parameters identified a high proportion of patients with subclinical evidence of liver injury. Supervised detoxification was completed in 170 patients.

Conclusion Alcohol related hospital admissions can be rapidly identified and managed by a dedicated specialist nursing team working in conjunction with hepatologists and acute physicians. Our cohort demonstrated strong links between poor socioeconomic status and early age of exposure to alcohol, age of regular alcohol misuse and long-term excessive drinking. We have now instituted formal screening of all hospital admissions in ED and MAU with direct electronic referral to the liaison service where alcohol misuse is a factor.

P27 REDUCTION IN ALANINE AMINOTRANSFERASE VALUES IN DIABETIC PATIENTS RECEIVING LONG-TERM ORAL ANTIBIOTICS: DOES MODULATION OF GUT FLORA AFFECT HEPATIC INFLAMMATION IN NON-ALCOHOLIC FATTY LIVER DISEASE?

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Introduction The gut microbiota may play a role in host metabolic processes and have been linked to the pathophysiology of non-alcoholic fatty liver disease (NAFLD). Murine studies have suggested beneficial effects of modulating the gut microbiota using antibiotics, however studies have not looked at the effect of long-term antibiotic therapy in humans.

Aim To investigate the effects of prolonged broad-spectrum antibiotics in patients attending the diabetic foot clinic who are likely to have NAFLD. It was hypothesised that long-term oral antibiotic administration would result in a decrease in serum alanine aminotransferase (ALT) values after 3 months compared to baseline.

Method 43 diabetic patients without known hepatic comorbidity, who had taken a minimum of 3 months' broad-spectrum oral antibiotics (predominantly co-amoxiclav) in the diabetic foot clinic were identified retrospectively. Demographic and clinical data were extracted from clinic letters, patient notes, and computer databases. The primary outcome measure was the change in ALT value at day 90 of antibiotics compared to day 0. Other outcome measures were a change in patient weight, glycosylated haemoglobin (HbA1c), white cell count, bilirubin and alkaline phosphatase at day 90 from day 0. The wilcoxon signed rank test was used for paired non-parametric data.

Results All patients with abnormal ALT at baseline (n=6) had a significant decrease in ALT from median 43 (41–48) U/l on day 0, to 32 (29–35) U/l on day 90 (p=0.03). 37 patients who had a normal ALT at baseline had a small but significant increase in ALT from median 17 (13–23) U/l on day 0, to 20 (14–28) U/l on day 90 (p=0.02). In the 20 patients with paired HbA1c values, there was a statistically significant decrease in HbA1c with antibiotic use (p=0.03). There were no significant associations in change in ALT at 90 days with weight change, white cell count, bilirubin, alkaline phosphatase, antibiotic regime or other medications.

Conclusion The robust decrease in ALT values in patients with abnormal baseline ALTs (and therefore likely to have NAFLD) provides indirect evidence that modulation of gut microbiota with oral antibiotics may reduce hepatic inflammation in NAFLD. The possibility of sepsis-induced liver damage accounting for the changes is countered by no change in white cell count, bilirubin or alkaline phosphatase, while reduction in HbA1c without weight change points to reduced insulin resistance. Prospective studies on patients with biopsy-proven non-alcoholic steatohepatitis are awaited.

P28 DEFECTIVE T-REGULATORY FUNCTION IN AUTOIMMUNE HEPATITIS MAY PARTIALLY DERIVE FROM A PRO-INFLAMMATORY SKEWING OF GAL9+T-REGS

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Introduction In autoimmune hepatitis (AIH) $CD4^+CD25^+$ regulatory T-cells (T-regs) are defective in their ability to control CD4 T-cell effector function. T-regs express Galectin9 (Gal9), a β-galactosidase-binding-protein that inhibits Th1-mediated immune-responses by binding the T-cell-immunoglobulin-and-mucin-domain3 (Tim-3) on CD4 effector cells. In AIH T-regs express reduced levels of Gal9.

Aim To characterise lineage-specific transcription factor and cytokine profiles of peripheral-blood-derived $Gal9^+$ T-regs in AIH.

Method 34 ANA/SMA+ patients (24 females; median age: 14.6 years) and 17 healthy subjects (HS, 12 females, median age: 29 years) were studied. The phenotype of circulating T-regs was determined by cytofluorimetry using CD4, CD25 and CD127 monoclonal antibodies. The frequency of cells positive for Gal9, FOXP3, T-bet, GATA3 and RORC and that of cells producing IFNγ, IL-10, TGF-β and IL-17 were determined by intracellular staining. T-reg suppressor function was evaluated in a proliferation assay following co-culture with $CD25^-Tim\text{-}3^+$ and $CD25^-Tim\text{-}3^-$ autologous target cells.

