



# Dansk Selskab for Gastroenterologi og Hepatologi

**Danish Society for Gastroenterology and Hepatology**

3. årsmøde

5.- 6. september 2014

på

Hindsgavl Slot



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## DSGH Årsmøde, Hindsgavl Slot 5-6 sept. 2014

Tidspunkt	Aktivitet/Sted
<i>FREDAG 5. sept.</i>	<b>Tranesalen</b>
09.30-10.00	<b>Registrering og kaffe</b>
10.00-10.15	<b>Velkomst, prisuddeling</b>
10.15-11.00	<b>Mavetarmkanalens mikroflora og glucosemetabolisme</b> <b>Filip Knop</b> <i>Chairman: Lars Vinter-Jensen</i>
11.00-12.00	<b>Nyt indenfor endoskopi</b> <b>Confocal Laser endomicroscopy, John G Karstensen</b> <b>HALO, Michael H Larsen</b> <b>Spy Glass, Søren Meisner</b> <b>Den endoskoperende sygeplejerske</b> <b>Karin Larsen, Lisbeth Laursen</b> <i>Chairman: Lasse Bremholm</i>
12.00-12.45	<b>Posterpræsentation (walk and talk)</b> <i>Chairmen: Henriette Ytting, Niels Kristian Aagaard, Alexander Krag, Søren Peter Jørgensen, Søren Schou Olesen</i>
12.45-13.45	<b>Frokost og besøg på udstilling</b>
13.45-14.45	<b>Drug Induced Liver Disease</b> <b>State of the art</b> <b>Professor Einar S Björnsson</b> <i>Chairman: Henning Grønbæk</i>
14.45-15.15	<b>Posterpræsentation (walk and talk)</b> <i>Chairmen: Som ved session 1</i>
15.15-16.00	<b>Kaffe og besøg på udstilling</b>
16.00-17.30	<b>Foredragskonkurrence</b> <i>Chairman: Henning Grønbæk, Mark Ainsworth</i>
17.30-17.40	<b>Ny dansk IBD database</b> <b>Niels Thorsgaard</b>
17.30-18.00	<b>DSGH generalforsamling</b>
19.00-	<b>Fest</b> <i>Band: Partyzone</i>
<i>LØRDAG 6 sept.</i>	
09.30-09.50	<b>Guideline APP</b> <b>Lasse Bremholm</b>
09.50-10.00	Pause m. Kaffe
10.00-12.00	<b>Diskussion af guidelines</b> <b>Cøliaki: diagnostik, behandling og kontrol</b> <b>Autoimmun hepatitis</b> <b>Diagnostik og behandling af kronisk pancreatitis</b> <b>Behandling af kronisk obstipation hos voksne</b> <i>Chairman Anette Mertz</i>
12.00	Frokost (sandwich), afrejse.

# Foredrag

1)

## **Risk factors on the development of new-onset gastroesophageal reflux symptoms. A population-based prospective cohort study: the HUNT study**

Andreas Hallan, Maria Bomme, Kristian Hveem\*, Jane Møller-Hansen, Eivind Ness-Jensen\*. *Dept. Medical Gastroenterology S, Odense University Hospital, \*HUNT Research Centre, Norwegian University of Science and Technology, Trondheim.*

**INTRODUCTION:** Gastroesophageal reflux disease (GERD) is highly prevalent in the western world and the incidence is increasing. This study aimed to investigate the risk factors of new-onset gastroesophageal reflux symptoms (GERS).

**METHODS:** The study was based on the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted from 1995–1997 to 2006–2009 in Nord-Trøndelag County, Norway. All inhabitants of the county from 20 years and above were invited. Association between risk factors and new-onset GERS were examined using logistic regression, providing odds ratios (OR) with 95% confidence intervals (CI).

**RESULTS:** 29,610 individuals (61% response rate) reported their degree of heartburn or acid regurgitation at baseline and follow-up. Participants reporting no complaints at baseline and severe complaints at follow-up ( $n=510$ ) were defined as having new-onset GERS, and compared to participants reporting no complaints at baseline and follow-up ( $n=14,406$ ). New-onset GERS was associated with increasing age (OR 1.01, 95%CI 1.01–1.02) and low education (OR 1.51, 95%CI 1.22–1.87). Education had a stronger influence on the risk of new-onset GERS among the younger than the old. New-onset GERS was dose-dependently associated with weight gain during follow-up (OR 1.31 per unit increase in BMI, 95%CI 1.26–1.37), irrespective of baseline weight. Stratification showed smoking cessation to be associated with new-onset GERS (OR 1.53, 95% CI 1.19–1.97), among those who gained weight upon quitting.

**CONCLUSIONS:** New-onset GERS were associated with; increasing age, low education and weight gain during follow-up. Smoking cessation was associated with new-onset GERS among those who gained weight upon quitting.

2)

## **Macrophage activation marker soluble CD163 is independently associated with liver inflammation and fibrosis in patients with non-alcoholic fatty liver disease**

Konstantin Kazankov<sup>1</sup>, Francisco Barrera<sup>2</sup>, Holger Jon Møller<sup>3</sup>, Saeed Esmaili<sup>2</sup>, Hendrik Vilstrup<sup>1</sup>, Jacob George<sup>2</sup>, Henning Grønbaek<sup>1</sup>

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**Background:** Macrophages play an important role in non-alcoholic fatty liver disease (NAFLD) and development of steatohepatitis (NASH) and liver fibrosis. Soluble (s)CD163 is a specific

macrophage activation marker and we hypothesized to find elevated sCD163 levels in association with disease severity and a good predictive capability of sCD163 in NAFLD/NASH.

**Methods:** sCD163 associations with biochemical and histological parameters of NAFLD severity were investigated in 171 and validated in 174 NAFLD/NASH patients. Data were assembled at the time of liver biopsy and sCD163 measured by ELISA.

**Results:** sCD163 increased in parallel with the NAFLD Activity Score (NAS) and Kleiner fibrosis score in both the estimation and validation cohorts. In the estimation cohort, sCD163 was higher in patients with  $NAS \geq 5$  compared to those with  $NAS < 5$  (3.8 (2.8–5.3) vs. 2.5 (1.9–3.4) mg/L,  $p < 0.001$ ) and in patients with  $F \geq 3$  compared to lower fibrosis stages (4.1 (3.2–4.7) vs. 2.5 (1.9–3.0) mg/L,  $p < 0.001$ ). Multivariate analysis demonstrated independent associations of sCD163 with inflammation and fibrosis in both cohorts. sCD163-based NASH score could accurately predict severe necroinflammation ( $NAS \geq 5$ ) (Estimation: AUROC 0.82 (95% CI: 0.74–0.90), Validation: 0.75 (95% CI: 0.66–0.84)). Similarly, sCD163-based fibrosis score showed excellent accuracy for advanced fibrosis ( $F \geq 3$ ) (Estimation: AUROC 0.85 (95% CI: 0.78–0.92), Validation: 0.83 (95% CI: 0.75–0.90)).

**Conclusion:** Soluble CD163 is increased in association with NAFLD severity, reflecting macrophage activation in NAFLD/NASH patients, and sCD163 is independently associated with liver inflammation and fibrosis. Further, sCD163-based models show very good accuracy for advanced disease in NAFLD patients.

3)

### **Profermin® is efficacious in patients with active ulcerative colitis – a randomised controlled trial**

Aleksander Krag<sup>1</sup>, Pia Munkholm<sup>2</sup>, Hans Israelsen<sup>3</sup>, Bjørn von Ryberg<sup>3</sup>, Klaus K Andersen<sup>4</sup>, Flemming Bendtsen<sup>5</sup>

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**Background:** Profermin® is developed for the dietary management of ulcerative colitis (UC). It consists of water, fermented oats, barley malt, lecithin and *Lactobacillus plantarum* 299v. The aim of this study was to assess the clinical efficacy of Profermin®.

**Methods:** 74 patients with a mild to moderate flare-up of UC (defined as Simple Clinical Colitis Activity Index (SCCAI) score  $\geq 5$  and  $\leq 11$ ) were randomly assigned to Profermin® (n=32) or Fresubin® (n=41). The primary endpoint was to assess whether addition of Profermin® in UC could significantly reduce SCCAI in comparison with Fresubin®.

**Results:** In the run in period the mean SCCAI was  $7.2 \pm 1.50$  in the Profermin® group and  $7.6 \pm 1.47$  in the Fresubin® group, NS. After 8 weeks treatment, the mean reduction of SCCAI score was higher in the Profermin® group, mean difference -1.77 SCCAI, 95% confidence interval (CI) (-2.97;-0.55),  $p < 0.005$ , in intention to treat analyses. Remission defined as  $SCCAI \leq 2.5$  was achieved in 10/32 (31 %) in the Profermin® group and in 6/41 (15 %) in the Fresubin® group,  $p = 0.048$ . The decrease in SCCAI scores of 50% or more was higher in the Profermin® group 17/32 (53%) vs. 11/41 (27%),  $p = 0.04$ . The risk of dropping out due to treatment failure/lack of effect was higher in the Fresubin® group 42% vs. 13%,  $p = 0.02$ .

**Conclusion:** Supplementation with Profermin® is safe, well tolerated, palatable and able to reduce SCCAI scores at a statistically and clinically significant level in patients with mild-to-moderate UC with a flare-up.

4)

#### **Markers of Collagen Remodeling Detect Clinically Significant Fibrosis in Chronic Hepatitis C Patients**

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**Background:** A Metavir Fibrosis stage F<sub>≥2</sub> is considered clinically significant for progressive liver disease and represents a threshold for antiviral treatment.

**Aim:** To assess the diagnostic value of novel serological extracellular matrix (ECM) protein fragments as potential biomarkers for clinically significant fibrosis.

**Methods:** C1M, C3M, C4M, C6M (MMP degraded type I, III, IV and VI collagen), Pro-C3 and P4NP7S (type III and IV collagen formation) specific protein fragments were assessed in plasma from 403 chronic hepatitis C (HCV) patients by specific ELISAs. Patients were stratified according to Metavir Fibrosis stage; F0 (n=46), F1 (n=161), F2 (n=95), F3 (n=44) and F4 (n=33) based on liver biopsy.

**Results:** Pro-C3 was significantly elevated in patients with significant fibrosis (≥F<sub>2</sub>) compared to F0-F1 (p<0.05), while the markers C3M, C4M, C6M and P4NP7S were significantly elevated in patients with ≥F<sub>3</sub> compared to F0-F2 (p<0.05). C1M showed no difference between fibrosis stages. Using Receiver Operating Characteristics analysis, the best markers for separation of ≥F<sub>2</sub> from F0-F1 were Pro-C3 and C4M (AUC=0.75 AUC=0.57). Combination of Pro-C3 and C4M with age, BMI and gender in a multiple ordered logistic regression model improved the diagnostic value for separating ≥F<sub>2</sub> from F0-F1 (AUC=0.80, p<0.0001). Similarly, the model could identify HCV patients with ≥F<sub>1</sub> compared to F0 (p<0.0001).

**Conclusion:** The Pro-C3 protein fragment provided clinically relevant diagnostic accuracy as a single marker of liver fibrosis. A model combining Pro-C3 and C4M along with patient's age, BMI and gender increased the diagnostic power for identifying clinically significant fibrosis.

5)

**Measurement of fecal calprotectin in ulcerative colitis: Association with Ulcerative Colitis Endoscopic Index of Severity, Mayo Endoscopic Score and histological inflammatory activity score**

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<sup>1</sup>*Gastrounit, Medical Division,* <sup>2</sup>*Department of Pathology, Copenhagen University Hospital Hvidovre, Denmark*

**INTRODUCTION:** Mucosal healing in ulcerative colitis (UC) has emerged as a treatment goal because mucosal healing leads to decreased risk of relapse and colectomy. Therefore, reliable non-invasive methods to assess the grade of inflammation and mucosal healing need to be developed. In this study we evaluate the correlation between fecal calprotectin (FC) and two endoscopic score modalities as well as histological inflammatory activity score.

**AIMS & METHODS:** In a prospective, cross-sectional study, 120 patients including subjects with both clinically active and inactive UC underwent sigmoidoscopy. Mayo Endoscopic Score (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) were used to evaluate the endoscopic inflammation. Rectal biopsies were evaluated for the grade of inflammation using a histological activity score with 4 categories based on the extent of cryptitis, crypt abscesses and the presence of erosions/ulcers.

**RESULTS:** The median age was 36 years, 58% were female and the median disease duration was 4.6 years. 32 (27 %) had endoscopic remission. We found a significant difference in FC between the MES-groups (0-3) ( $p < 0.0001$ ) and in FC between the histological groups ( $p < 0.0001$ ). Using linear regression, we found a significant relationship between FC and UCEIS ( $p < 0.0001$ ). Specifically, we found a significant difference in FC between MES=0 and MES=1 (median 87 mg/kg vs. 720 mg/kg,  $p < 0.0001$ ) as well as between UCEIS=3 and UCEIS=4 (median 71 mg/kg vs. 997 mg/kg,  $p < 0.034$ )

**CONCLUSION:** We compared FC with MES, UCEIS and histological inflammatory activity score and in all cases significant correlations were demonstrated. Especially, we found that FC is able to discriminate between MES 0 and 1 as well as between UCEIS 3 and 4, an important message regarding the evaluation of mucosal healing. Studies comparing FC with UCEIS and histological inflammation are lacking but in our study significant correlation between both of them were found.

6)

**No improvement in survival of Danish alcoholic liver disease patients since 1996: A nationwide study**

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**Background:** One in 500 Danish citizens suffer from alcoholic liver disease (ALD), so its prognosis has considerable implications for public health. Therefore, we examined time-trends in survival of Danish ALD patients diagnosed in 1996–2010.

**Methods:** We used nationwide health-care registries to identify all Danish ALD patients diagnosed in three periods: 1996–2000 (follow-up through 2001), 2001–2005 (follow-up through 2006), and 2006–2010 (follow-up through 2011). We compared the survival in each period by computing Kaplan-Meier curves and used Cox regression to compute hazard ratios (HRs) adjusted for age,

gender, ALD diagnosis, and comorbidity. A hospital contact for an alcohol disorder in the year after ALD diagnosis was used as a marker of continued alcohol intake.

**Results:** We included 24,885 patients (68% men). Patients' 1-year survival worsened from 74% (95% CI: 73–75) in 1996–2000, over 72% in 2001–2005, to 70% (95% CI: 69–71) in 2006–2010. Patients diagnosed with ALD in the later periods were older, had more comorbid diseases, and a higher prevalence of cirrhosis. After adjustment for these confounding factors we found no change in survival; the adjusted HRs for patients diagnosed in 1996–2000, 2001–2005, and 2006–2010 were 1.00 (reference), 1.01 (95% CI: 0.96–1.05), and 0.99 (95% CI: 0.95–1.04), respectively. However, during the study period, an increasing number of ALD patients continued their alcohol intake.

**Conclusion:** The survival of Danish ALD patients has not improved in 1996–2011. Stronger efforts to reduce alcohol consumption after ALD diagnosis are necessary.

7)

### **Establishment of human miniguts derived from human adult stem cells**

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**Background:** We have for several years been able to grow intestinal epithelial cells from humans in short term cultures at our laboratory. This is a powerful tool to examine simple immunological responses in epithelial cells, but due to low viability of the cultures, this model is unsuitable for the examination of processes like cell proliferation, cell differentiation and cell death. The aim was therefore to establish long term epithelial cell cultures derived from epithelial cells isolated from endoscopically obtained biopsies.

**Methods:** Stably transfected Wnt-3a producing fibroblast cell lines and R-Spondin1 producing HEK293 cells were grown to produce Wnt-3a/R-spondin1 conditioned DMEM media. This media was enriched with the growth factors Noggin, epidermal growth factor (EGF) and the p38 mitogen activated protein kinase (MAPK) inhibitor SB201290. The epithelium was isolated from standard colonic mucosal biopsies from control subjects by chelation and embedded in a 3D Matrigel (a basal membrane-like collagen gel; Invitrogen) gel. This gel was covered with the growth media, and the cells were grown at 37° C and 5% CO<sub>2</sub>.

**Results:** We were able to establish long term epithelial cell cultures viable for > 6 months. These cultures formed minigut-like structures: up to approx 1000 µM spheric structures (“organoids”) with surface epithelium and crypts with normal differentiation. Differentiation could be inhibited by adding inhibitors of transforming growth factor β1 signalling. The cultures could be passed every 2 weeks and expanded.

**Conclusion:** We have established a stem cell culture system of non-transformed human miniguts to be used for future experiments where carcinoma derived cell lines would otherwise have been used. This model is closer to the *in vivo* condition than models based on neoplastic cell lines. The technique is proposed to be usable in regenerative medicine in inflammatory bowel disease in the future.

