

Abstracts DSGH Årsmøde Kolding september 12-13

Foredrag holdes fredag d 12 september

Foredragskonkurrence: Abstracts nr 1-8; kl 16.30-18.00

Korte foredrag (ePosterpræsentation) session 1: abstracts nr 9-17, kl 11.10-12.00

Korte foredrag (ePosterpræsentation) session 2: abstracts nr 18-25, kl 14.00-14.45

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1. Serial cognitive testing in patients with obesity and MASLD: Cognitive impairments remain despite metabolic restoration

Charlotte W. Wernberg,^{1,2} Lea L. Grønkjær,¹ Birgitte Gade,¹ Karin Weissenborn,² Hendrik Vilstrup,³ Mette M. Lauridsen¹

1 Liver Research Group, Department of Gastroenterology and Hepatology, University Hospital of South Denmark, Esbjerg, Denmark; 2 Department of Neurology, Medizinische Hochschule Hannover, Hannover, Germany 3 Department of Gastroenterology and Hepatology, Aarhus University Hospital, Aarhus, Denmark

Background and Aims: Obesity is linked to cognitive dysfunction and metabolic dysfunction, particularly affecting executive functions and memory. This study investigates whether weight loss and improved severity in metabolic dysfunction associated steatotic liver disease (MASLD) can reverse cognitive deficits, and explores the relationship between cognitive impairment and obesity-related comorbidities.

Method: A prospective cohort study with liver biopsies, biometric evaluation, and cognitive assessments. Cognitive tests included the Continuous Reaction Time (CRT) test, the Portosystemic Encephalopathy Syndrome (PSE) test, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). PHES and RBANS batteries assess multidomain function, and only RBANS includes memory assessment. Participants ($\text{BMI} \geq 35 \text{ kg/m}^2$) were followed, with a third undergoing bariatric surgery after baseline visits. We analysed changes in test scores after surgery-induced weight loss and whether weight change or improvements in liver histology correlated with cognitive performance changes.

Results: We included 137 patients with serial cognitive testing and liver biopsies; 67% were women, aged 46 ± 12 years. In baseline liver biopsies, 26% did not meet the criteria for MASLD, 48% had MASLD, and 26% had MASH. 73% had low grades of fibrosis (F0-F1), 19% had F2, and 7% had F3-F4. Mean weight was 121 kg (SD 22), and 24% had type 2 diabetes. We used well-defined cut-offs for abnormal test results: CRT index <1.90 , PHES <-4 , and RBANS index <79 ; and found that the mean CRT index was 1.6 (SD 0.6), PHES 0.5 (SD 3.8), and RBANS 82 (SD 18). At follow-up, mean 2.7 years (SD 0.43), patients in the bariatric surgery arm ($n=43$) had lost a mean of 34.4 kg (± 17), while controls ($n=94$) had a weight change of -2.8 kg (± 13). There was no significant difference between the intervention and control groups in the change of the tests: CRT index score 0.17 (SD 0.7) vs. -0.02 (SD 0.52); PHES sum score 0.73 (SD 1.4) vs. 0.81 (SD 2.9); and the RBANS index 8.4 (SD 16) vs. 6.8 (SD 15). When stratifying patients in the intervention and control arm into worsened/stable/improved in NAFLD activity score (NAS), we observed no difference between the change in either the CRT index ($\Delta 0.08$), PHES sum score ($\Delta -0.04$), or the RBANS index ($\Delta 0.06$) ($p > 0.3$).

Conclusion: A large group of patients with severe obesity and mild MASLD had abnormal CRT and RBANS tests at baseline. Weight loss and liver histology changes were not associated with changes in

cognitive test results. This suggests that metabolic restoration does not reverse brain dysfunction, potentially due to neurodegeneration caused by premature brain aging.

2. Alcohol, Cardiometabolic Risk Factors, and Cirrhosis: Ten-Year Risk Estimates from a Nationwide Danish Cohort

Jonas Hedelund Rønn, Peter Jepsen, Hamish Innes, Jessica Mellinger, Marie H. Eliassen, Lone G. Madsen, Gro Askgaard

Introduction: Alcohol consumption and cardiometabolic risk factors increase the risk of cirrhosis, and their combined effects have gained recognition with the introduction of the MetALD term. We estimated 10-year risks of cirrhosis according to alcohol consumption and cardiometabolic risk factors.

Methods: We included participants from the population-based Danish National Health Surveys 2010-2017 and followed them in registries through 2022 for an incident hospital diagnosis of cirrhosis, linking data on alcohol consumption, smoking status, height and weight from questionnaires with data on diabetes and redeemed hypertension- and dyslipidemia prescriptions from health registries. A drink was defined as 12 grams of alcohol. We computed the 10-year risk of cirrhosis, accounting for death as a competing event and used inverse probability weights to adjust for the differences in age between participants across the strata of risk factors for cirrhosis.

Results: The study included 304,023 participants with a median age of 52 years (IQR 43-61); 54 % were female, 3% consumed more than 28 drinks per week, 17% had a BMI greater than 30, and 4.5% had diabetes. During 2,905,528 person-years of follow-up, 1010 participants were diagnosed with cirrhosis. The level of alcohol consumption had a powerful influence on the 10-year risk of cirrhosis with an 11-fold higher risk for 29-41 drinks/week of 2.29% and 30-fold higher risk of 5.2% for those consuming more than 42 drinks/week compared to 0.2% for those drinking 1-14 drinks/week. The largest number of cirrhosis cases occurred among participants consuming fewer than 29 drinks per week, where diabetes increased the 10-year risk of cirrhosis by fourfold, and other cardiometabolic risk factors (BMI over 30, hypertension, dyslipidemia, and smoking) increased the risk by two- to threefold. Among participants drinking more than 28 drinks/week, the influence of cardiometabolic risk factors on the 10-year cirrhosis risk weakened; however, notably, the highest 10-year risks of cirrhosis were found in participants drinking more than 28 drinks/week who also had diabetes or hypertension. A high BMI did not significantly affect the risk of cirrhosis in drinkers of 28-42 drinks/week, with 10-year risks of 1.9% vs. 1.8% for BMI of 18.5-25 vs. BMI $\geq$ 30.

Conclusion: The level of alcohol consumption has a substantial impact on the absolute 10-year risk of cirrhosis. The impact of cardiometabolic risk factors on the 10-year risk of cirrhosis is markedly weaker than alcohol, especially among those who consume more than 28 drinks/week. However, most cases of cirrhosis develop in the large population segment who drink small or moderate amounts of alcohol, indicating that preventive efforts should not be restricted to those who consume the most alcohol.

3. Hospitalised acute severe ulcerative colitis patients treated with rescue infliximab risk treatment failure due to underexposure caused by high drug clearance

Pernille Dige Ovesen^{1*}, Alix Démaris^{2,3*}, Johan F. K. F. Ilvemark¹, Jakob B. Seidelin⁴, Wilhelm Huisinga⁵, Robin Michelet³, Charlotte Kloft^{3†}, Casper Steenholdt^{6,7†}

¹Dept of Gastroenterology, Herlev Hospital, Denmark (DK). ²Dept of Clinical Pharmacy and Biochemistry, Freie Universitaet Berlin, DE. ³Graduate Research Training Program PharMetrX, Germany (DE). ⁴Dept of Digestive Diseases, Transplantation and General Surgery, Rigshospitalet, DK. ⁵Institute of Mathematics, Universitaet Potsdam, DE. ⁶Dept of Medical Gastroenterology, Odense University Hospital, DK. ⁷Research Unit of Medical Gastroenterology, Dept of Clinical Research, University of Southern Denmark, DK. *shared first authorship, † shared last authorship.

Background: Acute severe ulcerative colitis (ASUC) occurs in 25% of patients with ulcerative colitis resulting in hospital admission and treatment with corticosteroids followed by rescue therapy with infliximab (IFX), if needed. High baseline IFX clearance at admission has been associated with risk of colectomy supporting an intensified regimen in case of insufficient effect.¹ However, a recent randomized controlled trial did not find superior outcomes of different intensification regimens.² We investigated if admitted patients with ASUC have increased clearance of IFX during course of induction.

Methods: IFX concentrations from 154 patients with ulcerative colitis were retrieved from our biobank resulting in 248 (81%) induction phase and 58 (19%) maintenance phase samples. These data were used to construct a non-linear mixed effect model describing IFX pharmacokinetics (PK). Variables tested for potentially influencing IFX clearance comprised clinical disease activity according to Mayo or SCCAI scores, endoscopic severity defined by Mayo score, CRP, albumin, patient demographics, and whether patients were treated as outpatients or hospitalised, including fulfilment of Truelove and Witts criteria.

Results: In line with previous reports, a 2-compartment model with linear clearance accurately described IFX PK.³ Central and peripheral volumes of distribution were 6.52 L and 2.56 L, and intercompartmental clearance 0.146 L/day. Hospitalisation status was the most impactful variable significantly influencing IFX clearance in the model. Hence, hospitalised patients with ASUC (n=50, 32%) had 35% [95%CI: 14-56%, p<0.001] increased IFX clearance compared to outpatients (median clearance 0.463 L/day vs. 0.339, p<0.0001). This resulted in substantially decreased IFX exposure in ASUC patients from week 2 onwards and most pronounced during the early phase of induction. Thus, 74% of ASUC patients had sub-therapeutic IFX concentrations at week 2 (<20 ug/mL), 69% at week 6 (<15 ug/mL), and 56% at week 14 (<7 ug/mL).⁴ In contrast, only a minority of outpatients had sub-therapeutic IFX during the induction phase (week 2: 16%; week 6: 25%; week 14: 19%). There was no statistical difference in IFX clearance between ASUC patients formally fulfilling Truelove Witts criteria or not (0.442 L/day [0.250-0.636] vs. 0.516 [0.292-0.625], p=0.08). Addition of albumin did not significantly improve the model.

Conclusion: IFX clearance is substantially increased during ASUC, irrespective of formal fulfilment of Truelove Witts criteria, resulting in underexposure in the majority of patients treated with a standard dosing regimen. An intensified induction regimen should be considered for routine use.

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4. Beyond Ammann's pain classification: Multidimensional Pain Phenotyping and Cluster Analysis in Chronic Pancreatitis

Louise Kuhlmann¹, MD PhD, Ana Dugic², MD, Anna Evans Phillips³, MD, Dhiraj Yadav³, MD MPH, Divya Pillai⁴, MSC, Elaina Vivian⁵, MPH, Enrique de-Madaria⁶, MD PhD, Mahya Faghieh⁷, MD, Misbah Unnisa⁸, Pharm D, Patrick Michl², MD PhD, Paul Tarnasky⁵, MD, Péter Hegyi^{9,10,11,12}, MD PhD, Pramod Garg⁴, MD, Rasmus Bach Nedergaard^{1,13}, MD PhD, Rasmus Hagn-Meincke^{1,13}, MD, Rupjyoti Talukdar⁸, MD, Shagufta Farheen⁸, Pharm D, Soumya Jagannath⁴, MD, Vikesh Singh⁷, MD MSc, Zoltán Hajnádý^{9,10}, MD, Søren Schou Olesen^{1,13}, MD PhD, John A Windsor¹⁴, MD FRACS, Asbjørn Mohr Drewes^{1,13}, MD PhD DMSc *On behalf of the International Pancreatic Pain Consortium

Background: Assessment of pain to date in chronic pancreatitis (CP) has largely focused on intensity and pattern, unable to address its complexity. To evaluate pain in a multidimensional fashion, we aimed to identify pain phenotypes based on the Comprehensive Pain Assessment Tool Short Form (COMPAT-SF) questionnaire and examine their associations with clinical factors.

Methods: We studied 248 patients with painful CP from Asia, Europe, and the USA. A cluster analysis was performed, including the five pain dimensions from the COMPAT-SF questionnaire (severity, fluctuation, provocative factors, spreading pain, and qualitative descriptors). The resulting phenotypes were compared to demographic and clinical data, including patient-reported outcomes and quantitative sensory testing.

Results: Three distinct pain phenotypes were identified in the cluster analysis: A low-burden pain phenotype, Cluster 1 (n=151), a high-intensity, constant pain phenotype, Cluster 2 (n=61), and a widespread, multidimensional pain phenotype, Cluster 3 (n=36). Quality of life and sleep scores were worse in Cluster 3 than in the other phenotypes (all $p < 0.001$). The degree of anxiety, depression, and catastrophizing was also worst in Cluster 3 (all $p < 0.001$). Cluster 3 showed increased hyperalgesia on sensory testing with lower sum of pressure pain detection thresholds than Cluster 1 ($p = 0.009$) and higher temporal summation than Cluster 2 ($p = 0.007$).

Conclusion: The COMPAT-SF questionnaire identifies three pain phenotypes in CP. Widespread, multidimensional pain correlated with increased hyperalgesia, higher psychological distress, and worse overall well-being. Phenotyping based on the COMPAT-SF questionnaire may prove helpful in guiding treatment plans in CP and more accurately allocating patients in clinical trials.

