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Pantoprazole Prevents Gastrointestinal Events in Rivaroxaban or Aspirin Users

A randomized control trial showed that pantoprazole did not reduce upper gastrointestinal events among patients taking aspirin or rivaroxaban

Gastrointestinal bleeding is one of the most common adverse events in patients treated with antiplatelet or anticoagulation therapy. It is unclear whether proton pump inhibitors, a class of medications shown to prevent peptic ulcer bleeding among nonsteroidal anti-inflammatory drug users, reduce gastrointestinal events among patients taking aspirin or anticoagulants. In this issue of *Gastroenterology*, Moayyedi et al conducted a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease. Patients were randomly assigned to pantoprazole 40 mg/d or placebo, as well as rivaroxaban 5 mg twice daily, aspirin 100 mg/d, or rivaroxaban 2.5 mg twice daily plus aspirin 100 mg/d and followed for a mean of 3 years. The rivaroxaban-aspirin arm of the trial was terminated at a planned interim analysis based on overwhelming efficacy of rivaroxaban-aspirin combination compared with aspirin alone in decreasing major cardiovascular events. Upper gastrointestinal events, defined as a composite of overt bleeding with a gastroduodenal lesion (peptic ulcer or neoplasia) that is bleeding at the time of upper endoscopy, overt upper gastrointestinal bleeding of unknown origin, occult bleeding (hemoglobin drop at least 2 g/dL), or symptomatic gastrointestinal lesions (ulcers, erosions, obstruction, or perforation), were similar between the pantoprazole and placebo groups (hazard ratio, 0.88; 95% confidence interval, 0.67–1.15). Among the individual components of the composite endpoint, pantoprazole reduced bleeding from gastroduodenal lesions (hazard ratio, 0.52; 95% confidence interval, 0.28–0.94), but no difference in overt or occult upper gastrointestinal bleeding. The number needed to treat was 1770 (95% confidence interval, 934–17,111) for pantoprazole to prevent 1 overt bleeding from gastroduodenal lesions each year. The randomized clinical trial showed that routine use of proton pump inhibitors among patients taking aspirin or anticoagulant therapy did not decrease the overall gastroduodenal events, but may decrease bleeding from gastroduodenal lesions.

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Dietary Therapy for Crohn's Disease: A Randomized Trial

A randomized clinical trial showed that the Crohn's disease exclusion diet plus partial enteral nutrition-induced sustained remission in a high proportion of children with mild to moderate Crohn's disease compared with exclusive enteral nutrition.

Exclusive enteral nutrition, a liquid formula diet avoiding all other oral intakes, is a first-line treatment in pediatric patients with Crohn's disease based on its superiority to oral corticosteroids in inducing remission without medical side effects. However, implementation in clinical practice has been limited owing to the challenge of requiring children to avoid intake of all

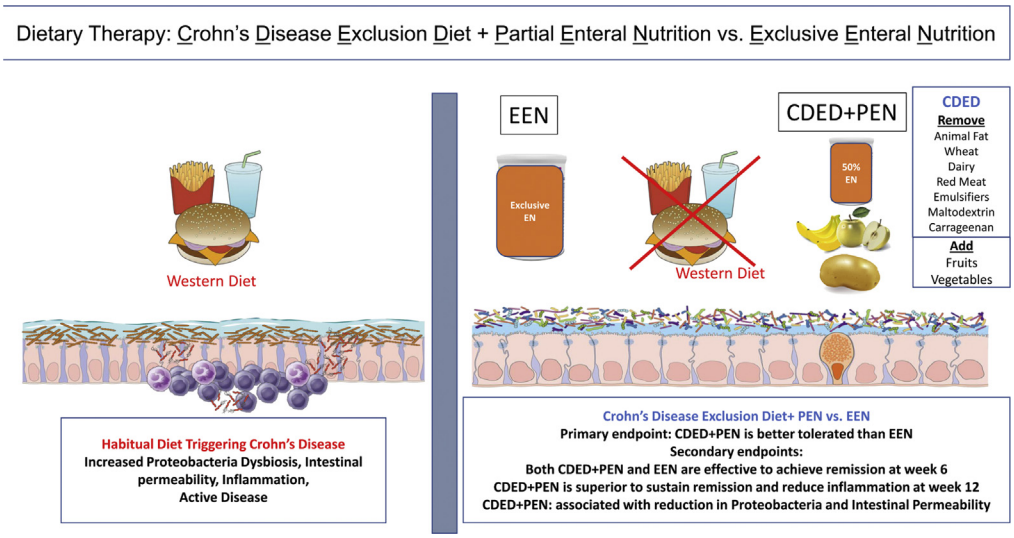

Figure 1. Crohn's disease exclusion diet plus partial enteral nutrition is well-tolerated and induced sustained remission in children with mild-to-moderate Crohn's disease. CDED, Crohn's disease exclusion diet; EEN, exclusive enteral nutrition; EN, enteral nutrition; PEN, partial enteral nutrition.

