ABSTRACT

Abstracts of the 19th American Neurogastroenterology and Motility Society Annual Scientific Meeting August 13–15, 2021 Boston, Massachusetts, USA

ORAL PRESENTATIONS

SESSION 1: BASIC ADVANCES MAKING AN IMPACT IN UNDERSTANDING GI PATHOPHYSIOLOGY

1 Gastric motility characterization from GI-MRI using a deep-learning-based automatic method

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**Purpose:** Peristaltic motility is a defining property of gastrointestinal function and can be visualized and quantified non-invasively using contrast-enhanced gastrointestinal MRI (GI-MRI). For assessing antral peristalsis quantitatively and accurately, in the present work, we established a deep-learning-based fully automatic pipeline using GI-MRI. We confirmed the reliability of our proposed analysis pipeline against simultaneously recorded multi-channel cutaneous electrogastrogram (EGG) and provided additional spatial characteristics of the peristalsis along the greater and lesser curvatures.

**Method:** In our proposed pipeline, we used a deep neural network to segment images automatically. We trained the network using an independent MRI dataset acquired from 48 rats and then applied the trained network to segment the newly acquired GI-MRI images directly. After minor post-processing to further improve the segmentation accuracy, we estimated the time-evolving displacement of the stomach contour perpendicular to the long axis along the greater or lesser curvature of the stomach.

**Results:** To evaluate our method, we performed simultaneous GI-MRI acquisition and EGG recording on six Sprague Dawley rats. We compared the frequency and power of the estimated displacements with corresponding EGG features within and across animals. The difference of dominant frequencies between EGG and peristaltic displacements was 0.0235 ± 0.0804 Cycles/minute (CPM) along the greater curvature, and −0.0052 ± 0.0787 CPM along the lesser curvature, suggesting a strong correspondence between the two. We then narrowed down the frequency range within 4–7 CPM and checked the relationship of the time-evolving power between EGG and peristaltic displacements. The result suggested high mutual information between two power estimations (z-score 0.633 ± 0.081 along the greater curvature and z-score 0.569 ± 0.068 along the...
lesser curvature). We further derived additional spatial features of the gastric motility unique to MRI and our analysis pipeline. We identified a spatially propagating sinusoid-like peristaltic pattern along the greater and lesser curvatures from the estimated displacements. The peristaltic wavelength is about 1.12 ± 0.40 cm along the greater curvature and 1.00 ± 0.36 cm along the lesser curvature. The estimated propagation velocity of the peristalsis wave fell in the range of 1.1–1.3 mm/s along both the greater and lesser curvatures. In conclusion, we have established a deep learning-based pipeline for the fully automatic characterization of gastric motility. Results from this analysis are consistent with the simultaneously recorded EGG in terms of time, frequency, and power, and in addition, provide more detailed spatial characteristics of gastric motility.

2 | Intracolonic administration of guanylate cyclase-c agonist linaclotide inhibits chronic psychological stress-induced activation of central nociceptive pathways to relieve visceral pain in rats

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Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits and frequently presents with co-morbid pain disorders such as bladder pain syndrome (BPS). Moreover, patients report an exacerbation of symptoms during periods of stress. Oral administration of the guanylate cyclase-c (GC-C) agonist linaclotide relieves stress-induced visceral pain via inhibition of afferent signaling at the level of the spinal cord and brain. However, it is unknown if intracolonic (i.c.) administration of linaclotide is similarly effective at attenuating stress-induced visceral pain. Here, we test the hypothesis that i.c. linaclotide relieves stress-induced colonic and bladder hypersensitivity by inhibiting afferent traffic to the spinal cord and brain nuclei involved in pain modulation.

Methods: Male and female rats were exposed to 1-hr of water avoidance stress (WAS) or sham stress for 10 days. On days 5–11 rats received i.c. linaclotide (3 µg/kg, q.d.) or vehicle. On day 10, referred bladder hyperalgesia was assessed by the frequency of withdrawal responses to von Frey filaments (0.16–15 g) applied to the suprapubic region (SWR). 24-h later rats received colorectal distensions (CRD) at 20–60 mmHg and the visceromotor response (VMR) was quantified. Brain and spinal cord were isolated for quantification of pERK+ neurons. Two-way ANOVA was used to analyze changes in SWR, VMR and pERK+ cells.

Results: Vehicle-treated WAS-exposed rats showed an increased VMR and SWR compared to sham stress (*p<0.05–###p<0.0001). WAS also increased CRD-evoked spinal and supraspinal neuronal activation as assessed via quantification of pERK+ neurons. Linaclotide inhibited the VMR to CRD and SWR in WAS-exposed rats compared to vehicle (#p<0.01–####p<0.00001). Additionally, linaclotide decreased the number of spinal and supraspinal CRD-evoked pERK+ neurons compared to vehicle in WAS rats. Linaclotide had no effect on pain behaviors or pERK immunoreactivity in sham stress rats compared to vehicle.

Summary: Intracolonic administration of linaclotide inhibits stress-induced colonic and bladder hypersensitivity by altering neuronal activation within the spinal cord and supraspinal pain modulation circuitry.

Conclusion: This study further highlights a role of GC-C mediated mechanisms in visceral pain processing and supports further evaluation of intracolonic linaclotide in human subjects.
activity and colon motility patterns as adults (Ednrb+/− mice did not live to adulthood), suggesting that even though they appear normal anatomically, Ednrb+/− mice may be a useful model to investigate long-term dysmotility and other chronic issues in HSCR. Some defects, however, were specific to Ednrb+/− mice that model HSCR aganglionosis. Lumbosacral parasympathetic input was dysfunctional only in Ednrb+/− mice, and also is needed to activate PHOX2B expression in these cells. Early loss (E8.5) of retinoic acid signaling therefore causes complete intestinal aganglionosis similar to the phenotype of Ret−/− and Phox2b−/− mice. Loss of cell-autonomous retinoic acid receptor signaling at later stages causes patterning defects and hypoganglionosis in the colon, loss of submucosal neurons, and changes in neuronal subtype identity. RNA sequencing from enteric nervous system cells at E11.5 and E13.5 demonstrated ~1000 genes regulated by retinoic acid at each age. Remarkably, different gene regulatory networks are activated by retinoid signaling at E11.5 and E13.5. Collectively, these data suggest that vitamin A deficiency (a very common global problem) and excess vitamin A can alter bowel motility in many ways and could contribute to the risk of Hirschsprung disease, chronic intestinal pseudo-obstruction, slow transit constipation, irritable bowel syndrome, and other bowel motility disorders.

4 | Cell-autonomous loss of retinoic acid receptor signaling causes diverse stage-specific enteric nervous system defects in mice

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Bowel motility disorders are caused by many genetic, toxic, infectious, metabolic, and immune-mediated defects that alter structure and function of the enteric nervous system, interstitial cells of Cajal and intestinal smooth muscle (among other cell types). The role of micronutrients in development and function of cells that control bowel motility is largely unexplored. A few papers show vitamin A deficiency or excess alters enteric nervous system development in mouse and avians at least in part via regulation of RET or PTEN in the enteric nervous system. Vitamin A is a precursor for retinoic acid, a regulator of gene expression that binds to retinoic acid receptors RAR/RXR to control many aspects of development and postnatal cell function. Retinoic acid signaling affects most cell types and many cells support enteric nervous system development. Prior studies in mutant animals or using chemical regulators of RAR did not unambiguously define which cells required retinoic acid signaling for normal development or evaluate the role of RAR signaling at later stages of development. To address these issues, we took advantage of a dominant negative retinoic acid receptor that is expressed after CRE-mediated DNA recombination in mice. We discovered that cell-autonomous retinoic acid receptor signaling within the enteric nervous system lineage is required to activate RET expression in enteric nervous system precursors as they migrate from neural tube to bowel (consistent with prior data), and also is needed to activate PHOX2B expression in these

5 | Evaluation of bidirectional gut and brain axis in patients with dyssynergic defecation

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Introduction: Dyssynergic defecation (DD) affects 40% of constipated patients. This abnormal behavioral problem of defecation may be associated with altered afferent or efferent gut and brain interactions. Whether the neurobiologic axis is dysfunctional in DD, and the abnormality affects the rectum or anus or both is unknown.

Aims: To examine the bidirectional anorectal-cortical axis by assessing cortical evoked potentials (CEP) and transcranial (TMS) and translumbarocral (TAMS) magnetic stimulation-induced motor evoked potentials (MEP) in DD patients and controls.

Methods: Patients with DD (Rome IV) and healthy controls were enrolled. CEPs were assessed by electrical stimulation of anus and rectum with a probe containing 2 pairs of bipolar steel ring electrodes. Anal and rectal MEPs were assessed by the same probe following bilateral TMS (cortex) and TAMS (lumbosacral) with a magnetic coil. Sensory thresholds for first sensation and pain, latencies (P1, N1, P2, N2) for rectal and anal CEPs, and bilateral latencies for rectal and anal MEPs were analyzed and compared.

Results: 33 patients (m/f = 1/32) with DD and 31 controls (m/f = 11/20) participated. Electrosensory thresholds (mA) for first sensation were significantly higher in rectum (29.3 ± 3.5 vs. 19.8 ± 2.1, p<0.02) and anus (18.8 ± 3 vs. 9.1 ± 6.3, p<0.001) in DD patients than controls, but not pain thresholds (p = 0.2). For CEP, both rectal and anal latencies (N1, P2 and N2) were significantly prolonged (p<0.02) in DD subjects compared to controls but not P1 (Table). For TMS, bilateral rectal and left anal MEP latencies were unchanged (p = 0.1) but right anal TMS was prolonged (p<0.02). All 8
Lumbo-anorectal and sacro-anorectal MEPs were significantly prolonged (p<0.0001) in DD patients compared to controls.

**Conclusion:** DD is associated with significant afferent gut-brain axis dysfunction as well as peripheral lumbosacral-anorectal axis, efferent dysfunction, characterized by prolonged conduction time. The transcranial-spinal axis appears to be intact. Furthermore, the dysfunction affects both the rectum and anus. Whether biofeedback therapy modifies this dysfunction merits further study.

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### Table 1

| Latency | ANAL | RECTAL |
|---------|------|--------|
|         | ms   | DD     | Healthy | DD     | Healthy |
| P1      | 78 ± 7 | 72 ± 3  | 68 ± 7  | 57 ± 3  |
| N1      | 117 ± 7 | 95 ± 3  | 109 ± 6 | 88 ± 3  |
| P2      | 178 ± 10 | 147 ± 7 | 177 ± 9 | 143 ± 8 |
| N2      | 214 ± 11 | 172 ± 6 | 217 ± 10 | 183 ± 10 |

**Parallel Session 3: Enteric neural neuroimmune signaling**

**6 | Modulation of visceral pain by the prefrontal cortex-bed nucleus of the stria terminals pathway**

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**Background:** Corticolimbic brain circuits demonstrate abnormal activity in patients with stress-induced visceral pain disorders, such as irritable bowel syndrome (IBS), characterized by colonic hypersensitivity. The prefrontal cortex (PFC) has been shown to participate in both pain and stress modulation. We have previously found that the pathway from the central amygdala to the bed nucleus of the stria terminalis (BNST) modulates colonic sensitivity in the rat. The BNST also receives signals from the PFC, but the role of the PFC in the modulation of stress-induced colonic nociception is unknown. The hypothesis for this study was that activation of PFC-BNST pathway could induce colonic hypersensitivity.

**Methods:** The role of PFC-BNST signaling was tested by infecting the PFC with viral vectors to express channelrhodopsin (ChR) or halorhodopsin (HR) and implanting fiber optic cannula at the BNST in male Fischer 344 rats (n = 4/group). A different cohort of rats had a single micropellet (30 µg) of the stress hormone, corticosterone (CORT) or cholesterol (CHOL) control implanted in the PFC (n = 8/group) to test the effect of stress on colonic sensitivity. In freely moving rats, colonic sensitivity was assessed as the number of abdominal contractions to graded, isobaric colorectal distension (20–60 mmHg, 10 min). In rats with opsin, colonic sensitivity was assessed with and without laser stimulation after 10 weeks. In rats with micropellets, colonic sensitivity was measured after 8 days at the peak diffusion of the micropellet. Results were analyzed with a repeated measure two-way ANOVA with Bonferroni’s post-hoc analysis (mean ± standard deviation).

**Results:** Inhibition of the PFC-BNST pathway via HR did not affect colonic sensitivity (60 mmHg: 22.0 ± 2.8 vs. 21.5 ± 3.3, p = 0.99). In contrast, activation of the PFC-BNST pathway with ChR induced colonic hypersensitivity (60 mmHg: 36.0 ± 8.8 vs. 28.5 ± 6.5, p<0.05). To demonstrate the role of stress on PFC signaling, rats with CORT implanted in the PFC developed colonic hypersensitivity compared to CHOL-implanted controls (60 mmHg: 37.9 ± 4.6 vs. 24.3 ± 2.7, p<0.01).

**Conclusions:** Both optogenetic and stress-induced signaling from the PFC to the BNST induced colonic hypersensitivity. These results support the role of the PFC-BNST pathway as part of a corticolimbic circuit that modulates visceral sensation in response to stress. Modulation of the PFC-BNST pathway could represent a valid target for novel therapies to treat disorders such as IBS.

**7 | Enteric glia sensitize nociceptor TRPV1 during acute inflammation through connexin-43-dependent prostaglandin-E2 release**

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Visceral pain involves processes that sensitize nociceptive nerve fibers in the intestine. Nociceptors innervate enteric ganglia where they interact with enteric glia but how enteric glia contribute to nociceptor sensitization is unknown. Here, we tested the hypothesis that acute inflammation promotes nociceptor sensitization through mechanisms that involve intercellular signaling between glia and nociceptors mediated by PGE2 and glial Cx43 channels. We used the DNBS model of acute colitis and tested the effects on enteric glia using multiplex immunoassays and ethidium bromide dye uptake to measure glial Cx43 channel activity. Specific interactions between glia and nociceptors were assessed using chemogenetics to activate glia while recording nociceptor activity with Ca²⁺ imaging in Gfap::hM3Dq:Trp1Cre;GCaMP5g-tdT mice. Sox10CreERT2;Cx43f/f mice were used to test how glial Cx43 channels modulate visceral sensitivity in visceromotor reflex recordings. At peak inflammation, DNBS colitis induced a 5-fold increase in IL1β expression in whole colon homogenates (n = 4–5, p < 0.05). IL1β increased Cx43-dependent glial dye uptake under basal conditions and potentiated ADP-stimulated dye uptake by 24% (n = 10–15, p<0.0001). Activating glia with clozapine-N-oxide in Gfap::hM3Dq:Trp1Cre;GCaMP5g-tdT mice did not affect nerve fiber responses to capsaicin under control conditions, but potentiated nerve fiber Ca²⁺ responses to capsaicin in the presence of IL1β (n = 5–7, p<0.05). The potentiating effects of glial activation were lost in the presence of the Cx43 mimic.
peptide 43Gap26 and ablating glial Cx43 in Sox10creERT2:Cx43fl/fl mice reduced visceromotor responses to colorectal distensions during inflammation in female (n = 8–10, p < 0.05), but not male mice. Glial RNA sequencing showed a significant increase in the PGE2 synthetizing enzyme, COX-2, in enteric glia during DNBS colitis (n = 3, p < 0.05); suggesting that PGE2 could mediate the effects of glial activation on nociceptors. In support, blocking nociceptor prostaglandin EP4 receptors eliminated the sensitizing effects of glial activation on nociceptor Ca2+ responses in the presence IL1β. Together, these data show that acute intestinal inflammation promotes visceral hypersensitivity through intercellular signaling between enteric glia and nociceptive nerve fibers in the periphery. Proinflammatory cytokines facilitate glial Cx43 opening and promote glial PGE2 production, which sensitizes nociceptors through actions at EP4 receptors.