Results Within $Gal9^+$ cells the frequency of: (1) $FOXP3^+$ cells was lower in AIH than in HS (14.4±2 vs 42.8±3.1, p<0.001); (2) $T\text{-}bet^+$, $GATA3^+$ and $RORC^+$ cells was similar in AIH and HS; (3) IL-10-producing cells was lower in AIH than in HS (5.1±0.6 vs 9.1±0.5, p<0.001) but higher than in the $Gal9^-$ T-reg fraction for both (AIH: 5.1±0.6 vs 2.3±0.2, p=0.001; HS: 9.1±0.5 vs 3.3±0.4, p<0.001); (4) TGF-β-producing cells was lower in AIH than in HS (6.4±0.7 vs 8.1±0.4, p=0.04); (5) IFNγ- and IL-17-producing cells was higher in AIH than in HS (IFNγ: 4.4±0.6 vs 2.1±0.3, p=0.002; IL-17: 4.1±0.6 vs 1.8±0.2, p=0.002). Treatment with anti-IL-10 neutralising antibodies reduced T-reg ability to suppress $CD25^-Tim\text{-}3^+$ cell proliferation (AIH: 42% inhibition in the absence of antibodies vs 36% in their presence, p=0.06; HS: 56% vs 48%, p=0.04), while did not affect $CD25^-Tim\text{-}3^-$ cell proliferation.

Conclusion A skewing towards a pro-inflammatory phenotype and a reduced proportion of $FOXP3^+$ and IL-10-producing cells within $Gal9^+$ T-regs may contribute to defective immunoregulation in AIH. The reduction of $Gal9^+$T-reg suppression following anti-IL-10 blockade both in health and AIH, suggests a role for IL-10 in $Gal9^+$T-cell immune-regulatory function.

P29 REDUCED EXPRESSION OF TIM-3 RENDERS TH1 AND TH17 EFFECTOR CELLS LESS AMENABLE TO T-REG CONTROL IN AUTOIMMUNE HEPATITIS

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Introduction In autoimmune hepatitis (AIH), CD4 effector immune responses are permitted by defective $CD4^+CD25^+$ regulatory T-cells (T-regs). In murine studies apoptosis of Th1 effector cells is mediated by binding of T-cell-immunoglobulin-and-mucin-domain3 (Tim-3) on their surface to Galectin-9 (Gal9) expressed by T-regs. In AIH, Tim-3 is down-modulated on CD4 effector cells.

Aim To test the frequency of $Tim\text{-}3^+$ cells within the Th1, Th2 and Th17 subsets and to evaluate whether Tim-3 expression by CD4 effectors affects their responsiveness to T-reg control.

Method 39 ANA/SMA$^+$ patients (23 females; median age: 13.9 years) and 16 healthy subjects (HS, 12 females; median age: 29.5 years) were studied. Cell phenotype was determined by cytofluorimetry using monoclonal antibodies to CD4, CD25 and TIM3. The frequency of cells positive for T-bet, GATA3 and RORC, transcription factors defining Th1, Th2 and Th17 cell subsets, was determined by intracellular staining. Proliferation of CD25$^-$, CD25$^-$Tim-3$^+$ and CD25$^-$Tim-3$^-$ target cells was assessed by ^{3}H-thymidine incorporation after 5-day co-culture with T-regs.

Results The frequency of Tim-3$^+$ cells within the Th1 and the Th17 subsets was lower in AIH than in HS (Th1: 5.1±0.7 vs 13.6±1.7, p<0.001; Th17: 3.9±0.3 vs 8.2±1.1, p=0.02), while there was no difference for Th2 cells. In AIH, there was a negative correlation between the frequency of Tim-3$^+$ cells and AST levels (r= −0.47, p=0.002) and a positive correlation between the frequency of T-bet$^+$ cells and AST levels (r=0.69, p<0.01). Addition of T-regs reduced cell proliferation by 26% (p=NS) in AIH and by 53% (p=0.007) in HS when undivided CD25$^-$ cells were used as targets; by 23% (p=NS) and by 25% (p=NS) when Tim-3$^-$ cells were the targets and by 47% (p=0.03) and by 62% (p=0.001) when the targets were Tim-3$^+$ cells.

Conclusion In AIH, reduced frequency of Tim-3 within the Th1 and Th17 effector cell subsets renders them less prone to T-reg control, CD4 effector cell proliferation depending on the expression of Tim-3. T-bet expression characterises effector T-cells likely to mediate liver damage in AIH.

P30 LUNG INJURY AND ITS PROGNOSTIC SIGNIFICANCE IN ACUTE LIVER FAILURE

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Introduction Acute liver failure (ALF) is a multi system illness. Data on the incidence and outcome of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) complicating ALF is scant[1]. We analysed radiological, gas exchange and ventilator data of consecutive patients admitted with ALF/subacute liver failure (SALF) to a tertiary liver intensive therapy unit (LITU).

