Results Six patients resolved HCV spontaneously (Resolvers), whilst six developed chronic infection (Chronics). At presentation, mean viraemia and ALT levels did not differ between Resolved and Chronic patients. In Resolvers HCV-RNA became undetectable at M3, which was then followed by ALT normalisation. Overall, Resolvers had higher proportions of total NKs than Chronics (p=0.023). Cytotoxic CD56dim NK cells were also higher in Resolvers (p=0.001), and became progressively predominant within their total NK pool, as shown by their progressive increase of the CD56dim/CD56bright ratio, which differentiated Resolvers from Chronics after M1 (p=0.01). In Chronic patients' cytotoxic CD56dim NK cells had, however, an overall greater expression of the cytotoxicity marker CD16 (p=0.008). Chronic patients also had higher proportions of both subsets of NK cells expressing the immunoinhibitory marker PD-1 (p=0.02), and stronger per-cell expression of the immunoinhibitory ligand PD-L1 on CD56dim NK cells (p=0.001). Analysis of clinical parameters revealed that in Resolvers the progressive increase of CD56dim/CD56bright ratio correlated with the decline of HCV-RNA over-time (r=−0.997, p=0.042), due to reduction of CD56bright (r=0.999, p=0.011) and expansion of CD56dim (r=−0.997, p=0.041). At M1, Resolvers' CD56dim were positively correlated with ALT (r=0.820, p=0.046).

Conclusion In patients with acute HCV infection the proportions and evolution of the two functionally distinct NK cell subsets differ in patients that resolve the infection compared to those who become chronically infected. A favourable outcome of infection is associated with the establishment of a defined NK profile, with predominance of CD56dim (cytotoxic) NK cells with low expression of the immunoinhibitory markers PD-1 and PD-L1, which may be linked to an improved early clearance of virus-infected hepatocytes, as shown by the correlation of this subset with serum HCV-RNA and ALT decline.

OP14 MEASUREMENT OF LOW DENSITY APOLIPOPROTEIN B ASSOCIATED HEPATITIS C VIRUS LIPOVIRAL PARTICLES IN GENOTYPE 1 INFECTION IS MORE CLINICALLY RELEVANT THAN TOTAL VIRAL LOAD

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Introduction The density of hepatitis C virus (HCV) in plasma is heterogeneous but the factors that influence this are poorly understood. Evidence from animal models and cell culture suggest that low-density apolipoprotein B (apoB)-associated HCV lipoviral particles (LVP) are more infectious than high density HCV.

Aim We measured HCV LVP in patients with chronic hepatitis C genotype 1 (CHC-G1) and examined metabolic determinants of LVP load and clinical correlates.

Method Fasting lipid profiles and HOMA-IR (homeostasis model assessment of insulin resistance) were determined in 51 CHC-G1 patients. LVP and non-LVP viral load were quantitated by real-time RT-PCR of plasma at density d<1.07 g/ml and d>1.07 g/ml, respectively, following iodixanol density gradient ultra-centrifugation. The LVP ratio was calculated using: LVP/(LVP+non-LVP)=LVP ratio.

Results The mean LVP ratio was 0.241 but varied 25-fold (0.029 to 0.74). When divided above and below the median value of 0.177, those with high LVP ratio had metabolic syndrome characteristics, higher liver stiffness and poorer early virological response rates (EVR) (see Abstract OP14 table 1).

Abstract OP14 Table 1 High vs low HCV LVP ratio—clinical and metabolic characteristics

	Low LVP ratio (n=25)	High LVP ratio (n=26)	p-value
Waist circum (cm)	85.7±11.1	92.7±12.2	0.037
Liver Stiffness (KPa)	9.53	19.54	0.001
Triglycerides mmol/l	1.08±0.46	1.62±0.15	0.015
HDL cholesterol mmol/l	1.36±0.33	1.11±0.25	0.015
TG/HDL ratio	0.84±0.4	1.62±1.1	0.003
HOMA IR	1.25±0.68	2.17±1.3	0.008
EVR (%)	31%	26%	0.037

Univariate analysis showed LVP ratio correlated with HOMA-IR (p=.004) and triglyceride (TG)/HDL-C ratio (p=0.004), but not with apoB. In multivariate analysis HOMA-IR was the main determinant of LVP load (log10 IU/ml) (p=0.037; R2=16.6%) but TG/HDL-C ratio was the strongest predictor of LVP ratio (p=0.019; R2=24.4%). Higher LVP ratios were associated with non-response to antiviral therapy (p=0.037) and with greater liver stiffness (p=0.001). There was no association between total viral load and host clinical and metabolic parameters.

