FALK GASTRO REVIEW JOURNAL

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79108 Freiburg | Germany

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Contents

Editorial

Dear colleagues,

Apart from endoscopic argon plasma coagulation (APC) there have been few drug therapy approaches to **gastrointestinal bleeding** due to small intestinal **angiodysplasia** to date, which is clinically often challenging. A randomized controlled trial showed that therapy with octreotide significantly reduced the number of transfusions and endoscopic interventions within a year compared to standard therapy (Goltstein et al., page 10). The detection of **gastric metaplasia** in the **distal esophagus** raises the question of its malignant potential and efficient endoscopic prevention strategies. A prospective surveillance study in the UK showed that gastric metaplasia of the distal esophagus has a significantly different clinical course and genetic pattern than intestinal metaplasia and a significantly lower malignant potential. For this reason, it appears to be questionable whether patients with gastric metaplasia need preventive care comparable to patients with Barrett's esophagus (Black et al., page 8).

Multiple publications in this edition concern new approaches to **colorectal cancer screening**. In a large-scale prospective study, an innovative **multitarget stool DNA test** showed superior sensitivity for colorectal cancer and advanced precancerous lesions than an immunological test of fecal blood, albeit with lower specificity (Imperiale et al., page 21). A **cell-free DNA blood-based test** also showed good sensitivity of 83% for the detection of colorectal cancer in an average risk population for colorectal cancer screening, but only of 13% for the detection of advanced precancerous lesions (Chung et al., page 21).

It is assumed that for **inflammatory bowel disease (IBD)**, **early consistent therapy with biologics** had a favorable impact on the disease progression. This was only partially confirmed by the results of a nationwide study in Israel. While in patients with Crohn's disease, early initiation of biologics was associated with a moderately lower risk of later Crohn's-associated surgery and steroid dependency, in patients with ulcerative colitis, it had no influence on colectomy or steroid dependency rates (Lujan et al., page 17). In this context, it is interesting that while in the LOVE-CD study, in which the response to vedolizumab was significantly better in patients with Crohn's disease and "early" (disease less than 2 years) initiation of therapy, in the LOVE-UC study of patients with early and late ulcerative colitis no significant differences were detected with regard to clinical, endoscopic, and histological outcomes in response to **vedolizumab** therapy (Vermeire et al., page 18).

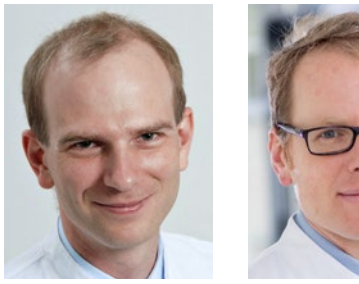
The treatment of **acute necrotizing pancreatitis** should not end with the discharge from the hospital. A cohort study conducted in the Netherlands showed that patients with acute pancreatitis often experience recurrence, require interventions, and develop endocrine and exocrine pancreatic insufficiency. Extensive (> 50%) pancreatic parenchymal necrosis seems to be an important predictor of the long-term need for interventions and complications during follow-up (Hollemans et al., page 27).

A current meta-analysis of **morbidity and mortality** in patients **coinfected with hepatitis B and hepatitis delta virus** shows that patients with HDV-RNA-positive status have a significantly greater risk of (decompensated) liver cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and liver-related mortality. These findings emphasize the importance of consistently screening patients with hepatitis B for coinfection with the hepatitis delta virus (Gish et al., page 32). In patients with **metabolic dysfunction-associated steatotic liver disease**

(MASLD), serum ferritin levels are typically elevated. A current study shows that the hyperferritinemia predicts the long-term prognosis and is associated with increased risk of liver-related events and all-cause mortality (Armandi et al., page 29). A current open-label controlled randomized trial on **induction therapy for autoimmune hepatitis** suggests that mycophenolate mofetil is superior to azathioprine as induction therapy for autoimmune hepatitis in combination with prednisolone, with better tolerability (Snijders et al., page 33).

We hope you find these articles, along with the other publications summarized in this issue, both stimulating and informative.

Yours sincerely,



Christoph Neumann-Haefelin and Peter Hasselblatt
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Passing the baton

For the past 10 years, I have had the pleasure of putting together a collection of abstracts on sensational developments in hepatology for the Falk Gastro Review Journal. These have included the revolution in hepatitis C therapy, the development of immunotherapy for hepatocellular carcinoma (HCC), and the development of the first targeted therapy for hepatitis delta. Effective September 2024, I will be starting my new position as a professor of gastroenterology and hepatology at the University of Cologne (Germany), where I will be succeeding Prof. Dr. Tobias Goeser. By tradition, the editor of the Falk Gastro Review Journal is based in Freiburg. I am delighted to pass on the hepatology editorial work to my long-standing colleague and the future head of the Gerok Liver Center in Freiburg, Prof. Dr. Tobias Böttler. Thank you for being such loyal readers, and I extend my gratitude to the Falk Foundation team for their outstanding support.

Sincerely,

Christoph Neumann-Haefelin

ESOPHAGUS TO SMALL INTESTINE

Achalasia and Motility Disorders

Gut. 2024;73(4):582–9

Boeckxstaens G, Elsen S, Belmans A, Annese V, Bredenoord AJ, Busch OR, Costantini M, Fumagalli U, Smout AJPM, Tack J, Vanuytsel T, Zaninotto G, Salvador R

10-year follow-up results of the European Achalasia Trial: A multicentre randomised controlled trial comparing pneumatic dilation with laparoscopic Heller myotomy

Objective: As achalasia is a chronic disorder, long-term follow-up data comparing different treatments are essential to select optimal clinical management. Here, the authors report on the 10-year follow-up of the European Achalasia Trial comparing endoscopic pneumatic dilation (PD) with laparoscopic Heller myotomy (LHM).
Design: A total of 201 newly diagnosed patients with achalasia were randomised to either a series of PDs (n = 96) or LHM (n = 105). Patients completed symptom (Eckardt score) and quality-of-life questionnaires, underwent functional tests and upper endoscopy. Primary outcome was therapeutic success defined as Eckardt score ≤ 3 at yearly follow-up. Secondary outcomes were the need for retreatment, lower oesophageal sphincter pressure, oesophageal emptying, gastro-oesophageal reflux and the rate of complications.
Results: After 10 years of follow-up, LHM (n = 40) and PD (n = 36) were equally effective in both the full analysis set (74% vs. 74%, p = 0.84) and the per protocol set (74% vs. 86%, respectively, p = 0.07). Subgroup analysis revealed that PD was superior to LHM for type 2 achalasia (p = 0.03) while there was a trend, although not significant (p = 0.05), that LHM performed better for type 3 achalasia. Barium column height after 5 minutes at timed barium oesophagram was significantly higher for patients treated with PD compared with LHM, while other parameters, including gastro-oesophageal reflux, were not different.

Conclusions: Pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM) are equally effective even after 10 years of follow-up with limited risk to develop gastro-oesophageal reflux. Based on these data, it was concluded that PD and LHM can both be proposed as initial treatment of achalasia.

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Am J Gastroenterol. 2024;119(4):635–45

Low EE, Demb J, Shah SC, Liu L, Bustamante R, Yadlapati R, Gupta S

Risk of esophageal cancer in achalasia: A matched cohort study using the nationwide Veterans Affairs Achalasia Cohort

Introduction: Achalasia is a postulated risk factor of esophageal cancer (EC); however, EC-associated risk in achalasia is understudied. The authors aimed to evaluate EC risk among individuals within the nationwide Veterans Affairs Achalasia Cohort.
Methods: They conducted a matched cohort study among US veterans aged 18 years or older from 1999 to 2019. Individuals with achalasia were age matched and sex matched 1:4 to individuals without achalasia. Follow-up continued from study entry until diagnosis with incident/fatal EC (primary outcome), death from non-EC-related causes, or end of the study follow-up (December 31, 2019). Association between achalasia and EC risk was examined using Cox regression models.
Results: 9315 individuals were included in the analytic cohort (median age, 55 years; 92% male): 1863 with achalasia matched to 7452 without achalasia. During a median 5.5 years of follow-up, 17 EC occurred (3 esophageal adenocarcinoma, 12 squamous cell carcinoma, and 2 unknown type) among individuals with achalasia, compared with 15 EC (11 esophageal adenocarcinoma, 1 squamous cell carcinoma, and 3 unknown type) among those without achalasia. EC incidence for those with achalasia was 1.4 per 1000 person-years, and the median time from achalasia diagnosis to EC development was 3.0 years (Q1–Q3: 1.3–9.1). Individuals with achalasia had higher cumulative EC incidence at 5, 10, and 15 years of follow-up compared with individuals without achalasia, and EC risk was 5-fold higher (hazard ratio = 4.6, 95% confidence interval: 2.3–9.2).

Discussion: Based on substantial esophageal cancer (EC) risk, individuals with achalasia may benefit from a high index of suspicion and endoscopic surveillance for EC.

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Celiac Disease, Gluten Sensitivity and Food Allergy

Gastroenterology. 2024;166(4):620–30

Shiha MG, Nandi N, Raju SA, Wild G, Cross SS, Singh P, Elli L, Makharia GK, Sanders DS, Penny HA

Accuracy of the no-biopsy approach for the diagnosis of celiac disease in adults: A systematic review and meta-analysis

Background and aims: Current international guidelines recommend duodenal biopsies to confirm the diagnosis of celiac disease in adult patients. However, growing

evidence suggests that immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody levels ≥ 10 times the upper limit of normal (ULN) can accurately predict celiac disease, eliminating the need for biopsy. The authors performed a systematic review and meta-analysis to evaluate the accuracy of the no-biopsy approach to confirm the diagnosis of celiac disease in adults.
Methods: They systematically searched Medline, Embase, Cochrane Library, and Web of Science from January 1998 to October 2023 for studies reporting the sensitivity and specificity of IgA-tTG ≥ 10 x ULN against duodenal biopsies (Marsh grade ≥ 2) in adults with suspected celiac disease. A bivariate random effects model was used to calculate the summary estimates of sensitivity, specificity, and positive and negative likelihood ratios. The positive and negative likelihood ratios were used to calculate the positive predictive value of the no-biopsy approach across different pretest probabilities of celiac disease. The methodological quality of the included studies was evaluated using the QUADAS-2 tool.
Results: A total of 18 studies comprising 12,103 participants from 15 countries were included. The pooled prevalence of biopsy-proven celiac disease in the included studies was 62% (95% confidence interval [CI]: 40–83%). The proportion of patients with IgA-tTG ≥ 10 x ULN was 32% (95% CI: 24–40%). The summary sensitivity of IgA-tTG ≥ 10 x ULN was 51% (95% CI: 42–60%), and the summary specificity was 100% (95% CI: 98–100%). The area under the summary receiver-operating characteristic curve was 0.83 (95% CI: 0.77–0.89). The positive predictive value of the no-biopsy approach to identify patients with celiac disease was 65%, 88%, 95%, and 99% if celiac disease prevalence was 1%, 4%, 10%, and 40%, respectively. Between-study heterogeneity was moderate (I^2 = 30.3%), and additional sensitivity analyses did not significantly alter these findings. Only 1 study had a low risk of bias across all domains.

Conclusion: The results of this meta-analysis suggest that selected adult patients with immunoglobulin A anti-tissue transglutaminase antibody levels ≥ 10 times the upper limit of normal and a moderate to high pretest probability of celiac disease could be diagnosed without undergoing invasive endoscopy and duodenal biopsy.

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Reflux

Am J Gastroenterol. 2024;119(5):803–13

Zhuang Q, Chen S, Zhou X, Jia X, Zhang M, Tan N, Chen F, Zhang Z, Hu J, Xiao Y

Comparative efficacy of P-CAB vs. proton-pump inhibitors for grade C/D esophagitis: A systematic review and network meta-analysis

Introduction: Los Angeles grade C/D esophagitis is a severe manifestation of gastroesophageal reflux disease that require active treatment and close follow-up. Potassium-competitive acid blockers (P-CABs) are promising alternatives to proton-pump inhibitors (PPIs). The authors aimed to compare the efficacy and safety of P-CABs and PPIs in healing grade C/D esophagitis to aid clinical decision-making.
Methods: A systematic literature search was performed using PubMed, Medline, and Cochrane Central Register of Controlled Trials. Randomized controlled trials were eligible for inclusion if efficacy of P-CABs and PPIs in healing grade C/D esophagitis was reported. Pooled risk ratios and risk difference with 95% credible intervals were used to summarize estimated effect of each comparison. The benefit of treatments was ranked using the surface under the cumulative probability ranking score.
Results: Of 5876 articles identified in the database, 24 studies were eligible. Studies included incorporated 3 P-CABs (vonoprazan, tegoprazan, and keverprazan) and 6 PPIs (lansoprazole, esomeprazole, omeprazole, rabeprazole extended-release [ER], pantoprazole, and dexlansoprazole). Based on the failure to achieve mucosal healing, 20 mg of vonoprazan once daily ranked the first among PPIs in initial and maintained healing of grade C/D esophagitis (surface under the cumulative probability ranking score = 0.89 and 0.87, respectively). Vonoprazan had similar risk of incurring adverse events, severe adverse events, and withdrawal to drug when compared with PPIs. For those who attempted lower maintenance treatment dose, 10 mg of vonoprazan once daily was a reasonable choice, considering its moderate efficacy and safety.

Discussion: Vonoprazan has considerable efficacy in initial and maintained healing of grade C/D esophagitis compared with proton-pump inhibitors, with moderate short-term and long-term safety.

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Gastritis and Helicobacter Pylori

Am J Gastroenterol. 2024;119(4):655–61

Yan TL, Wang JH, He XJ, Zhu YB, Lu LJ, Wang YJ, Wang ZW, Gao JG, Xu CF, Ma H, Luan SM, Li L, Chen Y

Ten-day vonoprazan-amoxicillin dual therapy vs. standard 14-day bismuth-based quadruple therapy for first-line Helicobacter pylori eradication: A multicenter randomized clinical trial

Introduction: Whether 10-day short-course vonoprazan-amoxicillin dual therapy (VA-dual) is non-inferior to the standard 14-day bismuth-based quadruple therapy (B-quadruple) against Helicobacter pylori eradication has not been determined. This trial aimed to compare the eradication rate, adverse events, and compliance of 10-day VA-dual regimen with standard 14-day B-quadruple regimen as first-line H. pylori treatment.
Methods: This prospective randomized clinical trial was performed at 3 institutions in eastern China. A total

of 314 treatment-naive, H. pylori-infected patients were randomly assigned in a 1:1 ratio to either 10-day VA-dual group or 14-day B-quadruple group. Eradication success was determined by ^{13}C-urea breath test at least 4 weeks after treatment. Eradication rates, adverse events, and compliance were compared between groups.
Results: Eradication rates of VA-dual and B-quadruple groups were 86.0% and 89.2% (p = 0.389), respectively, by intention-to-treat (ITT) analysis; 88.2% and 91.5% (p = 0.338), respectively, by modified ITT analysis; and 90.8% and 91.3% (p = 0.884), respectively, by per-protocol (PP) analysis. The efficacy of the VA-dual therapy remained non-inferior to B-quadruple therapy in all ITT, modified ITT, and PP analyses. The incidence of adverse events in the VA-dual group was significantly lower compared with that in the B-quadruple group (p < 0.001). Poor compliance contributed to eradication failure in the VA-dual group (p < 0.001), while not in the B-quadruple group (p = 0.110).

Discussion: The 10-day vonoprazan-amoxicillin dual therapy provided satisfactory eradication rates of > 90% (per-protocol analysis) and lower rates of adverse events compared with standard 14-day bismuth-based quadruple therapy as first-line Helicobacter pylori therapy.

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DOI: 10.14309/ajg.0000000000002592 ■

Am J Gastroenterol. 2024;119(4):646–54

Bujanda L, Nyssen OP, Ramos J, Bordin DS, Tepes B, Perez-Aisa A, Pavoni M, Castro-Fernandez M, Lerang F, Leja M, Rodrigo L, Rokkas T, Kupcinskas J, Jonaitis L, Shvets O, Gasbarrini A, Simsek H, Phull PS, Buzás GM, Machado JC, Boltin D, Boyanova L, Tonkić A, Marlicz W, Venerito M, Vologzanina L, Fadieienko GD, Fiorini G, Resina E, Muñoz R, Cano-Català A, Puig I, García-Morales N, Hernández L, Moreira L, Megraud F, O'Morain C, Montes M, Gisbert JP; Hp-EuReg investigators

Effectiveness of Helicobacter pylori treatments according to antibiotic resistance

Introduction: Antibiotic resistance is one of the main factors that determine the efficacy of treatments to eradicate Helicobacter pylori infection. The aim of the present study was to evaluate the effectiveness of first-line and rescue treatments against H. pylori in Europe according to antibiotics resistance.
Methods: Prospective, multicenter, international registry on the management of H. pylori (European Registry on H. pylori Management, Hp-EuReg). All infected and culture-diagnosed adult patients registered in the Spanish Association of Gastroenterology-Research Electronic Data Capture from 2013 to 2021 were included.
Results: A total of 2852 naive patients with culture results were analyzed. Resistance to clarithromycin, metronidazole, and quinolones was 22%, 27%, and 18%, respectively. The most effective treatment, regardless of resistance, were the 3-in-1 single capsule with bismuth, metronidazole, and tetracycline (91%) and the quadruple with bismuth, offering optimal cure rates even in the presence of bacterial resistance to clarithromycin or metronidazole. The concomitant regimen with tinidazole achieved an eradication rate of 99% (90/91) versus 84% (90/107) with metronidazole. Triple schedules, sequential, or concomitant regimen with metronidazole did not achieve optimal results. A total of 1118 non-naive patients were analyzed. Resistance to clarithromycin, metronidazole, and quinolones was 49%, 41%, and 24%, respectively. The 3-in-1 single capsule (87%) and the triple therapy with levofloxacin (85%) were the only ones that provided encouraging results.

Discussion: In regions where the antibiotic resistance rate of Helicobacter pylori is high, eradication treatment with the 3-in-1 single capsule, the quadruple with bismuth, and concomitant with tinidazole are the best options in naive patients. In non-naive patients, the 3-in-1 single capsule and the triple therapy with levofloxacin provided encouraging results.

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Gastroenterology. 2024;166(4):605–19

Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, Wu YX, Hsiao JL, Chen MJ, Lin KP, Wu CY, Lin JT, O'Morain C, Megraud F, Lee WC, El-Omar EM, Wu MS, Liou JM

Global prevalence of Helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022

Background and aims: The authors aimed to assess the secular trend of the global prevalence of Helicobacter pylori infection in adults and children/adolescents and to show its relation to that of gastric cancer incidence.
Methods: They performed a systematic review and meta-analysis to calculate overall prevalence, adjusted by multivariate meta-regression analysis. The incidence rates of gastric cancer were derived from the Global Burden of Disease Study and Cancer Incidence in Five Continents.
Results: Of the 16,976 articles screened, 1748 articles from 111 countries were eligible for analysis. The crude global prevalence of H. pylori has reduced from 52.6% (95% confidence interval [CI]: 49.6–55.6%) before 1990 to 43.9% (95% CI: 42.3–45.5%) in adults during 2015 through 2022, but was still as high as 35.1% (95% CI: 30.5–40.1%) in children and adolescents during 2015 through 2022. Secular trend and multivariate regression analyses showed that the global prevalence of H. pylori has declined by 15.9% (95% CI: -20.5% to -11.3%) over the last 3 decades in adults, but not in children and adolescents. Significant reduction of H. pylori prevalence was observed in adults in the Western Pacific, Southeast Asian, and African regions. However, H. pylori prevalence was not significantly reduced in children and adolescents in any World Health Organization regions. The incidence of gastric cancer has decreased globally and in various countries where the prevalence of H. pylori infection has declined.

Conclusions: The global prevalence of Helicobacter pylori infection has declined during the last 3 decades in adults, but not in children and adolescents. The results raised the hypothesis that the public health drive to reduce the prevalence of H. pylori as a strategy to reduce the incidence of gastric cancer in the population should be confirmed in large-scale clinical trials.