**8 | SARS-CoV-2 induces enteric neuronal production of vasoactive intestinal peptide as a potential mechanism of COVID-19-associated diarrhea**

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**Background:** Up to 36.6% of COVID-19 patients have diarrheal symptoms. The mechanism of SARS-CoV-2-associated diarrhea remains poorly understood. We hypothesize that the crosstalk between the enteric nervous system and enterocytes plays a critical role in COVID-19-associated diarrhea. SARS-CoV-2 infection induces endoplasmic reticulum (ER) stress and release of Damage Associated Molecular Patterns (DAMPs) by the enterocytes, which stimulate enteric neuronal production of neurotransmitters that disrupt gut electrolyte homeostasis.

**Methods:** SARS-CoV-2 was propagated in Vero-E6 cells. Colonic epithelial Caco-2 expresses SARS-CoV-2 entry receptor ACE2 and was used for infection. ER stress (phospho-PERK and Xbp1s) and DAMP (HMGB1) markers were examined by Western blotting (WB). Primary mouse enteric neurons were co-cultured with Caco-2 cells that were pre-treated with ER stress inducer, tunicamycin. Supernatants from enteric neurons were used to assess the expression of vasoactive intestinal peptide (VIP) by ELISA. Enteric neurons were treated with DAMP molecules (HMGB1 or ATP), and the expression of c-FOS, a marker of neuronal activity, was determined by WB and immunostaining.

**Results:** SARS-CoV-2 infection led to increased expression of phospho-PERK and Xbp1s in Caco-2 cells. Compared to uninfected control, infected cells secreted HMGB1 into culture media, indicating epithelial production of DAMPs in response to SARS-CoV-2 infection. Tunicamycin was then used to induce ER-stress and the secretion of HMGB1, mimicking SARS-CoV-2 infection. Importantly, enteric neurons co-cultured with tunicamycin-treated Caco-2 cells secreted significantly higher levels of VIP. Co-treatment of Caco-2 cells with tunicamycin (apical) and VIP (basolateral) induced a synergistic decrease in membrane expression of Na+/H+ exchanger (NHE3), an important transporter mediating intestinal Na+/fluid absorption. Moreover, HMGB1 and ATP both increased the expression of phospho-c-FOS in cultured enteric neurons, indicating DAMP-induced neuronal activation.

**Conclusions:** Our findings demonstrate that SARS-CoV-2 infection of the enterocytes stimulates DAMPs-dependent neuronal production of VIP, which in turn inhibits NHE3-mediated electrolyte absorption by the enterocytes. These findings identify potential targets for the treatment of SARS-CoV-2 infection of the gastrointestinal tract.

**9 | Esophagogastric junction compliance in pediatric eosinophilic esophagitis and achalasia**

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**Background:** Achalasia and eosinophilic esophagitis (EoE) are esophageal disorders that present with significant swallowing impairment. Using the functional luminal probe (FLIP) previous studies have shown a reduction in esophagogastric junction (EGJ) and esophageal distensibility in achalasia and EoE, respectively. However, no studies have described the potential role of EGJ compliance (EGJ-C) in the management of achalasia or EoE. Therefore, we sought to evaluate EGJ-C in children with achalasia and EoE.

**Methods:** Pediatric patients with achalasia and EoE undergoing clinically indicated FLIP studies at Children’s Hospital of Philadelphia and Rady Children’s Hospital, San Diego, respectively, were included in the study. Median EGJ-C was determined by assessing pressure and cross-sectional area (CSA) relationships during volumetric distentions.

**Results:** Thirteen patients with achalasia (6 treatment-naïve and 7 previously treated; mean age, 15.4 years) and twenty-seven EoE patients (15 active and 12 inactive; mean age, 14.3 years) were included. Achalasia patients had a pre-dilation EGJ-C of 14.6% volume/mmHg. EGJ-C was 30.7% lower in treatment-naïve subjects (12.55% volume/mmHg) compared to those previously treated (18.1% volume/mmHg). A significant change in EGJ-C was seen in achalasia subjects after dilation (+14.3% volume/mmHg, p < 0.01). EoE subjects had an EGJ-C of 10.4% volume/mmHg. EGJ-C in active EoE subjects (6.4% volume/mmHg) was 45.1% lower compared to subjects with inactive disease (11.6% volume/mmHg). Additionally, EoE subjects who reported experiencing dysphagia “almost always” had
32.8% lower EGJ-C compared to subjects who reported “never having dysphagia”.

**Conclusions:** These patterns suggest a potential role of reduced EGJ-C in EoE related symptomatology as the median EGJ-C in EoE is similar to untreated patients with achalasia. EGJ-C should be assessed during evaluation of achalasia and EoE in larger cohorts to further explore its potential role in disease management.

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### 10 | Comparison of patients diagnosed with ineffective esophageal motility according to the Chicago classification v3.0 and v4.0 definitions, 2011–2019

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**Background:** The Chicago Classification v4.0 (CCv4.0) of ineffective esophageal motility (IEM) requires ineffective contractions following >70% of swallows or failed contractions following >50% of swallows on esophageal high resolution manometry (HRM) and is more stringent than the CCv3.0 definition.

**Aims:** To compare the presentation and clinical features of patients at the Hershey Medical Center (HMC) meeting the CCv4.0 definition of IEM (Group 1) compared to those meeting CCv3.0 criteria but not CCv4.0 (Group 2).

**Methods:** We conducted a retrospective study of 183 adults diagnosed with IEM after HRM at HMC between 2011 to 2019 and reviewed charts for demographics, symptoms, medical problems, medications, manometric, endoscopic, and radiographic data. Data were compared using the Wilcoxon rank-sum tests and Fisher exact tests. Data are mean ± SD.

**Results:** 133 patients fell into Group 1 and 50 patients into Group 2. Age (53 ± 17 vs. 56 ± 16 years), female gender (70% vs. 72%), and BMI were not significantly different between Groups 1 and 2. Symptom of dysphagia was more prevalent (p = 0.03) in Group 2, but reflux and regurgitation symptoms were not different. Nervous system disorders were less prevalent in Group 1 (35% vs. 52%, p = 0.03), but prevalence of musculoskeletal/connective tissue, mood, and endocrine disorders was not different. There was no difference in frequency of common medications. On HRM for Group 1, percent of failed contractions was associated with bolus clearance (r = −0.2, p = 0.03) and bolus escape (r = 0.4, p = 0.0001); this association was not significant in Group 2. No correlation was found between motility findings on HRM and barium studies in either group. Percent of weak contractions on HRM and barium tablet delay were associated (p = 0.04) in Group 1, but not in Group 2. Dysphagia was associated with no delay in barium in Group 2 (p = 0.04), with no association in Group 1. Dysphagia—but not reflux, regurgitation, or opioid use—was associated with an abnormal IRP (p = 0.005) when all patients were combined. In all groups, mean LES pressure was not associated with an upper endoscopy finding of esophagitis or hiatal hernia, dysphagia, reflux, or regurgitation.

**Conclusions:** Most features studied did not differ between Groups 1 and 2. A CCv4.0 IEM diagnosis is associated with worse esophageal function (reduced bolus clearance, increased bolus escape, and barium tablet delay). Symptom of dysphagia is not associated with worse motility, suggesting that dysphagia is not primarily dependent on bolus transit.

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### 11 | Mitochondrial dysfunction in interstitial cells of Cajal predisposes female diabetic mice to gastroparesis

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**Background & Aims:** Recently, we reported that delayed gastric emptying (DGE) was associated with mitochondrial injury in the duodenal mucosa of patients with diabetic (DM) gastroenteropathy (PMID: 33491664). Previously, we established a causal link between systemic mitochondrial dysfunction, impaired ERK-ETV1-KIT signaling and loss of interstitial cells of Cajal (ICC) (PMID: 28438610), a common change in gastroparesis. Here, we investigated whether genetically induced mitochondrial injury in ICC could precipitate DGE.

**Methods:** Tricarboxylic acid (TCA) cycle metabolites were measured in buffy coats of DM and control patients by gas chromatography/mass spectrometry. The TCA cycle and respiratory chain enzyme complex succinate dehydrogenase (SDH) was deactivated in ICC by tamoxifen (Tam)-induced deletion of Sdhc in KitcreERT2/+ mice carrying Sdhcfl/fl or Sdhcfl/fl alleles. DM was induced with streptozotocin. Gastric emptying of solids (GES) was determined weekly by 13C-octanoic acid breath test. Protein levels in gastric muscles were determined by Western blotting.

**Results:** Succinate:2-ketogluutarate ratios were greater in DM patients vs. controls (n = 9/group; median[IQR]: 1.2 [0.9–1.7] vs. 0.6 [0.4–0.9]; p = 0.022), indicating systemic SDH dysfunction. Kit-specific deletion of Sdhc in mice reduced gastric KIT and ETV1 proteins and ERK1/2 phosphorylation. However, GES was not different 3–16 weeks post-Tam (7♂, 7♀) or post-vehicle (Veh: 6♂, 7♀) in either sex. Next, we induced DM in 11 Tam- and 8 Veh-treated ♀ KitcreERT2/+;Sdhcfl/fl mice and in 31 ♂ C57BL/6J mice (background strain). Mice with 2 consecutive GES T1/2 values > 97.5 percentile of the normal range for the strain were considered to have DGE. Three Tam-treated mice that died suddenly and displayed greatly enlarged stomach with food residue at necropsy were also considered to have DGE. In all, 9 of 11 (82%) of Tam-treated ♀ KitcreERT2/+;Sdhcfl/fl mice developed DGE between 0.6 and 7.7 weeks post-DM, whereas only 2 of 8 (25%) ♀ Veh-treated KitcreERT2/+;Sdhcfl/fl mice and 12 of
DMKitcreERT2/+ control mice (p-deleted and analysis showed significant difference between Sdhc
functionally distinct regions: the duodenum and colon. We used but more glia responded to ADP in the colon than in the duode
(64% and 47%, respectively) and colon (91% and 79%, respectively),
responded to ADP (100 µM) and CCK (100 nM) in the duodenum
to assess glial receptor patterns. Comparable proportions of glia
calcium sensors in enteric glia and used immunohistochemistry
development of the enteric nervous system (ENS) and loss-of
function mutations in RET cause Hirschsprung disease (HD), in which children
normal GI motility in males. This work highlights a novel mechanism
also important for the homeostatic regulation of gastrointestinal (GI)
motility. To test this hypothesis, we examined RET expression in the
postnatal gut and identified two populations of RET-expressing cells
involved in peristalsis, NOS1+/VIP+ inhibitory motor neurons in the
ENS and enteroendocrine cells (EECs) in the epithelium. We generated
mice lacking RET in each of these populations and found that
RET depletion in EECs, but not neurons, slowed GI transit. This mo-
tility defect was observed in males but not females. Pharmacologic
inhibition of RET kinase in wildtype mice phenocopied this defect.
EECs are a diverse group of cells that detect information from the
gut lumen. The majority of RET+ EECs were either enterochromaf-
fin cells, which release serotonin (5-HT), or L-cells, which release
peptide YY (PYY). Both 5-HT and PYY can signal to enteric neurons
rescued the motility defect in mice lacking RET in EECs. Together,
these findings indicate that RET signaling normally limits nutrient-
dependent PYY release in L-cells and that this activity is essential for
normal GI motility in males. This work highlights a novel mechanism
that could underlie chronic dysmotility in post-operative HD patients
and a new therapeutic target for modulating motility in functional GI
disorders.

ABSTRACT

31 (39%) ♀ C57BL/6J mice developed DGE. Kaplan-Meier survival
analysis showed significant difference between Sdhc-deleted and
control mice (p = 0.023). None of the 4 Tam- or the 4 Veh-treated,
DM shERT2/−/−Sdhcfl/fl mice developed DGE.

Conclusion: The severity of mitochondrial dysfunction in ICC may
determine whether ♀ DM mice develop gastroparesis. Grants: NIH
R01 DK58185, P30 DK084567.

12 | Functional and regional heterogeneity of glial cells in the enteric nervous system

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Enteric glia are a population of peripheral neuroglia associated with
neurons in the enteric nervous system (ENS). Enteric glia interact
with neurons in neurocircuits that control gastrointestinal functions,
but whether neuron-glial communication is heterogeneous in different
regions of the intestine remains unknown. We tested whether myenteric glia display regional and functional heterogeneity in two
functionally distinct regions: the duodenum and colon. We used in
situ calcium (Ca2+) imaging in whole-mount preparations of myen-
teric plexus from transgenic mice expressing genetically encoded
encoded calcium sensors in enteric glia and used immunohistochemistry
to assess glial receptor patterns. Comparable proportions of glia
responded to ADP (100 µM) and CCK (100 nM) in the duodenum
(64% and 47%, respectively) and colon (91% and 79%, respectively),
but more glia responded to ADP in the colon than in the duode-
num. Ca2+ responses to both neuromodulators were higher in the
colon than duodenum (ADP: p < 0.00010 colon vs duodenum; CCK:
p = 0.0005 colon vs duodenum), although CCK resulted in a greater
response in the duodenum than in the colon when compared to peak
ADP responses (p = 0.0167 for ADP vs CCK in the duodenum and
p < 0.0001 for ADP vs CCK in the colon). The changes in the per-
centage of glia responding to ADP and CCK upon treatment with TTX
(300 nM) or FA (5 mM) in the myenteric plexus of duodenum and
colon (~70% for ADP in FA-treated duodenum; ~27% and ~25% for
ADP in TTX- or FA-treated colon and ~58% for CCK in FA-treated
colon vs untreated tissues) and related glial Ca2+ responses (~36%
and ~70% for ADP in TTX- or FA-treated duodenum and +139% for
CCK in TTX-treated duodenum; ~67% and +27% for ADP in TTX-
or FA-treated colon and +23% and +60% for CCK in TTX- or FA-
treated colon vs untreated tissues) suggest that glial responses to
ADP require intercellular signaling with neurons in the duodenum,
and that glial responses to CCK involve intercellular signaling with
neurons in the duodenum. Our results also show that CCKBR are
mainly expressed by neurons in myenteric ganglia of the duodenum
(Pearson correlation coefficient for peripherin and GFAP = 0.5095
and 0.1486, respectively) and by myenteric glia in the colon (Pearson
correlation coefficient for GFAP and peripherin = 0.8191 and 0.334,
respectively). Similar and higher expression of P2Y1Rs is found in the
myenteric neurons of both regions (Pearson correlation coefficient
for peripherin = 0.6225 and 0.6530, and for GFAP = 0.2291 and
0.2476 in the duodenum and colon, respectively). Our findings sup-
port the conclusion that myenteric glia exhibit regional heterogene-
ity that could contribute to region-specific mechanisms that regulate
digestive functions. Glial heterogeneity adds an unexpected layer of
complexity in peripheral neurocircuits in the adult ENS.