5. Clinical management of *Clostridioides difficile* infection with faecal microbiota transplantation: a real-world cohort study

Sara Ellegaard Paaske, MD^{1,2}, Simon Mark Dahl Baunwall, PhD¹, Tone Rubak, MD^{2,3}, Nina Rågård, BSc¹, Jens Kelsen, PhD¹, Mette Mejlby Hansen, MSc¹, Anders Bergh Lødrup, PhD⁴, Lise Tornvig Erikstrup, PhD⁵, Susan Mikkelsen, PhD⁶, Christian Erikstrup, PhD⁶, Jens Frederik Dahlerup, DMSc^{1,2}, Christian Lodberg Hvas, PhD^{1,2}

¹Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

²Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

³Department of Geriatrics, Aarhus University Hospital, Aarhus, Denmark

⁴Department of Medicine, Section of Gastroenterology and Hepatology, Gødstrup Hospital, Herning, Denmark

⁵Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark

⁶Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark

Background: *Clostridioides difficile* infection (CDI) causes high morbidity and mortality. Faecal microbiota transplantation (FMT) is well-established for CDI, but therapeutic strategies may be optimised. We aimed to evaluate clinical outcomes by analysing therapeutic strategies in a real-life cohort of patients with CDI treated with FMT.

Methods: We conducted a multi-site cohort study, including 1,170 patients with CDI, treated with FMT through capsules, colonoscopy, or nasojejunal tube between May 2016 and December 2023. The primary outcome was cure of *C. difficile*-associated diarrhea (CDAD) eight weeks after treatment. We investigated antibiotic pretreatment type and length, FMT dosing and administration, and post-FMT prophylactic vancomycin during non-CDI antibiotic use, applying multivariable mixed-effect regression analysis including the patient as a random effect.

Results: The 1,170 patients received 1,643 FMT treatments. Patients' median age was 71 years (interquartile range 56-80 years). Following their first FMT treatment, 699 patients (60% (95% confidence interval: 57-63%)) were cured of CDAD. After repeated FMT treatments, 944 patients (81% (78-83%)) were cured. Prolonged antibiotic pretreatment was associated with higher cure rates (65% (59-70%), odds ratio (OR): 1.22, $p < 0.001$). FMT administration through oral, multi-dose capsules (69% (63-74%), OR: 1.19, $p < 0.001$) or colonoscopy (69% (61-76%), OR: 1.14, $p = 0.006$) resulted in the highest cure rates. Neither antibiotic pretreatment type nor prophylactic vancomycin during non-CDI antibiotics affected cure rates. In patients for whom FMT was initially unsuccessful, repeated FMT was more effective than antibiotic treatment alone.

Conclusion: CDI outcomes could be improved by optimising antibiotic pretreatment duration, selecting appropriate FMT delivery methods, and repeating FMT.

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6. Performance of six non-biomarkers versus liver biopsy as surrogate endpoints for clinical trials in ALD and MetALD

Authors: Ellen Lyngbeck Jensen^{1,2}, Maja Thiele^{1,2}, Nikolaj Torp^{1,2}, Stine Johansen^{1,2}, Johanne Kragh Hansen^{1,2}, Mia Dahl Sørensen³, Camilla Dalby Hansen^{1,2}, Mette Lehmann Andersen^{1,4}, Georg Semmler², Katrine Thorhauge^{1,2}, Helle Lindholm Schnefeld¹, Ida Villesen¹, Katrine Tholstrup Bech^{1,2}, Peter Andersen¹, Diana Julie Leeming⁵, Morten Karsdal⁵, Katrine Prier Lindvig¹, Torben Hansen⁶, Aleksander Krag^{1,2}, Sönke Detlefsen^{*2,3}, Mads Israelsen^{*1,2} *on behalf of the GALAXY and MicrobLiver consortia*

Background & Aims: Drug development for alcohol-related liver disease (ALD) and metabolic-associated and ALD (MetALD) is emerging, but clinical trial design remains challenging due to unknown disease progression rates and a lack of validated surrogate endpoints. This study assessed fibrosis progression and compared the prognostic accuracy of six non-invasive biomarkers to liver biopsy, as alternative surrogate endpoints for future trials.

Methods: We included patients with a history of excessive alcohol intake who underwent two liver biopsies and had concurrent measurement of VCTE, ELF, FIB-4, Agile 3+, PRO-C3, LiverPRO, and CPA. Fibrosis progression rates were calculated, and associations between histological and biomarker changes were analysed. We used C-statistics to compare how changes in liver biopsy and non-invasive biomarkers predicted hepatic decompensation or death after the second liver biopsy.

Results: Of 164 patients included, mean age of 59 (± 9) years, 75% had significant fibrosis ($\geq F2$). Median biopsy interval was 1.9 years, with a fibrosis progression rate of 0.22 stage per year, equivalent to one stage every 4.6 years. The progression rate was more than twofold faster in patients with active alcohol consumption at baseline compared to abstinent individuals (one stage every 3 years versus every 8 years). During a 2.1 year follow-up period after the second biopsy, twenty-one patients decompensated or died. Changes in Kleiner histological fibrosis stage and non-invasive biomarkers predicted these outcomes ($p \leq 0.001$). The Harrell's C-index for predicting hepatic decompensation or death for the delta values were as follows: LiverPRO (0.78), Agile 3+ (0.75), PRO-C3 (0.72), Kleiner histological fibrosis stage (0.70), FIB-4 (0.68), transient elastography (0.66), and ELF (0.64). Applying dichotomous cut-offs slightly reduced the C-index for all non-invasive tests.

Conclusion: NITs show promise as surrogate markers for disease monitoring and for their use in ALD and MetALD clinical trials which could improve feasibility, reduce costs, and enhance patient safety.

7. Diverging Incidence Trends in IBD-Associated Dysplasia

Jesper Winkler Andersen^{1,2}; Frederikke Schønfeldt Troelsen^{2,3}; Klaus Krogh^{1,2}; Rune Erichsen³; Ailsa Hart⁴; Anders Kirch Dige^{1,2}

¹ The Department of Hepatology and Gastroenterology, Aarhus University Hospital, DK

² The Faculty of Health Sciences, Aarhus University, DK

³ Department of Clinical Epidemiology, Aarhus University Hospital, DK

⁴ St Mark's Hospital & Imperial College, London, UK

Background: In inflammatory bowel disease (IBD), low-grade dysplasia (LGD) is recognised as a key risk factor for subsequent high-grade dysplasia (HGD) and colorectal cancer (CRC). Therefore, current guidelines recommend that the detection of LGD should guide clinical decision-making, often leading to intensified surveillance or, in some cases, colectomy to prevent the development of HGD or CRC. Consequently, the finding of LGD imposes a significant burden on affected individuals and healthcare systems. Despite these implications, there is limited literature describing temporal trends in the incidence of IBD-related LGD, HGD and CRC, especially over the past decade, a period marked by widespread use of biologic therapies and substantial advances in endoscopic technology and techniques. We therefore aimed to use nationwide Danish health registers to describe trends over time in the incidence of IBD-related LGD, HGD and CRC.

Methods: We conducted a nationwide cohort study using data from Danish national health registers covering the period from 1990 to 2022. All Danish residents with a first-time diagnosis of IBD, or with IBD-related LGD, HGD, or CRC during the study period, were included. A diagnosis of dysplasia or CRC was considered IBD-related if recorded within 180 days prior to, or at any time after, the first diagnosis of IBD. HGD and CRC were reported as a combined outcome (HGD/CRC), using the date of the earliest diagnosis where both were present. Incidence rates were reported per 100,000 person-years, along with corresponding incidence rate ratios using a Poisson approximation adjusted for age and standardised to the age distribution in Denmark in 2022. All results are followed by 95 percent confidence intervals (95% CI).

Results: From 1990 to 2022, a total of 92,717 new cases of IBD, 8,406 cases of IBD-related LGD, and 2,480 cases of IBD-related HGD/CRC were identified. The incidence rate of IBD increased from 29.88 per 100,000 person-years in 1990 (95% CI: 28.03 to 31.72) to 61.27 in 2020 (95% CI: 58.12 to 64.42). Over the same period, the incidence rate of IBD-related LGD rose from 0.55 (95% CI: 0.32 to 0.78) to 14.09 (95% CI: 12.76 to 15.42). For IBD-related HGD/CRC, the incidence increased from 1.16 (95% CI: 0.71 to 1.61) to 3.05 (95% CI: 2.62 to 3.47). While the incidence rates of IBD and HGD/CRC increased steadily before plateauing around 2008, a marked spike in the incidence rate of LGD was noted in 2014. This spike coincided with the introduction of the national CRC screening programme in Denmark. The relative increase in IBD-related LGD far exceeded that of advanced neoplasia, as illustrated by the incidence rate ratio between 1990 and 2020 of 25.60 (95% CI: 16.58 to 39.52) for LGD, compared to 2.63 (95% CI: 1.74 to 3.98) for HGD/CRC.

Conclusion: The incidence rate of IBD, IBD-related LGD, and IBD-related HGD/CRC has increased substantially in Denmark over the past 30 years. A plateau in the incidence rate of IBD and IBD-related HGD/CRC has been observed over the past decade. Notably, the overall increase in incidence rate

was far more pronounced for IBD-related LGD as compared to IBD-related HGD/CRC, with a steep rise observed in 2014. The rise coincided temporally with the introduction of the national CRC screening programme and, importantly, was not seen in the incidence rate of IBD-related HGD/CRC.

8. The mucosal- and lumen-associated mycobiome in treatment-naïve patients with new-onset inflammatory bowel disease

Johannes David Füchtbauer^{1,2,3}, Olga Brovkina⁴, Maria G Maseng^{5,6,7}, Simen Hyll Hansen^{7,8,9}, Anja Fejrskov^{1,3}, Loa Davíðsdóttir¹⁰, Michael Dam Jensen^{11,12}, Martin Rejler^{13,14}, Trond Espen Detlie^{7,15}, Dirk Repsilber¹⁶, Charlotte R H Hedin^{17,18}, Hesham Elabd⁴, Sussi B Mortensen¹⁹, Tone Bergene Aabrekk^{7,20}, Vendel Ailin Kristensen^{6,7}, Christine Olbjørn²¹, Gøri Perminow²², Svend Andersen²³, Johan D Söderholm²⁴, Johannes R Hov^{7,8,9,25}, Claus Aalykke^{2,26}, Vibeke Andersen²⁷, Jonas Halfvarson²⁸, Marte L Høivik^{6,7}, Andre Franke⁴, Corinna Bang⁴, Jens Kjeldsen^{1,3}

¹ Department of Medical Gastrointestinal Diseases S, Odense University Hospital, Odense, Denmark

² Department of Internal Medicine and Emergency, Section of Gastroenterology, Svendborg, Odense University Hospital and Svendborg Hospital, Denmark

³ Research Unit of Medical Gastroenterology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

⁴ Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany

⁵ Bio-Me, Oslo, Norway

⁶ Department of Gastroenterology, Oslo University Hospital, Oslo, Norway

⁷ Institute of Clinical Medicine, University of Oslo, Oslo, Norway

⁸ Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Oslo, Norway

⁹ Research Institute of Internal Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Oslo, Norway

¹⁰ Department of Gastroenterology, Landspítali National University Hospital of Iceland, Reykjavik, Iceland

¹¹ Institute of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

¹² Research Unit of Medical Gastroenterology and Hepatology, Hospital South West Jutland, Esbjerg, Denmark

¹³ Jönköping Academy for Improvement in Health and Welfare, Jönköping University, Jönköping, Sweden

¹⁴ Futurum-- Academy for Healthcare, Futurum Academy of Health and Care, Jönköping, Region Jönköping County, Sweden

- ¹⁵ Department of Gastroenterology, Akershus University Hospital, Lørenskog, Norway
- ¹⁶ School of Health and Medical Sciences, Örebro University, Örebro, Sweden
- ¹⁷ Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden
- ¹⁸ Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
- ¹⁹ Department of Clinical Immunology, Odense University Hospital, Odense, Denmark
- ²⁰ Department of Gastroenterology, Vestfold Hospital Trust, Tonsberg, Norway
- ²¹ Department of Paediatric and Adolescent Medicine, Akershus University Hospital, Akershus, Norway
- ²² Department of Paediatrics, Oslo University Hospital, Oslo, Norway
- ²³ Department of Paediatrics, Vestfold Hospital, Tonsberg, Norway
- ²⁴ Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Östergötland, Sweden
- ²⁵ Section of Gastroenterology, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Oslo, Norway
- ²⁶ Research Unit of Medicine, Svendborg, Department of Clinical Research, University of Southern Denmark, Odense, Denmark
- ²⁷ Institute of Regional Research, University of Southern Denmark, Odense, Denmark
- ²⁸ Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Background

Inflammatory bowel disease (IBD) pathogenesis may involve gut fungi (mycobiome), yet current knowledge largely relies on studies of long-standing, treated patients, with limited data from treatment-naïve individuals.

Objective

To investigate the gut mycobiome in treatment-naïve, new-onset patients with ulcerative colitis (UC) and Crohn's disease (CD) compared to symptomatic controls (SC), assessing diversity and fungal composition.

Design

Fungal communities were profiled using ITS2 sequencing from stool samples and colonic biopsies in two large Scandinavian inception cohorts - NORDTREAT and IBSEN III - comprising new-onset, treatment-naïve IBD patients and SCs. Alpha and beta diversity metrics, relative fungal abundances, and anti-*Saccharomyces cerevisiae* antibodies (ASCA) were analysed.