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BMJ. 2024;385:e076484

Kurlander JE, Laine L, Kim HM, Roberts CB, Saffar D, Myers A, Holleman R, Gao Y, Shank M, Nelson R, Forman J, Helfrich CD, Krein SL, Saini SD, Yang YX

Impact of large-scale, multicomponent intervention to reduce proton-pump inhibitor overuse in integrated healthcare system: Difference-in-difference study

Objective: To determine how a large-scale, multicomponent, pharmacy-based intervention to reduce proton-pump inhibitor (PPI) overuse affected prescribing patterns, healthcare utilization, and clinical outcomes.
Design: Difference-in-difference study.
Setting: US Veterans Affairs Healthcare System, in which 1 regional network implemented the overuse intervention and all 17 others served as controls.
Participants: All individuals receiving primary care from 2009 to 2019.
Intervention: Limits on PPI refills for patients without a documented indication for long-term use, voiding of PPI prescriptions not recently filled, facilitated electronic prescribing of H2 receptor antagonists (H2RAs), and education for patients and clinicians.
Main outcome measures: The primary outcome was the percentage of patients who filled a PPI prescription per 6 months. Secondary outcomes included percentage of days PPI gastroprotection was prescribed in patients at high risk for upper gastrointestinal bleeding, percentage of patients who filled either a PPI or H2RA prescription, hospital admission for acid peptic disease in older adults appropriate for PPI gastroprotection, primary care visits for an upper gastrointestinal diagnosis, upper endoscopies, and PPI-associated clinical conditions.
Results: The number of patients analyzed per interval ranged from 192,607 to 250,349 in intervention sites and from 3,775,953 to 4,360,868 in control sites, with 26% of patients receiving PPIs before the intervention. The intervention was associated with an absolute reduction of 7.3% (95% confidence interval: -7.6% to -7.0%) in patients who filled PPI prescriptions, an absolute reduction of 11.3% (-12.0% to -10.5%) in PPI use among patients appropriate for gastroprotection, and an absolute reduction of 5.72% (-6.08% to -5.36%) in patients who filled a PPI or H2RA prescription. No increases were seen in primary care visits for upper gastrointestinal diagnoses, upper endoscopies, or hospital admissions for acid peptic disease in older patients appropriate for gastroprotection. No clinically significant changes were seen in any PPI-associated clinical conditions.

Conclusions: The multicomponent intervention was associated with reduced proton-pump inhibitor use overall but also in patients appropriate for gastroprotection, with minimal evidence of either clinical benefits or harms.

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Am J Gastroenterol. 2024;119(5):837–45

Miceli E, Lenti MV, Gentile A, Gambini G, Petrucci C, Pitotti L, Mengoli C, Di Stefano M, Vanoli A, Luinetti O, Brondino N, Paulli M, Anderloni A, Klersy C, Corazza GR, Di Sabatino A

Long-term natural history of autoimmune gastritis: Results from a prospective monocentric series

Introduction: The natural history of autoimmune gastritis (AIG) has been poorly described. In this study, the authors report the long-term natural history and clinical clustering of the full spectrum of AIG, from the potential to the complicated stage.
Methods: Prospective single-center study conducted in a tertiary referral center. Patients with AIG at any stage (0 = potential; 1 = early; 2 = florid; 3 = severe; and 4 = complicated) were enrolled (January 2000 to December 2022). The histopathological evolution, the clinical presentation, and the correlates of evolution of potential AIG were assessed.
Results: 498 patients with AIG (mean age, 56.7 ± 15.2 years, female:male ratio 2.5:1) were included, of whom 93 experienced potential AIG. The maximum disease duration was 27 years (median, 18 years, interquartile range [IQR], 14–23), while the overall median follow-up was 52 months (IQR, 12–95). Age was significantly lower in stage 0 compared with that in the other stages. Accidental histologic evidence and hematologic findings were the most common clusters of diagnosis. The overall median rate of progression was 7.29 per 100 persons/year (95% confidence interval [CI]: 6.19–8.59), while the stage-specific rates of progression were 10.85 (stage 0; 95% CI: 7.75–15.18), 14.83 (stages 1–2; 95% CI: 11.89–18.49), and 2.68 (stage 3; 95% CI: 1.88–3.84). Newly onset neoplastic complications at follow-up occurred in 41 of 483 patients (8.5%; 23 neuroendocrine tumors and 18 epithelial dysplasia). No cases of adenocarcinoma were noticed. Male sex was associated with a greater likelihood of evolving from potential AIG to overt AIG.

Discussion: Autoimmune gastritis (AIG) is a progressive disorder, with a virtually absent risk of gastric adenocarcinoma. Patients with potential AIG should be monitored because they carry a high risk of evolving into overt AIG.

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Barrett's Esophagus, Esophageal and Gastric Cancer

Gut. 2024;73(5):729–40

Black EL, Ococks E, Devonshire G, Ng AWT, O'Donovan M, Malhotra S, Tripathi M, Miremadi A, Freeman A, Coles H, Fitzgerald RC; Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) Consortium

Understanding the malignant potential of gastric metaplasia of the oesophagus and its relevance to Barrett's oesophagus surveillance: Individual-level data analysis

Objective: Whether gastric metaplasia (GM) of the oesophagus should be considered as Barrett's oesophagus (BO) is controversial. Given concern intestinal metaplasia (IM) may be missed due to sampling, the UK guidelines include GM as a type of BO. Here, the authors investigated whether the risk of misdiagnosis and the malignant potential of GM warrant its place in the UK surveillance.
Design: They performed a thorough pathology and endoscopy review to follow clinical outcomes in a novel UK cohort of 244 patients, covering 1854 person years of follow-up. They complemented this with a comparative genomic analysis of 160 GM and IM specimens, focused on early molecular hallmarks of BO and oesophageal adenocarcinoma (OAC).
Results: The authors found that 58 of 77 short-segment (< 3 cm) GM (SS-GM) cases (75%) continued to be observed as GM-only across a median of 4.4 years of follow-up. They observed that disease progression in GM-only cases and GM+IM cases (cases with reported GM on some occasions, IM on others) was significantly lower than in the IM-only cases (Kaplan-Meier, p = 0.03). Genomic analysis revealed that the mutation burden in GM is significantly lower than in IM (p < 0.01). Moreover, GM does not bear the mutational hallmarks of OAC, with an absence of associated signatures and driver gene mutations. Finally, it was established that GM found adjacent to OAC is evolutionarily distant from cancer.

Conclusion: Short-segment gastric metaplasia (SS-GM) is a distinct entity from short-segment intestinal metaplasia (SS-IM) and the malignant potential of GM is lower than IM. It is questionable whether SS-GM warrants inclusion in Barrett's oesophagus surveillance.

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Endoscopy. 2024;56(5):325–33

Beaufort IN, Frederiks CN, Overwater A, Brosens LAA, Koch AD, Pouw RE, Bergman JJGHM, Weusten BLAM

Endoscopic submucosal dissection for early esophageal squamous cell carcinoma: Long-term results from a Western cohort

Background: Although endoscopic submucosal dissection (ESD) is established as first-choice treatment for early esophageal squamous cell carcinoma (ESCC) worldwide, most data are derived from Asian studies. The authors aimed to evaluate the long-term outcomes of ESD for patients with early ESCC in a Western cohort.
Methods: In this retrospective cohort study, patients with early ESCC amenable to ESD were included from 4 tertiary referral hospitals in the Netherlands between 2012 and 2017. All ESD procedures were performed by experienced endoscopists, after which the decision for additional treatment was made on a per-patient basis. Outcomes were curative resection rate, ESCC-specific survival, and overall survival.
Results: Of 68 included patients (mean age, 69 years; 34 males), ESD was technically successful in 66 (97%; 95% confidence interval [CI]: 93–100%), with curative resection achieved in 34 of 66 (52%; 95% CI: 39–64%). Among patients with non-curative resection, 15 of 32 (47%) underwent additional treatment, mainly esophagectomy (n = 10) or definitive chemoradiation therapy (n = 4). Endoscopic surveillance was preferred in 17 of 32 patients (53%), based on severe comorbidities or patient choice. Overall, 31 of 66 patients (47%) died during a median follow-up of 66 months; 8 of 31 (26%) were ESCC-related deaths. The 5-year overall and ESCC-specific survival probabilities were 62% (95% CI: 52–75%) and 86% (95% CI: 77–96%), respectively.

Conclusion: In this Western cohort with long-term follow-up, the effectiveness and safety of endoscopic submucosal dissection for early esophageal squamous cell carcinoma was confirmed, although the rate of non-curative resections was substantial. Irrespective of curative status, the long-term prognosis of these patients was limited mainly due to competing mortality.

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Nutrition and Obesity

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Lane MM, Gamage E, Du S, Ashtree DN, McGuinness AJ, Gauci S, Baker P, Lawrence M, Rebholz CM, Srour B, Touvier M, Jacka FN, O'Neil A, Segasby T, Marx W

Ultra-processed food exposure and adverse health outcomes: Umbrella review of epidemiological meta-analyses

Objective: To evaluate the existing meta-analytic evidence of associations between exposure to ultra-processed food (UPF), as defined by the Nova food classification system, and adverse health outcomes.
Design: Systematic umbrella review of existing meta-analyses.
Data sources: Medline, PsycINFO, Embase, and the Cochrane Database of Systematic Reviews, as well as manual searches of reference lists from 2009 to June 2023.
Eligibility criteria for selecting studies: Systematic reviews and meta-analyses of cohort, case-control,

and/or cross-sectional study designs. To evaluate the credibility of evidence, pre-specified evidence classification criteria were applied, graded as convincing ("class I"), highly suggestive ("class II"), suggestive ("class III"), weak ("class IV"), or no evidence ("class V"). The quality of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework, categorised as "high," "moderate," "low," or "very low" quality.
Results: The search identified 45 unique pooled analyses, including 13 dose-response associations and 32 non-dose-response associations (n = 9,888,373). Overall, direct associations were found between exposure to UPF and 32 (71%) health parameters spanning mortality, cancer, and mental, respiratory, cardiovascular, gastrointestinal, and metabolic health outcomes. Based on the pre-specified evidence classification criteria, convincing evidence (class I) supported direct associations between greater UPF exposure and higher risks of incident cardiovascular disease related mortality (risk ratio [RR] = 1.50, 95% confidence interval: 1.37–1.63; GRADE = very low) and type 2 diabetes (dose-response RR = 1.12, 1.11–1.13; moderate), as well as higher risks of prevalent anxiety outcomes (odds ratio [OR] = 1.48, 1.37–1.59; low) and combined common mental disorder outcomes (OR = 1.53, 1.43–1.63; low). Highly suggestive (class II) evidence indicated that greater exposure to UPF was directly associated with higher risks of incident all-cause mortality (RR = 1.21, 1.15–1.27; low), heart disease-related mortality (hazard ratio [HR] = 1.66, 1.51–1.84; low), type 2 diabetes (OR = 1.40, 1.23–1.59; very low), and depressive outcomes (HR = 1.22, 1.16–1.28; low), together with higher risks of prevalent adverse sleep-related outcomes (OR = 1.41, 1.24–1.61; low), wheezing (RR = 1.40, 1.27–1.55; low), and obesity (OR = 1.55, 1.36–1.77; low). Of the remaining 34 pooled analyses, 21 were graded as suggestive or weak strength (class III–IV) and 13 were graded as no evidence (class V). Overall, using the GRADE framework, 22 pooled analyses were rated as low quality, with 19 rated as very low quality and 4 rated as moderate quality.

Conclusions: Greater exposure to ultra-processed food (UPF) was associated with a higher risk of adverse

health outcomes, especially cardiometabolic, common mental disorder, and mortality outcomes. These findings provide a rationale to develop and evaluate the effectiveness of using population-based and public health measures to target and reduce dietary exposure to UPF for improved human health. They also inform and provide support for urgent mechanistic research.

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Upper and Middle Gastrointestinal Bleeding

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Goltstein LCMJ, Grooteman KV, Bernts LHP, Scheffer RCH, Laheij RJF, Gilissen LPL, Schrauwen RWM, Talstra NC, Zuur AT, Braat H, Hadithi M, Brouwer JT, Nagengast WB, Oort FA, Tenthof van Noorden J, Kievit W, van Geenen EJM, Drenth JPH

Standard of care versus octreotide in angiodysplasia-related bleeding (the OCEAN study): A multicenter randomized controlled trial

Background and aims: Gastrointestinal angiodysplasias are vascular anomalies that may result in transfusion-dependent anemia despite endoscopic therapy. An individual patient data meta-analysis of cohort studies suggests that octreotide decreases rebleeding rates, but component studies possessed a high risk of bias. The authors investigated the efficacy of octreotide in reducing the transfusion requirements of patients with angiodysplasia-related anemia in a clinical trial setting.
Methods: The study was designed as a multicenter, open-label, randomized controlled trial. Patients with angiodysplasia bleeding were required to have had at least 4 red blood cell (RBC) units or parental iron infusions, or both, in the year preceding randomization. Patients were allocated (1:1) to 40-mg octreotide long-acting release intramuscular every 28 days or standard of care, including endoscopic therapy. The treatment duration was 1 year. The primary outcome was the mean difference in the number of transfusion units (RBC + parental iron) between the octreotide and standard of care groups. Patients who received at least 1 octreotide injection or followed standard of care for at least 1 month were included in the intention-to-treat analyses. Analyses of covariance were used to adjust for baseline transfusion requirements and incomplete follow-up.
Results: 62 patients were enrolled (mean age, 72 years; 32 men) from 17 Dutch hospitals in the octreotide (n = 31) and standard of care (n = 31) groups. Patients required a mean number of 20.3 (standard deviation, 15.6) transfusion units and 2.4 (standard deviation, 2.0) endoscopic procedures in the year before enrollment. The total number of transfusions was lower with octreotide (11.0; 95% confidence interval [CI]: 5.5–16.5) compared with standard of care (21.2; 95% CI: 15.7–26.7). Octreotide reduced the mean number of transfusion units by 10.2 (95% CI: 2.4–18.1; p = 0.012). Octreotide reduced the annual volume of endoscopic procedures by 0.9 (95% CI: 0.3–1.5).

Conclusions: Octreotide effectively reduces transfusion requirements and the need for endoscopic therapy in patients with angiodysplasia-related anemia.

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Akiki K, Mahmoud T, Alqaisieh MH, Sayegh LN, Lescalleet KE, Abu Dayyeh BK, Wong Kee Song LM, Larson MV, Bruining DH, Coelho-Prabhu N, Buttar NS, Sedlack RE, Chandrasekhara V, Leggett CL, Law RJ, Rajan E, Gleeson FC, Alexander JA, Storm AC

A novel blood-sensing capsule for rapid detection of upper GI bleeding: A prospective clinical trial

Background and aims: Upper gastrointestinal bleeding (UGIB) is a common medical emergency associated with high resource utilization, morbidity, and mortality. Timely esophagogastroduodenoscopy (EGD) can be challenging from personnel, resource, and access perspectives. PillSense is a novel swallowed bleeding sensor for the detection of UGIB, anticipated to aid in patient triage and guide clinical decision-making for individuals with suspected UGIB.
Methods: This prospective, open-label, single-arm comparative clinical trial of a novel bleeding sensor for patients with suspected UGIB was performed at a tertiary care center. The PillSense system consists of an optical sensor and an external receiver that processes and displays data from the capsule as "Blood Detected" or "No Blood Detected." Patients underwent EGD within 4 hours of capsule administration; participants were followed up for 21 days to confirm capsule passage.
Results: A total of 126 patients were accrued to the study (59.5% male; mean age, 62.4 ± 14.3 years). Sensitivity and specificity for detecting the presence of blood were 92.9% (p = 0.02) and 90.6% (p < 0.001), respectively. The capsule's positive and negative predictive values were 74.3% and 97.8%, and positive and negative likelihood ratios were 9.9 and 0.08. No adverse events or deaths occurred related to the PillSense system, and all capsules were excreted from patients on follow-up.

Conclusions: The PillSense system is safe and effective for detecting the presence of blood in patients evaluated for upper gastrointestinal bleeding (UGIB) before upper GI endoscopy. It is a rapidly deployed tool, with easy-to-interpret results that will affect the diagnosis and triage of patients with suspected UGIB.

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Endoscopy of the Upper GI Tract

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Jiang X, Pan J, Xu Q, Song YH, Sun HH, Peng C, Qi XL, Qian YY, Zou WB, Yang Y, Jin SQ, Duan BS, Wu S, Chu Y, Xiao DH, Hu LJ, Cao JZ, Dai JF, Liu X, Xia T, Zhou W, Chen T, Zhou CH, Wu W, Liu SJ, Yang ZY, Wang F, Zhang L, Li CZ, Xu H, Wang JX, Wei B, Lin Y, Deng X, Qu LH, Shen YQ, Wang H, Huang YF, Bao HB, Zhang S, Li L, Shi YH, Wang XY, Zou DW, Wan XJ, Xu MD, Mao H, He CH, Li Z, Zuo XL, He SX, Xie XP, Liu J, Yang CQ, Spada C, Li ZS, Liao Z

Diagnostic accuracy of magnetically guided capsule endoscopy with a detachable string for detecting oesophagogastric varices in adults with cirrhosis: Prospective multi-centre study

Objective: To evaluate the diagnostic accuracy and safety of using magnetically guided capsule endoscopy with a detachable string (ds-MCE) for detecting and grading oesophagogastric varices in adults with cirrhosis.
Design: Prospective multicentre diagnostic accuracy study.
Setting: 14 medical centres in China.
Participants: 607 adults (> 18 years) with cirrhosis recruited between January 7, 2021, and August 25, 2022. Participants underwent ds-MCE (index test), followed by oesophagogastroduodenoscopy (OGD, reference test) within 48 hours. The participants were divided into development and validation cohorts in a ratio of 2:1.
Main outcome measures: The primary outcomes were the sensitivity and specificity of ds-MCE in detecting oesophagogastric varices compared with OGD. Secondary outcomes included the sensitivity and specificity of ds-MCE for detecting high-risk oesophageal varices and the diagnostic accuracy of ds-MCE for detecting high-risk oesophagogastric varices, oesophageal varices, and gastric varices.
Results: ds-MCE and OGD examinations were completed in 582 (95.9%) of the 607 participants. Using OGD as the reference standard, ds-MCE had a sensitivity of 97.5% (95% confidence interval: 95.5–98.7%) and specificity of 97.8% (94.4–99.1%) for detecting oesophagogastric varices (both $p < 0.001$ compared with a pre-specified 85% threshold). When using the optimal 18% threshold for luminal circumference of the oesophagus derived from the development cohort (n = 393), the sensitivity and specificity of ds-MCE for detecting high-risk oesophageal varices in the validation cohort (n = 189) were 95.8% (89.7–98.4%) and 94.7% (88.2–97.7%), respectively. The diagnostic accuracy of ds-MCE for detecting high-risk oesophagogastric varices, oesophageal varices, and gastric varices was 96.3% (92.6–98.2%), 96.9% (95.2–98.0%), and 96.7% (95.0–97.9%), respectively. Two serious adverse events occurred with OGD but none with ds-MCE.

Conclusion: The findings of this study suggest that magnetically guided capsule endoscopy with a detachable string is a highly accurate and safe diagnostic tool for detecting and grading oesophagogastric varices and is a promising alternative to oesophagogastroduodenoscopy for screening and surveillance of oesophagogastric varices in patients with cirrhosis.

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Functional Disorders of the Upper GI Tract

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Epidemiology, comorbidities, and treatment of cyclic vomiting syndrome in the United States

Introduction: Cyclic vomiting syndrome (CVS) imposes a substantial burden, but epidemiological data are scarce. This study aimed to estimate the incidence and prevalence of CVS, comorbid conditions, and treatment patterns, using administrative databases in the United States.
Methods: This cross-sectional study used claims data from Merative MarketScan Commercial/Medicare Supplemental and Medicaid databases in all health care settings. Incidence and prevalence rates for 2019 were calculated and stratified by age, sex, region, and race/ethnicity. Patient characteristics were reported among newly diagnosed patients with CVS (i.e., no documented claims for CVS before 2019). CVS was defined as having at least 1 inpatient and/or at least 2 outpatient CVS claims that were at least 7 days apart.
Results: The estimated prevalence of CVS was 16.7 (Commercial/Medicare) and 42.9 (Medicaid) per 100,000 individuals. The incidence of CVS was estimated to be 10.6 (Commercial/Medicare) and 26.6 (Medicaid) per 100,000 individuals. Both prevalence and incidence rates were higher among female individuals (for both Commercial/Medicare and Medicaid). Comorbid conditions were common and included abdominal pain (56–64%), anxiety (32–39%), depression (26–34%), cardiac conditions (39–42%), and gastroesophageal reflux disease (30–40%). Despite a diagnosis of CVS, only 32–35% had prescriptions for prophylactic treatment and 47–55% for acute treatment within the first 30-day period following diagnosis.

Discussion: This study provides the first population-level estimates of cyclic vomiting syndrome (CVS) incidence and prevalence in the United States. Comorbid conditions are common, and most patients with CVS do not receive adequate treatment. These findings underscore the need for improving disease awareness and developing better screening strategies and effective treatments.