other food for 6–8 weeks and the frequent need for use of nasogastric tube feeding. As an alternative, the Crohn's disease exclusion diet is a whole-food diet coupled with partial enteral nutrition designed to decrease exposure to dietary components hypothesized to negatively impact the gut microbiome, intestinal barrier, and intestinal immunity (Figure 1). In this issue of *Gastroenterology*, Levine et al conducted a randomized controlled trial comparing the 2 diets administered orally over 12 weeks in pediatric patients with mild to moderate Crohn's disease. Children were randomly assigned to either a Crohn's disease exclusion diet with 50% of calories from formula in the first 6 weeks, followed by Crohn's disease exclusion diet with 25% of calories from formula from weeks 7 to 12 (n = 40), or to exclusive enteral nutrition for the first 6 weeks, followed by a free diet with 25% of calories from formula from weeks 7 to 12 (n = 38). The Crohn's disease exclusion diet plus partial enteral nutrition was better tolerated (98% vs 74%; $P < .01$) compared with exclusive enteral nutrition. More children treated with the Crohn's disease exclusion diet plus partial enteral nutrition remained in steroid-free remission at week 6 (75% vs 59%; $P = .38$) and at week 12 (76% vs 45%; $P = .01$) and showed changes in the fecal microbiome associated with remission. These data support the use of Crohn's disease exclusion diet plus partial enteral nutrition as a first-line therapy to induce remission in children with mild to moderate Crohn's disease.

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Effects of Serotonin on Gastrointestinal Motility

Patients with depression also frequently suffer from gastrointestinal dysfunction, such as chronic constipation. A mutation in tryptophan hydroxylase-1 and -2 (TPH2), the rate-limiting step in serotonin production, occurs in depressed patients and TPH2 mutant mice had lower enteric serotonin levels, motility defects, and depressive symptoms, defects all rescued by bypassing TPH2 using sustained release 5-hydroxytryptophan.

Neurologic disorders, such as Parkinson's disease and Alzheimer's dementia, frequently have gastrointestinal (GI)-associated comorbidities and it is not uncommon for patients with depression to also suffer from constipation. Although the medications used to treat the primary disorder may contribute to GI symptoms, it is also possible that pathophysiology affecting central nervous system (CNS) function may also impact enteric nervous system (ENS) function, resulting in motility disorders such as constipation. Serotonin (5-HT) is a neurotransmitter common to both the CNS and ENS. Notably, neuronal 5-HT enhances GI motility and promotes gut neurogenesis. Tryptophan hydroxylase-1 and -2 (TPH2) are rate-limiting in 5-HT production, and TPH2 is expressed in both nervous systems. In fact, polymorphisms in TPH2 have been identified in patients with depression and specifically an arginine to histidine at codon 441 (R441H) identified in selective serotonin reuptake inhibitor–resistant depression. Transgenic mice engineered to express the murine TPH2 mutant homolog (R439H) have lower CNS 5-HT levels and have anxiety and depressive behaviors. In this issue of *Gastroenterology*, Israelyan et al determined whether TPH2 mutant mice also have intestinal phenotypes and tested the strategy of pharmacologic intervention with long-lasting 5-HT could effectively reverse neurologic and gut phenotypes. TPH2 mutant mice had decreased enteric 5-HT with associated ENS developmental defects and, not surprisingly, decreased gut motility with decreased frequencies of colonic migrating motor complex and magnitude as well as gut structural abnormalities such as reduced villus height and crypt perimeter. Bypassing TPH2 via dietary supplementation with sustained release 5-HTP effectively

