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Editorial

Dear colleagues,

In medicine, it is always particularly stimulating when long-established dogmata and treatment algorithms are critically reexamined and revised. Two studies featured in this issue exemplify this.

The BOSS trial by Old et al. (■ p. 6) challenges established surveillance strategies for Barrett's esophagus. In this randomized trial, 3453 patients with Barrett's esophagus were assigned to either 2-yearly surveillance endoscopy or endoscopy performed only when clinically indicated by symptoms. Over a minimum follow-up period of 10 years, no differences were observed in overall survival or cancer-specific survival between both groups. An accompanying health economic analysis further demonstrated that routine endoscopic surveillance, as practiced to date, is not cost-effective.

In recent years, several pivotal studies demonstrated the efficacy of immune checkpoint inhibitors in the treatment of gastrointestinal cancer. In colorectal cancer, immunotherapy has shown particularly impressive results in tumors characterized by high microsatellite instability or mismatch repair deficiency (dMMR). The STELLAR-303 trial, a phase 3 trial in patients with advanced colorectal cancer **without** microsatellite instability-high or dMMR tumors (■ Hecht et al., p. 22), now provides first evidence that an immunotherapy-based regimen with zanzalitinib and atezolizumab allows somewhat better overall survival compared with regorafenib. These results prompt renewed discussion about the potential role of immunotherapy-based approaches for the broader treatment landscape of colorectal cancer in the future.

Beginning with this issue, and alongside our established critical expert opinions, we are introducing a new feature in which 10 selected publications are highlighted as Editors' Choice ★ as shown below. This designation is intended to help readers more readily to identify articles of particular relevance and interest within each issue. Further developments and new content can be expected in forthcoming editions.

We hope you will find the articles in this issue both informative and inspiring.

Yours sincerely,



Peter Hasselblatt and Tobias Böttler
Department of Internal Medicine II,
University Medical Center Freiburg (Germany)

EDITORS' CHOICE



Watch out for the violet marker preceding certain abstracts: your guide to the editors' key selection! ■



ESOPHAGUS TO SMALL INTESTINE

Achalasia and Motility Disorders

Clin Gastroenterol Hepatol. 2025;23(13):2468-2476.e7

Forss A, Hansson MR, Holmberg D, Thuresson M, Ebrahimi F, Elbe P, Klevebro F, Håkanson B, Thorell A, Ludvigsson JF

All-cause and cause-specific mortality in achalasia: A nationwide matched cohort study

Background and aims: Achalasia has been linked to increased mortality, but evidence from large population-based cohorts is scarce. The study aimed to assess mortality in individuals with achalasia.

Methods: This nationwide cohort study included all adults in Sweden with incident achalasia (n = 704; 1969–2017; follow-up until December 31, 2021) without any other prior esophageal conditions. Achalasia was defined through International Classification of Disease codes in the Swedish National Patient Register in individuals who underwent endoscopic esophageal examination including biopsy as recorded in the histopathology cohort ESPRESSO. Individuals with achalasia were matched by age, sex, birth year, and county to up to 5 reference individuals (n = 3348) from the general population. In a secondary analysis, full siblings were used as secondary reference individuals. Mortality incidence rates (IRs) and multivariable-adjusted hazard ratios (aHRs) with 95% confidence intervals [CIs] for all-cause and cause-specific mortality were calculated using Cox proportional hazards modeling.

Results: During a median follow-up of 9.1 years, there were 270 deaths in individuals with achalasia, and 1023 in reference individuals (IR = 69.4 vs. 51.9/1,000 person-years). This corresponded to a 1.42-fold increased risk of death (95% CI: 1.21–1.65); or 1 extra death per every 6 individuals with achalasia followed for 10 years. Risk increases were seen for death from any cancer (IR = 17.4 vs. 11.8; aHR = 1.65; 95% CI: 1.21–2.23), esophageal cancer (IR = 2.7 vs. 0.2; aHR = 23.19; 95% CI: 3.27–164.55), and respiratory disease (IR = 7.4 vs. 3.9; aHR, 2.22; 95% CI: 1.28–3.87), but not from cardiovascular disease (IR = 22.7 vs. 19.6; aHR = 1.10; 95% CI: 0.84–1.45). Results remained robust across sensitivity analyses, including sibling comparisons.

Conclusions: Individuals with achalasia had a 42% increased mortality rate compared with the general population. The elevated mortality risk indicates a need for long-term follow-up.

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DOI: 10.1016/j.cgh.2025.02.011 ■

Celiac Disease, Gluten Sensitivity and Food Allergy

United European Gastroenterol J. 2025;13(7):1107-1115

Vujasinovic M, Blazevic N, Maisonneuve P, Forss A, Panic N, Bloch N, Dominguez Munoz JE, Ludvigsson JF, Löhr JM

Pancreatic exocrine insufficiency is not uncommon in celiac disease: A systematic review and meta-analysis

Introduction: Pancreatic exocrine insufficiency (PEI) is seen in primary pancreatic disease but has also been seen in extrapancreatic conditions including celiac disease (CeD). The symptoms of PEI and CeD often overlap, which makes diagnostics challenging. In this systematic review and meta-analysis, the authors aimed to investigate the prevalence of PEI in CeD.

Methods: With the assistance of a professional librarian, they searched five databases: PubMed, Embase, Cochrane, Web of Science Core Collection, and Google Scholar, up until October 21, 2024. The pooled prevalence of PEI in biopsy-confirmed CeD was estimated, and the quality of studies appraised.

Results: The authors identified and screened the titles and abstracts of 1432 publications, of which 60 were reviewed in full text and 12 were included in the analyses. The overall pooled weighted prevalence of PEI in CeD was 13.5% (95% CI: 7.2–21.0). The prevalence was similar among children (14.2%; 95% CI: 2.0–32.8) and adults (12.8%; 95% CI: 7.8–18.7) with CeD. The prevalence in studies that used secretory testing to define PEI was 13.1% (95% CI: 6.4–21.3) and in those requiring digestive tests 17.1% (95% CI: 5.8–32.1). The weighted prevalence of PEI was significantly higher among untreated CeD patients (18.2%) than patients on a gluten-free diet (6.9%) (p = 0.03), in both adults and children.

Conclusion: One in eight individuals with CeD may suffer from PEI. The prevalence was particularly high in untreated CeD. PEI should be considered in patients who do not respond to a gluten-free diet.

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DOI: 10.1002/ueg2.70076 ■

Reflux

Clin Gastroenterol Hepatol. 2025;23(13):2459-2467

Prakash Gyawali C, Rogers BD, Yadlapati R, Roman S, Carlson DA, Pandolfino J

pH impedance monitoring on proton pump inhibitor therapy impacts management decisions in proven GERD but not in unproven GERD

Background and aims: Ambulatory reflux monitoring off proton pump inhibitors (PPIs) is useful in unproven

gastroesophageal reflux disease (GERD). In this prospective clinical trial, the authors evaluated if on-PPI pH-impedance monitoring provides value in unproven GERD.

Methods: Patients with typical reflux symptoms with incomplete PPI response were studied both off-PPI (wireless pH monitoring) and on-PPI (pH-impedance monitoring) at two tertiary care centers. Patients and investigators were blinded to reflux testing findings, and patients were asked to self-resume PPI for uncontrolled symptoms despite rescue antacids. Data analysis determined if on-PPI pH-impedance findings correlated with off-PPI acid exposure time (AET) or influenced PPI-related decision making.

Results: Of 79 patients, all 26 (32.9%) with refractory GERD metrics on-PPI had proven GERD off-PPI. In 60 patients with proven GERD off-PPI, 56.7% had no ongoing GERD on-PPI. No on-PPI pH-impedance findings predicted PPI decision making among conclusive, borderline, or no reflux ($p = 0.872$); AET ($p = 0.107$); reflux episodes numbers ($p = 0.113$); mean nocturnal baseline impedance ($p = 0.621$); and reflux-symptom association categories ($p = 0.363$). In multivariable linear and logistic regression models, off-PPI AET modestly predicted refractory GERD (odds ratio [OR] = 1.34; 95% confidence interval [CI]: 1.11-1.63; $p = 0.003$), and reflux episode numbers were borderline in predicting conclusive GERD off-PPI (OR = 1.00; 95% CI: 1.00-1.10; $p = 0.04$).

Conclusions: A minority of symptomatic patients will have refractory GERD evidence on pH-impedance monitoring on PPI; this strategy risks missing over half of the cohort with proven GERD if testing off-PPI is unavailable. These findings support documenting GERD off-PPI first in PPI nonresponders and restricting on-PPI pH-impedance monitoring to identify refractory GERD only in patients with proven GERD with persisting symptoms.

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EoE

Clin Gastroenterol Hepatol. 2025;23(12):2144-2154.e6

Biedermann L, Schlag C, Straumann A, Lucendo AJ, Miehle S, Vieth M, Santander C, Ciriza de Los Rios C, Schmöcker C, Madisch A, Hruz P, Hayat J, von Arnim U, Bredenoord AJ, Schubert S, Halstead M, Pfurr S, Mueller R, Schoepfer AM, Attwood S; International EOS-2 Study Group

Efficacy and safety of budesonide orodispersible tablets for eosinophilic esophagitis up to 3 years: An open-label extension study

Background and aims: Budesonide orodispersible tablets (BOT) have been shown to be safe and effective in phase 3 double-blind trials of induction and 48-week maintenance therapy of eosinophilic esophagitis (EoE). The authors now analyzed the long-term efficacy and

safety of BOT in a 96-week open-label extension (OLE) study.

Methods: All patients with EoE in the 48-week double-blind maintenance study were eligible to receive BOT treatment for up to 96 weeks. Dosage was 0.5 or 1.0 mg BOT, twice daily, at investigator's discretion. Clinical, histologic, endoscopic, quality of life, and safety measures were assessed.

Results: A total of 186 patients participated in the OLE up to 96 weeks. At week 96, 81.9% of patients had clinical remission, defined as an EoE Symptom Activity Index (EEsAI) score of ≤ 20 vs. 77.7% at OLE baseline. A further 80.1% of patients were in histologic remission, defined as peak eosinophils per high-power field of < 5 , at week 96 vs. 91.8% at OLE baseline. Mean EoE endoscopic reference scores (EREFS) were 1 at all time points measured. Mean EoE Quality of Life (EoE-QoL-A) Scale scores improved from 3.3 at OLE baseline to 3.5 at week 96. No new safety concerns were observed across 96 weeks of treatment. Suspected symptomatic candidiasis occurred at similar rates to prior BOT studies and was predominantly mild and resolved with treatment.

Conclusions: Clinical and histologic remission of EoE could be maintained with BOT in a large majority of patients for up to 96 weeks, and for up to 144 weeks in patients with uninterrupted BOT therapy across all trials. No additional safety concerns were identified with long-term BOT treatment

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Clin Gastroenterol Hepatol. 2025;23(12):2155-2166.e5

Dellon ES, Katzka DA, Mikkada VA, Collins MH, Falk GW, Richmond CA, Terreri B, Thakur M, Boules M, Goodwin B, Hirano I

Long-term safety and efficacy of budesonide oral suspension for eosinophilic esophagitis: A 4-year, phase 3, open-label study

Background and aims: The authors investigated the long-term safety and efficacy of budesonide oral suspension (BOS) in eosinophilic esophagitis (EoE).

Methods: This study (SHP621-303) was a 4-year, phase 3, open-label study in patients with EoE who completed up to 52 weeks of BOS therapy in 2 preceding phase 3 studies. On the basis of treatment assignments in previous studies, patients were assigned to BOS-BOS or placebo-BOS groups. All patients received BOS 2.0 mg twice daily; dose reductions to once daily and interruptions were permitted. The safety and tolerability of BOS were primarily investigated, with exploratory efficacy endpoints also examined.

Results: Overall, 131 patients were included. BOS was well-tolerated, with no unexpected safety signals observed. Treatment-emergent adverse events (TEAEs) occurred in 76.3% of patients; most were mild/moderate in severity and unrelated to study drug. The most frequently reported BOS-related TEAEs included abnormal adrenocorticotropic hormone stimulation test results

(8.4%, 11/131; number of events [m] = 12) and adrenal insufficiency (2.3%, 3/131; m = 3). Esophageal candidiasis occurred in 3.1% of patients (4/131). The aforementioned TEAEs resolved in most patients. At month 48 of treatment, 50.0% and 58.3% of patients achieved/maintained a histologic response (≤ 6 and < 15 eosinophils per high-power field, respectively). The initial reduction (-3.6) in total EoE Endoscopic Reference Score from baseline to the first visit was maintained until month 48.

Conclusions: Long-term treatment with BOS was well-tolerated. Despite dosing changes/interruptions, approximately half of patients achieved/maintained a histologic response; initial improvements in endoscopic outcomes were maintained over 48 months.

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DOI: 10.1016/j.cgh.2024.12.024 ■

Barrett's Esophagus, Esophageal and Gastric Cancer

Am J Gastroenterol. 2025;120(11):2520-2528

Skef W, Haydel J, Rao A, Allencherril R, George R, Ketwaroo GA, Thrift AP, El-Serag HB, Nguyen Wenker T

High risk of persistence and risk of dysplasia after diagnosis of ultrashort Barrett's esophagus

Introduction: The management of ultrashort (< 1 cm) Barrett's esophagus (BE) remains unclear. The study aimed to determine the prevalence of ultrashort BE (USB) at index diagnosis, identify factors associated with persistent BE after USB diagnosis, and identify risk of dysplasia after initial USB in a population of US veterans.

Methods: This was a retrospective cohort study at the Veterans Affairs hospital in Houston, TX, of consecutive patients with new BE diagnosis from November 1990 to June 2022 with follow-up through April 2023. Using a pathology database, the authors identified patients with a new USB diagnosis and any subsequent follow-up esophagogastroduodenoscopy (EGD). They examined the association of sociodemographic and clinical risk factors of persistent USB cohort compared with longer-length segment BE and those with a negative follow-up EGD after index USB with χ^2 tests and logistic regression models. Last, they calculated the prevalence and incidence of any dysplasia in persistent BE after USB at index diagnosis compared with BE ≥ 1 cm. Patients without at least 1 follow-up endoscopy were excluded.

Results: Of 739 patients with BE, 167 (22.6%) had USB on index EGD. Of those with index USB, 86 (51.5%) had persistent BE and 67 (40.1%) had negative intestinal metaplasia on follow-up EGD. There was a greater proportion of non-Hispanic White and Hispanic than non-Hispanic Black patients with persistent BE after index USB and the negative follow-up of EGD cohorts

($p = 0.012$), but no significant difference in age, sex, smoking status, alcohol status, and body mass index between the 2 groups. White race (adjusted odds ratio [aOR] = 3.80; 95% confidence interval [CI]: 1.35-10.7) and Hispanic ethnicity (aOR = 4.85; 95% CI: 1.19-19.7; ref: non-Hispanic Black) were associated with an increased likelihood of persistent BE. During 3,880.7 person-years of follow-up, 112 patients (10 persistent BE after index USB) developed definite dysplasia/neoplasia. The incidence rate of definite dysplasia/neoplasia was 19.5 per 1,000 person-years (95% CI: 10.5-36.3 per 1,000 person-years) in those with persistent BE after USB and 33.8 per 1,000 person-years (95% CI: 27.9-41.1 per 1,000 person-years) in those with longer segment BE (p value by log-rank test = 0.23; hazard ratio = 0.67; 95% CI: 0.35-1.29). The authors did not identify any significant predictors of dysplasia in persistent BE after index endoscopy with USB.

Discussion: The prevalence of persistent BE after index USB is high, and there is a risk of developing dysplasia/neoplasia in persistent BE after USB. The authors were unable to detect a difference in the risk of dysplasia/neoplasia between persistent BE after index USB and BE ≥ 1 cm on index endoscopy in a cohort of US veterans. White race and Hispanic ethnicity are associated with persistent BE after index USB and may be target demographics for surveillance.

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DOI: 10.14309/ajg.0000000000003383 ■

J Clin Oncol. 2025;43(29):3152-3159

Shitara K, Rha SY, Wyrwicz L, Oshima T, Karaseva N, Osipov M, Yasui H, Yabusaki H, Afanasyev S, Park YK, Al-Batran SE, Yoshikawa T, Yanez P, Pietrantonio F, Lonardi S, Fang X, Guan Y, Valderrama A, Leconte P, Bhagia P, Bang YJ; KEYNOTE-585 Investigators

Pembrolizumab plus chemotherapy versus chemotherapy as perioperative therapy in locally advanced gastric and gastroesophageal junction cancer: Final analysis of the randomized, phase 3 KEYNOTE-585 study

The authors report results of the final analysis of overall survival (OS) and patient-reported outcomes from the phase 3 KEYNOTE-585. Participants with previously untreated, locally advanced, resectable gastric and gastroesophageal junction (G/GEJ) cancer were enrolled into the main ($n = 804$) and fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT; $n = 203$) cohorts, and randomly assigned 1:1 to neoadjuvant and adjuvant pembrolizumab plus chemotherapy or placebo plus chemotherapy. The primary end points were pathologic complete response (pathCR) by central review, event-free survival (EFS) by investigator, OS, and safety. Patient-reported outcomes was an exploratory end point. After a median follow-up of 59.9 months (range, 39-76), median OS was 71.8 versus 55.7 months (hazard ratio [HR] = 0.86 [95% CI: 0.71-1.06]) with pembrolizumab plus chemotherapy versus placebo plus chemo-

therapy in the main cohort. The EFS HR was 0.81 (95% CI: 0.67–0.98). Grade \geq 3 drug-related adverse event rates were 65% versus 63%. Perioperative pembrolizumab plus chemotherapy did not worsen health-related quality of life versus placebo. Pembrolizumab plus chemotherapy continued to show improved outcomes in pathCR and a trend toward longer EFS versus placebo in the main and main plus FLOT cohorts. Efficacy and safety outcomes with perioperative pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab in participants with untreated, locally advanced resectable G/GEJ cancer were consistent with previous analyses.

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DOI: 10.1200/jco-25-00486 ■

EDITORS' CHOICE



Endoscopic surveillance of Barrett's esophagus put into question: The BOSS study showed no benefit of regular surveillance endoscopies in patients with Barrett's esophagus. ■

Gastroenterology. 2025;169(6):1233-1243.e8



Old O, Jankowski J, Attwood S, Stokes C, Kendall C, Rasdell C, Zimmermann A, Massa MS, Love S, Sanders S, Deidda M, Briggs A, Hapeshi J, Foy C, Moayyedi P, Barr H; BOSS Trial Team

Barrett's oesophagus surveillance versus endoscopy at need study (BOSS): A randomized controlled trial

Background and aims: Barrett's esophagus (BE) is a precursor lesion for esophageal adenocarcinoma (EAC). Surveillance endoscopy aims to detect early malignant progression; although widely practiced, it has not previously been tested in a randomized trial.

Methods: BOSS (Barrett's Oesophagus Surveillance Versus Endoscopy at Need Study) was a randomized controlled trial at 109 centers in the United Kingdom. Patients with BE were randomized to 2-yearly surveillance endoscopy or "at-need" endoscopy, offered for symptoms only. Follow-up was a minimum of 10 years. The primary outcome was overall survival in the intention-to-treat population. Secondary outcomes included cancer-specific survival, time to diagnosis of EAC, stage of EAC at diagnosis, frequency of endoscopy, and serious adverse events related to interventions.

Results: There were 3,453 patients recruited; 1,733 patients were randomized to surveillance and 1,719 to at-need endoscopy. Median follow-up time was 12.8 years for the primary outcome. There was no evidence of a difference in overall survival between the surveillance arm (333 deaths among 1,733 patients) and the at-need arm (356 deaths among 1,719 patients; hazard ratio [HR] = 0.95; 95% CI: 0.82–1.10; stratified log-rank p = 0.503). There was no evidence of a difference for surveillance versus at-need endoscopy in cancer-specific survival (108 vs. 106 deaths from any cancer; HR = 1.01; 95% CI: 0.77–1.33; p = 0.926), time to diagnosis of EAC (40 vs. 31 patients had a diagnosis of EAC; HR = 1.32; 95% CI: 0.82–2.11; p = 0.254), or cancer stage at diagno-

sis. Eight surveillance patients (0.46%) and 7 at-need patients (0.41%) reported serious adverse events.

Conclusions: Surveillance did not improve overall survival or cancer-specific survival. At-need endoscopy may be a safe alternative for low-risk patients.

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DOI: 10.1053/j.gastro.2025.03.021 ■

Gastroenterology. 2025;169(6):1244-1252.e7

Deidda M, Old O, Jankowski J, Attwood S, Stokes C, Kendall C, Rasdell C, Zimmermann A, Massa S, Love S, Sanders S, Hapeshi J, Foy C, Briggs A, Barr H, Moayyedi P; BOSS Trial Team

Cost-effectiveness of regular surveillance versus endoscopy at need for patients with Barrett's esophagus: Economic evaluation alongside the Barrett's Oesophagus Surveillance Study (BOSS) randomized controlled trial

Background and aims: The Barrett's Oesophagus Surveillance Study (BOSS) was the first randomized study of surveillance. This study reports the costs and quality of life outcomes from the BOSS trial and models the outcomes and cost-effectiveness of surveillance beyond the follow-up period of the BOSS study. This trial showed similar stages and rates of esophageal cancer in both arms, but the regular surveillance arm did identify more high-grade dysplasia after a median of 12.8 years follow-up.

Methods: The authors used a decision tree model based on results from BOSS to conduct a cost-effectiveness analysis of costs and quality-adjusted life years (QALYs). A Markov model was used to extrapolate costs and outcomes over a further 10 years after the trial had ended, representing a 22.8-year time horizon. The proportion with high-grade dysplasia and QALYs was derived from the randomized trial.

Results: The total costs associated with 2-yearly surveillance was \$5,309 vs. \$3,182 in the at-need arm. Total QALYs in the 2-yearly endoscopy arm were 8.647 compared with 8.629 in the at-need arm. Compared with at-need endoscopy, 2-yearly surveillance costs \$115,563/QALY gained. In the sensitivity analyses around assumptions on the proportion of high-grade dysplasia that is undetected in the at-need endoscopy arm, surveillance had an incremental cost effectiveness ratio of \$94,513/QALY for the best-case and \$146,272/QALY for the worst-case scenario.

Conclusion: Barrett's esophagus surveillance every 2 to 3 years is unlikely to be a cost-effective strategy. Guidelines should take this into account when deciding on surveillance intervals.

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DOI: 10.1053/j.gastro.2025.04.026 ■



Prof. Dr. Michael Quante

Less is more? BOSS Study evaluates endoscopic surveillance in Barrett's esophagus

To date, the BOSS study (Barrett's Esophagus Surveillance Study) is the largest and methodologically strongest randomized study to examine whether regular endoscopic surveillance in non-dysplastic Barrett's esophagus (NDBE) provides clinically relevant benefits. In this multicenter UK study, 3,452 patients from 109 centers were observed over a median period of 12.8 years and randomly assigned to either 2-yearly surveillance endoscopy or a symptom-based "endoscopy at need" strategy. In the surveillance arm, significantly more esophago-gastroduodenoscopies (EGD) were performed (6,124 vs. 2,424), and dysplastic changes were detected more frequently. However, no advantages were found for either the primary or secondary clinical endpoints: Overall survival and cancer-specific survival did not differ between the two strategies. There was no significant difference in the incidence of esophageal adenocarcinoma (EAC), and the tumor stage at diagnosis remained comparable. The annual progression rate from NDBE to EAC was only -0.23% per year, confirming a very low absolute risk. Overall, 19.2% of patients in the surveillance arm and 20.7% in the control arm died, clearly missing the primary endpoint of demonstrating a survival benefit. Although Barrett's esophagus is traditionally considered an important risk factor for EAC, the question is also whether the Barrett's finding alone represents the central risk—or whether other, often overlooked factors deserve greater emphasis. There is growing evidence suggesting that chronic inflammation (GERD), obesity, metabolic factors, biliary reflux exposure, and genetic clonal alterations in the mucosa contribute significantly to cancer development and have greater impact on individual risk than the Barrett's diagnosis itself. In clinical practice, this means that instead of using Barrett's status as the sole basis for surveillance decisions, a comprehensive, multifactorial risk assessment should be performed, considering inflammatory burden, lifestyle factors, and molecular markers.

The BOSS study was accompanied by a health economic modeling exercise to evaluate the BOSS data over a period of almost 23 years (12.8 years of follow-up plus 10 years of model projection). The surveillance strategy resulted in significantly higher costs while generating only a minimal increase in quality-adjusted life years (QALYs). The total cost per patient was US\$5,309 compared to US\$3,182 in the "endoscopy at-need" group, while the additional health benefit was extremely low. The ratio of additional costs to additional benefits is thus well above what is generally considered efficient or acceptable in healthcare systems, demonstrating that close surveillance is not cost-effective under the given assumptions.

Overall, the clinical and economic analyses convey a consistent message: Routine 2-yearly surveillance endoscopy for NDBE does not improve survival, reduce tumor incidence, or lead to earlier-stage detection, but results in markedly higher endoscopic burden and significantly higher costs, while the absolute risk of progression remains very low.

Given this background, the key question is how the findings of the BOSS study should be translated into clinical practice. The accompanying editorial emphasizes the ethical principle *primum non nocere* and underscores that the procedural, psychological, and financial burdens associated with routine surveillance are disproportionate to a survival benefit that has not been demonstrated. This is especially true for patients with non-dysplastic Barrett's esophagus, exhibiting a very low progression rate but relevant competing mortality risks. For these individuals, routine, frequent endoscopic monitoring is difficult to justify.

The data support taking a critical look at current surveillance strategies and applying them in a more nuanced way. For patients with short-segment Barrett's esophagus, advanced age, limited treatment options, or no additional risk factors, symptom-driven approaches or substantially longer surveillance intervals may be clinically reasonable and ethically appropriate. At the same time, the findings highlight the need for more precise risk stratification: While intensive surveillance has shown no benefit for low-risk patients, uncertainty remains for those with longer Barrett's segments, confirmed low-grade dysplasia, a family history of the disease, or other risk factors. In these cases, ongoing surveillance and endoscopic therapy remain justified but should be implemented in a structured, quality-controlled, and targeted manner.

In conclusion, the current evidence does not suggest abandoning surveillance altogether. Instead, it supports a shift towards a more individualized, risk-adapted, and resource-conscious approach that fully acknowledges the very low absolute risk of progression and the lack of a survival benefit in many patients. ■

Nutrition and Obesity

N Engl J Med. 2025;393(18):1796-1806

Wharton S, Aronne LJ, Stefanski A, Alfaris NF, Ciudin A, Yokote K, Halpern B, Shukla AP, Zhou C, Macpherson L, Allen SE, Ahmad NN, Klise SR; ATTAIn-1 Trial Investigators

Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment

Background: Orforglipron, a small-molecule, nonpeptide oral glucagon-like peptide-1 (GLP-1) receptor agonist, is being investigated as a treatment for obesity.