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Hasler WL, Lee AA, Moshiree B, Surjanhata BC, Rao S, Parkman HP, Nguyen LA, Sarosiek I, Wo JM, Schulman MI, McCallum RW, Kuo B

Benefits of prokinetics, gastroparesis diet, or neuromodulators alone or in combination for symptoms of gastroparesis

Background and aims: Prokinetics have limited effectiveness for treating symptoms of gastroparesis. Thus, alternative or adjunct therapies, such as gastroparesis diets or neuromodulators, are often prescribed. Their therapeutic benefits alone or in combination remain unclear.
Methods: 129 patients with symptoms of gastroparesis underwent wireless motility capsule gastric emptying time and gastric emptying scintigraphy. Based on test results, changes in therapy were recommended. Changes in Gastroparesis Cardinal Symptom Index (GCSI) and individual symptom scores over 6 months were related to recommendations for prokinetics, gastroparesis diet, or neuromodulators given as solo new therapies or in dual combinations. Multivariate analyses were performed to adjust for gastric emptying and other variables.
Results: In the whole group regardless of therapy, GCSI scores decreased by 0.53 points (interquartile range, -1.25–0.05; $p < 0.0001$) over 6 months. GCSI did not decrease for prokinetics as solo new therapy ($p = 0.95$). Conversely, neuromodulators as solo therapy decreased GCSI scores ($p = 0.04$) and all individual symptoms except nausea/vomiting ($p = 0.86$). Prokinetics combined with gastroparesis diets or neuromodulators improved GCSI scores ($p \leq 0.04$) and most individual symptoms. Adjusting for gastric emptying time on multivariate analyses showed greater GCSI decreases for non-delayed emptying for neuromodulators as solo new therapy ($p = 0.01$). Gastric emptying scintigraphy, gender, diabetes, and functional dyspepsia did not influence responses to any treatment.

Conclusions: Initiating prokinetics as solo new therapy had little benefit for patients with symptoms of gastroparesis. Neuromodulators as the only new therapy decreased symptoms other than nausea and vomiting, especially with non-delayed gastric emptying. Adding gastroparesis diets or neuromodulators to prokinetics offered relief, suggesting that combination therapies may be more useful in managing these patients.

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Crohn's Disease

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Safety and efficacy of autologous haematopoietic stem-cell transplantation with low-dose cyclophosphamide mobilisation and reduced intensity conditioning versus standard of care in refractory Crohn's disease (ASTIClite): An open-label, multicentre, randomised controlled trial

Background: A previous controlled trial of autologous haematopoietic stem-cell transplantation (HSCT) in patients with refractory Crohn's disease did not meet its primary end point and reported high toxicity. The aim of this study was to assess the safety and efficacy of HSCT with an immune-ablative regimen of reduced intensity versus standard of care in this patient population.
Methods: This open-label, multicentre, randomised controlled trial was conducted in 9 National Health Service hospital trusts across the UK. Adults (aged 18–60 years) with active Crohn's disease on endoscopy (Simplified Endoscopic Score for Crohn's Disease [SES-CD] ulcer subscore of ≥ 2) refractory to 2 or more classes of biological therapy, with no perianal or intraabdominal sepsis or clinically significant comorbidity, were recruited. Participants were centrally randomly assigned (2:1) to either HSCT with a reduced dose of cyclophosphamide (intervention group) or standard care (control group). Randomisation was stratified by trial site by use of random permuted blocks of size 3 and 6. Patients in the intervention group underwent stem-cell mobilisation (cyclophosphamide 1 g/m^2 with granulocyte colony-stimulating factor [G-CSF] 5 µg/kg) and stem-cell harvest (minimum 2.0 × 10^6 CD34$^+$ cells per kg), before conditioning (fludarabine 125 mg/m^2, cyclophosphamide 120 mg/kg, and rabbit anti-thymocyte globulin [thymoglobulin] 7.5 mg/kg in total) and subsequent stem-cell reinfusion supported by G-CSF. Patients in the control group continued any available conventional, biological, or nutritional therapy. The primary outcome was absence of endoscopic ulceration (SES-CD ulcer subscore of 0) without surgery or death at week 48, analysed in the intention-to-treat population by central reading.
Findings: Between October 18, 2018, and November 8, 2019, 49 patients were screened for eligibility, of whom 23 (47%) were randomly assigned: 13 (57%) to the intervention group and 10 (43%) to the control group. In the intervention group, 10 participants (77%) underwent HSCT and 9 (69%) reached 48-week follow-up; in the control group, 9 (90%) reached 48-week follow-up. The trial was halted in response to 9 reported suspected unexpected serious adverse reactions in 6 patients (46%) in the intervention group, including renal failure due to proven thrombotic microangiopathy in 3 participants and 1 death due to pulmonary veno-occlusive disease. At week 48, absence of endoscopic ulceration

without surgery or death was reported in 3 of 7 participants (43%) in the intervention group and in 0 of 6 participants in the control group with available data. Serious adverse events were more frequent in the intervention group (38 in 13 [100%] patients) than in the control group (16 in 4 [40%] patients). A second patient in the intervention group died after week 48 of respiratory and renal failure.

Interpretation: Although haematopoietic stem-cell transplantation with an immune-ablative regimen of reduced intensity decreased endoscopic disease activity, significant adverse events deem this regimen unsuitable for future clinical use in patients with refractory Crohn's disease.

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Hernández-Rocha C, Walshe M, Birch S, Sabic K, Korie U, Chasteau C, Miladinova VM, Sabol WB, Mengesha E, Hanna M, Pozdnyakova V, Datta L, Kohen R, Milgrom R, Stempak JM, Bitton A, Brant SR, Rioux JD, McGovern DPB, Duerr RH, Cho JH, Schumm PL, Silverberg MS, Lazarev M

Clinical predictors of early and late endoscopic recurrence following ileocolonic resection in Crohn's disease

Background and aims: Multiple factors are suggested to place Crohn's disease patients at risk of recurrence after ileocolic resection with conflicting associations. The aim of this study was to identify clinical predictors of recurrence at first (early) and further (late) postoperative colonoscopy.
Methods: Crohn's disease patients undergoing ileocolic resection were prospectively recruited at 6 North American centres. Clinical data were collected and endoscopic recurrence was defined as Rutgeerts score ≥ i2. A multivariable model was fitted to analyse variables independently associated with recurrence.
Results: A total of 365 patients undergoing 674 postoperative colonoscopies were included with a median age of 32 years, 189 (51.8%) were male, and 37 (10.1%) were non-whites. Postoperatively, 133 (36.4%) used anti-tumour necrosis factor (anti-TNF) and 30 (8.2%) were smokers. At first colonoscopy, 109 (29.9%) had recurrence. Male gender (odds ratio [OR] = 1.95, 95% confidence interval [CI]: 1.12–3.40), non-white ethnicity (OR = 2.48, 95% CI: 1.09–5.63), longer interval between surgery and colonoscopy (OR = 1.09, 95% CI: 1.002–1.18), and postoperative smoking (OR = 2.78, 95% CI: 1.16–6.67) were associated with recurrence, while prophylactic anti-TNF reduced the risk (OR = 0.28, 95% CI: 0.14–0.55). Postoperative anti-TNF prophylaxis had a protective effect on anti-TNF-experienced patients but not on anti-TNF-naive patients. Among patients without recurrence at first colonoscopy, Rutgeerts score i1 was associated with subsequent recurrence (OR = 4.43, 95% CI: 1.73–11.35).

Conclusions: Independent clinical predictors of early and late Crohn's disease postoperative endoscopic recurrence were identified. Clinical factors traditionally used for risk stratification failed to predict recurrence and need to be revised.

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Real-world effectiveness of vedolizumab vs. anti-TNF in biologic-naive Crohn's disease patients: A 2-year propensity-score-adjusted analysis from the VEDO$_{IBD}$-study

Background: The aim of this observational, real-world evidence, modified intention-to-treat (mITT) study based on prospectively collected data from the VEDO$_{IBD}$ registry was to compare the effectiveness of vedolizumab (VEDO) versus anti-tumor necrosis factor (anti-TNF) in biologic-naive Crohn's disease (CD) patients.
Methods: Between 2017 and 2020, 557 CD patients starting therapy with VEDO or anti-TNF were consecutively enrolled in 45 inflammatory bowel disease (IBD) centers across Germany. Per study protocol, the analysis excluded biologic-experienced patients and those with a missing Harvey-Bradshaw Index score, resulting in a final sample of 327 biologic-naive CD patients. Clinical remission was measured using the Harvey-Bradshaw Index at the end of induction therapy and after 1 and 2 years. Switching to a different therapy was considered an outcome failure. Propensity score adjustment with inverse probability of treatment weighting was used to correct for confounding.
Results: The effectiveness of both VEDO (n = 86) and anti-TNF (n = 241) was remarkably high for induction treatment, but VEDO performed significantly less well than anti-TNF (clinical remission: 56.3% vs. 73.9%, $p < 0.05$). In contrast, clinical remission after 2 years was significantly better for VEDO compared with anti-TNF (74.2% vs. 44.7%; $p < 0.05$; odds ratio = 0.45; 95% confidence interval: 0.22–0.94). Remarkably, only 17% of patients switched from VEDO to another biologic versus 44% who received anti-TNF.

Conclusions: The results of this prospective, 2-year, real-world evidence study suggest that the choice of vedolizumab (VEDO) led to higher remission rates after 2 years compared with anti-tumor necrosis factor. This could support the role of VEDO as a first-line biologic therapy in Crohn's disease.

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Chanchlani N, Lin S, Bewshea C, Hamilton B, Thomas A, Smith R, Roberts C, Bishara M, Nice R, Lees CW, Sebastian S, Irving PM, Russell RK, McDonald TJ, Goodhand JR, Ahmad T, Kennedy NA; PANTS Consortium

Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study

Background: The authors sought to report the effectiveness of infliximab and adalimumab over the first 3 years of treatment and to define the factors that predict anti-tumour necrosis factor (anti-TNF) treatment failure and the strategies that prevent or mitigate loss of response.
Methods: Personalised Anti-TNF therapy in Crohn's disease (PANTS) is a UK-wide, multicentre, prospective observational cohort study reporting the rates of effectiveness of infliximab and adalimumab in anti-TNF-naive patients with active luminal Crohn's disease aged 6 years and older. At the end of the first year, sites were invited to enrol participants still receiving study drug into the 2-year PANTS-extension study. The authors estimated rates of remission across the whole cohort at the end of years 1, 2, and 3 of the study using a modified survival technique with permutation testing. Multivariable regression and survival analyses were used to identify factors associated with loss of response in patients who had initially responded to anti-TNF therapy and with immunogenicity. Loss of response was defined in patients who initially responded to anti-TNF therapy at the end of induction and who subsequently developed symptomatic activity that warranted an escalation of steroid, immunomodulatory, or anti-TNF therapy, resectional surgery, or exit from study due to treatment failure.
Findings: Between March 19, 2014, and September 21, 2017, 389 (41%) of 955 patients treated with infliximab and 209 (32%) of 655 treated with adalimumab in the PANTS study entered the PANTS-extension study (median age, 32.5 years [interquartile range, 22.1–46.8], 307 [51%] of 598 were female, and 291 [49%] were male). The estimated proportion of patients in remission at the end of years 1, 2, and 3 were, for infliximab 40.2% (95% confidence interval [CI]: 36.7–43.7), 34.4% (29.9–39.0), and 34.7% (29.8–39.5), and for adalimumab 35.9% (95% CI: 31.2–40.5), 32.9% (26.8–39.2), and 28.9% (21.9–36.3), respectively. Optimal drug concentrations at week 14 to predict remission at any later timepoints were 6.1–10.0 mg/l for infliximab and 10.1–12.0 mg/l for adalimumab. After excluding patients who had primary non-response, the estimated proportions of patients who had loss of response by years 1, 2, and 3 were, for infliximab 34.4% (95% CI: 30.4–38.2), 54.5% (49.4–59.0), and 60.0% (54.1–65.2), and for adalimumab 32.1% (26.7–37.1), 47.2% (40.2–53.4), and 68.4% (50.9–79.7), respectively. In multivariable analysis, loss of response at year 2 and 3 for patients treated with infliximab and adalimumab was predicted by low anti-TNF drug concentrations at week 14 (infliximab: hazard ratio [HR] for each 10-fold increase in drug concentration = 0.45 [95% CI: 0.30–0.67], adalimumab: 0.39 [0.22–0.70]). For patients treated with infliximab, loss of response was also associated with female sex (vs. male sex; HR = 1.47 [95% CI: 1.11–1.95]), obesity (vs. not obese 1.62 [1.08–2.42]), baseline white cell count (1.06 [1.02–1.11) per 1 x 10^9 increase in cells per l), and thiopurine dose quartile. Among patients treated with adalimumab, carriage of the HLA-DQA1*05 risk variant was associated with loss of response (HR = 1.95 [95% CI: 1.17–3.25]). By the end of year 3, the estimated proportion of patients who developed anti-drug antibodies associated with undetectable drug concentrations was 44.0% (95% CI: 38.1–49.4) among patients treated with infliximab and 20.3% (13.8–26.2) among those treated with adalimumab. The development of anti-drug antibodies associated with undetectable drug concentrations was significantly associated with treatment without concomitant immunomodulator use for both groups (HR for immunomodulator use: infliximab 0.40 [95% CI: 0.31–0.52], adalimumab 0.42 [95% CI: 0.24–0.75]), and with carriage of HLA-DQA1*05 risk variant for infliximab (HR for carriage of risk variant: infliximab 1.46 [1.13–1.88]) but not for adalimumab (HR = 1·60 [0.92–2.77]). Concomitant use of an immunomodulator before or on the day of starting infliximab was associated with increased time without the development of anti-drug antibodies associated with undetectable drug concentrations compared with use of infliximab alone (HR = 2.87 [95% CI: 2.20–3.74]) or introduction of an immunomodulator after anti-TNF initiation (1.70 [1.11–2.59]). In years 2 and 3, 16 (4%) of 389 patients treated with infliximab and 11 (5%) of 209 treated with adalimumab had adverse events leading to treatment withdrawal. Nine (2%) patients treated with infliximab and 2 (1%) of those treated with adalimumab had serious infections in years 2 and 3.

Interpretation: Only around a third of patients with active luminal Crohn's disease treated with an anti-tumour necrosis factor drug were in remission at the end of 3 years of treatment. Low drug concentrations at the end of the induction period predict loss of response by year 3 of treatment, suggesting higher drug concentrations during the first year of treatment, particularly during induction, might lead to better long-term outcomes. Anti-drug antibodies associated with undetectable drug concentrations of infliximab, but not adalimumab, can be predicted by carriage of HLA-DQA1*05 and mitigated by concomitant immunomodulator use for both drugs.

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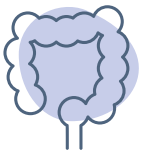

COLON TO RECTUM

Ulcerative Colitis, Crohn's Colitis

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Bokemeyer B, Plachta-Danielzik S, Steiner IM, Pohlschneider D, Urzica E, Hartmann P, Zemke J, Tappe U, Schreiber S, Steinkat N, Langbrandtner J, Hüppe A, Stargardt T

Inflammatory bowel disease (IBD) patients with impaired quality of life on biologic therapy benefit from the support of an IBD nurse specialist: Results of a randomised controlled trial in Germany ($IBD_{BIO\text{-}ASSIST}$ study)

Background: $IBD_{BIO\text{-}ASSIST}$ was a randomised controlled trial assessing the efficacy of care provided by inflammatory bowel disease (IBD) nurse specialists in Germany in improving health-related quality of life (QoL) in IBD patients on biologic therapy.
Aim: To evaluate patient-related outcomes and economic consequences associated with integrating IBD nurses into usual care.
Methods: The authors randomly assigned 1086 patients with IBD on biologic therapy to a control group (CG) receiving usual care or an intervention group (IG) receiving additional care from an IBD nurse specialist. The primary outcome was disease-specific QoL (sIBDQ) assessed at 6, 12 and 18 months.
Results: At baseline, patients in both groups were highly satisfied with their treatment situation and had relatively high sIBDQ values (range, 1–7; CG 5.12; IG 4.92). In the intention-to-treat analysis of the overall sample, there was no significant difference in sIBDQ between groups at the assessment time points. However, a per-protocol analysis of patients with impaired QoL at baseline (EQ-VAS < 75 [median]), showed improvement in sIBDQ over 6 months that became significant at month 12 and remained significant through month 18 (baseline: IG 4.24; CG 4.31; 18 months: IG 5.02; CG 4.76; p = 0.017).

Conclusion: High baseline satisfaction of inflammatory bowel disease (IBD) patients with treatment and the relatively high baseline disease-specific quality of life (sIBDQ) values may have contributed to the lack of significant difference in sIBDQ scores for the overall sample. However, patients with impaired quality of life derived significant benefit from additional care provided by an IBD nurse specialist, leading to meaningful improvements in sIBDQ over the long term.

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Guo A, Ludvigsson J, Brantsæter AL, Klingberg S, Östensson M, Størdal K, Mårild K

Early-life diet and risk of inflammatory bowel disease: A pooled study in 2 Scandinavian birth cohorts

Objective: The authors assessed whether early-life diet quality and food intake frequencies were associated with subsequent inflammatory bowel disease (IBD).
Design: Prospectively recorded 1-year and 3-year questionnaires in children from the All Babies in Southeast Sweden and The Norwegian Mother, Father and Child Cohort Study were used to assess diet quality using a Healthy Eating Index and intake frequency of food groups. IBD was defined as > 2 diagnoses in national patient registers. Cox regression yielded hazard ratios adjusted (aHRs) for child's sex, parental IBD, origin, education level and maternal comorbidities. Cohort-specific results were pooled using a random-effects model.
Results: During 1,304,433 person-years of follow-up, the authors followed 81,280 participants from birth through childhood and adolescence, whereof 307 were diagnosed with IBD. Compared with low diet quality, medium and high diet quality at 1 year of age were associated with a reduced risk of IBD (pooled aHR = 0.75, 95% confidence interval [CI]: 0.58–0.98, and 0.75, 95% CI: 0.56–1.00). The pooled aHR per increase of category was 0.86 (0.74–0.99). Pooled aHR for children 1 year old with high versus low fish intake was 0.70 (95% CI: 0.49–1.00) for IBD, and showed association with reduced risk of ulcerative colitis (pooled aHR = 0.46, 95% CI: 0.21–0.99). Higher vegetable intake at 1 year was associated with a risk reduction in IBD. Intake of sugar-sweetened beverages was associated with an increased risk of IBD. Diet quality at 3 years was not associated with IBD.

Conclusion: In this Scandinavian birth cohort, high diet quality and fish intake in early life were associated with a reduced risk of inflammatory bowel disease.

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Dignass A, Stremmel W, Horyński M, Poyda O, Armerding P, Fellermann K, Langhorst J, Kuehbacher T, Uebel P, Stein J, Novacek G, Avalueva E, Oliinyk O, Hasselblatt P, Dorofeyev A, Heinemann H, Mueller R, Greinwald R, Reinisch W; International PROTECT-1/2 Study Groups

Modified-release phosphatidylcholine (LT-02) for ulcerative colitis: Two double-blind, randomized, placebo-controlled trials

Background and aims: The aim of this study was to evaluate the efficacy of LT-02, a novel modified-release phosphatidylcholine (PC) formulation, for induction and

maintenance of remission in patients with mild-to-moderate ulcerative colitis and inadequate response to mesalazine.
Methods: LT-02 was evaluated in a multicenter double-blind, randomized, placebo-controlled study comprising a 12-week induction trial (PCG-2), followed by a 48-week maintenance trial (PCG-4). In PCG-2, patients were randomized 1:1:1 to treatment with 0.8 g LT-02 4 times daily (QID), 1.6 g LT-02 twice daily (BID), or placebo, respectively. All patients continued to take a standard dose of oral mesalazine (≥ 2.4 g/day). The primary end point in PCG-2 was deep remission. Patients achieving remission at week 12 were randomly assigned 2:1:1 to 1.6 g LT-02 BID, placebo, or 500 mg mesalazine (3 times daily), respectively, in PCG-4; the primary end point was remission at 48 weeks.
Results: PCG-2 was terminated early for futility after a prespecified interim analysis; 466 patients (of 762 planned) were randomized. There was no statistically significant difference in deep remission at week 12 (placebo, 13.5%; LT-02 BID, 14.2%; LT-02 QID, 9.7%). In PCG-4, 150 patients (of approximately 400 planned) were randomized. There was no statistically significant difference in remission rates at week 48 (LT-02 BID, 49.3%; mesalazine, 50.0%; placebo, 43.2%). LT-02 was safe.

Conclusions: Despite prior evidence of beneficial effects of phosphatidylcholine in phase 2 trials, the induction study with LT-02 in patients with mild-to-moderate ulcerative colitis was terminated prematurely for futility. Signals of efficacy in maintenance therapy require confirmation in an adequately powered maintenance trial. LT-02 was safe and well-tolerated.