# Posters

1)

## **Plasma Pro-C3 (N-terminal type III collagen propeptide) as marker of fibrosis progression in chronic hepatitis C**

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**Background & Aims:** Fibrogenesis results in release of certain extracellular matrix protein fragments into the circulation. We evaluated the diagnostic and prognostic performance of two novel serological markers, the precisely cleaved N-terminal propeptide of type III collagen (Pro-C3) and a peptide of helical collagen type III degradation (C3M), in chronic hepatitis C (CHC) patients.

**Methods:** Pro-C3 and C3M were measured by ELISA in plasma from CHC patients (n=194) from a prior phase II antifibrotic trial (NCT00244751). Plasma samples and paired liver biopsies were obtained at baseline and after 1-year. Patients were stratified according to Ishak stages 2-4. Internal cross-validation was performed by bootstrap analysis.

**Results:** Pro-C3 levels were significantly higher in CHC patients in Ishak stage 4 compared to stage 3 (p<0.05) or 2 (p<0.05). Pro-C3 could significantly distinguish moderate (stage 4) from mild fibrosis (stage 2/3) (AUC=0.72, p<0.001). Importantly, an overall significance in Pro-C3 (p=0.001) and C3M (p=0.025) levels was observed between the groups of -1, 0, +1 and +2 change in Ishak stage at 12 months. Pro-C3 was significantly increased in group +1 (p=0.012) and +2 (p=0.034) compared to group 0. C3M was significantly increased in group +2 compared to group 0 (p=0.049) and +1 (p=0.0103). In multivariate analysis, only baseline Pro-C3, but not FibroTest, had an independent association with fibrosis progression.

**Conclusions:** Pro-C3 is a useful test to predict fibrogenesis and monitor disease progression. Moreover, it could differentiate mild from moderate disease. Pro-C3 may become a promising blood parameter to assess the efficacy of antifibrotic therapies.

2)

## **Ciprofloxacin and Non-pathogenic *Escherichia coli* Nissle add-on treatment in active Ulcerative Colitis; a double-blind randomized placebo controlled clinical trial**

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<sup>a</sup>Department of Gastroenterology, Hvidovre University Hospital, Copenhagen, Denmark,

<sup>b</sup>Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark

**Background and aim:** Ulcerative colitis (UC) is a chronic inflammatory bowel disease. Current available treatments will often induce and maintain remission, however, without removing a continuous risk of disease flares and in some cases need for surgery. As a possible remission sustaining treatment, manipulation of the bacterial flora has been studied using the probiotic bacterium *Escherichia coli* Nissle 1917 (EcN). It has been shown in UC patients that treatment with EcN is equally as efficient in maintaining remission as the standard treatment with mesalazine. Furthermore, treatment with antibiotics such as ciprofloxacin has documented some, but not long-lasting, effect in UC. Our aim was, therefore, to test the effect of ciprofloxacin and/or EcN as add-on to conventional therapies in patients with active UC.

**Patients and methods:** Our single center double-blinded randomized placebo controlled study included patients with active UC with a Colitis Activity Index (CAI) score of at least 6. Patients were randomized to one of four treatment arms: ciprofloxacin-EcN, ciprofloxacin-placebo, placebo-EcN or placebo-placebo. Ciprofloxacin/placebo was given for 1 week, followed by EcN/placebo for 7 weeks. All treatments were given as add-on treatments.

**Results:** One hundred subjects with active ulcerative colitis were recruited for the study. Overall, in the two groups receiving EcN (cipro/EcN and placebo/EcN) fewer patients reached remission than in both groups receiving placebo instead of EcN (cipro/placebo and placebo/placebo), this difference was found to be statistically significant in an intention-to-treat analysis,  $p < 0.02$ . In the per-protocol analysis we, surprisingly, found that it was only the group receiving placebo/EcN that did significantly worse compared to the group receiving placebo/placebo,  $p < 0.05$ . Furthermore, the group receiving placebo/EcN had the largest number of withdrawals, 11 of 25 (44 %), compared to 15 of 75 (20 %) in any of the other groups,  $p < 0.05$ .

**Conclusions:** Our data suggest that there is no benefit in the use of *E. coli* Nissle as an add-on treatment to conventional therapies for active ulcerative colitis, and that treatment with *E. coli* Nissle without a previous antibiotic cure may even worsen the outcome in these patients.

3)

### **Time since last drug exposure in pregnancy determines Adalimumab and Infliximab levels in neonates (ERA study)**

Mette Julsgaard\*<sup>1,2</sup>, Lisbet A. Christensen<sup>1</sup>, Peter R. Gibson<sup>3</sup>, Jan Fallingborg<sup>4</sup>, Richard Gearry<sup>5</sup>, Alissa Walsh<sup>6</sup>, Jens Kjeldsen<sup>7</sup>, William Connell<sup>2</sup>, Miles P. Sparrow<sup>3</sup>, Graham Radford-Smith<sup>8</sup>, Jane M. Andrews<sup>9</sup>, Susan J. Connor<sup>10</sup>, Ian Lawrence<sup>11</sup>, Signe Wildt<sup>12</sup>, Gregory T. Moore<sup>13</sup>, Lise Svenningsen<sup>14</sup>, Ourania Rosella<sup>3</sup>, Anne Grosen<sup>1</sup>, Sally J. Bell<sup>2</sup>

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**Background:** Recent studies suggest no adverse pregnancy outcomes in babies exposed to anti TNF antibodies (ATA). However, the long term implications are unknown. Current guidelines suggest cessation of treatment in the last trimester of pregnancy to reduce fetal exposure but this is difficult for women with IBD who are not in deep remission, as active disease is a greater risk for adverse pregnancy outcome. This study aimed to examine drug levels of ATA in cord blood of newborns exposed to ATA in pregnancy, and to correlate these with maternal levels, the duration of therapy during pregnancy, and time to clearance of ATA in infants.

**Methods:** Women with IBD exposed to infliximab (IFX) or adalimumab (ADA) during pregnancy were included from 2012-present at 14 hospitals in Australia, New Zealand and Denmark. ATA levels were measured using an ELISA in cord and maternal blood at delivery (Matriks Biotek). If positive at birth, the infants were tested every third month until ATA were undetectable. Demographics, disease phenotype, disease activity in pregnancy, duration of ATA use in pregnancy, medication and pregnancy outcomes were prospectively collected by questionnaire and from the treating doctor.

**Results:** 80 pregnant women have been enrolled, and so far 53 mother-baby pairs have been tested (27 IFX and 26 ADA). An inverse correlation between duration since last exposure and cord ATA levels at birth was found (IFX:  $r = -0.58$ ,  $p = 0.002$ ; ADA:  $r = -0.42$ ,  $p = 0.047$ ). This was also the case for maternal levels at birth (IFX:  $r = -0.59$ ,  $p = 0.002$ ; ADA:  $r = -0.52$ ,  $p = 0.01$ ). There was a strong correlation between cord blood and maternal levels at delivery (IFX: Pearson's  $r = 0.80$ ,  $p < 0.0001$ ; ADA:  $r = 0.80$ ,  $p < 0.0001$ ). Drug was ceased prior to gestational week (GW) 30 in 15 (28%) women. In them, mean serum concentrations were 0.81  $\mu\text{g/ml}$  (IFX) and 0.08  $\mu\text{g/ml}$  (ADA), and the cord blood level at delivery was  $< 3 \mu\text{g/ml}$  in 11/15 (73%). So far 30 babies have completed testing for detectable ATA levels, and testing is ongoing in the remaining 23 babies. Complete clearance of ATA was seen in 7, 5, 12 and 6 babies at birth, by 3, 6 and 9 months, respectively. To date there has been one detectable ATA level at 9 months. Three women (5.7%) gave birth preterm (GW 33-35). No congenital malformations were detected and all babies are developing normally.

**Conclusion:** Maternal and neonatal ATA levels were inversely correlated with the duration since last exposure. Cord blood ATA levels were strongly correlated with maternal level at delivery. Maternal cessation of ATA prior to week 30 successfully reduced fetal exposure to drug in the vast majority of cases. Follow up will determine whether high neonatal levels have any negative consequences.

4)

#### **The macrophage activation marker soluble CD163 is associated with the severity of NAFLD in morbidly obese patients and normalized by bariatric surgery**

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**Background and aims:** Macrophages play an important role in non-alcoholic fatty liver disease (NAFLD). Blood soluble CD163 (sCD163) is a marker of macrophage activation, and we aimed to measure it in morbidly obese patients with varying degrees of NAFLD before and after bariatric surgery (BS).

**Methods:** Demographical, clinical and biochemical data of 196 patients were collected preoperatively and 3, 6 and 12 months after BS leading to significant weight loss. We secured perioperative liver biopsies for histological NAFLD Activity Score (NAS), and in a subset of patients, CD163 immunohistochemistry and real-time quantitative PCR for CD163 mRNA were performed. Plasma sCD163 was measured by ELISA.

**Results:** Patients with  $NAS \geq 5$  had higher sCD163 than those with  $NAS < 5$  (2.4(2.0–3.1) vs 1.9(1.5–2.3) mg/L,  $p < 0.001$ ). Subjects with bridging fibrosis ( $F \geq 3$ ) had higher sCD163 compared to those with lower fibrosis stages (2.6(2.0–4.9) vs 2.0(1.5–2.4) mg/L,  $p = 0.001$ ). Preoperative sCD163 was independently associated with the NAS ( $p = 0.002$ ) and the fibrosis score ( $p = 0.024$ ). sCD163 decreased after BS and was normalized after 12 months, more rapidly so in the patients with  $NAS \geq 5$  ( $p < 0.001$ ). Immunohistochemical analysis showed a different distribution of CD163-positive macrophages in  $NAS \geq 5$  with microgranulomas and macrophages containing lipid droplets and aligning fat-laden hepatocytes; however, CD163 mRNA expression was similar in the two subgroups.

**Conclusions:** Soluble CD163 was increased in parallel with the severity of NAFLD in morbidly obese patients, indicating macrophage activation. sCD163 normalized after BS even in patients with severe liver inflammation and fibrosis, suggesting full reversibility of macrophage activation with weight loss.

5)

### **Non-selective beta-blockers may reduce incidence of hepatocellular carcinoma: a meta-analysis of randomised trials**

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**Background & Aims:** Non-selective beta-blockers (NSBB) are used as bleeding prophylaxis in patients with cirrhosis and oesophageal varices. NSBB also inhibit neo-angiogenesis and reduces bacterial translocation. We propose that NSBB hereby may prevent the development of hepatocellular carcinoma (HCC).

**Methods:** Systematic review of randomised trials on NSBB for prevention of bleeding. Patients in the control group could receive any intervention other than NSBB. Our primary outcome was development of HCC. Fixed and random effects meta-analyses were performed with  $I^2$  as a measure of heterogeneity. Egger's test was performed to test for small-study effects and sequential analyses to adjust for multiple testing.

**Results:** Twenty-three randomised trials on 1391 patients were included. The mean trial duration was four years (follow up 8-82 months). In total, 47 of 694 patients randomized to NSBB developed HCC versus 65 of 697 controls. Fixed effects meta-analysis found that NSBB prevented HCC (risk difference -0.026; 95% confidence interval -0.052 to -0.001; number needed to treat 38 patients), but the result was not confirmed using random effects (RD -0.027; 95% CI -0.054 to -

0.000). There was no heterogeneity ( $I^2 = 0\%$ ) or evidence of small-study effects (Eggers  $P = 0.778$ ). The sequential analysis suggested that 3719 patients was needed for the result to be robust to multiple testing. NSBB reduced overall mortality (RD -0.067; 95% CI -0.093 to -0.041), but not HCC related mortality (RD -0.011; 95% CI -0.040 to 0.017).

**Conclusion:** Non-selective beta-blockers may prevent HCC in patients with cirrhosis, with a number needed to treat of 38 patients to prevent one HCC.

6)

### **Individualized therapy is long-term cost-effective compared to dose intensification in Crohn's disease patients failing infliximab treatment**

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**Background:** In Crohn's disease patients failing infliximab therapy, interventions defined by an algorithm based on infliximab and anti-infliximab antibody measurements have proven more cost-effective than intensifying the infliximab regimen. This study investigated long-term outcomes.

**Methods:** Follow-up from a 12-week, single-blind, clinical trial where patients with secondary infliximab failure were randomized to infliximab intensification (5 mg/kg every 4 weeks) (n=36), or algorithm-defined interventions (n=33). Accumulated costs, expressed as mean costs per patient, were based on the Danish National Patient Registry.

**Results:** At the scheduled week 20 follow-up study visit, response and remission rates were similar in all study subpopulations between patients treated by the algorithm or by infliximab intensification. However, the sum of all health care costs related to Crohn's disease was substantially lower (31%) for patients randomized to algorithm-based interventions than infliximab intensification in the intention-to-treat population: €8,652 vs. €12,490;  $p=0.005$ . For per protocol patients (n=55), costs at the week 20 follow-up visit were even lower (49%) in the algorithm group: €6,335 vs. €12,490;  $p=0.002$ . Figures were similar for patients having completed the 12-week trial as per protocol (n=45). Among patients continuing the allocated study intervention throughout the entire 20-week follow-up period (blinding maintained) (n=29), costs were reduced by 60% in algorithm-treated patients: €5,113 vs. €12,881;  $p<0.001$ . Cost reduction percentages remained stable throughout one year. Similar findings were observed also when evaluating the sum of all types of health care costs.

**Conclusion:** Economic benefit of algorithm-based interventions at infliximab failure is maintained throughout one year. (NCT00851565)

7)

**Pentoxifylline is superior to corticosteroids in reducing short term mortality in patients with alcoholic hepatitis: Results of a multiple-treatments meta-analysis**

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**Background & Aims:** The relative effect of different interventions for alcoholic hepatitis is highly debated. As a consequence of equivocal results in randomised controlled trials and meta-analyses international guidelines are conflicting. We performed a multiple-treatments meta-analysis of randomized controlled trials on corticosteroids (CS), pentoxifylline (PTX), n-acetylcysteine (NAC), CS with PTX, CS with NAC and placebo or no intervention for patients with alcoholic hepatitis.

**Methods:** Random effects model multiple-treatments meta-analyses were performed within a Bayesian framework. Results were expressed as relative risks (RR) with 95% credibility intervals. The Surface Under the Cumulative Ranking Area (SUCRA) was used to compare the efficacy of each intervention to the others. Consistency of the results was evaluated by comparing direct and indirect effect estimates. A common heterogeneity was assumed for each pairwise comparison. Primary outcomes were short-term (<6 months) and long-term mortality (≥6 months).

**Results:** Thirtyone randomised trials evaluated five interventions. Twentysix trials had a CS treated group, eight trials a PTX group, three trials a NAC group, three trials a CS with PTX group, and two trials a CS with NAC group. Twenty-three trials included a control group with placebo or no treatment. CS and PTX reduced short-term mortality compared with placebo or no intervention (31 trials; RR 0.63, 0.43-0.88 and RR 0.44, 0.26-0.73, respectively). PTX was more likely than CS to be the best treatment (SUCRA values 88% and 60%). The common heterogeneity was 0.39%. The results were consistent when comparing the direct and indirect effect estimates. Subgroup analyses of trials on severe alcoholic hepatitis and papers published in full confirmed the results. None of the interventions reduced long-term mortality (six trials).

**Conclusions:** Corticosteroids and pentoxifylline reduce short-term mortality in alcoholic hepatitis. The combined evidence suggests that pentoxifylline is the best treatment option.

8)

**Primært intracerebralt Hodgkin lymfom hos en patient med Crohn sygdom.**

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**Introduktion:** Hodgkin lymfom (HL) med involvering af centralnervesystemet (CNS) er ekstremt sjældent med en rapporteret incidens på mindre end 0,02%. Når det forekommer er det ofte som led i recidiv eller behandlingsfraktær sygdom. [1]. Primært intracerebralt HL er endnu mere sjældent og der er kun rapporteret 17 tilfælde i verdenslitteraturen[1,2]. Vi præsenterer et tilfælde af primær HL i CNS hos en patient med mb. Crohn.

**Case:** En 35-årig kvinde havde igennem 15 år haft Morbus Crohn lokaliseret til terminale ileum og recidiverende sygdomsaktivitet blev behandlet med mesalamin, prednisolon, budesonid og

remicade. Under sygdomsforløbet deltog hun i afprøvning med CDP 870 (Certrolizumab). Hun fik senere resseceret terminale ileum og lavet strikturplastik af anastomosen. I forløbet fik hun i alt 11 års profylaktisk behandling med azathioprin.

Hun blev indlagt i oktober 2013 efter en uges anamnese med kraftige opkastninger, hovedpine, flimren for øjnene, lysskyhed, vægttab og svimmelhed. Objektivt fandt man venstresidig nedre kvadrant-anopsi. MR-scanning af cerebrum viste multiple processer supra- og infratentorielt. Biopsier viste Hodgkins lymfom (Epstein-Barr virus associeret), og efterfølgende PET-CT viste let ukarakteristisk opladning i lever men ingen øvrige lokalisationer. Der blev ikke foretaget biopsi fra leveren. Pt. opnåede komplet remission af sin cerebrale HL efter 4 serier BEACOPP escalated (bleomycin, etoposid, doxorubicin, cyclophosphamid, vincristin, procarbazine, prednison) samt rituximab. Der blev herefter givet konsoliderende stråleterapi mod de cerebrale HL læsioner samt totale cerebrum.