Results

No significant differences in alpha or beta diversity were consistently observed between UC, CD, and SC groups in both cohorts. Stool and biopsy samples exhibited distinct fungal profiles, with *Saccharomyces* predominating in stool and *Malassezia* enriched in biopsies. *Candida* abundance was scarce and did not differ between patients and controls. No associations were detected between mycobiome diversity and disease extent, phenotype, or progression. ASCA levels were elevated in CD compared to SCs, without correlation to mycobiome diversity.

Conclusion

The gut mycobiome composition and diversity do not significantly differ between treatment-naïve, new-onset IBD patients and SCs, suggesting a limited role in early disease pathogenesis. Future studies should explore potential mycobiome contributions to disease progression and treatment response.

9. Assessment of transmural treatment response in known Crohn's disease – a prospective blinded study of the intermodality agreement between intestinal ultrasound and magnetic resonance enterocolonography

Jacob Broder Brodersen,^{1, 2} Søren Rafael Rafaelsen,^{2, 3} Nejatbakhsh E,¹ Michael Dam Jensen^{1, 2}

¹ Department of Internal Medicine, Section of Gastroenterology, Esbjerg Hospital – University Hospital of Southern Denmark, Esbjerg, Denmark

² Department of Regional Health Research, University of Southern Denmark, Denmark

³ Department of Radiology, Lillebaelt Hospital – University Hospital of Southern Denmark, Vejle, Denmark

Background: Transmural healing is an emerging treatment goal in Crohn's disease (CD). This study aimed to examine the intermodality agreement for assessing transmural response to medical treatment with intestinal ultrasound (IUS) and MR enterocolonography (MREC).

Methods: This was a post-hoc analysis of IUS and MREC performed in a prospective, blinded, multi-center study. Patients with endoscopically active CD completed IUS and MREC before and after medical treatment. Observers were blind to the result of the other modality. Findings and disease classification at baseline, as well as the intermodality agreement for transmural treatment response were determined.

Results: Thirty-five patients entered the analysis. IUS and MREC detected 59 (24.1%) and 42 (17.1%) segments with active CD at baseline, respectively ($P = 0.001$). Disease location and behavior were determined with a moderate intermodality agreement ($\kappa = 0.48$ and $\kappa = 0.43$, $P < 0.01$). Global IUS and MREC activity scores decreased after medical treatment ($P < 0.05$), and repeated measurement correlations were weak to moderate. The intermodality agreement for transmural treatment response was fair to moderate: IUS vs. MaRIA $\kappa = 0.43$ (CI 0.13-0.73, $P = 0.006$) and IUS vs. Clermont score $\kappa = 0.31$ (CI 0.01-0.60, $P = 0.026$). Normalization of BWT occurred in 12 (34.3%) patients with MREC and 11 (31.4%) patients with IUS. The intermodality agreement for transmural remission was moderate ($\kappa = 0.42$, CI 0.10-0.74, $P = 0.007$).

Conclusions: Transmural response and healing is determined with considerable variability. Maintaining consistency in imaging modality between assessments is essential to ensure accurate interpretation.

10. Chronic viral hepatitis B, C, and D in Greenland

Carina N. Naustdal^{1,2,3}, Gerda E. Villadsen^{4,5}, Karsten F. Rex^{6,8}, Henrik B. Krarup⁷, Henning Grønbæk^{4,5}, Michael L. Pedersen^{2,8}, Rasmus H. Gantzel^{2,4,5,9}

¹ Queen Ingrid's Hospital, Center of Primary Health Care, Nuuk, Greenland

² Steno Diabetes Center Greenland, Nuuk, Greenland

³ Section of Gastroenterology and Hepatology, Department of Medicine, Zealand University Hospital, Køge, Denmark

⁴ Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

⁵ Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

⁶ Department of Internal Medicine, Queen Ingrid's Hospital, Nuuk, Greenland

⁷ Department of Molecular Diagnostics, Aalborg University Hospital, Aalborg, Denmark

⁸ Greenland Center for Health Research, Institute of Health and Nature, University of Greenland, Nuuk, Greenland

⁹ Department of Medicine, Regional Hospital Gødstrup, Herning, Denmark

Background and Aim: Viral hepatitis B infection have been endemic in Greenland as in other Arctic areas. However, updated data are warranted after the implementation of screening, vaccination, and treatment programs during the past decades. We aimed to investigate the prevalence and disease characteristics of chronic viral hepatitis B virus (HBV), C (HCV) and delta (HDV) in Greenland.

Methods: We performed a cross-sectional nationwide study using national patient registries. Eligible patients were identified by either positive serologic or virologic tests, or by allocation of a relevant International Classification of Diseases – Tenth Revision or Anatomical Therapeutic Chemical classification code.

Results: We identified 299 HBV- and 45 HCV-positive patients, corresponding to an overall low prevalence of 0.53% (95%-CI: 0.49-0.57%) and 0.08% (95%-CI: 0.06-0.11%), respectively. The prevalence of HDV co-infection among patients with chronic HBV was 9.4%, of whom 82% was HDV-RNA positive indicating ongoing infection. Overall, most patients were living in Sermersooq municipality, middle-aged and male. Additionally, the occurrence of HBV and HCV was higher among women compared to men in the age category 20-39 years. The most recent liver biochemistry, including Fibrosis-4 score, was within reference values among HBV-positive patients. However, alanine and aspartate aminotransferase were slightly elevated among HCV-positive, and more than one-third had Fibrosis-4 scores >1.3 indicating significant liver fibrosis risk.

Conclusion: The prevalence of chronic HBV infection was markedly lower than reported in previous studies, and the prevalence was highest among adults, suggesting horizontal transmission is dominant. Yet, HDV co-infection is common and calls for increased awareness. Chronic HCV is rare, which is consistent with previous findings. This study provides valuable insights into the epidemiology of viral hepatitis in Greenland, supporting ongoing prevention strategies and informing future initiatives in circumpolar regions. **Corresponding author:** Carina N. Naustdal, email: carib@regsj.dk

11. Development and evaluation of AI-Assisted Intestinal Ultrasound for monitoring of IBD

Jakob Karrer¹ & Jonatan Ruiz-Molsgaard¹, Bjørn Leth Møller¹, Johan Burisch^{2,3,4}, Gorm Roager Madsen^{2,3}, Klaus Theede^{2,3}, Johan Fremberg Ilvemark^{2,3}, Bobby Lo^{2,3}, Bulat Ibragimov¹ & Trine Boysen^{2,3,4}

¹ Department of Computer Science, University of Copenhagen

² Gastro Unit, Medical Section, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark

³ Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents and Adults, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark

⁴ Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Objective

Intestinal ultrasound (IUS) is a valid and reliable alternative to endoscopy for monitoring inflammatory bowel diseases (IBD). However, IUS is a challenging to master and has a steep learning curve. Using IUS, thickness of intestinal bowel wall (BWT) is known to be the strongest predictor for activity in IBD. We propose an AI-powered IUS measuring system that produces interpretable BWT measurements in realistic images of varying quality.

Method

We constructed a system comprised of two neural networks and additional image-processing techniques. The neural networks were trained on 570 standard clinical images extracted from 144 videos. The system was validated against a clinical reference consisting of measurements made by four IBUS-certified experts on 55 images. Furthermore, we explored how well the system could differentiate between normal/diseased bowel thickness, using a standard 3 mm cutoff. We performed a leave-one-out study to compare model performance against that of an IBUS expert.

Result

When measuring BWT, our system was very close to measurements of IBUS experts as it achieved an average distance of 0.98mm (SD 1.1 mm) from the mean and 0.44mm (SD 0.89mm) from the bounds of the clinical reference measurements. In 59% of cases, the measurements were within the span of clinical reference measurements. When evaluating the system's ability to differentiate between normal bowels and bowels with disease active, we achieved a specificity of 0.94, sensitivity of 0.69, and accuracy of 0.77.

Conclusions

We have introduced the first AI model for assisting IUS monitoring of adult IBD-patients using real-world images with the only image criterion being, that the image was scorable by an IUS expert. The

model can identify the inner and outer bowel walls and place bowel wall measurements comparable to IBUS-certified experts.

12. DIAGNOSTIC ACCURACY OF SIMPLE MAGNETIC RESONANCE IMAGING MARKERS FOR DETECTION OF TREATMENT RESPONSE COMPARED TO COMPLEX DISEASE ACTIVITY SCORES IN PATIENTS WITH ACTIVE CROHN'S DISEASE

Nejatbakhsh E¹, Rafaelsen SR^{2,3}, Brodersen JB^{1,2}, Knudsen T^{1,2}, Kjeldsen J^{4,5,6}, Juel MA¹, Jensen MD^{1,2}

¹ Department of Internal Medicine, Section of Gastroenterology, Esbjerg and Grindsted Hospital – University Hospital of Southern Denmark, Esbjerg, Denmark

² Department of Regional Health Research, Odense, University of Southern Denmark, Denmark

³ Department of Radiology, Lillebaelt Hospital – University Hospital of Southern Denmark, Vejle, Denmark

⁴ Department of Medical Gastroenterology, Odense University Hospital, Odense, Denmark

⁵ Research Unit of Medical Gastroenterology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

⁶ OPEN Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark

Background: Minimally invasive modalities have shown significant potential for monitoring disease severity and treatment response in Crohn's disease (CD). Several magnetic resonance imaging (MRI) scoring systems have been validated in research settings. However, these calculations are time-consuming, which limit their widespread adoption in clinical practice. This analysis evaluated treatment response in patients with active CD using simple imaging markers and compared them to complex multifactorial scores.

Methods: A post-hoc analysis was conducted using data from a prospective, blinded, multicenter study (ClinicalTrials.gov: NCT03435016). The study included patients with endoscopically active CD and a clinical indication for medical treatment. All patients completed ileocolonoscopy (IC) and MRI-enterocolonography with intravenous contrast and diffusion-weighted sequences before and after treatment. IC served as the gold standard. Response was defined as a $\geq 50\%$ reduction of Simple Endoscopic Score for Crohn's Disease (SES-CD). The simple markers evaluated were bowel wall thickness (BWT) and the apparent diffusion coefficient (ADC). Measurements were performed on the most severely affected ileocolonic segment and were compared to Magnetic Resonance Index of Activity (MaRIA), Simplified MaRIA (sMaRIA), and the Clermont score.

Results: Forty-two patients with known CD were included in the analysis. Patient characteristics are shown in Table 1. Endoscopic response was achieved in 19 patients (45.2%) with a median SES-CD of 11.5 (interquartile range [IQR] 9-17) and 7.0 (IQR 0-13) before and after medical treatment, both $P < 0.001$. MaRIA, sMaRIA, Clermont score, BWT, and ADC all significantly improved in patients with endoscopic response compared to non-responders ($P < 0.05$). Receiver operating characteristics are shown in Figure 1. The diagnostic accuracy for the absolute difference in BTW (AUC 0.74, 95% CI 0.58-0.89) and ADC (AUC 0.75, 95% CI 0.60-0.90) appeared to be higher than MaRIA (AUC 0.60, 95% CI 0.42-0.78), $P = 0.12$ and $P = 0.13$, respectively. The relative reduction of BTW (AUC 0.76, 95% CI 0.61-0.91) trended towards higher diagnostic accuracy compared to MaRIA (AUC 0.63, 95% CI 0.45-

0.81, $P = 0.098$). A >17% decrease in BWT resulted in an optimal sensitivity and specificity of 78.9% (CI 54.40-93.90) and 85.2% (CI 66.30-95.80), respectively

Conclusion: Repeated measurements of BWT or ADC in the most diseased ileocolonic segment appear to be non-inferior to validated scores like MaRIA and sMaRIA at determining response to medical treatment in patients with active CD. These measurements are simple to perform and do not require intravenous contrast. (Tabel og Figur kan rekvireres fra førsteforfatter).

13. Efficacy and Safety of Dual Therapy for Complex Inflammatory Bowel Disease in a Danish Cohort

Haase, Anne-Mette¹, Kelsen, Jens¹, Agnholt, Jørgen Steen^{1,3}, Bendix, Mia²

¹Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark. ²Regional Hospital Randers, Medical department, Gastroenterology Section, Randers, Denmark. ³Aarhus University Hospital, National Center of Autoimmune Diseases, Department of Dermatology, Aarhus Denmark.

Abstract

Background: Patients with Crohn's disease (CD) and ulcerative colitis (UC) on monotherapy with biologics or small molecules may meet a therapeutic ceiling, not reaching the desired treatment targets. Dual therapy, combining different biologics and/or small molecules, has been proposed for this challenging population. Awaiting randomized studies, real-world data focusing on efficacy and safety are crucial.

Methods: Medical records from September 2018 to September 2023 were reviewed for CD and UC patients undergoing dual therapy with biologics and/or small molecules in the outpatient gastroenterology clinics at Aarhus University Hospital and Regional Hospital Randers. Patients treated for at least three months were included and followed until treatment discontinuation or the end of the study period. Patient characteristics, clinical outcomes, adverse events, and efficacy data were collected at baseline and follow-up.