13 | RET signaling in enteroendocrine cells regulates gut motility in a sex-
dependent manner

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The transmembrane RET receptor tyrosine kinase is required for de-
velopment of the enteric nervous system (ENS) and loss-of-function
mutations in RET cause Hirschsprung disease (HD), in which children
are born lacking enteric ganglia in bowel segments. Despite resection
of aganglionic bowel, up to 50% of HD patients experience chronic
defecatory dysfunction, raising the possibility that RET signaling is
also important for the homeostatic regulation of gastrointestinal (GI)
motility. To test this hypothesis, we examined RET expression in the
postnatal gut and identified two populations of RET-expressing cells
involved in peristalsis, NOS1+/VIP+ inhibitory motor neurons in the
ENS and enteroendocrine cells (EECs) in the epithelium. We gener-
ated mice lacking RET in each of these populations and found that
RET depletion in EECs, but not neurons, slowed GI transit. This mo-
tility defect was observed in males but not females. Pharmacologic
inhibition of RET kinase in wildtype mice phenocopied this defect.
EECs are a diverse group of cells that detect information from the
gut lumen. The majority of RET+ EECs were either enterochromaf-
fin cells, which release serotonin (5-HT), or L-cells, which release
peptide YY (PYY). Both 5-HT and PYY can signal to enteric neurons
rescued the motility defect in mice lacking RET in EECs. Together,
these findings indicate that RET signaling normally limits nutrient-
dependent PYY release in L-cells and that this activity is essential for
normal GI motility in males. This work highlights a novel mechanism
that could underlie chronic dysmotility in post-operative HD patients
and a new therapeutic target for modulating motility in functional GI
disorders.
14  |  α-Synuclein gene knockout disrupts cholinergic neuromuscular transmission causing colonic dysmotility

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Gastrointestinal (GI) complications are a significant clinical and economic burden in Parkinson’s disease (PD), with constipation being the most common GI symptom. α-Synuclein (α-syn), a presynaptic terminal protein and the pathological biomarker in PD, aggregates in the enteric nervous system (ENS) 10 years prior to CNS pathology. A role for endogenous α-syn is to regulate synaptic transmission and vesicle recycling. It is not clear if overexpression of α-syn in the ENS alters neuromuscular transmission. We hypothesize that endogenous α-syn in murine myenteric neurons is important for normal neuromuscular transmission. To study the role of α-syn within the ENS, we used α-syn KO mice and investigated colonic function by measuring fecal pellet output, isotonic longitudinal muscle tension using an isolated organ bath (ITIOB) and colonic migrating motor complex (CMMC) analysis combined with electrophysiological recordings from the circular muscle of proximal colon preparations. Our results show a significant increase in fecal pellet number, dry stool weight, and fecal pellet length in α-syn KO mice. We also observed a significant decrease in CMMC propagation speed in α-syn KO mice. There was a significant reduction in neurogenic contractions of the proximal colon longitudinal muscle of α-syn KO mice. Circular smooth muscle inhibitory junction potentials (IJPs) in α-syn KO mice showed no differences compared to WT mice. Taken together, these data suggest that loss of α-syn slows colonic transit by potentially impairing cholinergic neurotransmission in the proximal colon. Overall, these data support to a “loss-of-function” hypothesis of α-syn in the mouse enteric nervous system where α-syn is critical for ENS neurotransmission.

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Plenary Abstract Session

15  |  Symptoms improve more by combining diet or neuromodulator therapy with prokinetics vs. Prokinetics alone in suspected gastroparesis.

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Background: Prokinetics are mainstay gastroparesis treatments but may not improve symptoms. Clinicians often combine prokinetics with other therapies to manage suspected gastroparesis, but with little evidence to support these recommendations. Recent research emphasizes limitations of prokinetic only therapy and support multimodal treatment targeting diverse pathologic functions for symptoms of gastroparesis.

Methods: Therapy changes were recommended based on concurrent wireless motility capsule (WMC) and gastric scintigraphy tests for 138 patients with suspected gastroparesis. GCSI (0 = none, 5 = very severe) scores from baseline to 6-month followup were compared relating recommendations to take prokinetics alone or with diets or neuromodulators (tricyclics, mirtazapine, gabapentin, others). Multivariate models assessed WMC gastric emptying time (GET) impact on responses.

Results: GCSI scores in all patients given prokinetics with or without other therapy decreased 0.75±1.18 at 6 months (p < 0.01), but reduced only 0.02±1.26 (p = 0.95) in those on prokinetics as the sole new therapy. GCSI decreased 0.84±1.05 in those given prokinetics plus diets (p = 0.06) and 0.89±0.84 on prokinetics plus neuromodulators (p = 0.02 vs. prokinetics alone). Of individual symptoms, bloating increased on prokinetics alone (~0.38 ± 1.63) but decreased when combined with diet (0.96 ± 1.41) (p = 0.02) or neuromodulators (2.00±1.08) (p = 0.02). Fullness decreased more on prokinetics plus neuromodulators (2.06±0.80) vs. prokinetics alone (0.34±1.34) (p = 0.02). GCSI reductions were similar in all patients given prokinetics with and without GET delays (0.61±1.20 vs. 0.98±1.15) (p = 0.19). On multivariate models, GET delay predicted lesser response to prokinetics with or without neuromodulators (p = 0.04) but did not influence response to prokinetics and diet (p = 0.81).

Conclusions: Prokinetics given alone have limited benefit to reduce symptoms in suspected gastroparesis. Overall symptoms respond better by combining prokinetics with gastroparesis diets or neuromodulators vs. prokinetics alone. Of individual symptoms, bloating improves more on combined prokinetic therapy with diet or neuromodulators; fullness is better with prokinetics plus neuromodulators vs prokinetics alone. Responses to prokinetics with or without neuromodulators are influenced by gastric emptying delays. Our findings emphasize limitations of prokinetic only therapy and support multifaceted treatment targeting diverse physiologic functions for symptoms of gastroparesis.

16  |  Spectrum of gastrointestinal disorders in patients with eating disorders and relationship to eating disorder remission

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Introduction: Gastrointestinal (GI) symptoms are common in patients with eating disorders (ED). Less understood is if GI symptoms
ABSTRACT

Persist beyond ED remission or are a manifestation of ongoing ED pathology. We sought to determine the relationship between GI disorders and ED remission.

Methods: We constructed a retrospective review of 250 patients with an ED and GI encounter at a tertiary care center between 2010–2020. We determined diagnostic details, classifying GI diagnoses as “structural” or “functional” and EDs by DSM-IV-TR as anorexia nervosa (AN), bulimia nervosa (BN), or eating disorder not otherwise specified (EDNOS). We determined the temporal relationship between the ED diagnosis and GI consult and assessed ED remission. We used multivariable regression to determine factors associated with functional GI diagnoses and the relationship to ED remission.

Results: Among 250 patients, 180 had a GI consult. Mean age was 36.9 years, and 165 (91.7%) were female. There were 62 (34.4%) patients with AN, 48 (26.7%) BN, and 70 (38.9%) EDNOS. The most common diagnoses were irritable bowel syndrome (IBS) (21.1%) and constipation (17.2%). IBS was more common among patients with AN (27.4%). Functional disorders were more common than structural disorders (60% vs 40%). Younger age (OR 0.97, 95%CI 0.94–1.00) and >1 GI diagnosis (OR 5.52, 95%CI 2.25–15.77) were associated with likelihood of a functional GI diagnosis. There were 141 patients (78.3%) with an ED diagnosis prior to GI consult. Of those remitted (62 of 129 with known remission status), IBS (28.6%) and structural diagnoses (17.5%) were most common. Constipation was more common among non-remitted ED patients (24.4%), particularly in active AN and BN (33.3%). There was no difference in prevalence of functional disorders among remitted and non-remitted patients (61.3% vs 68.7% p = 0.38). Low BMI (OR 0.03, 95%CI 0.00–0.18) and EDNOS (OR 0.19, 95%CI 0.11–0.70) were associated with decreased likelihood of ED remission.

Conclusions: Over half of patients with EDs and GI symptoms were found to have a functional GI disorder. A subset of ED patients seeking GI care are less likely to be in remission and could benefit from ED-specific treatments. Additionally, the high prevalence of functional GI disorders seen in remitted ED patients suggests a role for past EDs in GI symptom pathogenesis.

17 | Altered gut afference-related brain connectivity in functional dyspepsia is linked to slower gastric peristalsis – a multimodal gut-brain axis MRI study

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Functional dyspepsia (FD) patients experience upper gastrointestinal (GI) symptoms possibly due to gastric motor or sensory dysfunction. Gastric afference is received by the nucleus tractus solitarius (NTS). We hypothesize that altered NTS connectivity to higher brain regions in FD will be associated with gastric dysmotility during a meal challenge. 15 FD and 14 healthy control (HC) subjects consumed the maximum tolerable amount of a 470 ml high-calorie pudding. Post meal, subjects alternated 3 times between stomach and brain MRI scans (Siemens 3T Skyra). Gastric 4D cine-MRI were collected continuously for 5 min (temporal resolution: 7 s). During brain scans, resting-state functional MRI data were acquired. Timeseries from left NTS (A) were used to generate seed-to-voxel whole-brain functional connectivity maps. Relative to HCs, FD patients demonstrated increased NTS connectivity to anterior medial prefrontal cortex (mPFC), superior frontal gyrus (SFG), and bilateral inferior frontal gyri (IFG) (B). Peristaltic propagation velocity in the antrum was calculated from the segmented gastric data (C). Reduced peristaltic propagation velocity was found in FD (HC = 5.58 ± 1.68 mm/s, FD = 3.76 ± 0.76, p = 0.003), and was negatively correlated to NTS connectivity (D). Our results reveal shifts in NTS functional connectivity from the self-referential processing Default Mode Network to the executive control processing FrontoParietal Control Network in the brain, potentially related to an altered cognitive processing of visceral GI sensations in FD. Furthermore, these altered connections are linked to physical properties of gastric peristalsis.

18 | A monoclonal anti-cGRP antibody decreases visceral hypersensitivity in experimental models of stress-induced irritable bowel syndrome

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Background: Pain, due to visceral hypersensitivity, is a characteristic feature of irritable bowel syndrome (IBS), a functional disorder of...
the gastrointestinal tract (GI). While the etiology of IBS remains unclear, stress has been shown to play a significant role in visceral pain. Here, we utilize a monoclonal anti-CGRP F(ab')2 antibody to test the hypothesis that inhibition of peripheral CGRP signaling will reverse colonic hypersensitivity induced by both a chronic psychological stress and early life stress (ELS) in a rodent model.

**Methods:** One cohort of adult rats were exposed to repeated water avoidance stress (WAS) (1 h/day for 10 days). Sham WAS-treated rats served as controls. A second cohort was exposed to an odor-attachment learning model of unpredictable ELS. Odor-only treated neonates serves as controls. In adulthood colonic sensitivity was quantified using a visceral motor response (VMR), quantified as the number of abdominal contractions, to graded pressures (0, 20, 40, 60 mmHg) of isobaric colorectal distension (CRD). Spinal extracellular signal-regulated kinase (ERK1/2) phosphorylation was assessed via immunohistochemistry. Stressed rats received a single intraperitoneal (i.p.) administration of anti-CGRP F(ab')2 (30 mg/kg), 24-hr prior to measuring colonic sensitivity.

**Results:** Rats exposed to WAS or ELS exhibited significantly increased colonic sensitivity compared to controls (WAS = 60 mmHg: 31.4 ± 1.2 vs. 16.1 ± 0.9 abdominal contractions, p < 0.0001; ELS = 60 mmHg: 36.1 ± 0.9 vs. 15.3 ± 0.8 abdominal contractions, p < 0.0001). In both cohorts, exposure to stress enhanced CRD-evoked ERK1/2 phosphorylation in the spinal cord (WAS = 4.1 ± 0.6 vs. 1.7 ± 0.9 p < 0.001; ELS: 6.9 ± 0.7 vs 1.2 ± 0.4 p < 0.0001). The anti-CGRP F(ab')2 antibody normalized stress-induced visceral hypersensitivity compared to isotype control (WAS = 60 mmHg: 19.5 ± 1.7 vs. 31.4 ± 1.2, p = 0.0001; ELS = 60 mmHg: 23.5 ± 1.9 vs. 36.1 ± 0.9, p = 0.05) and reduced CRD evoked spinal ERK1/2 phosphorylation (WAS: 0.9 ± 0.2 vs. 4.1 ± 0.6 p < 0.001; ELS: 1.2 ± 0.4 vs. 6.9 ± 0.7 p < 0.0001).

**Summary and conclusions:** Exposure to either a repeated psychological stress in adulthood or unpredictable stress during the neonatal period induces colonic hypersensitivity as well as enhanced evoked spinal ERK1/2 phosphorylation. These stress-induced phenotypes were reversed by inhibition of peripheral CGRP signaling, suggesting further investigation of an anti-CGRP antibody as a novel treatment strategy for IBS-related stress-induced visceral pain.

**Background/Aims:** Intestinal methanogen overgrowth (IMO) reflects a recent change in nomenclature distinguishing the overgrowth of methane-producing archaea from small intestinal bacterial overgrowth (SIBO). Recent clinical trends have favored the use of combination therapy with neomycin over rifaximin alone in treating IMO, though this practice is based on limited data. In this retrospective study, we aimed to quantify treatment response of IMO to rifaximin monotherapy.

**Methods:** All patients who underwent lactulose breath testing (BT) for SIBO at the University of Pennsylvania from February 2019 to March 2020 were identified for chart review. All breath tests were interpreted according to the 2017 North American Consensus. Symptom response to first antibiotic treatment was evaluated according to a 5-point subjective clinical scale (worsening, no improvement, minimal improvement, moderate improvement, resolution). Successful treatment was defined as moderate improvement or resolution of symptoms. Analyses were performed in SPSS using Fisher’s exact test.

**Results:** 336 patients underwent BT in the study period. Symptom response data were available for 153 patients. Among 74 patients with IMO, 48 were treated with rifaximin monotherapy, with 28 (58.3%) noting treatment response; 11 were treated with a combination of rifaximin and neomycin, with 5 (45.4%) noting treatment response; and 15 were treated with other regimens (summarized in a supplemental table, not presented herein due to length constraints). In the IMO subgroup, there was no significant difference in treatment response between rifaximin monotherapy and combination rifaximin and neomycin (p = 0.511). Among 58 patients with hydrogen-positive, methane-negative SIBO, 43 were treated with rifaximin monotherapy, with 21 (48.8%) noting treatment response. There was no significant difference in the treatment response to rifaximin monotherapy between the SIBO and IMO subgroups (p = 0.405).