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Chugh R, Long MD, Jiang Y, Weaver KN, Beaulieu DB, Scherl EJ, Mahadevan U

Maternal and neonatal outcomes in vedolizumab- and ustekinumab-exposed pregnancies: Results from the PIANO registry

Background: Pregnancy outcomes in inflammatory bowel disease (IBD) patients with quiescent disease are similar to those in the general population. Data from the Pregnancy Inflammatory bowel disease And Neonatal Outcomes (PIANO) registry have demonstrated the safety of anti-tumor necrosis factor (TNF) α agents and thiopurines in pregnancy. The objective of this study was to provide information from the PIANO registry on maternal and fetal outcomes in patients exposed to the newer biologics ustekinumab (UST) and vedolizumab (VDZ).
Methods: In this multicenter prospective observational study, the authors included pregnant women with singleton pregnancies and a diagnosis of IBD. Questionnaires were administered to women at study intake, each subsequent trimester, delivery, and at 4, 9, and 12 months after birth. Bivariate analyses were utilized to determine the independent effects of specific drug classes on outcomes. The exposure cohorts were VDZ, UST, anti-TNF, immunomodulators, and combination with anti-TNF and immunomodulators. All were compared to no exposure and to biologics/immunomodulators.
Results: There were 1669 completed pregnancies with 1610 live births. The maternal mean age was 32.1 years (standard deviation 4.6) at delivery with 66 VDZ and 47 UST exposed. Women on UST were more likely to have Crohn's disease. There was no increased risk of spontaneous abortion, small for gestational age, low birth weight, neonatal intensive care unit stay, congenital malformations, or intrauterine growth restriction with in utero VDZ or UST exposure. The rate of preterm birth was lower (0.0%) for the UST-exposed cohort when compared with other cohorts including VDZ (13.8%), anti-TNF (8.2%), combination therapy (14.2%), immunomodulators (12.3%), and unexposed (9.7%) (p = 0.03). Rates of serious infections at birth, 4 months, and within the first 12 months of life were comparable among all cohorts. Non-serious infections were lower at 12 months in UST-exposed pregnancies. There was no increased risk signal for placental complications in the VDZ cohort. UST infant concentrations at birth were increased whereas VDZ concentrations were overall decreased compared with maternal serum drug concentration.

Conclusion: This analysis of ustekinumab (UST) and vedolizumab (VDZ) exposure during pregnancy suggests no increase in complications compared with anti-tumor necrosis factor (TNF), immunomodulators and combination TNF/immunomodulators. No signal was found for increased placental events with either therapy. Continuation of UST and VDZ throughout pregnancy is recommended.

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Histologic remission in inflammatory bowel disease and female fertility: A nationwide study

Background and aims: Inflammatory bowel disease (IBD) is linked to reduced female fertility, but it is unclear how fertility rates vary by histologic disease activity.
Methods: Nationwide IBD cohort of Swedish women aged 15 to 44 years. The authors examined fertility rates during periods with versus without histologic inflammation (n = 21,046; follow-up, 1990–2016) and during periods with versus without clinical activity (IBD-related hospitalization, surgery, or treatment escalation) (n = 24,995; follow-up, 2006–2020). Accounting for sociodemographics and comorbidities, they used Poisson regression to estimate adjusted fertility rate ratios (aFRRs) for live births conceived during 12-month periods of histologic inflammation (vs. histo-

logic remission) and 3-month periods of clinically active IBD (vs. quiescent IBD).
Results: During periods with versus without histologic inflammation, there were 6.35 (95% confidence interval [CI]: 5.98–6.73) and 7.09 (95% CI: 6.48–7.70) live births conceived per 100 person-years of follow-up, respectively, or 1 fewer child per 14 women with 10 years of histologic inflammation (aFRR = 0.90; 95% CI: 0.81–1.00). In women with histologic inflammation, fertility was similarly reduced in ulcerative colitis (aFRR = 0.89; 95% CI: 0.78–1.02) and Crohn's disease (aFRR = 0.86; 95% CI: 0.72–1.04). Clinical IBD activity was associated with an aFRR of 0.76 (95% CI: 0.72–0.79) or 1 fewer child per 6 women with 10 years of clinical activity. Fertility was reduced in clinically active ulcerative colitis (aFRR = 0.75; 95% CI: 0.70–0.81) and Crohn's disease (aFRR = 0.76; 95% CI: 0.70–0.82). Finally, among women with clinically quiescent IBD, histologic inflammation (vs. histologic remission) was associated with reduced fertility (aFRR = 0.85; 95% CI: 0.73–0.98).

Conclusions: An association between histologic and clinical activity and reduced female fertility in Crohn's disease and ulcerative colitis was found. Notably, histologic inflammation was also linked to reduced fertility in women with clinically quiescent inflammatory bowel disease.

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Lujan R, Buchuk R, Focht G, Yogev D, Greenfeld S, Ben-Tov A, Loewenberg Weisband Y, Lederman N, Matz E, Ben Horin S, Dotan I, Nevo D, Turner D

Early initiation of biologics and disease outcomes in adults and children with inflammatory bowel diseases: Results from the epidemiology group of the nationwide Israeli Inflammatory Bowel Disease Research Nucleus cohort

Background and aims: In this nationwide study, the authors explored whether early initiation of biologics is associated with improved outcomes in children and adults with Crohn's disease (CD) and ulcerative colitis (UC).
Methods: All patients diagnosed with CD or UC in Israel (2005–2020) were included in the Epidemiology Group of the Israeli Inflammatory Bowel Disease Research Nucleus cohort, encompassing 98% of the population. They compared disease duration at biologics initiation (i.e., 0–3 months, > 3–12 months, > 1–2 years, and > 2–3 years) using the cloning, censoring, and weighting by inverse probabilities method to emulate a target trial, adjusting for time-varying confounders and selection bias.
Results: Of the 34,375 included patients (of whom 5240 [15%] were children), 7452 of 19,264 (39%) with CD and 2235 of 15,111 (15%) with UC received biologics. In CD, by 10 years postdiagnosis, the probability of CD-related surgery decreased gradually but modestly with earlier initiation of biologics; a significant difference was noted between > 2–3 years (31%) and 0–3 months (18%; p = 0.02; number needed to treat, 7.7), whereas there was no difference between the 0–3-month and > 3–12-month periods. The 10-year probability of steroid dependency for the 0–3-month period (19%) differed both from the > 2–3-year (31%; p < 0.001) and 1–2-year periods (37%; p < 0.001). In UC, no significant differences in colectomy or steroid dependency rates were observed between the treatment initiation periods. Similar trends were noted in the pediatric population.

Conclusions: Very early initiation of biologics was not associated with some outcomes except for a modest risk reduction of surgery and steroid dependency for Crohn's disease, which requires confirmation in future studies. In ulcerative colitis, early introduction of biologics was not associated with reduced risk of colectomy or steroid dependency.

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Verstockt B, Pivorunas V, Al Mahi N, Smaoui N, Guay H, Kennedy NA, Goodhand JR, Lin S, Bai BYH, Hanauer SB, Ferrante M, Panés J, Vermeire S

Baseline TREM-1 whole blood gene expression does not predict response to adalimumab treatment in patients with ulcerative colitis or Crohn's disease in the SERENE studies

Background and aims: This study assessed whether baseline triggering receptor expressed on myeloid cells (TREM-1) whole blood gene expression predicts response to anti-tumour necrosis factor (anti-TNF) therapy in patients with ulcerative colitis (UC) or Crohn's disease (CD).
Methods: TREM-1 whole blood gene expression was analysed by RNA sequencing in patients with moderately to severely active UC or CD treated with adalimumab in the Phase 3 SERENE-UC and SERENE-CD clinical trials. The predictive value of baseline TREM-1 expression was evaluated and compared according to endoscopic and clinical response versus non-response, and remission versus non-remission, at Weeks 8 and 52 (SERENE-UC), and Weeks 12 and 56 (SERENE-CD).
Results: TREM-1 expression was analysed in 95 and 106 patients with UC and CD, respectively, receiving standard-dose adalimumab induction treatment. In SERENE-UC, baseline TREM-1 expression was not predictive of endoscopic response (p = 0.48), endoscopic remission (p = 0.53), clinical response (p = 0.58), or clinical remission (p = 0.79) at Week 8, or clinical response (p = 0.60) at Week 52. However, an association was observed with endoscopic response (p = 0.01), endoscopic remission (p = 0.048), and clinical remission (p = 0.04997) at Week 52. For SERENE-CD, baseline TREM-1 expression was not predictive of endoscopic response (p = 0.56), endoscopic remission (p = 0.33),

clinical response (p = 0.07), or clinical remission (p = 0.65) at Week 12, or endoscopic response (p = 0.61), endoscopic remission (p = 0.51), clinical response (p = 0.62), or clinical remission (p = 0.97) at Week 56.

Conclusions: Baseline TREM-1 gene expression did not uniformly predict adalimumab response in SERENE clinical trials. Further research is needed to identify potential blood-based biomarkers predictive of response to anti-tumour necrosis factor therapy in patients with inflammatory bowel disease.

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Vermeire S, Hanzel J, Löwenberg M, Ferrante M, Bossuyt P, Hoentjen F, Franchimont D, Palatka K, Peeters H, Mookhoek A, de Hertogh G, Molnár T, van Moerkercke W, Lobatón T, Clasquin E, Hulshoff MS, Baert F, D'Haens G; LOVE-UC study group

Early versus late use of vedolizumab in ulcerative colitis: Clinical, endoscopic, and histological outcomes

Background and aims: The authors explored the potential for differential efficacy of vedolizumab between early and late ulcerative colitis (UC) with evaluation of clinical, endoscopic, and histological endpoints.
Methods: This was a multicentre, multinational, open-label study in patients with moderately-to-severely active UC, defining early UC by a disease duration < 4 years and bio-naive and late UC by a disease duration > 4 years and additional exposure to tumour necrosis factor antagonists. Patients received standard treatment with intravenous vedolizumab for 52 weeks (300 mg weeks 0, 2, 6, every 8 weeks thereafter without escalation). The primary endpoint was corticosteroid-free clinical remission with endoscopic improvement (total Mayo score ≤ 2 with no subscore >1) at both weeks 26 and 52.
Results: A total of 121 patients were included: in the "early" group, 25 of 59 (42.4%) achieved the primary endpoint versus 19 of 62 (30.6%) in the "late" group (p = 0.18). There were no significant differences between the 2 groups in endoscopic improvement (week 26: "early" 32/59 [54.2%] vs. "late" 29/62 [46.8%]; p = 0.412; week 52: 27/59 [45.8%] vs. 25/62 [40.3%]; p = 0.546) or in histological remission (Robarts Histopathology Index < 3 without neutrophils in the epithelium and lamina propria) (week 26: 24/59 [40.7%] vs. 21/62 [33.9%]; p = 0.439; week 52: 22/59 [37.3%] vs. 22/62 [35.5%]; p = 0.837).

Conclusions: No significant differences in clinical, endoscopic, and histological outcomes were observed between "early" and "late" disease.

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Understanding predictors of fatigue over time in persons with inflammatory bowel disease: The importance of depressive and anxiety symptoms

Introduction: Fatigue is a complex and frequent symptom in persons with inflammatory bowel disease (IBD), with detrimental impact. The authors aimed to determine predictors of fatigue over time.
Methods: 247 adults with IBD participated in a prospective study conducted in Manitoba, Canada, providing data at baseline and annually for 3 years. Participants reported fatigue impact (Daily Fatigue Impact Scale [DFIS]), depression and anxiety symptoms (Hospital Anxiety and Depression Scale [HADS]), and pain (Pain Effects Scale [PES]). Physician-diagnosed comorbidities, IBD characteristics, and physical and cognitive functioning were also assessed. The authors tested factors associated with fatigue using multivariable generalized linear models that estimated within-person and between-person effects.
Results: Most participants were women (63.2%), white (85.4%), and had Crohn's disease (62%). At baseline, 27.9% reported moderate-severe fatigue impact, 16.7% had clinically elevated anxiety (HADS-A ≥ 11), and 6.5% had clinically elevated depression (HADS-D ≥ 11). Overall fatigue burden was stable over time, although approximately half the participants showed improved or worsening fatigue impact between annual visits during the study. On multivariable analysis, participants with a 1-point higher HADS-D score had, on average, a 0.63-point higher DFIS score, whereas participants with a 1-point higher PES score had a 0.78-point higher DFIS score. Within individuals, a 1-point increase in HADS-D scores was associated with 0.61-point higher DFIS scores, in HADS-A scores with 0.23-point higher DFIS scores, and in PES scores with 0.38-point higher DFIS scores. No other variables predicted fatigue.

Discussion: Anxiety, depression, and pain predicted fatigue impact over time in inflammatory bowel disease, suggesting that targeting psychological factors and pain for intervention may lessen fatigue burden.

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IBS, Functional and Motility Disorders

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A low FODMAP diet plus traditional dietary advice versus a low-carbohydrate diet versus pharmacological treatment in irritable bowel syndrome (CARIBS): A single-centre, single-blind, randomised controlled trial

Background: Dietary advice and medical treatments are recommended to patients with irritable bowel syndrome (IBS). Studies have not yet compared the efficacy of dietary treatment with pharmacological treatment targeting the predominant IBS symptom. The authors therefore aimed to compare the effects of 2 restrictive dietary treatment options versus optimised medical treatment in people with IBS.
Methods: This single-centre, single-blind, randomised controlled trial was conducted in a specialised outpatient clinic at the Sahlgrenska University Hospital, Gothenburg, Sweden. Participants (aged ≥ 18 years) with moderate-to-severe IBS (Rome IV; IBS Severity Scoring System [IBS-SSS] ≥ 175) and no other serious diseases or food allergies were randomly assigned (1:1:1) by web-based randomisation to receive a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) plus traditional IBS dietary advice recommended by the UK National Institute for Health and Care Excellence (hereafter the LFTD diet), a fibre-optimised diet low in total carbohydrates and high in protein and fat (hereafter the low-carbohydrate diet), or optimised medical treatment based on predominant IBS symptom. Participants were masked to the names of the diets, but the pharmacological treatment was open-label. The intervention lasted 4 weeks, after which time participants in the dietary interventions were unmasked to their diets and encouraged to continue during 6 months' follow-up, participants in the LFTD group were instructed on how to reintroduce FODMAPs, and participants receiving pharmacological treatment were offered diet counselling and to continue with their medication. The primary endpoint was the proportion of participants who responded to the 4-week intervention, defined as a reduction of 50 or more in IBS-SSS relative to baseline, and was analysed per modified intention-to-treat (i.e., all participants who started the intervention). Safety was analysed in the modified intention-to-treat population.
Findings: Between January 24, 2017, and September 2, 2021, 1104 participants were assessed for eligibility and 304 were randomly assigned. Ten participants did not receive their intervention after randomisation and thus 294 participants were included in the modified intention-to-treat population (96 assigned to the LFTD diet, 97 to the low-carbohydrate diet, and 101 to optimised medical treatment). 241 (82%) of 294 participants were women and 53 (18%) were men and the mean age was 38 years (standard deviation 13). After 4 weeks, 73 (76%) of 96 participants in the LFTD diet group, 69 (71%) of 97 participants in the low-carbohydrate diet group, and 59 (58%) of 101 participants in the optimised medical treatment group had a reduction of 50 or more in IBS-SSS compared with baseline, with a significant difference between the groups (p = 0.023). 91 (95%) of 96 participants completed 4 weeks in the LFTD group, 92 (95%) of 97 completed 4 weeks in the low-carbohydrate group, and 91 (90%) of 101 completed 4 weeks in the optimised medical treatment group. Two individuals in each of the intervention groups stated that adverse events were the reason for discontinuing the 4-week intervention. Five (5%) of 91 participants in the optimised medical treatment group stopped treatment prematurely due to side-effects. No serious adverse events or treatment-related deaths occurred.

Interpretation: Two 4-week dietary interventions and optimised medical treatment reduced the severity of irritable bowel syndrome (IBS) symptoms, with a larger effect size in the diet groups. Dietary interventions might be considered as an initial treatment for patients with IBS. Research is needed to enable personalised treatment strategies.

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Colorectal Cancer

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Rahbari NN, Biondo S, Frago R, Feißt M, Kreisler E, Rossion I, Serrano M, Jäger D, Lehmann M, Sommer F, Dignass A, Bolling C, Vogel I, Bork U, Büchler MW, Folprecht G, Kieser M, Lordick F, Weitz J; SYNCHRONOUS and CCRe-IV Trial Groups

Primary tumor resection before systemic therapy in patients with colon cancer and unresectable metastases: Combined results of the SYNCHRONOUS and CCRe-IV trials

Purpose: Chemotherapy is established as primary treatment in patients with stage IV colorectal cancer and unresectable metastases. Data from non-randomized clinical trials have fueled persistent uncertainty if primary tumor resection (PTR) before chemotherapy prolongs survival. The authors investigated the prognostic value of PTR in patients with newly diagnosed stage IV colon cancer who were not amenable to curative treatment.
Patients and methods: Patients enrolled in the multicenter, randomized SYNCHRONOUS and CCRe-IV trials were included in the analysis. Patients with colon cancer with synchronous unresectable metastases were randomly assigned at 100 sites in Austria, Germany, and Spain to undergo PTR or up-front chemotherapy (No PTR group). The chemotherapy regimen was left at discretion of the local team. Patients with tumor-related symptoms, inability to tolerate surgery and/or systemic chemotherapy, and history of another cancer were excluded. The primary end point was overall survival (OS), and the analyses were performed with intention-to-treat.

Results: A total of 393 patients were randomly assigned to undergo PTR (n = 187) or no PTR (n = 206) between November 2011 and March 2017. Chemotherapy was not administered to 6.4% in the No PTR group and 24.1% in the PTR group. The median follow-up time was 36.7 months (95% confidence interval [CI]: 36.6–37.3). The median OS was 16.7 months (95% CI: 13.2–19.2) in the PTR group and 18.6 months (95% CI: 16.2–22.3) in the No PTR group (p = 0.191). Comparable OS between the study groups was further confirmed on multivariate analysis (hazard ratio = 0.944, 95% CI: 0.738–1.209; p = 0.65) and across all subgroups. Patients with serious adverse events were more common in the No PTR group (10.2% vs. 18.0%; p = 0.027).

Conclusion: Among patients with colon cancer and synchronous unresectable metastases, primary tumor resection before systemic chemotherapy was not associated with prolonged overall survival.

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Pinto C, Orlandi A, Normanno N, Maiello E, Calegari MA, Antonuzzo L, Bordonaro R, Zampino MG, Pini S, Bergamo F, Tonini G, Avallone A, Latiano TP, Rosati G, Cogoni AA, Ballestrero A, Zaniboni A, Roselli M, Tamberi S, Barone C

Fluorouracil, leucovorin, and irinotecan plus cetuximab versus cetuximab as maintenance therapy in first-line therapy for RAS and BRAF wild-type metastatic colorectal cancer: Phase 3 ERMES study

Purpose: The intensity of anti-epidermal growth factor receptor (EGFR)-based first-line therapy for RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC), once disease control is achieved, is controversial. A de-escalation strategy with anti-EGFR monotherapy represents a potential option to maintain efficacy while reducing cytotoxicity.
Methods: In this multicenter, open-label, phase 3 trial, patients with untreated RAS/BRAF wt mCRC were randomly assigned to receive either fluorouracil, leucovorin, and irinotecan/cetuximab (FOLFIRI/Cet) until disease progression (arm A) or FOLFIRI/Cet for 8 cycles followed by Cet alone (arm B). The co-primary end points were a non-inferior progression-free survival (PFS) in the modified per-protocol (mPP) population (> 8 cycles) and a lower incidence of grade (G) 3–4 adverse events (AEs) for arm B compared with arm A.
Results: Overall, 606 patients were randomly assigned, with 300 assigned to arm A and 306 to arm B. The median follow-up was 22.3 months. In the mPP population, 291 events occurred with a PFS of 10 versus 12.2 months for arms B and A, respectively (p of non-inferiority = 0.43). In the intention-to-treatment (ITT, ≥ 1 cycle) population, 503 events occurred with a PFS of 9 versus 10.7 months (p = 0.39). The overall survival was 35.7 versus 30.7 months (p = 0.119) and 31.0 versus 25.2 months (p = 0.32) in the mPP and ITT population, respectively. Arm B had lower G3–4 AEs during the maintenance period than arm A (20.2% vs. 35.1%).

Conclusion: The ERMES study did not demonstrate non-inferiority of maintenance with cetuximab (Cet) alone. Despite a more favorable safety profile, maintenance with single-agent Cet after induction with FOLFIRI/Cet cannot be recommended for all patients but could represent an option in selected cases.