**Diskussion:** Flere studier har vist at Morbus Crohn er forbundet med en øget risiko for ekstraintestinale cancersygdomme og herunder en 2-3 gange øget risiko for maligne hæmatologiske sygdomme især non-HL. Hvorvidt denne øgede risiko er relateret til thiopurin behandling er omdiskuteret. Aktuelle sygehistorie viser en meget atypisk præsentation af HL hos en patient med mangeårig mb Crohn og langvarig thiopurinbehandling.

**Konklusion:** Aktuelle sygehistorie er en reminder om at patienter med mb Crohn er i øget risiko for malign hæmatologisk sygdom. Hvorvidt den langvarige immunsuppression er en forklaring på denne meget atypiske præsentation af HL er uvist, men bør afdækkes i mere systematisk gennemgang af lymfom manifestationer hos IBD patienter

9)

### **Alcoholic liver cirrhosis increases the risk for autoimmune diseases: a nationwide registry-based cohort study.**

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**Background and aims:** Alcoholic cirrhosis is associated with hyper-activation and dysregulation of the immune system, so it may increase the risk for autoimmune diseases. We conducted a nationwide study of incidence of autoimmune diseases among alcoholic cirrhosis patients.

**Methods:** We used data from nationwide healthcare registries to identify and follow all Danish citizens diagnosed with alcoholic cirrhosis in 1977-2010. Each cirrhosis patient was matched with five random population controls of same gender and age. Incidence rates of various autoimmune diseases were compared between cirrhosis patients and controls.

**Results:** Of the 24,708 cirrhosis patients, 532 developed an autoimmune disease yielding an overall increased incidence rate ratio (IRR) of 1.55 (95% confidence interval (CI) 1.42 to 1.70). The strongest associations were with Addison's disease (IRR = 2.89, 95% CI 1.16 to 6.36), inflammatory bowel disease (IRR = 1.91, 95% CI 1.54 to 2.33), celiac disease (IRR = 5.14, 95% CI 2.79 to 9.10), pernicious anemia (IRR = 2.69, 95% CI 1.72 to 4.07), and psoriasis (IRR = 4.40, 95%

CI 3.62 to 5.31). There was no incidence increase for rheumatoid arthritis (IRR = 0.98, 95% CI 0.75 to 1.26), and for polymyalgia rheumatica the incidence was decreased (IRR = 0.55, 95% CI 0.38 to 0.77).

**Conclusion:** This nationwide follow up study showed that alcoholic cirrhosis contributes to the development of autoimmune diseases. Ectopic cellular immune hyperactivity is a likely explanation.

10)

**Circulating macrophage activation markers, CD163 and CD206, are associated with disease severity and treatment response in patients with autoimmune hepatitis.**

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**Introduction:** Autoimmune hepatitis is characterized by chronic inflammation and fibrosis. Soluble (s)CD163, a specific marker for activated macrophages, is a marker for disease activity, fibrosis, portal hypertension and prognosis in acute and chronic liver diseases. We hypothesized elevated sCD163 and sCD206 levels in patients with acute disease activity and higher levels in non-responders than non-responders.

**Methods:** We included 113 AIH patients (female/male 85/28, median age 50 (range: 17-79)), 93 with autoimmune hepatitis and 20 with overlap syndromes of AIH-PSC (n=7) and AIH-PBC (N=13). We measured sCD163 and sCD206 by ELISA and associated levels with parameters of disease activity and cirrhosis.

**Results:** Soluble CD163 was significantly elevated in AIH patients with acute disease activity compared to AIH responders (6.96(3.3-15.4) vs. 1.62(0.80-3.24) mg/L). sCD163 levels correlated significantly with ALT ( $\rho=0.47$ ,  $P<0.001$ ), IgG ( $\rho=0.48$ ,  $P<0.001$ ), bilirubin ( $\rho=0.30$ ,  $P<0.001$ ), alkaline phosphatase ( $\rho=0.38$ ,  $P<0.001$ ), coagulation factors(II,VII,X) ( $\rho=-0.30$ ,  $P<0.01$ ) and thrombocytes ( $\rho=-0.24$ ,  $P=0.014$ ). There was no difference in sCD163 levels between the different groups of patients with or without cirrhosis at time of diagnosis. sCD206 showed a similar but less significant pattern. Immunohistochemistry in patients with acute disease activity showed increased CD163 staining compared to controls.

**Conclusion:** sCD163 and sCD206 levels were markedly elevated in patients with acute activity in AIH and were normalized in patients on anti-inflammatory treatment, even in patients with cirrhosis. Our data support significant macrophage activation in AIH confirmed by immunohistochemistry thus sCD163 may serve as a marker for treatment response of AIH patients.

11)

### **Primary Sclerosing Cholangitis**

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**Background:** Primary sclerosing cholangitis (PSC) is an autoimmune disease in the liver that is most commonly seen in patients with inflammatory bowel disease. The disease causes the development of chronic liver disease and predisposes to the development of cholangiocarcinoma and a number of other gastrointestinal malignancies.

**Method:** Journals of 49 patients with registration of clinical manifestations and development of PSC were evaluated, and a calculation was made of the number of neoplasms and the mortality among the patient population. In addition, the frequency and form of surveillance were registered and compared with international guidelines.

**Results:** Of the 49 patients, 61.2 % had concomitant inflammatory bowel disease. Just 16.3% of patients were asymptomatic at the time of diagnosis, while others presented one or more clinical symptoms—most commonly abdominal pain, diarrhea, or increased fatigue. Out of 45 patients, 22.2% had undergone systematic surveillance with imaging or cancer-marker measurements within the first 12 months, whereas 75.5 % were followed with clinical and biochemical monitoring within the first 12 months. Eight patients had neoplasia developments with a distribution of cholangiocarcinoma of 75% and colon cancer of 25%. The mortality rate in the patient group was 14.9%, while the mortality rate in relation to the PSC diagnosis was 12.8%. Four patients were lost to follow-ups in relation to surveillance.

**Conclusion:** The review of the patient journals gives rise to a recommendation of systematic surveillance, as only a small proportion of the patients was followed regularly with actual neoplasia screening. Due to the increased risk of cholangiocarcinoma and colorectal cancer, it is recommended that a formalized annual surveillance program be administered, starting at the time of diagnosis, containing an MRCP of the bile ducts, measurements of the biochemical marker CA 19-9, and an ultrasound of the liver and gall bladder. In addition, patients should be monitored every six months through clinical monitoring and biochemical monitoring of the liver function so that patients may be referred for transplant evaluation in a timely manner. Patients with inflammatory bowel disease should also be followed up with colonoscopy once a year.

12)

### **Wireless Capsule Endoscopy as a tool in diagnosing Autoimmune Enteropathy**

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**Objective:** Autoimmune Enteropathy (AE) is a rare immune mediated illness of the intestinal mucosa. The cause is unknown, and the diagnosis relies on typical characteristics displayed in AE. The proposed criteria are chronic diarrhea with malabsorption, exclusion of other causes of small bowel villous atrophy and typical histologic findings. If anti-enterocyte antibodies are present, they are supportive of the diagnosis. Establishing the AE diagnosis is often challenging and time consuming. There is no gold standard for treatment.

**Methods:** Two previously healthy adult patients developed sudden onset severe diarrhea with marked weight loss and was admitted to our department at two separate occasions. Both were dependent of parenteral nutrition during admission for several months. Blood works showed

electrolytes out of range and sign of inflammation. Infectious and parasitic disease was excluded through culture, microscopy and a short course of antibiotics, inflammatory bowel diseases were excluded through ileocolonoscopy with biopsies and celiac disease through serologic screening and HLA-typing. Both patients were tested for lactose intolerance, HIV, gastrinoma, VIP-oma and pheochromocytoma without positive findings. An abdominal Computerized Tomography (CT) scan and Magnetic Resonance Imaging (MRI) did not reveal anything that brought us closer to diagnosis. In-111-Octreotide scan, flowcytometry on duodenal biopsies and a F-18 fluoro-fluorodeoxyglucose positron emission tomography/computed tomography excluded neuroendocrine tumor and lymphoma. In both patients, extensive villous atrophy in duodenum was found during upper endoscopy. When a wireless capsule endoscopy (WCE) was performed, this revealed extensive small bowel villous atrophy with inflammation and erosions in both patients, which raised suspicion of AE. Anti-enterocyte antibodies were found in one of the patients, but both patients fulfilled the above stated criteria. Anti-inflammatory treatment was instituted and the disease completely went in to remission.

These two cases demonstrates the broad and time-consuming workup and the difficulties in establishing the diagnosis of AE. WCE is minimal invasive and offers a complete visualization of the mucosal damage which often is extensive, and thereby different from celiac disease. In these two patients, WCE aided the determination of AE diagnosis.

**Conclusion:** We propose that wireless capsule endoscopy is an important diagnostic tool in determining the diagnosis of Autoimmune Enteropathy in both children and adults.

13)

### **Beta-blockers in cirrhosis and refractory ascites: A retrospective cohort study and review of the literature.**

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**Introduction:** It is currently discussed if beta-blockers exert harmful effects and increase mortality in patients with cirrhosis and refractory ascites. In this study we provide an overview of the available literature in this field in combination with a retrospective analysis of 61 patients with cirrhosis and refractory ascites in a tertiary unit.

**Material and methods:** We performed a systematic search of literature in May 2014. In addition, 61 patients with cirrhosis and ascites were identified and followed from development of refractory ascites until death or end of follow-up.

**Results:** Fourteen trials (9 trials on propranolol, 1 case-control study, and 4 retrospective analyses) were identified. One trial suggested an increased mortality in patients treated with beta-blockers and refractory ascites. The results of the remaining trials were inconclusive. No increase in mortality among beta-blocker treated patients was found in the present retrospective analysis.

**Conclusion:** Treatment with beta-blockers may increase mortality in patients with cirrhosis and refractory ascites. However, the current evidence is sparse and high quality studies are warranted to clarify the matter.

14)

### **Esophago-Gastric junction Distensibility is Increased in Patients with Hiatus Hernia: Evaluation Using the EndoFLIP**

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**Background & aim:** The Endoscopic Functional Lumen Imaging Probe (EndoFLIP) is a new tool to measure the functional properties of the esophago-gastric junction (EGJ). We aimed to use EndoFLIP to compare the EGJ of hiatus hernia (HH) patients and healthy controls.

**Materials and methods:** EndoFLIP assessments were made in 23 Barrett's esophagus patients with HH at endoscopy and in 10 healthy controls. The EndoFLIP probe was placed straddling the EGJ and the bag was distended stepwise to a maximal volume of 50 ml. When possible, the lower esophageal sphincter (LES) and crural diaphragm (CD) components were located and measured separately.

**Results:** Generally, EndoFLIP visualised the EGJ also in HH patients and diagnosed most HH. The LES in HH patients was more distensible ( $P=0.01$ ) than the common EGJ in healthy controls. In HH patients, the CD was more distensible ( $P<0.001$ ) than the LES. The CD sphincter component of HH patients was shorter when compared to the LES sphincter component in HH patients ( $P < 0.001$ ) as well as to the common EGJ in healthy controls ( $P<0.001$ ).

**Conclusions:** Overall, the EndoFLIP technique proved valuable in the assessment of functional EGJ properties in HH patients. HH patients were found to have a less competent EGJ than healthy controls, and the CD component of HH patients was found to be less important for the sphincter function than the LES component. In the future, EndoFLIP assessment is likely to improve the understanding of the function and pathophysiology of the EGJ.

15)

### **Telephone Reminders Reduces the Non-attendance Rate in a Gastroenterology Outpatient Clinic**

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*Herlev Hospital.*

**Objective:** Non-attendance is a global problem in the healthcare system. Our aim was to investigate the effect of a telephone reminder on the non-attendance rate in a Gastroenterology outpatient clinic. Secondly we examined reasons for non-attendance by a questionnaire and investigated if a permanent implementation would be economic beneficial.

**Material and methods:** We performed a comparative intervention study with a historical control group in a Gastroenterology outpatient clinic. The study lasted for six months and patients with a booked appointment in the first three-month period received no reminder (control group,  $n = 2705$ ), while patients in the following three-month period were attempted reminded by telephone one weekday day in advance of their appointment (intervention group,  $n = 2502$ ). Non-attending patients in the intervention group received a questionnaire. An economical cost-benefit analysis was made from the results.

**Results:** In the intervention group, 1577 patients answered the reminder telephone call. The non-attendance rate was significantly lower in the intervention group (6.1%), compared with the control group (10.5%) ( $P = < 0.00001$ ). Only 1% of the patients who answered the reminder, turned out as non-attendees. Non-attending patients in the intervention group stated forgetfulness as the most common explanation for non-attendance (27%). The reminder telephone call was found to be economical favourable.

**Conclusions:** Telephone reminders significantly reduced the non-attendance rate by 43% in the outpatient clinic of gastroenterology, and it would be economical beneficial to implement the reminder in a clinic like ours.

16)

**The intestinal mucosal proteom of ulcerative colitis is different from healthy controls**

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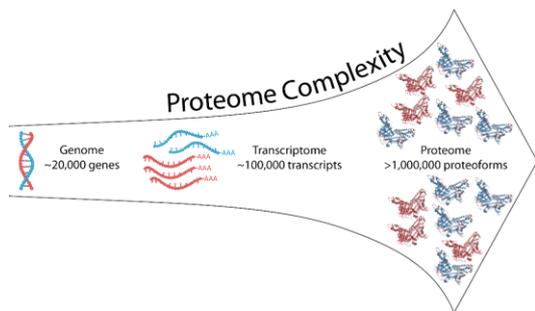
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Ulcerative colitis (UC) is a chronic inflammatory disease, characterized by inflammation to the colon, spreading continuously from the rectum and various distance proximal. The disease has great impact on the quality of life of the affected individuals, and for society due to lost labor and expenses to the health care system. The etiology of UC remain unclear, but involve a complex interplay between genetic and environmental factors. In this study, we investigate the relative protein abundances in intestinal mucosal biopsies of UC patients and healthy controls, to identify activated cellular pathways.<sup>1</sup>

Proteins function as the building blocks of the cells and tissue, and are responsible for the majority of the biological functions, making proteins an obvious target for studies seeking to describe disease etiologies.<sup>2,3</sup> Therefore, we established a biobank containing non-inflamed colonic biopsies from 10 well diagnosed UC patients and 10 healthy controls, extracted by standard sigmoidoscopy at Silkeborg Hospital.

Using mass spectrometry-driven protein identification and quantitation, we identified more than 6,000 proteins. Of these, 45 proteins demonstrated statistically significantly abundance change between the UC and control group, many of which were involved in specific parts of the innate immune system response to pathogens. The protein displaying the highest abundance change between the two groups (hundredfold) was lactotransferrin, a known disease marker for inflammation. Highly interestingly, the findings points to host-microbial interactions being involved in the disease etiology, which have been hypothesized by other groups to be altered in active inflammatory bowel disease.<sup>4,5</sup>

The study is ongoing, and we are currently following up on many of the findings, to better explain the disease etiology and identify diagnostic and prognostic markers.



17)

## Markers of Extracellular Matrix Remodeling Diagnose Early Fibrosis in Chronic Hepatitis B Patients

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**Background and aim:** Progressive disease with development of significant fibrosis and cirrhosis are important clinical events of chronic hepatitis B (HBV) infection. We aimed to evaluate the diagnostic value of extracellular matrix turnover (ECM) markers to detect clinically significant fibrosis (Metavir Fibrosis stage  $F \geq 2$ ) in chronic hepatitis B (HBV) patients.

**Methods:** Pro-C3 (Type III collagen formation), C1M and C4M (type I and IV collagen degradation) together with standard biochemical markers were assessed in plasma from 197 HBV patients. Patients were stratified according to Metavir Fibrosis score (F0-F4); F0 (n=41), F1 (n=97), F2 (n=37), F3 (n=17) and F4 (n=4). F3 and F4 were pooled in data analyses.

**Results:** Pro-C3 and C4M correlated to F stages ( $R=0.31$ ,  $p<0.001$  and  $R=0.23$ ,  $p<0.01$ ). Pro-C3 showed an overall significant difference between fibrosis stages ( $p<0.001$ ) and separated F0-F1 from F2-F4 (AUC=0.71). Combination of the markers and age, BMI, platelet count, and ALT in a linear regression model increased the correlation to F stages ( $R=0.51$ ,  $p<0.0001$ ). The diagnostic value of the algorithm was significant when separating patients without fibrosis (F0) from patients with fibrosis (F1-F4) (AUC=0.74,  $p<0.0001$ ) as well as when separating F0-F1 from F2-F4 (AUC=0.79,  $p<0.0001$ ).