Methods: In this phase 3, multinational, randomized, double-blind trial, the authors examined the safety and efficacy of once-daily orforglipron at doses of 6 mg, 12 mg, or 36 mg, as compared with placebo (assigned in a 3:3:3:4 ratio) as an adjunct to healthy diet and physical activity for 72 weeks. All the patients had obesity without diabetes mellitus. The primary end point was the percent change in body weight from baseline to week 72, as assessed according to the treatment-regimen estimand in the intention-to-treat population.

Results: A total of 3,127 patients underwent randomization. The mean change in body weight from baseline to week 72 was -7.5% (95% confidence interval [CI]: -8.2 to -6.8) with 6 mg of orforglipron, -8.4% (95% CI: -9.1 to -7.7) with 12 mg of orforglipron, and -11.2% (95% CI: -12.0 to -10.4) with 36 mg of orforglipron, as compared with -2.1% (95% CI: -2.8 to -1.4) with placebo ($p < 0.001$).

for all comparisons with placebo). Among the patients in the orforglipron 36-mg group, 54.6% had a reduction of 10% or more, 36.0% had a reduction of 15% or more, and 18.4% had a reduction of 20% or more, as compared with 12.9%, 5.9%, and 2.8% of the patients, respectively, in the placebo group. Waist circumference, systolic blood pressure, triglyceride levels, and non-HDL cholesterol levels significantly improved with orforglipron treatment as compared with placebo. Adverse events resulted in treatment discontinuation in 5.3% to 10.3% of the patients in the orforglipron groups and in 2.7% of those in the placebo group. The most common adverse events with orforglipron were gastrointestinal effects, which were mostly mild to moderate.

Conclusions: In adults with obesity, 72-week treatment with orforglipron led to significantly greater reductions in body weight than placebo; the adverse-event profile was consistent with that of other GLP-1 receptor agonists.

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Gastritis and *Helicobacter pylori*

Am J Gastroenterol. 2025;120(11):2644-2659

Casas Deza D, Alcedo J, Lafuente M, López FJ, Perez-Aisa Á, Pavoni M, Tepes B, Jonaitis L, Castro-Fernandez M, Pabón-Carrasco M, Keco-Huerga A, Vynovan I, Bujanda L, Lucendo AJ, Brglez Jurecic N, Denkovski M, Vologzanina L, Rodrigo L, Martínez-Domínguez SJ, Fadieienko G, Huguet JM, Abdulkhakov R, Abdulkhakov SR, Alcaide N, Velayos B, Hernández L, Bordin DS, Gasbarrini A, Kupcinskas J, Babayeva G, Gridnyev O, Leja M, Rokkas T, Marcos-Pinto R, Lerang F, Boltin D, Mestrovic A, Smith SM, Venerito M, Boyanova L, Milivojevic V, Douberis M, Kunovsky L, Parra P, Cano-Català A, Moreira L, Nyssen OP, Megraud F, Morain CO, Gisbert JP; Hp-EuReg investigators

Probiotics prescribed with *Helicobacter pylori* eradication therapy in Europe: Usage pattern, effectiveness, and safety. Results from the European Registry on *Helicobacter pylori* Management (Hp-EuReg)

Introduction: To evaluate the prescription patterns, effectiveness, and safety of adding probiotics to *Helicobacter pylori* eradication therapy, in Europe. **Methods:** International, prospective, noninterventional registry of the clinical practice of the European gastroenterologists. Data were collected and quality reviewed until March 2021 at AEG-REDCap. The effectiveness was evaluated by modified intention-to-treat analysis, differentiating by geographic areas. Adverse events (AEs) were categorized as mild, moderate, and severe. **Results:** Overall, 36,699 treatments were recorded, where 8,233 (22%) were prescribed with probiotics. Probiotics use was associated with higher effectiveness in the overall analysis (odds ratio [OR] = 1.631,

95% confidence interval [CI]: 1.456–1.828), as well as in triple (OR = 1.702, 95% CI: 1.403–2.065), quadruple (OR = 1.383, 95% CI: 0.996–1.920), bismuth quadruple (OR = 1.248, 95% CI: 1.003–1.554), and sequential therapies (OR = 3.690, 95% CI: 2.686–5.069). *Lactobacillus* genus was associated with a higher therapy effectiveness in Eastern Europe when triple (OR = 2.625, 95% CI: 1.911–3.606) and bismuth quadruple (OR = 1.587, 95% CI: 1.117–2.254) first-line therapies were prescribed. In Central Europe, the use of probiotics was associated with a decrease in both the overall incidence of AEs (OR = 0.656, 95% CI: 0.516–0.888) and severe AEs (OR = 0.312, 95% CI: 0.217–0.449). *Bifidobacterium* genus was associated with lower overall (OR = 0.725, 95% CI: 0.592–0.888) and severe (OR = 0.254, 95% CI: 0.185–0.347) AEs, and *Saccharomyces* was associated with reduced overall (OR = 0.54, 95% CI: 0.32–0.91) and severe (OR = 0.257, 95% CI: 0.123–0.536) AEs under quadruple-bismuth regimen.

Discussion: In Europe, the use of probiotics was associated with higher effectiveness and safety of *H. pylori* eradication therapy. *Lactobacillus* improved treatment effectiveness, whereas *Bifidobacterium* and *Saccharomyces* were associated with a better safety profile.

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EDITORS' CHOICE



After myocardial infarction, the risk of gastrointestinal bleeding is increased. It has therefore been speculated whether routine *Helicobacter* testing with urease tests could reduce this risk. However, this large Swedish study of 18,466 patients with myocardial infarction found no such risk. Hence, routine *Helicobacter* testing is not useful in patients with myocardial infarction. ■

JAMA. 2025;334(13):1160-1169

Hofmann R, James S, Sundqvist MO, Wärme J, Angerås O, Alfredsson J, Erlinge D, Arefalk G, Arstad G, Blomberg S, Fröbert O, Hambræus K, Hellström PM, Lauer mann J, Lidin M, Lindhagen L, Mourtzinis G, Schoede C, Thunström E, Voldberg B, Wagner H, Östlund O, Jernberg T, Bäck M

Helicobacter pylori screening after acute myocardial infarction: The cluster randomized crossover HELP-MI SWEDEHEART trial

Importance: Upper gastrointestinal bleeding is common after myocardial infarction.

Objective: To determine whether routine screening for *Helicobacter pylori* infection during hospitalization for myocardial infarction reduces bleeding events and improves clinical outcomes.

Design, setting, and participants: A nationwide, open-label, 2-period, 2-sequence, cluster randomized, crossover clinical trial using a clinical registry for study population definition and data collection merged with national Swedish health data registries. From

November 17, 2021, through January 17, 2024, thirty-five Swedish hospitals grouped into 18 clusters were randomized to a sequence of 1 year with routine *H. pylori* screening of all patients with acute myocardial infarction followed by a washout period of 2 months before crossing over to 1 year with usual care or vice versa. Patients were followed up until January 17, 2025.

Intervention: Routine addition of *H. pylori* screening by urea breath test to standard care in all patients hospitalized for myocardial infarction during the screening periods.

Main outcome and measure: Upper gastrointestinal bleeding, analyzed by a negative binomial model in the intention-to-treat population.

Results: A total of 18,466 patients (median age, 71 years [IQR, 61–79], 13,138 males [71%]) with myocardial infarction were followed up: 9,245 during the screening periods and 9,221 during the nonscreening periods. At admission, 2,284 during the screening periods and 2,275 during the nonscreening periods (both 24.7%) reported proton pump inhibitor use. During screening periods, 6,480 patients (70%) had undergone testing, of those 1,532 (23.6%) tested positive for *H. pylori*. After a median follow-up of 1.9 years, 299 patients in the screening group (incidence rate, 16.8 events per 1,000 person-years; cumulative hazard at 3 years, 4.1%) and 336 in the usual care group (incidence rate, 19.2 events per 1,000 person-years; cumulative hazard at 3 years, 4.6%) experienced the primary end point of upper gastrointestinal bleeding (rate ratio [RR] = 0.90; 95% CI: 0.77–1.05; *p* = 0.18). Predefined nonmultiplicity adjusted subgroup analyses showed a heterogeneous intervention effect; for no anemia (RR = 0.98; 95% CI: 0.80–1.21), mild anemia (RR = 0.64; 95% CI: 0.42–0.98), and moderate to severe anemia (RR = 0.44; 95% CI: 0.23–0.87; *p* for interaction = 0.03).

Conclusions and relevance: Among unselected patients with acute myocardial infarction, routine *H. pylori* screening did not significantly reduce the risk of upper gastrointestinal bleeding.

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Upper and Middle Gastrointestinal Bleeding

JAMA Intern Med. 2025;185(10):1194-1203

Prosty C, Noutsios D, Dubé LR, Baden R, Davar K, Freling S, Bhuket T, Yee HF, Jr., Spellberg B, McDonald EG, Lee TC

Prophylactic antibiotics for upper gastrointestinal bleeding in patients with cirrhosis: A systematic review and Bayesian meta-analysis

Importance: International guidelines recommend 5 to 7 days of antibiotic prophylaxis for patients with cirrhosis and upper gastrointestinal bleeding. However,

the evidence for this recommendation has not been reassessed recently.

Objective: To determine whether current evidence continues to support the recommended 5 to 7 days of antibiotic prophylaxis in patients with cirrhosis and upper gastrointestinal bleeding.

Data sources: Searches were performed of the Embase, Medline, and Central databases for randomized clinical trials (RCTs) from inception to September 25, 2024. The search query included the keywords gastrointestinal bleeding and prophylactic antibiotics.

Study selection: Included RCTs compared longer durations of antibiotic prophylaxis to shorter durations (or 0 days) in patients with cirrhosis and upper gastrointestinal bleeding. Observational and pediatric studies, gray literature, comparisons of systemic antibiotics, studies not reporting mortality or early rebleed, and studies of nonsystemic antibiotics were excluded.

Data extraction and synthesis: Data were extracted in duplicate by independent reviewers. Study quality was assessed in duplicate using the Cochrane Risk of Bias 2 tool. Data were pooled by random-effects Bayesian meta-analyses using a noninformative prior for the effect and a weakly informative prior for heterogeneity. To account for therapeutic advancements, a post hoc subgroup analysis was performed for studies published after 2004.

Main outcomes and measures: The primary outcome was all-cause mortality with a prespecified 5% noninferiority margin on the risk difference (RD) scale. Early rebleed and bacterial infections were secondary outcomes.

Results: The analysis included 14 RCTs totaling 1,322 participants (mean age range, 41.5–62.0 years; 981 male [74.2%] individuals), of whom 1,202 (90.9%) had a variceal source of bleeding. Study quality was low to moderate, bacterial infections were heterogeneously defined, and no studies reported adverse events. Two RCTs compared longer (5–7 days) to shorter (2–3 days) durations and 12 RCTs compared any prophylaxis (1–10 days) to none. Shorter durations (including none) had a 97.3% probability of noninferiority for all-cause mortality (RD, 0.9%; 95% credible interval [95% CrI]: -2.6 to 4.9). Shorter durations had a 73.8% probability of noninferiority for early rebleeding (RD, 2.9%; 95% CrI: -4.2 to 10.0) but were associated with more study-defined bacterial infections (RD, 15.2%; 95% CrI: 5.0–25.9). The probabilities of noninferiority of shorter durations for all 3 outcomes were higher in studies published after 2004.

Conclusions and relevance: The findings of this systematic review and Bayesian meta-analysis do not support the purported mortality benefit driving guideline recommendations for antibiotic prophylaxis in patients with cirrhosis and upper gastrointestinal bleeds. Although prophylaxis reduced reported infections, methodological concerns regarding infection definitions introduced high risk of bias. Higher-quality RCTs are needed to determine the benefit and optimal duration of antibiotic prophylaxis in the modern era of advanced interventions. Until these studies are available, clinicians should be aware that the current guideline recommendations are not based on high-quality evidence.

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Hemostatic powder after primary hemostasis in non-variceal upper gastrointestinal bleeding: The application of hemostatic powder following endoscopic hemostasis significantly reduced early (3 days) and late (30 days) rebleeding rates in a randomized trial. ■

Gut. 2025;74(11):1821-1827

Shin J, Cha B, Hong J, Kwon KS, Lee E, Maeng JH, Chung JW, Park DK, Kim YJ, Kwon KA, Kim JH, Seo KS, Hong SJ, Kim KO

Prevention of rebleeding after primary haemostasis using haemostatic powder in nonvariceal upper gastrointestinal bleeding: A multicentre randomised controlled trial

Background: Nonvariceal upper gastrointestinal bleeding (NVUGIB) remains a major cause of morbidity and mortality. Rebleeding rates following endoscopic treatment can reach up to 25% within 72 hours in patients with high-risk lesions.

Objective: To evaluate the efficacy of a haemostatic powder in reducing rebleeding rates after conventional endoscopic treatment in patients with NVUGIB.

Design: This was a prospective, multicentre, randomised controlled trial involving patients with acute NVUGIB from high-risk lesions who achieved initial endoscopic haemostasis. Participants were randomised 1:1 to receive either the haemostatic powder or no further therapy (control group). The primary outcome was the rebleeding rate within 72 hours post-treatment. Secondary outcomes included the 30-day rebleeding rate and the safety profile.

Results: A total of 341 patients (72.1% male; mean age 64.8 years) were included, with 173 in the powder group and 168 in the control group. Baseline characteristics were similar between groups. Ulcer bleeding was the predominant aetiology (n = 317), with Forrest type I bleeding observed in two-thirds of cases. The 72-hour rebleeding rate was significantly lower in the powder group (2.9%, 95% CI: 0.9–6.6%) compared with the control group (11.3%, 95% CI: 6.9–17.1%; p = 0.005). A significant reduction was also observed in the 30-day cumulative rebleeding rate (7.0% vs. 18.8%), with similar findings in the ulcer subgroup for the 3-day rebleeding rate (3.0% vs. 12.0%; p = 0.004). No adverse events related to the powder application were reported.

Conclusion: The application of haemostatic powder following endoscopic haemostasis significantly reduced both early (3 days) and late (30 days) rebleeding rates in patients with NVUGIB, particularly in cases of ulcer-related bleeding.

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Gastroenterology. 2025;169(7):1462-1474.e2

Aharoni-Frutkoff Y, Plotkin L, Pollak D, Livovsky J, Focht G, Lev-Tzion R, Ledder O, Assa A, Yogev D, Orlanski-Meyer E, Broide E, Kierkuś J, Kang B, Weiss B, Aloï M, Schwerd T, Shouval DS, Bramuzzo M, Griffiths AM, Yassour M, Turner D

Whole food diet induces remission in children and young adults with mild to moderate Crohn's disease and is more tolerable than exclusive enteral nutrition: A randomized controlled trial

Background and aims: Tasty&Healthy (T&H) is a whole food diet for Crohn's disease (CD) that excludes processed food, gluten, red meat, and dairy, without requiring formula or mandatory ingredients. TASTI-MM was a clinician-blinded, randomized controlled trial comparing tolerability and effectiveness of T&H versus exclusive enteral nutrition (EEN).

Methods: Patients with biologic-naïve mild to moderate CD and aged 6–25 years were randomized to either T&H or EEN for 8 weeks, receiving weekly dietary support. Tolerability was evaluated by weekly interviews, questionnaires, and intake diaries. Other outcomes included symptomatic remission, Mucosal-Inflammation Noninvasive index, calprotectin, C-reactive protein, and erythrocyte sedimentation rate. Fecal microbiome was analyzed by metagenomics at baseline, week 4, and week 8. Data were analyzed by the intention-to-treat approach unless specified otherwise.

Results: Among 83 included patients (n = 41 T&H, n = 42 EEN; mean ± SD age, 14.5 ± 3.7 years), 88% tolerated T&H versus 52% for EEN (adjusted odds ratio [aOR] = 7.7; 95% CI: 2.4–25; p < 0.001). Calprotectin, C-reactive protein, and erythrocyte sedimentation rate decreased significantly in both groups, with no between-group differences. Symptomatic remission was achieved in 56% of the T&H group versus 38% of the EEN group (aOR = 2.5; 95% CI: 0.98–6.3; p = 0.1; per-protocol: 67% vs. 76%; p = 0.47). Calprotectin < 250 µg/g was achieved in 34% versus 33% (aOR = 0.97; 95% CI: 0.37–2.6; p = 0.84) and Mucosal-Inflammation Non-invasive index score < 8 in 44% versus 31% (aOR = 1.8; 95% CI: 0.7–4.5; p = 0.33). Microbiome α-diversity improved in the T&H arm and declined in the EEN arm, showing superior species richness at both week 4 and week 8. Species associated with bowel inflammation, such as *Ruminococcus gnavus*, decreased in T&H and increased in EEN (q < 0.001).

Conclusions: T&H demonstrated better tolerability than EEN for inducing remission in mild to moderate CD, while positively affecting the microbiome.

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Endoscopy of the Upper GI Tract

Endoscopy. 2025;57(11):1185-1194

Chen S, Li Y, Wang H, Chen M, Wang C, Pan W, Ma J, Ji T, Hong J, Hu D, Sheng X, Jiang J, Wang S

A novel artificial intelligence-based system for quality monitoring during esophagogastroduodenoscopy: A multi-center randomized controlled study

Background: Esophagogastroduodenoscopy (EGD) is the pivotal procedure for diagnosis of upper gastrointestinal (UGI) lesions. However, significant variation in EGD performance among endoscopists impacts detection rates of UGI cancers and precursor lesions. The authors developed a novel EGD quality monitoring system and evaluated its effectiveness in a randomized controlled study.

Methods: The endoscopy quality control assistant (EQCA) was developed using deep convolutional neural networks and long short-term memory. Patients (≥ 18 years) undergoing EGD in seven hospitals were consecutively enrolled and randomly assigned to the EQCA-assisted group or control group. The primary outcome was the detection rate for cancer-related lesions (low- and high-grade intraepithelial neoplasia and cancer) and cancer (early and advanced cancer) in the UGI tract.

Results: After randomization and exclusions, 16,005 patients in the control group and 16,012 in the EQCA group were analyzed. Detection rates for UGI cancer-related lesions and cancer were significantly higher in the EQCA group than in the control group (8.00% vs. 5.55%; 1.93% vs. 1.21%; both $p < 0.001$). The EQCA group had a higher operation score, reflecting examination quality, and longer inspection time than the control group. The detection rate for UGI cancer-related lesions was positively correlated with operation score ($r = 0.9217$, $p < 0.001$) and inspection time ($r = 0.8943$, $p < 0.001$) for each hospital.

Conclusions: The use of EQCA during EGD was associated with increased detection of UGI cancer and precancerous lesions. This novel EQCA system can be an effective tool for monitoring real-time EGD quality.

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Gut. 2025;74(12):1989-1994

Welsch L, Friedrich-Rust M, Tal A, Haider N, Kim S, Schneider M, Schmitt L, Wittersheim L, Schmitt S, Heide A, Heilani M, Zeuzem S, Eickhoff A, Michael FA

Cutting waste in endoscopy: A multicentre observational study in the German health-care system

Background: Endoscopic procedures are a notable source of medical waste, contributing significantly to environmental pollution. Prior studies report 0.5–3.0 kg

of waste per procedure—compared with just 1.2 kg of household waste generated per person per day in Germany.

Objective: To quantify endoscopic waste in hospitals and outpatient settings, assess its impact on the health-care system and identify strategies for reduction.

Design: This prospective, multicentre, observational study was conducted over 4 weeks in two tertiary hospitals and two gastroenterology offices. Waste from 2,275 patients across 2,889 procedures was collected, sorted, weighed and categorised for recyclability. National waste generation from GI endoscopy was estimated using published insurance data.

Results: The average waste per procedure was 1,119 g (hospitals: 1,167 g; offices: 1,094 g). Office-based procedures produced significantly less waste than their hospital counterparts—by 51% for oesophagogastroduodenoscopy (EGD), 50% for colonoscopy, 47% for combined procedures and 69% for sigmoidoscopy (all $p < 0.001$). Performing consecutive procedures reduced waste by up to 39% for EGD and colonoscopy, and 33% for endoscopic ultrasound and endoscopic retrograde cholangiopancreatography. Switching from single-use to reusable gowns could reduce personal protective equipment waste by 54%. Overall, 23% of waste was potentially recyclable. Nationally, GI endoscopy generates an estimated 8,024 tonnes of waste annually—equivalent to the yearly household waste of 18,533 German citizens.

Conclusion: The waste generated by endoscopy per year in Germany rivals that of a small town. Adopting targeted waste reduction strategies—focusing on prevention, reduction, reuse, recycling and recovery—can substantially mitigate the environmental footprint of endoscopic practice.

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Gut. 2026;75(1): 24-32

Bang JY, Puri R, Lakhtakia S, Thakkar S, Waxman I, Siddiqui I, Arnold K, Chaudhary A, Mehta S, Singh A, Venkat Rao G, Basha J, Gupta R, Modak S, Singh S, Boone B, Dautel P, Dixon MEB, Kim HM, Sutton B, Arnoletti JP, Rösch T, Varadarajulu S

Endoscopic or surgical gastroenterostomy for malignant gastric outlet obstruction: A randomised trial

Background: Although surgical gastrojejunostomy (SGJ) is the standard method for palliation of gastric outlet obstruction (GOO), an endoscopic method—endoscopic ultrasound-guided gastroenterostomy (EUS-GE)—has been proposed as a novel, less invasive approach.

Objective: The authors compared both methods to determine whether clinical outcomes for EUS-GE are superior to surgery.

Design: They conducted a multicentre, randomised superiority trial of patients with malignant GOO to receive either EUS-GE or SGJ. Primary endpoint was

composite measure, consisting of Gastric Outlet Obstruction Scoring System (GOOSS) score of 0 or 1 at hospital discharge, need for reinterventions or supplemental nutrition, or procedure-related adverse events during 6-month follow-up or until death. Secondary endpoints were time to solid diet, length of hospitalisation, health-related quality of life (HRQoL) and treatment costs.

Results: 74 patients were randomly assigned to EUS-GE (38 patients) or SGJ (36 patients). Primary endpoint occurred in 7.9% of patients who received EUS-GE and 38.9% in SGJ (risk difference, -31.0%, 95% CI: -47.6% to -11.4%, $p = 0.002$). EUS-GE was associated with more rapid advancement to solid diet (median 2 days [P25-P75, 2-3] vs. 5 days [P25-P75, 3.5-9]), shorter hospitalisation (median 3 days [P25-P75, 3-6] vs. 9 days [P25-P75, 6-12.5]), better HRQoL for physical ($p = 0.0016$) and social functioning ($p = 0.011$) and lower treatment costs (US\$33,934 vs. US\$51,437, difference, -US\$17,503 [95% CI: -US\$27,807 to -US\$7,920]).

Conclusion: In this randomised trial, EUS-GE was superior to SGJ with regards to oral intake, need for reinterventions or supplemental nutrition, length of hospitalisation, quality of life and treatment costs.

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Lancet Gastroenterol Hepatol. 2025;10(12):1065-1074

van de Pavert YL, Kastelijan JB, Besselink MG, Booi DC, Boonstra JJ, Boot J, Bruno MJ, Busch OR, Daams F, Derksen WJM, Fockens P, Groot Koerkamp B, Hagendoorn J, van Hooft JE, Inderson A, Lammers WJ, Lips DJ, Mieog JSD, Molenaar IQ, Veenhof AAFA, Venneman NG, Verdonk RC, Voermans RP, van Wanrooij RLJ, Welsing PMJ, de Wijkerslooth TR, Moons LMG, van Santvoort HC, Vleggaar FP; Dutch Pancreatic Cancer Group

Endoscopic versus surgical gastroenterostomy for palliation of malignant gastric outlet obstruction (ENDURO): A randomised controlled trial

Background: In patients with malignant gastric outlet obstruction, endoscopic ultrasonography-guided gastroenterostomy might be superior to surgical gastroenterostomy, but randomised trials are scarce. The trial aimed to assess time to resumption of oral intake and the rate of persistent or recurrent obstructive symptoms requiring re-intervention following endoscopic ultrasonography-guided gastroenterostomy compared with surgical gastroenterostomy.

Methods: ENDURO was a multicentre, randomised controlled trial conducted at 12 Dutch academic and teaching hospitals. Hospitals with experience in at least 20 LAMS placements of any indication, at least ten endoscopic gastroenterostomies, and approved competence were eligible to perform endoscopic gastroenterostomy independently within the trial. Adults aged 18 years and older with symptomatic, malignant gastric outlet obstruction in a palliative setting were randomly

assigned (1:1) to endoscopic or surgical gastroenterostomy. Randomisation was performed with an electronic data capture system using randomly generated permuted blocks of 2 and 4 and stratified by WHO performance status (0-1 and 2-3). The first coprimary outcome was time to resumption of solid oral intake (Gastric Outlet Obstruction Scoring System score ≥ 2). The second coprimary outcome was non-inferiority for persistent or recurrent obstructive symptoms requiring re-intervention. The predefined non-inferiority margin of the risk difference was 20%. All outcomes were analysed in all randomly assigned participants.

Findings: Between February 18, 2022, and February 26, 2024, 250 patients were screened, 98 of whom were randomly assigned to endoscopic gastroenterostomy ($n = 48$) or surgical gastroenterostomy ($n = 50$). 43 (44%) patients were female and 55 (56%) were male. Endoscopic gastroenterostomy had a shorter time to solid oral intake than surgical gastroenterostomy (median 1 day [IQR, 1-3] vs. 3 days [1-6], hazard ratio = 2.21 [95% CI: 1.43-3.42]; $p = 0.0003$). Endoscopic gastroenterostomy was non-inferior to surgical gastroenterostomy for persistent or recurrent obstructive symptoms requiring re-intervention (5 [10%] vs. 6 [12%], risk difference 1.6% [upper limit of 90% CI: 8.9]). Overall adverse events were reported in 28 (58%) patients in the endoscopic gastroenterostomy group and 32 (64%) in the surgical gastroenterostomy group (relative risk = 0.91 [95% CI: 0.66-1.25]). One fatal event occurred in the endoscopic gastroenterostomy group and three fatal events occurred in the surgical gastroenterostomy group.

Interpretation: In patients with malignant gastric outlet obstruction, palliative treatment with endoscopic gastroenterostomy was superior to surgical gastroenterostomy for time to resumption of solid oral intake and was non-inferior for the rate of persistent or recurrent obstructive symptoms requiring re-intervention. Based on these results, endoscopic gastroenterostomy should be the preferred palliative treatment for patients with malignant gastric outlet obstruction.

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EXPERT OPINION



PD Dr. Armin Küllmer

Endoscopic gastroenterostomy: On the way to becoming the standard for malignant gastric outlet obstruction

Malignant gastric outlet obstruction is a severe complication of oncological diseases that markedly impairs patients' quality of life. In addition to the established standard of surgically created gastroenterostomy, obstruction may be treated endoscopically using duodenal stents, as well as endoscopic ultrasound-guided gastroenterostomy (EUS-GE), a procedure used with increasing

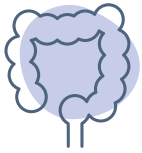
popularity in recent years. A high-impact study published in 2025 (Teoh et al., doi: 10.1016/S2468-1253(25)00136-0) demonstrated the superiority of EUS-GE over endoscopic duodenal stenting. The 2 studies discussed below now address the highly relevant question of how EUS-GE compares with surgically created gastroenterostomy in patients with malignant gastric outlet obstruction. Both randomized controlled trials—the ENDURO trial conducted in the Netherlands and the GOOSE trial conducted predominantly in the United States with participation from India and Germany—had a similar study design. The evaluated end points focused on clinically relevant outcomes, namely time to resumption of oral intake, the need for reintervention, and occurrence of complications. In simplified terms, the key question can be phrased as follows: does EUS-GE effectively relieve symptoms, and is this effect durable.