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Colorectal Cancer Screening/ Endoscopy

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Meulen LWT, Bogie RMM, Siersema PD, Winkens B, Vlug MS, Wolfhagen FHJ, Baven-Pronk M, van der Voorn M, Schwartz MP, Vogelaar L, de Vos tot Nederveen Cappel WH, Seerden TCJ, Hazen WL, Schrauwen RWM, Alvarez Herrero L, Schreuder RM, van Nunen AB, Stoop E, de Bruin GJ, Bos P, Marsman WA, Kuiper E, de Bièvre M, Alderlieste YA, Roomer R, Groen J, Bargeman M, van Leerdam ME, Roberts-Bos L, Boersma F, Thurnau K, de Vries RS, Ramaker JM, Vleggaar FP, de Ridder RJ, Pellisé M, Bourke MJ, Masclee AAM, Moons LMG

Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study): A multicentre cluster randomised trial

Objective: Endoscopic mucosal resection (EMR) is the preferred treatment for non-invasive large (≥ 20 mm) non-pedunculated colorectal polyps (LNPCPs) but is associated with an early recurrence rate of up to 30%. The authors evaluated whether standardised EMR training could reduce recurrence rates in Dutch community hospitals.
Design: In this multicentre cluster randomised trial, 59 endoscopists from 30 hospitals were randomly assigned to the intervention group (e-learning and 2-day training including hands-on session) or control group. From April 2019 to August 2021, all consecutive EMR-treated LNPCPs were included. Primary endpoint was recurrence rate after 6 months.
Results: A total of 1412 LNPCPs were included; 699 in the intervention group and 713 in the control group (median size 30 mm vs. 30 mm, 45% vs. 52% size, morphology, site and access [SMSA] score IV, 64% vs. 64% proximal location). Recurrence rates were lower in the intervention group compared with controls (13% vs. 25%, odds ratio [OR] = 0.43; 95% confidence interval [CI]: 0.23–0.78; p = 0.005) with similar complication rates (8% vs. 9%, OR = 0.93; 95% CI: 0.64–1.36; p = 0.720). Recurrences were more often unifocal in the intervention group (92% vs. 76%; p = 0.006). In sensitivity analysis,

the benefit of the intervention on recurrence rate was only observed in the 20–40 mm LNPCPs (5% vs. 20% in 20–29 mm, p = 0.001; 10% vs. 21% in 30–39 mm, p = 0.013) but less evident in ≥ 40 mm LNPCPs (24% vs. 31%; p = 0.151). In a post hoc analysis, the training effect was maintained in the study group, while in the control group the recurrence rate remained high.

Conclusion: A compact standardised endoscopic mucosal resection (EMR) training for large non-pedunculated colorectal polyps (LNPCPs) significantly reduced recurrences in community hospitals. This strongly argues for a national dedicated training programme for endoscopists performing EMR of ≥ 20 mm LNPCPs. Interestingly, in sensitivity analysis, this benefit was limited for LNPCPs ≥ 40 mm.

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Imperiale TF, Porter K, Zella J, Gagrat ZD, Olson MC, Statz S, Garces J, Lavin PT, Aguilar H, Brinberg D, Berkelhammer C, Kisiel JB, Limburg PJ; BLUE-C Study Investigators

Next-generation multitarget stool DNA test for colorectal cancer screening

Background: A next-generation multitarget stool DNA test, including assessments of DNA molecular markers and hemoglobin level, was developed to improve the performance of colorectal cancer screening, primarily with regard to specificity.
Methods: In a prospective study, the authors evaluated a next-generation multitarget stool DNA test in asymptomatic adults 40 years of age or older who were undergoing screening colonoscopy. The primary outcomes were sensitivity of the test for colorectal cancer and specificity for advanced neoplasia (colorectal cancer or advanced precancerous lesions). Advanced precancerous lesions included 1 or more adenomas or sessile serrated lesions measuring at least 1 cm in the longest dimension, lesions with villous histologic features, and high-grade dysplasia. Secondary objectives included the quantification of sensitivity for advanced precancerous lesions and specificity for non-neoplastic findings or negative colonoscopy and comparison of sensitivities for colorectal cancer and advanced precancerous lesions between the multitarget stool DNA test and a commercially available fecal immunochemical test (FIT).
Results: Of 20,176 participants, 98 had colorectal cancer, 2144 had advanced precancerous lesions, 6973 had non-advanced adenomas, and 10,961 had non-neoplastic findings or negative colonoscopy. With the next-generation test, sensitivity for colorectal cancer was 93.9% (95% confidence interval [CI]: 87.1–97.7), and specificity for advanced neoplasia was 90.6% (95% CI: 90.1–91.0). Sensitivity for advanced precancerous lesions was 43.4% (95% CI: 41.3–45.6), and specificity for non-neoplastic findings or negative colonoscopy was 92.7% (95% CI: 92.2–93.1). With the FIT, sensitivity was 67.3% (95% CI: 57.1–76.5) for colorectal cancer and 23.3% (95% CI: 21.5–25.2) for advanced precancerous lesions; specificity was 94.8% (95% CI: 94.4–95.1) for advanced neoplasia and 95.7% (95% CI: 95.3–96.1) for non-neoplastic findings or negative colonoscopy. As compared with FIT, the next-generation test had superior sensitivity for colorectal cancer (p < 0.001) and for advanced precancerous lesions (p < 0.001) but had lower specificity for advanced neoplasia (p < 0.001). No adverse events occurred.

Conclusions: The next-generation multitarget stool DNA test showed higher sensitivity for colorectal cancer and advanced precancerous lesions than fecal immunochemical test but also showed lower specificity.

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Chung DC, Gray DM II, Singh H, Issaka RB, Raymond VM, Eagle C, Hu S, Chudova DI, Talasaz A, Greenson JK, Sinicrope FA, Gupta S, Grady WM

A cell-free DNA blood-based test for colorectal cancer screening

Background: Colorectal cancer is the third most diagnosed cancer in adults in the United States. Early detection could prevent more than 90% of colorectal cancer-related deaths, yet more than one third of the screening-eligible population is not up to date with screening despite multiple available tests. A blood-based test has the potential to improve screening adherence, detect colorectal cancer earlier, and reduce colorectal cancer-related mortality.
Methods: The authors assessed the performance characteristics of a cell-free DNA (cfDNA) blood-based test in a population eligible for colorectal cancer screening. The coprimary outcomes were sensitivity for colorectal cancer and specificity for advanced neoplasia (colorectal cancer or advanced precancerous lesions) relative to screening colonoscopy. The secondary outcome was sensitivity to detect advanced precancerous lesions.
Results: The clinical validation cohort included 10,258 persons, 7861 of whom met eligibility criteria and were evaluable. A total of 83.1% of the participants with colorectal cancer detected by colonoscopy had a positive cfDNA test and 16.9% had a negative test, which indicates a sensitivity of the cfDNA test for detection of colorectal cancer of 83.1% (95% confidence interval [CI]: 72.2–90.3). Sensitivity for stage I, II, or III colorectal cancer was 87.5% (95% CI: 75.3–94.1), and sensitivity for advanced precancerous lesions was 13.2% (95% CI: 11.3–15.3). A total of 89.6% of the participants without any advanced colorectal neoplasia (colorectal cancer or advanced precancerous lesions) identified on colonoscopy had a negative cfDNA blood-based test, whereas 10.4% had a positive cfDNA blood-based test, which indicates a specificity for any advanced neoplasia of 89.6% (95% CI: 88.8–90.3). Specificity for negative colonoscopy (no colorectal cancer, advanced precancerous lesions, or non-advanced precancerous lesions) was 89.9% (95% CI: 89.0–90.7).

Conclusions: In an average-risk screening population, this cell-free DNA blood-based test had 83%

sensitivity for colorectal cancer, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions.

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Coronado GD, Jenkins CL, Shuster E, Johnson C, Amy D, Cook J, Sahnow S, Zepp JM, Mummadi R

Blood-based colorectal cancer screening in an integrated health system: A randomised trial of patient adherence

Objective: The authors evaluated whether people who had not completed a faecal immunochemical test (FIT) for colorectal cancer (CRC) screening would complete a blood-based testing option if offered one during health encounters. Blood-based screening tests for CRC could add to the total number of people screened for CRC by providing another testing alternative.
Design: Study participants were patients aged 45–75 years at a large, integrated health system who were offered but did not complete an FIT in the prior 3–9 months and were scheduled for a clinical encounter. Individuals were randomised (1:1) to be offered a commercially available CRC blood test versus usual care. The authors compared 3-month CRC screening proportions in the 2 groups.
Results: 2026 patients were randomised; 2004 remained eligible following postrandomisation exclusions (1003 to usual care and 1001 to blood draw offer; mean age, 60 years, 62% female, 80% non-Hispanic white). Of the 1001 allocated to the blood test group, 924 were recruited following chart-review exclusions; 548 (59.3%) were reached via phone, of which 280 (51.1%) scheduled an appointment with the research team. CRC screening proportions were 17.5 percentage points higher in the blood test group versus usual care (30.5% vs. 13.0%; odds ratio = 2.94, 95% confidence interval: 2.34–3.70; p < 0.001).

Conclusion: Among adults who had declined prior colorectal cancer (CRC) screening, the offer of a blood-based screening test boosted CRC screening by 17.5 percentage points over usual care. Further research is needed on how to balance the favourable adherence with lower advanced adenoma detection compared with other available tests.

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Lower Gastrointestinal Bleeding

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Aoki T, Sadashima E, Kobayashi K, Yamauchi A, Yamada A, Omori J, Ikeya T, Aoyama T, Tominaga N, Sato Y, Kishino T, Ishii N, Sawada T, Murata M, Takao A, Mizukami K, Kinjo K, Fujimori S, Uotani T, Fujita M, Sato H, Hayakawa Y, Fujishiro M, Kaise M, Nagata N; CODE BLUE-J Study collaborators

High-risk stigmata and treatment strategy for acute lower gastrointestinal bleeding: A nationwide study in Japan

Background: The rebleeding risks and outcomes of endoscopic treatment for acute lower gastrointestinal bleeding (ALGIB) may differ depending on the bleeding location, type, and etiology of stigmata of recent hemorrhage (SRH) but have yet to be fully investigated. The authors aimed to identify high-risk endoscopic SRH and to propose an optimal endoscopic treatment strategy.
Methods: They retrospectively analyzed 2699 ALGIB patients with SRH at 49 hospitals (CODE BLUE-J Study), of whom 88.6% received endoscopic treatment.
Results: 30-day rebleeding rates of untreated SRH significantly differed among locations (left colon 15.5% vs. right colon 28.6%) and etiologies (diverticular bleeding 27.5% vs. others [e.g. ulcerative lesions or angioectasia] 8.9%), but not among bleeding types. Endoscopic treatment reduced the overall rebleeding rate (adjusted odds ratio [aOR] = 0.69; 95% confidence interval [CI]: 0.49–0.98), and the treatment effect was significant in right-colon SRH (aOR = 0.46; 95% CI: 0.29–0.72) but not in left-colon SRH. The effect was observed in both active and non-active types but was not statistically significant. Moreover, the effect was significant for diverticular bleeding (aOR = 0.60; 95% CI: 0.41–0.88) but not for other diseases. When focusing on treatment type, the effectiveness was not significantly different between clipping and other modalities for most SRH, whereas ligation was significantly more effective than clipping in right-colon diverticular bleeding.

Conclusions: A population-level endoscopy dataset allowed to identify high-risk endoscopic stigmata of recent hemorrhage (SRH) and propose a simple endoscopic treatment strategy for acute lower gastrointestinal bleeding (ALGIB). Unlike upper gastrointestinal bleeding, the rebleeding risks for ALGIB depend on colonic location, bleeding etiology, and treatment modality.

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Microscopic Colitis

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Zheng T, Roda G, Zabana Y, Escudero-Hernández C, Liu X, Chen Y, Camargo Tavares L, Bonfiglio F, Mellander MR, Janczewska I, Vigren L, Sjöberg K, Ohlsson B, Almer S, Halfvarson J, Miehlke S, Madisch A, Lieb W, Kupčinskas J, Weersma RK, Bujanda L, Julià A, Marsal S, Esteve M, Guagnozzi D, Fernández-Bañares F, Ferrer C, Peter I, Ludvigsson JF, Pardi D, Verhaegh B, Jonkers D, Pierik M, Münch A, Franke A, Bresso F, Khalili H, Colombel JF, D'Amato M; MC-Europe GETECCU GWAS group

Human leukocyte antigen signatures as pathophysiological discriminants of microscopic colitis subtypes

Background and aims: Microscopic colitis (MC) is currently regarded as an inflammatory bowel disease that manifests as 2 subtypes: collagenous colitis (CC) and lymphocytic colitis (LC). Whether these represent a clinical continuum or distinct entities is, however, an open question. Genetic investigations may contribute important insight into their respective pathophysiologies.
Methods: The authors conducted a genome-wide association study (GWAS) meta-analysis in 1498 CC patients, 373 LC patients, and 13,487 controls from Europe and the USA, combined with publicly available MC GWAS data from UK Biobank and FinnGen (2599 MC cases and 552,343 controls in total). Human leukocyte antigen (HLA) alleles and polymorphic residues were imputed and tested for association, including conditional analyses for the identification of key causative variants and residues. Genetic correlations with other traits and diagnoses were also studied.
Results: The authors detected a strong HLA association with CC, and conditional analyses highlighted the DRB1*03:01 allele and its residues Y26, N77, and R74 as key to this association (best $p = 1.4 \times 10^{-23}$, odds ratio [OR] = 1.96). Nominally significant genetic correlations were detected between CC and pneumonia ($r_g = 0.77$; $p = 0.048$) and oesophageal diseases ($r_g = 0.45$, $p = 0.023$). An additional locus was identified in MC GWAS analyses near the CLEC16A and RMI2 genes on chromosome 16 (rs35099084, $p = 2.0 \times 10^{-8}$, OR = 1.31). No significant association was detected for LC.

Conclusion: These results suggest collagenous colitis (CC) and lymphocytic colitis have distinct pathophysiological underpinnings, characterised by a human leukocyte antigen-predisposing role only in CC. This challenges existing classifications, eventually calling for a re-evaluation of the utility of microscopic colitis umbrella definitions.

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XXVII International Bile Acid Meeting – Bile Acids in Health and Disease 2024

International Adolf Windaus Award Presented

Prof. Dr. Dieter Häussinger (Germany) honored with International Adolf Windaus Award at Symposium 237 in Edinburgh (UK)

The Falk Foundation e.V.'s XXVII International Bile Acid Meeting took place from July 5 to 6, 2024, in Edinburgh with over 400 participants in attendance. Internationally renowned speakers discussed topics including bile acid transport and signaling, the interaction between bile acids and the microbiome, and the role of bile acids in tumor development. New approaches to therapy using bile acid derivatives, receptor agonists, and transporter inhibitors were another focus of the symposium.

A highlight of the event was the presentation of the Adolf Windaus Award to Prof. Dr. Dieter Häussinger, Emeritus Director of the Department of Gastroenterology, Hepatology and Infectious Diseases at the University Medical Center of the Heinrich Heine University in Düsseldorf (Germany).

The Adolf Windaus Award was presented for the 23rd time in Edinburgh. The award is named after biochemist Adolf Windaus (1876–1959), who described the chemical structure of cholesterol and its connection with vitamin D metabolism, for which he received the Nobel Prize for Chemistry in 1928.

German researcher Häussinger was honored with the € 15,000 award, donated by the Falk Foundation e.V., for his outstanding contributions to bile acid research. Since 1980, the award has been presented every two years for exceptional scientific achievements in this medical field.

Prof. Dr. Ulrich Beuers from the Department of Gastroenterology and Hepatology at the University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, delivered the speech honoring the award winner:

"The price committee decided to give this year's Adolf Windaus prize 2024 to Dieter Häussinger for his contributions to the Bile Acid Field during the last 35 years.

Professor Dieter Häussinger was born in the medieval town of Nördlingen in Bavaria (Germany). After school, he decided to study medicine in Munich (Germany) and did at the same time his dissertation on a biochemical topic. After finishing the studies and getting first clinical work experience, he started in 1979 as a resident in Internal medicine in Freiburg (Germany) where Prof. Wolfgang Gerok was the Chair of Internal Medicine with a focus on Gastroenterology and Hepatology. During his 15 years in Freiburg, Dieter Häussinger finished his Habilitation, he became Internist and then Gastroenterologist, and a Professor of Internal Medicine. In 1991, he received an endowed Hermann und Lilly Schilling Chair and in the same year the highest and most prestigious scientific award for German speaking countries, the Gottfried Wilhelm Leibniz Award.

In 1994, Dieter Häussinger became Full Professor and Chair of the Department of Internal Medicine with focus on Gastroenterology, Hepatology and Infectious Diseases at the University of Düsseldorf, capital of the state North-Rhine Westphalia. During the next 25 years in Düsseldorf he was dean of Medicine and held many other administrative functions not only at the University of Düsseldorf, but also in national scientific committees in Germany and in international scientific

Prof. Dr. Dieter Häussinger

Prof. Dr. Ulrich Beuers

associations like the European Association for the Study of the Liver. In 2010, he founded and chaired the Hirsch Institute of Tropical Medicine, at the Ethiopian ARSI University in the south of Addis Abeba. An exchange program between medical fellows from Düsseldorf and those from the ARSI University was a win-win situation for medical learning and teaching.

The scientific bibliography is extensive and includes more than 700 original articles in all major journals and more than 15 books.

As many of those were directly related to the bile acid field, the Adolf Windaus committee decided to honour Prof. Dr. Dieter Häussinger with the 2024 Adolf Windaus Award for his unique achievements on this field. His lecture was entitled ***'Bile Acids and hepatic osmosensing/signaling pathways'.****"*

Professor Dieter Häussinger identified together with his team fundamental mechanisms on bile acid transport and signalling. He was among the first to describe and to characterize insertion and retrieval of canalicular transport ATPases such as Mrp2 and Bsep into or from the canalicular membrane as major mechanisms of short-term regulation of hepatobiliary transport. He discovered that the water content and accordingly the volume of the hepatocyte are dynamic parameters which potently regulate diverse hepatocyte functions. He discovered that the associated mechanosensing and mechanosignaling pathways can also be activated by specific bile acids. $ß_1$-integrins act as mechanosensors in response to hepatocyte swelling, but are also directly activated by the taurine conjugate of ursodeoxycholic acid, which thereby mediates choleresis and hepatoprotection. On the other hand hepatocyte shrinkage is sensed by hepatic endosomes and results in the generation of oxidative stress, which activates signaling pathways towards cholestasis and apoptosis induction. These shrinkage-induced sensing and signaling pathways are also activated by hydrophobic bile acids such as glycochenodeoxycholate and explain their proapoptotic and cholestatic action. These adverse effects are counteracted by a crosstalk with the $ß_1$-integrin-dependent signaling, shedding a new light on hepatoprotective mechanisms.

Prof. Dr. Dieter Häussinger (left) and Prof. Dr. Ulrich Beuers (right)

PANCREAS

Acute/Chronic Pancreatitis

Clin Gastroenterol Hepatol. 2024;22(5):994–1004.e10

Overbeek KA, Poulsen JL, Lanzillotta M, Vinge-Holmquist O, Macinga P, Demirci AF, Sindhunata DP, Backhus J, Algül H, Buijs J, Levy P, Kiriukova M, Goni E, Hollenbach M, Miksch RC, Kunovsky L, Vujasinovic M, Nikolic S, Dickerson L, Hirth M, Neurath MF, Zumblick M, Vila J, Jalal M, Beyer G, Frost F, Carrara S, Kala Z, Jabandziev P, Sisman G, Akyuz F, Capurso G, Falconi M, Arlt A, Vleggaar FP, Barresi L, Greenhalf B, Czakó L, Hegyi P, Hopper A, Nayar MK, Gress TM, Vitali F, Schneider A, Halloran CM, Trna J, Okhlobystin AV, Dagna L, Cahen DL, Bordin D, Rebours V, Mayerle J, Kahraman A, Rasch S, Culver E, Kleger A, Martínez-Moneo E, Røkke O, Hucl T, Olesen SS, Bruno MJ, Della-Torre E, Beuers U, Löhr JM, Rosendahl J; PrescrAIP Study Group

Type 1 autoimmune pancreatitis in Europe: Clinical profile and response to treatment

Background and aims: Autoimmune pancreatitis (AIP) is an immune-mediated disease of the pancreas with distinct pathophysiology and manifestations. The aims of this study were to characterize type 1 AIP in a large pan-European cohort and study the effectiveness of current treatment regimens.
Methods: The authors retrospectively analyzed adults diagnosed since 2005 with type 1 or not-otherwise-specified AIP in 42 European university hospitals. Type 1 AIP was uniformly diagnosed using specific diagnostic criteria. Patients with type 2 AIP and those who had undergone pancreatic surgery were excluded. The primary end point was complete remission, defined as the absence of clinical symptoms and resolution of the index radiologic pancreatic abnormalities attributed to AIP.
Results: They included 735 individuals with AIP (69% male; median age, 57 years; 85% white). Steroid treatment was started in 634 patients, of whom 9 (1%) were lost to follow-up. The remaining 625 had a 79% (496/625) complete, 18% (111/625) partial, and 97% (607/625) cumulative remission rate, whereas 3% (18/625) did not achieve remission. No treatment was given in 95 patients, who had a 61% complete (58/95), 19% partial (18/95), and 80% cumulative (76/95) spontaneous remission rate. Higher (≥ 0.4 mg/kg/day) corticosteroid doses were no more effective than lower (< 0.4 mg/kg/day) doses (odds ratio [OR] = 0.428; 95% confidence interval [CI]: 0.054–3.387) and neither was a starting dose duration > 2 weeks (OR = 0.908; 95% CI: 0.818–1.009). Elevated immunoglobulin G4 levels were independently associated with a decreased chance of complete remission (OR = 0.639; 95% CI: 0.427–0.955). Relapse occurred in 30% of patients. Relapses within 6 months of remission induction were independent of the steroid-tapering duration, induction treatment duration, and total cumulative dose.