Results: Seventy-four patients (47 with CD and 27 with UC) received a total of 79 dual therapies. The median dual therapy duration was 488 days for CD and 412 days for UC. The most common combinations were adalimumab/ustekinumab in CD (46%) and adalimumab/vedolizumab in UC (35%). Clinical remission at follow up was achieved in 56% of CD patients and 62% of UC patients and steroid-free follow-up in 81% of CD patients and 52% of UC patients. In CD, dual therapy significantly reduced stool frequency, bloody stools, calprotectin levels, and Harvey-Bradshaw Index (HBI) scores. In UC, stool frequency, nighttime stools, abdominal pain, CRP, calprotectin levels, and Simple Clinical Colitis Activity Index (SCCAI) scores significantly decreased, while hemoglobin and albumin levels significantly improved. Severe adverse events (SAEs) occurred in nine out of 79 dual therapies.

Conclusions: This retrospective study demonstrates a substantial rate of clinical remission and an acceptable safety profile in complex IBD patients receiving dual therapy. However, the risk of SAEs must be balanced against the therapeutic benefit.

14. High baseline infliximab clearance when starting rescue therapy for ASUC predicts need for dose intensification to achieve treatment outcomes comparable to patients with low drug clearance

Mathilde J Nissen^{1,2}, Pernille D Ovesen³, Frederik Ørtoft^{1,2}, Mark Ainsworth^{1,2}, Jens Kjeldsen^{1,2}, Casper Steenholdt^{1,2}

¹ Dept of Medical Gastroenterology, Odense University Hospital. ² Research Unit of Medical Gastroenterology, Dept of Clinical Research, University of Southern Denmark. ³ Dept of Gastroenterology, Herlev Hospital, Denmark.

Background: Acute severe ulcerative colitis (ASUC) is commonly treated with infliximab (IFX) rescue therapy in case of steroid refractoriness. However, 15% are colectomized due to treatment failure. We recently demonstrated that IFX clearance (CL) is significantly increased during ASUC compared to outpatients, resulting in sub-therapeutic drug levels in 74% of patients at week 2.¹ Additionally, high baseline IFX CL has been associated with colectomy.² Consequently, an intensified IFX induction regimen is frequently used to reduce risk of sub-therapeutic exposure and prevent pharmacokinetic treatment failure. The objective of this study was to evaluate whether baseline IFX CL upon starting rescue therapy for ASUC predicts the need for dose intensification and impacts treatment outcomes.

Methods: Retrospective cohort study including all IFX treated patients with ulcerative colitis (n=153) at Herlev Hospital from 2009-2019. An intensified IFX induction regimen was defined as increase in dose (>5 mg/kg) and/or reduction in dosing intervals, including additional infusions beyond the standard weeks of 0, 2, and 6. Baseline IFX CL was calculated using an established pharmacokinetic model:^{2,3} $CL = 0.407 \times (\text{albumin}/4.1)^{-1.54} \times 1.471^{\text{ATI}} \times 0.764^{\text{sex}}$, where albumin conc. (g/dL) was measured at first IFX infusion, anti-drug antibodies (ATI) status was 0 at baseline, and sex was coded as 1 for females and 0 for males.

Results: Baseline IFX CL data was available for 37 of 49 (76%) patients with ASUC and 33 of 104 (32%) outpatients. ASUC patients exhibited significantly higher baseline IFX CL compared to outpatients (median 0.477 L/day, IQR 0.323–0.392 vs. 0.353 L/day, 0.414–0.559, $p < 0.0001$). Fourteen (29%) ASUC patients received an intensified IFX induction regimen (7 had dose increases, 6 had shortened intervals or extra infusions, 1 excluded due to missing data) based on clinical grounds and by consensus at the department. Notably, patients selected for intensification had significantly higher baseline IFX CL (median 0.545 L/day, IQR 0.493–0.626 vs. 0.440, 0.397–0.519, $p = 0.01$). ROC analysis ($AUC^{\text{ROC}} 0.77$ [0.61–0.92], $p = 0.001$) with Youden Index identified a baseline IFX CL threshold of ≥ 0.477 L/day for optimal prediction of need for intensified IFX induction regimen (sensitivity 0.83 [0.75–1.00], specificity 0.68 [0.27–0.85]). Subgroup analysis of patients complying with Truelove Witts criteria (n=27, 55%) showed similar results (IFX CL median 0.497 L/day, IQR 0.397–0.596 vs. 0.455, 0.429–0.529, $p = 0.74$). No other variables (Mayo score, Montreal classification, CRP, hemoglobin, leucocytes, age, disease

duration, BMI, and Truelove-Witts criteria) significantly associated with dose intensification in logistic regression analysis. Importantly, there were no significant differences in long-term outcomes between ASUC patients who received intensified or standard IFX induction regimens. Thus, persistent IFX therapy at 1 year was 40% in the intensified group vs. 59% in the standard group ($p=0.47$), and colectomy rates were 21% vs. 14% ($p=0.63$). Baseline IFX CL did not correlate with either outcome ($p>0.05$).

Conclusion: ASUC patients with high baseline IFX clearance require intensified IFX induction to achieve adequate drug exposure. When applied, dose intensification results in similar 1-year treatment outcomes as in patients with lower IFX clearance. Further validation in larger cohorts is needed to refine the IFX CL threshold for guiding intensification strategies.

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15. International consensus on objective structured assessment of intestinal ultrasound technical skills: a multidisciplinary Delphi process

AUTHOR LIST:

Zainab G. Nagras¹, Frauke Petersen², Pia Iben Pietersen³, Johan Fremberg Ilvemark⁴, Jacob Bjerrum⁵, Bram Verstockt⁶, Christian Maaser⁷, Dan Carter⁸, Federica Furfaro⁹, Gauraang Bhatnagar¹⁰, Hien Huynh¹¹, Kerri L. Novak¹², Krisztina Gecse¹³, Lauren White¹⁴, Mariangela Allocca¹⁵, Marjorie Costa Argollo¹⁶, Marios Katsaros¹⁷, Noa Krugliak Cleveland¹⁸, Shintaro Sagami¹⁹, Stuart Taylor²⁰, Torsten Kucharzik²¹, Michael Dolinger²², Rune Wilkens¹.

AFFILIATIONS:

¹ Bispebjerg Hospital, University of Copenhagen, Digestive Disease Center, Research Department, Copenhagen, Denmark

² Department of Gastroenterology, Lüneburg Hospital, University of Hamburg, Lüneburg, Germany

³ Research and Innovation Unit of Radiology, Department of Clinical Research, University of Southern Denmark & Department of Radiology, Odense University Hospital, Odense, Denmark

⁴ Gastrounit, Medical Section, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark

⁵ Department of Gastroenterology, Medical Section, Herlev Hospital, University of Copenhagen, Herlev, Denmark

⁶ Department of Gastroenterology and Hepatology, University Hospitals Leuven & Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium

⁷ Outpatients Department of Gastroenterology, IBD Center, Städtisches Klinikum Lüneburg gGmbH, Lüneburg, Niedersachsen, Germany

⁸ Institute of Gastroenterology, Chaim Sheba Medical Center (Tel Hashomer), Ramat Gan; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

⁹ Department of Gastroenterology and Digestive Endoscopy, IRCCS San Raffaele Hospital, Milan, Italy

¹⁰ Centre for Medical Imaging, University College London Hospitals NHS Foundation Trust, London, United Kingdom

¹¹ Division of Pediatric Gastroenterology & Nutrition, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, AB, Canada

¹² Division of Gastroenterology and Hepatology, Department of Medicine, University of Calgary & Foothills Medical Centre, Calgary, Alberta, Canada

¹³ Department of Gastroenterology and Hepatology, Amsterdam University Medical Center (Location AMC), Amsterdam, The Netherlands

¹⁴ Sunshine Coast University Hospital, Buderim, Australia

¹⁵ *Department of Gastroenterology and Digestive Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy*

¹⁶ *Department of Medicine, Paulista School of Medicine, Federal University of São Paulo (UNIFESP), Brazil*

¹⁷ *Gastroenterology and Hepatology Division, Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki, Greece*

¹⁸ *Section of Gastroenterology, Inflammatory Bowel Disease Center, Department of Medicine, University of Chicago Medicine*

¹⁹ *Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan*

²⁰ *Centre for Medical Imaging, University College London (UCL), London, UK*

²¹ *University of Münster; Head of Internal Medicine and Gastroenterology, Municipal Hospital of Lüneburg, Lüneburg, Germany*

²² *NYU Langone, New York, United States of America*

Background and Aim: Intestinal ultrasound (IUS) is increasingly utilized to objectively assess inflammatory bowel disease (IBD), yet operator proficiency evaluation lacks a structured framework; we aimed to develop international consensus criteria for an Objective Structured Assessment of IUS Skills (OSAIUS) via a multidisciplinary Delphi process.

Methods: Experts in gastroenterology, radiology, internal medicine, and pediatrics were recruited worldwide; a three-round modified Delphi survey was conducted. In round 1, 23 experts rated 20 predefined technical-skill topics across four OSAIUS domains using a five-point Likert scale and suggested additional items. Round 2 re-rated two original and four new topics with standardized anchor text. Round 3 finalized wording. Items achieving $\geq 70\%$ rating of 4 or 5 were included in the final assessment.

Results: Twenty-one experts responded in round 1 and 19 in round 2 (15 gastroenterologists); 18 topics were accepted in round 1, with two revisited alongside four new items. In round 2, three more topics met criteria, yielding 21 final OSAIUS topics. Discarded items included advanced machine settings, appendix evaluation, examiner position, and transperineal ultrasound.

Conclusion: This international, multispecialty Delphi study defined core technical competencies for intestinal ultrasound (IUS) proficiency—encompassing patient positioning and preparation (95–100 % agreement, mean scores 4.7–4.9), machine care and probe selection (79–95 % agreement, mean 4.4–4.7), image optimization steps (90–100 % agreement, mean 4.5–4.7), systematic examination techniques (90–100 % agreement, mean 4.5–4.9), and documentation practices (71–90 % agreement, mean 4.1–4.7). These robust consensus metrics establish a foundation for a globally recognized OSAIUS framework that may support certification pathways, reduce operator variability, and enable objective comparison of educational interventions.

16. Management of Wilson disease across Europe: An international physician-oriented survey by the ERN-RARE Liver group

Frederik Teicher Kirk^{1,2,†}, Karina Stubkjær Rewitz^{1,2}, Zoe Mariño^{1,3}, Eduardo Couchonnal^{1,4}, Nicolas Lanthier^{1,5}, Wiebke Papenthin^{1,6}, Marina Berenguer^{1,7}, Aurelia Poujois^{8,9}, Dominique Debray^{1,9}, Aftab Ala^{1,10}, Luis García-Villarreal^{1,11}, Tudor Lucian Pop^{1,12}, Gerald Denk^{1,13}, Piotr Socha^{1,14}, Thomas Damgaard Sandahl^{1,2}

¹European Reference Network on Rare Liver Disorders (ERN-RARE Liver) ²Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark ³Liver Unit, Hospital Clínic, IDI-BAPS, CIBERehd, Barcelona, Spain. ⁴Unité d'Hépatologie, gastroentérologie et Nutrition pédiatrique, Hospices Civils de Lyon, Bron, France. ⁵Service d'Hépatogastroentérologie, Cliniques universitaires Saint-Luc, Brussels, Belgium ⁶German Association for Wilson Disease Patients (Morbus Wilson e.V.) ⁷Hepatology and Liver Transplant Unit, University and Politecnical Hospital La Fe, Valencia, Spain ⁸European Reference Network for Hereditary Metabolic Disorders (MetabERN) ⁹Centre de Référence de la Maladie de Wilson et autres Maladies Rares Liées au Cuivre, Paris, France. ¹⁰Institute of Liver Studies, King's College Hospital, London, UK ¹¹Digestive Diseases Service, Universidad Las Palmas Gran Canaria, Spain ¹²Center of Expertise in Pediatric Liver Rare Disorders, Emergency Clinical Hospital for Children Cluj-Napoca, Romania ¹³Department of Medicine II, University Hospital, LMU Munich, Munich, Germany. ¹⁴Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, Children's Memorial Health Institute, Warsaw, Poland.

Background and Aims: Diagnosis and treatment of Wilson Disease (WD) is complex and highly specialized. Understanding differences in WD management across the European Union is important, as international clinical and scientific collaboration becomes more common. In this study we aimed to investigate differences in WD management, patient related perspectives and guideline adherence across European centers.

Method: A 37-item questionnaire was distributed among physicians involved in the management of WD patients across European WD centers. Each physician responded on behalf of a WD center. Questions related to diagnosis, treatment, and monitoring of WD as well as questions addressing patient perspectives and background information from the respondent. Responding centers were classified as small or large by number of patients seen per year ($\leq$ / $>$ 30). Data was assessed in total as well as by managing specialty and center size.

Results: 58 physicians from 20 countries responded to the survey. 91% adhered to international guidelines and 88% utilized the Leipzig diagnostic criteria. Most centers had a wide range of diagnostic tools available, e.g. 24-hour urinary copper, slit-lamp examination and genetics (98%, 95% and 93% respectively). Some were less commonly available, e.g. liver biopsy for copper quantification, penicillamine challenge test and non-ceruloplasmin bound copper (74%, 53% and 43%), these were more commonly available in large centers.

