

IN BRIEF

CROHN'S DISEASE

Perianal fistula surgical closure in Crohn's disease

A multicentre patient-preference randomized control trial (PISA-II) included 94 patients with Crohn's disease and an active high perianal fistula assigned to surgical closure combined with short-term anti-TNF therapy ($n=38$) or to anti-TNF therapy alone ($n=56$). At 18 months, radiological healing (primary outcome) was more in the surgical group than in the anti-TNF group (32% versus 9%, $P=0.005$), whereas there was no significant difference in clinical closure (secondary outcome) between the two groups (68% versus 52%). Perianal Disease Activity Index score was lower in the surgical group than in the anti-TNF group ($P=0.031$). Adverse effects were similar in both treatment groups.

ORIGINAL ARTICLE Meima-van Praag, E. M. et al. Short-term anti-TNF therapy with surgical closure versus anti-TNF therapy in the treatment of perianal fistulas in Crohn's disease (PISA-II): a patient preference randomised trial. *Lancet Gastroenterol. Hepatol.* [https://doi.org/10.1016/S2468-1253\(22\)00088-7](https://doi.org/10.1016/S2468-1253(22)00088-7) (2022)

LIVER

Anti-SARS-CoV-2 vaccine in liver transplantation

Liver transplant recipients ($n=61$) showed improved humoral immune response after a third BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ($P<0.0001$). The activated T cell counts and the levels of anti-RBD IgG and neutralizing antibodies were increased after the third dose ($P=0.008$, $P<0.0001$ and $P<0.0001$, respectively). Adverse effects, reported by 37% of recipients, were mild.

ORIGINAL ARTICLE Davidov, Y. et al. A third dose of the BNT162b2 mRNA vaccine significantly improves immune responses among liver transplant recipients. *J. Hepatol.* <https://doi.org/10.1016/j.jhep.2022.03.042> (2022)

PANCREATIC CANCER

Microbial signatures in pancreatic cancer

Metagenomics of faecal and salivary samples from Japanese patients with treatment-naive pancreatic ductal carcinoma (PDAC) ($n=47$) and individuals with non-PDAC as controls ($n=235$) revealed 30 gut and 18 oral bacterial species, and 58 bacteriophages associated with PDAC. Among the gut bacterial species significantly (FDR <0.1) associated with PDAC were *Veillonella* spp. and *Streptococcus* spp., which were also enriched in Spanish ($n=57$) and German ($n=43$) patients with PDAC.

ORIGINAL ARTICLE Nagata, N. et al. Metagenomic identification of microbial signatures predicting pancreatic cancer from a multinational study. *Gastroenterology* <https://doi.org/10.1053/j.gastro.2022.03.054> (2022)

RELATED ARTICLE Kartal, E. et al. A faecal microbiota signature with high specificity for pancreatic cancer. *Gut* <https://doi.org/10.1136/gutjnl-2021-324755> (2022)

GUT MICROBIOTA

Water chlorination and intestinal microbiota

In a cluster-randomized automated water chlorination trial, faecal metagenomes from 130 Bangladeshi children ($n=64$ control and $n=66$ treatment group) were analysed. Water chlorination was associated with a higher abundance (FDR-adjusted $P<0.05$) of bacterial genera, such as *Akkermansia* spp. (treatment coefficient 2.4, 95% CI 1.9–3.0), but it did not affect overall richness or diversity. No significant difference was observed in the presence or absence of clinically relevant antibiotic-resistant genes (ARGs) between the two groups. In the treatment group, differences were detected in the relative abundance of ARGs, such as a higher relative abundance of *mdf(A)*, which correlated strongly with *Enterobacteriaceae* ($\rho>0.9$).

ORIGINAL ARTICLE Nadimpalli, M. L. et al. Drinking water chlorination has minor effects on the intestinal flora and resistomes of Bangladeshi children. *Nat. Microbiol.* <https://doi.org/10.1038/s41564-022-01101-3> (2022)

Journal Club



ABDOMINAL PAIN IN IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) affects 10–15% of the general population worldwide and is characterized by abdominal pain and altered bowel habits. Abdominal pain is considered the core IBS symptom by the **Rome IV criteria**, and its severity constitutes a major driver for care-seeking behaviour in patients with IBS. Early mechanistic studies mainly focused on understanding the causes of motility disorders at the cellular and molecular level. However, gut motor abnormalities were poorly correlated with patients' abdominal pain and discomfort. As psychological factors highly influence colonic sensitivity, it was considered that the prominent mechanism of abdominal pain was related to the central nervous system. Thus, research on centrally acting visceral analgesics was thought to be needed, rather than focusing on peripheral inputs.

The study by Barbara et al. in 2004 changed this paradigm. It was generally accepted that peripheral sensitization of sensory neuronal endings could be involved in visceral hypersensitivity onset in IBS; however, links between abdominal pain and peripheral events in gut tissues were poorly explored. Barbara et al. demonstrated that mast cells were increased in number and were more degranulated in the colonic mucosa of patients with IBS compared with healthy individuals. Most importantly, the researchers showed that mast cells were closer to nerve endings in patients with IBS than in healthy individuals. A significant positive correlation was observed between nerve-to-mast cell proximity and degranulation of mast cells ($P=0.002$). This study documented for the first time a nerve-to-mast cell phenotype in peripheral (colonic) tissues of patients with IBS and correlated colonic mast cell parameters (such as mediator release) with the severity and frequency of abdominal pain. This study paved the way for the concept of peripherally acting analgesics in IBS abdominal pain treatment.

To study the effects of peripheral IBS mediators, the investigators worked with cultures of freshly harvested colonic biopsy samples from patients and collected their supernatants. Since then, hundreds of studies have used this approach and enabled the identification of several peripheral IBS mediators and their function. The roles of proteases, histamine, serotonin, prostaglandins, cytokines or chemokines in patients' tissues on submucosal, myenteric or spinal neurons firing or on epithelial barrier functions have been elucidated. One could envision that individual profiling of peripheral tissue mediators of patients with IBS could aid patient stratification in the future.

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Advancements have arisen from this first demonstration of peripheral input in the mechanisms of abdominal pain associated with IBS. For example, Cibert-Goton et al. suggested that peripheral pronociceptive changes in the colon are more important than psychological factors to explain pain severity. Pain management in IBS is still a research priority and an important clinical need. Treatment approaches based on targeting peripheral tissue mediators augur well for additional efficacious treatments that could even aid precision medicine.

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Competing interests

The author declares no competing interests.

ORIGINAL ARTICLE Barbara, G. et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* **126**, 693–702 (2004)

RELATED ARTICLE Cibert-Goton, V. et al. Pain severity correlates with biopsy-mediated colonic afferent activation but not psychological scores in patients with IBS-D. *Clin. Transl Gastroenterol.* **12**, e00313 (2021)