The answer is clearly affirmative. In both studies, EUS-GE showed advantages with regard to the aforementioned end points, with the ENDURO trial designed as a non-inferiority study. These findings now confirm, with substantially higher-quality evidence, the results of previous retrospective analyses.

The rapid resumption of oral intake after successful EUS-GE and the short length of hospital stay are well-known clinical observations and can be readily explained by the less invasive nature of the procedure. EUS-GE does not require pneumoperitoneum or suturing, and while a surgical anastomosis must be created at its final diameter, EUS-GE requires only a small, transmural opening—approximately 3.5 mm—between the stomach and small intestine for stent deployment. For most patients, the modest time advantage in resuming oral intake compared with surgical gastroenterostomy is unlikely to be clinically decisive; similarly, the initiation of systemic therapy did not differ significantly between treatment groups.

More surprising is the lower reintervention rate observed over a follow-up period of up to 6 months. In the palliative setting of this patient population, this represents a clinically meaningful time frame. A longer follow-up would likely not have been informative given the high disease-related mortality.

Does this mean that EUS-GE is on its way to becoming the new standard of care? For centers with appropriate expertise, both trials provide strong arguments in favor of selecting an endoscopic approach as first-line therapy and potentially establishing it as the preferred standard. Nevertheless, the procedure remains technically demanding, and management of complications can be complex. Careful patient selection and substantial expertise in interventional endoscopic ultrasound are therefore essential to ensure safe and successful implementation. ■



COLON TO RECTUM

Ulcerative Colitis, Crohn's Colitis

EDITORS' CHOICE



This population-based study from Denmark reveals an alarmingly high frequency of chronic opioid use in patients with Crohn's disease (27.4%) or ulcerative colitis (22.3%). ■

Am J Gastroenterol. 2025;120(11):2632-2643

Mertz Nørgård B, Thingholm Thorarinsson C, Nielsen J, Dalal RS, Andersen ML, Lund K, Friedman S, Knudsen T, Kjeldsen J

Predictors for chronic opioid use in patients with inflammatory bowel disease: A population-based cohort study

Introduction: A significant proportion of patients with Crohn's disease (CD) and ulcerative colitis (UC) become opioid users, but data pertaining to predictors of chronic opioid use remain sparse. The authors examined predictors for chronic opioid use in CD/UC.

Methods: This is a nationwide cohort study based on Danish registries, comprising incident patients with CD/UC (≥ 18 years) from January 1, 1996, to December 31, 2021. Chronic opioid use was defined as ≥ 1 prescriptions in at least 2 of 3 consecutive quarters. Cox regression models were used to estimate adjusted hazard ratios for predictors for chronic opioid use. Several variables and time-varying covariates (inflammatory bowel disease surgery, inflammatory bowel disease, and psychotropic medications) were included.

Results: In 15,092 patients with CD, 4,141 (27.4%) became chronic opioid users (median follow-up 7.35 years, 25–75% percentiles [interquartile range], 3.40–13.66 years). The 3 most important predictors were surgery (4.20, 95% confidence interval [CI]: 3.72–4.75), hypnotics/sedatives (2.02, 95% CI: 1.81–2.25), and age ≥ 50 years (1.92, 95% CI: 1.77–2.09). In 30,416 patients with UC, 6,777 (22.3%) became chronic users (median follow-up 8.80 years, interquartile range, 4.20–15.22 years). The 3 most important predictors were surgery (4.81, 95% CI: 4.20–5.52), age ≥ 50 years (2.62, 95% CI: 2.44–2.82), and hypnotics/sedatives (2.11, 95% CI: 1.95–2.29).

Discussion: An alarming proportion of patients became chronic opioid users. These results are helpful to risk stratify patients to prevent chronic opioid use. Clinicians should be particularly attentive in patients who have had surgery, who use hypnotics/sedatives, and who are elderly. The authors need evidence regarding pain management strategies, efficacy of nonopioid analgesics, and opioid cessation strategies.

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Ben Hur D, Issaschar G, Moshe R, Lebedenko B, Lujan R, Haklai Z, Loewenberg Weisband Y, Ben-Tov A, Lederman N, Matz E, Dotan I, Turner D, Pinto GD, Waterman M

Risk of age-related and disease-related complications and mortality in elderly-onset inflammatory bowel disease: A population-based study

Background and aims: In this nationwide cohort from Israel (Epi-IIRN), the authors aimed to characterize risks for age-related complications, mortality, and inflammatory bowel disease (IBD)-related surgeries in patients with elderly-onset IBD (EO-IBD).

Methods: Data of patients with EO-IBD (≥ 65 years) diagnosed during 2005 to 2020 were retrieved from the epi-IIRN database. Patients with EO-IBD were compared with 3 age-, sex-, and district-matched non-IBD individuals, for age-related outcomes. Patients with incident EO-IBD were matched to 4 adult-onset (AO) IBD (≥ 18 –65 years) by IBD subtype, sex, and district. Cumulative incidence functions were calculated to estimate event probabilities over time, accounting for death as a competing risk. Proportional subdistribution hazards models were used to assess predictors of medication use, surgery, and complications.

Results: Of 2,826 EO-IBD cases, 2,162 had 3 matched non-IBD controls. Mortality rates per 1,000 person-years (PY) were similar in EO-IBD and non-IBD controls (292.32; 95% confidence interval [CI]: 273.53–311.85 vs. 291.24; 95% CI: 280.31–302.42, respectively) as were mortality causes and risk for pneumonia (adjusted hazard rate [aHR] = 1.04; 95% CI: 0.84–1.29), fractures (aHR, 1.03; 95% CI: 0.82–1.29), bacteremia (aHR = 2.16; 95% CI: 0.87–5.40), and thromboembolism (aHR = 0.58; 95% CI: 0.27–1.23). When matching 2,826 patients with EO-IBD to 11,304 patients with AO-IBD, the EO-IBD group had lower exposure to thiopurines (aHR = 0.44; 95% CI: 0.39–0.49) and anti-tumor necrosis factor (TNF) (aHR = 0.37; 95% CI: 0.32–0.42) and higher risk for abdominal surgery (aHR = 1.23; 95% CI: 1.04–1.46) in Crohn's disease [CD]; aHR = 1.51; 95% CI: 2.04–3.08 in ulcerative colitis [UC], respectively) but lower perianal surgery risk (hazard ratio [HR] = 0.27; 95% CI: 0.16–0.47) in CD. The calculated frequencies of repeat perianal and abdominal surgery in the EO-CD and AO-CD groups at 3 years were 7.1% and 36%, respectively, and 29% and 21%, respectively.

Conclusions: Compared with non-IBD elderly, patients with EO-IBD have similar risks for death and complications. Compared with AO-IBD, patients with EO-IBD are at higher risk for abdominal surgery, but not for perianal surgery.

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Granot M, Kopylov U, Talmor Y, Nachum N, Krauthammer A, Berger T, Abitbol CM, Dotan A, Borenstein E, Ben-Horin S, Weiss B, Haberman Y

Elderly-onset inflammatory bowel disease has distinct disease characteristics and treatment patterns

Background and aims: Elderly-onset inflammatory bowel disease (IBD) patients (age ≥ 60 at diagnosis) have unique characteristics that require special consideration. Using a real-life registry-based cohort, the authors compared disease phenotypes and treatment exposures between adult-onset (18 \leq age < 60 years) and elderly-onset IBD patients.

Methods: Demographics, disease characteristics, and treatment were compared between adult- and elderly-onset IBD patients diagnosed during 2000–2022 with ≥ 12 months follow-up.

Results: Of 3,307 adult IBD patients, 290 (9%) were elderly-onset. This group exhibited a higher prevalence of colon-only involvement, with higher rates of ulcerative colitis (UC, 38.3% vs. 31.4%, $p = 0.02$) and more colonic L2 Crohn's Disease (CD, 21% vs. 12%, $p < 0.001$) than adult-onset group. Elderly-onset CD also showed less ileocolonic L3 disease (14% vs. 29%, $p < 0.001$), less penetrating B3 phenotype (7.4% vs. 19%, $p < 0.001$), and less perianal involvement (10% vs. 20%, $p < 0.001$). Elderly-onset CD and UC patients received more 5-ASA (36% vs. 17%, $p < 0.001$ in CD and 75% vs. 63%, $p = 0.02$ in UC). In contrast, these patients were exposed to considerably less biologics and/or JAK inhibitors (37% vs. 56% for CD and 20% vs. 35% for UC, $p < 0.001$), with higher 15-year biologic-free survival among elderly-onset IBD. First-line biological choices also substantially differed, with adult-onset receiving more anti-TNFs and elderly-onset receiving more vedolizumab. The authors did not observe higher rates of IBD-related surgeries and steroid use between the groups.

Conclusions: Elderly-onset IBD shows higher prevalences of colon-only IBD (UC and L2 CD). Treatment strategies in elderly-onset IBD favor 5-ASA and show reduced biological use, with preferences for vedolizumab over anti-TNFs.

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EXPERT OPINION



Prof. Dr. Peter Hasselblatt

Inflammatory bowel disease (IBD) in older adults: An often underestimated challenge

The prevalence of inflammatory bowel disease (IBD) among older adults (> 60 years) is steadily increasing.

It is estimated that by 2030, approximately one-third of patients treated in specialized IBD practices will belong to this age group. This population includes, on the one hand, patients with longstanding IBD diagnosed in childhood or adulthood who often experience chronic and complex disease courses. On the other hand, IBD is newly diagnosed in approximately 5% of patients older than 60 years, a condition referred to as elderly onset IBD (EO-IBD). The treatment of older patients with IBD is obviously challenging because of increased risks of infection, higher rates of adverse events related to immunosuppressive therapies, frequent comorbidities, and potential drug interactions due to polypharmacy. Many aspects of caring for aging IBD patients were recently summarized in an excellent review (Singh et al., *Lancet Gastro. Hepatol.* 2023;8(4):368-382; [https://doi.org/10.1016/S2468-1253\(22\)00358-2](https://doi.org/10.1016/S2468-1253(22)00358-2)). It is often assumed that the disease course of EO-IBD patients may be less complicated and therefore requires less advanced therapy. However, in the cited review, the disease course in EO-IBD is by no means considered less serious than that of patients diagnosed at a younger age. Moreover, EO-IBD is associated with a higher likelihood of long-term and potentially harmful corticosteroid therapy. However, the available data on the manifestation and clinical course of EO-IBD are limited, and this subgroup is clearly underrepresented in clinical trials. Some of these aspects are addressed by 2 Israeli studies focusing on EO-IBD. In the evaluation of a large IBD cohort from a tertiary center, Granot et al. compared disease progression in 290 patients with EO-IBD with that in 2,068 patients with adult onset disease (ages 18–60 years). Patients with EO-IBD were significantly more likely to develop IBD in the colon (diagnosis of ulcerative colitis or Crohn's colitis), while the risk of penetrating disease or perianal fistulas was significantly lower. Patients with EO-IBD and Crohn's disease were significantly more likely to be treated with mesalamine, which is ineffective for Crohn's disease. In addition, EO-IBD patients received significantly fewer prescriptions for biologics or Janus kinase inhibitors. EO-IBD patients treated with biologics were more likely to receive vedolizumab, while younger patients were more likely to be treated with tumor necrosis factor (TNF) antibodies. This study found no differences in the frequency of corticosteroid prescriptions or surgical procedures. In a nationwide registry study from Israel (Epi-IIRN), Ben Hur et al. evaluated outcomes in patients with EO-IBD, defined here as initial diagnosis at 65 years or older, compared with 3 matched control subjects without IBD in order to assess the impact of EO-IBD on mortality and severe complications. In this analysis of 2,162 EO-IBD patients, mortality and specific risks for pneumonia, bone fractures, sepsis, and venous thrombosis were comparable to those of controls without IBD. However, this study also revealed significant differences in IBD therapy when comparing EO-IBD patients with 11,304 IBD patients diagnosed at an earlier age. On the one hand, EO-IBD patients received treatment with thiopurines or TNF antibodies significantly less often. On the other hand, abdominal surgery was performed slightly but significantly more often, with a 1.2-fold increased risk in Crohn's disease and a 1.5-fold increased risk in ulcerative colitis. Postoperatively, EO-IBD patients more frequently received corticosteroids, while postoperative TNF-antibody therapy was prescribed less often. The rate of repeat abdominal surgery within 3 years was also higher in EO-IBD patients (29% vs. 21%). In contrast, the risk of perianal (0.27-fold)

or perianal repeat surgery was significantly lower in EO-IBD patients. Both studies provide important information about EO-IBD. EO-IBD likely manifests more frequently in the colon, while penetrating Crohn's disease is less common. However, the reported therapies suggest that many patients with EO-IBD receive inadequate drug therapy due to concerns about adverse effects. Therefore, it is reassuring that the risk of severe infections and mortality in EO-IBD is not increased compared to the general population. These findings support the use of TNF inhibitors in selected older patients. The availability of vedolizumab, ustekinumab, and IL-23 antibodies also offers safe and well-tolerated treatment options. However, their effectiveness in older patients should be assessed in prospective registries in order to better address the anticipated demographic shift in IBD care. ■

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Danese S, Allegretti JR, Schreiber S, Peyrin-Biroulet L, Jairath V, D'Haens G, Kierkuś J, Leong RW, Yarur AJ, Vincent MS, Banerjee A, Chandra DE, Peeva E, Neelakantan S, Hung KE, McBride JM, Bojic D, Lasch K, Schiffman C, Feagan BG

Anti-TL1A antibody, afimkibart, in moderately-to-severely active ulcerative colitis (TUSCANY-2): A multicentre, double-blind, treat-through, multi-dose, randomised, placebo-controlled, phase 2b trial

Background: TNF-like ligand 1A (TL1A) is an emerging therapeutic target for inflammatory bowel disease. The authors evaluated the safety and efficacy of multiple doses of afimkibart, a TL1A-directed antibody, in patients with moderately-to-severely active ulcerative colitis. **Methods:** The multicentre, double-blind, treat-through, multi-dose, randomised, placebo-controlled, phase 2b, TUSCANY-2 trial was conducted at 114 centres in 23 countries across North America, Europe, Asia, Africa, Australia, and South America. Adults (aged 18–75 years) with moderately-to-severely active ulcerative colitis (total Mayo score [tMS] 6–12, endoscopic subscore ≥ 2) were randomly assigned (2:2:2:2:3:1:1) to one of nine treatment sequences to receive subcutaneous afimkibart 50 mg, 150 mg, 450 mg, or matched placebo every 4 weeks during the 12-week induction period, and subcutaneous afimkibart 50 mg, 150 mg, or 450 mg during the treat-through 40-week maintenance period. Investigators and patients were masked to treatment. Study drugs were administered by masked site personnel following preparation by an unmasked pharmacist at the investigational site. Efficacy was assessed at weeks 14 and 56 in the intent-to-treat populations. The primary efficacy endpoint of clinical remission at week 14 by tMS (defined as tMS ≤ 2 , with no individual subscore > 1) was assessed in those who received at least one dose of drug or placebo during induction, excluding patients who had missing data due to complications resulting from COVID-19. Safety endpoints were also analysed in those who were randomly assigned and received at least one dose of assigned treatment. **Findings:** Between December 19, 2019, and October 25, 2022, 246 patients were randomly assigned treatment, of whom 245 were treated, 228 completed induction, and 178 completed maintenance. Median age was 39 years

(IQR, 30.0–51.0), 99 (40%) patients were female and 146 (60%) were male; median disease duration was 4.7 years (IQR, 2.5–10.2). At week 14, the primary endpoint of clinical remission by tMS was reported in 12 (26%) of 47 patients in the afimkibart 50 mg group (risk difference vs. placebo [RD] 13.9% [90% CI: -0.2 to 27.7]; $p = 0.0545$), 14 (23%) of 60 patients in the afimkibart 150 mg group (RD 11.7% [-1.7 to 24.1]; $p = 0.0823$), and 21 (24%) of 88 patients in the in the afimkibart 450 mg group (RD 12.2% [-0.6 to 22.9]; $p = 0.0642$) versus five (12%) of 43 patients in the placebo group. In alignment with updated US Food and Drug Administration guidance, clinical remission using the modified Mayo score at week 14 was reported in 14 (30%) of 47 patients in the afimkibart 50 mg group (RD 18.2% [90% CI: 3.3–32.2]), 21 (35%) of 60 patients in the in the afimkibart 150 mg group (RD 23.4% [6.2–36.3]), and 28 (32%) of 88 patients in the in the afimkibart 450 mg group (RD 20.2% [3.2–31.3]) versus five (12%) of 43 patients in the placebo group. Overall, 117 (48%) of 245 patients in the induction phase and 132 (59%) of 224 patients in the maintenance phase reported at least one treatment-emergent adverse event; incidences of treatment-emergent adverse events during induction were similar with placebo and afimkibart. The most common treatment-emergent adverse events (occurring in $\geq 5\%$ of patients) during induction were nausea, urinary tract infection, ulcerative colitis, anaemia, fatigue, headache, and pyrexia. Six serious adverse events were reported during induction in the active treatment groups and four in the placebo group. Two patients who completed induction and did not receive the study drug during maintenance had serious adverse events during safety follow-up. During the maintenance period, 12 (5%) of 224 patients had 13 serious adverse events. No deaths occurred.

Interpretation: Differences in the primary endpoint of clinical remission by tMS were not significantly different for any dose of afimkibart compared with placebo. However, secondary endpoints suggest that afimkibart was associated with a favourable benefit-risk profile, with clinically meaningful improvements in clinical remission with the modified Mayo score for patients with moderately-to-severely active ulcerative colitis. These results support the continued development of afimkibart.

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Appendectomy is not associated with a milder clinical course of ulcerative colitis: A nationwide Danish population-based study

Background: Appendectomy may have a beneficial effect on the course of ulcerative colitis (UC), but the association remains debated. **Aim:** To examine if appendectomy influences the clinical course of UC.

Methods: The authors identified all patients diagnosed with UC in Denmark from 1977 to 2017 from the Danish National Patient Registry. Patients who underwent appendectomy were matched for age, sex, calendar year and disease duration with up to 10 comparators with UC and no appendectomy. They compared UC-related admission rates, rates of initiating treatment with biologics, and colorectal resection rates between patients with UC with and without appendectomy.

Results: 22,098 patients with UC (2014 with and 20,084 without appendectomy) were followed for a median 10.3 years (interquartile range, 5.1–18.5). Hospitalisation rates were higher for those who underwent appendectomy of a normal appendix after UC (IRR = 1.11 [95% CI: 1.01–1.22]) and for those who underwent appendectomy for appendicitis before UC (IRR = 1.22 [95% CI: 1.15–1.31]). Appendectomy performed for appendicitis after UC was associated with a higher rate of colorectal resections 5–20 years after appendectomy (aHR_{5–10 years} = 2.08 [95% CI: 1.03–4.17]), aHR_{10–20 years} = 3.25 (95% CI: 1.31–8.08) and 5–10 years after appendectomy if not performed for appendicitis (aHR = 2.51 [1.01–6.23]). Rates of initiating treatment with biologics were comparable between patients with and without prior appendectomy.

Conclusion: Patients with UC who underwent appendectomy did not experience a milder clinical course compared to those without appendectomy, regardless of underlying appendicitis.

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Macaluso FS, Fries W, Viola A, Cappello M, Melatti P, Mocchiari F, Scrivo B, Di Caro S, Muscarella S, Ferracane C, Giangreco E, Minissale MG, Grova M, Li Voti R, Mistretta G, Renna S, Casà A, Armetta S, Morello S, Orlando A; Sicilian Network for Inflammatory Bowel Disease

Switching to subcutaneous administration may offer more profound remission compared to intensified intravenous therapy in patients with inflammatory bowel disease and partial response following induction with intravenous vedolizumab: The PRIVEDO study

Background and aims: The optimal management of inflammatory bowel disease (IBD) patients with a partial response after intravenous (IV) vedolizumab (VDZ) induction remains unclear.

Methods: PRIVEDO was an observational, non-randomized, open-label, prospective cohort study conducted within the Sicilian Network for IBD. It compared subcutaneous (SC) VDZ (108 mg every 2 weeks) versus intensified IV VDZ (300 mg every 4 weeks) in Crohn's disease (CD) or ulcerative colitis (UC) patients with a partial response at Week 14 post-induction. Partial response was defined as: (1) clinical remission with fecal calprotectin > 250 µg/g and/or steroid use, or (2) a reduction in the Harvey-Bradshaw Index by ≥ 3 points (for CD) or in the Partial Mayo Score by ≥ 2 points (for UC) from baseline, without fulfilling clinical remission

criteria. The primary endpoint was steroid-free clinical remission with fecal calprotectin < 250 µg/g at Weeks 26 and 52. The secondary endpoints were clinical benefit (remission or partial response), regardless of calprotectin values, and treatment persistence.

Results: 107 patients were enrolled (CD: 58/107, 54.2%; UC: 49/107, 45.8%), allocated to SC (n = 52) or IV (n = 55) groups. The primary endpoint was met more often with SC VDZ at Week 26 (30/52, 57.7% vs. 14/55, 25.5%; p < 0.001; odds ratio [OR] = 3.57, p = 0.004 at multivariable analysis) and at Week 52 (25/52, 48.1% vs. 14/55, 25.5%; p = 0.016; OR = 3.05, p = 0.029 at multivariable analysis). Clinical benefit was also higher in the SC group at both timepoints, though not statistically significant. Treatment persistence was comparable between the 2 groups (log-rank test, p = 0.225).

Conclusions: In IBD patients with partial response to IV VDZ induction, switching to SC VDZ may lead to more profound remission than continuing IV optimization.

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Radia C, Danso Y, Ritchie S, Hale M, Elford AT, Patel C, Hicks L, Kalyanji S, Dong C, Yeung K, Yeo JH, Allah-Ditta M, Bishara M, Sethi-Arora K, Pillay L, Johnston EL, Rudling R, Rees F, Harvey P, Trodden-Mitnacht H, Davis E, Fraser A, Sawan NJ, Hussain MA, Campbell R, George B, Rawcliffe M, Choon XY, Shah K, Al-Zarrad D, Toft J, Chhabra P, Burr N, Hewitt A, Kumar R, McCartney S, Rosiou K, Dhar A, Lees CW, Lamb CA, Speight A, Ahmad T, Limdi J, Raine T, Walsh A, Cooney R, Harrow P, Patel K, Samaan M, Pavlidis P, Kent A, Selinger C, Kok KB

Is 2nd JAKi treatment for UC worth the effort? A retrospective, multicentre UK study

Background and aims: Janus kinase inhibitors (JAKi) provide effective treatment for ulcerative colitis (UC), but inadequate response (IR) or intolerance occurs frequently. This study aimed to assess the effectiveness of a second JAKi in a real-world UC cohort.

Methods: A retrospective multicentre cohort study encompassing 19 UK hospitals was undertaken. Primary outcome was clinical remission (Simple Clinical Colitis Activity Index/partial Mayo Score ≤ 1) at weeks 8 and 24, based on available assessments. Biochemical (CRP ≤ 5 mg/L and fecal calprotectin ≤ 200 µg/g) and endoscopic (Ulcerative Colitis Endoscopic Index of Severity/Mayo Endoscopic Subscore ≤ 1) remission were also assessed.

Results: A total of 131 patients with active UC were included. The majority (60%) had exposure to ≥ 3 advanced therapies and 50% required corticosteroids at induction. Clinical remission rates were 59% and 51% at weeks 8 and 24. Biochemical and endoscopic remission rates were 61% and 60% at week 8, and 47% and 32% at week 24. All disease activity parameters significantly reduced by week 8 (p < 0.001). At week 24 no difference was detected in clinical remission rates between

those with primary non-response (42%) or secondary loss of response (52%) to their first JAKi ($p = 0.518$). Clinical remission did not differ between upadacitinib (54%) and filgotinib (36%), $p = 0.253$. Adverse events occurred in 27% of patients, and serious adverse events in 8%.

Conclusions: In this highly refractory cohort with active UC a second JAKi effectively achieved remission following IR to first JAKi. Type of first JAKi failure did not appear to influence clinical remission. No new safety signals were found.

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Bourgonje AR, Andreu-Sánchez S, Gacesa R, Innocenti G, Kalka IN, Klompus S, Leviatan S, Schlesinger Y, Krongauz D, Weinberger A, van der Vegt B, Fu J, Segal E, Zhernakova A, Vogl T, Weersma RK

Crohn's disease and ulcerative colitis exhibit prediagnostic antibody signatures with shared and divergent changes towards disease onset

Background: The development of IBD is known to involve early immunological alterations, but the authors' understanding of the changes in antibody epitope repertoires moving from the prediagnostic phase towards disease onset remains incomplete.

Objective: In this study, the authors comprehensively characterised systemic antibody responses in patients with IBD before and after disease onset, aiming to identify prediagnostic disease biomarkers.

Design: Within Lifelines, a population-based cohort study collecting and storing longitudinal samples from 167,000 individuals over ~15 years, they identified 178 individuals with blood samples taken both before and after IBD-onset. In these prediagnosis and postdiagnosis serum samples (median time span 3.9 years), they profiled antibody epitope repertoires against 344,000 rationally selected microbial, food and immune antigens using phage-display immunoprecipitation sequencing.

Results: Postdiagnosis, the authors observe reduced antibody frequencies against herpesviruses, particularly for Epstein-Barr virus and varicella zoster virus, and elevated antibody frequencies against specific enteroviruses, including adenovirus C and enterovirus types B and C. Even before diagnosis, individuals who ultimately developed Crohn's disease (CD) displayed elevated antibody reactivity against flagellins of both commensal and pathogenic bacteria. This CD-specific profile became even more pronounced postdiagnosis, suggesting the formation of IBD-specific antibody responses years before disease onset.

Conclusion: This study is the first comprehensive high-resolution analysis of the exact antigenic nature of systemic antibody responses during the transition from prediagnostic to established IBD. The antibody signatures the authors found may represent a route to developing biomarkers that identify individuals at high risk of developing disease.

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How long is long enough? Timing of pre-conceptual remission predicts relapse risk during pregnancy in IBD

Background and aims: Inflammatory bowel disease (IBD) often coincides with pregnancy, and disease activity during pregnancy increases the risk of adverse outcomes. The study aimed to determine how disease course before conception influences relapse risk during pregnancy, adjusting for established risk factors.