**Conclusions:** In this retrospective cohort series, the response rate to rifaximin monotherapy among patients with IMO was similar to the response rate among patients with SIBO. Additionally, in the IMO subgroup, there was a similar response to rifaximin alone or in combination with neomycin. Current practice patterns favoring dual-antibiotic therapy for IMO merit further review.
and BT results, including intestinal methanogen overgrowth (IMO). In this retrospective, single-center study, we aimed to identify clinical predictors of lactulose BT positivity.

**Methods:** All patients who underwent BT for SIBO at the University of Pennsylvania from February 2019 to March 2020 were identified for chart review. All breath tests were performed and interpreted according to the 2017 North American Consensus. Tests with equivocal interpretations on the basis of elevated baseline hydrogen levels were excluded from analysis for hydrogen ($H_2$) correlations but included for analysis of methane ($CH_4$) correlations. Clinical variables of interest were selected *a priori* and included demographic variables, presenting symptoms (mutually inclusive), comorbid diagnoses, and medications. Statistical analyses were performed in SPSS using Fisher’s exact test.

**Results:** 336 patients underwent BT in the study period. 142 tests were positive for $H_2$, 114 tests were positive for $CH_4$, and 43 tests were equivocal. 55 tests were positive for both $H_2$ and $CH_4$, while 92 tests were negative for both $H_2$ and $CH_4$. Bloating ($p = 0.001$) was associated with $H_2$ positivity. Constipation was associated with $CH_4$ positivity ($p = 0.016$). Vomiting was associated with $H_2$ negativity ($p = 0.028$) and $CH_4$ negativity ($p = 0.020$). Mood disorders (depression and/or anxiety) were associated with $H_2$ positivity ($p = 0.029$) while inflammatory bowel disease was associated with $CH_4$ negativity ($p = 0.004$). Other clinical variables were not associated with BT results (descriptive tables excluded herein due to size constraints).

**Conclusions:** Presenting complaints of bloating and constipation were associated with BT positivity for $H_2$ and $CH_4$ respectively. The majority of clinical variables evaluated demonstrated no association with BT positivity, including variables classically associated with SIBO (e.g. acid suppressing drugs, opiates, diabetes, and irritable bowel syndrome). Unexpectedly significant associations with BT results included a presenting complaint of vomiting and comorbid mood disorder. Further research is still needed to clarify our prevailing clinical assumptions regarding SIBO and IMO.

**Table 1** Percent of people with and without Rome IV IBS reporting sensitivities to 11 types of foods

| Food sensitivity          | Rome IV IBS (n = 103) | Controls (Rome IV IBS criteria not met) (n = 1397) | Risk Ratio |
|---------------------------|-----------------------|--------------------------------------------------|------------|
| Milk/dairy products       | 52.4\* (42.6–62.2)    | 23.8 (21.6–26.1)                                 | 2.2        |
| Soy/soy products          | 16.5 (9.2–23.8)       | 8.7 (7.2–10.2)                                   | 1.9        |
| Eggs                      | 24.3\* (15.9–32.7)    | 11.0 (9.4–12.7)                                  | 2.2        |
| Meat                      | 21.4\* (13.3–29.4)    | 10.6 (9.0–12.2)                                  | 2.0        |
| Gluten/wheat flour        | 24.3\* (15.9–32.7)    | 9.4 (7.8–10.9)                                   | 2.6        |
| Fish/seafood              | 18.4 (10.8–26.1)      | 10.5 (8.9–12.1)                                  | 1.8        |
| High fat foods            | 45.6\* (35.8–55.4)    | 20.0 (17.9–22.1)                                 | 2.3        |
| Nuts                      | 17.5 (10.0–24.9)      | 8.7 (7.3–10.2)                                   | 2.0        |
| Onions and/or garlic      | 15.5 (8.4–22.6)       | 12.6 (10.9–14.4)                                 | 1.2        |
| Spicy food                | 42.7 (33.0–52.4)      | 29.8 (27.4–32.3)                                 | 1.4        |
| Sugary food /sweets       | 40.7\* (31.1–50.4)    | 17.8 (15.7–19.8)                                 | 2.3        |

\* **Significantly higher** using Bonferroni-adjusted alpha of $p < 0.0042$. 

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**Background/Aims:** IBS patients often report food-associated symptoms and sensitivities and many alter their diet to control symptoms. It is unknown to what extent this is also true for people with IBS in the general population.

**Methods:** A nationwide Internet survey of United States adults in January 2020 used quota-based sampling to match the national population in distribution of sex, age, race/ethnicity, education, and geographic regions. The survey included demographics, Rome IV IBS diagnostic questions, questions about sensitivity to 11 classes of foods, use of special diets, the PHQ-15 (somatization), and PHQ-4 (anxiety and depression). Those with inflammatory bowel disease, celiac disease, diverticulitis and peptic ulcer were excluded from Rome IV IBS case definition.

**Results:** 1,500 adults completed the survey (50% females; mean age 46.9 years, range 18–92 years). IBS criteria were met by 103 (6.9%), of whom 34 were clinically diagnosed. People with IBS reported more food sensitivities than those without (Mean [95% CI]: 3.2 [2.7–3.8] vs. 1.6 [1.5–1.7], $p < 0.0001$), with significantly more prevalent sensitivities to 6 of 11 food types; Table 1. Follow-up analyses showed elevated number of reported food sensitivities in IBS diarrhea (IBS-D) and mixed (IBS-M) subtypes, but not in IBS with constipation (IBS-C).

Number of food sensitivities reported by those with IBS corre- lated modestly with somatization ($r = 0.24$, $p = 0.01$) and was not
correlated with anxiety or depression. IBS respondents were not more likely to be on special diets than those without IBS (31.1% vs. 23.9%, p = 0.12). Only 34% of IBS individuals using diets (11/32) reported doing so to control GI symptoms.

**Conclusions:** People with IBS in the general population report more sensitivities to foods than those without IBS. The tendency toward excess food sensitivities in IBS may not include those with IBS-C.

22 | Withdrawn

23 | Withdrawn

24 | Brain fMRI activity follows the gastric rhythm and encodes the power fluctuations of gastric electrical activity in rats

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**Purpose:** The stomach-brain interaction is critical for regulating gastric function. This interaction is better understood in terms of the vago-vagal reflex but remains largely unclear beyond. A prior study suggests that the human brain maintains a slow rhythm coupled to the gastric slow wave [1]. Here, we further hypothesize that the rat brain not only maintains neural copies of gastric rhythms but also encodes their frequency and power fluctuations. To test this hypothesis, we acquired concurrent fMRI and electrogastrogram (EGG) from eight rats and assessed the relationship between the fMRI signal and the frequency and power fluctuations of gastric slow wave.

**Results:** With simultaneous recordings of EGG and fMRI, we assessed the relationship between BOLD activity and various features of EGG in rats. First, the dominant frequency of gastric slow waves was identified for every 4-min segment. The coherence at the dominant frequency was then calculated between EGG and fMRI to assess whether fMRI signals were phase-coupled to the gastric slow waves. The result showed that EGG and fMRI activity were coherent at the dominant frequency in various brain regions, covering the somatomotor, emotion-cognitive, reward-modulation, and olfactory-related areas. We also extracted temporal fluctuations of narrow-band EGG rhythms and tested their relationship with the BOLD activity. The EGG rhythms at five cycles per minute, a hallmark feature of gastric pace-making activity, could linearly explain the BOLD signal at regions, such as the ventromedial thalamic nucleus, insular cortex, and orbital cortex.

**Conclusion:** The rat brain is not only synchronized with the gastric slow wave but also encodes the power fluctuation of gastric pace-making activity via the NTS-insula-somatosensory network.

[1] Rebollo I, Devauchelle AD, Béranger B, Tallon-Baudry C. Stomach-brain synchrony reveals a novel, delayed-connectivity resting-state network in humans. Elife. 2018 Mar 21;7:e33321.

25 | 3D imaging and computational quantitation of extrinsic and intrinsic cholinergic innervation in the enteric nervous system (ENS) of the pig colon: implications in the cholinergic anti-inflammatory pathway (CAP)

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Central or peripheral vagal nerve stimulation reduces inflammation in GI diseases by activating CAP as shown recently in Crohn’s diseases. However, little is known on the spatial configuration of extrinsic (ext) and intrinsic (int) cholinergic innervation in the pig colon, a relevant translational research animal model for human colon. The full thickness colon samples were collected from proximal, transverse and distal regions (pC, tC, dC) of 6 adult naïve Yucatan minipigs (3 of each sex) and processed for tissue clearing and 3D imaging. Int- and ext-cholinergic innervations were double-labeled by a novel human peripheral and a common type of choline acetyltransferase (hpChAT and cChAT) antibodies respectively, cChAT and hpChAT immunoreactive (ir) fibers and neurons in the 3D structure of inner and outer submucosal and myenteric plexi (ISP, OSP and MP) were traced and quantified using Imaris 9.5. Single cell RNA-sequencing (scRNA-seq) was performed on isolated myenteric cholinergic neurons from the pC for mapping transcriptomic profiling. In 3D images, hpChAT-ir neurons were closely surrounded by cChAT-ir varicose fibers and dot-like structures, presumably ext-cholinergic nerve terminals. No cChAT-ir fibers were visualized in ISP. The density order of cChAT-ir fibers was dC>tC>pC in both OSP (dC vs tC or pC: p = 0.16 or < 0.001; tC vs pC: p < 0.05) and MP (dC or tC vs pC: p < 0.001 or p < 0.001) with significant higher density in the MP than OSP in pC, tC or dC. There was no significant difference between two sexes. hpChAT-ir fibers showed no significant difference among plexi and segments. A large portion of genes in the myenteric cholinergic neurons are involved in coping with defense response to inflammation via TNF signaling pathway. In parallel, electrical stimulation of the celiac branch of the vagus nerve (CBVN, 2 Hz, 0.3 ms, 5 mA) caused a dramatic increase (>60-fold, compared to baseline) in the plasma IL1ra levels immediately and at 30 min post-stimulation periods. These results revealed for the first time the regional difference in the autonomic cholinergic innervation in 3D structure and provide neuroanatomical and transcriptomic evidence for CAP in the pig colon. The increased plasma IL1ra in response to CBVN stimulation extends the anti-inflammatory effects of vagal neuromodulation and possible activation of CAP in pigs.
**Background:** Anorectal Manometry (ARM) and Balloon Expulsion Testing (BET) are utilized to diagnose functional defecation disorders (FDD). Data suggests inflating the rectal balloon enhances the desire to defecate during simulated defecation (SD) in ARM limiting over diagnosing a FDD. The London Consensus (LC) was developed to standardize the evaluation process for ARM procedures. Our objective is to compare intra-patient responses to 4 different incremental balloon inflations during simulated defecation (SD) related to LC Part III (LC-3).

**Methods:** Prospective analysis of adults who underwent ARM and BET using the International Anorectal Physiology Working Group protocol at a single GI center: Jan – Mar, 2021. Data including demographics (age, sex, BMI, and race), SD measurements during ARM (percent anal relaxation [PAR] and intrarectal pressure [IRP] mmHg), and BET results (normal = defeca a 50 ml water filled balloon in ≤60 s) were obtained. The 4 incremental balloon inflation volumes (ml) were: 0, 30, 60, & 90. Post balloon inflation, a 30-second latency phase occurred allowing basal anal pressure to return post the recto-anal inhibitory reflex. LC-3 categories were based on BET, coordination, and rectal propulsion: Abnormal (AB) BET & Dysynergia [ABET-D], AB BET & Poor Propulsion [ABET-P], and AB BET with Poor Propulsion & Dysynergia [ABET-P+D]. Normal PAR and IRP were defined using ROME IV criteria for FDD. Statistical analysis included chi-square with linear-by-linear association. A p-value of <0.05 was considered statistically significant.

**Results:** 24 subjects (mean age of 55.3 ± 13.8; Range: 28–74; mean BMI: 29.0 ± 6.9; 62.5% female; 66.7% Caucasian) were included. The primary indication for the ARMs was constipation (58.3%). 62.5% of subjects had an AB BET. The likelihood of ABET-P+D significantly decreased as rectal balloon volume increased: 0 ml = 50.4%; 30 ml = 14.3%; 60 ml = 18.2%; 90 ml = 8.3%, p = 0.03. With balloon incremental inflations IRP increased, the mean PAR decreased with incremental balloon volumes: 0 ml = 11.8%; 30 ml = 4.5%; 60 ml = 4.9%; 90 ml = 5.7%, p = 0.49.

**Conclusion:** Although underpowered, the data suggests that the LC-3 profile provides opportunities for future anorectal interventions such as bulking agents for high IRP versus biofeedback therapy for decreasing PAR.
on colon contractility and function. A novel defecatory test device termed Fecobionics (CGH 2018;16:981-983) was used for colon application (preliminary data in Gastroenterology 2020). The aim was to study colon transit properties after colonoscopic delivery of the device to the ascending colon in canines. Fecobionics is a 10 cm-long wireless device with shape and deformability mimicking feces. A 3 cm long encapsulated battery package was tethered to support long-term colon transit studies. The device was dropped 16 times in the proximal colon of five 25-35 kg Mongrel dogs. The bag was distended to volumes between 10-30 ml. Multiple pressures and cross-sectional areas (CSAs) measured by impedance planimetry were recorded. Fluoroscopy was done to confirm the device location at various time points. Fecobionics made successful recordings in most cases. Bag leakage occurred in three experiments and one experiment had sensor problems. Fecobionics was expelled after 3.5-18 h without clear dependence on the bag volume. The first 30 min showed relatively little activity and movement due to the Propofol administered during colonoscopy. Pressure recordings demonstrated intermittent antegrade peristaltic activity with amplitudes of 30-50 cm H2O. Independent hereof, slowly moving waves of CSA indentations were recorded at a frequency of approximately 4 min. The waves were most often moved in retrograde direction but antegrade and stationary contractions were also recorded. The waves were most often detected in the ascending and transverse colon. The CSA waves were recorded even during the antegrade peristaltic contractions. The waves were best observed at the 30 ml bag volume. In conclusion, Fecobionics obtained novel recordings of colonic contractility in vivo. The CSA waves have a striking resemblance to a myogenic motor pattern of antegrade and retrograde waves named ripples. These waves are believed to originate from interstitial cells of Cajal. Similar waves have previously been recorded in vitro in small animal species by spatiotemporal mapping and were not detectable with manometry. The function of the waves is likely to mix colonic content and slowing transit. Fecobionics may be used to detect segments with impaired function and provide insight into mechanisms of colonic disorders, e.g. to detect whether contractility remains in segments for pharmacological treatment, or if patients are eligibility for partial or total colectomy.

29 | Biofeedback efficacy assessed using the Fecobionics device

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Introduction: Anorectal disorders with fecal incontinence and constipation symptoms are common. Biofeedback is a behavioral therapy used to treat people with constipation or fecal incontinence, which do not respond to standard treatment. The aim was to use Fecobionics (Gregersen et al, CGH 2018, CTG 2019) to assess anorectal physiological function during biofeedback therapeutic intervention. Pressure and expulsion data were compared to high-resolution anorectal manometry (HRAM) and the balloon expulsion test (BET).