Conclusions: Patients with type 1 autoimmune pancreatis and elevated immunoglobulin G4 level may need closer monitoring. For remission induction, a starting dose of 0.4 mg/kg/day for 2 weeks followed by a short taper period seems effective. This study provides no evidence to support more aggressive regimens.

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Hart PA, Osypchuk Y, Hovbakh I, Shah RJ, Nieto J, Cote GA, Avgaitis S, Kremzer O, Buxbaum J, Inamdar S, Fass R, Phillips RW, Yadav D, Mendoza Ladd A, Al-Assi MT, Gardner T, Conwell DL, Irani S, Sheikh A, Nuttall J; TACTIC Study Investigators

A randomized controlled phase 2 dose-finding trial to evaluate the efficacy and safety of camostat in the treatment of painful chronic pancreatitis: The TACTIC study

Background and aims: Chronic pancreatitis (CP) causes an abdominal pain syndrome associated with poor quality of life. The authors conducted a clinical trial to further investigate the efficacy and safety of camostat, an oral serine protease inhibitor that has been used to alleviate pain in CP.
Methods: This was a double-blind randomized controlled trial that enrolled adults with CP with a baseline average daily worst pain score ≥ 4 on a numeric rating system. Participants were randomized (1:1:1:1) to receive camostat at 100, 200, or 300 mg 3 times daily or placebo. The primary end point was a 4-week change from baseline in the mean daily worst pain intensity score (0–10 on a numeric rating system) using a mixed model repeated measure analysis. Secondary end points included changes in alternate pain end points, quality of life, and safety.
Results: A total of 264 participants with CP were randomized. Changes in pain from baseline were similar between the camostat groups and placebo, with differences of least squares means of -0.11 (95% confidence interval [CI]: -0.90–0.68), -0.04 (95% CI: -0.85–0.78), and -0.11 (95% CI: -0.94–0.73) for the 100-mg, 200-mg, and 300-mg groups, respectively. Multiple subgroup analyses were similar for the primary end point, and no differences were observed in any of the secondary end points. Treatment-emergent adverse events attributed to the study drug were identified in 42 participants (16.0%).

Conclusion: The authors were not able to reject the null hypothesis of no difference in improvements in pain or quality of life outcomes in participants with painful chronic pancreatitis (CP) who received camostat compared with placebo. Studies are needed to further define mechanisms of pain in CP to guide future clinical trials, including minimizing placebo responses and selecting targeted therapies.

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Hollemans RA, Timmerhuis HC, Besselink MG, Bouwense SAW, Bruno M, van Duijvendijk P, van Geenen EJ, Hadithi M, Hofker S, Van-Hooft JE, Kager LM, Manusama ER, Poley JW, Quispel R, Römkens T, van der Schelling GP, Schwartz MP, Spanier BWM, Stommel M, Tan A, Venneman NG, Vleggaar F, van Wanrooij RLJ, Bollen TL, Voermans RP, Verdonk RC, van Santvoort HC; Dutch Pancreatitis Study Group

Long-term follow-up study of necrotising pancreatitis: Interventions, complications and quality of life

Objective: To describe the long-term consequences of necrotising pancreatitis, including complications, the need for interventions and the quality of life.
Design: Long-term follow-up of a prospective multicentre cohort of 373 necrotising pancreatitis patients (2005–2008) was performed. Patients were prospectively evaluated and received questionnaires. Readmissions (i.e., for recurrent or chronic pancreatitis), interventions, pancreatic insufficiency and quality of life were compared between initial treatment groups: conservative, endoscopic/percutaneous drainage alone and necrosectomy. Associations of patient and disease characteristics during index admission with outcomes during follow-up were assessed.
Results: During a median follow-up of 13.5 years (range, 12–15.5 years), 97 of 373 patients (26%) were readmitted for recurrent pancreatitis. Endoscopic or percutaneous drainage was performed in 47 of 373 patients (13%), of whom 21 of 47 patients (45%) were initially treated conservatively. Pancreatic necrosectomy or pancreatic surgery was performed in 31 of 373 patients (8%), without differences between treatment groups. Endocrine insufficiency (126/373 patients; 34%) and exocrine insufficiency (90/373 patients; 38%), developed less often following conservative treatment ($p < 0.001$ and $p = 0.016$, respectively). Quality of life scores did not differ between groups. Pancreatic gland necrosis > 50% during initial admission was associated with percutaneous/endoscopic drainage (odds ratio [OR] = 4.3; 95% confidence interval [CI]: 1.5–12.2), pancreatic surgery (OR = 3.2; 95% CI: 1.1–9.5) and development of endocrine insufficiency (OR = 13.1; 95% CI: 5.3–32.0) and exocrine insufficiency (OR = 6.1; 95% CI: 2.4–15.5) during follow-up.

Conclusion: Acute necrotising pancreatitis carries a substantial disease burden during long-term follow-up in terms of recurrent disease, the necessity for interventions and development of pancreatic insufficiency, even when treated conservatively during the index admission. Extensive (> 50%) pancreatic parenchymal necrosis seems to be an important predictor of interventions and complications during follow-up.

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de Pretis N, Carlin M, Calderini E, Caldart F, Conti Bellocchi MC, Amodio A, De Marchi G, Campagnola P, Crinò SF, Bernardoni L, Gabbrielli A, Martinelli L, Frulloni L

Clinical features and long-term outcomes of patients with type 2 autoimmune pancreatitis

Objectives: Type 2 is a rare form of autoimmune pancreatitis (AIP). Despite being considered a benign disease, only few studies with limited sample size and short follow-up have been published on type 2 AIP. The aim of this observational study was to evaluate long-term outcomes, such as the risk of relapse, pancreatic insufficiency and cancer in a large type 2 AIP cohort with long follow-up.
Methods: Patients with definitive or probable diagnosis of type 2 AIP by International Consensus Diagnostic Criteria (ICDC) present in the authors' prospectively maintained database since 1995 at 31.12.2021 were identified. All patients were clinically evaluated during the year 2022. Clinical, radiological, serological, and pathological data were evaluated.
Results: 88 out of 420 patients present in the database (21%) were diagnosed with type 2 AIP (mean age, 33.5 ± 13.5 years). According to the ICDC, 21 patients (23.8%) had a definitive and 67 (76.2%) had a probable diagnosis of type 2 AIP. The mean follow-up was 9.2 ± 7.1 years (range, 1–27 years). No differences were observed when comparing patients with definitive and probable type 2 AIP diagnosis. Concomitant inflammatory bowel disease was reported in 77 patients (87.5%). The probability of disease relapse was lower in patients treated with steroids versus surgery (at 5 years: 13% vs. 33%; $p = 0.038$), but this difference was not statistically significant at multivariable analysis. The risk of endocrine or severe exocrine insufficiency was low (5% and 25%). Four extrapancreatic malignancies (5%) were diagnosed, none pancreatic. One patient died in a car accident.

Conclusions: Type 2 autoimmune pancreatitis has benign long-term clinical outcomes. Mortality and cancer rates are low and no specific follow-up is needed after radiological remission.

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Pancreatic Tumors

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De La Fouchardière C, Malka D, Cropet C, Chabaud S, Raimbourg J, Botsen D, Launay S, Evesque L, Vienot A, Perrier H, Jary M, Rinaldi Y, Coutzac C, Bachet JB, Neuzillet C, Williet N, Desgrippes R, Grainville T, Aparicio T, Peytier A, Lecomte T, Roth GS, Thirot-Bidault A, Lachaux N, Bouché O, Ghiringhelli F

Gemcitabine and paclitaxel versus gemcitabine alone after 5-fluorouracil, oxaliplatin, and irinotecan in metastatic pancreatic adenocarcinoma: A randomized phase 3 PRODIGE 65-UCGI 36-GEMPAX UNICANCER study

Purpose: GEMPAX was an open-label, randomized phase 3 clinical trial designed to assess the efficacy and tolerability of gemcitabine plus paclitaxel versus gemcitabine alone as second-line treatment for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who previously received 5-fluorouracil, oxaliplatin, and irinotecan (FOLFIRINOX).
Methods: Patients with histologically or cytologically confirmed mPDAC were randomly assigned (2:1) to receive GEMPAX (paclitaxel 80 mg/m^2 + gemcitabine 1000 mg/m^2; i.v.; once at day (D)1, D8, and D15/arm A) or gemcitabine alone (arm B) once at D1, D8, and D15 every 28 days until progression, toxicity, or patient's decision. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), objective response rate (ORR), quality of life, and safety.
Results: Overall, 211 patients (median age, 64 [30–86] years; 62% male) were included. After a median study follow-up for alive patients of 13.4 versus 13.8 months in arm A versus arm B, the median OS (95% confidence interval) was 6.4 (5.2–7.4) versus 5.9 months (4.6–6.9; hazard ratio [HR] = 0.87 [0.63–1.20]; p = 0.4095), the median PFS was 3.1 (2.2–4.3) versus 2.0 months (1.9–2.3; HR = 0.64 [0.47–0.89]; p = 0.0067), and the ORR was 17.1% (11.3–24.4) versus 4.2% (0.9–11.9; p = 0.008) in arm A versus arm B, respectively. Overall, 16.7% of patients in arm A and 2.9% in arm B discontinued their treatment because of adverse events (AEs). One grade 5 AE associated with both gemcitabine and paclitaxel was reported in arm A (acute respiratory distress), and 58.0% versus 27.1% of patients experienced grade ≥ 3 treatment-related AEs in arm A versus arm B, among which 15.2% versus 4.3% had anemia, 15.9% versus 15.7% had neutropenia, 19.6% versus 4.3% had thrombocytopenia, 10.1% versus 2.9% had asthenia and 12.3% versus 0.0% had neuropathy.

Conclusion: While gemcitabine plus paclitaxel did not meet the primary end point of overall survival versus gemcitabine alone in patients with metastatic pancreatic ductal adenocarcinoma in the second-line setting, both progression-free survival and objective response rate were significantly improved.

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Revisiting the performance of cyst fluid carcinoembryonic antigen as a diagnostic marker for pancreatic mucinous cysts: A comprehensive 20-year institutional review

Objective: Elevated pancreatic cyst fluid carcinoembryonic antigen (CEA) has been routinely used to classify mucinous cysts. This study incorporates original data that established the CEA ≥ 192 ng/ml threshold with over 20 years of additional data and re-assesses the diagnostic performance of CEA for differentiating mucinous from non-mucinous cysts.
Design: 1169 pancreatic cysts (1999–2021) with CEA results were identified. 394 cases had histological confirmation as the diagnostic standard. Additionally, 237 cysts without histological confirmation demonstrated KRAS, GNAS, or RNF43 mutations by molecular testing and were combined with the histologically confirmed cysts for separate analysis on a total cohort of 631 cysts.
Results: Median CEA was significantly higher in mucinous cysts (323.9 ng/ml, n = 314) versus non-mucinous cysts (204.6 ng/ml, n = 80) (p < 0.001). Receiver-operating characteristic curve analysis demonstrated an optimal CEA cut-off of 20 ng/ml (area under the curve, 80%), though the specificity was lower than desired (sensitivity 89%, specificity 64%). At the previously established threshold of 192 ng/ml, sensitivity and specificity were 56% and 78%, respectively. To achieve a specificity of 85% as originally reported, a CEA threshold of 250 ng/ml was needed; the 13 false-positive cases at this threshold included 4 benign simple cysts, 2 squamoid cysts, 1 serous cystadenoma, 1 lymphoepithelial cyst and 5 more uncommon entities. All results remained similar within the total cohort after including additional cases with KRAS/GNAS/RNF43 mutations only.

Conclusion: Cyst fluid carcinoembryonic antigen (CEA) continues to be a useful test in the diagnosis of mucinous pancreatic cysts but does not appear as specific as previously reported. Raising the CEA threshold to 250 ng/ml to maintain specificity for differentiating mucinous from non-mucinous cysts may be considered.

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LIVER AND BILE

MASH/MASLD*

* MASH/MASLD: formerly non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD). The new international terms "MASH" (metabolic dysfunction-associated steatohepatitis) and "MASLD" (metabolic dysfunction-associated steatotic liver disease) were introduced by the multi-society Delphi panel in June 2023.

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Armandi A, Sanavia T, Younes R, Caviglia GP, Rosso C, Govaere O, Liguori A, Francione P, Gallego-Duràn R, Ampuero J, Pennisi G, Aller R, Tiniakos D, Burt A, David E, Vecchio F, Maggioni M, Cabibi D, McLeod D, Pareja MJ, Zaki MYW, Grieco A, Stål P, Kechagias S, Fracanzani AL, Valenti L, Miele L, Fariselli P, Eslam M, Petta S, Hagström H, George J, Schattenberg JM, Romero-Gómez M, Anstee QM, Bugianesi E

Serum ferritin levels can predict long-term outcomes in patients with metabolic dysfunction-associated steatotic liver disease

Objective: Hyperferritinaemia is associated with liver fibrosis severity in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), but the longitudinal implications have not been thoroughly investigated. The authors assessed the role of serum ferritin in predicting long-term outcomes or death.
Design: They evaluated the relationship between baseline serum ferritin and longitudinal events in a multicentre cohort of 1342 patients. Four survival models considering ferritin with confounders or non-invasive scoring systems were applied with repeated 5-fold cross-validation schema. Prediction performance was evaluated in terms of Harrell's C-index and its improvement by including ferritin as a covariate.
Results: Median follow-up time was 96 months. Liver-related events occurred in 7.7%, hepatocellular carcinoma in 1.9%, cardiovascular events in 10.9%, extrahepatic cancers in 8.3% and all-cause mortality in 5.8%. Hyperferritinaemia was associated with a 50% increased risk of liver-related events and 27% of all-cause mortality. A stepwise increase in baseline ferritin thresholds was associated with a statistical increase in C-index, ranging between 0.02 (lasso-penalised Cox regression) and 0.03 (ridge-penalised Cox regression); the risk of developing liver-related events mainly increased from threshold 215.5 µg/l (median hazard ratio [HR] = 1.71 and C-index = 0.71) and the risk of overall mortality from threshold 272 µg/l (median HR = 1.49 and C-index = 0.70). The inclusion of serum ferritin thresholds (215.5 µg/l and 272 µg/l) in predictive models increased the performance of Fibrosis-4 and Non-Alcoholic Fatty Liver Disease Fibrosis Score in the longitudinal risk assessment of liver-related events (C-indices > 0.71) and overall mortality (C-indices > 0.65).

Conclusions: This study supports the potential use of serum ferritin values for predicting the long-term prognosis of patients with metabolic dysfunction-associated steatotic liver disease.

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Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease

Background and aims: Recently, the term metabolic dysfunction-associated steatotic liver disease (MASLD) has replaced non-alcoholic fatty liver disease (NAFLD). Concern remains regarding whether the evidence generated under the NAFLD definition can be used for MASLD. The authors compared the clinical profile and outcomes of NAFLD to MASLD using tertiary care- and population-based data.
Methods: Comparison data were obtained from their NAFLD database and the National Health and Nutrition Examination Survey (NHANES III). Clinical profiles and non-invasive tests (enhanced liver fibrosis [ELF] score, fibrosis-4 index [FIB-4] and vibration-controlled transient elastography) were compared. Mortality data were obtained from NHANES-National Death Index. All-cause mortality was assessed by Cox proportional hazards regression models and cause-specific mortality by competing risk analysis.
Results: There were 6429 patients in the NAFLD database (age, 54 ± 12 years, 42% male, body mass index [BMI] 35.4 ± 8.3, waist circumference 112 ± 17 cm, 52% type 2 diabetes). Average scores for ELF, FIB-4 and liver stiffness were 9.6 ± 1.2, 1.69 ± 1.24, 14.0 ± 11.8 kPa, respectively; 99% met MASLD criteria; 95% met MASLD on BMI only. Predictive accuracy of ELF and FIB-4 were identical between MASLD and NAFLD. 12,519 eligible participants from NHANES were included (age, 43.00 years, 47.38% male, 22.70% obese, 7.28% type 2 diabetes, 82.51% ≥ 1 cardiometabolic criteria). Among the NHANES study population, there was excellent concordance between MASLD and NAFLD diagnoses: Cohen's kappa coefficient: 0.968 (95% confidence interval: 0.962–0.973) with 5.29% of NAFLD cases not meeting MASLD criteria. After a median follow-up of 22.83 years, there were no mortality differences between MASLD and NAFLD diagnoses (p values ≥ 0.05).

Conclusions: Non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) are similar except individuals with MASLD seem to be older with slightly higher mortality

risk, likely owing to cardiometabolic risk factors. Clinical profiles and non-invasive test thresholds were also identical. These data provide evidence that NAFLD and MASLD terminologies can be used interchangeably. For the small proportion of patients with NAFLD who do not meet MASLD criteria, further consideration is needed.

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Randomized trial of anakinra plus zinc vs. prednisone for severe alcohol-associated hepatitis

Background and aims: Severe alcohol-associated hepatitis (SAH) is associated with high 90-day mortality. Glucocorticoid therapy for 28 days improves 30- but not 90-day survival. The authors assessed the efficacy and safety of a combination of anakinra, an interleukin-1 antagonist, plus zinc (A+Z) compared to prednisone using the Day-7 Lille score as a stopping rule in patients with SAH.
Methods: In this phase 2b double-blind randomized trial in adults with SAH and Model for End-stage Liver Disease (MELD) scores of 20–35, participants were randomized to receive either daily anakinra 100 mg subcutaneously for 14 days plus daily zinc sulfate 220 mg orally for 90 days, or daily prednisone 40 mg orally for 30 days. Prednisone or prednisone placebo was stopped if Day-7 Lille score was > 0.45. All study drugs were stopped for uncontrolled infection or ≥ 5-point increase in MELD score. The primary endpoint was overall survival at 90 days.
Results: 73 participants were randomized to prednisone and 74 to A+Z. The trial was stopped early after a prespecified interim analysis showed prednisone was associated with higher 90-day overall survival (90% vs. 70%; hazard ratio [HR] for death = 0.34, 95% confidence interval [CI]: 0.14–0.83, p = 0.018) and transplant-free survival (88% vs. 64%; HR for transplant or death = 0.30, 95% CI: 0.13–0.69, p = 0.004) than A+Z. Acute kidney injury was more frequent with A+Z (45%) than with prednisone (22%) (p = 0.001), but rates of infection were similar (31% in A+Z vs. 27% in prednisone, p = 0.389).

Conclusions: Participants with severe alcohol-associated hepatitis treated with prednisone using the Day-7 Lille score as a stopping rule had significantly higher overall and transplant-free 90-day survival and lower incidence of acute kidney injury than those treated with anakinra plus zinc.

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Analyzing the utility of renal replacement therapy to manage hepatorenal syndrome in alcoholic hepatitis without liver transplantation: A nationwide analysis

Background: Hepatorenal syndrome (HRS) frequently complicates alcoholic hepatitis (AH) and portends poor survival in this population. Published literature indicates mixed benefits from renal replacement therapy (RRT) for HRS refractory to medical management. Therefore, the authors sought to assess the utilization of RRT in AH and clinical outcomes at a national level.
Methods: Using the International Classification of Diseases, 10th Revision (ICD-10) codes, they identified adult patients with AH with a coexisting diagnosis of HRS from the National Readmission Database 2016 through 2019. Mortality, morbidity, and resource utilization were compared. Additionally, proportions using the Fisher exact test and computed adjusted p-values based on multivariate regression analysis were compared. Analyses were performed using Stata, version 14.2, considering a 2-sided p < 0.05 as statistically significant.
Results: A total of 73,203 patients with AH were included in the analysis (mean age, 46.2 years). A total of 3620 individuals had HRS diagnosis (5%), of which 14.7% (n = 532) underwent RRT. HRS patients receiving RRT had a higher mortality rate than those who did not (adjusted odds ratio [aOR] = 1.8, 95% confidence interval [CI]: 1.3–2.6, p = 0.01), along with higher resource utilization. Only those patients with HRS who underwent liver transplantation experienced a mortality reduction (24.4% for those not receiving RRT and 36.5% for those receiving RRT).