Methods: In this multicenter, retrospective cohort study, the authors included adult women with IBD who were pregnant during treatment at one of three university hospitals between 2017 and 2022. Using generalized estimating equations, they evaluated associations between relapse during pregnancy and pre-conceptual flares, categorized into three time intervals. Analyses were adjusted for phenotype, disease duration, surgical history, biologic use, smoking, and assisted reproduction. Interaction analyses were conducted with matched non-pregnant women.

Results: The authors included 386 women (63.4% Crohn's disease, 36.6% ulcerative colitis) with 476 pregnancies. Pre-conceptual flares were significantly associated with relapse if they occurred < 3 months (adjusted odds ratio [aOR] = 5.289, 95% CI: 2.6-10.8, $p < 0.001$) or 3-6 months prior to conception (aOR = 2.910, 95% CI: 1.0-8.2, $p = 0.043$), but not 6-12 months prior (aOR = 1.636, 95% CI: 0.8-3.2, $p = 0.146$). Other predictors were not significantly associated with relapse. There was no significant interaction between pregnancy and pre-conceptual disease activity.

Conclusions: This large multicenter study demonstrates that disease activity within 6 months before conception significantly increases the risk of relapse during pregnancy in women with IBD. This study is the first to assess both the pre-conceptual disease course and a broad set of known risk factors in a real-world cohort.

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IBS, Functional and Motility Disorders

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Yang JW, Qi LY, Yan SY, She YF, Li Y, Chi LL, Hu H, Wang LQ, Ji CC, Wu BQ, Fu ZT, Li SJ, Yang NN, Wang Y, Liu CZ

Efficacy of Acupuncture in Irritable Bowel Syndrome (ACTION): A multicenter randomized controlled trial

Background and aims: Irritable bowel syndrome (IBS) affects 4.1% of the adult population, with many reporting ongoing symptoms despite first-line therapies. Acupuncture is widely used for IBS, but without sufficient evidence. This trial aimed to assess the efficacy of acupuncture in patients with diarrhea-predominant IBS (IBS-D).

Methods: This was a multicenter randomized controlled trial in 6 hospitals in China. Patients aged 18 to 75 years with IBS-D per Rome IV diagnostic criteria were randomly allocated (1:1) to receive 15 sessions of acupuncture or sham acupuncture (blunt-tipped needle at non-acu-points) over 6 weeks with a 12-week follow-up. The primary outcome was the composite response rate at week 6, defined as at least a 30% improvement in the mean worst abdominal pain and a 50% or more reduction in the number of days with diarrhea from baseline during week 6.

Results: Between May 2021 and August 2022, 584 patients were assessed for eligibility, of whom 280 were randomly allocated. The primary outcome was reached by 71 (57.9%) patients in the acupuncture group compared with 47 (41.4%) patients in the sham acupuncture group (risk ratio = 1.40; $p = 0.008$). The between-group difference became significant from week 3 and was maintained throughout the study except week 16. No severe adverse event was reported.

Conclusions: Acupuncture improved abdominal pain and stool consistency in patients with IBS-D, with sustained efficacy over 18 weeks. The results of this trial suggest that acupuncture may serve as an alternative treatment for IBS-D.

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Wang Y, Kuo B, Berschback M, Huttenhower C, Chan AT, Staller K

Dietary patterns and incident chronic constipation in three prospective cohorts of middle- and older-aged adults

Background and aims: Current literature on diet-constipation associations is limited by small sample sizes and cross-sectional designs. The study aimed to com-

prehensively examine the associations among 5 dietary patterns, their components, and incident constipation. **Methods:** In 3 large cohorts, the Nurses' Health Study (NHS), NHSII, and the Health Professional Follow-up Study, the authors identified chronic constipation based on repeatedly measured self-reported constipation symptoms for ≥ 12 weeks in the past year. They assessed long-term adherence to 5 dietary patterns (alternate Mediterranean diet [aMED], low-carbohydrate diet, Western diet) and indices (plant-based dietary index [PDI], empirical dietary inflammatory pattern) using validated quadrennial food frequency questionnaires. They used a log-binomial model adjusted for a wide range of confounders, including fiber or ultra-processed food intake, to estimate relative risk (95% confidence interval) for constipation.

Results: In the pooled cohort of 27,774 (78.4 ± 5.6 years) NHS, 55,906 (60.5 ± 4.6 years) NHSII, and 12,237 (78.6 ± 5.6 years) Health Professional Follow-up Study participants, the authors documented 7,519 incident constipation cases after 2 to 4 years of follow-up. Compared with the lowest quintiles, the top quintiles of aMED and PDI were associated with 16% (9–22%) and 20% (14–27%) reduced risk for constipation, whereas the top quintiles of empirical dietary inflammatory pattern, Western diet, and low-carbohydrate diet were associated with 24% (15–33%), 22% (11–33%), and 3% (-3% to 11%) increased risk for constipation, respectively. These associations were independent of total fiber or ultra-processed food intake. Vegetable and nut intake, which is enriched in aMED and PDI, was associated with decreased constipation risks.

Conclusion: These findings suggest that dietary patterns emphasizing plant-based foods and healthy fats may protect against constipation, informing future dietary interventions and treatments for chronic constipation.

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Colorectal Cancer Screening/Endoscopy

Am J Gastroenterol. 2025;120(10):2432-2439

Plys E, Bulliard JL, Chaouch A, Durand MA, van Duuren LA, Braendle K, Auer R, Froehlich F, Lansdorp-Vogelaar I, Corley DA, Selby K

Colorectal cancer screening based on predicted risk: A randomized controlled trial

Introduction: Colorectal cancer (CRC) screening relies primarily on colonoscopy and fecal immunochemical testing (FIT). Aligning utilization of these options with individual CRC risk may optimize benefit with lower risks, individual burden, and societal costs. The authors studied the effect of communicating personalized CRC risk and corresponding screening recommendations on risk-appropriate screening uptake in an organized screening setting.

Methods: Randomized controlled trial among residents aged 50–69 years not yet invited for screening in Vaud, Switzerland. The intervention was a mailed brochure communicating individual 15-year CRC risk and screening recommendation. The control group received a usual brochure comparing FIT and colonoscopy. The primary outcome was self-reported risk-appropriate screening (FIT if < 3% risk, FIT or colonoscopy if ≥ 3% and < 6%, and colonoscopy if ≥ 6%) at 6 months. A secondary outcome was overall screening uptake.

Results: Of 5,396 invitations, 1,059 people responded (19%) of whom 258 were randomized to intervention and 257 to control materials (average 15-year risk 1.4% [SD = 0.5], age 52.2 years [SD = 2.2], 51% women). Risk-appropriate screening completion was 37% in the intervention group and 23% in the control group (absolute difference 14%, 95% confidence interval 6–22%). Overall screening uptake was 50% in the intervention group and 49% in the control group (absolute difference 1%, 95% confidence interval: -7% to 10%).

Discussion: In a population not known to be at elevated CRC risk, brochures providing personalized CRC risk and screening recommendations improved risk-appropriate screening without impacting overall screening uptake. This approach could be helpful for aligning screening methods, risks, and benefits with cancer risk and resource allocation.

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Gut. 2025;74(11):1804-1813

Pohl H, Rex DK, Barber J, Moyer MT, Elmunzer BJ, Rastogi A, Gordon SR, Zolotarevsky E, Levenick JM, Ahsanian HR, Elatrache M, von Renteln D, Wallace MB, Brahmabhatt B, Keswani RN, Kumta NA, Pleskow DK, Smith ZL, Abu Ghanimeh MK, Simmer S, Sanaei O, Mackenzie TA, Piraka C

Cold snare endoscopic resection for large colon polyps: A randomised trial

Background: Complications of endoscopic mucosal resection (EMR) of large colorectal polyps remain a concern.

Objective: The trial aimed to compare safety and efficacy of cold EMR (without electrocautery) to hot EMR (with electrocautery) of large colorectal polyps.

Design: In this multicentre randomised trial, patients with any large (≥ 20 mm) non-pedunculated colon polyp were assigned to cold or hot EMR (primary intervention), and to submucosal injection with a viscous or non-viscous solution (secondary intervention) following a 2×2 design. The primary outcome was the rate of severe adverse events (SAEs). The secondary outcome was polyp recurrence. In this study, the authors report results of the primary intervention.

Results: 660 patients were randomised and analysed. An SAE was observed in 2.1% of patients in the cold EMR group and in 4.3% in the hot EMR group (p = 0.10) (per protocol analysis 1.4 vs. 5.0%, p = 0.017) with fewer perforations following cold EMR (0%) compared with hot EMR (1.6%, p = 0.028). Postprocedure bleeding did

not differ (1.5% vs. 2.2%, p = 0.57). The effect of cold resection was independent of the type of submucosal injection solution, polyp size or antithrombotic medications. Recurrence was detected in 27.6% and 13.6% in the cold and hot EMR groups, respectively (p < 0.001). Recurrence was not significantly different for 20–29 mm polyps (18.6% vs. 13.4%, p = 0.24) and for sessile serrated polyps (14.1% vs. 8.5%, p = 0.33).

Conclusion: Universal application of cold EMR did not significantly lower SAEs (unless cold EMR could be completed) and doubled the recurrence rate compared with hot EMR.

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Lancet Gastroenterol Hepatol. 2025;10(10):896-903

Budzyń K, Romańczyk M, Kitala D, Kołodziej P, Bugajski M, Adami HO, Blom J, Buszkiewicz M, Halvorsen N, Hassan C, Romańczyk T, Holme Ø, Jarus K, Fielding S, Kunar M, Pellise M, Pilonis N, Kamiński MF, Kalager M, Bretthauer M, Mori Y

Endoscopist deskilling risk after exposure to artificial intelligence in colonoscopy: A multicentre, observational study

Background: It is not known if continuous exposure to artificial intelligence (AI) changes endoscopists' behaviour when conducting colonoscopy. The authors assessed how endoscopists who regularly used AI performed colonoscopy when AI was not in use.

Methods: They conducted a retrospective, observational study at four endoscopy centres in Poland taking part in the ACCEPT (Artificial Intelligence in Colonoscopy for Cancer Prevention) trial. These centres introduced AI tools for polyp detection at the end of 2021, after which colonoscopies had been randomly assigned to be conducted with or without AI assistance according to the date of examination. The authors evaluated the quality of colonoscopy by comparing two different phases: 3 months before and 3 months after AI implementation. They included all diagnostic colonoscopies, excluding those involving intensive anticoagulant use, pregnancy, or a history of colorectal resection or inflammatory bowel disease. The primary outcome was change in adenoma detection rate (ADR) of standard, non-AI assisted colonoscopy before and after AI exposure. Multivariable logistic regression was done to identify independent factors affecting ADR.

Findings: Between September 8, 2021, and March 9, 2022, 1443 patients underwent non-AI assisted colonoscopy before (n = 795) and after (n = 648) the introduction of AI (median age 61 years [IQR, 45–70], 847 [58.7%] female, 596 [41.3%] male). The ADR of standard colonoscopy decreased significantly from 28.4% (226 of 795) before to 22.4% (145 of 648) after exposure to AI, corresponding with an absolute difference of -6.0% (95% CI: -10.5 to -1.6; p = 0.0089). In multivariable logistic regression analysis, exposure to AI (odds ratio = 0.69 [95% CI: 0.53–0.89]), male versus female patient sex (1.78 [1.38–2.30]), and patient age ≥ 60 years versus < 60 years (3.60 [2.74–4.72]) were the independent factors significantly associated with ADR.

Interpretation: Continuous exposure to AI might reduce the ADR of standard non-AI assisted colonoscopy, suggesting a negative effect on endoscopist behaviour.

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Gut. 2025;74(12):1995-2003

van der Schee L, Albers SC, Didden P, Lacle MM, Farina Sarasqueta A, Richir MC, Intven MPW, Tuijnman JB, Hompes R, Dekker E, Vleggaar FP, Bastiaansen BAJ, Moons LMG

Results of endoscopic intermuscular dissection for deep submucosal invasive rectal cancer: A three-year follow-up study

Background: Endoscopic intermuscular dissection (EID) is a promising new technique for managing rectal deep submucosal invasive cancer (D-SMIC), but long-term outcome data are currently lacking.

Objective: This multicentre study evaluated the three-year oncological outcomes of EID, focusing specifically on patients with rectal D-SMIC who underwent active surveillance following the procedure.

Design: Data from consecutive, prospectively recorded EID procedures for suspected rectal D-SMIC-based on optical diagnosis-performed at two academic centres between 2019 and 2023 were analysed. D-SMIC was defined as submucosal invasion of sm2-sm3 depth. Histological risk factors included poorly differentiated tumours (G3), lymphovascular invasion, high-grade tumour budding and positive or indeterminate resection margins (R1/Rx). Study outcomes included three-year rates of locoregional recurrence (intramural and nodal), distant recurrence (metastatic disease), non-salvageable recurrence, cancer-specific mortality and secondary rectal surgery. Cumulative incidence was estimated using the Aalen-Johansen method.

Results: Among the 188 included cases, EID achieved an en bloc resection rate of 94.1% and RO resection rate of 82.5%, respectively. Of the 177 procedures that were completed, 16% showed non-invasive histology (low-grade dysplasia/high-grade dysplasia; 20/177 = 11%) or superficial submucosal invasive cancer (sm1, 9/177 = 5%), and 31% (54/177) showed deeper (\geq pT2) invasion. The remaining 94 D-SMIC cases (53%) represented the main target group. Of these, 37% (n = 35) were classified as low risk (no histological risk factors), 34% (n = 32) as intermediate risk (one risk factor) and 29% (n = 27) as high risk (\geq 2 risk factors). Active surveillance was initiated in all low-risk patients, in 72% of the intermediate-risk cases and in 22% of the high-risk group. The remaining patients underwent completion surgery or adjuvant chemoradiotherapy. At three years, locoregional recurrence occurred in 7% (1/35, 95% CI: 1-28%) of low-risk and 13% (2/15, 95% CI: 2-35%) of intermediate-risk patients managed with active surveillance. All were successfully salvaged. Among the six high-risk patients under surveillance, locoregional recurrence was seen in two. No distant recurrences or cancer-specific deaths occurred in any D-SMIC group. Secondary rectal surgery was finally performed in 5.3%, 25.0% and 59.6% of the low, intermediate and high-risk groups, respectively.

Conclusion: Despite the challenges associated with accurate preoperative staging, EID followed by active surveillance may offer a viable alternative to radical surgery for patients with low- and intermediate-risk rectal D-SMIC, avoiding rectal surgery in most cases while maintaining oncological safety.

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Endoscopy. 2025;57(11):1243-1250

Kemper G, Turan AS, Schreuder RM, Schrauwen RWM, Hadithi M, Didden P, Bastiaansen BAJ, van der Spek BW, Teerhaar sive Droste JS, Schwartz MP, Hazen WL, Straathof JWA, Boonstra JJ, Alkhalaf A, Voogd FJ, Allajar D, de Graaf W, Koehestanie P, Roomer R, de Ridder RJJ, Moons LMG, Siersema PD, van Geenen EJM; Dutch EMR Study Group

The effect of prophylactic clipping on delayed bleeding after proximal colonic endoscopic mucosal resection: A multicenter, randomized controlled trial (CLIPPER)

Background: Delayed bleeding is the most common complication after endoscopic mucosal resection (EMR) of large colorectal polyps. Randomized controlled trials in high volume centers have suggested that prophylactic clipping of the resection defect reduces delayed bleeding in patients with a high risk for delayed bleeding. The trial aimed to evaluate the role of prophylactic clipping in reducing delayed bleeding in patients undergoing EMR for large, proximal, nonpedunculated polyps in daily clinical practice.

Methods: The authors performed a randomized controlled trial in 19 Dutch hospitals in patients referred for EMR of laterally spreading and sessile polyps \geq 20 mm in the proximal colon. Patients were randomly assigned (1:1) into groups receiving or not receiving prophylactic clipping. The primary end point was delayed bleeding, and analyses were performed according to intention-to-treat analysis.

Results: Between May 2018 and December 2021, 356 patients with a median polyp size of 30 mm (interquartile range, 25-40) in the proximal colon were randomized (177 to the prophylactic clipping group and 179 to the control group). Delayed bleeding occurred in 16 patients (9.0%) receiving prophylactic clipping and 11 control patients (6.1%; p = 0.30). No deaths were reported.

Conclusions: Prophylactic clipping did not reduce delayed bleeding in patients undergoing EMR for large laterally spreading and sessile polyps in the proximal colon in daily clinical practice.

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Colorectal Cancer

EDITORS' CHOICE



This is the first phase 3 trial to demonstrate a significant overall survival benefit from an immunotherapy-based regimen in patients with refractory or relapsed colorectal cancer that is not microsatellite instable or mismatch repair deficient. ■

Lancet. 2025;406(10517):2360-2370



Hecht JR, Park YS, Tabernero J, Lee MA, Lee S, Virgili AC, Van den Eynde M, Fontana E, Fakih M, Asghari G, So J, Stein A, Dubreuil O, Bodnar L, He CS, Wang G, Smith R, Eng C, Saeed A; STELLAR-303 study investigators

Zanzalintinib plus atezolizumab versus regorafenib in refractory colorectal cancer (STELLAR-303): A randomised, open-label, phase 3 trial

Background: Zanzalintinib is a multitargeted tyrosine-kinase inhibitor that, when combined with atezolizumab, showed promising antitumour activity and manageable toxicity in a phase 1 study. The study aimed to compare the efficacy and safety of zanzalintinib-atezolizumab versus regorafenib in patients with previously treated metastatic colorectal cancer.

Methods: STELLAR-303 is a global, randomised, open-label, phase 3 trial done at 121 centres (including hospitals, academic medical centres, and specialised cancer research facilities) in 16 countries. Patients aged 18 years and older with confirmed metastatic adenocarcinoma of the colon or rectum, who had previously received standard-of-care therapy, and did not have microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours were randomly assigned (1:1) in blocks of four to oral zanzalintinib (100 mg daily) plus intravenous atezolizumab (1200 mg every 3 weeks) or oral regorafenib (160 mg daily on days 1-21 of each 28-day cycle) using an interactive response technology system, stratified by geographical region, RAS status, and presence of liver metastases. Dual primary endpoints were overall survival in the intention-to-treat (ITT) population and in the subset of patients without liver metastases. Safety was assessed in all patients who received at least one dose of study drug. This report is based on a planned overall survival analysis (data cutoff April 30, 2025); the trial is active but not recruiting and continues to the final overall survival analysis in the subset of patients without liver metastases.

Findings: 1325 patients were screened for eligibility; between September 7, 2022, and July 15, 2024, 901 patients were randomly assigned to zanzalintinib-atezolizumab (n = 451) or regorafenib (n = 450). 528 (59%) patients were male and 373 (41%) were female; 485 (54%) were White, 338 (38%) were Asian, 18 (2%) were Black, 24 (3%) were other races, and 36 (4%) had race not reported. At a median follow-up of 18.0 months (IQR, 14.6–21.5), zanzalintinib-atezolizumab showed a significant overall survival benefit versus regorafenib in the ITT population (stratified hazard ratio [HR] = 0.80 [95% CI: 0.69–0.93]; p = 0.0045) with a median overall survival of 10.9 months (95% CI: 9.9–12.1) versus 9.4

months (8.5–10.2). At the interim analysis of overall survival in the subset of patients without liver metastases, the stratified HR for zanzalintinib-atezolizumab versus regorafenib was 0.79 (95% CI: 0.61–1.03); p = 0.087 (median overall survival 15.9 months [95% CI: 13.5–17.6] vs. 12.7 months [10.9–15.5]). Grade 3 or worse treatment-related adverse events occurred in 268 (60%) of 446 patients receiving zanzalintinib-atezolizumab and 161 (37%) of 434 patients receiving regorafenib. There were 5 (1%) treatment-related deaths in the zanzalintinib-atezolizumab group and one (< 1%) in the regorafenib group.

Interpretation: STELLAR-303 is the first phase 3 trial to show a significant improvement in overall survival with an immunotherapy-based regimen, zanzalintinib-atezolizumab, in patients with relapsed or refractory metastatic colorectal cancer that is not MSI-H or dMMR. This combination represents a chemotherapy-free treatment option with a novel mechanism of action for heavily pretreated patients in need of improved therapies.

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N Engl J Med. 2025;393(11):1051-1064

Martling A, Hed Myrberg I, Nilbert M, Grönberg H, Granath F, Eklund M, Öresland T, Iversen LH, Haapamäki C, Janson M, Westberg K, Segelman J, Ersson U, Prytz M, Angenete E, Bergström R, Mayrhofer M, Glimelius B, Lindberg J; ALASCCA Study Group

Low-dose aspirin for PI3K-altered localized colorectal cancer

Background: Aspirin reduces the incidence of colorectal adenoma and colorectal cancer among high-risk persons. Observational studies suggest that aspirin may also improve disease-free survival after diagnosis, particularly among patients with tumors harboring somatic *PIK3CA* mutations. However, data from randomized trials are lacking.

Methods: The authors conducted a double-blind, randomized, placebo-controlled trial involving patients with stage I, II, or III rectal cancer or stage II or III colon cancer with somatic alterations in PI3K pathway genes. The patients were assigned in a 1:1 ratio to receive 160 mg of aspirin or matched placebo once daily for 3 years. Patients with prespecified *PIK3CA* hotspot mutations in exon 9 or 20 (group A alterations) and those with other moderate- or high-impact somatic variants in *PIK3CA*, *PIK3R1*, or *PTEN* (group B alterations) were eligible for randomization. The primary end point was colorectal cancer recurrence, assessed in a time-to-event analysis, in patients with group A alterations. Secondary end points included colorectal cancer recurrence in patients with group B alterations, disease-free survival, and safety.

Results: Alterations in PI3K pathway genes were detected in 1,103 of 2,980 patients (37.0%) with complete genomic data. Of 515 patients with group A alterations and

588 patients with group B alterations, 314 and 312, respectively, were assigned to receive aspirin or placebo. The estimated 3-year cumulative incidence of recurrence was 7.7% with aspirin and 14.1% with placebo (hazard ratio [HR] = 0.49; 95% confidence interval [CI]: 0.24–0.98; $p = 0.04$) among patients with group A alterations and 7.7% and 16.8%, respectively (HR = 0.42; 95% CI: 0.21–0.83), among those with group B alterations. The estimated 3-year disease-free survival was 88.5% with aspirin and 81.4% with placebo (HR = 0.61; 95% CI: 0.34–1.08) among patients with group A alterations and 89.1% and 78.7%, respectively (HR = 0.51; 95% CI: 0.29–0.88), among those with group B alterations. Severe adverse events occurred in 16.8% of aspirin recipients and 11.6% of placebo recipients.

Conclusions: Aspirin led to a significantly lower incidence of colorectal cancer recurrence than placebo among patients with *PIK3CA* hotspot mutations in exon 9 or 20 and appeared to have a similar benefit among those with other somatic alterations in PI3K pathway genes.

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DOI: 10.1056/nejmoa2504650 ■

Gastrointestinal Infections, Diverticular Disease, Other Inflammatory Disorders

Gut. 2025;74(12):2004-2011

Ma W, Ha J, Neylan CJ, Munro H, Skerrett D, Downie JM, Sevilla-González M, Steinwandl M, Mumma M, Zheng W, Maguire LH, Giovannucci EL, Strate LL, Chan AT

Lifestyle factors, genetic susceptibility and risk of incident diverticulitis: An integrated analysis of four prospective cohort studies and electronic health records-linked biobank

Background: Both lifestyle factors and genetic predisposition contribute to the development of diverticulitis. **Objective:** To examine whether lifestyle modification can reduce the genetic risk of diverticulitis.

Design: The authors derived an overall healthy lifestyle score for diverticulitis based on smoking, body mass index (BMI), physical activity, fibre and red meat among 179,564 participants in three prospective cohorts—the Nurses' Health Study (NHS), NHSII and the Health Professionals Follow-Up Study. The association between the healthy lifestyle score and incident diverticulitis was confirmed among 30,750 participants in the Southern Community Cohort Study (SCCS). They assessed genetic risk using a polygenic risk score among 36,077 individuals with genotype data available. They further validated the authors' findings in the Mass General Brigham Biobank (MGBB).

Results: A healthy lifestyle score was associated with a decreased risk of diverticulitis. Compared with a score of 0, the multivariable-adjusted HR for a score of 5 was

0.50 (95% CI: 0.44–0.57; p trend < 0.0001). This association was consistent across the SCCS in both non-Hispanic black and white populations. Each unit increase in the healthy lifestyle score was associated with a reduced diverticulitis risk similarly across genetic risk categories, with HRs of 0.89 (95% CI: 0.83–0.95) for low, 0.86 (0.81–0.92) for mid and 0.87 (0.83–0.91) for high genetic risk. In the MGBB cohort, a higher BMI was associated with an increased diverticulitis risk across genetic risk categories.

Conclusion: Maintaining a healthy lifestyle was associated with a reduced risk of developing diverticulitis, regardless of population differences and genetic susceptibilities.

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EDITORS' CHOICE



According to the study below, the transfer of lyophilized sterile filtrate from intestinal microbiota is less effective than fecal microbiota transfer with live bacteria for the treatment of recurrent *Clostridioides difficile* infection. ■

Lancet Gastroenterol Hepatol. 2025;10(11):986-997

Kao D, Wong K, Lee C, Steiner T, Franz R, McDougall C, Silva M, Schmidt TSB, Walter J, Loebenberg R, Monaghan TM, Giebelhaus RT, Harynuk JJ, Xu H, Yaskina M, MacDonald KV, Marshall DA, Louie T

Effects of lyophilised faecal filtrate compared with lyophilised donor stool on *Clostridioides difficile* recurrence: A multicentre, randomised, double-blinded, non-inferiority trial

Background: Faecal microbiota transplantation (FMT) is highly effective in preventing recurrent *Clostridioides difficile* infection. However, it is not known whether live microbes are necessary in mediating FMT efficacy.

This study aims to determine whether lyophilised sterile faecal filtrate (LSFF), free of live bacteria, is non-inferior to lyophilised donor stool (LFMT) in efficacy.

Methods: This multicentre, randomised, double-blinded, non-inferiority trial was done at four academic centres in Canada. Eligible patients were adults aged 18 years or older with recurrent *C. difficile* infection (at least two recurrences). Eligible patients were randomly assigned (1:1 using a prespecified computer-generated randomisation list with permutation blocks of 2 and 4, stratified by age > 65 years or < 65 years) to receive oral LSFF or LFMT. Each treatment dose consisted of 15 capsules that appeared identical. Participants and investigators were masked to treatment allocation. The primary outcome was the proportion of participants without recurrent *C. difficile* infection (absence of more than three Bristol type 6 or 7 bowel movements per 24 h persisting more than 2 consecutive days) at 8 weeks. Analysis was done in the per protocol population, in which participants with unknown outcome status at

8 weeks due to death or loss to follow-up were excluded. Non-inferiority was established if the lower bound of the one-sided 95% CI for the difference in proportions of participants without recurrent *C. difficile* between the LSFF and LFMT groups was above the non-inferiority margin of -10%.