**Conclusion:** This study is the first to demonstrate the diagnostic value and potential of the ECM Protein Fingerprint markers in chronic hepatitis B patients. Pro-C3 provided clinically relevant information both as single marker and in a regression model of combined markers.

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### **MUSCLE WEAKNESS, OSTEOPENIA AND DISTURBED METABOLIC ACTIVITY IN PATIENTS WITH CIRRHOSIS AND ASCITES**

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**Rationale:** Patients with cirrhosis and ascites often suffer from metabolic disturbances and it is currently unclear how ascites affects the resting energy expenditure (REE).

**Methods:** In 19 patients with cirrhosis and ascites, measurements of REE with indirect calorimetry were performed before and after paracentesis. Handgrip strength (HGS) was measured as well as body composition by Dual X-ray Absorptiometry (DXA).

**Results:** Low HGS (M:<30 kg; F<20 kg) was evident in 68% of patients. T-scores revealed osteopenia and osteoporosis in 58% and 16% respectively. Reduced vitamin D levels (<50 nmol/l) were found in 68% suggesting a component of osteomalacia. Patients who had reduced REE in response to paracentesis had higher MAP (p=0.02), p-Sodium (p=0.02) and p-PTH (p=0.03). In this group MAP decreased from 107 ± 18 mmHg before paracentesis to 89 ± 12 mmHg after paracentesis, a mean difference of 19 mmHg (95% CI: 10 - 27)(p=0.001). Calculated and measured REE was different in 63%. By including the weight of ascites REE is overestimated by mean 126 ± 1344 kJ/day, and by subtracting the weight of ascites REE is underestimated by mean 934 ± 1835 kJ/day.

**Conclusions:** Tense ascites increases REE and an abnormal REE is related to circulatory disturbances. Calculating REE may lead to erroneous assessments of nutritional needs. More than 2/3 of patients with ascites suffer from muscle weakness and/or osteopenia.

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### **BLOOD CULTURE POSITIVE INFECTIONS IN PATIENTS WITH ALCOHOLIC HEPATITIS**

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#### **ABSTRACT**

Acute alcoholic hepatitis (AH) is a life-threatening disease and its course is often determined by infections. However, the pattern of pathogens has not been studied. We examined which microbiological pathogens that caused blood borne infection in AH patients. We included 32 AH patients without infection at inclusion. Patients were followed for 1 month and their infection status was recorded based on clinical records, radiologic exams and cultures of different secretions. Nine patients (28%) developed blood culture positive infections. The agents were of heterogeneous aetiology and came from various sites of infection. Candida species accounted for three of these (33%). Five patients (16%) died, two of which had positive blood cultures. A high fraction was invasively infected by a heterogeneous spectrum of microbes including yeasts and commensal

bacteria. This may reflect the severe immune impairment of AH and suggests thorough infection screening and an immediate broad-spectrum antibiotic approach if infection is suspected.

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### **Effects of resveratrol treatment on experimental non-alcoholic steatohepatitis**

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**Background and aims:** Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis is an increasing clinical problem for which treatments are required. The polyphenol resveratrol prevents the development of fatty liver disease and we hypothesized that it could revert steatohepatitis, including hepatic inflammation and fibrosis in a well-characterised rodent model.

**Methods:** A 65% fat, 2% cholesterol diet was used to induce hepatic steatosis in rats for 1 week. Subsequently, the diet was supplemented (or not) with resveratrol (100 mg/rat/day) to 5 intervention groups; weeks 2-5, 2-8, 5-8, 11-17 and 17-23. Treated animals were sacrificed at the end of each intervention period like appropriate control and high-fat diet controls. Blood and liver were harvested for analysis.

**Results:** Resveratrol treatment partially mitigated hepatic enlargement and transaminase elevations when commenced early from the second week. There was however no effect on plasma bilirubin or  $\alpha$ 2-MG elevations. Resveratrol treatment did not alter the levels of hepatic triglyceride or histological steatohepatitis. The expression of Coll1 $\alpha$ 1 was typically lower in the resveratrol groups than in the positive controls and the difference was significant when treated with resveratrol from week 17 to 23 ( $P < 0.03$ ). We observed no reduction in mRNA expression of TGF $\beta$ , TNF $\alpha$ ,  $\alpha$ 2-MG, PGC-1 $\alpha$  or SREBP-1c.

**Conclusion:** Contrary to the findings in experimental steatosis, resveratrol treatment had no consistent therapeutic effect in alleviating experimental steatohepatitis.

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### **Hepatopulmonalt syndrom – En vigtig årsag til hypoxæmi hos patienter med portal hypertension**

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Dyspnø er en hyppig gene hos patienter med leversygdom. De almindeligste årsager er kardiopulmonale sygdomme og væskeretention. Man skal dog altid overveje hepatopulmonalt syndrom (HPS) som differentialdiagnose.

Patienterne klager typisk over snigende dyspnø med platypnø. Objektivt findes der ortodeoksi. Hypoksæmien starter med desaturering ved mobilisering og progredierer til et invaliderende kronisk problem.

Der er ikke sammenhæng mellem sværhedsgraden af HPS og sværhedsgraden af leversygdom. Diagnosen kan stilles ved kontrastekkokardiografi med saltvandsmikrobler, der ved betydelige

intrapulmonal shunting kan påvises i venstre ventrikel mindst tre hjerteslag senere end i højre ventrikel.

HPS er defineret ved intrapulmonal mikrovaskulær vasodilatation og angiogenese, hvilket medfører arteriel hypoksæmi og arteriovenøs shunting hos patienter med portal hypertension, hyppigst pga. cirrose. Leverskade frigør endothelin, som øger frigørelse af NO. NO diffunderer ind i glatmuskelceller og medfører vasodilatation. Vasodilatation og nedsat oxygenisering af blodet øger den pulmonale angiogenese.

Patienter med HPS har statistisk halveret levetid i forhold til patienter med leversygdom alene. Levertransplantation forbedrer prognosen fra en forventet femårsoverlevelse på under 25% til ca. 75%. Medicinsk behandling er ikke mulig. Levertransplantation giver mulighed for helbredelse af både lunge- og leversygdommen.

To patient cases er brugt til at illustrere den kliniske problematik ved HPS.

En 34 årig mand med arvelig hepatopulmonal sklerose, som fik påvist HPS og helbredtes ved transplantation. Samt en 50 årig kvinde kendt med alkoholisk levercirrose og svær HPS. Patienten kunne ikke transplanteres pga. vedvarende alkoholforbrug.

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### **Flow cytometric detection of vitamin D receptor changes during vitamin D treatment in Crohn's disease**

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**Introduction:** Crohn's disease (CD) is characterized by a dysregulated host response towards the intestinal microflora. Vitamin D deficiency is common in CD and *in vitro* vitamin D has immune modulatory effects on T cells through the nuclear vitamin D receptor (VDR). It is uncertain how vitamin D treatment affects the VDR expression *in vivo*.

**Aim:** To establish a flow cytometric protocol, including both nuclear and cytoplasmic VDR expression, to investigate the VDR expression in T cells from CD patients during vitamin D treatment.

**Methods:** We established a flow cytometry protocol enabling the detection of both cytoplasmic and nuclear VDR expression. The protocol was applied on anti-CD3/CD28 stimulated peripheral blood mononuclear cells (PBMCs) from vitamin D3-treated (n = 9) and placebo-treated (n = 9) CD patients. Cultured PBMCs were stained with anti-VDR antibody and examined by flow cytometry. *VDR*, *CYP27B1* and *RXR $\alpha$*  mRNA expression levels were measured by quantitative reverse transcriptase polymerase chain reaction in magnetic separated CD4+ T cells. Cytokine production in supernatants was measured with cytokine bead array.

**Results:** The established flow cytometry protocol enabled detection of both cytoplasmic and nuclear VDR-expression in PBMCs. This was confirmed by confocal microscopy and supported by correlation with VDR-gene expression. VDR expression in T cells increased following anti-CD3/CD28 stimulation. Vitamin D treatment reduced the activation-induced VDR up-regulation with 30% in CD4+ T cells. VDR expression correlated to *in vitro* interferon- $\gamma$  production in stimulated PBMCs.

**Conclusion** Flow cytometry is a useful method to measure the vitamin D receptor expression in Crohn's disease. Vitamin D treatment in CD patients reduces VDR up-regulation following T cell-receptor stimulation.

23)

### **Hemolysin in IBD associated *E coli* disrupts tight junctions**

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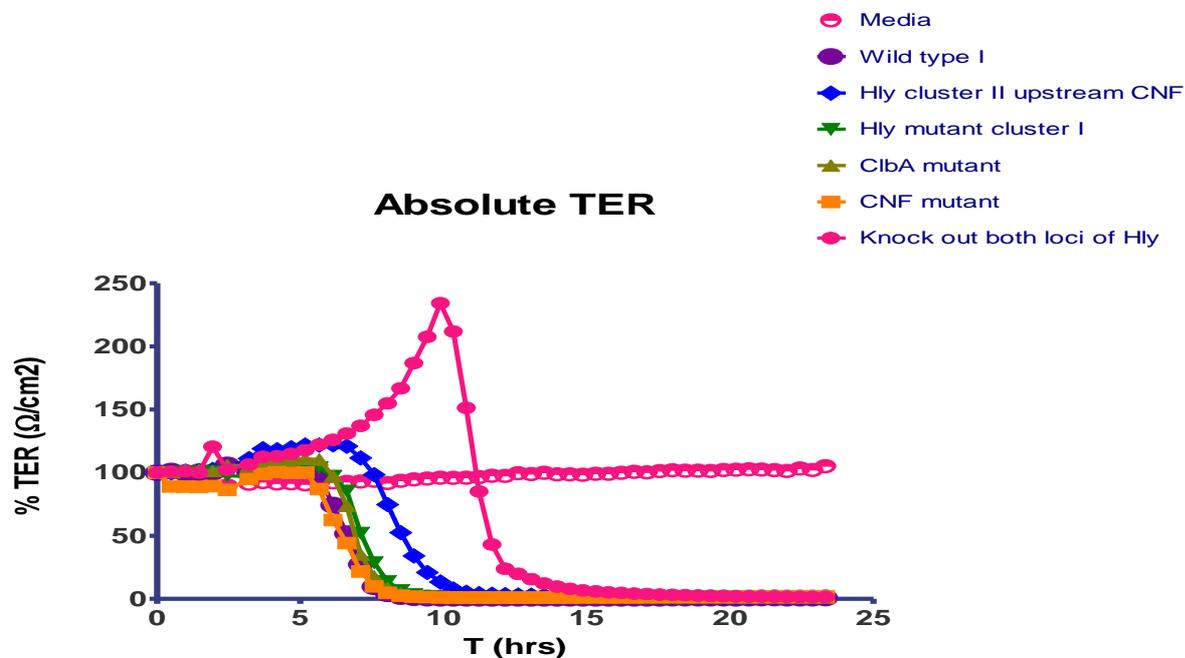
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**Background:** An increased prevalence of phylogenetic group B2 Escherichia coli (*E. coli*) has been associated with active disease in Inflammatory Bowel Disease (IBD) patients. Many of the B2 group strains harbor virulence genes present in extra intestinal pathogenic *E. coli* including  $\alpha$ -haemolysin (*hly*) and cytotoxic necrotizing factor type 1 (*cnf1*) the loci of which are often linked. Here we investigated the potential of phylogenetic group B2 *E. coli* isolated from IBD patients to damage the integrity of the intestinal epithelium and the potential contribution of *hly* and *cnf1*.

**Method:** Nine IBD associated *E. coli* and 3 *E. coli* isolates from healthy controls were selected for measurement of trans-epithelial electric resistance (TER) after co-culture with a monolayer of Caco2 cells. In order to investigate the role of *hly* and *cnf1* in disruption of the epithelial integrity, mutants of IBD associated *E. coli* “p19A” were created and hemolytic activity was tested using a hemolytic titration assay. Neutral Red uptake of viable Caco-2 cells assay was performed in order to investigate the possible cytotoxic effects of  $\alpha$ -haemolysin.

**Results:** Three of five *E. coli* strains from patients with active Ulcerative Colitis (strains p7, p19A and p22) disrupted epithelial cell tight junctions after only 6 hours of co-culture with Caco2 cells, in contrast to none of four *E. coli* isolated from patients with inactive UC and none of three *E. coli* strains from healthy controls. The three strains disrupting tight junctions in epithelial cells were all  $\alpha$  hemolysin positive. IBD associated *E. coli*, p19A was chosen for further experiments elucidating the role of  $\alpha$  haemolysin. P19a was found to possess two copies of the *hly* gene cluster one of which was located upstream of the *cnf1* gene. Knockout mutants lacking the individual haemolysin gene cluster as well as a *cnf1* mutant retained the ability to damage Caco-2 cell tight junctions after less than 6 hrs of co-culture. However, this phenotypic characteristic was lost in a mutant lacking both *hly* determinants. There were no differences in cytotoxicity between p19A wt and mutants.

**Conclusion:** IBD associated *E. coli* harboring  $\alpha$  haemolysin can cause rapid loss of tight junction integrity in differentiated Caco-2 cell monolayers. This effect is abolished in a mutant unable to express  $\alpha$ -haemolysin. These results suggest that high  $\alpha$  hemolysin expression may be a mechanism by which specific strains of *E. coli* pathobionts can contribute to epithelial barrier dysfunction and pathophysiology of IBD.



24)

### Novel biomarkers of extracellular matrix remodeling in inflammatory bowel disease: Different patterns of gut injury in UC and CD

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**Introduction:** About 10 % of patients with IBD have symptoms that match both Crohn's disease (CD) and ulcerative colitis (UC), termed inflammatory bowel disease unclassified (IBDU). The hallmark of both diseases is inflammation, which leads to excessive extracellular matrix remodeling and release of specific protein fragments, called neoepitopes. However, the pathophysiology, clinical manifestations and treatment is still different among the two diseases. Consequently, to ensure the best possible patient care, accurate diagnosis is essential. Therefore, we speculate that the biomarker profile panel of UC and CD represents a heterogeneous expression pattern, and thus these biomarkers will be a valuable non-invasive diagnostic tool to aid the diagnosis of UC and CD.

**Methods:** 37 patients with active CD (>150 CDAI) of which 24 had inflammation in colon or colon/ileum, and 56 patients with active UC (St. Marks score >2) were included in this study. All patients had standardized work-up at inclusion, including medical history, physical examination, endoscopy, C-reactive protein. Biomarkers of degraded collagens I, III-IV (C1M, C3M, and C4M), collagen type 1 formation (PINP) and citrullinated and MMP-degraded vimentin (VICM) were evaluated by a competitive ELISA assay system. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the discriminative power of the biomarkers. The combination of biomarkers was investigated by a backward logistic regression model.

**Results:** The serum level of the biomarkers, C3M and VICM, was significantly different between patients with either active UC or CD. C3M was significantly elevated in patients with UC compared to CD ( $P=0.039$ ). In contrast, VICM was highly elevated in patients with CD compared to UC ( $P<0.0001$ ). The biomarkers with the highest discriminative value were seen in C3M and VICM, calculated by ROC analysis. The biomarkers were adjusted for demographic variations (age,

gender, BMI, and smoking). VICM showed an AUC of 0.76 ( $P<0.0001$ ) (CD vs. UC) while C3M showed a more modest AUC of 0.62 ( $P=0.039$ ) (CD vs. UC). However, since the inflammation in UC is limited to the colon, ROC-curve analysis was then carried out, including only CD patients with inflammation limited to the colon or ileocolonic areas. Furthermore a logistic regression model was developed to find the best combination of the biomarkers. The best combination of biomarkers was VICM, C3M, and C4M with an AUC of 0.92 ( $P<0.0001$ ) (See table).

**Conclusion:** These data provide new insights into differences in mechanisms of gut injury in CD and UC. We observed a clinical relevant potential of VICM and C3M as novel biomarkers to differentiate between UC and CD, underlining the value of measuring extracellular matrix turnover in IBD. These results warrant further investigation as diagnostic markers in larger clinical studies.

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### **Endoskopisk ultralydsvejledt behandling af pankreatiske ansamlinger er en sikker procedure med få komplikationer - Aalborg Universitetshospital 2006-2012**

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**Baggrund:** Pankreatiske nekroser og pseudocyster er alvorlige komplikationer til akut og kronisk pankreatitis. Endoskopisk ultralyds (EUS) vejledt drænage kan ofte erstatte åben operation. Behandlingen består i etablering af et stoma mellem ventrikel eller duodenum og den pankreatiske ansamling med samtidig anlæggelse af stent(s) til sikring af dræningen og at stomat holder sig åbent.

Flere studier tyder på, at denne minimal invasive behandling har færre alvorlige komplikationer, kortere indlæggelsestid og er billigere sammenlignet med åben kirurgisk behandling.

På Aalborg Universitetshospital har man siden 2001 foretaget EUS-vejledt behandling af pankreatiske ansamlinger og fra 2006 også endoskopiske nekrosektomier.