Methods: Nine female fecal incontinent patients aged 61.9 ± 4.0 years underwent biofeedback treatment and were enrolled. They were assessed with Fecobionics, HRAM, and BET. The subjects filled in the validated Fecal Incontinence Severity Index (FISI) before and after 8 weeks biofeedback treatment. The Fecobionics device was 10 cm long and 12 mm diameter with a distensible bag that was filled to urge-to-defecate level. Fecobionics measured front, bag and rear pressures.

Results: The FISI score was 34.4 ± 3.8 before treatment and 27.1 ± 3.5 post-treatment. The urge volume for Fecobionics was 26.1 ± 6.1 ml and 21.7 ± 6.8 ml pre- and post-treatment (p > 0.5). The urge volume for BET was 83.2 ± 5.1 and 74.1 ± 6.9 ml pre- and post-treatment (p > 0.5). The urge volume was significantly lower for Fecobionics compared to BET (p < 0.01). The expulsion duration for Fecobionics was 4.6 ± 1.5 and 5.0 ± 2.0 s pre- and post-treatment (p > 0.5). The BET expulsion duration was 30.6 ± 6.5 and 19.3 ± 2.4 s pre- and post-treatment (p < 0.01). The expulsion duration for Fecobionics was significantly lower than the duration for BET (p < 0.01). The resting pressure for Fecobionics was 17.8 ± 4.9 and 20.4 ± 5.6 cm H2O pre- and post-treatment (p > 0.5). The resting pressure for HRAM was 40.9 ± 5.6 and 20.4 ± 5.6 mmHg pre- and post-treatment (p > 0.5). The resting anal pressure for Fecobionics was significantly lower than that for BET (p < 0.01). The max squeeze pressure for Fecobionics was 70.5 ± 8.9 and 69.3 ± 8.1 cm H2O pre-and post-treatment (p > 0.5). The max squeeze pressure for HRAM was 127.9 ± 5.6 and 103.4 ± 11.0 mmHg pre- and post-treatment (p > 0.4). The maximum squeeze pressure data for Fecobionics were lower than those for BET (p < 0.01). The improvement in FISI score correlated better with Fecobionics expulsion duration than with BET expulsion duration (r = 0.69 vs 0.36).

Conclusion: Biofeedback therapy resulted in modest improvement (20%) of the FISI score. Fecobionics differed from HRAM-BET data. Fecobionics data correlated best with the improvement in FISI score.

30 | How accurate is patient’s recall of bowel symptoms for fecal incontinence: A comparative study of self-report vs prospective stool diary

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Background: An accurate history of symptoms is important for making a clinical diagnosis, particularly for motility disorders such as fecal incontinence (FI). However, whether a subject’s history of
bowel habit is reliable, especially when it is irregular or unpredictable is unknown. Furthermore, whether there is recall bias in reporting symptoms is unclear.

**Aim:** To examine the prevalence of FI-related bowel symptoms as assessed by a questionnaire (recall) and compare this with a prospective FI stool diary.

**Methods:** FI patients filled out a FI bowel symptom questionnaire that assessed 9 symptoms including stool frequency, number of leakage episodes and amount (none = 0, mild = 1, moderate = 2, excessive = 3), mean stool consistency (Bristol scale), time of leakage, awareness of leakage, urgency for stooling and use of pads. Subsequently they completed a prospective one-week validated FI stool diary that enquired similar symptoms. Data were compared for agreement and correlation between recall and prospective stool diary.

**Results:** One hundred patients (f/m = 61/39, mean age: 61 years) were assessed. Fifty-two percent completed under-graduation, 33% had high school diploma and 15% were post-graduates. When compared to FI diary, 22% of patients accurately reported the number of FI episodes, whereas 45% underestimated and 33% overestimated using recall. Similarly, the concordance for number of BMs was 25%, and under/overestimation rates were 44%/31% respectively. Urgency was accurately reported in 50% patients. The stool consistency either with a bowel movement or a FI event was concordant in 12.5% and 17.8%, and was overestimated in 50% and underestimated in 30%-37.5% of patients. The occurrence of nocturnal FI events was concordant in 57% and discordant in 43% of patients. The use of pads and lack of awareness for FI events were concordant in 77% and 73% respectively. Finally, the amount of leakage (FI severity) had the lowest concordance at 11% and under/overestimation rates of 43%/46% respectively.

**Conclusion:** There is very poor concordance for key FI symptoms such as FI episodes, BMs, urgency, stool consistency and FI severity, suggesting a significant recall bias in symptom reports, when compared to prospective FI diary assessment. Thus, historical recall of bowel symptoms appears to be inaccurate for the assessment of FI. To improve accuracy and better management, a prospective stool diary is recommended for FI evaluation.

**31 | Rectal sensation in patients with chronic constipation: What factors are associated with rectal hyposensitivity?**

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**Introduction:** Intact rectal sensation is important to normal bowel function. Rectal hyposensitivity (RH) has been reported in up to 68% of chronically constipated (CC) patients but its clinical significance, particularly related to dyssynergic defecation (DD), is not well understood.

**Aim:** To clinically characterize CC patients with altered rectal sensation and evaluate the impact on dyssynergic defeation.

**Methods:** Retrospective analysis of consecutive adults with CC presenting at a tertiary care center (2018–2020) for anorectal manometry (ARM). Demographics and clinical data were analyzed. Rectal sensory testing was accomplished during ARM via standardized ramp balloon air distension protocol. Required air volumes for three established sensation thresholds (“FIRST sensation”, “URGE to defecate”, “MAXIMUM tolerated”) were determined. DD was defined as both the inability to relax the anal sphincter during simulated defecation and an abnormal balloon expulsion test (BET). Statistical analyses included the Mann-Whitney test and multivariable regression model.

**Results:** 1630 CC patients (78.7% female, 48.1 years mean age) were included in this study. DD was diagnosed in 419 CC patients (25.7%). CC patients with DD had required significantly higher distension volumes to achieve all three (FIRST/URGE/MAX) sensation thresholds (p < 0.01 for all comparisons). Notably, absolute median volume difference was highest for the “MAX” sensation threshold (DD = 150 cc’s vs. No DD = 120 cc’s, p = 0.001). On the multivariable regression model, higher URGE sensory threshold volume (rectal hyposensitivity) was associated with male gender (β = 11.93, p < 0.01), diabetes mellitus (β = 11.99, p < 0.01), higher body-mass index/BMI (β = 0.36, p = 0.02), and presence of DD (β = 13.22, p < 0.01) These differences were statistically significant for each of the 3 sensation thresholds (p < 0.05 for all comparisons).

**Conclusion:** Amongst patients with CC, dyssynergic defecation, male gender, diabetes and higher BMI are associated with rectal hyposensitivity, measured by ramp balloon distension. Future studies delineating the predictive value of RH related to CC therapy outcomes in these patient subgroups may be useful.

**32 | Withdrawn**

**33 | Withdrawn**

**34 | Longterm impact of constipation drug therapies on upper gastrointestinal symptom profiles and quality of life of patients with suspected gastroparesis with normal versus delayed colonic transit**

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**Background:** Patients with upper gastrointestinal (GI) symptoms suggestive of gastroparesis (GP) often have extra-gastric transit delays in the colon. Laxatives have been shown to improve QOL in patients with constipation and colonic transit time as assessed by
Wireless Motility Capsule (WMC). However, the long-term impact of Constipation Drug Therapies (CDT) on upper GI symptoms in patients with normal versus delayed colonic transit (NCT vs DCT) is unknown.

Methods: Subjects with suspected GP had concurrent WMC and gastric scintigraphy. Based on test results, medication management decisions were made including laxatives, prokinetics, neuromodulators and others. Questionnaires (GCSI. PAGI-SYM and PAGI-QOL) were administered at baseline, 3 and 6 months. CDT included linaclotide (22), lubiprostone (9), PEG (19), pyridostigmine (4) and others (4). Subjects placed on CDT were compared to those without laxatives and categorized into NCT or DCT based on their colonic transit. Multivariate models were used to assess the impact of covariates including gastric emptying delay, gender and meeting ROME III functional dyspepsia criteria on treatment response.

Results: Of 150 subjects, 45/150 (30%) had DCT, 102/150 (68%) had NCT, and 3/150 (2%) had no transit data. In subjects with NCT, GCSI scores and individual bloating scores improved at 6 months without CDT (N = 74, p < 0.0001 for both) but not in subjects with NCT on CDT (n = 28). Subjects with DCT (N = 39) had significant decreases in GCSI (0.69 ± 0.18, p < 0.0002), PAGISYM (0.64 ± 0.16, p < 0.0001), and individual symptoms of bloating and constipation (p < 0.033, p < 0.0053, respectively) with improved PAGIQOL (0.78 ± 0.17, p < 0.0001) on CDT. Six subjects with DCT were not on CDT and symptoms did not improve in these subjects at 6 months.

Conclusion: DCT is seen in 30% of patients with suspected GP. Treatment with CDT is associated with overall long-term improvements in upper GI symptoms, constipation, and QOL in subjects with DCT when compared to NCT. Upper GI symptoms and QOL improve in patients with NCT irrespective of CDT therapy. Prokinetics, neuromodulator and dietary management may drive symptom improvement in patients with NCT. Delayed colonic transit may be a predictor of favorable gastroparesis symptom outcomes with CDT. Assessment of colonic transit time in patients with suspected GP could improve treatment outcomes.

Joint hypermobility, autonomic dysfunction, gastrointestinal dysmotility and autoimmunity (JAG-A) – Clinical associations and the response to intravenous immunoglobulin therapy

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Background: The role of autoimmunity in the pathogenesis of GI dysmotility and dysautonomia in patients with joint hypermobility syndrome (JHS) remains unclear. We conducted a hypothesis-generating study to examine markers of immune dysregulation in patients with unexplained GI symptoms with various combinations of JHS and autonomic dysfunction (AGA) and prospectively treated a subset with IVIG.

Methods: A cohort of 318 patients with suspected idiopathic dysmotility was evaluated for evidence of autoimmunity, neuropathy, JHS, and GI dysmotility. A subset was treated empirically with IVIG, and subjective/objective responses to treatment were systemically tracked and compared to data from controls in the same cohort who did not receive IVIG.

Results: 238/318 patients (75%) had at least one marker indicative of autoimmunity (range: 0–7; IQR: 0.2); 212 (66.7%) had JHS defined by Beighton scores, and 123 (38.7%) had evidence of dysautonomia. Gender, Beighton scores, GI symptoms, and GI transit objective tests were similar in patients with and without autoimmunity. Patients with autoimmunity were slightly older and had a higher prevalence of objective dysautonomia, migraine, generalized body pain, and elevated CRP or ESR. Patients treated with IVIG (n = 34) showed more overall treatment effect than controls and a higher GI specific quality of life compared with controls at the end of 4 months, along with clinically meaningful improvements over baseline in multiple GI and autonomic scores (upper GI: PAGI-SYM and subscales, lower GI (PAC and PFDI), upper and lower abdominal pain (PAGI-SYM), and autonomic function (COMPASS and subscales). Patients with JHS just as likely to have autoimmune markers than those without but were younger and more likely to be females with IgG2 and IgA deficiencies.

Conclusions: Autoimmunity markers are common in patients with GI dysmotility and are more often associated with evidence of AGA and robust response to IVIG with symptomatic improvement in GI and autonomic symptoms. Patients with JHS form a distinct subgroup but are not different in terms of autoimmunity. These results need to be corroborated by prospective randomized clinical trials.

Stiff person syndrome is commonly associated with gastrointestinal symptoms and dysmotility

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Background: Stiff person syndrome (SPS) is a rare neurological disorder denoted by progressive rigidity of axial and limb muscles with painful intermittent muscular cramps. The prevalence of gastrointestinal (GI) pathophysiology has not been systematically described.

Methods: Relevant clinical data were collected retrospectively by chart review of patients from 2006–2021, which yielded 30 individuals with SPS & GI manifestations presenting to a tertiary referral center.

Results: 25 are females. 23 Caucasian, 4 African American, 1 Asian and 2 Hispanic. GI symptom onset started approximately 7 years prior the SPS diagnosis. GI symptoms included heartburn (86.7%),
abdominal pain (80%), constipation (76.7%), dysphagia (76.7%), nausea (66.7%), bloating (63.3%), vomiting (46.7%), early satiety (33.3%), diarrhea (30%), alternating constipation & diarrhea (16.7%). The most bothersome symptom was constipation (40%). 17 reported autoimmune diseases: Hashimoto’s (8) and Sjogren’s (5). 26/30 tested positive for anti-glutamic acid decarboxylase antibodies (GAD65) and a minority (8/25) for anti-neuronal antibodies, including neuronal AChR (2/25), voltage gated calcium channel (2/25), Anti-GAD 65, (2/25) and anti-striational (2/25) antibodies. Motility workup consisted of whole gut scintigraphy (WGTTS) completed by 12/30 patients and pelvic floor workup (anorectal manometry “ARM” and/or MR defecography) completed by 9/30 patients. WGTTS findings were notable for gastroparesis in 6/12 patients and colonic inertia in 9/12 patients. ARM findings were notable for dyssynergia in 7/9 patients. MR defecography was completed by 2 patients and both reported rectocele. Skin biopsy was completed by 7 patients (4 of which were consistent with small fiber neuropathy). Tilt table tests performed in 5 patients revealed 2 with neurally mediated hypotension and 1 with postural orthostatic tachycardia syndrome.

Conclusion: GI symptoms are common in SPS, often precede the diagnosis, and are associated with objective delays in transit, suggesting a generalized dysmotility and autonomic dysfunction. Constipation was the dominant symptom and was associated with colonic inertia. Gastroparesis was seen in half the patient who did the WGTTS. Studies are ongoing to further investigate the mechanism of dysmotility in these patients but SPS should be added to the list of autoimmune diseases that has a prominent effect on gastrointestinal function and symptoms.

38 | Gastrointestinal symptom burden and quality of life in patients with anorectal spastic motor disorders and irritable bowel syndrome (IBS)

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Introduction: Anorectal spastic motor disorders (ASD) have been linked to functional disease and affective disorders, but these associations have not been systematically assessed. This case-control study compares GI- and non-GI-symptom burdens and psychometric profiles of subjects with ASD to IBS and healthy control groups.

Methods: Subjects presenting to outpatient neurogastroenterology clinics were prospectively recruited to complete self-report questionnaires to determine Rome III functional gastrointestinal disease, affective disorders, health related quality of life (HRQOL) and symptom burden. High resolution manometry (HRM) of the anorectum determined presence of ASD. Demographics, clinical and psychometric profiles were compared between subjects with ASD to IBS and healthy controls.

