological evidence of hepatitis¹³. In patients with negative HBsAg but positive anti-HBc, anti-TNF- α therapy appears to be quite safe. Nevertheless, careful monitoring is necessary¹³⁻¹⁵. In a recent report on sixty patients with negative HBsAg but positive anti-HBc receiving DMARD, 2 patients (3.3%) experienced reactivation of viral replication (<2.1 log copies/ml). One had been receiving tacrolimus, prednisolone, and methotrexate (MTX); the other had been treated with adalimumab, prednisolone, and MTX. The use of biological and nonbiological DMARDs is relatively safe in most RA patients with past HBV infection, even when no anti-HBV prophylaxis is administered. Considering the high prevalence of past HBV infection in RA patients in Asia, and the high cost of prophylaxis against HBV reactivation, universal prophylaxis is impractical. Regular monitoring of serum viral DNA seems to be the most rational approach to preventing the development of clinically apparent hepatitis 16

4. Immunosuppressant therapy for Inflammatory Bowel Disease

Inflammatory bowel disease patients may require long-term immunosuppression. They should receive antiviral treatment if they have active chronic hepatitis B infection. Particular attention is needed if TNF- α is used¹⁷. 3 Crohn's disease patients with chronic HBV infection suffered severe reactivation after withdrawal of infliximab therapy and one died. The third patient was treated with lamivudine at the time of infliximab therapy, had no clinical or biochemical worsening of liver disease during or after therapy¹⁸. Patients negative for HBsAg should be considered candidates for vaccination against new HBV infection as well as prophylaxis against HBV reactivation prior to immunosuppressive therapy¹⁹.

5. Immunosuppression Therapy for Respiratory Diseases

Patients with asthma and chronic obstructive airway diseases may require intermittent or long-steroid therapy and are also at risk of HBV reactivation. Glucocorticoid facilitates HBV replication and increases viral load. On steroid withdrawal, the immune rebound will lead to varying degree of hepatitis flare. The risk is higher if the duration of steroid therapy is prolonged or high dosage is required. In a retrospective study on 198 patients with asthma or COPD who were also HBsAg positive, HBV reactivation occurred in 11.1% of patients treated with systemic corticosteroid. It was significantly higher than in patients treated with inhaled steroid. HBV reactivation was more frequent among those on continuous and medium-to-high-dose systemic corticosteroid²⁰.

CHOICE OF ANTIVIRAL THERAPY

Currently there are five nucleos(t)ide analogues approved for treatment of hepatitis B infection. Lamivudine has been used to rescue patients from HBV reactivation since late 1990's and therefore has most data. Newer and more potent agents such as entecavir, telbivudine and tenofovir are likely more effective and data is emerging. The APASL Guidelines for HBV management was drawn up in 2007. It recommends screening for HBsAg before patients receive immunosuppression or chemotherapy (III). If HBsAg is positive, prophylactic therapy with lamivudine before starting and up to 12 weeks after the end of immunosuppression or chemotherapy is recommended (I). It mentions that other direct antiviral can be also used²¹.

In 2009, AASLD updated guidelines recommended HBsAg and anti-HBc testing (II-3) before chemotherapy. Prophylactic antiviral therapy with lamivudine for HBV carriers at onset of chemotherapy or for a finite course of immunosuppressive therapy is recommended. If baseline HBV DNA <2,000IU/mL, antiviral therapy should be maintained for 6 months after completion of chemotherapy or immunosuppressive therapy (III); if baseline HBV DNA >2,000IU/mL, continue treatment till endpoint is reached as in immune competent patients (III). With regard to the choice of antiviral, it recommends that lamivudine and telbivudine can be used if anticipated therapy for <12 months and baseline HBV DNA undetectable. (Lam I TBV III). This will reduce the risk of resistant mutants emerging and other side-effect such as myositis and neuropathy associated with telbivudine. However, if longer duration of therapy anticipated, entecavir and tenofovir are the preferred choice (III). Interferon should be avoided because of marrow suppression (II-3)²².

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Autoimmune Hepatitis in Children

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SUMMARY

Autoimmune hepatitis in children is a progressive inflammatory liver disorder of unknown aetiology characterised by the presence of autoantibodies, raised aminotransferase levels, elevated immunoglobulin G (IgG) and interface hepatitis. The mode of presentation of autoimmune hepatitis in childhood is variable. Hence, it should be suspected and excluded in all children presenting with symptoms and signs of prolonged or severe liver disease. Other conditions such as drug-induced liver diseases, liver infections and hereditary conditions like Wilson disease must be excluded by appropriate investigations. Although standard immunosuppressive treatment is usually effective, severe liver failure may unfortunately develop after years of satisfactory control, with about 10% of patients needing transplantation 10 to 15 years after diagnosis.