Der er gennemført en retrospektiv opgørelse af alle patientforløb i perioden 2006–2012 for at belyse procedurerelaterede komplikationer og opgøre det kliniske resultat.

**Metode.** Patienter, der blev forsøgt dræneret i perioden 2006-2012, blev identificeret efter procedurekoder og data blev retrospektivt indsamlet og opdateret frem til 30/6-2013.

Alle patienter var præoperativt vurderet til enten at have én eller flere pseudocyster eller indkapslede nekroser ud fra CT-skanning. Alle procedurer blev udført med anvendelse af tre billedmodaliteter: endoskopi, EUS og røntgengennemlysning. Der blev anlagt 1-3 stents og procedurerne blev udført i generel anæstesi under antibiotikadække.

**Resultater:** 80 patienter, hvoraf 51 havde pseudocyster og 29 havde indkapslede nekroser, blev forsøgt behandlet endoskopisk. Medianalderen var 53 år (20-81år) og 53 var mænd. Ætiologien for pankreatitten var galdesten (40%), alkohol (34%), idiopatisk (18%), traume (4%), medicin (3%), post-ERCP (1%) samt hyperlipidæmi (1%). Ansamlingens størrelse varierede fra 1,3x5,3cm til 14x22cm.

Proceduren kunne gennemføres hos 75 patienter (94%). Årsagen til manglende gennemførelse var anatomiske forhold hos 3 patienter og tekniske vanskeligheder hos 2 patienter. Proceduren blev gentaget efter behov, median 1 (1-6 procedurer). 48 patienter (64%) kunne behandles succesfuldt med ét indgreb. Behandlingskrævende procedurerelaterede komplikationer opstod i 6 tilfælde (8%) af de gennemførte procedurer. 3 patienter blev behandlet for pneumoperitoneum med drænage og 3 patienter for blødning fra stoma (2 endoskopisk og 1 med åben operation). Der var ingen procedurerelaterede dødsfald.

**Konklusion:** EUS-vejledt behandling af pankreatiske ansamlinger har en høj succesrate og få procedurerelaterede komplikationer.

26)

### **GASTROINTESTINAL MOTILITY DURING SLEEP - AMBULATORY TRACKING OF TELEMETRIC CAPSULES COMBINED WITH POLYSOMNOGRAPHY**

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Studies of gastrointestinal function during sleep are hampered by lack of proper and easy to use techniques. We introduce a novel ambulatory telemetric capsule system (3D-Transit) which in conjunction with polysomnography confronts this problem.

3D-Transit (Motilis Medica SA, Neuchatel, Switzerland) consists of ingestible electromagnetic capsules traceable through an extracorporeal portable detector while traversing the gut. Sixteen healthy subjects (9 females, median age 34 years) ingested a capsule in the morning (C1) and another in the evening (C2). Polysomnography was carried out as unattended portable sleep monitoring. Technical problems in relation to the polysomnography prevented complete data collection in six subjects. 3D-Transit failed in one case.

We found that the amplitude of gastric contractions decreased with depth of sleep. Progression through the small intestine did not change with depth of sleep and there was no association between nocturnal awakenings or arousals and the occurrence of colonic and small intestinal propagating movements (capsule displacement of  $\geq 3$ cm). Propagating movements were, however, significantly more common during light sleep than during the additional sleep stages. Furthermore we found a significant decrease in basic colonic activity (capsule displacement of  $< 3$ cm) during both deep sleep ( $P < 0.0001$ ) and light sleep ( $P < 0.0001$ ) as compared to nocturnal wake periods. In conclusion, the novel ambulatory 3D-Transit system in combination with polysomnography allows minor invasive and completely ambulatory investigation of associations between sleep patterns and gastrointestinal motility.

27)

### **The association between endoscopic and histological inflammation in ulcerative colitis**

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**INTRODUCTION:** Mucosal healing (MH) in ulcerative colitis has emerged as a treatment goal because mucosal healing leads to decreased risk of relapse and colectomy. Histological inflammation seems to be a predictor of relapse independent of endoscopic MH. Different activity indices to assess the endoscopic and histological inflammation have been developed. We evaluate the relationship between Mayo Endoscopic Score (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the histological inflammation.

**METHODS:** In a prospective cross-sectional study, 120 patients underwent sigmoidoscopy. MES and UCEIS were used to determine the grade of endoscopic inflammation. Biopsies were evaluated by two “blinded” pathologists for the inflammatory activity using a four-point grading system (0-3), which included extent of cryptitis, crypt abscesses and the presence of erosions/ulcers.

**RESULTS:** The median age was 36 years, 58% were female and the median disease duration was 4.6 years. 27% had endoscopic remission, 18 % proctitis, 13% proctosigmoiditis, 23% left-sided colitis and 18% pancolitis.

Comparing the two endoscopic scores with the histology index we found Gamma=0.83, CI95% (0.73-0.93) for MES-histology, and Gamma=0.76, CI95% (0.65-0.86) for UCEIS-histology. Comparing MES with UCEIS, we found Gamma=0.99, CI95% (0.98-1). Furthermore, we found that 16% of the patients with MES=0 and 15% with UCEIS=3 had active histological inflammation (histology score=1)

**CONCLUSION:** We found a very strong significant association between the MES and the UCEIS, in both endoscopic active and inactive disease confirming that UCEIS is as accurate as MES in monitoring endoscopic inflammation and mucosal healing. Both MES and UCEIS correlated significantly with the histological inflammatory activity, suggesting a close relationship between endoscopic and histological inflammation. Reports indicate that histological inflammation without endoscopic lesions can be present in some cases, independently indicating a worse prognosis. Accordingly, we found that 15-16% of patients with endoscopic mucosal healing did have histological inflammatory activity.

28)

#### **Specific fragments of extracellular matrix proteins reflect disease activity in ulcerative colitis.**

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**Background:** The hallmark of ulcerative colitis (UC) is chronic inflammation, which is a key driver of excessive extracellular matrix (ECM) remodeling partly through an increased activity of matrix metalloproteinases (MMP). This leads to the release of specific ECM fragments, so called neoepitopes, to the circulation. Changes to the ECM, reflected by the circulating neo-epitopes, provide information on the damage and quality of the affected tissue and may therefore act as objective and non-invasive measures of disease burden and severity. We investigated the potential of such neoepitopes as biomarkers reflecting disease activity in UC patients.

**Methods:** 62 patients with UC were included. Patients had a standardized work-up at inclusion with medical history, physical examination, clinical activity index (St. Marks score), C-reactive protein. Blood samples were drawn at each visits, where visit 1=active UC and visit 2=UC in remission. Following neoepitopes were measured by competitive ELISAs; MMP-mediated of type I, III, IV collagen (C1M, C3M, C4M), N-terminus pro-collagen type I (P1NP), and MMP-degraded, citrullinated vimentin (VICM). Patients were subdivided into groups based on their St. Marks score: (a) All samples; Group 1, score 0-3 (n=52) and group 2, score 4-9 (n=41). (b) Active UC; Group 1, score 3 (n=15); group 2, score 4-5 (n=20), and group 3, score 6-9 (n=20). Correlations between disease activity and biomarkers were investigated by Spearman’s correlation (rho). The data was log transformed, and parametric statistical tests were applied (Students t-test and one-way ANOVA with Bonferroni correction). Non-parametric test was applied if normal distribution was not achieved (Mann Whitney’s t-test).

**Results:** Biomarkers of collagen degradation correlated with CRP in patients with active UC (n=55); C1M ( $\rho=0.70$ ,  $P<0.0001$ ), C3M ( $\rho=0.49$ ,  $P<0.0001$ ), C4M ( $\rho=0.37$ ,  $P<0.01$ ), as well as in patients with UC in remission (n=37); C1M ( $\rho=0.70$ ,  $P<0.0001$ ) and VICM ( $\rho=0.37$ ,  $P=0.031$ ). When investigating the level of biomarkers including patients with a low (group 1) or high (group 2) St. Marks score, there was a significant difference between the two groups; C1M ( $P=0.0025$ ), C3M ( $P=0.0040$ ), and C4M ( $P=0.042$ ) (table 1). In addition, ROC-curve analysis showed that C1M and C3M had significant discriminative power, area under the curve and  $P$ -values are listed in table 1. In patients with active UC, a significant difference was seen in C1M between group 3 and 1 ( $P=0.013$ ) (table 1).

**Conclusion:** In active ulcerative colitis biomarkers of the ECM turnover is increased compared to patients with less active disease or in remission and may therefore serve as biomarkers of disease severity and activity in UC. Further studies are warranted to reveal the true potential of these markers.

Table			
All patients	Group 1 N=51 St. Marks score 0-3 Mean (SD)nmol/L	Group 2 N=40 St. Marks score 4-9 Mean (SD)nmol/L	AUC (p-value)
C1M	82.02 ( $\pm 39.5$ )	129.2 ( $\pm 87.60$ )	<b>0.66 (<math>P=0.008</math>)</b>
C3M	27.56 ( $\pm 5.99$ )	32.10 ( $\pm 8.494$ )	<b>0.67 (<math>P=0.004</math>)</b>
C4M	65.7 ( $\pm 16.5$ )	75.42 ( $\pm 24.86$ )	0.60 ( $P=0.08$ )
VICM	6.83 ( $\pm 3.76$ )	8.13 ( $\pm 5.61$ )	0.55 ( $P=0.44$ )
P1NP	100.4 ( $\pm 56.70$ )	106.0 ( $\pm 59.24$ )	0.52 ( $P=0.71$ )
Active colitis	Group 1 N=15 St. Marks score 3 Mean (SD)nmol/L	Group 2 N=20 St. Marks score 4-5 Mean (SD) nmol/L	Group 3 N=20 St. Marks score 6-9 Mean (SD)nmol/L
C1M	66.4 ( $\pm 29.7$ )	128.2 ( $\pm 98.37$ )	132.9 ( $\pm 80.10$ )
C3M	26.92 ( $\pm 33.53$ )	33.53 ( $\pm 9.25$ )	30.73 ( $\pm 7.68$ )
C4M	65.26 ( $\pm 18.43$ )	79.48 ( $\pm 26.97$ )	71.56 ( $\pm 22.70$ )
VICM	6.64 ( $\pm 2.83$ )	8.05 ( $\pm 6.41$ )	8.20 ( $\pm 4.88$ )
P1NP	115.8 ( $\pm 55.17$ )	118.6 ( $\pm 63.69$ )	93.39 ( $\pm 53.04$ )

29)

### Increased extracellular matrix proteins turn-over in patients with Crohn's disease

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**Background:** Ongoing inflammation in Crohn's disease (CD) may lead to development of intestinal fibrosis and patients may present with stenosis. Inflammation is a dynamic process with a permanent remodeling of the extracellular matrix (ECM). Small fragments of the ECM generated during this process, so called neopeptides, are released into the circulation and could be used as

biochemical markers of disease activity or markers of fibrosis. This study investigates a panel of these novel developed markers in patients with suspected or known CD

**Methods:** 106 patients referred for evaluation of CD had serum samples drawn. Patients were evaluated with colonoscopy, small-bowel imaging (capsule endoscopy, MR enterography, and CT enterography), fecal calprotectin, and C-reactive protein. Thirty five patients had newly diagnosed CD, 26 had CD with active inflammation or stenosis, 11 had known CD without inflammation or complication, and 34 had no evidence of Crohn's disease. The following neopeptides were measured by competitive ELISAs; MMP-mediated of type I, III, IV collagen (C1M, C3M, C4M), N-terminus pro-collagen type I (P1NP), and MMP-degraded, citrullinated vimentin (VICM).

**Statistic:** Data were not normally distributed and Kruskal-Wallis one-way analysis of variance was used for comparison. ROC-curve analysis were used to test the biomarkers ability to discriminate CD from non-CD.

**Results:** Serum levels of C3M were significantly elevated in patients with CD compared to patients without CD (median 24.4 and 19.1, respectively;  $P = 0.01$ ). C3M discriminated CD from non-CD with an AUC of 0.66. Concentrations of C1M and C4M were also elevated but statistical significance was not reached (C1M: median 68.9 and 62.9;  $P = 0.12$ . C4M: median 70.5 and 67.2;  $P = 0.15$ ). In patients with CD, C1M and C3M concentrations were higher in clinically active disease (CDAI > 150) compared to quiescent disease (C1M: median 75.0 and 63.2;  $P = 0.02$ . C3M: median 24.5 and 22.7;  $P = 0.10$ ), and C3M concentrations were higher in CD involving the colon compared to small bowel CD (median 26.2 and 22.1;  $P = 0.05$ ). C1M, C3M and C4M correlated with CRP (Spearman's rho 0.76, 0.40, and 0.45, respectively;  $P < 0.001$ ) but not with fecal calprotectin. Concentrations of ECM degradation markers were not significantly increased in patients with stricturing CD compared to patients without CD. In subgroup analysis of patients with diagnosed CD and elevated CRP compared to non-CD and normal CRP C1M, C3M and C4M discriminated CD from non-CD (AUC of 0.95, 0.88 and 0.90).

**Conclusions:** Turnover of ECM proteins is increased in patients with CD. These neopeptides may distinguish between patients with CD and patients without CD and between active CD and disease in remission. Further studies of these markers of the ECM are warranted.

30)

### **Vaccination routines during anti-TNF treatment in IBD: Do patients adhere to guidelines?**

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**Background:** Immunosuppressive therapy with TNF-inhibitors is a keystone in the treatment of inflammatory bowel disease (IBD). Although generally well tolerated, these agents increase the risk of infectious diseases including reactivation of latent infections. International guidelines therefore recommend routine screening and vaccination in connection to anti-TNF therapy. Clinical observations indicate, that these guidelines are challenging to use in everyday clinical practice.

**Aim:** To investigate if patients receive information about recommended vaccinations in a routine clinical setting, and if this information increases adherence to guidelines. Further, to identify reasons for non-adherence.

**Methods:** Observational, retrospective cohort study of IBD patients in ongoing anti-TNF therapy per March, 2013. Vaccination details were obtained by a validated questionnaire. Guidelines from European Crohn's and Colitis Organisation (ECCO) served as gold standard.

**Results:** 130 (83%) of 157 IBD patients responded to the questionnaire. Of these, 83 (64%) received anti-TNF therapy with infliximab and 47 (36%) received adalimumab. Sixty-two patients (48%) reported to have received information from a health care professional about recommended vaccinations either before or during anti-TNF therapy. This information significantly increased adherence to guidelines. Hence, the hepatitis B vaccination rate increased from 24% prior to information to 52% after information ( $p<0.001$ ), pneumococcal vaccination rate from 7% to 24% ( $p<0.001$ ), human papilloma virus vaccination from 19% to 32% ( $P<0.01$ ), and annual influenza vaccinated from 26% to 58% ( $P<0.001$ ). Main barriers for lack of adherence to vaccination guidelines were forgetfulness (36%) and financial reasons (32%).

**Conclusion:** Patients' adherence to recommended vaccinations in connection with anti-TNF therapy is improved by targeted information from health care professionals. However, despite relevant information, the majority of patients do not completely adhere to the guidelines. This introduces risk of potentially severe side effects. Proposed strategies for improved adherence include focus on the problem by healthcare professionals, repeated information to patients, and financial support.

31)

### **Clinical outcome of adalimumab therapy in patients with ulcerative colitis previously treated with infliximab: a single-center cohort study**

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**Background:** Immunosuppressive therapy with TNF-inhibitors is effective for treatment of ulcerative colitis. Adalimumab (ADL) is increasingly used in the clinic both as primary anti-TNF drug and in patients switching from infliximab (IFX) due to treatment failure or side effects.

**Aim:** To investigate short- and long-term clinical outcomes of ADL therapy in a real-life clinical setting, where IFX had been used as preferred choice of anti-TNF agent and followed by ADL as second line agent.

**Methods:** Observational, retrospective, single-center cohort study including all ulcerative colitis patients treated with ADL at a tertiary Danish center until 2014.

**Results:** The study population comprised 33 patients. The cohort consisted solely of IFX-to-ADL switchers. Main reasons for switching to ADL were infusion reactions to IFX (45%) or incomplete clinical effect of IFX (33%). Short-term efficacy of ADL assessed after 12 weeks, revealed 15 (45%) with clinical response and 6 patients (18%) in clinical remission. Twenty-three patients continued ADL for more than 12 weeks. At long-term follow-up after one year of ADL treatment, 8 patients (24%) had clinical response and 6 patients (18%) were in clinical remission. Five patients (15%) were colectomized within the one-year follow-up period, and this was generally due to primary non-response (4 of 5 patients).

**Conclusion:** Real-life efficacy of ADL therapy in ulcerative colitis patients previously treated with IFX is relatively low with an estimated colectomy rate that is 3-fold higher than reported in the randomized controlled registration trials.