Findings: Between March 27, 2019, and November 6, 2023, the authors assessed 409 patients for eligibility. 271 were excluded and the remaining 138 were enrolled and randomly assigned to receive LSFF (n = 72) or LFMT (n = 66). Participants' mean age was 61.2 years (SD 18.6); 91 (66%) of 138 patients were women and 47 (34%) were male. 127 participants (92%) were White. 130 (94%) of 138 participants completed the trial. At the planned interim analysis, 47 (65%) of 72 participants in the LSFF group and 57 (88%) of 65 participants in the LFMT group did not have *C. difficile* recurrence at 8 weeks (difference -23%, one-sided 95% CI: -33.8% to infinity; p = 0.96). Given the pre-specified non-inferiority margin of -10%, non-inferiority of LSFF to LFMT could not be established and the study was terminated at the recommendation of the data safety monitoring board. Serious adverse events included one death (LFMT group) and 5 hospitalizations (4 unrelated, one possibly related to interventions [LSFF group]). One event occurred before treatment and all others 2–20 weeks after study intervention. The most common adverse events were abdominal discomfort (48 [67%] of 72 patients in the LSFF group and 36 [55%] of 66 patients in the LFMT group) and nausea (13 [18%] in the LSFF group and 21 [32%] in LFMT group).

Interpretation: Among adults with recurrent *C. difficile* infection, non-inferiority of LSFF to LFMT was not established for the prevention of recurrent *C. difficile* infection over 8 weeks, supporting the crucial role of live microbes in mediating clinical efficacy.

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Maitland K, Ouattara SM, Sainna H, Chara A, Ogundipe OF, Sunyoto T, Hamaluba M, Olupot-Olupot P, Alaroker F, Connon R, Saidou Maguina A, Okiror W, Amorut D, Mwajombo E, Oguda E, Mogaka C, Langendorf C, Dewez JE, Ciglenecki I, Gibb DM, Coldiron ME, Petrucci R, George EC; GASTROSAM Trial Group

Intravenous rehydration for severe acute malnutrition with gastroenteritis

Background: International recommendations advise against the use of intravenous rehydration therapy in children with severe acute malnutrition because of the concern about fluid overload, but evidence to support this concern is lacking. Given the high mortality associated with the current recommendations, the adoption of intravenous rehydration strategies might improve outcomes.

Methods: The authors conducted a factorial, open-label superiority trial in four countries in Africa. Children 6 months to 12 years of age with severe acute malnutrition with gastroenteritis and dehydration underwent

randomization in a 2:1:1 ratio to one of three rehydration strategies: oral rehydration, plus intravenous boluses for shock; a rapid intravenous strategy that consisted of lactated Ringer's solution (100 ml per kilogram of body weight) administered over a period of 3 to 6 hours, with boluses for shock; or a slow intravenous strategy that consisted of the same solution administered over a period of 8 hours, with no boluses. The primary end point was death at 96 hours.

Results: A total of 272 children underwent randomization; 138 were assigned to the oral strategy, 67 to the rapid intravenous strategy, and 67 to the slow intravenous strategy. Participants were followed for 28 days. A nasogastric tube was used for oral rehydration in 126 of 135 participants (93%) in the oral group and in 82 of 126 (65%) in the intravenous groups. Intravenous boluses were administered at admission in 12 participants (9%) in the oral group, 7 (10%) in the rapid intravenous group, and none in the slow intravenous group. At 96 hours, 11 participants (8%) in the oral group and 9 (7%) in the intravenous groups (5 in the rapid group and 4 in the slow group) had died (risk ratio = 1.02; 95% confidence interval [CI]: 0.41–2.52; p = 0.69). At 28 days, 17 participants (12%) in the oral group and 14 (10%) in the intravenous groups had died (hazard ratio = 0.85; 95% CI: 0.41–1.78). Serious adverse events occurred in 32 participants (23%) in the oral group, 14 (21%) in the rapid intravenous group, and 10 (15%) in the slow intravenous group. No evidence of pulmonary edema, heart failure, or fluid overload was noted.

Conclusions: Among children with severe acute malnutrition and gastroenteritis, no evidence of a difference in mortality at 96 hours was noted between oral and intravenous rehydration strategies.

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Microscopic Colitis

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Bergman D, Ebrahimi F, Sun J, Maret-Ouda J, Lindkvist B, Peery A, Ludvigsson JF

Cholecystectomy is a risk factor for microscopic colitis: A nationwide population-based matched case control study

Background and aims: Studies have linked bile acid malabsorption and microscopic colitis (MC), with some patients with MC responding to treatment with bile acid sequestrants. However, the literature on cholecystectomy as a risk factor for MC is inconclusive. Therefore, the authors investigated the relationship between cholecystectomy and MC on a nationwide scale to provide more definitive insights.

Methods: They conducted a nationwide matched case-control study involving 13,554 patients diagnosed with MC between 1981 and 2017 in Sweden who were matched to 64,886 controls. Data on MC were obtained from

Swedish pathology registers, and controls were randomly selected from the general population and matched according to birth year, sex, county of residence, and calendar year. Moreover, MC-free full siblings to patients with MC were identified. Information on cholecystectomy was collected from the Swedish National Patient Register. Adjusted odds ratios (aORs) were calculated using multivariable-adjusted conditional logistic regression.

Results: The median age at diagnosis was 63.5 years (interquartile range [IQR], 51.0–73.4 years), and 72.3% of MC patients were women. Among patients with MC, 342 (2.5%) had undergone a cholecystectomy before diagnosis, compared with 687 (1.1%) in the control group. This yielded an aOR of 2.36 (95% confidence interval [CI]: 2.07–2.69) for earlier cholecystectomy in patients with MC. The corresponding aORs for collagenous colitis and lymphocytic colitis were 1.87 (95% CI: 1.48–2.36) and 2.65 (95% CI: 2.26–3.12), respectively. When compared with siblings, the aOR was 1.49 (95% CI: 1.21–1.85).

Conclusions: Cholecystectomy is associated with an increased risk of subsequent MC. These findings have implications for surgeons and general practitioners and underscore the need for further research into the underlying association between bile acid and MC.

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Advances in Hepatology – From Mechanistic Insights to Novel Therapeutic Concepts

Current Status and Progress in Understanding and Management of Liver Diseases: Insights from the Berlin Symposium

by *eickhoff kommunikation GmbH, Cologne, Germany*

Liver diseases are an increasing challenge for health-care systems worldwide, not only in Western industrialized nations. The 242nd International Symposium of the Falk Foundation e.V., “Advances in Hepatology – From Mechanistic Insights to Novel Therapeutic Concepts”, held on October 24 and 25, 2025, in Berlin, focused on the molecular and cellular mechanisms of liver diseases, novel therapeutic targets and approaches, as well as innovative research methods, and diagnostic options. It also became clear to what extent liver diseases affect other organs and vice versa, underscoring the importance of considering this interplay in diagnosis and management.

News on epidemiology, pathophysiology, and therapy

In his keynote lecture opening the event, **Prof. Vlad Ratziu** (Paris, France) highlighted recent advances in hepatology. Metabolic dysfunction-associated steatotic liver disease (MASLD) is no longer solely a problem of affluent Western societies. In North Africa, the Middle East, and Asia, the number of cases is rising significantly and is increasingly affecting younger individuals. MASLD is associated with overweight, obesity, hypertension, and diabetes. Recent data specifically indicate that hypertension increases the risk of MASLD progression [1]. Conversely, liver disease itself can contribute to the development of both diabetes and hypertension [2]. One challenge in clinical practice is that, according to a data-based cluster analysis, groups of people with similar morphology can differ significantly in their risk of developing associated diseases [3]. This underscores the urgent need for effective diagnostic and therapeutic strategies, as well as risk stratification models tailored to individual risk profiles.

For example, some MASLD patients are at increased risk for cardiometabolic complications, while others are primarily at risk for liver complications. New classes of drugs, some of which are already available in hepatology and others in clinical development, are demonstrating promising effects in studies on liver fat content, liver inflammation, metabolism, and antifibrotic outcomes. According to Prof. Ratziu, personalized therapy will play an increasingly important role in the future due to the diversity of mechanisms of action. In metabolic dysfunction-associated steatohepatitis (MASH), the most promising drug candidates include analogues or mimetics of fibroblast growth factor 21 (FGF21).

Through coordinated effects on both the central nervous system (CNS) and the liver, these agents are capable of reversing MASH [4].

Many years of research into therapies for primary biliary cholangitis (PBC) are also yielding results. Among other things, there are promising studies on agonists of the peroxisome proliferator-activated receptor (PPAR) [5,6]. Additional therapeutic options are currently in development.

Prof. Ratziu also reported on advances in liver cancer therapy and transplant medicine. A recent study demonstrated that immunotherapy prior to liver transplantation offers advantages in terms of survival and safety for patients with hepatocellular carcinoma [7]. For a recent auxiliary xenotransplantation of a genetically modified pig liver in a patient with advanced liver cancer.

Role of HSCs in fibrosis and hepatocyte regulation

Hepatic stellate cells (HSCs) play a central pathogenetic role in the development and regression of liver fibrosis. However, fibrosis-independent and homeostatic functions of HSCs remain poorly understood. **Prof. Robert F. Schwabe** (New York, USA) presented a study in which genetic HSC depletion in mice was combined with conditional knockout of candidate genes to analyze fibrosis-independent functions of HSCs [8]. This study identified hepatocyte-regulating functions of HSCs that control hepatic zoning, metabolism, injury, and regeneration via R-spondin 3 (Rspo3) and subsequent activation of WNT signaling, a major regulator of liver zonation and function. It has been shown that genetic depletion of HSCs affects WNT activity and hepatocyte zonation, leading to significant changes in liver regeneration, cytochrome P450 metabolism, and liver injury. Rspo3 is an HSC-enriched modulator of WNT signaling and has been identified as responsible for these hepatocyte-regulating effects of HSCs. HSC-selective deletion of Rspo3 mimics the effects of HSC depletion on hepatocyte gene expression, zonation, liver size, regeneration, and cytochrome P450-mediated detoxification, and exacerbates alcohol-related liver disease (ALD) and MASLD. Rspo3 expression decreases with HSC activation and is inversely related to outcomes in patients with these two disease entities. Since the protective and hepatocyte-regulating functions of HSCs via Rspo3 are similar to those of the R-spondin-expressing stromal niche in other organs, Prof. Schwabe believes that these

mechanisms should be integrated into current therapeutic concepts.

The development of therapies for PSC is a challenge

The cause of primary sclerosing cholangitis (PSC) remains unknown. However, PSC frequently occurs in conjunction with inflammatory bowel disease (IBD), and other autoimmune and inflammatory diseases are also more common, as **Prof. Tom Hemming Karlsen** (Oslo, Norway) explained. Elevated serum levels of alkaline phosphatase (ALP) may indicate PSC and, according to the guidelines of the European Association for the Study of the Liver (EASL), warrant further investigation [9]. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), the cholangiographic features of PSC, together with the exclusion of secondary sclerosing cholangitis, are sufficient for diagnosis, as a significant proportion of PSC patients may have normal ALP levels [10]. The course of PSC is highly variable, and critical processes often cannot be reliably tracked. While inflammation progresses to cholestasis and fibrotic processes lead to cirrhosis, disease activity as assessed by blood tests, including ALP determination, fluctuates. This affects their usefulness as surrogate endpoints in clinical trials. The severity of IBD also fluctuates during the course of PSC. Blood-based fibrosis markers show less spontaneous fluctuation than ALP and generally increase during the course of the disease, as does elastographically measured liver stiffness. Various microbial biomarkers in the intestine often remain stable over the course of the disease, and some may remain elevated after liver transplantation and influence the risk of PSC recurrence [11]. Cholestasis, bacterial cholangitis, and malignancies are common clinical events. Regular screening of PSC patients for malignancies is essential [9,10]. The limited understanding and difficult monitoring of critical disease processes make it challenging to identify relevant mechanisms of action for potential drugs. For ursodeoxycholic acid, the study data for PSC are inconsistent, and guidelines therefore offer only limited recommendations [9,10]. Agonists of the peroxisome proliferator-activated receptor (PPAR) show efficacy at least for some endpoints [12,13]. Various immunosuppressive therapies and antibiotics have not yet led to a breakthrough and are not clearly recommended in guidelines. IBD with PSC should be treated like IBD without PSC, with the goal of mucosal healing [9-11]. Prof. Karlsen concluded by noting that various drugs are currently being investigated in studies to address the urgent need for effective treatment options.

First xenotransplantation of a pig liver into a living patient

Dr. Beicheng Sun (Hefei, China) reported on the world's first xenotransplantation of a genetically modified pig liver in a patient with advanced liver cancer [14]. Previously, only hearts and kidneys from pigs had been transplanted. Due to additional physiological incompatibilities, much more extensive genetic modifications are necessary in the liver to avoid rejection. Ten targeted genetic modifications were made to the pig liver before it was transplanted as an auxiliary organ into the patient's right liver lobe. In the first 31 days after transplantation, no hyperacute or acute rejection reactions, infections,

or significant complications were observed, and the patient's liver and kidney functions remained stable. The xenotransplant produced bile acids, albumin, and coagulation factors. An early postoperative coagulation disorder, manifested by elevated D-dimer and fibrin degradation products, was treated with anticoagulants. On the 38th postoperative day, the xenotransplant had to be removed due to associated thrombotic microangiopathy (xTMA). Subsequent treatment with eculizumab and plasma exchange led to successful healing of xTMA. Repeated bleeding in the upper gastrointestinal tract ultimately led to the patient's death on day 171. Nevertheless, this case demonstrates that auxiliary xenotransplantation of a pig liver can help bridge the time until a human liver becomes available [14].

Targeted case finding in risk groups instead of mass screenings

Personalized treatment concepts first require the earliest possible identification of affected individuals, especially those with fibrosis or compensated cirrhosis. Early identification can improve treatment outcomes, delay progression, and enhance quality of life. However, **Prof. Maja Thiele** (Odense, Denmark) emphasized that there is currently no evidence supporting general, population-wide liver screening. Mass screening carries risks such as overdiagnosis, overtreatment, and psychological and somatic distress. Furthermore, there is no evidence that it can reduce liver-related morbidity and mortality [15,16]. Prof. Thiele proposed that expectations for general population screening should be scaled back. Instead, she advocated for targeted case finding in risk groups, particularly in individuals with high alcohol consumption and/or cardiometabolic risk factors such as obesity and diabetes. Her assessment was based on a study showing that 70% of individuals with these risks had steatotic liver disease, 10% had increased liver stiffness, and 2% had advanced liver fibrosis confirmed by biopsy [17]. The tests used to identify at-risk individuals should be practical, widely available, and scalable. These include, in particular, blood-based scoring systems and ultrasound-based liver elastography, a non-invasive imaging technique. National and international guidelines already recommend the appropriate use of these diagnostic tools [18-20].

Baveno VIII aims to provide answers to questions from the research agenda

To improve the management of portal hypertension, experts have been meeting every five years since 1990 in Baveno (Lake Maggiore, Italy) to discuss the available evidence, adopt definitions and consensus statements, and answer questions raised by new evidence in the years leading up to the next meeting. In patients with compensated cirrhosis or compensated advanced chronic liver disease (cACLD), clinically significant portal hypertension (CSPH) can play an important role in the progression to decompensation. As **Prof. Annalisa Berzigotti** (Bern, Switzerland) explained, the Baveno VII consensus on portal hypertension no longer focused on the management of bleeding episodes. Instead, the therapeutic goal was defined as preventing any decompensation. Ideally, simple, non-invasive tools should be used to rule out or confirm CSPH and treat patients at risk of decompensation as early as possible [21].

Prof. Berzigotti presented some of the results achieved in recent years from the Baveno VII consensus research agenda, which should lead to corresponding statements and recommendations at the Baveno VIII workshop in March 2026: Important improvements in the non-invasive risk stratification of CSPH and decompensation include non-invasive tests for CSPH in obese MASLD patients, the measurement of spleen stiffness for stratification and prognosis, alternative blood tests, reduction of ambiguous cases with unclear CSPH (liver stiffness 15–25 kPa), and assessment of CSPH in hepatocellular carcinoma (HCC). In addition, the concept of recompensation is to be validated and refined. Recommendations on non-pharmacological and pharmacological therapies that act on portal hypertension and liver fibrosis prevent (further) decompensation and promote recompensation will be updated. New findings on the optimal use of intrahepatic portosystemic shunts (e.g., risk stratification) are also expected.

Influence of the immunological environment on the development and treatment of HCC

Prof. Mathias Heikenwälder (Heidelberg, Germany) emphasized the importance of the immunological environment in liver cancer. Chronic hepatitis promotes the development of HCC through necroinflammation, i.e., the inflammatory response to necrotic cell death. Inflammation is also promoted by lifestyle factors, especially alcohol abuse and metabolic risk factors, partly due to the Western diet. Systemic factors of the gut microbiome and the immune system may also be involved. Kinase inhibitors, VEGF receptor blockers, and immune checkpoint inhibitors are part of the standard therapy for advanced HCC. However, the effectiveness of the therapies may depend on the etiology (viral or non-viral) [22]. There are now approaches to using metformin in combination with other tumor therapies [23]. Using MASH-HCC mouse models, Prof. Heikenwälder's research group demonstrated that the combination of metformin and immune checkpoint inhibitors can control tumor growth. This occurs through the infiltration of CD8 T cells into the tumor and indirectly through the reduction of fatty acid accumulation in MASH-HCC. As yet unpublished data confirm the effectiveness of the combination, with prolonged survival in diabetic HCC patients. Antiplatelet therapy is also established for MASH and HCC. Since glycoprotein Iba (GPIba) plays an important role in platelet activation, Prof. Heikenwälder's research group engineered a GPIba antibody that has already proven effective in preclinical trials. Platelet enrichment in HCC may be associated with resistance to immunotherapy. Mouse models have shown that blocking GPIba and thus platelet activation can improve the effectiveness of immunotherapy.

Current and future therapies for MASH

MASLD is associated with increased cardio-renal-metabolic outcomes. According to **Dr. Arun J. Sanyal** (Richmond, USA), understanding its pathogenesis provides a rationale for targeting common disease processes and is important for developing multi-organ therapies based on mechanisms of action. The liver is a fat-accumulating organ whose fat can be broken down again if weight and visceral fat are reduced, e.g.,

through treatment with glucagon-like peptide-1 (GLP-1) receptor antagonists [24]. GLP-1 receptor antagonists can also promote the regression of MASH and fibrosis [25]. A new approach is the use of a selective agonist of the thyroxine β -receptor in patients with MASH and fibrosis [26]. MASH and fibrosis can also be improved by sodium-glucose-linked transporter 2 (SGLT-2) inhibitors [27].

According to Dr. Sanyal, combination therapies with new approaches that build on the benefits of currently available drugs such as GLP-1 receptor antagonists or SGLT-2 inhibitors will be important in the future. One example of this is the combination of a fibroblast growth factor-2 (FGF-2) analogue with a GLP-1 receptor antagonist, which has been shown to reduce hepatic fat fraction and fibrosis markers in patients with MASH and type 2 diabetes [28].

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Scientific Organization

Stefan Fichtner-Feigl (Freiburg, Germany)
Tom Hemming Karlsen (Oslo, Norway)
Sophie Lotersztajn (Paris, France)
Frank Tacke (Berlin, Germany)

Bringing Innovations into Clinical Practice

Prof. Dr. Frank Tacke, Director of the Department of Hepatology and Gastroenterology at Charité, Berlin (Germany), co-organized the symposium “Advances in Hepatology”. The event focused on the molecular and cellular mechanisms of liver diseases, novel therapeutic approaches, innovative research methods, and diagnostic options. We spoke with Prof. Tacke during the symposium.

What were your main objectives for the symposium “Advances in Hepatology”, and what impact did it have?

Prof. Dr. Frank Tacke: Our goal was to take stock of the current landscape in hepatology: What has changed, what are the most pressing unresolved issues, and what new solutions have emerged? This includes the detection and management of liver diseases, especially in cases where there were no therapeutic options a decade ago. Today, new treatment possibilities are emerging, for example, for fatty liver diseases, now called MASLD, or for rare diseases like primary sclerosing cholangitis.

Which topics and areas of research do you currently consider particularly important?

Prof. Dr. Frank Tacke: Thanks to technological advances, we’ve seen an enormous increase in knowledge in basic science. Today, we can partially characterize what happens in a diseased liver at the single-cell level. The challenge lies in translation; using these findings to better understand disease mechanisms and develop new interventions. This is the beginning of a new wave of truly personalized, tailored therapy options.

How are fatty liver diseases, hepatocellular carcinoma, and liver immunology interconnected?

Prof. Dr. Frank Tacke: Any type of liver damage triggers an inflammatory response that can lead to fibrosis or cirrhosis, and it increases the risk of liver cancer. These processes are closely linked and represent different stages of disease progression. Fatty liver disease is the biggest challenge because it affects so many people.

What progress has been made in diagnostics and therapy?

Prof. Dr. Frank Tacke: Non-invasive diagnostic procedures have led to significant advances. Liver biopsies used to be essential, but today we can accurately determine the severity of liver diseases using tests like elastography or magnetic resonance imaging. In terms of therapy, the approval of the first medication for fatty liver diseases was a milestone. There have also been advances in cancer therapy, such as immunotherapies. For diseases like primary biliary cholangitis, new second-line medications are available.

How important is interdisciplinary collaboration?

Prof. Dr. Frank Tacke: It is essential. Progress in research requires collaboration among cell biologists, immunologists, data scientists, and computer scientists. In clinical

practice, interdisciplinarity means close cooperation between radiologists, pathologists, surgeons, and hepatologists. Other specialties—such as nephrology, cardiology, and diabetology, where the liver isn’t the primary focus—should also be more involved, as they can often contribute to diagnosing liver diseases.

What role does a symposium like this play in that context?

Prof. Dr. Frank Tacke: It’s important to open up to other disciplines and, for example, consider the cardiometabolic consequences of liver diseases within hepatology, and vice versa. We also need to raise awareness in other fields that the liver is often affected, such as in cases of long-term diabetes. When it comes to liver diseases, you always have to consider their impact on the entire organism. For example, interventions that influence the microbiome can affect—or even improve—the gut-liver or gut-liver-brain axis.

Precision medicine: The presentations covered organoids, single-cell omics, multi-omics, and AI. How do you assess the potential of these technologies, especially for personalized medicine?

Prof. Dr. Frank Tacke: The potential is enormous, but we’re currently using only a small part of it. Technologies like organoids, which are produced from stem cells, could allow us to analyze signaling pathways and test potential therapies. Single-cell and multi-omics, as well as AI, help us develop personalized therapies. These approaches aren’t fully explored yet, but they offer great promise. They help us determine who should receive which therapy in a personalized way to achieve the best outcomes.

What would you recommend to colleagues who didn’t attend the symposium?

Prof. Dr. Frank Tacke: Stay informed about the latest developments, for example, by visiting the symposium website, and try not to miss the next Falk Symposium. It was a fantastic event with leading experts who showed us where we stand, what questions remain unanswered, and how we can implement innovations in clinical practice.



Prof. Dr. Frank Tacke in Berlin © Falk Foundation



PANCREAS

Acute/Chronic Pancreatitis

EDITORS' CHOICE



This multinational retrospective cohort study suggests that cholecystectomy is safe and effective during the second and third trimester of pregnancy, while ERCP is safe in any trimester. ■

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Tarján D, Szalai EÁ, Erőss B, Hegyi PJ, Drug VL, Chooklin S, Hirth M, Sandblom G, Sandblom V, Edergren Å, Tlili A, Fendri S, Sirtl S, de la Iglesia Gracia D, Kurti F, Wu D, Gherbon A, Nawacki Ł, Constantinescu A, Shirinskaya NV, Zolotov AN, Pandanaboyana S, Ikeura T, Cúrdia Gonçalves T, Rasmussen L, Andersson B, Bouzid A, Saidani A, Ács N, Sipos Z, Farkas N, Tihanyi B, Teutsch B, Nilsson J, Mikó A, Hegyi P

Safety and effectiveness of cholecystectomy and endoscopic retrograde cholangio-pancreatography in biliary pancreatitis during pregnancy: BORN study

Background: Biliary acute pancreatitis (AP) during pregnancy is a challenging situation, and current guidelines for AP, pregnancy care, and surgery do not specifically address its management. This study investigated the safety and effectiveness of cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy in AP.

Methods: This international retrospective multicenter cohort study encompassed questions related to demographic information, clinical presentation, management strategies, timing of cholecystectomy, approaches to the procedure, complications, and outcomes. Continuous variables were summarized as medians with interquartile ranges, and categorical variables as frequencies and percentages. Group comparisons used Welch's t-test, Pearson's chi-squared, or Fisher's exact tests.

Results: A total of 101 cases from 14 countries and 19 centers were enrolled. Cholecystectomy after mild AP during pregnancy had a lower rate of readmission due to recurrent AP or other gallstone-related complications compared with those who did not undergo surgery after a mild AP during pregnancy (0% vs. 24%; $n = 0/17$ vs. $n = 12/49$, $p = 0.027$). Cholecystectomy performed during pregnancy was associated with a low surgical complication rate, identical to that seen in postpartum procedures (12% vs. 10%; $n = 2/17$ vs. $n = 3/30$; $p > 0.999$). Preterm birth occurred in 7.1% ($n = 1/14$) of patients with cholecystectomy versus 11% ($n = 5/45$) without. Fetal loss after surgery occurred only in the first trimester ($n = 3/17$ vs. $n = 1/49$). No difference

was seen in readmission (5%, $n = 1/21$ vs. 27%, $n = 4/15$; $p = 0.138$), fetal loss (5%, $n = 1/21$ vs. 27%, $n = 4/15$; $p = 0.138$) and preterm birth (6%, $n = 1/17$ vs. 8%, $n = 1/12$; $p > 0.999$) between the surgical and ERCP groups. The fetal loss (9.1%, $n = 2/22$ vs. 5.4%, $n = 4/74$; $p = 0.618$) and preterm birth rates (5.9%, $n = 1/17$ vs. 12%, $n = 8/65$; $p = 0.677$) did not significantly differ between patients with and without ERCP during pregnancy.

Conclusion: Cholecystectomy is effective and safe in pregnant patients during the second or third trimester in cases of mild biliary pancreatitis. ERCP is safe in any trimester.

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Deng H, Peng K, Zhang L, Lu J, Mei W, Shi X, Peng Y, Xu K, Li H, Wang Z, Lu G, Wang G, Lu Z, Cao F, Wen L; Chinese Hypertriglyceridemia-associated Pancreatitis Study Group (CHPSG)

Clinical outcomes in a multicenter cohort involving 919 patients with hypertriglyceridemia-associated acute pancreatitis

Introduction: Hypertriglyceridemia-associated acute pancreatitis (HTG-AP) is one of the most common etiologies of acute pancreatitis (AP) worldwide. Compared with other etiologies, patients with HTG-AP may develop more severe AP, but previous studies yielded controversial conclusions due to the lack of adequate adjustment for the confounders. Therefore, the aim of this study was to examine the possibility and risk factors of developing severe AP in HTG-AP.