Conclusion Measurement of HCV LVP is of more direct clinical relevance than total HCV viral load. Insulin resistance and associated dyslipidaemia are the major determinants of low-density apoB-associated LVP in fasting plasma. This provides a novel mechanism to explain why insulin resistance is associated with more rapidly progressive liver disease and poorer treatment outcomes.

Transplant

OP15 EARLY BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION: INCIDENCE, RISK FACTORS AND CENTRE EFFECT

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Introduction Although biliary disease is one of the most common complications of liver transplantation, its incidence and risk factors have not been previously determined in a large risk-adjusted analysis.

Method Using the United Kingdom and Ireland Liver Transplant Database, we sought to identify the incidence of and independent risk factors for early biliary complications (EBC, defined as the occurrence of a biliary tract leak, or stricture either of which required endoscopic, percutaneous or surgical intervention or culminated in graft loss within the first 3 months after transplantation) among 7044 adult, orthotopic, single-organ liver transplants between March 1994 and February 2007. Univariate and multivariable logistic regression models were fitted to examine the association between EBC and a wide range of recipient, donor and graft risk factors.

Results The incidence of EBC in the cohort was 8.5%, of which 5.2% were strictures and 4.7% were bile leaks. Multivariable analysis identified the following independent risk factors for EBC: lower donor-recipient age difference (per year, OR 0.99 p<0.003), lower pre-transplant serum albumin (per g/dL, OR 0.84 p<0.009), higher pre-transplant serum bilirubin (per mg/dl, OR 1.01 p<0.008), longer cold ischaemia time (per hour, OR 1.04 p=0.01), negative donor rhesus antigen (OR 1.39 p<0.003), higher donor haemoglobin (per g/dl, OR 1.05 p<0.03), presence of donor urinary tract infection (OR 2.63 p<0.04), use of live (vs brain-dead) donors (OR 5.89 p<0.005) and utilisation of biliary stent vs duct-to-duct reconstruction (OR 2.22 p<0.03). In addition, 5 of the 8 transplant centres in the UK and Ireland experienced a significantly higher adjusted risk of EBC compared to the centre with the lowest incidence, the ORs ranging between 1.48 (p<0.02) and 3.76 (p<0.001).

Conclusion This multi-centre analysis, the largest reported to date, has identified several novel recipient, donor and graft risk factors that could be utilised to stratify the risk of EBC among patients

undergoing liver transplantation. Significant variations exist among liver transplant centres in the risk of post-transplant biliary disease that cannot be accounted for by differences in recipient, donor or graft characteristics.

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Clinical hepatology

OP16 EVIDENCE FOR COMPARTMENTALISED ENDOTOXAEMIA AND ITS EFFECT ON NEUTROPHIL FUNCTION IN THE PORTAL CIRCULATION IN CIRRHOSIS

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Introduction Bacterial translocation and endotoxaemia are important in the pathogenesis of neutrophil dysfunction in cirrhosis. At present, it is not clear whether systemic endotoxaemia occurs as a consequence of a defect at the gut barrier interface or diminished hepatic function and associated portosystemic shunting.
Aim The aims of this study were (1) to quantify the degree of portal endotoxaemia and the contribution of the liver in the regulation of systemic endotoxin (ET) levels, (2) to determine intestinal production of cytokines and adhesion molecules and (3) to determine whether the portal and hepatic milieu modulates neutrophil function.
Method 12 patients with cirrhosis (54±3.2 yr, Pugh 10.2±1.0, eight male, four female) were studied prior to and 1-h after TIPSS insertion. Blood was sampled from the artery, hepatic vein (HV), portal vein (PV) and its tributaries. PV blood was sampled before insertion of the TIPSS. Endotoxin (ET) (LAL assay), LBP, BPI, IL-6, IL-10, TNFR55, TNFR75, sICAM and sELAM (using ELISA) were measured. Neutrophil respiratory burst and phagocytosis was measured using FACS in neutrophils derived from the HV and PV, prior to and following cross-incubation with PV and HV plasma, respectively.
Results TIPSS insertion resulted in a significant increase in arterial ET levels from 0.08±0.02 to 0.19±0.02 EU/ml (p=0.0001). Mean ET levels in the PV and HV pre-TIPSS insertion were 0.22±0.02 and 0.04±0.02 EU/ml respectively. Transintestinal (TI) and transhepatic (TH) ET fractional extraction (FE) rates were 2.7±0.7 and −0.5±0.06, respectively. HV neutrophil resting burst was significantly increased from 52±5.3 to 78±4.5% after incubation with PV plasma (p<0.0001). Conversely PV neutrophil resting burst was significantly reduced from 85±3.5 to 60±5.3% (p<0.0001) after incubation with HV plasma. Positive intestinal FE rates were observed most markedly with BPI, IL-6 and IL-10. Neutrophil phagocytosis was reduced post-TIPSS from 66±7.5 to 42±6.5% (p=0.0004) and resting burst increased from 62±5.6 to 87±2.8% (p=0.0001).
Conclusion This study provides direct evidence for portal endotoxaemia in cirrhosis. The data suggest that the liver is responsible for compartmentalising ET and associated neutrophil dysfunction within the portal circulation. Intestinal production of IL-6 and IL-10 was also demonstrated. TIPSS insertion disturbs this compartmentalisation and exposes the systemic circulation to portal endotoxaemia. Strategies to diminish portal endotoxaemia or enhance hepatic ET clearance capacity are important therapeutic targets to minimise neutrophil dysfunction in cirrhosis.