21% of small centers did not offer trientine, cost was a limiting factor to some. Initial treatment of hepatic WD was uniform, whereas variability was observed for neurological presentations with 56% of centers using chelation therapy $\pm$ zinc. Neurological departments were more likely to offer

chelation therapy (80% of centers, n=5). Similar differences were seen for psychiatric presentation and asymptomatic patients. Recommendations for copper restricted diet varied widely, with 48% recommending temporary low copper diet and 38% recommending it indefinitely.

Large centers were more likely to follow guidelines and offer more diagnostic tools and therapies, though overall there was little difference between small and large centers.

Conclusion: This physician-oriented survey shows a relatively high degree of adherence to international WD guidelines among European centers. The survey also uncovers important differences amongst centers particularly related to the initial treatment of non-hepatological WD, availability of trientine and recommendations for low copper diet. The survey thusly highlights numerous areas in WD management in which evidence is lacking, and may lead the way for future improvement in WD care and future research projects.

17. Phosphatidylethanol and Self-Reported Alcohol Intake to Classify MASLD, MetALD, and ALD in Individuals At Risk of Steatotic Liver Disease: A Prospective Cohort Study

Nikolaj Torp^{1,2}, Katrine Tholstrup Bech^{1,2}, Helle Lindholm Schnefeld¹, Stine Johansen¹, Camilla Dalby Hansen¹, Georg Semmler¹, Javier Vega Benjumea³, Katrine Prier Lindvig¹, Katrine Holtz Thorhauge^{1,2}, Ellen Lyngbeck Jensen^{1,2}, Ellen Elise Petersen^{1,2}, Johanne Kragh Hansen^{1,2}, Ida Falk Villesen¹, Peter Andersen¹, Marianne Lerbæk Bergmann⁴, Aleksander Krag^{1,2}, Mads Israelsen^{1,2}, Maja Thiele^{1,2}

1) Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark

2) Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

3) Department of Clinical Biochemistry, Puerta de Hierro University Hospital, Madrid, Spain

4) Department of Biochemistry and Immunology, Lillebaelt Hospital - University Hospital of Southern Denmark, Vejle, Denmark

Background: Phosphatidylethanol (PEth) is a direct alcohol biomarker of consumption within the past 1-4 weeks, making it a potential tool in the subclassification of patients with steatotic liver disease (SLD). However, the clinical utility of PEth among individuals at risk of SLD remains to be established. This study evaluated the correlation between PEth and self-reported alcohol intake among individuals at risk of SLD due to excessive alcohol consumption or metabolic dysfunction.

Methods: We included 2,924 participants aged 30–75 years with a history of excessive alcohol use, ongoing or prior (alcohol group, n=1,482) and metabolic dysfunction (metabolic group, n=1,442). Alcohol intake was assessed as self-reported (past 1-week and 3-month average) together with AUDIT-C. Hepatic steatosis (controlled attenuation parameter ≥ 248 dB/m), cardiometabolic risk factors and past 3-month alcohol intake subclassified into metabolic dysfunction-associated SLD (MASLD), metabolic and alcohol-related liver disease (MetALD) or alcohol-related liver disease (ALD). We quantified PEth with liquid chromatography-mass spectrometry according to standard procedures.

Results: Median PEth was 172 ng/mL (IQR: 45-434) in the alcohol group and 11 ng/mL (IQR: 5-37) in the metabolic group. PEth correlated with past 1-week self-reported intake (alcohol: $p=0.638$, 95%CI: 0.600-0.676; metabolic: $p=0.655$, 95%CI: 0.623-0.688), and the average preceding 3-months self-reported intake (alcohol: $p=0.628$, 95%CI: 0.586-0.669; metabolic: $p=0.725$, 95%CI: 0.697-0.753). 40% and 9% from the alcohol and metabolic group respectively, underestimated alcohol intake with a higher PEth than self-report. <1% with a high self-reported intake ($\geq 50/\geq 60$ g/day for $\text{♀}/\text{♂}$) had PEth <20 ng/mL. For the 2,042 participants with SLD, PEth was diagnostically redundant for those 812 (40%) with either a self-reported alcohol intake corresponding to MASLD and a low AUDIT-C or solely a self-report corresponding to ALD.

Conclusion: PEth reveals significant underestimation of alcohol intake, especially in those with a history of excessive alcohol consumption. Incorporating PEth into diagnostic SLD algorithms could aid in patient subclassification.

18. Point of care measurements of prothrombin in patients with cirrhosis and ascites – an exploratory study

Markus Maagaard^{1,2}; Nikolaj Torp^{1,2}; Cecilie Løbel^{1,2}; Katrine Tholstrup Bech^{1,2}; Helle Lindholm Schnefeld^{1,2}; Georg Semmler^{1,2}; Katrine Prier Lindvig¹; Katrine Holtz Thorhauge^{1,2}; Stine Johansen^{1,2}; Johanne Kragh Hansen^{1,2}; Camilla Dalby Hansen¹; Ida Falk Villesen¹; Peter Andersen¹; Mark Haastrup³; Niels Foged³; Maja Thiele^{1,2}; Mads Israelsen^{1,2}; Aleksander Krag^{1,2}

1) Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, Denmark

2) Institute of Health Sciences, University of Southern Denmark, Denmark

3) Solsten Diagnostics International, Aarhus, Denmark

Background and Aims: Prothrombin (coagulation factor II) is a coagulation cascade protein synthesized exclusively by the liver which results in decreased concentrations in patients with cirrhosis. The international normalized ratio (INR) is normally used to estimate prothrombin but is only an indirect measure, as INR also reflects coagulation factors VII and X, and can furthermore be affected by physiological factors and medications.

We aimed to validate a novel aptamer-based biosensor to quantify prothrombin as a potential point of care biomarker.

Method: We included 23 patients with cirrhosis and ascites together with 5 healthy individuals who served as controls. The endogenous molar concentration of prothrombin (C_{PT}) was quantified directly in EDTA-plasma stored at -80°C until sample analysis for the patients with cirrhosis. EDTA-plasma was taken from controls immediately ahead of analysis. Measurements were performed in a single 5 min reaction step by the aptamer-based electrochemical biosensor. We correlated C_{PT} levels with INR and albumin while assessing if C_{PT} was associated with liver disease severity. We followed patients from time of study inclusion (2014-2018) until November 2024.

Results: Mean age of patients with cirrhosis and ascites was 57 years (± 8) while 30% were female. In the patients with cirrhosis and ascites median MELD-Na=10 (IQR: 8-14) and Child-Pugh class distribution was B: 74% and C: 26%.

Prothrombin levels were significantly lower in patients with cirrhosis ($C_{PT}=753$ nM IQR: 531-961) compared to healthy controls ($C_{PT}=1654$ nM IQR: 1511-1816, $p<0.001$). In the patients with cirrhosis, prothrombin was negatively associated with INR ($r=-0.6488$, $p<0.001$) and positively with serum albumin ($r=0.6495$, $p<0.001$). Similarly, INR exhibited a negative correlation with albumin ($r=-0.7408$, $p<0.001$).

There were lower prothrombin levels in patients with MELD-Na >10 ($C_{PT}=614$ nM IQR: 499-753) compared to MELD-Na ≤ 10 ($C_{PT}=886$ nM IQR: 696-1065, $p=0.03$). Similarly, we observed a trend towards lower prothrombin levels in Child-Pugh C ($C_{PT}=503$ nM IQR: 439-717) compared to Child-Pugh B ($C_{PT}=830$ nM IQR: 696-960, $p=0.0524$). At end of follow up 8 of 23 patients were alive. 3 of these 8

(38%) scored low MELD-Na (≤ 10). Replacing INR with C_{PT} in MELD (MELD- Na_{PT}) resulted in 6 of 8 (75%) being classified with a low MELD- Na_{PT} (≤ 10).

Conclusion: Prothrombin levels measured using an aptamer-based biosensor were significantly reduced in patients with cirrhosis and correlated with established markers of liver function and disease severity. These findings suggest that the biosensor provides a fast and direct method for quantifying prothrombin as point of care diagnostics which in turn opens avenues for expanding home or remote testing of liver function in patients with cirrhosis.

19. Prevalence and clinical impact of primary sclerosing cholangitis in newly-diagnosed inflammatory bowel disease - a prospective population-based cohort study

Mohamed Attauabi¹⁻³ (MD, PhD), Gorm Roager Madsen^{2,3} (MD, PhD), Jakob M Møller⁴ (PhD), Yousef Jesper Wirenfeldt Nielsen⁴ (MD, PhD), Annette Bøjer Jensen⁵ (MD, PhD), Hartwig Roman Siebner⁶⁻⁸ (MD, PhD, DMSc), Eva Fallentin⁹ (MD), Flemming Bendtsen^{2,3,8} (MD, DMSc), Jakob Benedict Seidelin^{8,10} (MD, PhD, DMSc), Johan Burisch^{2,3,8} (MD, PhD, DMSc)

Affiliations:

¹ Department of Gastroenterology and Hepatology, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark

² Gastrounit, Medical Section, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark

³ Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents, and Adults, Hvidovre Hospital, Hvidovre, Denmark.

⁴ Department of Radiology, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark

⁵ Section of Radiology, Department of Radiology and Nuclear Medicine, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark

⁶ Danish Research Centre for Magnetic Resonance, Department of Radiology and Nuclear Medicine, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark

⁷ Department of Neurology, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark.

⁸ Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

⁹ Department of Radiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark.

¹⁰ Department of Digestive Diseases, Transplantation and General Surgery, IBD Section, Rigshospitalet, Copenhagen, Denmark.

Background

Primary sclerosing cholangitis (PSC) is a chronic, premalignant liver disease linked to ulcerative colitis (UC) and Crohn's disease (CD), yet its true prevalence in newly diagnosed inflammatory bowel disease (IBD) is unclear. We aimed to determine the prevalence and clinical impact of PSC at IBD diagnosis.

Methods

In this prospective population-based inception cohort study, all adult patients with newly diagnosed UC or CD in a defined catchment area of Copenhagen, Denmark (May 2021 – to May 2023), were offered magnetic resonance cholangiopancreatography (MRCP) and hepatobiliary blood tests at the time of IBD diagnosis. Primary outcome was the prevalence of PSC at IBD diagnosis. Cox proportional hazards models (adjusted hazard ratios [aHR]) were used to evaluate the association between PSC and disease outcomes over two years.

Findings

Of 389 patients with IBD, a total of 31 (8.0%; UC: 16/242 [6.6%] and CD: 15/147 [10.2%]) were diagnosed with radiological PSC, while seven (1.8%; UC: 5 [2.1%] and CD: 2 [1.4%]) patients had non-diagnostic PSC-like lesions, bringing the total to 38 of 389 (9.8%) with radiological PSC or PSC-like lesions. PSC prevalence did not vary by sex, age, or IBD activity level, but was significantly higher in patients with extensive colitis compared to those without (9/77 [11.8%] vs. 3/97 [3.1%], $p=0.03$).

Half of those with PSC (14/31 [45.2%]) presented with abnormal liver biochemistry at diagnosis, including 11 (35.5%) who had persistently elevated alkaline phosphatase.

The majority of patients had both intra- and extrahepatic bile duct involvement (21 [67.7%]) of moderate severity (18 [58.1%]), as assessed by the DiStrict Score. Radiological PSC was associated with an increased risk of CD-related hospitalization (aHR=2.30, 95% CI 1.12–4.75) and biological therapy (aHR=2.53, 95% CI 1.02–6.28).

Interpretation

Approximately 8% of patients with newly diagnosed IBD harbored previously undetected radiological PSC. The frequent absence of biochemical abnormalities and the negative impact of radiological PSC on IBD support routine MRCP screening at IBD diagnosis to improve early detection and potentially optimize long-term management.

Funding sources:

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20. The Resistant Microbiome: Insights from Pouchitis and Healthy Ileal Pouches

Sabrina Just Kousgaard^{1,2}, Alberte Holm Møllekær³, Sebastian Mølvang Dall³, Mads Albertsen³, Lone Larsen^{1,4}, Ole Thorlacius-Ussing²

¹*Department of Gastroenterology, Aalborg University Hospital, Aalborg, Denmark;* ²*Department of Gastrointestinal Surgery, Aalborg University Hospital, Aalborg, Denmark;* ³*Center for Microbial Communities, Department of Chemistry and Bioscience, Aalborg University, Aalborg, Denmark;* ⁴*Center for Molecular Prediction of Inflammatory Bowel Disease, PREDICT, Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark*

Objective: Chronic pouchitis is a common complication after ileal pouch-anal anastomosis (IPAA), with limited effective treatments. While antibiotics are first-line therapy, prolonged use in chronic cases leads to increased antimicrobial resistance in the ileal pouch microbiome.¹ Although fecal microbiota transplantation (FMT) can shift microbial composition, randomized trials show no clinical benefit over placebo.² Given the lack of efficacy of FMT using stool from healthy donors, the present study aims to characterize the microbiome of a healthy ileal pouch and to evaluate the impact of high antibiotic exposure in patients with chronic pouchitis.