Methods: Data from patients with an established diagnosis of AP were collected from January 2013 to December 2023 using a predesigned data collection form and were gathered from 5 tertiary cross-regional centers of China. HTG-AP was defined as serum triglyceride (TG) levels > 500 mg/dL and excluded other etiologies. The possibility and risk factors of severe AP were assessed by multivariable logistic regressions after adjusting potential confounders. A prediction model was established and validated.

Results: Between 2013 and 2023, the authors identified a total of 6,996 patients with AP, of whom 4,378 were included in the final analysis. Compared with other etiologies, patients with HTG-AP had a higher risk of developing severe AP (odds ratio = 1.897; 95% confidence interval: 1.380–2.608; $p < 0.001$) and organ failure. HTG-AP patients showed higher possibility for developing respiratory and circulation failure, but renal failure compared with other etiologies. In HTG-AP patients, risk factors of severe AP included age, fasting blood glucose, white blood cell counts, and presence of pleural effusion. TG level was found not to be significantly associated with severity in HTG-AP patients. A prediction model incorporating these risk factors demonstrated an area under the curve (AUC) of 0.837 in the training and 0.883 in the testing set, with adequate calibration.

Discussion: Using a multicenter cross-regional cohort, the authors demonstrated that HTG-AP had a higher risk of developing severe AP and organ failure. A risk prediction model for predicting severe AP was developed and effectively stratified patients.

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Frequency and predictors of delayed clearance of prophylactic pancreatic stents after ERCP

Background and aims: Timely evaluation and removal of prophylactic pancreatic stents (PSs) placed during endoscopic retrograde cholangiopancreatography (ERCP) are recommended. The aim of the study was to examine the proportion of patients whose prophylactic PSs passed or were removed within 4 weeks of ERCP.

Methods: Consecutive patients who received ERCP with prophylactic PS placement (May 2014 to October 2022) at a tertiary center were identified. The primary endpoint was clearance of the PS \leq 4 weeks from ERCP confirmed by radiologic studies or endoscopy. Multivariate analysis was used to identify endoscopist-, patient-, and procedure-related factors associated with the primary endpoint.

Results: Of 4,724 patients undergoing ERCP, 262 (5.5%) received a prophylactic PS (mean age, 56.6 \pm 18.5 years; 168 [64%] women). After ERCP, PSs were evaluated in \leq 2 weeks in 177 patients (68%; 95% CI: 62-73). Furthermore, PSs were cleared at \leq 4 weeks in 135 patients (52%; 95% CI: 46-58) by radiologic studies in 86 (33%) or endoscopic removal in 49 (19%). On multivariate analysis, biliary stent placement (adjusted odds ratio [aOR] = 0.5; 95% CI: 0.3-0.8) reduced the odds of timely PS clearance after adjusting for endoscopist-specific clearance rates: top (aOR = 11.1; 95% CI: 4.0-30.5), second (aOR = 5.4; 95% CI: 2.5-11.9), and third (aOR = 4.1; 95% CI: 1.9-9.0) compared with the bottom quartile. During follow-up of 20.1 \pm 23.5 months, 47 of 127 patients (37%) with delayed PS clearance demonstrated a median stent dwelling time of 55 days (range, 29-929).

Conclusions: Prophylactic PSs were cleared within 4 weeks in only half of the patients after ERCP. In addition to primarily endoscopist-driven factors, biliary stent placement was associated with delayed clearance of prophylactic PSs.

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Pancreatic Tumors

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Janssen QP, van Dam JL, van Bekkum ML, Bonsing BA, Bos H, Bosscha KP, Bouwense SAW, Brouwer-Hol L, Bruynzeel AME, Busch OR, Coene PPLO, van Eijck CHJ, de Groot JWB, Haberkorn BCM, de Hingh IHJT, Karsten TM, Kazemier G, van der Kolk MB, Liem MSL, Loosveld OJL, Luelmo SAC, Luyer MDP, Mekenkamp LJM, Mieog JSD, Nieuwenhuijs VB, Nuyttens JJME, Patijn GA, van Santvoort HC, Stommel MWJ, Versteijne E, de Vos-Geelen J, de Wilde RF, Zonderhuis BM, van der Holt B, Homs MYV, van Tienhoven G, Besselink MG, Wilmink JW, Groot Koerkamp B; Dutch Pancreatic Cancer Group

Neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy in resectable and borderline resectable pancreatic cancer (PREOPANC-2): A multi-centre, open-label, phase 3 randomised trial

Background: The PREOPANC-2 trial aimed to evaluate whether neoadjuvant FOLFIRINOX improved overall survival compared with neoadjuvant gemcitabine-based chemoradiotherapy followed by adjuvant gemcitabine in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma (PDAC).

Methods: In this investigator-initiated, open-label, nationwide, phase 3 randomised trial, patients aged 18 years or older with resectable or borderline resectable PDAC and a WHO performance status of 0 or 1 were enrolled across 19 Dutch centres. Patients in the FOLFIRINOX (FFX) group received FOLFIRINOX (85 mg/m² intravenous oxaliplatin, 180 mg/m² intravenous irinotecan, 400 mg/m² intravenous leucovorin, followed by a 400 mg/m² intravenous fluorouracil bolus and then continuous infusion at 2,400 mg/m² intravenously over 46 h every 14 days for eight cycles) followed by surgery without adjuvant treatment. Patients in the chemoradiotherapy (CRT) group received three cycles of neoadjuvant gemcitabine (1,000 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle and on days 1 and 8 only for cycles one and three) combined with hypofractionated radiotherapy (36 Gy in 15 fractions) during the second cycle only, followed by surgery and four cycles of adjuvant gemcitabine. Randomisation (1:1) was done using a minimisation technique and stratified by resectability status (resectable vs. borderline resectable disease) and centre. The primary endpoint was overall survival in the modified intention-to-treat population, after excluding ineligible patients. Data on race and ethnicity were not collected.

Findings: From June 5, 2018, to January 28, 2021, 375 patients were randomly assigned to the FFX group (n = 188) or the CRT group (n = 187). Six patients (three per group) were excluded due to ineligibility (n = 4) or immediate withdrawal of informed consent after randomisation (n = 2). 208 (56%) of 369 patients were male and 161 (44%) were female. After a median follow-up of 42.3 months (IQR, 35.7-48.7), median overall survival was 21.9 months (95% CI: 17.7-27.0) in the FFX group versus 21.3 months (16.8-25.5) in the CRT group (HR = 0.88 [95% CI: 0.69-1.13], p = 0.32). The most common grade 3-4 adverse events were neutropenia (43 [25%] of 175 in the FFX group vs. 38 [22%] of 176 in the CRT

group), diarrhoea (41 [23%] vs. 2 [1%]), and leukopenia (14 [8%] vs. 26 [15%]). Serious adverse events occurred in 85 (49%) patients in the FFX group compared with 75 (43%) in the CRT group ($p = 0.26$). Adverse events of grades 3 or worse occurred in 117 (67%) patients in the FFX group versus 106 (60%) patients in the CRT group ($p = 0.20$). Treatment-related deaths occurred in 2 (1%) patients in the FFX group (multi-organ failure and intestinal mucositis) and 1 (1%) patient in the CRT group (upper gastrointestinal haemorrhage).

Interpretation: This randomised trial did not show a difference in overall survival between neoadjuvant FOLFIRINOX and neoadjuvant gemcitabine-based chemoradiotherapy in patients with resectable or borderline resectable PDAC. Both neoadjuvant treatment regimens may be considered in these patients.

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J Clin Oncol. 2025;43(30):3266-3278

Fietkau R, Ghadimi M, Grützmann R, Wittel UA, Jacobasch L, Uhl W, Croner RS, Bechstein WO, Neumann UP, Waldschmidt D, Boeck S, Moosmann N, Reinacher-Schick AC, Golcher H, Adler W, Semrau S, Lubgan D, Kallies A, Hecht M, Tischoff I, Tannapfel A, Frey B, Oettle H; CONKO Study Group

Benefit of chemoradiotherapy versus chemotherapy after induction therapy for conversion of unresectable into resectable pancreatic cancer: The randomized CONKO-007 trial

Purpose: To determine the benefit, measured as complete removal of a tumor so that no tumor cells are detectable during histopathologic examination of the resection margin (R0 resection rate), of induction chemotherapy plus chemoradiotherapy (CRT) compared with chemotherapy alone for unresectable pancreatic tumors.

Patients and methods: CONKO-007, an investigator-initiated open-label, multicentric, phase III randomized clinical trial, enrolled 525 patients with unresectable tumors, and 495 patients received induction chemotherapy (402 with fluorouracil, irinotecan, and oxaliplatin [FOLFIRINOX] and 93 with gemcitabine). Patients without progression after 3 months of induction chemotherapy ($n = 336$) were randomly assigned for continuation of the same chemotherapy ($n = 167$) or CRT ($n = 169$; 50.4 Gy concurrently with gemcitabine). Resectability was centrally reassessed by a panel of surgeons. Surgery was recommended if possible. After an interim analysis, the primary end point was changed from overall survival (OS) to overall R0 resection rate because of slow recruitment. The median follow-up was 76 months. Important planned secondary end points were R0 resection rate in the surgically treated population and OS.

Results: The primary end point (overall R0 resection rate) was not significantly different between treatment arms with 25% (43 of 169) in the CRT arm versus 18% in

the chemotherapy arm (30 of 167; $p = 0.113$). Secondary end point analysis showed that surgery was performed equally often ($p = 0.91$); R0 resection rate in patients who underwent surgery was higher after CRT, 69.4% (43 of 62) compared with chemotherapy alone: 50.0% (30 of 60 patients, $p = 0.04$). Other parameters of resection (ratio of R0/R1/R2/no resection) also favored CRT ($p = 0.02$). No difference in OS was seen between treatment arms (hazard ratio [HR] = 0.937 [95% CI: 0.747–1.174]; $p = 0.57$; randomly assigned intention-to-treat patients). Surgery was associated with longer OS ($p < 0.001$, HR = 0.525 [95% CI: 0.408–0.676]).

Conclusion: Although not improving overall R0 resection rate or survival, CRT enables a R0 resection in surgically treated patients more often than chemotherapy alone.

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LIVER AND BILE

Viral Hepatitis

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Hui RWH, Wu TKH, Ho KCY, Leung RHM, Chung MSH, Wong DKH, Fung J, Seto WK, Mak LY, Yuen MF

Large-scale profile study on hepatitis B surface antigen levels in chronic hepatitis B: Implications for drug development targeting functional cure

Background: Quantitative hepatitis B surface antigen (qHBsAg) is an important biomarker in chronic hepatitis B (CHB).

Objective: Establish qHBsAg profiles to guide novel drug development.

Design: Baseline qHBsAg profiles, longitudinal qHBsAg trajectories and predictors of HBsAg seroclearance were determined in a large CHB cohort.

Results: This study included 4,287 patients with qHBsAg measurements between 2009 and 2020 (62.5% male; mean age 48.0; 45.2% on nucleos(t)ide analogues [NUC]) with median baseline qHBsAg of 630.8 (117.1–1875.5) IU/mL. 3,437 (80.2%), 2,516 (58.7%) and 997 (23.3%) patients had baseline qHBsAg < 3,000 IU/mL, < 1,000 IU/mL and < 100 IU/mL, respectively (69.2%, 46.9% and 22.9% in treatment-naïve; 93.4%, 73.0% and 23.6% in NUC-treated patients correspondingly). Among patients with recent qHBsAg measurements in 2018 (n = 1,593), 98.9%, 71.1% and 26.9% of patients had baseline qHBsAg < 3,000 IU/mL, < 1,000 IU/mL and < 100 IU/mL, respectively (99.3%, 67.1% and 34.2% in treatment-naïve; 98.7%, 73.1% and 23.0% in NUC-treated patients correspondingly). Age (OR = 1.019–1.049), hepatitis B e antigen positivity (OR = 0.264–0.349) and HBV DNA (OR = 0.675–0.832) were independent determinants of qHBsAg < 100 or 1,000 IU/mL, respectively (all p < 0.05). Among patients with serial qHBsAg measurements, the median qHBsAg reduction was 0.10 (0.02–0.27) log IU/mL/year. After median follow-up for 6.3 (5.7–14.3) years, 526 patients (12.3%) achieved HBsAg seroclearance. Baseline alanine aminotransferase/qHBsAg ratio \geq 0.27 independently predicted HBsAg seroclearance (HR = 4.904, p < 0.001).

Conclusion: In an endemic population, > 40% of patients with CHB have qHBsAg > 1,000 IU/mL. These patients are unlikely to achieve spontaneous HBsAg seroclearance, but also have suboptimal responses to novel antivirals. These data have important implications for novel antiviral development.

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EXPERT OPINION



Prof. Dr. Tobias Böttler

Quantifying the interplay between hepatitis B virus and antiviral immunity: The ALT/qHBsAg ratio

Quantitative measurement of hepatitis B surface antigen (HBsAg) has gained substantial importance in recent years. Although quantitative HBsAg levels (qHBsAg) do not directly correlate with the number of hepatitis B virus (HBV)-infected hepatocytes, several studies have demonstrated that low HBsAg levels are predictive of spontaneous HBsAg loss or HBsAg seroconversion, which is commonly defined as a functional cure. These findings have now been convincingly confirmed in a large Asian cohort study conducted by Hui et al. Functional cure of chronic HBV infection is an immune-mediated event. A substantial body of evidence, including data from studies evaluating nucleos(t)ide analogue (NUC) discontinuation, indicates that a certain degree of immune activation is required to achieve this outcome. This activation is often reflected by an increase in serum transaminases, particularly alanine aminotransferase (ALT), commonly referred to as “HBV flares.” In their study, the authors introduce a novel integrative marker that captures the interaction between viral burden and host immune response: the ALT/qHBsAg ratio. This ratio relates biochemical inflammatory activity, with ALT serving as a surrogate marker of immune-mediated hepatocyte injury, to the viral antigen load as reflected by quantitative HBsAg. In doing so, it provides an estimate of immune activation relative to the amount of viral antigen. The ALT/qHBsAg ratio specifically addresses an important limitation of conventional prognostic markers such as age, HBeAg status, or HBV DNA levels, which insufficiently capture the dynamic virus-host equilibrium. It also complements other virological markers that are less widely available in clinical practice. By integrating ALT activity and qHBsAg levels, the ratio allows a functional interpretation of whether ALT activity is sufficiently high relative to the existing HBsAg level to indicate meaningful immunological control. The data presented demonstrate that the ALT/qHBsAg ratio is a significant predictor of long-term HBsAg seroclearance and favorable qHBsAg trajectories in both treatment-naïve and treated patients, with consistent performance across different subgroups. Because both parameters are routinely measured, the ratio is also well suited for longitudinal monitoring of immunovirological dynamics. Beyond the natural course of disease, the ALT/qHBsAg ratio may also play an important role for emerging antiviral therapies currently under development. Indeed, the efficacy of almost all compounds in clinical testing with HBsAg loss as a primary end point, efficacy appears to be greatest in patients with low baseline qHBsAg levels. However, selecting patients solely on the basis of qHBsAg levels may exclude potentially “immunoactive” patients with high qHBsAg values. In contrast to isolated qHBsAg measurement, the ratio therefore allows a more nuanced assessment of immune activity, including whether changes in HBsAg levels are accompanied by evidence of immune response. This aspect may become particularly relevant for future personalized combination therapies with immunomodulators, such

as RNA interference-based strategies or therapeutic vaccination.

In summary, the ALT/qHBsAg ratio appears to be a simple, biologically plausible, and clinically relevant tool for estimating immune activity over the course of chronic HBV infection. Nevertheless, further validation and standardization in prospective studies are required. ■

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Chen Z, Liu L, Situ J, Li G, Guo S, Lai Q, Wu S, Jiang Y, Fan J, Tang Z, Li Y, Wen G, Wang S, Ying D, Liang Y, Siu-Fung Ho S, Ma X, Yiu-Hung Tsoi J, Shun EH, Chew NF, Ma W, Mao W, Li T, Chen Z, Fang M, Wang Y, Yu H, Zhang F, Zhang AJ, Li S, Xia N, Sridhar S, Zheng Q, Zheng Z

Antibodies elicited by hepatitis E vaccination in humans confer cross-genus protection against rat hepatitis E virus

Background and aims: Paslahepevirus balayani (bHEV), also known as hepatitis E virus (HEV), encompasses eight genotypes, five of which infect humans. Rats are natural reservoirs of Rocahepevirus ratti genotype 1 (HEV-r-1; rat HEV; rHEV), which has recently been implicated in viral hepatitis. Despite the antigenic divergence between bHEV and rHEV, studies on shared protective antibodies remain rare.

Methods: Polyclonal and monoclonal antibody responses against bHEV and rHEV were analyzed using antibody enzyme-linked immunosorbent assays. The efficacy of six potent bHEV-elicited cross-reactive antibodies in preventing rHEV infection was evaluated via challenge assays in rats. Cryo-electron microscopy was performed to assess the structural basis for the differential protective efficacy of the six antibodies. The viral lysis ability of these antibodies was assessed by separately reacting purified HEV-b-1 and HEV-r-1 virions with each antibody.

Results: The authors determined that antibody responses to bHEV infection and vaccination possess limited cross-reactivity to rHEV and identified two cross-reactive antigenic sites within the E2s domain. Structural analysis and animal challenge studies pinpointed potent cross-reactive antibodies targeting antigenic site 1, indicating its prophylactic efficacy against rHEV. Conversely, antibodies recognizing antigenic site 2 were found to facilitate viral lysis of bHEV but not rHEV.

Conclusions: These findings underscore the importance of antigenic site 1 in the design of broad-spectrum vaccines and therapeutics to mitigate the impact of diverse HEV genotypes on human health.

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Liver Tumors

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Lai JCT, Yang B, Lee HW, Lin H, Tsochatzis EA, Petta S, Bugianesi E, Yoneda M, Zheng MH, Hagström H, Boursier J, Calleja JL, Goh GBB, Chan WK, Gallego-Durán R, Sanyal AJ, de Lédinghen V, Newsome PN, Fan JG, Castera L, Lai M, Fournier-Poizat C, Wong GL, Pennisi G, Armandi A, Nakajima A, Liu WY, Shang Y, Saint-Loup M, Llop E, Teh KKJ, Lara-Romero C, Asgharpour A, Mahgoub S, Chan MSW, Canivet CM, Romero-Gómez M, Kim SU, Wong VWS, Yip TCF

Non-invasive risk-based surveillance of hepatocellular carcinoma in patients with metabolic dysfunction-associated steatotic liver disease

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of the general population and is the fastest growing cause of hepatocellular carcinoma (HCC). Current guidelines recommend HCC surveillance in patients with cirrhosis when annual HCC incidence exceeds 1% without specifying the role of non-invasive tests in patient selection.

Objective: To define non-invasive test thresholds to select patients with MASLD for HCC surveillance.

Design: A multicentre longitudinal study of adults with MASLD from 16 tertiary centres in the USA, Europe and Asia between February 2004 and January 2023. Primary outcome was incident HCC.

Results: 12,950 patients had Fibrosis-4 index (FIB-4) and liver stiffness measurement (LSM) (mean age 51.7 years; 41.1% male). At a median follow-up of 47.7 (IQR, 23.3-72.3) months, 109 (0.8%) developed HCC. FIB-4 was below the low cut-off (< 1.3 if aged < 65 years and < 2.0 if aged ≥ 65 years), between the low cut-off and < 2.67, 2.67 to < 3.25, and ≥ 3.25 in 66.3%, 23.9%, 3.4% and 6.4% of patients; the corresponding annual HCC incidence was 0.07%, 0.17%, 0.77% and 1.18%. As a stand-alone test, the annual HCC incidence exceeded 0.2% for LSM ≥ 10 kPa and 1% for LSM ≥ 20 kPa. If LSM was performed as a second step only among patients with FIB-4 above the low cut-off, the annual HCC incidence exceeded 0.2% for LSM ≥ 10 kPa and 1% for LSM ≥ 15 kPa.

Conclusion: HCC surveillance should be offered to patients with MASLD with FIB-4 ≥ 3.25 or LSM ≥ 20 kPa. When a two-step approach is adopted, LSM ≥ 15 kPa in patients with increased FIB-4 predicts a high HCC risk.

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Franssen S, Rousian M, van Verschuer V, Bruno M, Doukas M, van Driel L, Homs M, Mohseny B, de Wilde R, de Jonge J, Polak W, Porte R, Bijdevaate D, Moelker A, Groot Koerkamp B

Primary percutaneous stenting for palliative biliary drainage of patients with malignant hilar biliary obstruction: TESLA trial

Background and aims: Palliative patients with malignant hilar biliary obstruction typically undergo endoscopic or internal/external percutaneous biliary drainage. Both approaches may cause bacterial colonization of the bile ducts, requiring multiple reinterventions. The 90-day mortality rate after palliative drainage is reported to be up to 36%. Few patients become eligible for systemic treatment. Primary percutaneous stenting may avoid infectious complications. The aim of this study was to investigate primary percutaneous stenting in palliative patients with malignant hilar biliary obstruction.

Methods: The authors performed a single-arm phase II trial. Primary percutaneous stenting was performed with uncovered self-expandable metal stents across the hilar tumor without crossing the ampulla. The puncture tract was sealed without leaving an external drain. Outcomes included drainage-related severe complications and the proportion of patients receiving systemic treatment after drainage.

Results: From October 2020 until June 2023, 67 patients were included, with perihilar cholangiocarcinoma in 27 patients (40.3%), intrahepatic cholangiocarcinoma in 23 patients (34.3%), gallbladder cancer in nine patients (13.4%), and other tumors in eight patients (12.0%). Drainage-related severe complications within 90 days were observed in 12 patients (17.9%); two patients (3.0%) developed acute cholecystitis, one patient (1.5%) had a biliary leak, three patients (4.5%) had hemorrhage, and six patients (9.0%) had persistent jaundice. No drainage-related 90-day mortality was observed. Cholangitis or pancreatitis was never observed after the first drainage. Palliative systemic treatment was started in 42 patients (62.7%).

Conclusions: Primary percutaneous stenting for patients with malignant hilar biliary obstruction had a low incidence of drainage-related complications without any cholangitis or pancreatitis after the first drainage. Palliative systemic treatment was never withheld because of drainage-related complications or inadequate drainage. These results compare favorably to both endoscopic and internal/external percutaneous drainage.

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Steatotic Liver Disease

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Jara M, Norlin J, Skalshøi Kjær M, Almholt K, Bendtsen KM, Bugianesi E, Cusi K, Galsgaard ED, Geybels M, Gluud LL, Harder LM, Loomba R, Mazzoni G, Newsome PN, Nitze LM, Palle MS, Ratziu V, Sejling AS, Wong VWS, Anstee QM, Knudsen LB

Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis

Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic liver disease strongly associated with cardiometabolic risk factors. Semaglutide, a glucagon-like peptide-1 receptor agonist, improves liver histology in MASH, but the underlying signals and pathways driving semaglutide-induced MASH resolution are not well understood. Here the authors show that, in two preclinical MASH models, semaglutide improved histological markers of fibrosis and inflammation and reduced hepatic expression of fibrosis-related and inflammation-related gene pathways. Aptamer-based proteomic analyses of serum samples from patients with MASH in a clinical trial identified 72 proteins significantly associated with MASH resolution and semaglutide treatment, with most related to metabolism and several implicated in fibrosis and inflammation. An independent real-world cohort verified the pathophysiological relevance of this signature, showing that the same 72 proteins are differentially expressed in patients with MASH relative to healthy individuals. Taken together, these data suggest that semaglutide may revert the circulating proteome associated with MASH to the proteomic pattern observed in healthy individuals.

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Noureddin M, Harrison SA, Loomba R, Alkhouri N, Chalasani N, Sheikh MY, Tomah S, Gutierrez JA, Urbina S, Suschak JJ, Brown R, Odili O, Yang J, Keeton S, Neff G, Mena E, Roberts MS, Browne SK, Harris MS

Safety and efficacy of weekly pemvidutide versus placebo for metabolic dysfunction-associated steatohepatitis (IMPACT): 24-week results from a multicentre, randomised, double-blind, phase 2b study

Background: GLP-1-glucagon dual receptor agonists such as pemvidutide have shown promise in treating metabolic dysfunction-associated steatohepatitis (MASH). The aim of this trial was to assess the effects of pemvidutide on MASH resolution and fibrosis improvement in patients with liver fibrosis stage F2 or F3 MASH at 24 weeks of treatment.

Methods: IMPACT is an ongoing 48-week international, randomised, double-blind, placebo-controlled, phase

2b trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3. Patients from 83 sites in the USA and Australia were randomly assigned 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg), administered without dose titration, or placebo. The dual primary endpoints were MASH resolution without worsening of fibrosis or at least one stage liver fibrosis improvement without worsening of MASH at 24 weeks in the intention-to-treat population.

Findings: From July 27, 2023, to April 29, 2025, 1,557 patients were screened and 212 patients were randomly assigned. MASH resolution without fibrosis worsening was observed in 18 (20%) of 86 patients in the placebo group, 24 (58%) of 41 patients in the 1.2 mg pemvidutide group (difference of 38% [95% CI: 21–56]; $p < 0.0001$), and 45 (52%) of 85 patients in the 1.8 mg pemvidutide group (difference of 32% [95% CI: 19–46]; $p < 0.0001$). Fibrosis improvement without worsening of MASH was observed in 24 (28%) of 86 patients in the placebo group, 13 (33%) of 41 patients in the 1.2 mg pemvidutide group (difference of 5% [95% CI: -13 to 22]; $p = 0.59$), and 30 (36%) of 85 patients in the 1.8 mg pemvidutide group (difference of 8% [95% CI: -6 to 22]; $p = 0.27$). Adverse events were reported in 32 (78%) of 41 patients receiving 1.2 mg pemvidutide, 69 (81%) of 85 patients receiving 1.8 mg pemvidutide, and 58 (67%) of 86 patients receiving placebo, the majority of which were mild or moderate in severity. Pemvidutide was well tolerated, with discontinuations due to adverse events in none of 41 patients in the 1.2 mg pemvidutide group, one (1%) of 85 patients in the 1.8 mg pemvidutide group, and two (2%) of 86 patients in the placebo group.

Interpretation: Pemvidutide treatment met the primary endpoint of MASH resolution without worsening of fibrosis at 24 weeks but did not meet the other primary endpoint of fibrosis improvement without worsening of MASH at this timepoint. Additional trials of longer duration are planned.

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Hansen CD, Hansen JK, Israelsen M, Andersen P, Pikkupeura LM, Lindvig KP, Stinson SE, Lindholm Schnefeld H, Tellerup J, Fogt M, Torp N, Kjærgaard M, Bech KT, Holtz Thorhauge K, Johansen S, Spedtsberg I, Deluran E, Falk Villesen I, Detlefsen S, Hansen T, Krag A, Thiele M

Prevalence, severity and determinants of steatotic liver disease among individuals with metabolic and alcohol risk from the community

Background and aims: Individuals with steatotic liver disease (SLD) are affected by metabolic dysfunction and/or high alcohol consumption; however, the prevalence of SLD in at-risk individuals remains underexplored. The study aimed to investigate the prevalence and severity of SLD and its subclasses: metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic- and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD) in at-risk individuals.