32)

## **Antibodies against infliximab (IFX) are associated with *de novo* development of antibodies to adalimumab (ADL) and therapeutic failure in IFX-to-ADL switchers with inflammatory bowel disease**

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**Background:** A notable proportion of inflammatory bowel disease (IBD) patients are switched from infliximab (IFX) to adalimumab (ADL). We investigated if immunogenicity of IFX influenced immunogenicity and clinical outcomes of later ADL therapy.

**Methods:** Single-center cohort study including all IBD patients assessed for antibodies (Abs) against IFX or ADL.

**Results:** Anti-IFX Abs were evaluated in 187 patients treated with IFX as first line anti-TNF agent. Approximately half (49%) were positive. Detected anti-IFX Abs had functional capacity as judged by a median IFX concentration below limit of detection (IQR 0.0-0.0 µg/ml) vs. 3.8 µg/ml (IQR 1.3-7.9) in anti-IFX Ab-negative patients,  $p < 0.0001$ ; but did not cross-react with ADL. Anti-ADL Abs were assessed in 57 ADL treated patients. Twelve (21%) tested positive. Patients with previous anti-IFX Ab development were significantly more prone to develop anti-ADL Abs (33%) than those without (0%): OR estimated 11,  $p = 0.04$ . The anti-ADL Abs were also functional as ADL was undetectable in all anti-ADL Ab-positive patients vs. median 8.3 µg/ml (IQR 5.0-11.0) in anti-ADL-negative patients,  $p < 0.0001$ . The presence of anti-ADL Abs increased the risk of secondary ADL treatment failure with OR 28 [3-248],  $p < 0.001$ . ADL trough levels, irrespectively of anti-ADL Ab status, associated with efficacy of ADL maintenance therapy:  $AUC^{ROC} 0.77 [0.62-0.93]$ ,  $p < 0.01$ .

**Conclusion:** Switchers with anti-IFX Abs are prone to develop *de novo* anti-ADL Abs which may result in therapeutic failure. Assessment of ADL immunogenicity in anti-IFX Ab-positive switchers is required to ensure optimal interventions at inadequate treatment responses and to avoid inappropriate ADL intensification regimens.

33)

## **Systemic appearance of antibodies against adalimumab in patients with inflammatory bowel disease**

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**Background:** Antibodies (Abs) against adalimumab (ADL) have been associated with low ADL serum levels and treatment failure in patients with inflammatory bowel disease (IBD).

**Aim:** To evaluate the formation and temporal appearance of anti-ADL Abs including associations with low serum trough levels of ADL and clinical outcomes.

**Methods:** Single-center cohort study including all IBD patients assessed for anti-ADL Abs by radioimmunoassay.

**Results:** Anti-ADL Abs were evaluated in 133 serum samples obtained from 72 patients. Of these, 17 patients (24%) were positive for anti-ADL Abs after a median of 194 days, IQR 66-361. Most patients (76%) developed anti-ADL Abs within first year of ADL therapy. Kaplan-Meier analysis showed that 78% were free of anti-ADL Abs after 1 year, and 68% from 21 months onwards. Anti-ADL Abs generally persisted at repeat assessments during continued ADL therapy (n=9). Rarely, previously detected anti-ADL Abs became undetectable during continued ADL therapy due to false negative testings (n=1) or yet unknown reasons (n=2). Detected anti-ADL Abs appeared pharmacologically active as judged by a median ADL concentration below limit of detection (IQR 0.0-0.0 µg/ml) vs. 7.7 µg/ml (4.9-11.4) in anti-ADL Ab-negative patients, p<0.0001. Anti-ADL Abs associated with loss of treatment response (OR estimated 67, p<0.0001), and shorter time on ADL (p<0.0001).

**Conclusion:** Antibodies against ADL usually develop within the first year of therapy, and strongly associate with diminished serum drug trough levels and treatment failure. However, anti-ADL Abs may become undetectable during continued therapy due to false negative testings or yet unknown reasons.

34)

**Changes in serum trough levels of infliximab during treatment intensification but not in anti-infliximab antibody detection are associated with clinical outcomes after therapeutic failure in Crohn's disease**

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**Background:** It is recommended to intensify the infliximab (IFX) regimen in case of inadequate treatment effect. However, the rationale is not well defined as underlying mechanisms varies.

**Aim:** To explore if changes in serum IFX and anti-IFX antibodies (Abs) after IFX intensification are associated with clinical outcomes.

**Methods:** *Post hoc* analysis of randomized clinical trial including 42 Crohn's disease patients with IFX treatment failure all treated by an intensified IFX regimen (5 mg/kg every 4 week) throughout 12 weeks. Trough serum IFX and anti-IFX Abs were measured by homogeneous mobility shift binding assay (HMSA) and functional cell-based reporter gene assay (RGA) at treatment failure and end of trial.

**Results:** 21 patients (50%) regained clinical response on intensified IFX regimen. The increase in serum trough levels of IFX during treatment intensification was higher among responders than non-responders (RGA: 8.8 µg/ml vs. 3.0, p=0.035; HMSA: 9.9 µg/ml vs. 4.7, p=0.040), and differentiated patients by clinical outcome ( $AUC^{ROC}_{RGA}$  0.75 [0.53-0.97], p=0.035;  $AUC^{ROC}_{HMSA}$  0.74 [0.53-0.95], p=0.042). All responders exhibited IFX increase  $\geq 2.6$  µg/ml (sensitivity 100%, specificity 50%). Anti-IFX Abs detected by HMSA in 13 patients (32%) were often non-functional and became undetectable during IFX intensification. However, even functional anti-IFX Abs detected by RGA in 6 patients (15%) became undetectable.

**Conclusion:** Increase in IFX levels following treatment intensification is associated with improved clinical outcomes indicating insufficient drug levels in a subgroup of patients. Anti-IFX Abs may become undetectable during treatment intensification suggesting lowered production or formation of immune complexes.

35)

### **ALCOHOLIC HEPATITIS MARKEDLY DECREASES THE CAPACITY FOR UREA SYNTHESIS**

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**Background and aims:** Urea synthesis serves a key regulatory role in nitrogen (N) homeostasis. Its capacity decreases in patients with compromised liver function. In contrast, it increases in patients with inflammation. Alcoholic hepatitis (AH) involves both mechanisms, but it is unknown how their effects on urea synthesis are balanced. Our aim was to investigate how AH affects the capacity for urea synthesis.

**Methods:** We included twenty patients (m/f, 17/3; age 39-59 years) with a clinical diagnosis of AH. Eleven had severe AH: a Glasgow alcoholic hepatitis score (GAHS)  $\geq 9$ . We measured blood  $\alpha$ -amino-N concentrations (AAN) and urea-N synthesis rates (UNSR) before, during, and after a 4-h constant infusion of alanine (2mmol/kg/h). The capacity for urea synthesis was quantified by the Functional Hepatic Nitrogen Clearance (FHNC), i.e. the slope of the linear dependence of UNSR on AAN. The FHNC was related to another metabolic liver function, the Galactose Elimination Capacity (GEC), and to clinical liver status assessed by the Model for End-Stage Liver Disease (MELD) and the Child-Pugh (C-P) score.

**Results:** FHNC was markedly decreased to  $7.2 \pm 4.9$  l/h (mean $\pm$ SD) in the patients (normal range 20-35 l/h) and most so in those with severe AH ( $4.9 \pm 3.6$  l/h vs.  $9.9 \pm 4.9$  l/h,  $P < 0.05$ ). The GEC was less markedly reduced than the FHNC and they were dissociated. There was an inverse relation between the FHNC and the liver status scores (MELD  $r^2 = 0.27$ ,  $P < 0.05$ , C-P  $r^2 = 0.22$ ,  $P < 0.05$ ).

**Conclusions:** Alcoholic hepatitis markedly decreases the capacity for urea synthesis and to a level previously only measured in acute liver failure. In AH, thus, the metabolic failure prevails so that the liver cannot appropriately deliver the metabolic up-regulation found in other stressful states including inflammation. This may contribute towards the frail prognosis of the patients.

36)

### **Milk is an excellent source for vitamin B12 - An experimental study in a rat model.**

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**BACKGROUND:** In general, food-bound vitamin B12 (B12) has a poor bioavailability. Curiously, some studies indicate that B12 present in milk is absorbed even more efficiently than free B12.

**OBJECTIVE:** To explore the uptake of free B12, B12 bound to milk protein (recombinant transcobalamin (rTC)) and B12 in milk.

**METHODS:** Radioactive B12 ( $^{57}\text{Co}$ -B12), either free or bound to rTC, was administered by gastric gavage to two groups of 15 rats. Five rats from each group were sacrificed after 2, 24, and 48 hours.

Likewise, groups of rats (n=10) were fed with <sup>57</sup>Co-B12 in its free form, present in milk, or bound to rTC added to milk and sacrificed 24 hours later. Weight quantities of tissue were homogenized, and <sup>57</sup>Co-B12 was measured employing a gammacounter. All results were expressed as percentage of given dose per organ.

**RESULTS:** After feeding with free B12, the highest percentage at 2, (24) and [48] hours expressed as median and (range) was recovered in the kidney: 0.061% (0.052-0.075); (14% (10-17)) and [18% (13-20)] followed by the small intestine: 3.9% (2.0-5.6); (1.8% (1.1-2.2)) and [1.2% (0.8-1.9)] and liver: 0.056% (0.017-0.090), (1.1% (0.70-1.6)) and [1.1% (0.68-1.2)]. No significant difference was observed between the uptake of free B12 and B12 bound to rTC or present in milk.

**CONCLUSION:** We document that B12 present in milk is absorbed as efficiently as is free vitamin B12. Our results confirm milk as an excellent source for vitamin B12, but does not support that milk is a better source than free vitamin B12.

37)

### **KCa3.1 channels are upregulated in hepatocytes of cirrhotic patients**

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**Introduction:** KCa3.1 is a calcium activated potassium channel, which regulates proliferation, migration and cell volume. KCa3.1 has been identified in circulating blood cells (erythrocytes, lymphocytes and macrophages), endothelial and epithelial cells in colon and airway. Its inhibition is suggested as target for therapy of lung and kidney fibrosis. Little is known about its role in liver fibrosis. Recently, we found that KCa3.1 deficient mice show augmented hepatic fibrosis upon liver injury. The present study investigated KCa3.1 expression in hepatic stellate cells (HSC), hepatocytes and Kupffer cells *in vitro*, as well as expression and cellular localization in human liver biopsies.

**Methods:** *Cellular studies:* In primary isolated hepatocytes, Kupffer cells and HSC we measured KCa3.1 gene expression by quantitative polymerase chain reaction. We incubated quiescent and culture-activated hepatic stellate cells with the specific KCa3.1 inhibitor TRAM-34 and the activator SKA-31 and evaluated effect on mRNA expression of collagen 1, smooth muscle actin and tumor growth factor  $\beta$ .

*Human biopsies:* liver biopsies from 54 patients representing normal, alcoholic cirrhosis, autoimmune disease or severe inflammation or fibrosis due to other aetiologies were included. Immunohistochemical stain was performed for KCa3.1 expression. Double fluorescent immune stain was performed to investigate KCa3.1/macrophage co-localization.

**Results:** KCa3.1 inhibition with TRAM-34 suppressed collagen production in HSC, but did not change the myofibroblastic phenotype. KCa3.1 mRNA was 300 and 100 times higher in macrophages and hepatocytes compared to HSC.

In normal human biopsies KCa3.1 was low or absent, but an abundant expression was seen in hepatocytes of cirrhotic livers. KCa3.1 was also found in a minor percentage of the macrophages.

**Conclusion:** Our study questions the potential anti-fibrotic effect of channel blockers, but demonstrates an upregulation of KCa3.1 channels in hepatocytes during cirrhosis, which might play a pathogenic role.

38)

### **Stine Hald**

#### **A diet rich in arabinoxylan and resistant starch increases colonic butyrate concentration and occludin expression in subjects with metabolic syndrome**

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**Background:** The metabolic syndrome (MetS) is associated with a decreased intestinal mucosal defense barrier leading to low-grade inflammation and endotoxemia. The defense barrier consists of epithelial tight junctions including occludin and mucins (primarily MUC2). In *in vitro* models and animal studies, butyrate modulates occludin and MUC2 expression. We hypothesized that a diet rich in arabinoxylan (AX) and resistant starch (RS) would improve colonic health by increasing the colonic butyrate production and the expression of occludin and MUC2 in subject with MetS.

**Methods:** Nineteen adults with MetS completed a 4-week, randomized crossover study with two diet interventions; a healthy carbohydrate diet (HCD) rich in AX (16 g/d) and RS (21 g/d), and a low-fiber western style diet (WSD) containing AX 4 g/d and RS 3 g/d.

Before and after each intervention endoscopy with tissue samples was done, and stool samples were collected. Colonic MUC2 and occludin expression were analyzed by quantitative RT-PCR, while gas-liquid chromatography was used to detect fecal butyrate concentration.

**Results:** After HCD fecal butyrate concentration increased ( $p<0.01$ ), and the colonic expression of occludin was 1.15 ( $p=0.005$ ) and MUC2 was 1.20 ( $p=0.07$ ) fold higher compared to WSD.

**Conclusion:** Consumption of a 4-week diet rich in AX and RS increased fecal butyrate and colonic occludin expression and tended to enhance MUC2 expression compared to a western style diet suggesting an enhanced colonic defense barrier in subjects with MetS.

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#### **NOD2 is not of importance for the course of mycobacterial infections in humans**

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**Background:** Peptidoglycan-derived muramyl dipeptide (MDP) constitutes a key component in bacterial cell envelopes which is recognized by nucleotide oligomerization domain 2 (NOD2). NOD2 gene variants are associated with Crohn's disease (CD). Most bacteria carry the N-acetylated form of MDP (A-MDP), whereas N-glycolyl MDP (G-MDP) is found on mycobacteria. Clinical studies have linked CD to mycobacterial infections, and animal studies reports that G-MDP has greater NOD2-stimulating capacity than A-MDP.

**Aims:** To identify how A-MDP and G-MDP producing bacteria are affected by CD associated NOD2-gene variants in order to determine if NOD2 gene variants could cause bacteria-species specific changes in bacterial handling in CD patients.

**Methods:** PBMCs were isolated from **healthy human volunteers wild-type (*wt*) in both NOD2 (n=8), wt CD patients (n=9), NOD2-variant CD patients (n=7), and wt NOD2 variant CD patients (n=6) and stimulated A-MDP or G-MDP, *Listeria monocytogenes* (LM; an A-MDP producing bacteria), or *Mycobacterium avium paratuberculosis* (MAP; a G-MDP producing bacteria). The tumor necrosis factor  $\alpha$  (TNF) response was measured by ELISA. Pathway identifying studies were also performed.**

**Results:** A-MDP induced significantly stronger TNF response in wt NOD2 PBMCs compared with G-MDP. LM resulted in a low TNF release compared to MAP. MAP activated NOD2 and Toll-like receptor (TLRs)-mediated responses whereas LM mainly activated NOD2 pathways. Responses to LM was therefore reduced in NOD2 mutated cells, whereas responses to MAP were unaffected.

**Conclusions:** Our results demonstrate a distinct NOD2 and TLR mediated immune response in humans determined by the species of the bacteria that are significantly different from previous findings in rodents. Mycobacteria are not mainly recognized by NOD2 and the results suggest impairment towards a broader array of A-MDP producing bacteria in CD patients with NOD2 mutations.

40)

#### **A kinetic *in vivo* characterization of experimental human colonic mucosal wound healing in ulcerative colitis**

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**Background** Dysfunctional colonic mucosal wound healing plays a key role in ulcerative colitis (UC) and are correlated to the disease burden in UC, risk of surgery, and risk of developing colorectal cancer. Unfortunately, *in vivo* research in human wound healing in the intestine largely remains unexploited.

**Aim** This study aims at characterizing the kinetics of wound healing *in vivo* in the human colonic mucosa on the macroscopic level in healthy control subjects and UC patients.

**Methods** Establishing an *in vivo* wound healing assay: an experimental wound is made in the recto-sigmoidum during endoscopy using a standard disposable biopsy forceps. The kinetics of wound healing is subsequently documented by successive macroscopic high definition imaging through a standard endoscope at time points 24h and 48h post-wounding. Based on the well-known kinetics of wound healing in the skin a wound scoring system for the colonic mucosa was developed prior to the experiments, see Table 1. Fourteen UC patients in endoscopic remission and 11 healthy controls were included.

**Results** The colonic mucosal wound healing score was significantly different between controls and UC patients at 24h ( $p=0.02$ ), but not at 48h ( $p=0.11$ ). Distinct wound phenotypes were identified: Wounds from UC patients had marked peripheral hyperemia and edema whereas wounds in control subjects had less inflammation with no hyperemia and less or no edema.

**Conclusions** A kinetic *in vivo* characterization of experimental human colonic mucosal wound healing has been performed for the first time, and the wound healing seems to be characterized by

distinct yet intertwined phases of fibrin clot formation and inflammation (hyperemia and edema). A subsequent molecular identification of these potentially dysfunctional tissue repair mechanisms *in vivo* might provide excellent therapeutic targets for a better wound healing process in UC patients.