Methods: In this cohort study, stool samples were collected from four groups: patients with a normally functioning IPAA, patients with chronic pouchitis, patients with ulcerative colitis, and healthy controls. Microbiome composition and antibiotic resistance genes were analyzed across these groups. Fecal samples underwent metagenomic sequencing, and metagenome-assembled genomes (MAGs) were reconstructed. For *Escherichia coli* MAGs, the antibiotic resistance gene (ARG) profiles and plasmid content were specifically examined.

Results: This study included 197 participants. A clear pattern emerged in the microbial composition, revealing that reduced alpha diversity is directly associated with declining gut function and clinical health. Both species richness and Shannon diversity were lowest in patients with chronic pouchitis and highest in healthy individuals, with intermediate levels observed in the other groups. Notably, the ileal pouch microbiome of many chronic pouchitis patients was dominated by *E. coli*. The *E. coli* MAGs from chronic pouchitis patients exhibited a significantly higher frequency of single nucleotide polymorphisms (SNPs) associated with resistance to fluoroquinolones compared to MAGs from the normally functioning IPAA and healthy control cohorts. Furthermore, *E. coli* MAGs from chronic pouchitis patients harbored a greater number of plasmids, with an increased presence of plasmid-borne ARGs conferring resistance to antibiotics commonly administered in this group, relative to the other cohorts.

Conclusions: These findings demonstrate that the composition of the ileal pouch microbiome—both in chronic pouchitis and normally functioning IPAA—differs significantly from that of individuals with normal gut physiology. This suggests that the microbiome of a normally functioning IPAA may serve

as a more appropriate baseline for comparative studies than the healthy gut microbiome. Additionally, our results indicate that antibiotic use exerts increased selective pressure on *E. coli* strains carrying antibiotic resistance genes, directly correlating with the types of antibiotics administered.

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21. The total cross-sectional area of spontaneous portosystemic shunts improves overt hepatic encephalopathy risk stratification among patients with minimal hepatic encephalopathy

Elise Jonasson¹, Elise Humerfelt¹, Lea Ladegaard Grønkjær¹, Birgitte Gade¹, Bassam Mahdi², Mette Munk Lauridsen¹

¹Department of Gastroenterology, University Hospital of Southern Denmark, Finsensgade 35, 6700 Esbjerg, Denmark

²Department of Radiology, University Hospital of Southern Denmark, Finsensgade 35, 6700 Esbjerg, Denmark

Introduction: Minimal hepatic encephalopathy (MHE) is associated with an increased risk overt hepatic encephalopathy (OHE). However, not all patients with MHE develop OHE, indicating the need for improved risk stratification and early intervention. Spontaneous portosystemic shunts (SPSS) are a sign of portal hypertension and can be visualized on abdominal CT scans, a routine modality in the assessment of patients with cirrhosis. We hypothesize that large SPSS are more prevalent among patients with MHE and that SPSS measurement can help identify the subgroup of patients at highest risk of OHE.

Aim: This prospective cohort study aimed to examine the association between the size of SPSS and two key outcomes in patients with liver cirrhosis: The presence of MHE at baseline and the development of OHE.

Method: Patients diagnosed with cirrhosis underwent contrast-enhanced abdominal CT scan and psychometric testing to detect MHE (defined by a portosystemic hepatic encephalopathy score below -4). CT images were assessed for the presence of SPSS and the total cross-sectional area (TCA) of SPSS was calculated. Large SPSS were defined as a TCA >83 mm². Patients were followed for development of OHE, liver transplantation and death.

Results: A total of 102 patients were included. Patients diagnosed with MHE (n = 34) had significantly larger SPSS (TCA = 261 mm² vs. 108 mm², p = 0.03), smaller portal vein diameter (15.1 mm vs. 17.1 mm, p = 0.02) and higher ammonia levels (46.9 umol/L vs. 36.3 umol/L, p = 0.025) compared to patients without MHE. The median follow-up period was 297 days (range: 13-758 days). During this period, 16 patients (16%) developed OHE; among them, 11 (69%) had MHE at baseline (p = 0.001), 8 (50%) had large SPSS (p = 0.014) and 6 (38%) had both (p = 0.000).

Conclusion: MHE was associated with larger SPSS at baseline, and patients with both MHE and large SPSS had the highest risk of OHE followed by patients with MHE without SPSS. These findings suggest that routine evaluation of SPSS might improve OHE risk stratification.

22. Therapeutic Drug Monitoring of Ustekinumab and Vedolizumab in IBD: Expanding Flexibility Through PK–PD Time-Based Thresholds

Ella Widigson^{1,2*}, Camilla Frimor^{3,4*}, Casper Steenholdt^{3,4}, Zrinka Duvnjak^{1,2}, [Wilhelm Huisinga](#)⁵, Jens Kjeldsen^{3,4}, Franz Weber^{1,2}, Mark Ainsworth^{3,4*}, Charlotte Kloft^{1,2*}

¹Department of Clinical Pharmacy and Biochemistry, Freie Universität Berlin, Berlin, Germany. ²Graduate Research Training Program: Pharmacometrics & Computational Disease Modelling (PharMetrX), Berlin Germany. ³Department of Medical Gastrointestinal Diseases, Odense University Hospital, Odense, Denmark. ⁴Institute of Clinical Research, University of Southern Denmark, Odense, Denmark. ⁵Institute of Mathematics, University of Potsdam, Germany. * denotes shared first/last authorship.

Background: Personalized dosing is primarily used in anti-TNF-alpha agents, guided by therapeutic drug monitoring (TDM) and relying on trough-level measurements to inform treatment decisions. However, model-informed precision dosing (MIPD) allows greater flexibility by enabling drug-level assessments at any timepoint. Previously, our group identified Pharmacokinetic/Pharmacodynamic (PK/PD) targets for vedolizumab (VDZ) and ustekinumab (UST) to ensure endoscopic remission (ER). Here, we present time-based thresholds derived from PK-models fitted to literature PK/PD thresholds.

Aim: To put the literature PK/PD thresholds into clinical perspective by Probability of Target Attainment (PTA) analysis, and to bridge the gap between TDM and MIPD by introducing model-derived continuous PKPD threshold profiles which combine the flexibility of MIPD with TDM's ease of clinical implementation.

Methods: Published PK-models (Rosario 2015 and Adedokun 2022) were used to stochastically simulate (n=1000) the standard dosing regimens of VDZ and UST for virtual reference patients, corresponding to the respective medians of the model building populations. Their trough concentrations (C_{min}) were compared to median PK/PD thresholds identified in prior literature to calculate the PTA. To derive continuous PK/PD threshold curves for any time-point, PK parameters (e.g. CL, V, etc.) that best-fit the median of literature PK/PD thresholds were estimated and used for subsequent deterministic simulations.

Results: PTA analysis showed that only ~50% of UST-treated patients hit the treatment target during induction, dropping to ~30% during maintenance. For VDZ ~80% hit the treatment target during induction, decreasing to ~42% in late induction and maintenance. Full concentration-time profiles were simulated for i) UST weight-based induction for different weights, ii) VDZ induction with doses at weeks 0, 2 and 6, and iii) UST subcutaneous- and VDZ intravenous maintenance dosing every 4-12 weeks. The generated PK/PD profiles are thus allowing to measure drug-concentrations at any given time point, and compare this to the corresponding thresholds derived from the respective concentration-time profile.

Conclusion: Our findings suggest a need for dose optimization, as current regimens may not ensure adequate target attainment for all patients. The proposed PK/PD threshold profiles allow for flexible, time-independent TDM. Further clinical validation is warranted before implementation.

23. Up-front vedolizumab versus conventional treatment for checkpoint inhibitor mediated colitis – VEICO: An open label randomized clinical trial

Emilie Dahl^{1,2}, Jacob Bjerrum², Katrine Christensen², Anita Wozniak², Johan Ilvemark², Mathias Kock³, Paul Blanche³, Nicolai Vad⁴, Marco Donia⁵, Inge Marie Svane⁵, Jakob Seidelin¹

¹Department of Digestive Diseases, Transplantation and General Surgery, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

²Department of Gastroenterology, Copenhagen University Hospital, Herlev, Denmark

³Department of Biostatistics, Copenhagen University, Denmark

⁴Department of Gastroenterology, Copenhagen University Hospital, North Zealand, Denmark

⁵Department of Oncology, National Center for Cancer Immune Therapy (CCIT-DK) Copenhagen University Hospital, Herlev, Denmark

Background and aim: Immune checkpoint inhibitor (ICI) mediated enterocolitis (IMC) may lead to treatment discontinuation. Corticosteroids for IMC is associated with serious side effects and might affect cancer progression in addition to preclude continued ICI treatment. We hypothesized that vedolizumab, a gut selective $\alpha 4\beta 7$ integrin inhibitor, is effective as a first-line treatment and investigated whether vedolizumab reduces corticosteroid exposure and facilitate ICI resumption.

Patients and methods: We conducted a single center, open-label, explorative phase 2 trial including patients treated with ICI who developed IMC. Patients were randomized 1:1 ratio to receive vedolizumab (300 mg) or standard treatment with corticosteroids, with infliximab used as rescue therapy for corticosteroid failure. The primary outcome was cumulative corticosteroid dose at week 30. Key secondary outcomes included cumulative corticosteroid dose at week 10, corticosteroid free remission at week 10 and ICI resumption rates.

Results: Twenty-two patients received vedolizumab, and 19 patients received standard treatment. At week 10, the mean cumulative corticosteroid use was significantly lower in the vedolizumab arm (1157 mg vs. 2207 mg). By week 30, the mean corticosteroid use remained lower but not statistically significant (1378 mg vs. 2390 mg, estimated difference 1012 mg, 95% CI -229 to 2253, $p=0.107$). Among patients with less severe IMC, who did not need corticosteroids during screening, vedolizumab-treated patients used in average 1729 mg less corticosteroid (95% CI 631 to 2827). Corticosteroid-free remission at weeks 2 and 10 was more common with vedolizumab. Seven patients (33.3%) in the vedolizumab group resumed with ICI compared to three (16.7%) in the standard arm. In patients with severe colitis, who required upfront corticosteroid treatment, a trend towards longer hospitalization in the vedolizumab arm was observed.

Conclusion: For patients with less severe colitis, not needing corticosteroids during screening, vedolizumab may be a viable corticosteroid-sparing option, enabling faster remission and ICI resumption.

24. Vitamin and mineral deficiency following cancer treatment in the colon and pelvic organs

Fredrika Sofia Magnuson¹, Jakob Lykke Poulsen,^{2,3} Louise Kuhlmann³, Mette Borre^{1,2}, Peter Christensen^{2,4}, Asbjørn Mohr Drewes,^{2,3} Søren Laurberg^{2,4}, Klaus Krogh^{1,2}, Janne Fassov^{1,2}

Background: With the increased survival of cancer patients, a growing focus on late adverse effects due to cancer treatment has emerged. This study aimed to uncover potential vitamin B12-, D-, or iron deficiencies in patients treated for cancer in the colon and pelvic organs.

Methodology: All patients referred to our tertiary gastroenterological Late Adverse Effects Clinic between 2017 and 2022 were included and had blood samples taken at the initial baseline examination to identify vitamin and mineral deficiencies. To exclude known deficiencies or uncover deficiencies that arose after cancer treatment which were already supplemented, data was collected retrospectively from patients' medical journals. Cut-off values for vitamin B12, vitamin D, and ferritin were set to 250 pmol/l, 50 nmol/l, and 30 µg/l, respectively.

Results: In total, 324 cancer patients were included with registered cancers as follows: 129 right-sided colon cancers, 27 left colon cancers, 5 colon cancers necessitating subtotal colectomy, 54 rectal cancers, 21 anal cancers, 18 prostate cancers, 48 cervix cancers, 5 ovarian cancers, and 41 with other localization. Following right-sided hemicolectomy for right-sided colon cancer patients 41 patients (33%) presented with vitamin B12 deficiency and 29 patients (24%) with iron deficiency after surgery. As for the cervical cancer patients, 22 (46%) were observed with B12 deficiency and 12 (26%) with iron deficiency after cancer treatment. In the rectal cancer group 11 patients (22%) had B12 deficiency after cancer treatment. 4 patients (20%) of anal cancer patients and 5 patients (28%) of prostate cancer patients presented with vitamin B12 deficiency. No major deficiencies of B12 or ferritin were observed in the other cancer groups. Likewise, no major deficiencies of vitamin D were seen in any of the cancer groups.

Conclusion: In this study a higher prevalence of B12 deficiency was observed in late adverse cancer patients treated for right-sided colon, cervical, rectal, anal and prostate cancer. Also, iron deficiency was more prevalent in patients treated for right-sided colon and cervical cancer.