Methods: Between October 2017 and November 2022, citizens aged 30–75 years were recruited 1:1 into: a) the metabolic cohort, comprising individuals with BMI $> 30 \text{ kg/m}^2$ and/or type 2 diabetes without prolonged increased alcohol consumption; or b) the alcohol cohort, comprising individuals with ongoing/prior increased alcohol consumption. The authors assessed liver steatosis by controlled attenuation parameter (CAP), liver fibrosis by liver stiffness measurements (LSM) and performed liver biopsies in participants with $\text{LSM} \geq 8 \text{ kPa}$.

Results: They included 3,123 participants; 1,599 in the metabolic cohort and 1,524 in the alcohol cohort. In total, 2,197 (70%) were diagnosed with SLD: 1,603 (51%) with MASLD, 398 (13%) with MetALD, and 196 (6.3%) with ALD. Of 307 (9.8%) with $\text{LSM} \geq 8 \text{ kPa}$, 169 underwent liver biopsy (55%). In the metabolic cohort, 1,237 (77%) had SLD, 147 (9.2%) had $\text{LSM} \geq 8 \text{ kPa}$, and 24 (1.5%) had biopsy-confirmed advanced liver fibrosis. In the alcohol cohort, 960 (63%) had SLD, 160 (10.5%) had $\text{LSM} \geq 8 \text{ kPa}$, and 46 (3.1%) had biopsy-confirmed advanced liver fibrosis. Across subclasses, ALD demonstrated the highest liver disease severity ($\text{LSM} \geq 8 \text{ kPa}$: 25%; biopsy-confirmed advanced fibrosis: 8%), and severity was comparable between MASLD and MetALD ($\text{LSM} \geq 8 \text{ kPa}$: 12%, biopsy-confirmed advanced fibrosis: 3%).

Conclusions: Among individuals with cardiometabolic and/or alcohol risk factors, 70% had SLD, 10% had elevated liver stiffness, and 2% had biopsy-confirmed advanced liver fibrosis.

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Oh JH, Yoon EL, Park H, Lee S, Jo AJ, Cho S, Kwon E, Nah EH, Lee JH, Park JH, Ahn SB, Jun DW

Efficacy and safety of time-restricted eating in metabolic dysfunction-associated steatotic liver disease

Background and aims: Time-restricted eating (TRE) may improve weight loss, insulin resistance, and body composition, which are key factors in the pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD). However, evidence on the efficacy of TRE in patients with MASLD is limited. This study aimed to evaluate the potential benefits of TRE in patients with overweight or obesity and MASLD.

Methods: In this 16-week randomized controlled trial, patients with overweight or obesity and MASLD were randomized into three groups in a 1:1:1 ratio: standard of care (SOC), calorie restriction (CR), and TRE. The primary endpoint was an improvement in hepatic steatosis, measured using MRI-proton density fat fraction. Changes in liver fibrosis, body composition, lipid profiles, glucose homeostasis, and sleep quality were also analyzed.

Results: Among the 337 participants randomized, 333 were included in the full analysis set (113 in SOC, 110 in CR, and 110 in TRE). After the 16-week intervention, hepatic steatosis significantly decreased in the TRE group (-25.8%) compared to the SOC group (0.7%),

$p < 0.001$), with no significant difference between TRE and CR (-24.7%, $p > 0.999$). The TRE group also showed greater reductions in body weight, waist circumference, and body fat mass compared to the SOC group, while changes were comparable between TRE and CR. Liver stiffness, glucose homeostasis, and sleep quality were similar between the TRE and CR groups. No serious adverse events were reported.

Conclusions: TRE effectively reduces hepatic steatosis in MASLD, with comparable benefits on weight loss, body composition, and metabolic parameters as CR.

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EXPERT OPINION



Dr. Dr. Natascha Röhlen

What is the significance of time-restricted eating in the treatment of metabolic dysfunction-associated steatohepatitis (MASLD)?

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects between 30% and 40% of the adult population worldwide, with a continuing rise in incidence. Obesity is one of the most important risk factors. Accordingly, irrespective of the pharmacological treatment options now available for patients with MASLD-associated liver fibrosis, weight loss through lifestyle modification is the first-line and central therapeutic approach for MASLD patients. A reduction in body weight of at least 5% leads to improvement in steatosis, while greater weight loss may result in improvements in inflammatory activity and even fibrosis. To date, however, no large randomized clinical trials have directly compared different diets head-to-head regarding their effectiveness in the treatment of MASLD. Available individual studies and meta-analyses suggest that magnitude and durability of weight loss, rather than the specific type of diet (e.g., low-carbohydrate, low-fat, ketogenic) are the key determinants of therapeutic benefit.

This assessment is supported by the study by Oh JH et al. published in the *Journal of Hepatology*. In this randomized controlled trial, 337 overweight or obese patients with MASLD received dietary guidance for 16 weeks and were assigned to 3 study groups: “standard of care” (SoC), “calorie reduction” (CR), and “time-restricted eating” (TRE). At baseline, all patients were advised to reduce daily calorie intake by 500 kcal relative to individually calculated daily energy requirements and received personalized nutritional counselling. Patients in the SoC group ($n = 114$) additionally received monthly feedback on their diet via text messaging. Participants

in the CR ($n = 112$) and TRE ($n = 111$) groups received the same dietary recommendations but underwent more intensive monitoring. Using a special mobile application, these patients were encouraged to closely track meals and body weight and received feedback on calorie intake and nutritional quality from nutritionists twice a week. Patients in the TRE group also followed a 16:8 intermittent fasting regimen, consisting of 16 hours of fasting and an 8-hour eating window.

Intensive monitoring and counselling resulted in significantly greater reductions in calorie intake in the TRE and CR groups compared with the SoC group (mean calorie reduction from baseline: -851.2 kcal for TRE, -878.7 kcal for CR, and -434.0 kcal for SoC). After 16 weeks, patients who received intensive dietary support demonstrated significant improvements in the primary end point, liver fat content measured by MRI-proton density fat fraction (MRI-PDFF) (-23.7% for TRE, -24.7 for CR, and -0.7% for SoC). However, the timing of calorie restriction did not result in significant differences between the CR and TRE groups. The other cardiometabolic parameters recorded, including body weight and body fat percentage, also improved significantly with close dietary supervision, without evidence of benefit or harm associated with time-restricted eating. In all groups, nearly two-thirds of participants regained at least 80% of the weight lost or exceeded 95% of baseline body weight within 6 months after completion of the intervention. In line with previous studies, loss of skeletal muscle mass during the intervention was a particular risk factor for subsequent weight regain.

In summary, this trial confirms the effectiveness of a calorie-restricted diet for reducing hepatic steatosis in patients with MASLD but demonstrates no additional benefit of implementing calorie restriction through time-restricted eating. The data also highlight the potential value of close and sustained nutritional counselling for weight loss. Important limitations include the predominant implementation of intermittent fasting as “late” food intake in the afternoon and evening. The beneficial effects of “early” TRE on insulin sensitivity and glycemic control described in other studies are not captured. In addition, the relevance of the findings to specific hepatological end points is also limited, as the study largely consisted of patients with only slightly elevated aminotransferase levels (mean alanine aminotransferase [ALT] levels: 44.3 IU/L for TRE, 44.0 IU/L for CR, and 41.4 IU/L for SoC) and normal liver stiffness, indicating the absence of liver fibrosis. The study period was also too short to expect meaningful results on prognostically relevant outcomes. As expected, the hepatological parameters mentioned were unaffected at the end of the intervention. The study likewise provides no new insights into the potential benefits of a specific diet. Based on the strongest long-term evidence for reducing cardiometabolic risk and mortality, both European and US guidelines recommend a Mediterranean diet for MASLD patients. Overall, however, the optimal diet should be individualized to align with patients’ daily routine and long-term adherence, which may explain why this study conducted in Korea deviated from guideline-based recommendations for cultural reasons. ■

Immune-mediated Liver Disease

EDITORS' CHOICE



Using patient samples as well as mouse and organoid models, this study shows that the tight junction protein Claudin-1 is a key disease mediator and a promising therapeutic target in primary sclerosing cholangitis. ■

J Hepatol. 2025;83(6):1305-1319

Del Zompo F, Crouchet E, Ostyn T, Nehme Z, Messé M, Jühling F, Désert R, Vieira AT, Moehlin J, Nakib D, Andrews T, Perciani C, Chung S, Bader GD, McGilvray I, Caime C, Scaravaglio M, Carbone M, Invernizzi P, Yaqub S, Folseraas T, Karlsen TH, Shankar G, Primeaux M, Dhawan P, Banales JM, Roehlen N, Iacone R, Teixeira G, Heikenwälder M, Mailly L, MacParland S, Roskams T, Govaere O, Schuster C, Baumert TF

Claudin-1 is a mediator and therapeutic target in primary sclerosing cholangitis

Background and aims: Primary sclerosing cholangitis (PSC) is a cholangiopathy associated with a high risk of progression to end-stage liver disease and hepatobiliary cancer. Its pathogenesis remains poorly understood, and current clinical management offers limited therapeutic options, primarily liver transplantation. Claudin-1 (CLDN1), a transmembrane protein highly expressed in liver epithelial cells, plays a critical role in cell-cell communication and signaling. The authors aimed to investigate the functional role of CLDN1 as both a mediator and potential therapeutic target for PSC using patient cohorts alongside murine and patient-derived intervention models.

Methods: CLDN1 expression patterns and associated cellular phenotypes were analyzed in liver tissues from five PSC patient cohorts using single-cell RNA sequencing, spatial transcriptomics, and multiplex proteomics. Proof-of-concept studies employing CLDN1-specific monoclonal antibodies (mAbs) and genetic loss-of-function approaches were performed in state-of-the-art mouse models of PSC and cholangiopathies. Perturbation studies in human cell-based models were conducted to explore underlying mechanisms.

Results: In liver tissues from patients with PSC, CLDN1 expression was markedly upregulated and correlated with disease progression. Spatial transcriptomics and proteomics revealed elevated CLDN1 expression in diseased cholangiocytes and cholestatic periportal hepatocytes, accompanied by activation of pro-inflammatory and pro-fibrotic signaling pathways. Therapeutic administration of CLDN1-specific mAbs or genetic knockout improved liver function in PSC mouse models by reducing hepatobiliary fibrosis and cholestasis. Mechanistic studies indicated that mAb treatment inhibited pro-inflammatory and pro-fibrotic signaling in cholangiocytes and hepatocytes perturbed in PSC liver tissues.

Conclusions: These findings demonstrate a functional role for CLDN1 in the pathogenesis of PSC and biliary fibrosis. In vivo proof-of-concept studies, combined with expression analyses in patients with PSC, support the clinical development of CLDN1-specific mAbs as a therapeutic strategy for PSC.

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Lancet Gastroenterol Hepatol. 2026;11(1):46-58

Trauner M, Levy C, Tanaka A, Goodman Z, Thorburn D, Joshi D, Salminen K, Yimam K, Isayama H, Montano-Loza AJ, Caldwell S, Danta M, Farkkila M, Gallegos-Orozco JF, Gordon SC, Hinrichsen H, Invernizzi P, Vuppalanchi R, Zhu K, Xu J, Liu X, Lu X, Crans G, Bolbolan S, Boyette L, Alani M, Barchuk WT, Watkins TR, Genovese MC, Bowlus CL

Cilofexor in non-cirrhotic primary sclerosing cholangitis (PRIMIS): A randomised, double-blind, multicentre, placebo-controlled, phase 3 trial

Background: There is currently no pharmacological therapy proven to alter the natural course of primary sclerosing cholangitis (PSC). The PRIMIS trial evaluated the efficacy and harms of the farnesoid X-activated receptor agonist cilofexor in participants with non-cirrhotic PSC.

Methods: In this phase 3, double-blind, placebo-controlled, multicentre trial (205 sites across 16 countries), adults aged 18–75 years with non-cirrhotic (FO–F3 [Ludwig classification]) large-duct PSC were randomly assigned (2:1) via an interactive web response system to receive cilofexor 100 mg or placebo (identical in appearance) orally once daily for 96 weeks. Randomisation was stratified by ursodeoxycholic acid use (yes or no) and the presence of bridging fibrosis (F3 vs. FO–F2), with a block size of six within each stratum. Participants, personnel directly involved in the conduct of the study, and outcome assessors were masked to treatment assignment. The primary endpoint was the proportion of participants with histological progression of liver fibrosis (a stage increase of one or more [Ludwig classification]) at week 96. After study termination, the primary endpoint analysis set was amended to include all participants in the harms analysis set (all who received at least one dose of the study drug) who had biopsy data at baseline and week 96.

Findings: Between June 13, 2019, and July 22, 2021, 419 participants were randomly assigned, and 416 were included in the full and harms analysis sets (cilofexor: n = 277; placebo: n = 139); 257 (62%) men and 159 (38%) women. The study was terminated early on September 26, 2022, after a planned interim futility analysis after 160 patients had reached 96 weeks of follow-up indicated a 6.8% probability of detecting a significant difference between cilofexor over placebo (futility boundary $\leq 10\%$). In the final analysis of the primary endpoint, for which 133 patients in the cilofexor group and 64 in the placebo group had liver biopsy results available, fibrosis progression occurred in 41 (31%) participants in the cilofexor group and 21 (33%) in the placebo group at week 96 (treatment difference -1.4% [95% CI: -15.2 to 12.3]; p = 0.42). The most common adverse events were pruritus (cilofexor: 136 [49%] of 277 patients; placebo: 50 [36%] of 139 patients; grade 3 or higher in 11 [4%] patients in the cilofexor group and one [1%]

patient in the placebo group), COVID-19 (cilofexor: 65 [23%]; placebo: 26 [19%]), and upper abdominal pain (cilofexor: 40 [14%]; placebo 20 [14%]). The proportion of serious adverse events was similar between groups (cilofexor: 53 [19%]; placebo: 26 [19%]). There were no treatment-related deaths.

Interpretation: Cilofexor did not significantly reduce the rate of fibrosis progression (vs. placebo) in participants with non-cirrhotic PSC. A greater percentage of cilofexor-treated participants had pruritus than placebo-treated participants; this study provides valuable harms data for cilofexor and other drugs in its class.

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JHEP Rep. 2025;7(11):101562

Díaz-González Á, Schregel I, Carballo L, Álvarez-Navascués C, Frisancho-Morales E, Miquel M, Retortillo MG, Gómez J, Horta D, Mateos B, Engel B, Volmer F, Barrio MD, Rodríguez-Tajes S, Olivas I, Hartl J, González CA, Hernández-Guerra M, Castello I, Pérez-Medrano I, González-Santiago JM, Arencibia A, Gómez A, Rodríguez-Perálvarez M, Crespo J, Sala M, Salcedo M, Barreira-Díaz A, Riveiro-Barciela M, Taubert R, Schramm C, Londoño MC; ColHai Registry

Isolated IgG elevation in patients with persistently normal transaminases does not affect the outcome of autoimmune hepatitis

Background and aims: The goal of treatment for autoimmune hepatitis is to achieve a complete biochemical response, defined as normalization of transaminases and immunoglobulin G (IgG) levels. Recent data suggest that IgG normalization does not significantly affect survival. The authors evaluated the impact of persistently elevated IgG levels (IgGe) and IgG flares (IgGf) on fibrosis progression and cirrhosis development.

Methods: This retrospective multicenter cohort study included 493 patients with autoimmune hepatitis and persistently normal transaminase levels during follow-up. The inverse probability of treatment weighting (IPTW) propensity score method was used to balance the cohorts.

Results: 349 (70.8%) patients had persistently normal IgG (IgGn) levels, 89 (18.1%) had IgGe, and 55 (11.1%) had IgGf during follow-up. After a median follow-up of 6.2 years (IQR, 4.1-10.1 years) with normal transaminase levels, median liver stiffness measurement (LSM) values remained stable, with no significant differences between groups. During the follow-up, 24 patients developed cirrhosis. Predictive factors for cirrhosis were age (hazard ratio [HR] = 1.10, $p < 0.001$), albumin (HR = 0.20, $p < 0.001$), IgG (HR = 1.00, $p = 0.001$), and platelet count (HR = 0.99, $p = 0.001$) at diagnosis; LSM (HR = 1.30, $p < 0.001$) at transaminase normalization; and transaminase normalization at 6 months (HR = 0.24, $p = 0.025$). In the multivariate analysis, only LSM was independently

associated with a higher risk of developing cirrhosis. After IPTW application, elevated IgG (IgGe or IgGf) did not affect fibrosis progression ($p = 0.275$) or cirrhosis development ($p = 0.211$).

Conclusions: Persistent or temporary serum IgG elevation in patients with normal transaminase levels did not significantly affect autoimmune hepatitis disease progression, thus challenging the current definition of complete biochemical response.

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or

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Hirschfield GM, Bowlus CL, Jones DEJ, Kremer AE, Mayo MJ, Tanaka A, Andreone P, Jia J, Jin Q, Macías-Rodríguez RU, Cobitz AR, Currie BM, Gorey C, Lazic I, Podmore D, Ribeiro A, Shannon JB, Swift B, McLaughlin MM, Levy C; GLISTEN Study Group

Linerixibat in patients with primary biliary cholangitis and cholestatic pruritus (GLISTEN): A randomised, multicentre, double-blind, placebo-controlled, phase 3 trial

Background: Cholestatic pruritus is common and undertreated in primary biliary cholangitis (PBC) and negatively affects patients' lives. The trial aimed to evaluate the safety and efficacy of linerixibat, an ileal bile acid transporter inhibitor, as a specific antipruritic therapy in patients with PBC.

Methods: The authors conducted a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Patients with PBC and moderate-to-severe pruritus (Worst Itch Numerical Rating Scale [WI-NRS] ≥ 4) were recruited at 115 centres in 19 countries. Patients were randomly assigned to receive either oral linerixibat 40 mg twice a day or a matching placebo through an interactive online response system, with pruritus severity (moderate or severe) and concomitant pruritus treatment (bile acid binding resins, other treatments, or none) as stratification factors. The primary endpoint was change in pruritus over 24 weeks assessed using the WI-NRS, ranging from 0 (no itching) to 10 (worst imaginable itching). Efficacy analyses included all randomly allocated patients; safety analyses included all randomly allocated patients who received one dose of study treatment or more.

Findings: From December 1, 2021, to May 13, 2024, a total of 238 patients were randomly assigned to receive either linerixibat ($n = 119$) or placebo ($n = 119$). One ($< 1\%$) of 119 patients randomly allocated to receive placebo withdrew before receiving treatment. Patients receiving linerixibat experienced significant improvement in pruritus over 24 weeks compared with placebo

(least-squares mean change from baseline -2.86 [95% CI: -3.23 to -2.50] for linerixibat vs. -2.15 [-2.51 to -1.78] for placebo; adjusted mean difference -0.72 [95% CI: -1.15 to -0.28]; $p = 0.0013$). Gastrointestinal adverse events were more frequent in patients treated with linerixibat than with placebo (72 [61%] of 119 vs. 21 [18%] of 118 had diarrhoea; 22 [18%] vs. four [3%] had abdominal pain). Treatment discontinuations due to gastrointestinal adverse events occurred in eight (7%) of 119 patients in the linerixibat group (of which five were due to diarrhoea) and one (< 1%) of 118 in the placebo group. Serious adverse events were reported in 14 (12%) of 119 patients receiving linerixibat and four (3%) of 118 receiving placebo. No deaths were reported during the study.

Interpretation: Linerixibat significantly improved pruritus versus placebo, supporting its potential to address a major symptom of PBC. An expected increase in diarrhoea in linerixibat-treated patients was observed.

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Alcohol and Toxicity

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Dong Y, Zhang Z, Zhi Y, Li X, Guo T, He L, Zhao S, Yang X, Tang J, Zhong W, Niu Q, Ma M, Huang Z, Mao Y

Evaluating large language models' performance in answering common questions on drug-induced liver injury

Background and aims: Drug-induced liver injury (DILI) is a complex condition often linked to medication behaviors, with patient education having a crucial role in optimizing outcomes. Large language models (LLMs) could serve as promising tools for scalable patient support, but their utility remains unclear. This study systematically evaluated the capability of six popular open- and closed-source LLMs in addressing common DILI-related queries, focusing on patient-centered education.

Methods: Twenty-eight frequently asked DILI questions were collected with input from hepatologists and patients ($n = 15$), and categorized into six clinical domains. Responses from six LLMs (GPT-4, GPT-3.5, Claude-2, Claude-1.3, Gemini, and LLaMA-3.1-405B) were anonymized, randomized, and independently evaluated by three hepatologists for accuracy, comprehensiveness, and safety. Additional analyses included automated readability assessment, domain-specific analysis, detailed expert-led error analysis, and direct comparison with physician responses.

Results: LLaMA-3.1-405B achieved the highest performance across most domains, with mean accuracy, comprehensiveness, and safety scores of 8.18 ± 1.68 , 3.86 ± 0.70 , and 4.02 ± 0.84 , respectively, significantly surpassing other models (Dunn's post hoc test, all

$p < 0.05$). O1-preview ranked second (accuracy, 7.29 ± 1.38 ; safety, 3.80 ± 0.92), whereas GPT-3.5-Turbo consistently performed worst (accuracy, 4.61 ± 1.17 ; comprehensiveness, 2.13 ± 0.79). In direct comparison with physicians, both LLaMA-3.1-405B and o1-preview significantly outperformed residents and primary care physicians across all metrics ($p < 0.05$). Error analysis showed that omission of crucial information accounted for 72% of errors, predominantly in GPT-3.5-Turbo, whereas hallucinations were rare (< 10%) but notable in LLaMA outputs.

Conclusion: This study represents the first systematic evaluation of LLMs for DILI-focused patient education. High-performing, publicly accessible LLMs demonstrate the potential to deliver accurate, comprehensive, and safe health information, even surpassing physician responses.

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JAMA Intern Med. 2025;185(9):1070-1078

Florian J, Salcedo P, Burkhart K, Shah A, Chekka LMS, Keshishi D, Patel V, Yang S, Fein M, DePalma R, Matta M, Strauss DG, Rouse R

Cannabidiol and liver enzyme level elevations in healthy adults: A randomized clinical trial

Importance: The wide use of unregulated cannabidiol (CBD) products among consumers raises safety concerns. Most research on CBD has studied the relatively high doses used by patients taking prescription CBD. However, limited safety data are available at lower doses.

Objective: To study the effects of 4-weeks of twice-daily CBD use on the liver and endocrine hormones using a dose within the range consumers are taking with unregulated CBD products.

Design, setting, and participants: This randomized double-blinded placebo-controlled trial from January to August 2024, using per-protocol analysis, included healthy adults recruited from a clinical pharmacology unit (Spaulding Clinical Research in West Bend, Wisconsin).

Interventions: Healthy participants were randomized to CBD, 5 mg/kg/day (2.5 mg/kg/day twice daily), or placebo for 28 days with weekly laboratory assessments.

Main outcomes and measures: The primary end point was the percentage of participants with an alanine aminotransferase or aspartate aminotransferase level elevation greater than 3 times the upper limit of normal during the study.

Results: In 201 healthy participants (median age, 36 years [IQR, 30–43 years]; 89 women [44%]), 8 participants (5.6%; 95% CI: 1.8–9.3%) in the CBD group and 0 participants (0%; 95% CI: 0–7.6%) in the placebo group had liver enzyme level elevation greater than 3 times the upper limit of normal. Seven participants met withdrawal criteria for potential drug-induced liver injury, detected at day 21 in 2 participants and day 28 in 5 participants.

No differences in change from baseline were observed between the CBD and placebo groups for total testosterone and inhibin B in male participants or thyrotropin, total triiodothyronine, and free thyroxine in all participants.

Conclusions and relevance: In this study, the incidence of elevated alanine aminotransferase or aspartate aminotransferase coupled with the finding of increased eosinophilia underscores the need for further investigation on the long-term effects of CBD use, its impact on various populations, and the safety of lower doses commonly used by consumers.

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Liver Transplantation

Gut. 2025;74(12):2058-2069

Lucas-Ruiz F, Vidal-Correoso D, Mateo SV, de la Torre-Álamo MM, Jover-Aguilar M, Alconchel F, Martínez-Alarcón L, Lopez-Lopez V, Ríos-Zambudio A, Cascales P, Pelegrín P, Pons JA, Ramírez P, Baroja-Mazo A

Intrahepatic donor microbiota-based metataxonomic signature detected in organ preservation solution enables prediction of short-term liver transplant outcomes

Background: Liver transplantation (LT) remains hampered by post-transplant complications. While gut microbiota dysbiosis has been linked to transplant outcomes, the role of the intrahepatic graft's native microbiota remains unexplored.

Objective: To characterise the microbial profile detected in organ preservation solution (OPS) and determine whether specific microbial taxa are associated with short-term clinical outcomes, and to develop predictive models for risk stratification.

Design: The authors analysed the OPS microbiota-based metataxonomic signature from 110 LT donors (discovery cohort) and an independent validation cohort (n = 29) using 16S rRNA sequencing. Microbial DNA signatures associated with clinical outcomes were identified through MaAsLin2-adjusted models, and relevant gene pathways were uncovered via data mining and enrichment analysis. Machine learning (ML) models were developed to predict outcomes based on microbial features, and host-microbiome interactions were validated through RNA sequencing (RNA-seq of matched liver biopsies).

Results: OPS-derived microbial DNA signature closely resembled liver/bile microbiomes (Proteobacteria-dominated). Specific genera (e.g., *Bacillus*, *Prevotella*) were differentially abundant in adverse outcomes (p < 0.05): hyperabundant in non-survivors and hepatic artery thrombosis, hypoabundant in acute rejection (AR). Gene mining linked these taxa to immune/metabolic pathways relevant to LT outcomes. RNA-seq vali-

dated upregulation of chemokines (CCL/CXCL families) in liver grafts from non-surviving recipients. ML models accurately predicted global survival (area under the curve [AUC] = 0.95) and AR (AUC = 0.96) based on microbial features, with generalisability confirmed in the validation cohort (AUC = 0.85–0.88).

Conclusion: Donor intrahepatic microbial DNA signature predicts LT outcomes via immune-metabolic modulation. While causality requires further study, these findings position the graft microbiome as a novel biomarker and potential therapeutic target, paving the way for microbiome-informed precision care in transplantation.

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EDITORS' CHOICE



This international cohort study provides the first robust clinical evidence to guide safe timing of immune checkpoint inhibitor washout before liver transplantation. ■

Hepatology. 2025;82(5):1122-1137

Moeckli B, Wassmer CH, El Hajji S, Kumar R, Rodrigues Ribeiro J, Tabrizian P, Feng H, Schnickel G, Kulkarni AV, Allaire M, Asthana S, Karvellas CJ, Meeberg G, Wei L, Chouik Y, Kumar P, Gartrell RD, Martinez M, Kang E, Sogbe M, Sangro B, Schwacha-Eipper B, Schmiderer A, Krendl FJ, Goossens N, Lacotte S, Compagnon P, Toso C

Determining safe washout period for immune checkpoint inhibitors prior to liver transplantation: An international retrospective cohort study

Background and aims: Immune checkpoint inhibitors (ICIs) are increasingly used in patients with advanced HCC patients awaiting liver transplantation (LT). However, concerns about the risk of posttransplant rejection persist.