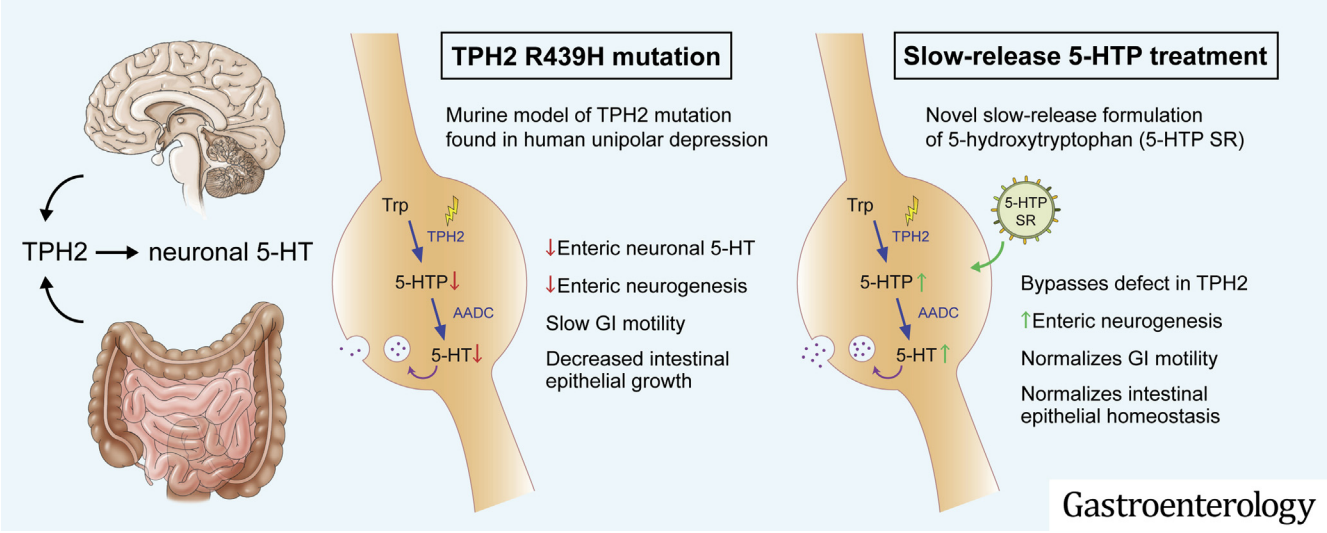

Figure 2. Graphical Abstract from article by Israelyan et al.

reversed these abnormalities as well as brain and behavioral deficits (Figure 2). This study further reveals the complexity of and interrelationships between CNS and ENS function and considerable plasticity in the ENS, allowing for the postnatal correction of development ENS deficits in adult mice. Sustained release 5-HTP may have therapeutic potential in treating patients with low 5-HT, depression, and constipation.

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Metabolomes, Proteomes, Transcriptomes and Hepatitis C Virus-Related Diseases

Multi-omics approaches coupled with combined cell line and humanized hepatitis C virus mouse model identify defects in peroxisome function, metabolism, and STAT3 signaling in hepatitis C virus infection.

Although over the past 3 decades we have made significant progress in understanding the pathophysiology of hepatitis C, there remains much to learn about hepatitis C virus (HCV) infection and resultant liver disease, its progression to cirrhosis, and to hepatocellular carcinoma. Recent advances in genomic and proteomics technologies and in newly developed sophisticated humanized mouse modeling of HCV infection allow never before possible interrogation of the impact of early HCV infection on reprogramming basic hepatocyte biology. In this issue of *Gastroenterology*, Lupberger et al use a combination of genomic, transcriptomic, metabolic, and proteomic analysis of HCV infected Huh7^{dif} (hepatocyte-like cells) and a uPA/SCID humanized liver mouse model infected with serum from HCV-infected patients to establish early events in HCV infection. Pathway analysis in both models identified metabolic impacts and dysregulation of transcripts and proteins previously implicated in hepatocarcinogenesis. Interestingly, HCV infection increased transcripts involved in innate immunity; however, protein levels were unaffected. Metabolic perturbations included increased glucose metabolism and STAT3 signaling with decreased peroxisome function, resulting in reduced beta oxidation of very long chain fatty acids, resulting in their accumulation. Last, analysis of patients with HCV liver disease had similar alterations in peroxisome function. This report presents a detailed multi-omics atlas of HCV infection, identifies high concordance between animal modeling and human disease, and may yield novel therapeutic strategies in the management of HCV.

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