¹ Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

² Danish Cancer Society Centre for Research on Survivorship and Late Adverse Effects after Cancer in the Pelvic Organs, Aarhus University Hospital, Aarhus, Denmark

³ Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aarhus, Denmark

⁴ Department of Surgery, Aarhus University Hospital, Aarhus, Denmark

25. Vævsbaserede prædiktorer for sygdomsrecidiv efter resektion for stenoserende Crohns sygdom

M. Pedersen¹, L. Riis², P. Ovesen^{1,3}, J. Rasmussen⁴, MD Wewer⁵, I. Gögenur⁶, J. Burisch⁵, J. Seidelin¹, A. Poulsen¹

1. Afdeling for transplantation og sygdomme i fordøjelsessystemet, Klinik for IBD, Rigshospitalet, 2. Patologisk afdeling, Copenhagen University Hospital, Herlev og Gentofte Hospital, 3. Afdeling for mave-, tarm- og leversygdomme, Herlev og Gentofte Hospital, 4. Medicinsk afdeling, Sjællands Universitetshospital, Køge, 5. Gastroenheden – Medicinsk sektion, Amager og Hvidovre Hospital, 6. Center for Surgical Science, Sjællands Universitetshospital, Køge

Formål

Fibrose i resektionsranden ved Crohns sygdom (CD) er ikke tidligere undersøgt. Formålet var at karakterisere inflammation og fibrose i resektionsrandene og vurdere deres betydning for sygdomsrecidiv inden for ét år efter resektion ved stenoserende sygdom.

Materiale og metoder

Af 63 inkluderede patienter med resektionskrævende CD gennemgik 54 (86 %) koloskopi inden for ét år. Recidiv blev defineret som endoskopisk aktivitet (Rutgeerts-score $\geq$ i2b). Vævsprøver fra resektionsrande og stenoser blev blindet vurderet histologisk med fibrosescore og D'Haens' inflammationscore. Multivariat regressionsanalyse blev anvendt.

Resultater

Fuldvægsbiopsier viste mere udtalt fibrose og inflammation i de stenotiske områder sammenlignet med resektionsrandene. Alle stenoser udviste transmural fibrose. Fibrose i den orale resektionsrand blev påvist hos 20 patienter (32 %), heraf 15 (24 %) med submukosal involvering. I den anale resektionsrand fandtes fibrose hos 13 patienter (21 %), hvoraf 12 (19 %) havde submukosal fibrose. Inflammationen var ligeledes mest udtalt i de stenotiske områder, hvor 61 patienter (97 %) havde aktiv inflammation (D'Haens-score > 0), med en median score på 9 (IQR: 4–11). Til sammenligning havde 9 patienter (14 %) aktiv inflammation i den orale resektionsrand og 21 (33 %) i den anale.

Endoskopisk sygdomsrecidiv blev fundet hos 3 patienter (5 %) inden for 6 måneder og hos 20 patienter (32 %) inden for 12 måneder. Der blev ikke observeret fibrostenotisk recidiv.

Ved isoleret ileocecal resektion (n=49) viste en multivariat analyse, at højere inflammationscore i den orale rand var associeret med reduceret recidivrisiko (OR = 0,38; 95% CI [0,13–0,77]; p = 0,027), mens højere fibrosescore var associeret med øget risiko (OR = 4,72; 95% CI [1,71–22,26]; p = 0,015). Fund i den anale rand var ikke associeret med recidiv.

Konklusion

Postoperativt recidiv ved stenoserende CD er hyppigt og ses primært oralt for anastomosen. Fibrose i den orale rand øger recidivrisikoen, mens inflammation kan være beskyttende.

26. Usefulness of Circulating Fibrosis Markers in the Initial Screening and Detection of Carcinoid Heart Disease in Patients with Neuroendocrine Neoplasms

Tobias Stemmann Lau^{1,2}, Elisavet Angeli³, Riina Karoliina Oksjoki⁴, Vibeke Guldbrand Rasmussen⁴, Federica Genovese³, Linda Skibsted Kornerup¹, Henning Grønbaek^{1,2}, Gitte Dam^{1,2}

¹Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark ²Department of Clinical Medicine, Aarhus University, Aarhus, Denmark ³Nordic Bioscience A/S, Herlev, Denmark ⁴Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Background and aim: Carcinoid heart disease (CHD) is a potential serious fibrotic complication in patients with neuroendocrine neoplasms (NEN), affecting the heart valves. Early detection is crucial to avoid severe manifestations. The value of the currently recommended screening biomarker, NT-proBNP, is questionable. Fibrosis markers are circulating fragments of the extracellular matrix reflecting fibrosis formation. We aimed to investigate the usefulness of circulating fibrosis markers in the initial screening and detection of CHD.

Methods: We included patients with disseminated small-intestinal NEN. We performed transthoracic echocardiography (TTE) for the diagnosis of CHD, and blood samples were drawn for measurement of different circulating fibrosis markers (CALC2, MIM, PRO-C3, PRO-C6, TIM, C2M, C3M, C6Ma3). The area under the receiver operating characteristic (AUROC) curve was calculated to evaluate the usefulness of fibrosis markers as a screening tool for detection of CHD.

Results: Ninety-eight (98) patients were included in the study of whom 16 (16%) had CHD. Mean age was 66 years (+ 9.3), 51% were men and 49% were female. The levels of the specific fibrosis marker, PRO-C3, were significantly increased in patients with CHD compared to patients without CHD (127 ng/ml (IQR: 102 – 158) vs. 94 (IQR: 82 – 115), $p = 0.002$). The AUROC for PRO-C3 for detection of CHD was 0.77 (95% CI: 0.64 – 0.90).

Conclusion: PRO-C3 demonstrated good performance in detection of CHD, outperforming the currently recommended screening biomarker, NT-proBNP. However, as an initial screening tool to determine whether patients should undergo TTE, PRO-C3 cannot stand alone.

Abstracts som fremgår af DSGH hjemmesiden

Muscle ammonia metabolism; contribution to systemic ammonia clearance and effects of cirrhosis and experimentally induced hyperammonaemia

Peter Lykke Eriksen^{1,2}, Lars Djernes^{3,4}, Nicolai J. Wewer Albrechtsen⁵, Hendrik Vilstrup¹, Peter Ott¹

1: Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

2: Department of Internal Medicine, Horsens Regional Hospital, Horsens, Denmark.

3: Department of Anaesthesiology and Intensive Care, Viborg Regional Hospital, Viborg, Denmark

4: Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, Aarhus Denmark

5: Department of Clinical Biochemistry, Copenhagen University Hospital - Bispebjerg, Copenhagen, Denmark

Introduction

Ammonia is toxic and implicated in hepatic encephalopathy (HE). While liver-based urea cycle is responsible for final elimination, muscles may be a key site for transient ammonia detoxification. In cirrhosis, sarcopenia may impair muscle ammonia scavenging, exacerbating hyperammonaemia and HE. Despite clinical relevance, quantitative data on muscle ammonia handling are limited. This study examines muscles contribution to systemic ammonia metabolism in cirrhosis and healthy individuals under basal and experimentally induced hyperammonaemic conditions.

Methods

Ten patients with cirrhosis and ten healthy individuals studied at baseline and during a standardised intravenous ammonium chloride infusion. Systemic ammonia removal and leg ammonia and amino acid fluxes were determined by arterial and femoral venous sampling and leg blood flow Doppler ultrasound, and leg and total skeletal muscle mass by bioelectrical impedance.

Results

In cirrhosis, muscle mass was reduced by 18% ($p = 0.02$) and arterial and venous ammonia levels increased at baseline and during infusion ($p < 0.001$). Overall, muscles demonstrated net ammonia removal with comparable leg fluxes between groups at both time points ($p = 0.45$ and $p = 0.94$). 3/10 patients showed a small basal net ammonia release ($1.3\text{--}2.9 \mu\text{mol/min}$), which transitioned to net removal during infusion in 2 of these 3. Muscle ammonia removal increased with increasing ammonia levels and was higher in patients at both time points ($1.1 [0.2\text{--}2.1]$ vs. $0.4 [0.2\text{--}0.5]$, $p = 0.09$ and $5.3 [2.8\text{--}7.7]$ vs. $4.3 [3.4\text{--}5.1] \mu\text{mol/min/kg muscle}$, $p = 0.14$). Muscle contribution to systemic removal was similar between groups: 24% vs. 25% at baseline ($p = 0.86$) increasing to 31% vs. 33% during infusion ($p = 0.78$).

Conclusions

Despite reduced overall ammonia clearance in cirrhosis, total and fractional muscle ammonia removal was intact and does not explain the ammonia problem. Still, the results support role of muscles in buffering ammonia in health and cirrhosis and its potential as a therapeutic target.

Semaglutid til kronisk idiopatisk diarre – erfaringer fra 5 cases

Gunnar Lauge Nielsen, Aalborg UH, Farsø (guln@rn.dk)

Baggrund: Kronisk idiopatisk diarre er en hyppig tilstand, der ofte er socialt invaliderende for de ramte patienter. Behandlingen er empirisk og den introduceres typisk trinvist(1). En mindre gruppe patienter har dog stadig diarre efter at have gennemgået vanlige behandlinger (psyllium, loperamid, dropizol).

Intervention: På baggrund af dokumenteret evidens for brug af liraglutide (Victoza®) til patienter med galdesaltsbetinget diarre(2) har vi i udvalgte cases med idiopatisk diarre forsøgt behandling med semaglutid (Ozempic®).

Patienter: Alle patienter havde gennemgået vanlig diarreudredning med gastro- og koloskopi med biopsitagning incl. normal transglutaminase og lactosegentest. Ingen af patienter varolecystektomerede, alle var kvinder. Se-HCAT viste hhv. 24%, 24% og 11% retention. Ved patient D og E er der pga manglende effekt af behandling med Questran ikke lavet se-HCAT test. Se tabel.

Alder, år	A: 23	B: 38	C: 65	D: 74	E: 59
Afføringer, no	15-20	8-10	5-6	10-15	10-15
Natlige aff.	1-2	1-2	-	2-3	-
Kapsel	Ja	-	-	Ja	-
Se-HCAT	11%	24%	24%	Ej lavet	Ej lavet
Aff. volumen	-	-	-	631/289/663	-
Questran	Marginal effekt	Ej prøvet	Ej prøvet	Ingen effekt	Ingen effekt
Dropizol	Ej prøvet	Ej prøvet	Ej prøvet	Ingen effekt	Ingen effekt
Imodium	Marginal effekt	Marginal effekt	Marginal effekt	Ingen effekt	Marginal effekt
Ozempic®	0,25 mg/5 dag	0,5 mg/uge	1,7 mg/uge	0,25 mg/5 dag	0,5 mg/uge
Start Ozempic	Aug. 2024	Nov. 2024	Aug. 2024	Juli 2024	Jan. 2025
Status juni 25	Normalisering	Normalisering	Normalisering	Normalisering	Normalisering

Efter succesfulde behandlingsforsøg ansøgte om individuelt tilskud til Ozempic®, hvilket er bevilget til alle patienter. Ved telefoninterview juni 2025 bekræfter alle vedvarende normalisering af afføringen.

Konklusion: Semaglutid kan i udvalgte tilfælde benyttes til behandling af idiopatisk diarre.

Artificial Intelligence Predicts Progression from Low-Grade Dysplasia in IBD

Jesper Winkler Andersen^{1,2}; Frederikke Schønfeldt Troelsen^{2,3}; Klaus Krogh^{1,2}; Trevor Graham⁵; Nicholas Trahearn⁵; Ailsa Hart⁴; Anders Kirch Dige^{1,2}

¹ The Department of Hepatology and Gastroenterology, Aarhus University Hospital, DK

² The Faculty of Health Sciences, Aarhus University, DK

³ Department of Clinical Epidemiology, Aarhus University Hospital, DK

⁴ St Mark's Hospital & Imperial College, London, UK

⁵ Centre for Evolution and Cancer, The Institute of Cancer Research, London, UK

Background

The finding of low-grade dysplasia (LGD) in inflammatory bowel disease (IBD) guides clinical decision-making and carries major implications for affected individuals, often leading to intensive surveillance, repeated pathological assessments, and, in some cases, surgery. Progression rates from LGD to advanced dysplasia, including high-grade dysplasia (HGD) or colorectal cancer (CRC) vary considerably across studies, and defining individual risk remains challenging. One major challenge is the pathological assessment, which is time-consuming and complicated by morphological heterogeneity, concomitant inflammation, and interobserver variability. A recently developed and validated artificial intelligence (AI)-based cell quantifier enables automated identification and quantification of cells on digital histology slides. This cell quantifier is validated and predicts relapse-free survival in CRC. We investigated whether macrophage density differed in areas with LGD versus surrounding tissue, and whether the density of macrophages in the area of LGD was related to progression from LGD to advanced dysplasia.

Methods

We conducted a case-control study including individuals diagnosed with IBD and LGD between 1994 and 2018 in the Central Denmark Region. Cases were defined as individuals who progressed from LGD to either HGD or CRC, and controls were matched on age, sex, and follow-up time using risk set sampling. For each participant, the first available LGD sample was identified, and H&E-stained slides were prepared and digitised. Areas with LGD were annotated by an expert pathologist, and the slides were subsequently analysed using the cell quantifier. When multiple samples were available, each was analysed separately. T-tests were used to compare macrophage density in the area LGD-marked area between cases and controls, and for each sample between areas with LGD and the surrounding tissue. Kernel density plots and Cox regression analyses with clustering and robust standard error were used to further investigate the impact on progression.