Results: Study cohorts consisted of individuals undergoing HRM, within which ASD was identified in 42 subjects (ASD+) (53 ± 2.4 years, 6 F). Of the 42 subjects with ASD, 23 were found to have IBS overlap (ASD+/IBS+). Comparator groups consisted of 112 subjects with IBS alone (ASD-/IBS+) (47.9 ± 1.3 years, 89 F), and 57 healthy controls (58.1 ± 2.1 years, 32 F). When compared
to healthy controls, ASD+ subjects reported increased GI symptoms severity, bother, and frequency (p < 0.01 for each), lower HRQOL (p < 0.01) as well as increased depression (BDI) and anxiety scores (BAI) (p < 0.001 for each). When compared to subjects with IBS alone (ASD-/IBS+), ASD+/IBS+ subjects had similar GI symptom burden, HRQOL, anxiety and depression scales, while ASD+/IBS+ overlap subjects reported increased anxiety (p < 0.001), increased depression (p < 0.05), and demonstrated a trend towards increased GI symptom frequency (p = 0.10).

**Conclusions:** ASD subjects, especially those with ASD/IBS overlap, demonstrate increased GI symptom burden and affective comorbidity, similar to subjects with IBS alone. Recognition and directed treatment of both ASD and IBS may be an important strategy in decreasing symptom burden and improving HRQOL in patients with ASD and ASD/IBS overlap.

Enteric nervous system neurobiology and circuitry: neurons, glia, smooth muscle cell, ICC

39 | **Rhythmic organization of Ca\(^{2+}\) transient clusters in ICC-MY of the stomach**

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**Background & Aims:** Interstitial cells of Cajal (ICC) in the myenteric plexus region (ICC-MY) of the gastric corpus and antrum are pacemakers that generate and propagate electrical slow waves. Slow waves depend upon activation of Ano1 channels which are Ca\(^{2+}\)-activated Cl\(^{-}\) channels and activated by Ca\(^{2+}\) transients in ICC. We investigated how Ca\(^{2+}\) signaling is organized and regulated in gastric ICC and characterized regional differences in the pattern of Ca\(^{2+}\) signaling in corpus and antrum.

**Key results:** Gastric slow waves have different intrinsic frequencies in isolated muscles of the corpus and antrum. In the mouse slow waves occur at ~8 cycles per min and in the corpus and ~4 cycles per min in the antrum. Propagation from corpus to antrum entrains antral slow waves to the frequency of the corpus. We found that Ca\(^{2+}\) waves spread through ICC-MY networks at the frequency of slow waves. High resolution imaging showed important differences in Ca\(^{2+}\) signaling in corpus and antral ICC-MY. ICC-MY displayed multiple discrete firing sites with highly localized Ca\(^{2+}\) transients organized into clusters temporally (Ca\(^{2+}\) transients clusters; CTCs). There was a relatively high frequency of firing of Ca\(^{2+}\) transients during the intra-slow wave period in the corpus in comparison to the antrum. The propagating Ca\(^{2+}\) transients that initiated the clusters of localized Ca\(^{2+}\) events were due to Ca\(^{2+}\) entry through voltage-dependent Ca\(^{2+}\) channels. L-type and T-type Ca\(^{2+}\) channel antagonists and membrane potential hyperpolarization by pinacidil reduced the durations of CTCs. The localized Ca\(^{2+}\) transients were due to release from intracellular stores. CPA and thapsigargin reduced the duration and frequency of the clustered events. The durations of CTCs were also reduced by the Orai antagonist GSK-7975A, suggesting that store-operated Ca\(^{2+}\) entry maintains Ca\(^{2+}\) stores. Ca\(^{2+}\) release and activation of Ano1 channels appears to be responsible for both initiation of slow waves and the amplitude and duration of the plateau phase of slow waves, the major electrical component associated with excitation-contraction coupling and phasic contractions.

**Conclusions:** Ca\(^{2+}\) handling mechanisms provide the mechanisms for generation, propagation, and complex waveform features of gastric slow waves.

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40 | **Abnormalities of the enteric nervous system may contribute to post pull-through dysmotility in Hirschsprung disease**

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Hirschsprung disease (HSCR), a congenital colorectal disorder which affects 1 in 5000 newborns, is characterized by absence of the enteric nervous system (ENS) along variable lengths of the colon. Surgical removal of aganglionic bowel segment is lifesaving, however, gastrointestinal motility disorders, including constipation, enterocolitis, and fecal incontinence, commonly persist in about 50% of patients. The broad objective of this study was to test the hypothesis that abnormalities of the proximal ganglionated intestine contribute to continuing intestinal morbidity following pull-through surgery. In this study, we utilized an Ednrb-knockout (KO) mouse model of HSCR. Morphometric analysis of the ENS was performed following immunostaining of the myenteric plexus with neuronal markers, Hu and Tuj1. KO mice demonstrated a hypoganglionic phenotype as compared to wild-type (WT) controls, including smaller ganglia with decreased neuronal fiber density in the proximal colon, and significantly fewer ganglia and decreased neuronal fiber density in the distal small intestine. To study the ENS composition of the ganglionic intestine in KO mice, we performed single-cell gene expression analysis on ENS cells isolated from the small intestine of Wnt1-GCaMP5\(^{fluorehua}\);Ednrb KO and WT mice. Our data showed decreased expression of certain immune-pathway genes in the glial cell population in the KO group. We also measured calcium activity of ENS cells ex vivo in whole-mount preparations of the proximal colon of Wnt1-GCaMP5\(^{fluorehua}\);Ednrb KO mice, where all Wnt1-expressing cells co-express the calcium indicator, GCaMP5. As compared to WT, significantly fewer ENS cells in the KO group demonstrated calcium transients in response to serotonin and electric field stimulation. These morphometric and cellular abnormalities in HSCR mice were accompanied by functional motility defects, namely diminished colonic migrating motor complexes in the proximal colon and...
Background: All living organisms rely on sensory systems to survive. Sensory systems interpret and transduce environmental stimuli into physiologic responses. The GI tract has a highly developed sensory system that is based on the physical interaction between luminal contents and the gut wall. Therefore, it is critical that we understand GI mechanosensing. To process mechanical stimuli, the gut requires specialized sensory neurons called intrinsic primary afferent neurons (IPAN) that reside within both submucosal and myenteric plexuses. While previous studies demonstrated that some IPANs are mechanosensitive, the molecular mechanisms of mechanotransduction in IPANs remain poorly understood.

Methods: Recent studies from our group show that the gut uses Advillin+ cell as IPANs. We used Avil creERT2/−;tdTomato/GCaMP5f/− mice to lineage trace and functionally assess the IPANs. We dissociated the small intestine myenteric plexus to study Advillin cells (tdTomato+) using whole cell electrophysiology and Ca2+ imaging with direct membrane displacement by a piezo-electrically driven microprobe.

Results: In whole-cell patch clamp, we found that 6 of 6 Advillin+ neurons displayed rapidly adapting mechano-currents (peak −316.02 ± 74.08 pA, inactivation time constant τi = 5.06 ± 0.77 ms) induced by direct membrane displacement (up to 7 μm). In Ca2+ imaging experiment, we found Ca2+ increase when Advillin+ neurons were subjected to membrane displacement (2 μm, 68%). Force-induced Ca2+ increases were reversibly inhibited by Piezo channel blockers: gadolinium (Gd3+, 30 μM, n = 4) and D-GsMTx4 (10 μM, n = 6) (ΔF/F0: ctrl 1.07 ± 0.53 vs. Gd3+ 0.0005 ± 0.0003 and ctrl D-GsMTx4 1.74 ± 0.48 vs. D-GsMTx4 0.24 ± 0.19), and were also inhibited by siRNA Piezo2 knockdown (ΔF/F0: Piezo2-siRNA 0.41 ± 0.09 vs. NT-siRNA 3.51 ± 3.15).

Conclusions: A population of mouse small bowel myenteric Advillin+ neurons are mechanosensitive, likely used Piezo2 as a primary mechanotransducer. Current and future studies to determine the mechanoreceptors and mechanotransduction mechanisms may provide novel drug targets.

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Gastrointestinal toxicity is a common dose-limiting adverse effect of platin chemotherapy treatment. Notably, for 50% of cancer survivors symptoms of chronic constipation or diarrhea induced by their chemotherapy treatment do not resolve. This drug toxicity is largely attributed to damage to the enteric nervous system. The enteric nervous system controls gastrointestinal motility, but a variety of biological perturbations can alter its function, making it especially challenging to dissect the direct effects of platinoids on the enteric nervous system at the organismal level. Therefore, the precise mechanisms underlying platin-induced enteric neuron death and potential preventative strategies remain unknown. Here, we use human pluripotent stem cell derived enteric neurons as an innovative strategy to overcome these technical challenges and establish a model capable of uncovering the mechanism of platin-induced enteric neuropathy. Utilizing this scalable platform, we performed a high throughput phenotypic screen, identifying molecules that prevent or exacerbate platin toxicity in enteric neurons. Utilizing the pharmacologic dataset, we identified 22 high confidence proteins predicted to be involved in the disease mechanism. These proteins are primarily composed of neurotransmitter receptors, revealing neurotransmission as a key modulator of platin-induced enteric neuropathy. Furthermore, antagonizing specific classes of receptors reduced the drug toxicity, particularly in the most vulnerable enteric neuron subtypes. These findings provide important insights into the cell type specific mechanisms underlying platin-induced enteric neuropathy and this novel approach serves as a proof of concept for uncovering cell type specific responses to cellular stress underlying numerous intractable peripheral neuropathies.

44 | Establishing a stem cell model to uncover the mechanism of chemotherapy-induced enteric neuropathy

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Interplay between embryonic enteric neural stem cells (ENSCs) and enteric mesenchymal cells (EMCs) in the embryonic gut is essential for normal development of the enteric nervous system. Disruption of these interactions underlies the pathogenesis of intestinal aganglionosis in Hirschsprung disease (HSCR). ENSC therapy has been proposed as a possible treatment for HSCR, but whether the survival and development of postnatal-derived ENSCs similarly rely on signals from the mesenchymal environment is unknown and has important implications for developing protocols to expand ENSCs for cell transplantation therapy. Enteric neural crest derived cells (ENCDCs) and EMCs were cultured from the small intestine of Wnt1-Rosa26-tdTomato mice. EMCs promoted the expansion of ENCDCs 9.5-fold by inducing ENSC properties, including expression of Nes, Sox10, Sox2 and Ngfr. EMCs enhanced the neurosphere-forming ability of ENCDCs, and this persisted after withdrawal of the EMCs. These effects were mediated by paracrine factors and several ligands known to support neural stem cells were identified in EMCs. Using the optimized expansion procedures, neurospheres were generated from
ABSTRACT

Small intestine of the Ednrb⁻/⁻ mouse model of HSCR. These ENSCs had similar proliferative and migratory capacity to Ednrb⁺/⁺ ENSCs, albeit neurospheres contained fewer neurons. ENSCs derived from Ednrb⁻/⁻ mice generated functional neurons with similar calcium responses to Ednrb⁺/⁺ ENSCs and survived after transplantation into the aganglionic colon of Ednrb⁻/⁻ recipients. EMCs act as supporting cells to ENSCs postnatally via an array of synergistically acting paracrine signaling factors. These properties can be leveraged to expand autologous ENSCs from patients with HSCR mutations for therapeutic application.

46 | Cholinergic and nitrergic neurons in the submucosal plexuses of the human sigmoid colon

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The colonic submucosal neurons play an important role in maintaining intestinal homeostasis by controlling electrolyte balance, colonic fluid and motility. We have shown differences in the neuronal density in the inner submucosal plexus (ISP) located near the mucosa and the outer submucosal plexus (OSP) located near the circular muscle layer in the ascending and descending porcine and human colon. In this study, we focused on the quantification of the overall neuronal population and of excitatory and inhibitory neurons in the ISP and OSP and the distribution of nerve fibers to the different layers of the gut wall in the human sigmoid colon. We obtained specimens from the uninvolved resection margin of sigmoid colon from 8 patients (2 F, age 41–80) undergoing elective surgery for colon adenocarcinoma. The lack of pathologic involvement was confirmed by histological analysis. We processed whole mount preparations of the ISP and OSP and tissue sections of the sigmoid colon for multiple labeling immunofluorescence with antibodies to HuC/D or PGP9.5 (as pan-neuronal markers for the identification of neuronal cell bodies and fibers, respectively), and to choline acetyltransferase (ChAT) or neuronal nitric oxide synthase (nNOS) as markers for excitatory and inhibitory neurons, respectively. Immunoreactive (IR) staining was analyzed with high-resolution confocal microscopy and Imaris software for quantification. The number of HuC/D-IR/mm² in the ISP and OSP of the sigmoid colon were comparable (169.9±12.4 and 168.7±17.4), however there were more neurons/ganglia in the ISP compared to OSP (18.11±1.7 vs. 13.19±1.2, p < 0.05). There was a dense innervation of the mucosa with PGP9.5-IR fibers running in the lamina propria and near the epithelium layer and distributed to the muscle layer. The distribution and density of ChAT-IR and nNOS-IR neurons were comparable in the ISP and OSP of the sigmoid colon with ChAT-IR neurons comprising 42% of HuC/D-IR neurons in the OSP and 50% in the ISP, and the nNOS-IR neurons being 33% of HuC/D-IR neurons in the OSP and 38% in the ISP. This study shows higher number of neurons/ganglion in the ISP compared to the OSP, with similar density of excitatory and inhibitory neurons and dense neuronal innervation of the mucosa and muscle layer supporting the concept that submucosal neurons regulate both secretory and motility functions. Characterization of submucosal neurons is important for a better understanding of the reflex pathways underlying disturbances in motility and secretion occurring in many gastrointestinal disorders.

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Epidemiology, genetics, cross-cultural and psychosocial factors in functional GI disorders in adults

47 | Factors of early life abuse, stressful life events, and family history for developing abdominal pain disorders of gut-brain interaction

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Background: Irritable Bowel Syndrome (IBS) is a multifactorial disorder of gut-brain interaction (DGBI), which familial and environmental factors are thought to play a role. A systematic review of studies measuring the association between IBS and other abdominal pain DGBI (AP-DGBI) and early adverse life events (EAL), negative life events (NLE), perceived stress (PS), and family history (FH) of AP-DGBI was conducted.

Methods: A comprehensive literature search was performed in PubMed, Medline, and Embase (Jan 1987 – Mar 2019). A tier-review process was utilized for identifying qualified adult studies. Manuscript inclusion criteria included fully published peer reviewed studies with a control group; exclusion criteria excluded treatment
studies. A validated quality rating scale (0–9) was completed; higher scores equaled higher quality.

Results: The search populated 64 citations, 51 (79.7%) of including [EAL (n = 12), NLE (n = 17), PS (n = 18), FH (n = 4)]. EALs were assessed by 3 domains: emotional (EA)/verbal abuse (VA), sexual abuse (SA), and physical abuse (PA). History of EA was associated with an increased risk of IBS or AP-DGBI (8/8 studies). The majority of studies showed an association between IBS pts who had experienced PA or SA as a child; however, these domains were not consistently found to be significant risk factors for developing IBS/AP-DGBI. NLE were defined by the experience of stressful situations. Majority of studies (15/17), from both community and population-based samples, showed either a greater number and/or impact of NLEs were associated with an increased risk of IBS. PS was assessed by validated and non-validated questionnaires and defined as increased psychological/emotional stress, sensitivity to stress, work-related stress, or daily stress. Majority of studies (15/18) found a positive association between increased stress and IBS/AP-DGBI. A positive FH of IBS was found to be a RF for IBS (4/4 studies), although interestingly, having an adoptive parent with IBS was not associated with developing IBS (1/1 studies).