Approach and results: The authors conducted an international retrospective cohort study including 119 HCC patients who received ICIs prior to LT. They analyzed the incidence of allograft rejection, graft loss, and post-transplant recurrence with a particular focus on the washout period between the last ICI dose and LT. In this study, 24 of the 119 (20.2%) patients experienced allograft rejection with a median time to rejection of 9 days (IQR, 6–10) post-LT. A linear relationship was observed between shorter washout periods and higher rejection risk. Washout periods < 30 days (OR = 21.3, 95% CI: 5.93–103, p < 0.001) and between 30 and 50 days (OR = 9.48, 95% CI: 2.47–46.8, p = 0.002) were significantly associated with higher rejection rates in the univariate analysis compared to the washout period above 50 days. Graft loss as a result of rejection occurred in 6 patients (25%) with rejection. No factors related to grafts were associated with rejection. A longer washout

period was not associated with a lower recurrence-free survival posttransplantation at 36 months (71% vs. 67%, $p = 0.71$).

Conclusions: These findings suggest that a washout period longer than 50 days for ICIs before LT appears to be safe with respect to rejection risk. While these results may help guide clinical decision-making, future prospective studies are essential to establish definitive guidelines.

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DOI: 10.1097/hep.0000000000001289 ■

General Hepatology

EDITORS' CHOICE



This large randomized trial shows that a shorter acetylcysteine regimen for paracetamol overdose provides an equally effective and safe alternative to the established standard regimen. ■

J Hepatol. 2025;83(4):881-887

Isbister G, Chiew A, Buckley N, Harris K, Berling I, Downes M, Page C, Isoardi K

A non-inferiority randomised controlled trial of a shorter acetylcysteine regimen for paracetamol overdose – The SARPO trial

Background and aims: Paracetamol is a commonly overdosed medication worldwide. Early acetylcysteine treatment can prevent hepatotoxicity. Multiple intravenous acetylcysteine regimens exist; the commonest recommending 300 mg/kg over 20 h. The authors investigated the effectiveness and safety of a shorter regimen in paracetamol overdoses ≤ 30 g.

Methods: In a multicentre, non-inferiority, randomised-controlled trial performed at three hospitals, 204 patients with acute paracetamol overdose ≤ 30 g, presenting within 8 h, were randomised to the standard 20 h acetylcysteine (200 mg/kg/4 h, 100 mg/kg/16 h) regimen or a short 12 h acetylcysteine (200 mg/kg/4 h, 50 mg/kg/8 h) regimen. The primary outcome was the absolute difference between alanine aminotransferase (ALT) 24 h post-ingestion and at admission (Δ ALT₂₄). Secondary outcomes included ALT > 150 U/L and $\geq 2x$ admission value at 24 h, systemic hypersensitivity and gastrointestinal adverse effects.

Results: The two groups were similar in terms of age, gender, dose ingested, paracetamol concentration, baseline ALT, hospital, charcoal administration and time until acetylcysteine treatment. The shorter regimen was non-inferior to the standard regimen. The median Δ ALT₂₄ for 107 patients given the shorter regimen was

-2 U/L (IQR, -7 to 1 U/L) compared to -1 U/L (IQR, -5 to 1.5 U/L) for the 97 patients given the standard regimen; difference in medians of -1 U/L (95% CI: -3 to 1 U/L) were less than the upper non-inferiority margin of 5. No patient receiving the shorter regimen had a 24 h ALT of $\geq 2x$ admission value and > 150 U/L, compared to one receiving the standard regimen. No patient had an ALT $> 1,000$ U/L. The frequency of systemic hypersensitivity reactions was similar between groups (9/107 [8%] for short vs. 10/97 [10%] for standard regimens). Gastrointestinal adverse effects occurred in 78/107 patients (73%) receiving the short vs. 63/97 (65%) receiving the standard regimen.

Conclusions: The shorter 12 h acetylcysteine regimen had the same effectiveness and safety as the standard 20 h regimen in acute paracetamol overdoses ≤ 30 g, almost halving the length of treatment required.

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Cirrhosis and Portal Hypertension

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Swaroop S, Janeela AM, Valsan A, Biswas S, Alexander V, Gamanagatti S, Gupta S, Goyal A, Sharma R, Agarwal S, Moorthy S, Babu KBS, Keshava SN, Sudhindran S, Nair G, Mohamed ZU, Nair P, Chavan A, Chaudhary S, Aggarwal A, Agarwal A, Goel A, Shalimar

Long-term outcomes of transjugular intrahepatic portosystemic shunt in Budd-Chiari syndrome: A multicenter study

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an important therapeutic option for Budd-Chiari syndrome (BCS), but long-term data are limited.

Aim: Evaluate response rates, long-term outcomes, complications, and predictors of mortality, new decompensation, hepatic encephalopathy (HE), and restenosis after TIPS.

Methods: Retrospective analysis of symptomatic BCS patients who underwent TIPS at three centers in India (2010–2025) from a prospectively maintained database. The authors evaluated response rates, new decompensations (HE, variceal bleed, ascites), restenosis and survival outcomes and their predictors.

Results: Among 318 patients (mean age 29.4 ± 9.8 years, 50.6% males, median follow-up 4.4 years), 244 (76.7%) had a clinical response to TIPS; non-response (23.3%) was mainly persistent ascites (two re-bleeds). Of 282 with ascites at presentation, complete/partial resolution at 3-months was 75.2%/17.0%. New decompensation developed in 32.7%, HE in 14.8%, and restenosis in 33.6%. Transplant-free survival at 1, 5, and 10 years were 95.5%, 87.4%, and 78.4%, respectively. Predictors of mortality included non-response to TIPS, bilirubin, albumin, and HE at 3 months. Age, non-response to TIPS, creatinine, and albumin predicted new decompensation. Post-TIPS complications occurred in 8.2%.

Conclusion: TIPS is a safe, effective intervention for symptomatic BCS, leading to high response rates and long-term survival. Non-response to TIPS and liver function identifies high-risk patients who should be evaluated for transplantation.

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EXPERT OPINION



PD Dr. Michael Schultheiß

Budd-Chiari-Syndrome and TIPS: Nothing new!

The study by Swaroop et al. on Budd-Chiari syndrome (BCS) is a retrospective analysis without any substantial new insights. Nevertheless, it provides a welcome opportunity to address the topic of BCS. With an incidence of fewer than 1 case per 1,000,000 persons per year, BCS is a rare disease and therefore an uncommon condition even for hepatologists. This rarity likely contributes to the persistent “uncertainty” regarding the therapeutic algorithm. Given the young age of the patients and the often severe, potentially life-threatening clinical course, a more focused and systematic approach to BCS is warranted to support rational well-informed treatment decisions.

Today, the use of a transjugular intrahepatic porto-systemic shunt (TIPS) is a clearly established standard of care in BCS. This insight is supported in part by work from the Freiburg TIPS group led by Prof. Martin Rössle in the 1990s. Interestingly, data published both by Rössle et al. in 2004 (1) from the Freiburg cohort and by Garcia-Pagán et al. in 2008 (2) from a multicenter European cohort demonstrate survival rates that are largely comparable with those presented by Swaroop et al. Transplant-free 1-year survival was 93% in Rössle, 88% in Garcia-Pagán, and 95.5% in Swaroop et al. Five-year survival was 74%, 78%, and 87.4% respectively, and 10-year survival was 69% in Garcia-Pagán and 78.4% in Swaroop et al.

Rates of stent thrombosis or need for revision also remain relatively high—even following the introduction of covered TIPS stents: 54% in Rössle et al. (23% covered stents), 41% in Garcia-Pagán et al. (51% covered stents), and 33.6% in Swaroop et al.

However, comparison of the studies also reveals several striking differences, which may be explained by the long time interval between the studies, as well as by differences between patient cohorts. As mentioned above, an important distinction is the proportion of covered TIPS stents used. In the European cohorts, coagulopathies are typically reported in 70% to 80% of patients, which may help explain the high rates of

TIPS stenosis, dysfunction, and subsequent revision. In contrast, the Indian cohort studied by Swaroop et al. included only about 28% of patients with a coagulation disorder.

The introduction of TIPS has fundamentally revolutionized the treatment of BCS. Whereas long-term survival among untreated BCS patients was previously less than 10%, contemporary data indicate that 70% to 80% of patients are still alive 10 years after initial diagnosis. Nevertheless, we need to do better. The current study suggests that survival has improved only marginally compared with the first TIPS studies published more than 20 years ago. Ten-year mortality in the Swaroop et al. cohort is still greater than 20%. From my perspective, this is essentially a catastrophe for a patient cohort with a median age of 29 years.

Accordingly, the timing of TIPS placement must therefore continue to be discussed in the future. The updated European Association for the Study of the Liver (EASL) guidelines continue to recommend a stepwise approach with anticoagulation, angioplasty, TIPS, and finally liver transplant (3). But how long can and should we wait before TIPS placement? Several findings—including those from the study by Swaroop et al.—argue in favor of early TIPS placement:

- Hepatic encephalopathy in BCS (15% in this study) is often attributed to hypoxic liver failure and may be preventable with timely TIPS.
- Failure of TIPS therapy is associated with worse outcomes.
- Two-thirds of BCS patients ultimately require TIPS despite initial anticoagulation or angioplasty (3).

The logical consequence would therefore be early TIPS placement in BCS to allow prompt evaluation for liver transplant if treatment fails. ■

References:

- (1) Doi: 10.1016/j.surg.2003.09.005
- (2) Doi: 10.1053/j.gastro.2008.05.051
- (3) Doi: 10.1016/j.jhep.2025.08.001

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Tapper EB, Chen X, Parikh ND

Testosterone replacement reduces morbidity and mortality for most patients with cirrhosis

Background and aims: Many men with cirrhosis have low testosterone levels. This is associated with sarcopenia, anemia, and poor quality of life. Data are lacking, however, regarding the clinical impact of testosterone replacement.

Methods: The authors conducted an emulated clinical trial evaluating the impact of testosterone replacement among men who were diagnosed with hypogonadism at the same time as their diagnosis of cirrhosis (new user design). They used nationally representative Medicare data (2008–2020) to examine the risk of death, decompensation events, and fractures in patients who did or did not receive testosterone. They balanced treated and untreated with inverse probability of treatment weighting and evaluated outcomes using an intention-to-treat design.

Results: A total of 282 patients (7.4%) with testicular hypofunction and cirrhosis received testosterone replace-

ment after diagnosis. Patients started on testosterone spent 28.6% of patient-days on therapy, and patients not started would spend 0.5% of patient-days on therapy ($p < 0.0001$). Testosterone use was associated with lower mortality (subdistribution hazard ratio [sHR] = 0.92; 95% confidence interval [CI]: 0.85–0.99). Testosterone also led to a lower risk of new decompensation events (sHR = 0.92; 95% CI: 0.86–0.99) and especially for ascites requiring paracentesis (sHR = 0.82; 95% CI: 0.76–0.89) and variceal hemorrhage (sHR = 0.67; 95% CI: 0.54–0.85) with less effect on hepatic encephalopathy requiring hospitalization (sHR = 0.92; 95% CI: 0.84–1.01) and fractures (sHR = 0.99; 95% CI: 0.91–1.08) and without increased risk of hepatocellular carcinoma (sHR = 1.09; 95% CI: 0.91–1.3). There was substantial heterogeneity of treatment effect across baseline subgroups.

Conclusions: In the authors' target trial emulation of a nationally representative cohort of older patients with cirrhosis and hypogonadism, testosterone use improved clinical outcomes.

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TRANSLATIONAL SCIENCE CORNER

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Jiang Z, Wang Y, Gong J, Chen X, Hang D, Chen C, Hong X, Zhang J, Qiu K, Liao Y, Li P, Wang H, Yang Z, Qiu T, Zhou Y, Chen Z, Zhou H, Shan X, Zhou N, Liu L, Feng F, Su F, Ma H, Liu Z, He W, Fang L, Xuan J, Gan Z, Gao X, Zhang J, Chen H, Wang F, Zhang X, Zhu M

An *Aeromonas* variant that produces aerolysin promotes susceptibility to ulcerative colitis

Introduction: Ulcerative colitis (UC) is a multifactorial disease involving immune dysregulation, genetic susceptibility, aberrant inflammatory responses to intestinal microbiota, and environmental factors. UC is characterized by an unpredictable clinical course, often alternating between periods of exacerbation and remission. Because the inflammation and ulceration associated with UC are typically confined to the mucosal layer, UC has been often considered a disease of the epithelial barrier. The initiating factors responsible for epithelial barrier impairment remain unclear and elucidating them could reveal how UC develops and inform new treatment strategies. Rationale: The gut epithelium contains one of the largest populations of tissue-resident macrophages, which serve as the first line of defense against pathogens invading from the intestinal lumen. We hypothesized that gut-resident macrophages are compromised in UC, leading to impaired epithelial integrity, and we therefore examined macrophages in UC colon tissues.

Results: In colon tissues isolated from UC patients, we found that tissue-resident macrophages were depleted in areas that did not show indications of inflammation. We hypothesized that macrophage loss preceded overt inflammation. In mouse models, chemical or genetic ablation of macrophages increased susceptibility to intestinal injury. To identify potential factors that might impair the function of macrophages, we examined bacteria present in fecal samples from UC patients. We identified a toxin-producing bacterium belonging to the *Aeromonas* genus, designated *Aeromonas* sp. MTB (macrophage-toxic bacteria), which expressed the virulence factor aerolysin. Macrophages exhibited higher sensitivity to aerolysin-induced cell death than epithelial cells, a result that we hypothesized could lead to barrier impairment without direct epithelial damage. MTB persistently colonized mice under pathological conditions, depleting macrophages and enhancing sensitivity to enteric stimuli. MTB promoted colitis in mice exposed to dextran sulfate sodium or lacking interleukin-10 expression, with phenotypes resembling UC, but not in germ-free mice. An aerolysin-deficient MTB mutant failed to cause colitis,

supporting the role of this toxin. In mice, pretreatment with polyclonal anti-aerolysin antibodies prevented MTB-induced colitis, and a monoclonal anti-aerolysin ameliorated established disease. To determine the prevalence of this bacterium in UC patients versus healthy individuals, we developed a real-time polymerase chain reaction assay to detect *Aeromonas* species. *Aeromonas* species were detected more frequently in stools from UC patients compared with healthy controls. We also detected aerolysin in colon tissues isolated from UC patients.

Conclusion: We identified a variant of *Aeromonas* in UC patients and demonstrated its ability to promote colon inflammation in mice through aerolysin-mediated impairment of tissue-resident macrophages. Treatment with an anti-aerolysin antibody alleviated disease severity in mice exposed to MTB. Our findings highlight how microbes may contribute to UC pathogenesis and suggest that targeting bacterial virulence factors could be a therapeutic strategy for UC.

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EXPERT OPINION



Dr. Lena Sophie Mayer

Bacterial virulence factors as therapeutic targets in ulcerative colitis?

Ulcerative colitis (UC) is an inflammatory bowel disease characterized by a highly variable clinical course. Although treatment options have increased considerably in recent years, durable remission is often not achieved. Organ damage may occur, and up to one-quarter of patients eventually require colectomy. The pathogenesis of UC is still incompletely understood; multiple factors, including dysregulation of the intestinal immune system, dysbiosis, and defects of the mucosal barrier contribute to disease development. However, the mechanisms underlying disruption of the epithelial barrier have not yet been fully elucidated. Tissue-resident macrophages, as part of the innate immune system, constitute a central first line of defense against pathogens and play an important role in maintaining the epithelial barrier. In their study, Jiang et al. observed a reduction in subepithelial, tissue-resident macrophages not only in inflamed tissue but in areas that had not yet exhibited inflammation, leading them to conclude that macrophage

loss precedes the onset of inflammation. Bacteria-free supernatants derived from stool cultures of patients with UC exerted cytotoxic effects on murine bone marrow-derived macrophages in vitro. The authors identified an *Aeromonas* variant that produces the macrophage-toxic protein aerolysin. In vitro experiments and additional mouse models demonstrated that macrophages are more susceptible to aerolysin-induced cell death than epithelial cells, suggesting that aerolysin-mediated barrier dysfunction occurs without direct epithelial damage. The identified *Aeromonas* strain, referred to as macrophage-toxic bacteria (MTB), was able to persistently colonize mice following pretreatment with antibiotics or dextran sulfate sodium (DSS), whereas colonization under physiological conditions was not sustained. MTB promoted inflammation in 2 different murine colitis models, and aerolysin production was required for this effect. Polyclonal anti-aerolysin antibodies prevented MTB-induced colitis, whereas monoclonal anti-aerolysin antibodies attenuated inflammation. Furthermore, the authors demonstrated that *Aeromonas* species were detected more frequently in stool samples from patients with UC than from healthy donors, and aerolysin was identified in intestinal biopsy specimens from patients with UC. The authors conclude that MTB and aerolysin may represent diagnostic biomarkers and potential therapeutic or preventive targets for antimicrobial or antibody-based treatments. However, UC is a complex, multifactorial, immune-mediated disease in which bacterial toxins do not represent the primary pathogenic factor. Antitoxin antibodies neutralize toxin-mediated effects but do not eliminate toxin-producing bacteria and lack immunomodulatory properties, making their efficacy during active inflammation uncertain.

Moreover, it remains unclear which additional bacterial toxins may be pathogenic and would require simultaneous targeting. The use of multiple antibody-based therapies would be costly and potentially associated with increased adverse effects. Antibiotic therapy in UC is currently indicated only in cases of confirmed infection or specific complications and is not recommended for modulation of the gut microbiota, as protective bacteria may also be depleted or eliminated. Fecal microbiota transplantation is presently under investigation as a treatment for UC in clinical trials. Overall, this study is convincingly conducted and sheds light on a mechanism that contributes to UC pathogenesis. Further investigations focusing on interactions between the intestinal immune system and the gut microbiome are essential to advance understanding of disease mechanisms. ■

Liver

Nature. 2026;649(8098):991-1002

Gridley J, Pak D, Kumari A, Shupak J, Holland B, Shi Y, Trivedi S, Wang Y, Kasturi SP, Kapoor A, Chung RT, Grakoui A

iHALT unlocks liver functionality as a surrogate secondary lymphoid organ

Upon viral infection, the current paradigm of humoral immunity posits that germinal centre reactions occurring

within secondary lymphoid organs (SLOs) yield effector plasma cells that subsequently traffic to infected organs or the bone marrow. However, it is not well understood how viral tissue tropism may govern the spatiotemporal dynamics of such responses. Here we demonstrate that infection with a prototypical systemic virus indeed induces liver-trafficking plasma cells generated in SLOs, whereas strictly hepatotropic hepatitis viral infection elicits locally primed, virus-specific plasma cells in the liver independently of SLO contribution. Such locally derived progenies emerged from inducible hepatic-associated lymphoid tissue (iHALT) structures containing generative foci of T follicular helper cells, myeloid cells and germinal centre-like B cells, often arising from single founder clones unique to individual periportal structures and locally supporting somatic hypermutation. Critically, the cellular composition, cell-cell contact partners and microarchitecture of such iHALT structures in mice were closely mirrored upon hepatitis viral infection in humans. Functionally dependent upon CD40L signalling and cognate B cell receptor specificity, emerging CXCR4(+)VLA-4(+)LFA-1(+)CD44(+)CD138(+) plasma cells were immediately retained along CXCL12(+)fibronectin(+)ICAM2(+)osteopontin(+)type I collagen(+) periportal fibroblast tracts, acting as cognate anchoring pairs that were critical to their maintenance therein. In summary, we characterize humoral immunity exclusively generated and maintained within its extralymphoid site of viral infection in the liver amidst SLO dormancy, in which functional iHALT successfully compensates for strictly hepatotropic virus-induced SLO-evasion strategies to prevent persistent infection.

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EXPERT OPINION



Prof. Dr. Dr. Bertram Bengsch

The dynamic liver immune system: An iHALT to infection

The liver has long been recognized as an immunologically active organ, with a primarily tolerogenic role in maintaining homeostasis; however, it is also recognized as a site of primary immune activation suitable for T-cell priming during infection. Our understanding of the role of the liver in humoral immunity is less well-defined. Effective antiviral B-cell responses typically require germinal center (GC) reactions that are associated with the generation of high-affinity antibodies and the development of memory B cells and antibody-producing plasma cells. These reactions canonically take place in secondary lymphoid organs (SLO), most notably draining lymph nodes. Nevertheless, tertiary lymphoid structures (TLSs) are also frequently described in liver diseases. In recent work, Gridley et al. examined whether liver tropism influences the generation of local antiviral humoral responses. The authors studied a murine model system of a strictly hepatotropic infection (the HCV-

related rodent hepacivirus [RHV]). The authors compared immune responses with those elicited by lymphocytic choriomeningitis virus (LCMV), a systemic infection that also affects the liver. A key result was that, during strictly hepatotropic infection, intrahepatic numbers of antibody-secreting cells (plasma cells) closely correlated with virus-specific serum IgG titers. Moreover, even splenectomized mice and mice treated with FTY720, a sphingosine-1-phosphate receptor inhibitor that blocks lymph node egress, were able to clear RHV infection and maintained intrahepatic antibody-secreting cell and GC B-cell numbers comparable to those in untreated mice. These findings were in stark contrast to systemic infection, in which FTY720 treatment resulted in markedly impaired humoral immunity.

These observations support a prominent role for antiviral control through intrahepatic local immune reactions. The authors compared the intrahepatic development of humoral immunity and identified an intrahepatic formation of GC-like responses in RHV over time. Interestingly, the development of intrahepatic GC-like structures occurred approximately 3 weeks after intrahepatic infection, later than the canonical GC formation observed at around 2 weeks in SLOs during systemic infection. Intriguingly, in the RHV model, the formation of GC-like responses with an expansion of B-cell signatures in the liver occurred despite minimal changes in systemic SLOs, a phenomenon the authors describe as SLO dormancy and in line with a primary intrahepatic immune reaction. Spatial transcriptomic analysis showed the induction of intrahepatic lymphoid aggregates with features of blasting B cells, indicating intrahepatic compartmentalization, but lacked the level of structural organization inherent to SLOs, such as segmentation into spatially distinct B- and T-cell zones or specialized macrophage populations. The authors chose to not classify these structures as TLS but instead referred to them as induced intrahepatic-associated lymphatic tissue (iHALT) to highlight their dynamic character. The iHALT structures were primarily identified in periportal areas of the liver, an area also described to act as the primary micro-anatomic site for effective T-cell help mediated by intrahepatic dendritic cells (<https://doi.org/10.1038/s41467-024-45612-5>).

The Grakoui lab further investigated potential molecular mechanisms and cellular interaction partners that could underlie the generation and localization of iHALTs. They found that multiple cell-adhesion molecules were expressed by plasma cells that fit to ligands expressed by neighboring perivascular fibroblasts, including VLA-4-fibronectin, CXCR4-CXCL12, and CD44-osteopontin interactions. Blocking these ligand-receptor interactions by inhibitory antibodies strongly reduced the number of antibody-secreting cells in the liver and, in combination, resulted in impaired virus control.

These findings thus highlight a crucial role for these “makeshift” iHALT structures in mediating control of a hepatotropic infection. Notably, similar iHALT structures were observed in chronic HCV infection, a disease known for its TLS formation and high production of antibodies. Comparison to other liver diseases, such as HBV infection or autoimmune hepatitis revealed similarities but also cellular differences in iHALT composition, suggesting that disease-specific cues drive the formation of local sites for prolonged immune interactions as a dynamic process.

These data establish intrahepatic immune responses as key contributors to the control of hepatotropic infections and identify periportal areas, which are the typical site

of iHALTs. Understanding the cues inducing them may help identify therapeutic targets for modulating liver immunity. Nevertheless, while the work shows an important role of iHALTs in humoral immune response, T cells, a major component of adaptive immunity in the diseases studied, may also be present within iHALTs independently of them. The role of iHALTs in determining T-cell immunity warrants further study. ■

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e-mail: info@cicsud.it
<https://www.sanita.puglia.it/web/>

April 17–21, 2026, Munich, Germany
ESCMID Global 2026
36th European Congress of Clinical Microbiology & Infectious Diseases
e-mail: info@escmid.org
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April 22–25, 2026, Istanbul, Turkey
APASL 2026
35th Annual Meeting of the Asian Pacific Association for the Study of the Liver
e-mail: secretariat@apasl2026istanbul.org
<https://www.apasl2026istanbul.org/>

April 24–25, 2026, Warsaw, Poland
Symposium 243
Gastrointestinal Inflammation and Neoplasia
e-mail: meeting@falkfoundation.org
<https://falkfoundation.org>

May 2–5, 2026, Chicago, IL, USA & Online
Digestive Disease Week (DDW 2026)
<https://ddw.org>

May 9–12, 2026, Tampa, FL, USA
American Society of Colon & Rectal Surgeons (ASCRS) Annual Scientific Meeting
e-mail: ascrs@fascrs.org
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<https://ascrsasm2026.eventscribe.net/>

May 14–16, 2026, Milan, Italy
ESGE Days 2026
Reimagining endoscopy
e-mail: esgedays@esge.com
<https://esgedays.org>

May 18–20, 2026, Cologne, Germany
ESDE 2026 – 28th European Conference on Esophageal Diseases
e-mail: esde@wikonect.de
<https://esde2026.com>

May 21, 2026, Geneva, Switzerland
EASL – WHA Side Event, From Vision to Action: A Holistic Approach to Metabolic Health and NCD Prevention and Care
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May 27–30, 2026, Barcelona, Spain
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June 9–12, 2026, Montpellier, France
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37th Annual Meeting and Postgraduate Course
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June 12–13, 2026, Hamburg, Germany
Primary Sclerosing Cholangitis: From Pathogenetic Insights to Novel Therapies
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<https://easl.eu>
<https://easl.eu/event/psc-from-pathogenetic-insights-to-novel-therapies/>

June 12–13, 2026, Stockholm Sweden
Clinical Research Study Design
e-mail: easloffice@easloffice.eu
<https://easl.eu>
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June 13–16, 2026, Chicago, IL, USA
ENDO 2026
e-mail: meetings@endocrine.org
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June 19–20, 2026, Frankfurt, Germany
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38th Annual Conference of the German Working Association for Chronic Inflammatory Bowel Diseases
e-mail: daced@kompetenznetz-darmerkrankungen.de
<https://kompetenznetz-darmerkrankungen.de/fortbildung/>

June 22–25, 2026, Liverpool, United Kingdom
BSG Live'26
e-mail: conference@bsg.org.uk
<https://live.bsg.org.uk>

June 24–27, 2026, Lille, France
58th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
e-mail: office@espghan.org
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June 24–27, 2026, Istanbul, Turkey
58th European Pancreatic Club (EPC) / International Association of Pancreatology (IAP) Joint Meeting
e-mail: info@europeanpancreaticclub.org
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June 26–27, 2026, Dresden, Germany
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