Aim The main objective of this assessment was to identify the incidence of ALI/ARDS in ALF/SALF and the impact it has on outcome.

Method All patients with ALF/SALF receiving mechanical ventilation who were admitted between January 2007 and February 2011 were included. Patients were categorised according to the ARDS network consensus definition as: No lung injury present (NALI), ALI (P/F <300 mm Hg) and ARDS (P/F <200 mm Hg). Chest radiographs were independently assessed by two observers for the presence of bilateral infiltrates. Absence of left atrial pressure elevation was based on haemodynamic and echocardiographic assessment.

Results 146 (M: F 71:75) patients with ALF/SALF were studied. 31 patients (21%) fulfilled ARDS network criteria, 14 ARDS (9.6%), 17 ALI (11.6%), within the first 72 h following LITU admission. ARDS patients required higher levels of positive end expiratory pressure (10 vs 6 ALI and 7cmH_2O NALI, p=0.016) and had a worse oxygenation index (10.7 vs 4.3 ALI, 4.5 NALI, p≤0.001). There was a trend towards reduced compliance of the respiratory system in ARDS and ALI patients (p=0.07 vs NALI) and an increased number of ventilator days (NALI 10d, ALI 12d, ARDS 17d). Duration of LITU stay (p=0.175) and survival (p=0.877) were not affected by the presence of ALI/ARDS. Type of liver disease presentation ALF/SALF, poor prognostic markers of liver failure, that is, lactate, INR, bilirubin, presence of encephalopathy and intracranial hypertension did not correlate with lung injury presentation. Also no association with inotrope requirements (p=0.495), need for extracorporeal renal support (p=0.565) and severity of organ failure scores was found.

Conclusion The incidence of lung injury is relatively low in ALF of mixed aetiology. Less than 10% of patients fulfilled ARDS criteria. Overall presence of ALI/ARDS appeared to have a limited impact on outcome.

REFERENCE

1. **Baudouin SV,** *et al*. ALI in FHF following paracetamol poisoning. *Thorax* 1995; **50**:399–402.

P31 PREDICTORS OF FLUID RESPONSIVENESS IN PATIENTS WITH ACUTE LIVER FAILURE

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Introduction Profound haemodynamic changes are invariably seen in ALF and resemble those found in later stages of septic shock. Vasopressor support is frequently required and in discriminatory fluid resuscitation can worsen intracranial hypertension (ICH) and lung injury. Markers of preload dependency have thus far not been studied in this patient group and response to dynamic manoeuvres such as passive leg raising or end expiratory hold cannot be considered safe in this population due to the high incidence of ICH.

Method Patients admitted to a tertiary referral specialist ICU with ALF. All patients were in vasoplegic shock, requiring multiorgan support including controlled mechanical ventilation. Cardiac output monitoring via transpulmonary thermodilution (TPTD) and pulse contour analysis (PiCCO_, Pulsion Munich) was performed. Markers of fluid responsiveness were compared between responders (CI≥15%) and non-responders to a colloid fluid challenge (5 ml/kg IBW). All patients had a transthoracic echocardiogram (TTE) performed before and after fluid administration. The predictive capacity of stroke volume—pulse pressure variation (SVV, PPV) and respiratory change in peak aortic velocity (DV peak) for preload dependency was analysed.

Results 26 patients (mean age 40 (13), 15 M: 11 F,) with mixed aetiology ALF were assessed. The mean APACHE II score was 23 (4) and mean SOFA 15 (2). Change in CI and SVI were closely correlated (R=0.726, p<0.001). There was no difference between those defined as responders using a cut-off of CI or SVI of 10%. When using 15%, 7 patients would have been classified differently. Intraclass correlation coefficient (ICC) for CI and SVI change was 0.83 (0.62–0.92), confirmed using Pasing & Blakock regression (A= −0.278, −0.88 to 0.16, B=1.26, 0.88 to 1.72) suggesting haemodynamic changes in both measures are interchangeable. Using a cut-off of a change in CI of 15% only PPV predicted fluid responsiveness (AUROC 0.79, 0.58–0.93, p=0.005, cut-off >9%, sensitivity 75%, specificity 62%). SVV weakly predicted fluid responsiveness in this cohort (AUROC 0.73, 0.52–0.87, p=0.005, cut-off >11%), While there was a trend towards reduction in DV peak (mean difference −3%, p=0.080) this was not different between those defined as fluid responders by CI (Repeated measures ANOVA p=0.124) and AVV prior to fluid bolus did not predict a CI response (AUROC 0.637, 0.413–825, p=0.322).

Conclusion Baseline PiCCO parameters predict fluid responsiveness but the respiratory variability in DV peak did not predict a CI response to fluid bolus in this cohort of ALF patients. PPV may be a more suitable PiCCO index for assessing fluid requirements in patients with ALF than SVV.