Conclusion: This comprehensive systematic review overall found that familial and environmental factors, particularly stressful life events, increase the risk for developing IBS and other AP-DGBI. Addressing these risk factors may help to understand their impact in a patient’s health-related outcomes and are targets for treatment intervention.

48 | Prevalence of undiagnosed acute hepatic porphyria in cyclic vomiting syndrome

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Background: Acute hepatic porphyria (AHP), a rare genetic disorder, presents with non-specific clinical symptoms: diffuse abdominal pain, nausea, and vomiting that can mimic cyclic vomiting syndrome (CVS). There is a lack of knowledge of overlap of clinical symptoms between CVS and AHP and the prevalence of undiagnosed AHP in these patients.

Aims: To characterize clinical features of CVS that overlap with AHP and determine the prevalence of AHP via molecular analysis of the 4 AHP-associated genes: HMBS, CPOX, PPOX, and ALAD.

Methods: A prospective study of 188 patients diagnosed with CVS based on Rome IV criteria was performed. Patients completed a clinical questionnaire. They were eligible for AHP genetic testing if they had recurrent episodes of severe/diffuse abdominal pain with ≥2 of the following: red/brownish urine, blistering skin lesions, peripheral nervous system (PNS) dysfunction (muscle weakness/aching, numbness, tingling), central nervous system (CNS) (confusion, anxiety, seizures, hallucinations) or autonomic nervous system (ANS) (hyponatremia, tachycardia, hypertension, constipation, nausea/vomiting) during a CVS attack. Family history of AHP or elevated urinary porphobilinogen (PBG)/aminolevulinic acid (ALA) levels were also criteria for genetic testing. Genetic testing was performed in eligible patients.

Results: Mean age was 38.6 ± 14 years, 146 (78%) were female and 165 (88%) were Caucasian. Most (79%) had abdominal pain > 24 h during an episode. They also had PNS, CNS, ANS symptoms or red/brownish urine. Eligible patients were more likely to report numbness/tingling (p = 0.0146), fast or irregular heartbeat (p = 0.0159), or hyponatremia (p = 0.0259). Patients who experienced PNS (p = 0.0018), CNS (p ≤ 0.001), ANS (p = 0.0035) symptoms or had red/brownish urine (p = 0.001) were more likely to be hospitalized. Of 125 (66.5%) eligible patients, 66 completed genetic testing for AHP and none were found to carry pathogenic variants in the AHP genes. Variants of uncertain significance in the HMBS gene were identified in two patients, one of whom had normal urinary ALA and PBG concentrations. Biochemical porphyrin analysis for the other patient was not completed.

Conclusion: A significant overlap of symptoms with AHP (particularly neurological) was seen in CVS. There were no cases of AHP detected through genetic testing but the true prevalence will need a larger sample size and is ongoing.

49 | Diagnostic testing delays and telemedicine: Motility patient pandemic perspectives

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Background: Mandated delays in elective care during the COVID-19 pandemic have been determined with limited patient input. Continued disruption is possible with procedure backlogs and new virus variants. This may be especially problematic in neurogastroenterology/motility (NGM) patients who are known to have existing difficulty seeking care. We aimed to describe the NGM patient experience with these changes.

Methods: Thirty NGM patients who had diagnostic gastrointestinal testing within our motility laboratory canceled pursuant our state’s “stay-at-home” advisory during the initial viral surge underwent a semi-structured interview with a survey. Codes were derived from interview transcripts using the constant comparative method of inductive data acquisition.

Results: Five main themes arose including (1) understanding of the rationale for delays in gastrointestinal testing, although 68% of respondents expressed concern surrounding delay and 40% were at least somewhat upset; (2) varying degrees of fear surrounding COVID-19 itself in comparison to their health; (3) both satisfaction and frustration with telemedicine; (4) unhappiness with the function of outpatient practices; (5) factors independent of COVID-19 contributing to patients’ states-of-mind, with 76% of respondents stating at least good mood/mental health resilience.
Conclusions: While healthcare systems determine parameters of institutional function, NGM patients tolerate these top-down only within certain limits. It is difficult to predict patient preferences and as much flexibility as possible should be offered where favorable local COVID-19 parameters permit.

| Demographics/ Socioeconomics | Diagnostic Testing |
|-------------------------------|--------------------|
| Percent total (N)             | Percent total (N)  |
| Gender                        | Catheter foregut   |
| Female 66.7 (20)              | testing            |
| Male 33.3 (10)                | Esophageal manometry (HREM) |
| Race/ ethnicity               | Catheter pH testing |
| White 83.3 (25)               | HREM + catheter pH |
| Non-White 16.7 (5)            | testing            |
| Age                           | Endoscopy foregut  |
| 18–34 13.3 (4)                | testing            |
| 35–44 13.3 (4)                | EGD + wireless pH |
| 45–54 20 (6)                  | testing            |
| 55–64 40 (12)                 | Anorectal manometry |
| 65 and over 13.3 (4)          | 43.3 (13)          |
| Annual household income       | Dysphagia (not specified) |
| Below $10,000                 | Achalasia 16.7 (5) |
| $10,001–$50,000               | GERD 30 (9)        |
| $50,001–$100,000              | Lung transplantation 6.7 (2) |
| $100,001–$150,000             | Hindgut complaints |
| Over $150,000                 | Constipation 30 (9) |
| No response given             | Fecal incontinence 13.3 (4) |

50 | Long-term burden of hospitalizations and readmissions in achalasia

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Introduction: Achalasia is associated with significant morbidity. Thirty-day readmission rates, while a nationally important quality metric, is not sufficient in capturing the readmission burden, costs, and morbidity associated with this condition. In addition to analyzing long-term (180-day) readmission rates, associated costs, and trends we hope to identify characteristics of high utilizers of hospital services.

Methods: Nationwide Readmissions database (NRD), an all-payer claims database, was interrogated to identify patients with achalasia who had index admissions between January and June of each year between 2010–2014. Summary statistics was performed to evaluate readmissions within 180 days and important events during over these hospitalizations (pneumonia/respiratory arrest, procedures, deaths). High utilizers were defined as patients with ≥3 admissions in 180 days, and summary statistics was used to highlight morbidity and costs associated with this group.

Results: N = 6680 index admissions with achalasia (age 69 years, 59% female) resulted in 44% readmissions within 180 days. Only 7% first readmission occurred within 30 days, compared to 20% between 31–90 days, and 18% between 91 to 180 days. Over 180 days, average length of stay (LOS) per patient was 12 days and average hospital charges per patient was $102,341. Over this period, 57% of patients experienced pneumonia or respiratory, 19% were diagnosed with nutritional deficiencies, and 9% of patients died. Overall, 26% patients underwent upper endoscopy, 6% of patients underwent dilation, and 0.5% patients underwent esophagectomy. 21% of patients were identified as being high utilizers (age 67, 59% female). Over 180 days, high-utilizers incurred $213,277 in charges, with average LOS of 27 days. Between 2010–2014, 180-day readmission rates, average 180-day LOS, deaths, respiratory events, and proportion of high utilizers remained the same. However, total charges increased by $2,676 per year.

Conclusions: Achalasia is associated with a high rate of long-term hospitalizations, with most hospitalizations occurring later than 30 days of admission. Efforts at reducing healthcare costs, morbidity, and hospitalization burden associated with achalasia need to focus on ongoing, long-term, quality improvement efforts—especially geared towards high-utilizers.

51 | Impact of COVID-19 on irritable bowel syndrome in a Minnesota population

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Background: The COVID-19 pandemic has led to life disruptions directly and indirectly through mitigation measures, leading to increased stress, isolation and variable access to health care. As stress is a known trigger of irritable bowel syndrome (IBS), we sought to understand the impact of the pandemic on IBS patients.

Methods: We identified residents of Olmsted County, MN, diagnosed consecutively with IBS at Mayo Clinic from 2010–2020. Eligible participants received mailed surveys evaluating COVID-19 impact (March-May 2020) and IBS symptoms (past 10 days).

Results: Among 213 eligible, 38 surveys (18%) were returned. Of six symptomatic participants who did not seek care, four cited...
COVID-19 related concerns. Eight respondents (21%) had a friend/relative diagnosed with COVID-19, and 12 (32.4%) reported developing significant financial concerns. Participants with friends/family diagnosed with COVID-19 (n = 8) had higher anxiety (p = 0.028) and depression (p = 0.027) scores and those reporting financial concerns (n = 12) had higher anxiety (p = 0.03). IBS-QOL total increased with both anxiety (R² = 0.35, p < 0.0001) and depression scores (R² = 0.51, p < 0.0001) on linear regression. Both anxiety and depression were correlated with pain (A: R² = 0.17, p = 0.016; D: R² = 0.19, p = 0.01), distension (A: R² = 0.17, p = 0.018, D: R² = 0.14, p = 0.03), dissatisfaction (A: R² = 0.11, p = 0.048, D: R² = 0.22, p = 0.003), and interference (A: R² = 0.34, p = 0.0001, D: R = 0.34, p = 0.0001) on IBS-SSS. Subgroup analysis was performed on symptomatic respondents who did not seek care due to COVID related concerns (n = 4) compared to others. This group had statistically significant higher HAD-depression scores (9.8 vs. 4.6, p = 0.02), IBS-SSS pain levels (67.5 vs. 23.9, p = 0.04), dissatisfaction (88.75 vs. 46.5, p = 0.014), interference to life (67.5 vs. 23.9, p = 0.004), and IBS-QOL Totals (111.5 vs. 67.9, p = 0.0095). Respondents who had friends/relatives diagnosed with COVID-19 were significantly more likely to have abdominal distension (LR 5.3, p = 0.02) and reported their symptoms to have higher interference on their life (61.3 vs. 27.9, p = 0.0096).

Discussion: The COVID-19 pandemic has impacted IBS patients from direct infection and mitigation efforts leading to increased isolation, financial pressures, and stress. Cross-sectional evaluation of patients in Olmsted County showed that symptomatic patients who did not seek care due to COVID-19 concerns had more GI symptoms and worsened quality of life. Respondents with financial concerns had higher anxiety, increased abdominal distension, and life disruption from GI symptoms. Care should be taken to provide access and support to this patient population as the pandemic progresses.

Esophageal physiology, pathophysiology, and clinical disorder

52 | Manometric esophagogastric junction barrier metric as predictors of gastroesophageal reflux

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Introduction: High-resolution manometry (HRM) tools, such as esophagogastric junction contractile integral (EGJ-CI), total EGJ-CI and EGJ subtypes have been designed to assess EGJ barrier function. There is evidence to suggest that it may allow for better differentiation of patients with and without pathological reflux. The aim of this study was to evaluate the relationship between manometric EGJ metrics with esophageal acid exposure found on ambulatory reflux monitoring.

Methods: We conducted a retrospective review of patients off PPI who underwent both HRM and ambulatory reflux testing between 11/2017–1/2020. Patients were excluded if they had incomplete data, achalasia, EGOO, or prior esophagogastric surgery. The EGJ-CI was calculated using the distal contractile integral (DCI) tool box during three consecutive respiratory cycles. The value was then divided by the duration of these cycles. Cross sectional evaluation of patients with and without pathological reflux. The EGJ-CI was defined as pH < 4 with esophageal acid exposure time (EAET) exceeding 6.0%. Pearson's correlation, univariable and multivariable regression models were used to assess the relationship between pathological GERD and manometric parameters. ROC analysis and a Youdex index were used to optimize sensitivity and specificity thresholds for EGJ-CI and total EGJ-CI values.

Results: 275 patients ≥18 years old who underwent HRM and ambulatory reflux monitoring were included. Majority of patients (74.17%) had a manometric diagnosis of IEM with a predominant Type 2 EGJ. On univariable analysis, GIDR patients had increased odds of having lower mean basal LES pressure, EGJ-CI, total EGJ-CI and integration relaxation pressures than non-GIDR patients. There was no difference in EGJ subtype between GIDR and non-GIDR patients. Patients with GIDR had increased odds of IEM (OR 1.80, 95% CI 1.05–3.09). On multivariable analysis, age, EGJ-CI and Mean DCI were significant predictors of pathological GERD. There were significant, though weak, correlations between EAET and EGJ-CI and total EGJ-CI (r = −0.18, −0.19, p < 0.01, respectively). An EGJ-CI cutoff of 44.16 as a predictor for pathologic GERD had a sensitivity of 46% and specificity of 42% (AUC 0.60). Total EGJ-CI cutoff of 11.461.3 for pathologic GERD had a sensitivity of 44% and a specificity of 43% (AUC 0.62).

Conclusions: EGJ-CI can independently predict pathological GERD. However, the poor correlation between EGJ-CI and esophageal acid exposure indicates that mechanisms other than baseline EGJ barrier function play a role in GERD development. Factors such as age and integrity of peristalsis also contribute. Calculated thresholds for EGJ-CI and total EGJ-CI yield low sensitivity and specificity for the diagnosis of GERD. Larger studies are required to assess the roles of these manometric tools as independent predictors in the pathophysicsology of GERD.
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Background: Pneumatic dilations are often used in children for the management of achalasia. EsoFLIP\textsuperscript{tm} is a novel hydraulic dilation device, previously used to successfully dilate the esophago-gastric junction (EGJ) in adult achalasia patients without the need of fluoroscopy. Data on the use of EsoFLIP\textsuperscript{tm} in children is limited. Thus, we sought to describe our center’s experience using EsoFLIP\textsuperscript{tm} in children with achalasia.

Methods: We performed a retrospective chart review of patients undergoing dilations using EsoFLIP\textsuperscript{tm} (EsoFLIP-ES-330, Medtronic, Inc) and functional luminal probe (FLIP) measurements at the time of dilation. EGJ measurement using FLIP are typically obtained before and immediately after dilations. FLIP data was used to generate pressure geometry measurement and calculate EGJ distensibility index (EGJ-DI).
which is defined as the minimal cross-sectional area (CSA) at the EGJ versus the intraballoon pressure (IBP) at an inflation volume of 40 ml.

**Results:** Nine achalasia patients (ages 10.2–17.5 years, 5 females) underwent hydraulic dilation with a 30 mm diameter EsoFLIP™ dilator balloon. Fluoroscopy was not used during the dilation procedures. Hydraulic dilations using EsoFLIP™ where performed per manufacturer’s recommendations. The EsoFLIP™ dilator balloon was always inflated twice for 60 s until effacement of the EGJ segment was seen. The EsoFLIP™ balloon pressure ranged between 13 and 18 pounds per square inch (PSI), measured by an external manometer during the dilation phase. EGJ measurements prior to dilation included EGJ-DI (median, 3.0 mm²/mmHg; range 1.4–5.1 mm²/mmHg), diameter (median 9.7 mm; range 7.0–13.1 mm) and IBP (median, 25.4 mmHg; range 18.2–45.9 mmHg). A significant within subject improvement in EGJ-DI (median \( \Delta \), +3.2 mm²/mmHg; range, +1.8–8.3 mm²/mmHg; \( p < 0.001 \)) and diameter (median \( \Delta \), +4.0 mm; range +2.1–5.7 mm, \( p < 0.001 \)) was seen. No significant changes in IBP were observed post dilation (median \( \Delta \), −2.5 mmHg; range, −0.9, −16.7 mmHg, \( p = 0.08 \)). No significant post procedural adverse events were reported.