<b>Colonic Mucosal Wound Healing Score</b>	
<i>Wound</i>	Score
Complete fibrin coverage	1
Partial fibrin coverage	2
No fibrin coverage (clotting only)	3
<i>Inflammation</i>	
Peripheral hyperemia	1
Edema	1
Total score	

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## **DIAGNOSIS AND PERSISTENCE OF HISTOLOGICAL CHANGES IN LYMPHOCYTIC COLITIS**

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**INTRODUCTION:** The topographic distribution of histological changes in microscopic colitis (MC) remains controversial. The main conception has been that in order to detect or rule out MC, biopsies from the right colon is necessary. However this has to some extent been proposed on the basis of a selected population of patients included in randomised trials with collagenous colitis (CC). A sigmoideoscopy is more gentle with the patient, cheaper and often more accessible and thus could in some cases be preferred in detecting MC.

**AIMS & METHODS:** To access the topography of histological changes in the colon diagnostic of lymphocytic colitis (LC) in a complete series of consecutive, non-selected patients and to provide the sensitivity of left- and right-side biopsies respectively. Furthermore to analyse the persistence of changes in repeated endoscopies.

**Methods:** Retrospective review of the pathologic descriptions in the Danish National Pathology Database in patients diagnosed with lymphocytic colitis in the coverage area of Køge Hospital from 2000 through March 2014. Biopsies from the rectum were excluded.

**RESULTS:** LC was diagnosed in 238 patients; in 81 (34%) by sigmoideoscopy and in 136 (57%) by colonoscopy. A medical history of watery diarrhoea could be retrieved in 196, 1 did not have diarrhoea. The median number of biopsies taken was 6 (mean 7.6). Biopsies were taken from both right and left colon in 122 (51%) and showed LC in both left and right colon of 119 (98%). At the diagnostic endoscopy 3 patients (2%) had changes in the left colon only and no one had changes in the right colon only. The histological diagnosis in the right colon were: normal (1), chronic inflammation (1) and incomplete LC (1). The sensitivity of left sided biopsies for the primary diagnosis of LC were 100% (95% CI: 97-100%) and right sided 98% (94-100%). A second endoscopy following the diagnostic one was performed in 50 (21%) of the 238 patients after a

median of 13.5 months (mean 27.2) with a median of 6.5 biopsies (mean 7.1). LC was reconfirmed in 28 (56%). Other histological changes found were: normal (4), chronic inflammation (2), incomplete LC (2), CC (2) and non specific changes (10). In 3 patients histological changes diagnostic of collagenous colitis were found in one or more of the endoscopies following the diagnostic one. Looking at the total number (161) of colonoscopies diagnostic of LC (with biopsies from both right and left colon) done in the population, 1 patient (1%) had changes in the right colon only and 3 patients (2%) had changes in the left colon only. Prior non-diagnostic endoscopies were performed in 22 patients (9%) with a median of 4 (mean 5) biopsies. In these histological changes were: normal (4), chronic inflammation (10), incomplete LC (4) and non specific changes (4).

**CONCLUSION:** While a full colonoscopy can be necessary in order to exclude other diagnoses, biopsies from the left colon are suffice for diagnosing or excluding LC in patients with chronic watery diarrhoea. The histological findings are not permanent and can change from one type of microscopic colitis to another suggesting that the different types of microscopic colitis are closely related.

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### **Regional Cerebral Water Contents in Hepatic Encephalopathy measured by MRI.**

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**Background & Aims:** The pathophysiology of hepatic encephalopathy (HE) may involve cellular cerebral edema due to osmotic swelling caused by glutamine accumulation. However, it has only been studied in patients with covert HE or by indirect methods.

**Methods:** We measured the absolute brain water contents with anatomical resolution by MRI in 7 cirrhosis patients during an episode of overt HE type C. Six patients with cirrhosis and no history of HE and 12 healthy age matched control subjects were also scanned. Two patients were rescanned after recovery from HE. The images were normalized to standard space and the image analysis used volumes of interest from a probabilistic brain atlas.

**Results:** The average whole brain water contents in both patients with HE and cirrhosis patients who never suffered from HE was 85 %  $\pm$  0.03 vs. 83 %  $\pm$  0.02 ( $P = 0.14$ ) in the healthy controls. Temporal lobe water was 86 %  $\pm$  0.03, 85 %  $\pm$  0.04, and 82 %  $\pm$  0.04 in HE, cirrhosis, and controls, respectively. The corresponding cerebellum water was 86 %  $\pm$  0.02, 84 %  $\pm$  0.03, and 82 %  $\pm$  0.02. The frontal lobe water was 84 %  $\pm$  0.03 in both HE and cirrhosis patients and 82 %  $\pm$  0.02 in the controls ( $P < 0.05$ , all regions HE vs. controls). The brain water contents of the two patients with overt HE fell after recovery by 0.9 % and 1.3%.

**Conclusions:** Our data quantitatively demonstrate low-grade cerebral edema in several brain regions in patients with overt HE and suggest that it may be reversible with recovery from HE. Cirrhosis patients without HE may also have slightly increased brain water.

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### **Leverens transport af konjugerede galdesyre bestemt med <sup>11</sup>C-cholylsarcosine PET/CT.**

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**Introduktion:** Galdeudskillelsen er en essentiel leverfunktion, som ikke kan stimeres med konventionelle målemetoder. Vi undersøgte om PET/CT, med den radioaktivt mærket galdesyre analog [N-methyl-<sup>11</sup>C]cholylsarcosine (<sup>11</sup>C-CSar) som tracer, tillod kvantitative bestemmelser af denne udskillelse i mennesker.

**Metode:** Ti raske individer og ti patienter med varierende grad af kolestase deltog. Hver enkelt blev undersøgt med to dynamiske PET/CT undersøgelser af 60 minutters varighed. <sup>11</sup>C-CSar blev givet intravenøst enten som bolus eller som konstant infusion. Blodkoncentrationerne af <sup>11</sup>C-CSar blev bestemt i prøver fra både en radial arterie og fra en levervene. <sup>11</sup>C-CSar koncentrationen i levervævet og i galdegangene blev optaget af PET kameraet. Gennemblødningen af leveren blev bestemt med intravenøs ICG-infusion og Fichs princip. Den hepatiske ekstraktionsfraktion blev beregnet ud fra <sup>11</sup>C-CSar koncentrationerne målt i arterie og levervene. Den fraktionelle galdeudskillelse til et givent tidspunkt blev beregnet som ratioen mellem det udskilte <sup>11</sup>C-CSar og den totale mængde <sup>11</sup>C-CSar tilbudt til leveren.

**Resultater:** For både raske individer og patienter med kolestase steg koncentrationen af <sup>11</sup>C-CSar i levervævet hurtigt efter traceradministration. Den efterfølgende udskillelse af <sup>11</sup>C-CSar fra levervævet og ud i galden var signifikant reduceret hos patienter med kolestase. Hos patienter med kolestase var udskillelsen til galdegangen (ductus hepaticus communis) forsinket og nåede en mindre maksimal koncentration end hos raske individer.

Hos raske individer var den hepatiske ekstraktionsfraktion konstant 90% (85 - 94%) gennem hele den 60 minutter lange PET optagelse. Hos patienter med kolestase faldt ekstraktionsfraktionen fra initialt 86% (77 - 93%; p=0,09) til 50% (28 - 59%; p<0,0001). Dette viser, at hos patienterne med kolestase er optagelsen af konjugerede galdesyre fra blod til hepatocytter normal, men samtidigt koblet med et signifikant tilbageløb fra hepatocytter til blod. Hos de raske individer er der imidlertid ikke tilbageløb til blodet.

Den fraktionelle galdeudskillelse af <sup>11</sup>C-CSar ved 50 minutter var 73% (55 - 80%) hos raske individer og 38% (17 - 70%) hos patienter med kolestase (p<0,001). Dette demonstrerer en nedsat udskillelse af <sup>11</sup>C-CSar fra hepatocytter til galde hos patienter med kolestase.

**Konklusion:** Med <sup>11</sup>C-CSar PET/CT var det muligt at bestemme leverens optagelse og udskillelse af konjugerede galdesyre. Hos patienter med kolestase var leverens optagelse af <sup>11</sup>C-CSar normal, mens udskillelsen til galden var nedsat og med betydeligt tilbageløb til blodet. Disse resultater viser et fremtidigt potentiale for kvantitative undersøgelser af leverens galde-transport med <sup>11</sup>C-CSar PET/CT.

44)

### **Vitamin D status and response to anti-TNF $\alpha$ therapy in inflammatory bowel disease**

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**Background and aims:** Vitamin D has immune modulating potential in inflammatory bowel disease (IBD) and might have a synergistic effect on anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$ )

therapy. We wanted to investigate whether pre-treatment vitamin D levels affect IBD-patients' response to anti-TNF $\alpha$  therapy.

**Methods:** We performed a retrospective, single-centre study on all IBD-patients receiving anti-TNF $\alpha$  therapy from November 2011 to February 2014. Patients' vitamin D status, clinical scores (Harvey Bradshaw Index and Simple Clinical Colitis Activity Index) and inflammatory markers prior to and during one year of treatment were collected. Patients were categorised according to their vitamin D status as either insufficient (P-25-hydroxy vitamin D < 50 nmol/L) (D-low) or sufficient (P-25-hydroxy vitamin D > 50 nmol/L) (D-high).

**Results:** 78 patients were included. At baseline, D-low patients (n = 15) were more ill than D-high patients (n = 63), measured by CRP (median: 10.75 mg/L vs. 3.4 mg/L,  $p < 0.001$ ), albumin (median: 35.5 g/L vs. 38 g/L,  $p < 0.05$ ) and haemoglobin (median: 7.9 mmol/L vs. 8.5 mmol/L,  $p < 0.05$ ). Clinical scores and f-calprotectin did not reach statistical significance. Both groups responded to anti-TNF $\alpha$  treatment and ended up at the same levels regarding clinical scores, CRP, albumin and haemoglobin. However, f-calprotectin levels were consistently higher in D-low patients and this difference reached statistical significance at follow-up week 14.

**Conclusion:** Vitamin D insufficiency is associated with increased disease activity in IBD. More studies are needed to clarify whether vitamin D status affects these patients' response to anti-TNF $\alpha$  therapy.

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#### **Effects of Niemann-Pick Type C2 protein treatment on non-alcoholic steatohepatitis in a rat model**

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**Background and aim:** Patients with non-alcoholic steatohepatitis (NASH) have an increased risk of cirrhosis, liver cancer, diabetes and death from cardiovascular disease, but we lack effective means to treat the condition. The Niemann-Pick type C2 (NPC2) protein, a small soluble protein mediating intracellular cholesterol trafficking from the lysosome to post-lysosomal destinations. We hypothesized that NPC2 treatment could prevent or reduce steatosis and inflammatory changes in a rat NASH model.

**Material and methods:** NASH was induced in rats by feeding a high-fat, high-cholesterol (2%) diet (HFHC) for 4 weeks. Animals received two weekly intravenous injections of 5 mg/kg bovine NPC2 or placebo throughout the study period or for the last 2 weeks. We investigated liver/body weight ratio and plasma concentrations of alanine and aspartate aminotransferases (ALT and AST), gamma-glutamyl transpeptidase (GGT) and bilirubin along with triglycerides, cholesterols and various cytokines. Further, we assessed liver fat and inflammation by immunohistochemistry.

**Results:** The HFHC fed rats had significantly elevated liver and spleen weights, liver/body weight ratio, liver enzymes (ALT, AST, GGT, bilirubin), cholesterols (HDL, LDL, total cholesterol) and pro-inflammatory cytokines iL-1 $\beta$ , iL-6, TNF- $\alpha$  and KC/GRO ( $p < 0,005$ ) compared to controls on isocaloric diet. The anti-inflammatory cytokines iL-10 and iL-13 were lowered in HFHC fed animals. NPC2 treatment did not change liver/body weight ratio or concentrations of ALT, AST, GGT, bilirubin, or most cytokines. However, the anti-inflammatory cytokine IL-4 was significantly

up-regulated by NPC2 treatment (5,6 vs. 4,0, p=0,03). There was a trend towards higher HDL- and total cholesterol in NPC2-treated animals as well as serum triglycerides (0,48 vs. 0,39, p=0,05).

**Conclusion:** Our preliminary data in this HFHC rat NASH model indicate that NPC2 treatment could not prevent or reduce steatosis and inflammatory changes.

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### **Soluble PD-1 levels are associated with disease activity and treatment response in patients with autoimmune hepatitis**

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**Background:** Autoimmune hepatitis (AIH) is a chronic liver disease caused by impaired immune regulation. Programmed death 1 (PD-1) and its ligands PD-L1/L2 play an important role in preventing auto-reactivity. PD-1 is a cell surface inhibitory receptor mainly expressed by T-lymphocytes while the ligands, PD-L1 and PD-L2 are present on antigen presenting cells. Both PD-1 and its ligands exist in soluble forms. Previous studies in AIH suggest that PD-1 mediated immune-regulation is involved in AIH and we hypothesized AIH to be associated with a dysfunctional PD-1/PD-L1/2 mediated immune regulation. We studied this, in AIH, by examining patients systemic levels of soluble (s) PD-1. Further, we also stimulated CD4+ T cells to evaluate their ability to up-regulate PD-1 .

**Methods:** We included 72 AIH patients (female/male 48/24, median age 49 (range: 20-81)) receiving different immune-suppressive treatments. Both patients with active and quiescent disease were included. Forty-seven healthy volunteers were included as controls. We measured sPD-1 by ELISA and PD-1 up-regulation on T cells following 48 hours of *in vitro* stimulation with CD3/CD28 in 26 AIH patients and in 10 of the healthy controls.

**Results:** Soluble PD-1 was significantly elevated both in AIH patients with active disease (0.25±0,11 ng/mL) and in AIH patients who were non-responders to standard therapy (0,29±0,47 ng/mL) compared with AIH patients who were responders to standard therapy (0.16±0,17 ng/mL, p=0,003 and 0,018, respectively) and HC (0,14±0,11 ng/mL, p=0,003 and p=0,017, respectively). PD-1 was significantly up-regulated by times 3.3 on T cells from AIH patients following *in vitro* activation compared to HC.

**Conclusion:** In the present study we observed increased sPD-1 and increased *in vitro* up-regulation of PD-1 following T cell stimulation, supporting an increased PD-1 mediated immune-regulation in AIH patients.

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### **Biochemical diagnosis of bile acid diarrhoea using FGF19**

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**Introduction:** Bile acid diarrhoea (BAD) is a common and less acknowledged cause of chronic watery diarrhoea. The 7-day radiolabeled <sup>75</sup>Selenium homocholelic acid taurine (SeHCAT) test is not generally available, is cumbersome and expensive. Patients suffering from undetected BAD have a poor quality of life and are withheld effective therapy with sequestrants. New insight into the regulation of bile acid physiology have identified fibroblast growth factor FGF19 and 7 $\alpha$ -hydroxycholest-4-en-3-one (C4) as possible markers of BAD and demonstrated a correlation with SeHCAT. FGF19 concentrations are easily measured but subject to diurnal variation and postprandial increase. C4 is measured by high performance liquid chromatography and thus less available. Further studies of FGF19 as a test for BAD are warranted.

**Objective** To confirm the association between SeHCAT and FGF19 in a prospective patient series, to examine the inter-and intra-individual variation on FGF19 levels, and to explore values in patients cholecystectomised, and whether the overlap between normal and individuals with BAD could be reduced by measuring the meal induced change in FGF19. **Methods** FGF19 was measured by commercially available quantitative sandwich enzyme immunoassay technique (Quantikine® ELISA, R&D Systems Europe, Ltd.) before and one hour after meals and after 1 week in healthy volunteers, in patients with previous diagnosed BAD or cholecystectomy, and in consecutive patients referred to SeHCAT. The median (range) FGF 19 values are given as pg/mL. No correction for cholesterol values or weight was performed. The interassay variation was 9.6 % in our laboratory. **Results** The median FGF19 was lower for patients with BAD but with a wide overlap to both healthy controls and cholecystectomied patients. The least squares linear correlation coefficient  $r = 0.5$  for the relation between SeHCAT, and FGF19 in the prospective series in which the breakfast induced increase in FGF19 did not differ significantly (Mann-Whitney). Neither single values nor meal induced changes in FGF19 could predict or rule out BAD. The inter-individual variation of fasting FGF19 values in all 56 participants was large.

#### **Conclusion**

- The overall results confirm that FGF19 is lower in patients with BAD and correlates to SeHCAT.
- FGF19 varies over time for any individual. Neither fasting nor single postprandial values of BAD can identify patients with BAD.
- The utility and timing of FGF19 values as a diagnostic test for BAD using a more powerful and uniform stimulation of the bile acid transporter should be tested.