OP17 CLINICAL EFFECT OF ALBUMIN DIALYSIS IN PATIENTS WITH INTRACTABLE PRURITUS CORRELATES CLOSELY WITH CHANGES IN AUTOTAXIN ACTIVITY BUT NOT BILE SALT LEVELS

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Introduction About 5% of patients with severe cholestatic liver disease have intractable pruritus. Albumin dialysis is an effective treatment for these patients but the mechanism through which it reduces the severity of pruritus is not clear. Autotaxin (ATX) is a 125 kD protein which cleaves a choline group of lysophosphatidylcholine (LPC) thereby forming the biological active lysophosphatidic acid (LPA). Increased serum ATX activity has been described in patients with cholestatic pruritus (*Gastroenterology*, 2010; in press).
Aim The aim of the study was to determine the effect of albumin dialysis using molecular adsorbents recirculating system (MARS) on autotaxin activity and bile salts and their relationship to the severity of pruritus.
Method 15 patients (11F/4M, PBC 10, PSC 2, other 3) with severe pruritus that was resistant to medical therapy were treated in 31 sessions (each consisting of 3, 8-h treatments; median follow-up of 12.8 months) with MARS. The intensity and severity of itch was quantified using an itch severity scale (ISS) and the visual analogue scale (VAS) pre and post treatment and then weekly for up to 12 weeks. ATX activity was measured in diluted serum samples and albumin dialysate before and after MARS treatments using a fluorescence assay. ATX protein levels were determined by Western blotting. Bile salts were measured by LCMS.
Results MARS treatment was associated with immediate, significant and complete response (R) in 11 patients, two patients had a partial response (PR) and two patients had no response (NR). Median ATX activities were not different between responders and non-responders (R=216.5; NR=306.6). A mean reduction of ATX activity of 27.6±4.13% was seen in R, 10.7±10.3% in PR and 1.5±1.48% in NR. This change in ATX activity was directly correlated with the reduction in ISS (r2=0.59; p<0.005) and VAS (r^2=0.47; p<0.02). The change in serum ATX activity correlated closely with the change in serum ATX protein level (r^2=0.5; p<0.01). Expectedly, no ATX activity was measureable in the albumin dialysate. ATX levels returned to pre-treatment values with relapse of itching which occurred in all responders between 6 weeks and 4 months. No significant changes in serum bile salts were observed.
Conclusion Our study suggests an important role for ATX activity in modulating the severity of pruritus in cholestatic patients providing novel insights into the pathogenesis of itch in cholestatic disease. The reduction is not due to removal of circulating ATX into the dialysate suggesting that MARS treatment either reduces the production of ATX or enhances its hepatic clearance. Alternatively, or in addition, either a substrate or co-factor of ATX is extracted by the MARS system.

OP18 ABNORMAL LIVER HISTOLOGY IN PATIENTS TAKING METHOTREXATE CORRELATES POORLY WITH DOSAGE OR DURATION OF THERAPY AND REFLECTS ESTABLISHED RISK FACTORS FOR STEATOHEPATITIS

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Introduction Chronic liver injury has been described in patients taking low dose methotrexate (MTX) for psoriasis or rheumatological