Conclusions: Renal replacement therapy (RRT) is associated with higher mortality and morbidity when offered to patients with alcoholic hepatitis (AH) and hepatorenal syndrome (HRS), who do not undergo liver transplantation. Therefore, these results suggest careful selection of AH patients when deciding to initiate RRT for HRS.

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Gratacós-Ginès J, Avitabile E, Montironi C, Guillamon-Thiery A, Hernández-Évole H, Moreta MJ, Blaya D, Ariño S, Rubio AB, Pérez-Guasch M, Cervera M, Carol M, Fabrellas N, Soria A, Juanola A, Graupera I, Sancho-Bru P, Díaz A, Coll M, Bataller R, Ginès P, Pose E

Alcoholic foamy degeneration, an entity resembling alcohol-associated hepatitis: Diagnosis, prognosis, and molecular profiling

Background and aims: Alcoholic foamy degeneration (AFD) is a condition with similar clinical presentation

to alcohol-associated hepatitis (AH), but with a specific histologic pattern. Information regarding the prevalence and prognosis of AFD is scarce and there are no tools for a non-invasive diagnosis.
Methods: A cohort of patients admitted to the Hospital Clinic of Barcelona for clinical suspicion of AH who underwent liver biopsy was included. Patients were classified as AFD, AH, or other findings, according to histology. Clinical features, histology, and genetic expression of liver biopsy specimens were analyzed. The accuracy of National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria and laboratory parameters for differential diagnosis were investigated.
Results: Of 230 patients with a suspicion of AH, 18 (8%) met histologic criteria for AFD, 184 (80%) had definite AH, and 28 (12%) had other findings. In patients with AFD, massive steatosis was more frequent, and the fibrosis stage was lower. AFD was characterized by down-regulation of liver fibrosis and inflammation genes and up-regulation of lipid metabolism and mitochondrial function genes. Patients with AFD had markedly better long-term survival (100% vs. 57% in AFD vs. AH; p = 0.002) despite not receiving corticosteroid treatment, even in a Model for End-stage Liver Disease-matched sensitivity analysis. Serum triglyceride levels had an area under the receiver-operating characteristic of 0.886 (95% confidence interval: 0.807–0.964) for the diagnosis of AFD, whereas the NIAAA criteria performed poorly. A 1-step algorithm using triglyceride levels of 225 mg/dl (sensitivity, 0.77; specificity, 0.90; and Youden index, 0.67) is proposed for differential diagnosis.

Conclusions: Alcoholic foamy degeneration (AFD) in the setting of suspicion of alcohol-associated hepatitis is not uncommon. A differential diagnosis is important because prognosis and treatment differ largely. Triglyceride levels successfully identify most patients with AFD and may be helpful in decision making.

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HBV

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Non-linear association of baseline viral load with on-treatment hepatocellular carcinoma risk in chronic hepatitis B

Objective: The association between baseline pretreatment serum HBV DNA levels and on-treatment hepatocellular carcinoma (HCC) risk remains controversial in patients with chronic hepatitis B (CHB). The authors aimed to investigate the association between baseline hepatitis B virus (HBV) viral load and on-treatment HCC risk in CHB patients without cirrhosis.
Design: Using a multicentre historical cohort study including 4693 hepatitis B e antigen (HBeAg)-negative and HBeAg-positive, adult CHB patients without cirrhosis who initiated antiviral treatment, HCC risk was estimated by baseline HBV viral load as a categorical variable.
Results: During a median of 7.6 years of antiviral treatment, 193 patients developed HCC (0.53 per 100 person-years). Baseline HBV DNA level was independently associated with on-treatment HCC risk in a non-linear, parabolic pattern. Patients with moderate baseline viral loads (5.00–7.99 $\log_{10}$ IU/ml) exhibited the highest HCC risk (hazard ratio [HR] = 2.60; p < 0.001), followed by those with low viral loads (3.30–4.99 $\log_{10}$ IU/ml; HR = 1.66; p = 0.11). Patients with high viral loads (≥ 8.00 $\log_{10}$ IU/ml) presented the lowest HCC risk. Particularly, patients with baseline HBV DNA levels 6.00–6.99 $\log_{10}$ IU/ml had the highest on-treatment HCC risk (HR = 3.36; p < 0.001) compared with those with baseline HBV DNA levels ≥ 8.00 $\log_{10}$ IU/ml. These findings were more prominent among HBeAg-positive patients, younger patients, or those with less advanced hepatic fibrosis.

Conclusion: Patients with moderate baseline viral load, particularly around 6 $\log_{10}$ IU/ml, demonstrated the highest on-treatment hepatocellular carcinoma (HCC) risk, despite long-term antiviral treatment. Early initiation of antiviral treatment, tailored to viral load, should be considered to minimise HCC risk in adult patients with chronic hepatitis B without cirrhosis.

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Long-term use of tenofovir disoproxil fumarate increases fracture risk in elderly patients with chronic hepatitis B

Background and aims: The use of tenofovir disoproxil fumarate (TDF) is associated with a reduction in bone mineral density and an increase in bone metabolism biomarkers. However, data on clinical bone fractures remain limited. The authors evaluated the impact of TDF compared to entecavir on the risk of fracture in elderly patients with chronic hepatitis B (CHB).
Methods: Patients with CHB aged ≥ 60 years receiving entecavir or TDF between January 2008 and December 2022 were identified using a territory-wide database in Hong Kong. The risk of incident fracture in entecavir- and TDF-treated patients before and after month 24 were compared after propensity score matching.
Results: A total of 41,531 patients with CHB (mean age, 69.8 ± 7.8 years, 61.6% male) receiving entecavir (n = 39,897 [96.1%]) and TDF (n = 1634 [3.9%]) were analysed. At a median follow-up of 25.3 (9.1–58.5) months, 1733 (4.2%) patients developed incident fracture. Patients with incident fracture were more likely to have diabetes, hypertension, congestive heart failure, rheumatoid arthritis, osteoporosis, and a history of fracture. Compared with propensity score-matched

entecavir-treated patients, the risk of incident fracture in TDF-treated patients was comparable in the first 24 months (weighted subdistribution hazard ratio [sHR] = 0.99, 95% confidence interval [CI]: 0.56–1.73, p = 0.960) but increased after month 24 (weighted sHR = 1.80, 95% CI: 1.11–2.93, p = 0.019). The 24-, 60-, and 96-month cumulative incidences (95% CI) of fracture in TDF-treated and entecavir-treated patients were 2.3% (1.6–3.4%) versus 2.6% (1.9–3.5%), 6.4% (5.0–8.2%) versus 4.7% (3.8–6.0%), and 10.2% (8.3–12.6%) versus 6.8% (5.4–8.5%), respectively.

Conclusions: The risk of fracture increased with tenofovir disoproxil fumarate treatment for ≥ 24 months in elderly patients with chronic hepatitis B. Selection of nucleos(t)ide analogues should be individualised based on age and comorbidities.

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HDV

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Gish RG, Wong RJ, Di Tanna GL, Kaushik A, Kim C, Smith NJ, Kennedy PTF

Association of hepatitis delta virus with liver morbidity and mortality: A systematic literature review and meta-analysis

Background and aims: Studies have suggested that patients with chronic hepatitis B, either co- or superinfected, have more aggressive liver disease progression than those with the hepatitis delta virus (HDV). This systematic literature review and meta-analysis examined whether HDV RNA status is associated with increased risk of advanced liver disease events in patients who are hepatitis B surface antigen- and HDV antibody-positive.
Approach and results: A total of 12 publications were included. Relative rates of progression to advanced liver disease event for HDV RNA+/detectable versus HDV RNA-/undetectable were extracted for analysis. Reported odds ratio (OR) and hazard ratios (HRs) with 95% confidence interval (CI) were pooled using the Hartung-Knapp-Sidik-Jonkman method for random-effects models. The presence of HDV RNA+ was associated with an increased risk of any advanced liver disease event (random effect [95% CI]: risk ratio = 1.48 [0.93–2.33]; HR = 2.62 [1.55–4.44]). When compared to the patients with HDV RNA- status, HDV RNA+ was associated with a significantly higher risk of progressing to compensated cirrhosis (risk ratio = 1.74 [1.24–2.45]) decompensated cirrhosis (HR = 3.82 [1.60–9.10]), hepatocellular carcinoma (HR = 2.97 [1.87–4.70]), liver transplantation (HR = 7.07 [1.61–30.99]), and liver-related mortality (HR = 3.78 [2.18–6.56]).

Conclusions: The patients with HDV RNA+ status have a significantly greater risk of liver disease progression than the patients who are HDV RNA-. These findings highlight the need for improved hepatitis delta virus (HDV) screening and linkage to treatment to reduce the risk of liver-related morbidity and mortality.

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AIH/PBC/PSC

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A new and simple score to predict adequate and deep response to ursodeoxycholic acid in patients with primary biliary cholangitis: The ALP-A score

Background: Ursodeoxycholic acid (UDCA) is the standard treatment for primary biliary cholangitis (PBC), but a significant proportion of patients do not respond adequately, leading to increased risk of adverse outcomes. This study aims to develop a new and straightforward predictive score to identify PBC patients likely to achieve a complete response to UDCA.
Methods: A logistic regression analysis was conducted using a derivation cohort of PBC patients to identify pretreatment variables associated with response to UDCA. This analysis led to the development of the ALP-A score, calculated as: age at diagnosis divided by (alkaline phosphatase [ALP] at diagnosis/upper limit of normal). ALP-A score accuracy was evaluated using the area under the receiver-operating characteristic curve, validated with a large external cohort from Brazil. Additionally, the correlation between the ALP-A score and the previously validated UDCA response score (URS) was assessed.
Results: The ALP-A score had good predictive power for adequate (area under the curve [AUC], 0.794; 95% confidence interval [CI]: 0.737–0.852) and deep (AUC, 0.76; 95% CI: 0.69–0.83) UDCA response at 1 year of treatment. A cut-off score of 17 and 23 points was determined to be the optimal threshold for distinguishing adequate and deep responders, respectively, from non-responders. ALP-A score demonstrated a sensitivity of 73%, specificity of 71%, positive predictive value of 65%, negative predictive value of 78%, and overall accuracy of 72% for biochemical response.

The URS displayed similar discriminative ability (AUC, 0.798; 95% CI: 0.741–0.855).

Conclusion: The ALP-A score performs comparably to the ursodeoxycholic acid (UDCA) response score but offers the great advantage of simplicity for routine clinical use. It serves as a valuable tool to identify primary biliary cholangitis patients less likely to respond to UDCA treatment, facilitating early consideration of alternative therapeutic approaches.

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An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis

Background and aims: Patients with autoimmune hepatitis (AIH) almost invariably require lifelong immunosuppressive treatment. There is genuine concern about the efficacy and tolerability of the current standard combination therapy of prednisolone and azathioprine. Mycophenolate mofetil (MMF) has emerged as an alternative option. The aim of this study was to compare MMF to azathioprine as induction therapy for AIH.
Methods: In this 24-week, prospective, randomised, open-label, multicentre superiority trial, 70 patients with treatment-naive AIH received either MMF or azathioprine, both in combination with prednisolone. The primary endpoint was biochemical remission defined as normalisation of serum levels of alanine aminotransferase and immunoglobulin G after 24 weeks of treatment. Secondary endpoints included safety and tolerability.
Results: 70 patients (mean 57.9 years [standard deviation 14.0]; 72.9% female) were randomly assigned to the MMF plus prednisolone (n = 39) or azathioprine plus prednisolone (n = 31) group. The primary endpoint was met in 56.4% and 29.0% of patients assigned to the MMF group and the azathioprine group, respectively (difference, 27.4 percentage points; 95% confidence interval: 4.0–46.7; p = 0.022). The MMF group exhibited higher complete biochemical response rates at 6 months (72.2% vs. 32.3%; p = 0.004). No serious adverse events occurred in patients who received MMF (0%) but serious adverse events were reported in 4 patients who received azathioprine (12.9%) (p = 0.034). Two patients in the MMF group (5.1%) and 8 patients in the azathioprine group (25.8%) discontinued treatment owing to adverse events or serious adverse events (p = 0.018).

Conclusions: In patients with treatment-naive autoimmune hepatitis, mycophenolate mofetil (MMF) with prednisolone led to a significantly higher rate of biochemical remission at 24 weeks compared to azathioprine combined with prednisolone. Azathioprine use was associated with more (serious) adverse events leading to cessation of treatment, suggesting superior tolerability of MMF.

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Hatoum S, Rockey DC

Long-term outcomes of patients with autoimmune hepatitis-induced cirrhosis after immunosuppressive treatment

Introduction: Autoimmune hepatitis (AIH) is an immune-mediated liver disease that results in hepatic inflammation and subsequent fibrosis. The authors aimed to assess the natural history of AIH in patients who had cirrhosis at the time of diagnosis.
Methods: They examined consecutive patients with AIH (based on the revised International Autoimmune Hepatitis Group criteria) and cirrhosis who had long-term follow-up between 2012 and 2018. Complete clinical data, including longitudinal data, was obtained for each patient to determine clinical and biochemical outcomes. Decompensating events were defined as complications of portal hypertension.
Results: 34 patients presenting with AIH-induced cirrhosis (age 50 [17–81] years; 71% women) were followed for an average of 8 years post-diagnosis. 14 patients (41%) had a decompensating event at diagnosis. All patients were begun on treatment; index decompensating events resolved in all patients. 26 patients (76%) had normalization of transaminases; in this group, 4 patients (15%) developed 1 or more new decompensating events and 1 patient (4%) died. Of the 8 patients (24%) who did not have transaminase normalization, 6 (75%) developed 1 or more new decompensating events and 5 (62%) died or underwent liver transplant. There was a significant association between achieving normalization of transaminases and protection from developing a decompensating event (p = 0.003) and liver transplant or death (p = 0.001).

Conclusion: Most patients with autoimmune hepatitis with cirrhosis at presentation achieved normalization of transaminases with treatment and rarely developed further decompensating events. It is speculated that some of these patients had stabilization or reversal of portal hypertension.

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Inherited Liver Disease

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Schönauer R, Sierks D, Boerrigter M, Jawaid T, Caroff L, Audrezet MP, Friedrich A, Shaw M, Degenhardt J, Forberger M, de Fallois J, Bläker H, Bergmann C, Gödiker J, Schindler P, Schlevogt B, Müller RU, Berg T, Patterson I, Griffiths WJ, Sayer JA, Popp B, Torres VE, Hogan MC, Somlo S, Watnick TJ, Nevens F, Besse W, Cornec-Le Gall E, Harris PC, Drenth JPH, Halbritter J; Genomics England Research Consortium

Sex, genotype, and liver volume progression as risk of hospitalization determinants in autosomal dominant polycystic liver disease

Background and aims: Autosomal dominant polycystic liver disease is a rare condition with a female preponderance, based mainly on pathogenic variants in 2 genes, PRKCSH and SEC63. Clinically, autosomal dominant polycystic liver disease is characterized by vast heterogeneity, ranging from asymptomatic to highly symptomatic hepatomegaly. To date, little is known about the prediction of disease progression at early stages, hindering clinical management, genetic counseling, and the design of randomized controlled trials. To improve disease prognostication, the authors built a consortium of European and US centers to recruit the largest cohort of patients with PRKCSH and SEC63 liver disease.
Methods: They analyzed an international multicenter cohort of 265 patients with autosomal dominant polycystic liver disease harboring pathogenic variants in PRKCSH or SEC63 for genotype-phenotype correlations, including normalized age-adjusted total liver volumes and polycystic liver disease-related hospitalization (liver event) as primary clinical end points.
Results: Classifying individual total liver volumes into predefined progression groups yielded predictive risk discrimination for future liver events independent of sex and underlying genetic defects. In addition, disease severity, defined by age at first liver event, was considerably more pronounced in female patients and patients with PRKCSH variants than in those with SEC63 variants. A newly developed sex-gene score was effective in distinguishing mild, moderate, and severe disease, in addition to imaging-based prognostication.

Conclusions: Both imaging and clinical genetic scoring have the potential to inform patients about the risk of developing symptomatic disease throughout their lives. The combination of female sex, germline PRKCSH alteration, and rapid total liver volume progression is associated with the greatest odds of polycystic liver disease-related hospitalization.

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Liver Cirrhosis

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Prognostic value of procalcitonin in patients with cirrhosis hospitalized for acute infection

Background: In patients with cirrhosis, infections significantly increase the risk of short- and long-term mortality. During infection, the levels of procalcitonin increase, but it has not yet been clarified its prognostic value in subjects with cirrhosis. Therefore, the aim of this study was to evaluate the prognostic role of procalcitonin in patients with liver cirrhosis hospitalized for acute infection, and to compare it with other markers of infection.
Patients: The authors included 279 patients hospitalized because of infection, 133 with liver cirrhosis. At admission the levels of the main biochemical parameters of infection, i.e. leukocytes, procalcitonin, C-reactive protein and lactate, were considered.
Results: The duration of hospitalization and antibiotic therapy were longer in patients with cirrhosis, while no difference was observed for mortality. In both groups, a correlation with the duration of hospitalization and antibiotic therapy was observed for high levels of procalcitonin. In the cirrhotic population, in particular, higher procalcitonin values were associated with an increase in the length of hospitalization and antibiotic therapy, suggesting an even greater predictive value for those patients. High levels of leukocytes and lactate were positively associated with the duration of hospitalization, but not with the duration of antibiotic therapy. For mortality, the strongest correlation was found for high serum lactate levels, regardless of the presence of cirrhosis.

Conclusion: In patients with cirrhosis and acute infection, the value of procalcitonin at admission is a good prognostic indicator for the course of hospitalization and could be useful for guiding the management and treatment of hospitalized patients.

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Tonon M, D'Ambrosio R, Calvino V, Tosetti G, Barone A, Incicco S, Gambino C, Gagliardi R, Borghi M, Zeni N, Piano S, Lampertico P, Angeli P

A new clinical and prognostic characterization of the patterns of decompensation of cirrhosis

Background and aims: The prognostic impact of acute decompensation (AD), i.e. the development of complications that require hospitalization, has recently been

assessed. However, complications of cirrhosis do not necessarily require hospitalization and can develop progressively, as in the recently defined non-acute decompensation (NAD). Nevertheless, there is no data regarding the incidence and prognostic impact of NAD. The aim of the study was to evaluate the incidence and the prognostic impact of NAD and AD in outpatients with cirrhosis.
Methods: A total of 617 outpatients with cirrhosis from 2 Italian tertiary centers (Padua and Milan) were enrolled from January 2003 to June 2021 and followed prospectively until the end of the study, death or liver transplantation. The complications registered during follow-up were considered as AD if they required hospitalization, or NAD if managed at the outpatient clinic.
Results: During follow-up, 154 patients (25.0% of total patients) developed complications, 69 patients (44.8%) developed NAD and 85 (55.2%) developed AD, while 29 patients with NAD (42.0%) developed a further episode of AD during follow-up. 60-month survival was significantly higher in patients with no decompensation than in patients with NAD or AD. On multivariable analysis, AD (hazard ratio [HR] = 21.07, p < 0.001), NAD (HR = 7.13, p < 0.001), the etiological cure of cirrhosis (HR = 0.38, p < 0.001) and Model for End-stage Liver Disease score (HR = 1.12, p = 0.003) were found to be independent predictors of mortality.

Conclusions: The first decompensation is non-acute in almost 50% of outpatients, though such events are still associated with decreased survival compared to no decompensation. Patients who develop non-acute decompensation must be treated with extreme care and monitored closely to prevent the development of acute decompensation.