Further studies should explore the utility of using the area under the curve of FGF19, FGF19 values following stimulation of the intestinal bile acid transporter and the combination with other markers such as C4

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#### **Risk of unemployment, sick leave and work disability among patients with inflammatory bowel disease: A 7 year follow-up study of a Danish inception cohort**

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**Objective.** To assess the occurrence and risk of unemployment (UE), sick leave (SL) and work disability (WD) in incident patients with IBD after 7 years of follow-up compared to the background population.

**Methods:** The study population encompassed patients aged 18-67 years (N=379) from an IBD-inception cohort registered Jan 1, 2003 to Dec 31, 2004 in a Copenhagen area. Clinical data were collected from the medical records. Data on UE, SL and WD were retrieved from national registers. A random subset of the general population (n=1,435) were matched on sex, age and residency to IBD cases. Cumulative probabilities of UE, SL and WD were calculated. Cox proportional hazard regression was performed to identify possible predictors.

**Results:** There was no difference in unemployment rates between IBD patients and controls (P = .23). More IBD patients than controls experienced more than 4 consecutive weeks of SL (P<0.01) and more IBD patients than controls obtained WD (P=0.05). Compared to controls, IBD patients were not at increased risk of UE, however the risk of SL was significantly increased in IBD patients (HR 2.0; 95% CI 1.7-2.4) and highest in patients of younger age as the risk of WD was increased in IBD patients (HR 2.1; 95% CI 1.2-3.8) and most pronounced in male patients aged above 55 years. The rate of WD in CD (5.8%) was markedly lowered compared to previous studies.

**Conclusions:** The observed increased risk of SL and WD in patients with IBD underscores the need for early identification of risk factors. A multidisciplinary approach to patients in order to secure IBD patients' participation on the labour market is recommended.

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#### **Can a mouse model aid the understanding of CD163 in alcoholic liver disease?**

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**Introduction:** CD163 is a phenotypic marker of resident macrophages such as Kupffer cells and of alternatively activated macrophages. Soluble CD163 (sCD163) is highly up-regulated in patients with alcoholic cirrhosis and alcoholic hepatitis where the levels are associated with disease severity. The functional role of CD163 in alcoholic liver disease is, however, still poorly understood. To accommodate this, we aimed to investigate whether a well-established mouse model of alcoholic liver disease can be used study the role of CD163 in alcoholic liver disease.

**Methods:** We employed a chronic-binge-model of alcoholic liver disease along with pair feed controls. Serum sCD163, ALT, AST and bilirubin were measured. Liver leukocytes were isolated using enzymatic digestion and analysed by flow cytometry for the expression of F4/80<sup>hi</sup>CD11b<sup>low</sup> (Kupffer cells) and F4/80<sup>int</sup>CD11b<sup>hi</sup> (infiltrating monocytes) and a viability marker. Histological HE and trichrome stainings were performed on paraffin embedded tissue sections.

**Results:** In the ethanol feed mice, soluble CD163 was 355.8ng/ml±74.5 compared with 337.7ng/ml±73.6 in the control mice (p=0.2). Both ALT (62.8U/ L±25.4 vs. 25.3±7.5, p=0.001) and AST (149±41 vs. 69.6±15.1, p=0.002) levels were increased in ethanol fed mice compared with control mice, but no difference in bilirubin levels (p=0.1). SCD163 correlated positively with AST (r=0.51, p=0.05) but not with ALT. Among the isolated leukocytes, we were able to detect both F4/80<sup>hi</sup>CD11b<sup>low</sup> Kupffer cells (ethanol feed mice 3.64%±2.11 vs. control mice 1.67%±0.95) and infiltrating F4/80<sup>low</sup>CD11b<sup>hi</sup> monocytes (18.95%±5.25 vs. 20.50%±7.10). Cell viability was above

85% in all experiments. The histological stainings demonstrated steatosis in the ethanol feed mice but not in the control mice. No difference in leukocyte infiltration was evident on the HE stainings.

**Conclusion:** We were able to detect and quantify levels of sCD163 and monocyte/macrophage numbers. The sCD163 and cell numbers were not as increased in ethanol feed mice as expected based on human studies, but neither was the liver injury. Mice may, therefore, be used to assess basic mechanistics of CD163 although changes in the alcoholic liver injury model may be needed.

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### **Leveradenomer ved Aarhus Universitetshospital i perioden 2000-2013**

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**Baggrund:** Leveradenom (hepatocellulært adenom, HCA) er en sjælden benign primær levertumor udgående fra hepatocytter i en ellers rask lever. HCA optræder langt overvejende (85%) hos yngre p-pille-brugende kvinder, er ofte asymptomatisk, men kan afhængigt af størrelse og placering give anledning til smerte, ruptur og blødning. Sammen med adenomstørrelse er mandligt køn og beta-catenin-aktivering risikofaktorer for malign transformation til hepatocellulært carcinom (HCC).

**Formål og metode:** Et retrospektivt, deskriptivt studie af tidligere og nuværende HCA patienter tilknyttet Aarhus Universitetshospital mhp. patologisk/genetisk subtypeinddeling samt kvalitetssikring af håndteringen af adenompatienter. Ud af 135 konsekutive patienter med ICD-10-diagnosekode: DD134, "Godartet tumor i leveren" med kontakt til Medicinsk Hepato-Gastroenterologisk Afdeling V, Kirurgisk Gastroenterologisk Afdeling L og/eller multidisciplinær leverkonference, MDT, identificeredes 32 patienter med HCA, 28 kvinder og 4 mænd.

**Resultater:** HCA patienterne havde en median alder på 35(range 20-74) år. 88% af kvinderne var tidligere eller aktuelt behandlet med oral kontraktion, 62% af patienterne havde BMI > 25, og for 22% var der billeddiagnostisk og/eller histologisk tegn til steatose. HCA optrådte solitært hos 56% og multipelt og som adenomatose ( $\geq 10$  adenomer) hos 34% respektivt 9%, med en medianstørrelse af største adenom på 80(12-180) mm. Hyppigste symptom, der førte til undersøgelse og dermed fund af HCA, var abdominal smerte/ubehag (53%). 6(19%) patienter, heraf 5 som debut af HCA, præsenterede sig med blødning og 59% af patienterne blev behandlet med kirurgisk resektion, RFA og/eller embolisering. Der var ingen med transformation til HCC.

**Konklusion:** Den overordnede demografi og patienternes kliniske karakteristika afspejler tidligere studiers. På baggrund af ny viden om diagnostik og behandling af leveradenomer herunder risikoen for størrelsesprogression og malignitet, giver foreløbige resultater på de 32 patienter anledning til fortsatte kontroller og/eller bioptering af 6 ellers afsluttede patienter. Subtypeinddeling ud fra immunohistokemisk undersøgelser inkl. farvning for beta-catenin-aktivering (øget malignitetspotentiale) og sammenholdning med fænotype afventes fortsat.

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### **Restoration of enteroendocrine and pancreatic function after internal hernia and short bowel syndrome in a woman with previous gastric bypass surgery**

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**Introduction:** Roux-en-Y gastric bypass (RYGB) surgery leads to altered gastrointestinal anatomy and increased postprandial secretion of gut hormones from enteroendocrine cells. We analysed gut hormone concentrations in plasma from a 22-year old non-diabetic woman with a history of RYGB, suffering from severe internal hernia. The patient underwent extensive bowel resection resulting in short bowel syndrome (saliva-fistula from upper part of the stomach to stoma, intact duodenum, 15 cm of jejunum and 35 cm jejunum and colon). Analyses were carried out before and after reconstructive surgery where the intestinal continuity was re-established (Fig. 1).

**Methods:** A standardized meal test was performed 7 days before and 60 days after reconstructive surgery. Blood samples were drawn for measurement of plasma glucose, insulin, C-peptide, glucagon, glucose-dependent insulintropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), polypeptide YY (PYY), glucagon-like peptide-2 (GLP-2), cholecystokinin (CCK) and gastrin.

**Results:** As expected, preoperative plasma concentrations of glucose, insulin, C-peptide, glucagon and gut hormones remained at baseline throughout the meal test. After reconstructive surgery glucose, insulin and C-peptide concentrations exhibited bi-phasic profiles with peaks at 30 min and 150 min. Glucagon concentrations increased slowly and peaked after 180 min at 8 pmol/l. GIP increased steadily between 30 to 120 min, where peak concentrations were reached (~50 pmol/l). During the same period, GLP-1 and GLP-2 concentrations reached 50 pmol/l and 100 pmol/l, respectively, and high peak concentrations (~150 pmol/l) were observed at 150 min. PYY concentrations increased progressively reaching 1400 pg/ml at 180 min. At 30 and 150 min, CCK concentrations displayed 2 major peaks (~10 pmol/l), whereas gastrin concentrations were still rising after 240 min (~50 pmol/l).

**Conclusion:** Our patient experienced severe complications after RYGB surgery and underwent extensive bowel resections resulting in short bowel syndrome and disappearance of normal postprandial enteroendocrine and pancreatic endocrine responses. However, following reconstructive surgery postprandial plasma concentrations of gut and pancreatic hormones were fully restored. GIP, GLP-1 and GLP-2 concentrations were comparable to levels observed after RYGB surgery, whereas PYY concentrations were markedly higher (~1400 pg/ml).

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### **Drug induced liver injury in Danish patients, a 5-year retrospective database study**

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**Introduction:** The idiosyncratic sub type of drug induced liver injury (DILI) is a rare side effect of medical treatment that in severe cases can lead to acute liver failure and death.

**Methods:** We identified all inpatients (n=44) at the Department of Hepatology, Rigshospitalet, diagnosed with DILI within a 5-year retrospective period from 2007 to 2012. The following parameters were registered: symptoms, comorbidity, biochemistry levels, treatment and outcome.

**Results:** Of 44 patients, 26 (59,1%) were women, mean age was 53,9 years. The two most common drugs inducing DILI were Disulfiram (29,5%) and antibiotics (18,2%) The most common symptoms were jaundice, nausea, tiredness and gastrointestinal discomfort. At the time of diagnosis a moderately or highly raised ALT (88,6 %), INR (68,2 %) and bilirubin (56,8%) was most

frequently seen. Twentythree patients were treated with glucocorticoids. 52,3 % patients had a severe course of illness and needed intensive treatment. Seven patients (15,9%) were liver transplanted and 9 patients died. 5 of 9 of the patients who died had a history of abuse of alcohol and/or liver cirrhosis. Twentyseven patients survived and recovered completely.

**Conclusion:** In this retrospective study 36% of the patients with DILI died or developed fulminant liver failure treated with liver transplantation. The patients are from a tertiary hospital and thus represent a selected population, but the results underline that DILI can be severe and run a fatal course. The symptoms and biochemistry resemble those of other parenchymal liver diseases.

**Key words:** Drug induced liver injury, DILI, idiosyncratic, liver transplantation, Disulfiram, Antibiotics, green tea, Nitrofurantoin.

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### **Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study**

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**Background and aims:** Alcohol is the major contributing factor of alcoholic cirrhosis, but less is known about the significance of drinking pattern. We examined two hypotheses regarding drinking pattern and risk of alcoholic cirrhosis: (1) if daily drinking is associated with an increased risk compared to drinking less frequently and (2) if drinking wine is associated with a decreased risk compared to drinking beer and liquor.

**Methods:** We investigated risk of alcoholic cirrhosis among 55,971 participants from the Danish Cancer, Diet, and Health study (1993-2011). Baseline information on alcohol intake, drinking pattern, and confounders came from questionnaire. Follow-up information came from national registers. We calculated hazard ratios (HR) for alcoholic cirrhosis in relation to alcohol drinking frequency (drinking days per week) and percentage of wine of weekly alcohol consumption in strata of weekly alcohol consumption.

**Results:** We observed 257 and 85 incident cases of alcoholic cirrhosis among men and women, none among never drinkers. Compared to drinking 2-4 days/week, in men, HR were 1.30 (95%CI: 0.59;2.87), 1.43 (95%CI: 0.84;2.43), and 3.65 (95%CI: 2.39; 5.55) when drinking 1 day/week, 5-6 days/week, and in daily drinkers, respectively (p for trend <0.001). In women, compared to drinking 2-4 days/week HR were 1.45 (95%CI:0.71;2.96), 2.30 (95%CI: 1.14;4.67), and 1.73 (95%CI: 0.85; 3.52) when drinking 1 day/week, 5-6 days/week, and in daily drinkers, respectively (p for trend 0.14).

In men drinking 14-28 drinks/week, HR were 7.47 (95%CI: 1.68; 33.12), 3.12 (95%CI: 1.53; 6.39), and 1.69 (95%CI: 0.79; 3.65) in drinkers of little (<1% of alcohol consumption), some (1-15%), and mostly wine (50-100%), respectively. In women, due to few cases it was not possible to model a risk function for percentage of wine of weekly alcohol consumption.

**Conclusions:** In men, daily drinking, especially, increase the risk of alcoholic cirrhosis and compared to beer and liquor, wine might be associated with a lower risk of alcoholic cirrhosis. In women, we are unable to draw firm conclusions due to low statistical power though in general we found the same trends regarding drinking pattern and risk of alcoholic cirrhosis.

**A retrospective cohort study of patients with autoimmune hepatitis followed at department of hepatology, Rigshospitalet, Copenhagen, Denmark**

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**Introduction and aim:** Autoimmune hepatitis (AIH) is a condition with chronic inflammation in the liver of unknown etiology that – if untreated, leads to liver cirrhosis and increased mortality. AIH occurs in children and adults of all ages, more frequent in women than men (female-male ratio of 3.6 to 1). The incidence in Denmark is 2 per 100.000 per year and the prevalence 11 to 25 per 100.000 inhabitants. The aim in this retrospective study is to describe characteristics and treatment regimens of all patients with AIH followed at a tertiary center.

**Patients and Methods:** Patients diagnosed with AIH and patients with AIH with overlap syndrome (concomitant PBC or PSC), and seen at least once in department of Hepatology in the period the department from 1st of January 2008 to 30rd of June 2013, were included in the study. In all patients screening and exclusion of liver disease of other etiologies had been performed, thus no viral, toxic hepatitis, metabolic or genetic causes of liver diseases were demonstrated.

Data were collected from the patient files data included age, race, gender, other autoimmune diseases, laboratory data, histopathological findings, smoking habits, alcohol consumption and presence of cirrhosis. Cirrhosis was diagnosed based on biopsy or blood analyses combined with clinical findings (ascites, varices, spiders) and imaging. Laboratory data at the time of diagnosis were registered before initial immunosuppressive treatment. All treatment regimens and the indications for changes treatment were registered.

**Results:** 254 patients were identified. 26 patients were excluded due to lack of clinical data, insufficient diagnostics or incorrect diagnosis coding, leaving 228 evaluable patients. The patients were followed for a median time of 84 months. 167 were female and 61 male; a ratio of 2.7:1. In the female patients AIH was most frequently diagnosed between the ages of 40-50 years, whereas in men no peak age was observed. In our data set, only few were diagnosed with AIH in childhood ( $n=26$ ; 11%) and at ages over 70 years ( $n=7$ ; 4%). Median age at the time of diagnosis is 42 years. 144 (63%) patients did not have any concomitant autoimmune diseases. 83 (37%) patients had one or more other autoimmune diseases, most commonly other autoimmune liver disease, namely 22 cases of PBC (9.6%) and 20 cases of PSC (18.4%). Sixty-six patients (30%) had cirrhosis at the time of diagnosis. 48 of those were female with median age of 46 (range 9-70) and 18 male with median age of 18 (range 14-69) giving a female: male ratio of 2.7:1. Up to 83% ( $n=55$ ) of patients with cirrhosis were diagnosed by biopsy and the remaining 11 (17%) cases based on a combination of clinical findings, blood analyses and imaging. In the period the patients were followed, the treatment regimens were changed due to side effects (71 cases), treatment failure (29 cases), remission (64 cases) or because the patients were not interested in any treatment (11 cases). By the end of the study recruitment in June 2013, 18 patients (7.8%) were in remission without treatment. 71 patients (31%) were on monotherapy, with either azathioprine ( $n=36$ ; 15.6%), prednisolone ( $n=17$ ; 7.5%), mycophenolate mofetil ( $n=7$ ; 3%), tacrolimus ( $n=2$ ; 0.8%) or budesonide ( $n=9$ ; 3.9%). 71 patients (31%) were on standard treatment with prednisolone and azathioprine whereas 48 patients (21%) were treated with alternative two-drug combinations. Eleven patients (4.7%) were treated with a combination of three different drugs. In cases where standard treatment could not induce remission, budesonide and mycophenolate mofetil were the most used second line/alternative drugs. 9 patients were dead or transplanted.

**Conclusion:** In this cohort of Danish AIH patients, age and gender distribution and the occurrence of cirrhosis at diagnosis is similar to that observed in other cohorts<sup>8</sup>. Autoimmune comorbidity was frequent, and the high frequency of overlapping autoimmune liver reflects that the cohort is treated at a tertiary center. In order to gain disease control and avoid side effects many different treatment regime has been used.

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