Results

We identified 64 cases and matched 116 controls between 1994-2018, representing 236 samples with LGD due to multifocality. For all samples, sufficient tissue was retrieved, and the AI-based cell quantifier was applied without requiring alterations to standard slide preparation or model structure. A marked difference in macrophage density was observed between surrounding tissue and areas with LGD (mean: 233.6 vs. 129.3, $p = 0.000$). Kernel density plots demonstrated a minor leftward shift among cases. Belonging to the lowest quartile of macrophage density within the LGD area, compared

to the combined higher quartiles, was associated with an almost twofold increased risk of progression to advanced dysplasia

Conclusion

AI-based tools enable novel and scalable quantification of cellular distribution in digital histological sections. In this study, a markedly higher macrophage density was observed within LGD areas compared to the surrounding tissue. Importantly, being in the lowest quartile of macrophage density within LGD areas was associated with an increased risk of progression from LGD to advanced dysplasia.

Acute severe infusion reactions to infliximab in patients with checkpoint inhibitor-induced enterocolitis

Pernille Dige Ovesen^{1,2}, Emilie Kristine Dahl², Mirabella Zhao³, Anja Poulsen², Johan Burisch³, Casper Steenholdt^{4,5}, Jakob B. Seidelin²

¹ Department of Gastroenterology, Herlev University Hospital, Herlev, Denmark

² Department of Digestive Diseases, Transplantation and General Surgery, Section for IBD, Copenhagen University Hospital, Rigshospitalet, Denmark

³ Gastrounit, Medical Division, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark

⁴ Department of Medical Gastroenterology, Odense University Hospital, Denmark

⁵ Research Unit of Medical Gastroenterology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Background:

Immune checkpoint inhibitor therapy has revolutionized oncologic treatment. The treatment primarily targets T-cells but also modulate B-cells directly and via activated CD4⁺ T-cells. As a result, immune related adverse events such as immune related enterocolitis (irC) are common and can be potentially life-threatening. Treatment of irC often involves infliximab (IFX) in cases of steroid refractoriness. However, IFX can lead to acute severe infusion reactions, primarily due to anti-drug antibodies (ADAs). The on-demand nature of irC treatment, along with the presence of activated B-cells may elevate ADA levels, potentially increasing risk of infusion reactions compared to IFX use in chronic immune-inflammatory diseases such as inflammatory bowel disease (IBD). We aim to investigate the incidence and characteristics of infusion reactions in a population of patients with irC as well as subsequent management of irC following reaction.

Methods:

This was a retrospective cohort study including patients with irC treated with IFX from 2020 through 2024. Patients were followed one year from initiation of IFX. Reactions were defined as acute reactions during infusion with IFX and scored using the Universal Standardized Drug Allergy Reaction (USDAR) grading scale. Secondary, subsequent management of irC following reactions was reported. A cohort of 176 bio-naïve and thiopurine-unexposed patients initiating IFX for IBD was used as a pseudo control group.

Results:

Ninety-nine patients with irC were treated with IFX during the study period, 93% of whom received concomitant CS. The median number of CS treatment days prior to IFX initiation was 21 (IQR:10-72). Twenty-five percent received a single IFX infusion, 50% received two, 15% received three and 9% received four or more infusions. Diarrhea resolved within 14 days following the first infusion in 63% of patients. Overall, 4 (4.0%) patients experienced acute severe infusion reactions. This incidence was comparable to the IBD control group where 8 (4.5%) of 176 patients had reactions (p=1.0). Infusion

reactions occurred in two patients during their second IFX infusion and two during their third. Three patients had a USDAR grade of one, while one patient had a grade of two. All cases were managed with intravenous anti-histamine and corticosteroids, and none resulted in hospital admission. In one of the cases, the patient had been treated with IFX four years prior, thus having a reaction at the second infusion when reintroduced. Three patients were subsequently treated with golimumab (100 mg every four weeks, n=2 attained remission), and one went successfully into remission with vedolizumab (300 mg every eight weeks). Other drug related adverse events to IFX such as dermatitis, drug induced liver injury or infections, were not significantly different in the two groups (irC: 8/99 (8.1%) vs IBD: 18/176 (10.2%), $p=0.67$).

Conclusion:

The risk of acute severe infusion reactions to IFX is not increased in patients with irC compared to patients with IBD despite risk factors such as episodic use and an activated state of immune response. Switching to another TNF-inhibitor can be successful following a reaction.

Alcohol, Inequality, and Liver Cirrhosis: Can Drinking Patterns and Cardiometabolic Risk Factors Explain the Socioeconomic Gap?

Jonas Hedelund Rønn, Peter Jepsen, Jessica Mellinger, Merete Osler, Matilde Winther-Jensen, Anne I. Christensen, Marie H. Elisassen Lone G. Madsen, Gro Askgaard

Introduction

There is socioeconomic inequality in the incidence of cirrhosis. We investigated 1) the contribution of alcohol drinking patterns and cardiometabolic factors to socioeconomic inequality in cirrhosis incidence, and 2) whether the association of these risk factors with cirrhosis risk depended on socioeconomic status.

Methods

We included participants from the population-based Danish National Health Surveys 2010-2017 and followed them until December 31st, 2022, for an incident hospital diagnosis of cirrhosis, linking data from questionnaires and health registries. Socioeconomic position was measured by educational length. The socioeconomic inequality of cirrhosis risk was estimated as the hazard ratio (HR) of cirrhosis in those with short (≤ 9 years) vs. long (≥ 17 years) educational length. 1) The contribution of alcohol drinking patterns (drinks per week, drinking days per week, drinking outside of meals) and cardiometabolic factors (body mass index (BMI), diabetes, hypertension, dyslipidemia, smoking) to socioeconomic inequality was measured by the socioeconomic inequality in HR for cirrhosis with versus without adjustments for them. 2) We used interaction tests to examine whether the effects of alcohol and cardiometabolic risk factors on cirrhosis incidence depend on socioeconomic position. All analyses were weighted for sampling procedure and differential participation in the health surveys according to sociodemographic and health variables.

Results

The study included 301,559 participants with a median age of 49 years (IQR 40.3-59.1), 50% were female, 19% had a short education length, and 12% had a long education length. There was a gradual increase with decreasing educational length in the prevalence of drinking above 28 drinks/week, smoking, BMI >30 , and the other cardiometabolic risk factors. During 2,711,309 person-years of follow-up, 1015 participants were diagnosed with cirrhosis. The HR for cirrhosis in short vs. long education length was attenuated from 3.85 (95% CI: 2.60; 5.71) in the age- and sex adjusted analysis to 3.67 (95% CI, 2.49; 5.41) when further adjusted for alcohol drinking pattern, and to 2.72 (95% CI, 1.84; 4.03) when fully adjusted for alcohol drinking pattern and cardiometabolic factors. The strength of the association between alcohol drinking patterns and any cardiometabolic risk factor on cirrhosis risk did not depend on education length (p-values for interactions were all > 0.4).

Conclusion

When alcohol drinking pattern and cardiometabolic factors were considered, there was still a nearly three-fold higher risk of cirrhosis in short vs. long educated. The relative harmful effect of alcohol was irrespective of educational level, and a similar pattern was observed for the influence of cardiometabolic factors.

Model-Informed Precision Dosing (MIPD) of Ustekinumab and Vedolizumab in Inflammatory Bowel Disease (the MOVE-IT study): protocol for an Independent randomized, controlled, multi-center Trial

Camilla Frimor^{1,2}, Casper Steenholdt^{1,2}, Ella Widigson^{3,4}, Jens Kjeldsen^{1,2}, Lone Larsen^{5,6}, Johan Burisch^{7,8}, Maiken Thyregod Jørgensen⁹, Morten Lee Halling¹⁰, Charlotte Kloft^{3,4}, Mark Ainsworth^{1,2}

¹ Department of Medical Gastrointestinal Diseases, Odense University Hospital, Odense, Denmark. ² Institute of Clinical Research, University of Southern Denmark, Odense, Denmark. ³ Department of Clinical Pharmacy and Biochemistry, Freie Universität Berlin, Berlin, Germany. ⁴ Graduate Research Training Program: Pharmacometrics & Computational Disease Modelling (PharMetrX), Berlin Germany. ⁵ Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark. ⁶ Center of Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Aalborg University, Aalborg, Denmark. ⁷ Copenhagen IBD-center, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark. ⁸ Gastrounit, Medical Section, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark. ⁹ Department of Internal Medicine, Section of Gastroenterology, Sygehus Lillebælt, Vejle, Denmark. ¹⁰ Department of Internal Medicine, Section of Gastroenterology, Sydvestjysk Sygehus, Esbjerg, Denmark

Background: Biologic therapies, such as vedolizumab (VDZ) and ustekinumab (UST), offer effective treatment options for inflammatory bowel disease (IBD). In spite of limited evidence, it is common practice to escalate the dosing regimen if clinical symptoms or biomarkers raise suspicion of waning effect or loss of response.

Aim: This study aims to determine whether Model-Informed Precision Dosing (MIPD) can provide equal efficacy and possibly superior cost-effectiveness compared to conventional symptom-based management.

Methods and analysis: This is a prospective, unblinded, randomized controlled trial, conducted at eight centers in Denmark. A total of 166 patients diagnosed with CD or UC who have been on stable VDZ or UST therapy for at least three months will be enrolled. Participants will be randomized to receive either continued symptom and biomarker-based dosing (control group) or dosing guided by TDM using pharmacokinetic (PK) models together with pharmacokinetic-pharmacodynamic (PKPD) targets (=MIPD; intervention group). The primary endpoint is the proportion of patients in steroid-free remission after 48 weeks. Secondary endpoints include mucosal healing, clinical remission, biochemical disease control, PK assessment, and cost-effectiveness. Recruitment will be initiated by medio 2025. Results are expected in 2027.

Ethics and dissemination: The trial has been approved by the Danish Medicines Agency and The Medical Research Ethics Committee. Results will be published in peer-reviewed journals and presented at international conferences. The study is registered under EU CT number: 2024-517123-39-00 and <https://clinicaltrials.gov/study/NCT06788340>.

Therapeutic Drug Monitoring of Ustekinumab and Vedolizumab in Inflammatory Bowel Disease: A Systematic Review to Define Exposure Thresholds for Endoscopic Remission

Camilla Frimor^{1,2*}, Ella Widigson^{3,4*}, Casper Steenholdt^{1,2}, Zrinka Duvnjak^{3,4}, Wilhelm Huisinga⁵, Franz Weber^{3,4}, Charlotte Kloft^{3,4*}, Mark Ainsworth^{1,2*}

¹ Department of Medical Gastrointestinal Diseases, Odense University Hospital, Odense, Denmark. ² Institute of Clinical Research, University of Southern Denmark, Odense, Denmark. ³ Department of Clinical Pharmacy and Biochemistry, Freie Universität Berlin, Berlin, Germany. ⁴ Graduate Research Training Program: Pharmacometrics & Computational Disease Modelling (PharMetrX), Berlin Germany. ⁵ Institute of Mathematics, University of Potsdam, Germany

* denotes shared first/last authorship

Background: Personalized treatment in IBD, through Therapeutic Drug Monitoring (TDM) is gaining popularity in treatment of Inflammatory Bowel Disease with Anti-TNF-alfa agents. Pharmacokinetic/Pharmacodynamic (PK/PD) thresholds have been well established for anti-TNF-alfa agents, however, such a consensus is still lacking for vedolizumab (VDZ) and ustekinumab (UST). The aim of this study was to identify exposure thresholds for endoscopic remission (ER).

Methods: PubMed and Embase was searched on the 7th of April 2025, for the following key terms 'Ustekinumab OR Stelara OR Vedolizumab OR Entyvio' AND 'Therapeutic Drug Monitoring OR Exposure-Response' AND 'Inflammatory Bowel Disease' AND 'Endoscopy', to find studies identifying exposure-response relationships between drug-exposure and ER. All studies yielded from the search were processed blinded, and in parallel, by two investigators (E.W. and C.F.), using Covidence. Only full-length, original research articles on adults were included. If complicated disease such as fistulizing or structuring disease was the main scope, articles were excluded. Relevant reviews were screened by one investigator (CF) to reveal relevant studies not found in our search of PubMed and Embase. The median of PK/PD thresholds were chosen as summary statistics of optimal minimal drug-exposure to eliminate the impact of outliers and avoid assumptions on normal distribution of thresholds.

Results: A total of 282 studies were retrieved, 104 duplicates were removed, 178 abstracts were screened, 88 studies were screened for eligibility. Relevant reviews were also screened for eligible studies that had not been identified in the initial search. A total of 18 studies were included (VDZ n=9 studies of n=1.245 patients, UST n=9 studies of n=906 patients). Median PK/PD threshold for ER on UST at week 8 was 8,4 µg/mL (ER w8-24), and 3.5 µg/mL during the maintenance phase (ER w16-52). The median PK/PD threshold for ER on VDZ was 27,0 µg/mL at week 2 (ER w14-52), 23,5 µg/mL at week 6 (ER w14-52), 15,3 µg/mL at week 14 (ER w14-54) and 10.4 µg/mL during maintenance (ER w22-52).

Conclusion: We have found a clear exposure-response relationship for both VDZ and UST, and provide reference values for assessing adequate exposure. These thresholds can be used to guide dosing in select patients.