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Yang TC, Chen WC, Hou MC, Chen PH, Lee PC, Chang CY, Lu HS, Chen YJ, Hsu SJ, Huang HC, Luo JC, Huang YH, Lee FY

Endoscopic variceal ligation versus propranolol for the primary prevention of oesophageal variceal bleeding in patients with hepatocellular carcinoma: An open-label, 2-centre, randomised controlled trial

Objective: This randomised trial aimed to address whether endoscopic variceal ligation (EVL) or propranolol (PPL) is more effective at preventing initial oesophageal variceal bleeding (EVB) in patients with hepatocellular carcinoma (HCC).
Design: Patients with HCC and medium-to-large oesophageal varices (EVs) but without previous EVB were randomised to receive EVL (every 3–4 weeks until variceal eradication) or PPL (up to 320 mg daily) at a 1:1 ratio. Long-term follow-up data on EVB, other upper gastrointestinal bleeding (UGIB), non-bleeding liver decompensation, overall survival (OS) and adverse events (AEs) were analysed using competing risk regression.
Results: Between June 2011 and April 2021, 144 patients were randomised to receive EVL (n = 72) or PPL (n = 72). In the EVL group, 7 patients experienced EVB, and 30 died; in the PPL group, 19 patients had EVB, and 40 died. The EVL group had a lower cumulative incidence of EVB (Gray's test, p = 0.009) than its counterpart, with no mortality difference (Gray's test, p = 0.085). For patients with Barcelona Clinic Liver Cancer (BCLC) stage A/B, EVL was better than PPL in reducing EVB (p < 0.001) and mortality (p = 0.003). For patients beyond BCLC stage B, between-group outcomes were similar. Other UGIB, non-bleeding liver decompensation and AEs did not differ between groups. A competing risk regression model confirmed the prognostic value of EVL.

Conclusion: Endoscopic variceal ligation (EVL) is superior to propranolol in preventing initial oesophageal variceal bleeding (EVB) in patients with hepatocellular carcinoma. The benefits of EVL on EVB and overall survival may be limited to patients with Barcelona Clinic Liver Cancer (BCLC) stage A/B and not to those with BCLC stage C/D.

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Evaluation of terlipressin-related patient outcomes in hepatorenal syndrome-acute kidney injury using point-of-care echocardiography

Background and aims: Treatment of hepatorenal syndrome-acute kidney injury (HRS-AKI), with terlipressin and albumin, provides survival benefits, but may be associated with cardiopulmonary complications. The authors analyzed the predictors of terlipressin response and mortality using point-of-care echocardiography (POC-Echo) and cardiac and renal biomarkers.
Approach: Between December 2021 and January 2023, patients with HRS-AKI were assessed with POC-Echo and lung ultrasound within 6 hours of admission, at the time of starting terlipressin (48 h), and at 72 hours. Volume expansion was done with 20% albumin, followed by terlipressin infusion. Clinical data, POC-Echo data, and serum biomarkers were prospectively collected. Cirrhotic cardiomyopathy (CCM) was defined per 2020 criteria.
Results: 140 patients were enrolled (84% men, 59% alcohol-associated disease, mean MELD-Na 25 ± standard deviation [SD] 5.6). A median daily dose of infused terlipressin was 4.3 mg/day (interquartile range, 3.9–4.6); mean duration 6.4 ± SD 1.9 days; the complete response was in 62% and partial response in 11%. Overall mortality was 14% and 16% at 30 and 90 days, respectively. Cut-offs for prediction of terlipressin non-response were cardiac variables (ratio of early mitral inflow velocity

and mitral annular early diastolic tissue doppler velocity > 12.5 [indicating increased left filling pressures, C-statistic: 0.774], tissue doppler mitral velocity < 7 cm/s [indicating impaired relaxation; C-statistic: 0.791], > 20.5% reduction in cardiac index at 72 hours [C-statistic: 0.885]; p < 0.001) and pretreatment biomarkers (cystatin C > 2.2 mg/l, C-statistic: 0.640 and N-terminal brain natriuretic peptide > 350 pg/ml, C-statistic: 0.655; p < 0.050). About 6% of all patients with HRS-AKI and 26% of patients with CCM had pulmonary edema. The presence of CCM (adjusted hazard ratio [aHR] = 1.9; 95% confidence interval [CI]: 1.8–4.5, p = 0.009) and terlipressin non-response (aHR = 5.2; 95% CI: 2.2–12.2, p < 0.001) were predictors of mortality independent of age, sex, obesity, diabetes mellitus, etiology, and baseline creatinine.

Conclusions: Cirrhotic cardiomyopathy (CCM) and reduction in cardiac index, reliably predict terlipressin non-response. CCM is independently associated with poor survival in hepatorenal syndrome-acute kidney injury.

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The clinical and financial burden of non-hepatocellular carcinoma focal lesions detected during the surveillance of patients with cirrhosis

Background and aims: Hepatocellular carcinoma (HCC) surveillance is challenged by the detection of hepatic focal lesions (HFLs) of other types. This study aimed to describe the incidence, characteristics, outcomes, and costs of non-HCC HFLs detected during surveillance.
Approach and results: The authors retrospectively analyzed non-standardized work-up performed in French patients included in HCC surveillance programs recruited in 57 French tertiary centers (ANRS CirVir and CIRRAL cohorts, HCC 2000 trial). The overall cost of work-up was evaluated, with an estimation of an average cost per patient for the entire population and per lesion detected. A total of 3295 patients were followed up for 59.8 months, 391 (11.9%) patients developed HCCs (5-year incidence: 12.1%), and 633 (19.2%) developed non-HCC HFLs (5-year incidence: 21.8%). Characterization of non-HCC HFLs required a median additional of 0.7 exams per year. A total of 11.8% of non-HCC HFLs were not confirmed on recall procedures, and 19.6% of non-HCC HFLs remained undetermined. A definite diagnosis of benign liver lesions was made in 65.1%, and malignant tumors were diagnosed in 3.5%. The survival of patients with benign or undetermined non-HCC HFLs was similar to that of patients who never developed any HFL (5-year survival: 92% vs. 88%, p = 0.07). The average cost of the diagnostic work-up was 1087 Euro for non-HCC HFL and 1572 Euro for HCC.

Conclusions: Non-hepatocellular carcinoma hepatic focal lesions are frequently detected in patients with cirrhosis, and do not impact prognosis, but trigger substantial costs. This burden must be considered in cost-effectiveness analyses of future personalized surveillance strategies.

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Determinants of clinical response to empirical antibiotic treatment in patients with cirrhosis and bacterial and fungal infections – Results from the ICA "Global Study" (EABCIR-Global Study)

Background: The administration of an appropriate empirical antibiotic treatment is essential in cirrhosis and severe bacterial infections. The authors aimed to investigate the predictors of clinical response of empirical antibiotic treatment in a prospective cohort of patients with cirrhosis and bacterial and fungal infections included in the International Club of Ascites (ICA) "Global Study."
Methods: Patients hospitalized with cirrhosis and bacterial/fungal infection were prospectively enrolled at 46 centers. Clinical response to antibiotic treatment was defined according to changes in markers of infection/inflammation, vital signs, improvement of organ failure, and results of cultures.
Results: From October 2015 to September 2016, 1302 patients were included at 46 centers. A clinical response was achieved in only 61% of cases. Independent predictors of lack of clinical response to empirical treatment were C-reactive protein (odds ratio [OR] = 1.16; 95% confidence interval [CI]: 1.02–1.31), blood leukocyte count (OR = 1.39; 95% CI: 1.09–1.77), serum albumin (OR = 0.70; 95% CI: 0.55–0.88), nosocomial infections (OR = 1.96; 95% CI: 1.20–2.38), pneumonia (OR = 1.75; 95% CI: 1.22–2.53), and ineffective treatment according to antibiotic susceptibility test (OR = 5.32; 95% CI: 3.47–8.57). Patients with a lack of clinical response to first-line antibiotic treatment had a significantly lower resolution rate of infections (55% vs. 96%; p < 0.001), a higher incidence of second infections (29% vs. 15%; p < 0.001), shock (35% vs. 7%; p < 0.001) and new organ failures (52% vs. 19%; p < 0.001) than responders. Clinical response to empirical treatment was an independent predictor of 28-day survival (subdistribution = 0.20; 95% CI: 0.14–0.27).

Conclusions: Four out of 10 patients with cirrhosis do not respond to the first-line antibiotic therapy, leading

to lower resolution of infections and higher mortality. Broader-spectrum antibiotics and strategies targeting systemic inflammation may improve prognosis in patients with a high degree of inflammation, low serum albumin levels, and severe liver impairment.

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Refractory hepatic hydrothorax is associated with increased mortality with death occurring at lower MELD-Na compared to cirrhosis and refractory ascites

Background and aims: Although refractory hepatic hydrothorax (RH) is a serious complication of cirrhosis, waitlisted patients do not receive standardized Model for End-stage Liver Disease (MELD) exemption because of inadequate evidence suggesting mortality above biochemical MELD. This study aimed to examine liver-related death (LRD) associated with RH compared to refractory ascites (RA).
Approach and results: This was a retrospective cohort study of Veterans with cirrhosis. Eligibility criteria included participants with RH or RA, followed from their first therapeutic thoracentesis/second paracentesis until death or transplantation. The primary outcome was LRD with non-LRD or transplantation as competing risk. Of 2552 patients with cirrhosis who underwent therapeutic thoracentesis/paracentesis, 177 met criteria for RH and 422 for RA. RH was associated with a significantly higher risk of LRD (adjusted hazard ratio [aHR] = 4.63, 95% confidence interval [CI]: 3.31–6.48) than RA overall and within all MELD-sodium (MELD-Na) strata (< 10 aHR = 4.08, 95% CI: 2.30–7.24; 10–14.9 aHR = 5.68, 95% CI: 2.63–12.28; 15–24.9 aHR = 4.14, 95% CI: 2.34–7.34; ≥ 25 aHR = 7.75, 95% CI: 2.99–20.12). LRD was higher among participants requiring 1 (aHR = 3.54, 95% CI: 2.29–5.48), 2–3 (aHR = 4.39, 95% CI: 2.91–6.63), and ≥ 4 (aHR = 7.89, 95% CI: 4.82–12.93) thoracenteses relative to RA. Although participants with RH and RA had similar baseline MELD-Na, LRD occurred in RH versus RA at a lower MELD-Na (16.5 vs. 21.82, p = 0.002) but higher MELD 3.0 (27.85 vs. 22.48, p < 0.0001).

Conclusions: Refractory hepatic hydrothorax (RH) was associated with higher risk of liver-related death (LRD) than refractory ascites at equivalent MELD-sodium. By contrast, MELD 3.0 may better predict risk of LRD in RH.

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Statin use in cirrhosis and its association with incidence of portal vein thrombosis

Background and aim: Statin use has shown a reduction in hepatic decompensation and portal hypertension. Its association with portal vein thrombosis (PVT) incidence is unknown. The authors aim to compare the incidence of PVT in patients with and without statin use.
Methods: They excluded patients with a history of hepatocellular cancer, liver transplants, Budd-Chiari syndrome, and intra-abdominal malignancies. Patients with cirrhosis were followed from their first hepatologist clinical encounter (January 1, 2016, to January 31, 2021) for 180 days to determine PVT incidence. The association of statin use with PVT using 1:1 propensity score matching and Cox proportional hazard regression was tested.
Results: 2785 patients with cirrhosis (mean age, 61.0 ± 12.3 years, 44.3% female, 63.8% white, mean MELD-Na score, 11.7 ± 6.1, and statin use, 23.1%) were analyzed. A total of 89 patients developed PVT during the follow-up, which was lower in patients with statin use as compared to no statin use (1.3% vs. 3.8%, p = 0.001, unadjusted hazard ratio [HR] = 0.28, 95% confidence interval [CI]: 0.13–0.62, p = 0.001). After matching for demographics, comorbidities, and hepatic decompensation events, patients with statin use had a lower risk of developing PVT in 180-day follow-up as compared to those without statin use (HR = 0.24, 95% CI: 0.10–0.55, p = 0.001). Subgroup analysis showed that statin use was associated with lower PVT incidence in non-NASH (HR = 0.20, 95% CI: 0.07–0.54, p = 0.002) and decompensated cirrhosis (HR = 0.12, 95% CI: 0.03–0.53, p = 0.005) than no statin use.

Conclusion: Portal vein thrombosis incidence was lower in decompensated cirrhosis patients with statin use than in those with no statin use. However, this finding needs to be further tested in randomized controlled trials.

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Nardelli S, Riggio O, Marra F, Gioia S, Saltini D, Bellafante D, Adotti V, Guasconi T, Ridola L, Rosi M, Caporali C, Fanelli F, Roccarina D, Bianchini M, Indulti F, Spagnoli A, Merli M, Vizzutti F, Schepis F

Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt does not increase mortality in patients with cirrhosis

Background and aims: Overt hepatic encephalopathy (OHE) is a major complication of transjugular intrahepatic portosystemic shunt (TIPS) placement, given

its high incidence and possibility of refractoriness to medical treatment. Nevertheless, the impact of post-TIPS OHE on mortality has not been investigated in a large population.
Methods: The authors designed a multicenter, non-inferiority, observational study to evaluate the mortality rate at 30 months in patients with and without OHE after TIPS. They analyzed a database of 614 patients who underwent TIPS in 3 Italian centers and estimated the cumulative incidence of OHE and mortality with competitive risk analyses, setting the non-inferiority limit at 0.12.
Results: During a median follow-up of 30 months (interquartile range, 12–30), 293 patients developed at least 1 episode of OHE. 27 (9.2%) of them experienced recurrent/persistent OHE. Patients with OHE were older (64 [57–71] vs. 59 [50–67] years, p < 0.001), had lower albumin (3.1 [2.8–3.5] vs. 3.25 [2.9–3.6] g/dl, p = 0.023), and had a higher prevalence of pre-TIPS OHE (15.4% vs. 9.0%, p = 0.023). Child-Pugh and Model for End-stage Liver Disease (MELD) scores were similar. The 30-month difference in mortality between patients with and without post-TIPS OHE was 0.03 (95% confidence interval [CI]: -0.042–0.102). Multivariable analysis showed that age (subdistribution hazard ratio [SHR] = 1.04, 95% CI: 1.02–1.05, p < 0.001) and MELD score (SHR = 1.09, 95% CI: 1.05–1.13, p < 0.001), but not post-TIPS OHE, were associated with a higher mortality rate. Similar results were obtained when patients undergoing TIPS for variceal rebleeding prophylaxis (n = 356) or refractory ascites (n = 258) were analyzed separately. The proportion of patients with persistent OHE after TIPS was significantly higher in the group of patients who died. The robustness of these results was increased following propensity score matching.

Conclusion: Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS) is not associated with mortality in patients undergoing TIPS, regardless of the indication.

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Kjaergaard M, Prier Lindvig K, Holtz Thorhauge K, Johansen S, Kragh Hansen J, Andersen P, Dalby Hansen C, Lindholm Schnefeld H, Tholstrup Bech K, Torp N, Israelsen M, Detlefsen S, Graupera I, Gines P, Krag A, Thiele M

Screening for fibrosis promotes lifestyle changes: A prospective cohort study in 4796 individuals

Background and aims: Early detection of liver fibrosis is believed to promote lifestyle changes. The authors evaluated self-reported changes in alcohol intake, diet, exercise, and weight after participating in a screening study for liver fibrosis.
Methods: They conducted a prospective screening study of individuals at risk of alcohol-related liver disease (ALD) or metabolic dysfunction-associated steatotic liver disease (MASLD). Lifestyle advice was provided to all participants and lifestyle changes were evaluated by questionnaires after 1 week and 6 months, with re-examination of a subgroup after 2 years.
Results: A total of 1850 at risk of ALD and 2946 at risk of MASLD were included, of whom 383 (8%) were screening-positive (transient elastography ≥ 8 kPa). A total of 84% replied to the 6-month questionnaire. In ALD participants, excessive drinking decreased from 46% to 32% after 6 months. Only 15% reported increased drinking, without differences between screening-positive and -negative individuals (p = 0.698). In high-risk drinkers, a positive screening test predicted abstinence or decreased alcohol use after 6 months (odds ratio [OR] = 2.45; 95% confidence interval [CI]: 1.32–4.57; p = 0.005). After 2 years, excessive drinking decreased from 52% to 41% in a subgroup of 752 individuals and a positive screening test predicted abstinence or decreased alcohol use after 2 years (OR = 1.84; 95% CI: 1.09–3.11, p = 0.023). MASLD participants showed similar improvements: 35% improved their diet, 22% exercised more, and 13% reported a weight loss ≥ 5% after 6 months.

Conclusions: Screening for liver fibrosis is associated with sustained improvements in alcohol consumption, diet, weight, and exercise in at-risk alcohol-related liver disease and metabolic dysfunction-associated steatotic liver disease. The changes are most pronounced in screening-positive participants but not limited to this group.

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Jachs M, Hartl L, Simbrunner B, Semmler G, Balcar L, Hofer BS, Schwarz M, Bauer D, Stättermayer AF, Pinter M, Trauner M, Reiberger T, Mandorfer M

Prognostic performance of non-invasive tests for portal hypertension is comparable to that of hepatic venous pressure gradient

Background and aims: Non-invasive tests to assess the probability of clinically significant portal hypertension (CSPH) – including the ANTICIPATE±NASH models based on liver stiffness measurement (LSM) and platelet count±body mass index, and the von Willebrand factor antigen to platelet count ratio (VITRO) – have fundamentally changed the management of compensated advanced chronic liver disease (cACLD). However, their prognostic utility has not been compared head-to-head to the gold standard for prognostication in cACLD, i.e. the hepatic venous pressure gradient (HVPG).
Methods: Patients with cACLD (LSM ≥ 10 kPa) who underwent advanced characterization via same-day HVPG/non-invasive test assessment from 2007 to 2022 were retrospectively included. Long-term follow-up data on hepatic decompensation was recorded.
Results: 420 patients with cACLD of varying etiologies, with a CSPH prevalence of 67.6%, were included. The cumulative incidence of hepatic decompensation at

1 and 2 years was 4.7% and 8.0%, respectively. HVPG, VITRO, and ANTICIPATE±NASH-CSPH probability showed similar time-dependent prognostic value (areas under the receiver-operating characteristic curve, 0.683–0.811 at 1 year and 0.699–0.801 at 2 years). In competing risk analyses adjusted for Model for End-stage Liver Disease score and albumin, HVPG (adjusted subdistribution hazard ratio [aSHR] = 1.099 [95% confidence interval {CI}: 1.054–1.150] per mmHg; $p < 0.001$), or VITRO (aSHR = 1.134 [95% CI: 1.062–1.211] per unit; $p < 0.001$), or ANTICIPATE±NASH-CSPH probability (aSHR = 1.232 [95% CI: 1.094–1.387] per 10%; $p < 0.001$) all predicted first decompensation during follow-up. Previously proposed cut-offs (HVPG ≥ 10 mmHg vs. < 10 mmHg, VITRO ≥ 2.5 vs. < 2.5, and ANTICIPATE-CSPH probability ≥ 60% vs. < 60%) all accurately discriminated between patients at negligible risk and those at substantial risk of hepatic decompensation.

Conclusions: The prognostic performance of ANTICIPATE±NASH-CSPH probability and VITRO is comparable to that of hepatic venous pressure gradient, supporting their utility for identifying patients who may benefit from medical therapies to prevent first hepatic decompensation.

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Congresses 2024

October 2–4, 2024, London, UK
Basic Science School 2024:
Precision Cut Liver Slices and Liver Organoids – versatile ex-vivo models of liver disease
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http://www.easl.eu
https://easl.eu/event/basic-science-school-2024/

October 3–4, 2024, Bad Ischl, Austria
9. Österreichisches Crohn Colitis Symposium
E-Mail: oecco-ced@media.co.at
http://www.oecco-ced.at

October 8–11, 2024, Harrogate, UK
BASL Annual Meeting 2024
E-Mail: admin@basl.org.uk
https://www.basl.org.uk

October 12–15, 2024, Vienna, Austria
32nd United European Gastroenterology Week (UEG Week)
E-Mail: office@ueg.eu
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ILCA 2024 – 18th Annual Conference
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https://www.ilca-online.org
https://ilcalive.org/annual-conference-2024-front/

October 25–30, 2024, Philadelphia, PA, USA
ACG 2024 Annual Scientific Meeting & Postgraduate Course
E-Mail: registration@gi.org
https://acgmeetings.gi.org

October 31 – November 3, 2024, Kobe, Japan (+ online)
Japan Digestive Disease Week (JDDW) 2024
E-Mail: kobe2024en@jddw.jp
https://www.jddw.jp/jddw2024/en/

November 6–9, 2024, Hollywood, FL, USA
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E-Mail: naspghan@naspghan.org
https://members.naspghan.org/annualmeeting
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November 8–9, 2024, Florence, Italy
Symposium 238
Immuno-Mediated Diseases of the GI Tract: Where Do We Stand?
E-Mail: meeting@falkfoundation.org
https://falkfoundation.org

November 15–19, 2024, San Diego, CA, USA
The Liver Meeting 2024
E-Mail: education@aasld.org
E-Mail: meetings@aasld.org
https://www.aasld.org/the-liver-meeting

November 21–24, 2024, Bali, Indonesia
Asian Pacific Digestive Disease Week (APDW) 2024
E-Mail: secretariat@apdw2024bali.com
https://www.apdw2024bali.com/

December 7–8, 2024, Savannah, GA, USA
EASL-AASLD Masterclass 2024
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