Acute Alcoholic Hepatitis

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SUMMARY

Although alcoholic hepatitis is defined by pathological criteria, acute alcoholic hepatitis is a clinical syndrome. It is characterised by jaundice, low-grade fever, neutrophilia, prolonged INR and often, ascites. Not all patients with histological alcoholic hepatitis have the clinical features of acute alcoholic hepatitis. Most cases will also have underlying alcoholic cirrhosis. It is not known why patients with alcoholic hepatitis suddenly develop acute alcoholic hepatitis. Typically patients will have stopped drinking a week or two prior to admission to hospital and liver function tests deteriorate for a period despite abstinence. Mathematical scoring systems have been developed to assess severity and prognosis– Maddrey’s discriminant function, Glasgow alcoholic hepatitis score, the MELD score and the Lille index. Falling serum bilirubin or improved MELD score in the first week (> 2 points) suggests a good prognosis. Patients with severe alcoholic hepatitis may be in hospital for 4-6 weeks and gradually improve. Complications include sepsis, bleeding and hepatorenal syndrome. Treatment options include oral nutritional support, steroids and pentoxifylline. Unfortunately there has been little improvement in the prognosis for patients with alcoholic liver disease/acute alcoholic hepatitis has over the past few decades. TNF levels are high in patients with alcoholic hepatitis. However clinical results with anti-TNF antibodies have been mixed and the large French randomised trials reported an increase in mortality compared to standard treatment. Because of the high mortality with severe acute alcoholic hepatitis some centres consider these patients for urgent liver transplantation. In carefully selected patients the results to date have been promising but long term abstinence rates are not yet available.

Gastroenterology & Hepatology - To Merge or Not to Merge – That is the Question

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SUMMARY

Traditionally training in Hepatology has been part of the Gastroenterology training programme. This has long been observed in the USA and Europe . Hepatology is now regarded as a clinically distinct but closely allied subspeciality. Malaysia is currently facing an acute shortage of hepatologists and Liver units. Furthermore the majority of hepatologists are disproportionately centred in the Klang Valley. The current Gastroenterology training programme of the Ministry of Health is a four-year training programme. Trainees in Hepatology would then undergo two years of general gastroenterology followed by two years of Hepatology training. The initial two years would involve some exposure to inpatient as well as outpatient experiences in Hepatology in addition to upper GI endoscopy. The final two years would involve spending at least one year in a specialized Liver unit and at least 6 months in a liver transplant service. The goal of training in a two-year module allied to gastroenterology would be to produce hepatologists who are competent to manage the broad spectrum of hepatological problems encountered in a typical gastroenterological practice. In addition the trainee would also be able to manage complex cases of liver failure, hepatitis and problems associated with liver transplantation. By fulfilling the competencies of the gastroenterological curriculum, the Hepatologist would then be able to handle emergencies in Gastroenterology including variceal bleeding. This would be particularly relevant to the Malaysian scenario as hepatologists may be required to manage these conditions on their own in a referral hospital setting. Current logistic and manpower constraints considered , Hepatology training should preferably be a part of Gastroenterology training in the Malaysian context.

Abnormal Liver Function Tests

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SUMMARY

Most patients with liver disease have no symptoms. Those who present with jaundice may have progressed to advanced liver disease or have obstructive jaundice. Our first clue usually is an abnormal liver function test, which is a simple and non-invasive test. On looking at a liver function test, with its various components we are able to tease out a likely cause. Certain raised values point to hepatitis or cholestatic jaundice whilst the vast majority of patients have a 'mixed' picture. We will analyze in a stepwise fashion on how to use the liver function test and determine what may have caused these derangements in an individual patient.

Hepatitis and Pregnancy - The Do's and Dont's

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SUMMARY

Acute viral hepatitis is the most common cause of jaundice during pregnancy. In women with acute hepatitis A, B, C, or D, pregnancy does not worsen the course of hepatitis. HAV infection during 2nd & 3rd trimester of pregnancy is associated with a high rate of gestational complications and pre term labour. Hepatitis A vaccination and passive immunoglobulin are both considered safe in pregnancy. Breast feeding is safe in acute hepatitis A. Acute Hepatitis B in pregnancy is associated with low birth weight, prematurity and increased transmission rate with advanced pregnancy. Lamivudine improves the outcome of severe acute Hepatitis B. Hepatitis E is associated with abortions, stillbirth and neonatal death. There is evidence of vertical transmission and neonatal infection. More than 20% of pregnant women with Hepatitis E virus develop Fulminant Hepatic Failure especially in the 3rd trimester. Chronic hepatitis B viraemia increases significantly with elevation of ALT late in pregnancy and shortly after delivery. There is positive association between chronic HBV and gestational diabetes mellitus, antepartum haemorrhage, placenta previa and pre-term delivery. Risk factors for mother to child transmission include HBeAg +ve mothers, highly viremic mothers (>10⁸ copies /ml), intrauterine infection and preterm labour. All pregnant women should be screened for the presence of HBsAg. The children of the HBsAg +ve mothers should receive prophylaxis using HBIG and HBV vaccine. The HBIG and the 1st dose of vaccine should be administered within 12 hours of birth. Antiviral treatment should be considered in highly viraemic mothers during the last trimester. Lamivudine and Telbivudine use in late pregnancy have been shown to safely prevent HBV intra-uterine infection and mother to child transmission. HBV infected mothers who are on treatment before pregnancy should continue therapy with the least toxic agent and they should switch from interferon to nucleoside analogue. In chronic hepatitis C, the serum HCV RNA levels increase during the 2nd and 3rd trimester. However there is a significant reduction in mean ALT levels during pregnancy with a rebound in the post partum period. The overall rate of mother-to-child transmission for HCV is 1.7%. If the mother is known to be viremic, that is HCVRNA -positive, the rate is 4.3%. Co-infection with HIV increases the rate of mother -to- child transmission up to 19.4%. Risk factors for vertical transmission of HCV include a high viral load defined as at least 2.5x10⁶ copies /ml, HIV coinfection and invasive procedures. Both interferon and ribavarin are contraindicated during pregnancy. Breast feeding need not be avoided in HCV infection.