**Conclusions:** EsoFLIP™ is a feasible dilation method for patients with achalasia without the need for fluoroscopy. EsoFLIP™ dilations achieve a significant improvement in EGJ-DI and diameter. Prospective studies to further assess safety and symptomatic outcomes in children are greatly needed.

### Sars-CoV-2 (COVID-19) prospective quality control project: exploring a patient profile relative to scheduling a motility laboratory procedure related to Sars-CoV-2 anxiety

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**Background:** Motility Laboratories (ML) have been impacted by the Sars-CoV-2 (COVID-19) pandemic. Gastroenterology society task forces published COVID-19 recommendations for operating a safe motility laboratory protecting staff and patients. Data is nonexistent to the role COVID-19 anxiety plays in patients scheduling their motility studies. Our aims were: (i) Determine if COVID-19 anxiety impacts patients’ willingness to schedule ML tests. (ii) Explore differences between scheduling specific ML tests related to COVID-19 anxiety.

**Methods:** Prospective, single-center, analysis (Jan – Nov, 2020); 353 patients were invited to participate in a 5-minute online survey administered via Survey Monkey. A ML scheduler contacted all patients; then, the survey was sent to motility patients. Motility test orders were: Esophageal Manometry (EM), pH testing (pH), Esophageal Manometry and pH (EM-pH), Anorectal Manometry (ARM), and Hydrogen Breath Test (HBT). The survey included the

| Patient characteristics | Total cohort n = 252 | Under 65 n = 138 | Elderly n = 114 |
|-------------------------|---------------------|-----------------|----------------|
| Age (year)**            | 61.3 ± 17.4         | 49 ± 12.9       | 76 ± 7.8       |
| Female                  | 116 (45.3)          | 61(44.2)        | 53 (46.5)      |
| Known type achalasia    | 125 (49.2)          | N = 52          | N = 72         |
| Type 1                  | 18 (14.4)           | 6 (11.5)        | 12 (16.7)      |
| Type 2                  | 96 (76.8)           | 41 (78.8)       | 54 (75)        |
| Type 3                  | 11 (10.6)           | 5 (9.6)         | 6 (8.5)        |
| Complications           | 18 (7.1)            |                 |                |
| Esophageal perforation  | 6 (2.4)             | 4 (2.9)         | 2 (1.8)        |
| Chest pain-ER**         | 12 (4.8)            | 11 (8)          | 1 (0.9)        |
| Chest pain-hospitalization* | 9 (3.6)          | 8 (5.8)         | 1 (0.9)        |
| Mean ± SD/ n (%)        | * p < .05           |                 |                |

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| Mean ± SD/ n (%)        | * p < .05           |                 |                |
validated Coronavirus Anxiety Scale (CAS), income, education, residence (North [NC] or South Carolina [SC]), and underlying medical conditions (risk factors for COVID-19): hypertension, COPD, diabetes mellitus, smoker, coronary artery disease, liver and renal disease. A CAS score ≥ 9 indicated a dysfunctional level of COVID-19 anxiety. Statistical analyses included chi-square and independent t-tests.

Results: 82 (23.2%) of 353 invitees completed the online survey. Mean age was 53.8 ± 15.3 years, participants were 87.8% female, 85.2% Caucasian, and 82.3% from NC. Specific test orders: 36.6% ARM, 25.6% EM-ph, 23.2% EM, 2.4% pH, and 12.2% HBT. 76.8% of ML patients scheduled their test. No mean CAS difference was seen between patients who scheduled their test vs. those foregoing testing: 6.2 ± 2.8 vs. 6.8 ± 4.7, p = NS. Similar CAS categorization was seen among all ML tests. No differences in scheduling or foregoing ML testing related to income, education attainment, geographical residency, and underlying medical conditions excluding coronary artery disease (p = 0.001; forego testing). Of the 12 patients with a CAS ≥ 9, 100% resided in NC vs. 0% from SC; p = 0.08.

Conclusion: Motility Laboratory patients are willing to schedule their test during cycles of the COVID-19 pandemic, despite COVID-19 anxiety. However, patients with elevated levels of CAD risk may be more reluctant to schedule a ML test during the pandemic. Future studies are warranted to identify optimal testing options for these patients and whether state leadership strategies impact COVID-19 CAS levels for ML patients should be explored.

55 | Pneumatic dilation is safe in elderly patients with achalasia: a multicenter cross-sectional study

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Background: Pneumatic dilation (PD) is an effective treatment option for achalasia, but may result in esophageal perforation or bleeding. Data about PD in elderly patients are limited. Our study aimed to explore the periprocedural safety profile of PD in elderly patients.

Methods: This was a retrospective study of consecutive achalasia patients undergoing PD in the Massachusetts General Hospital (MGH) between 2013–2020, and the Tel Aviv Medical Center (TLVMC) between 2006–2020. Records were reviewed and periprocedural complications (up to a month) were compared between elderly (65 and older) and younger patients.

Results: The 252 patients [TLVMC-197 (78%), MGH-55 (22%)] included underwent 318 PDs: 251 a single PD, 58 a second, and 9 a third PD. One hundred-fifteen (45.2%), 86 (33.6%), and 53 (20.7%) patients were older than 65, 70, and 75 years, respectively. Ages ranged between 17.9–97.9. In 318 PDs, 18 (5.7%) complications occurred (see table): 6 (1.9%) perforations, 12 (3.8%) ER visits with chest pain, 9 (2.8%) non-perforation-related hospitalizations. All events occurred in TLVMC. No bleeding occurred. Perforation was not associated with age. Moreover, there was no association with balloon diameter or number of PDs and risk of all complications. Two (18.2%) patients with type 3 achalasia had post procedural chest pain vs 2 (1.8%) in type 1/2 p = 0.04. One of the two elderly patients (aged 83) with a perforation, died of septic complications following perforation clip closure of the perforation.

Conclusions: PD is safe in elderly patients. When complications do occur, elderly patients may have worse outcomes. Younger patients should be advised on potential for chest pain post-PD. This may affect informed consent discussions.

56 | Utility of baseline impedance ratio measured during high resolution impedance manometry in identification of erosive esophagitis and/or Barrett’s esophagus

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Background: The baseline impedance measured during high-resolution impedance manometry (HRIM) is a new modality that showed promising performance in distinguishing patients with gastroesophageal acid reflux disease (GERD) from controls. However, data on its utility in erosive esophagitis or Barrett’s esophagus (BE) is limited. We evaluated the performance of baseline impedance measured during HRIM, as well as three other proposed modifications, in identifying severe esophagitis and BE diagnosed on esophagogastroduodenoscopy (EGD).

Method: We retrospectively included patients with pH study proven GERD, who underwent an EGD and HRIM at the University of Kentucky between 7/2012 to 10/2019. Using the manometry smart mouse tool, we measured four variables: (1) lower baseline impedance (LBI) measured at the landmark section, (2) total lower baseline impedance (TLBI) measured across the whole study, (3) baseline impedance ratio (BIR) measured as lower divided by upper impedance within the landmark section and (4) total baseline impedance ratio (TBIR) measured as lower to upper impedance measured across the whole study. Measurements were done 3 cm above the lower esophageal sphincter and 3 cm below upper esophageal sphincter. We used receiver operator curves (ROC) to assess the performance of these metrics.
Results: We identified 22 cases with severe esophagitis (grade C and D) and/or BE and 42 controls. TLBI for esophagitis/BE group was 0.65 (IQR 0.41–0.79) and 1.04 for the control group (IQR 0.8–1.25, p < 0.001) (Table 1). Using a cutoff value of 0.8, TLBI had an area under the curve [AUC] of 0.77. We found no significant difference between the two groups in upper esophageal impedance. However, we found significantly lower BIR and TBIR in the severe esophagitis/BE group (0.27 and 0.31 respectively) compared to the controls (0.52 and 0.49 respectively). AUCs for the 4 metrics were statistically similar (Figure 1).

Conclusion: The four studied impedance metrics were significantly lower in the severe esophagitis/BE group; they all showed modest ability in distinguishing these patients from controls. Being the most simple to calculate, BLI can help identify these complications of GERD in patients who decline or cannot perform an EGD.

Table 1 Patient characteristics

|                      | Controls        | Severe esophagitis (Grade C or D)/Barrett’s esophagus | p-value |
|----------------------|-----------------|--------------------------------------------------------|---------|
| n                    | 42              | 22                                                     |         |
| Age, years, mean (SD)| 54.9 (12.7)     | 52.27 (17.55)                                          | 0.494   |
| Males, n (%)         | 13 (31)         | 8 (36.4)                                               | 0.781   |
| Ethnicity, Caucasian (%) | 39 (92.9)       | 22 (100)                                               | 0.545   |
| Symptoms (%)         |                 |                                                        |         |
| Heartburn, n (%)     | 25 (59.5)       | 14 (63.6)                                              | 0.793   |
| Dysphagia, n (%)     | 21 (50)         | 8 (36.4)                                               | 0.428   |
| Chest pain, n (%)    | 9 (21.4)        | 8 (36.4)                                               | 0.24    |
| Regurgitation, n (%) | 24 (57.1)       | 15 (68.2)                                              | 0.431   |
| Acid exposure time, median [IQR] | 10.55 [6.6, 13.75] | 13.2 [9.95, 16.42]                                     | 0.066   |
| Baseline lower impedance, kΩ, median [IQR] | 1.23 [0.84, 1.76] | 0.59 [0.5, 0.73]                                       | <0.001  |
| Baseline upper impedance, kΩ, median [IQR] | 2.36 [1.74, 3.19] | 2.12 [1.67, 2.79]                                      | 0.344   |
| Total lower impedance, kΩ, median [IQR] | 1.04 [0.8, 1.25] | 0.65 [0.41, 0.79]                                      | <0.001  |
| Total upper impedance, kΩ, median [IQR] | 1.89 [1.6, 2.3] | 1.95 [1.52, 2.41]                                      | 0.838   |
| Baseline lower/upper impedance ratio, median [IQR] | 0.52 [0.33, 0.77] | 0.27 [0.2, 0.48]                                       | 0.001   |
| Total lower/upper impedance ratio, median [IQR] | 0.49 [0.43, 0.65] | 0.31 [0.24, 0.51]                                      | 0.002   |

SD, standard deviation; AET, Acid exposure time; IQR, Interquartile range.

Figure 1 Receiver operating characteristic (ROC) curve
57 | Paraneoplastic achalasia in the setting of a neuroendocrine tumor: A case report

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Introduction: Achalasia in the paraneoplastic setting has primarily been associated with anti-neuronal nuclear antibody-1 (ANNA-1) and is usually related to small cell lung cancer. While other onconeural antibodies have also been described, to date there has been no association between paraneoplastic achalasia and neuroendocrine tumors (NET).

Case Report: 60-year old male with significant tobacco use presented to the hospital with 1 year of progressive weakness in all his extremities, unsteadiness of gait, hypophonia, dysphagia and 70-lb unintentional weight loss. Both endoscopy and manometry had classic findings of achalasia type 2. Patient was a poor surgical candidate so he underwent botox injection into distal esophagus with improvement of symptoms. MRI brain demonstrated T2 intensity in involving centrum pons and semi-ovale. Electromyelogram revealed demyelinating polyneuropathy. Cross-sectional imaging revealed 8 mm spiculated lesion within right upper lobe of lung but also 4 cm porta hepatis mass. Biopsy of the porta hepatis mass revealed strong expression of nuclear TTF-1, cynaptophysin, CD 56, and cytokeraatin 7—consistent with NET with possible lung origin. Paraneoplastic panel sent to Mayo Clinic revealed positivity of ANNA-1 and collagen response-mediator protein-5 immunoglobulin G (CRMP-5 IgG). Patient is being considered for steroid therapy after improvement of complicated aspiration pneumonia.

Discussion: This case report is the first to describe an association between paraneoplastic achalasia and NET. While further study of this association is warranted, our case report suggests clinicians should have greater vigilance for paraneoplastic causes amongst patients with NET

58 | Decreased distal esophageal impedance in Barrett’s esophagus: Variations with dysplasia

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Background: Barrett’s esophagus (BE) has decreased distal esophageal impedance (DEI) measured on high-resolution esophageal manometry (HREM). The aim of this study was to determine differences in DEI in BE patients with varying grades of dysplasia both before and after BE treatment.

Methods: Patients with a current or previous diagnosis of BE who underwent HREM were included in this retrospective study. BE status at time of HREM was recorded. Landmark DEI values were calculated from HREM tracings using the impedance channel directly above the LES and compared among patients without BE, with BE with no dysplasia (NDBE), indefinite for dysplasia (IND), low-grade dysplasia (LGD), and high-grade dysplasia (HGD). DEI also was compared among patients who had and had not received ablative treatment prior to HREM. Kruskal-Wallis and Mann-Whitney tests were used to compare groups.

Results: There were 70 patients with active or previously treated BE who underwent HREM, with an overall mean DEI (kΩ) of 1.56 ± 1.62. At the time of HREM, 24 patients had no BE, 34 had NDBE, 6 had IND, 5 had LGD, and 1 had HGD. DEI for these respective groups differed: 2.31 ± 1.99, 1.33 ± 1.38, 0.75 ± 0.64, 0.81 ± 0.58, and 0.27 ± 0 (p = 0.003). DEI remained significantly different among groups when dysplastic BE was grouped together: non-BE vs. NDBE vs. BE with any grade of dysplasia (IND, LGD, and HGD) (p = 0.001). Patients with BE of any kind had a significantly lower DEI than non-BE patients (any BE = 1.17 ± 1.24, non-BE = 2.31 ± 1.99; p < 0.001). DEI was significantly lower in both NDBE patients and in BE with any dysplasia patients compared to non-BE patients (respectively, p = 0.014 and p = 0.001). The DEI among BE patients with any grade of dysplasia trended lower than that of NDBE patients (BE any dysplasia = 0.74 ± 0.57, NDBE = 1.33 ± 1.38; p = 0.099). Patients who received ablation prior to HREM (n = 13) and had not (n = 57) had no difference in DEI (ablation = 1.51 ± 0.69; no ablation = 1.57 ± 1.76; p = 0.308), even when adjusted for BE grade at HREM (p = 0.392).

Discussion: Patients with NDBE or BE with any dysplasia have a lower DEI than non-BE patients. There is also a trend toward lower DEI with worsening grades of dysplasia. This can potentially be used as a guide for BE surveillance and management. There was no change in DEI after BE treatment.

59 | Cannabis use is associated with esophageal motility disorders characterized by impaired inhibition

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Background: Data regarding cannabis effects on esophageal function are limited. Small studies have shown that cannabinoid receptor agonists decrease transient lower esophageal sphincter relaxations (TLESRs), suggesting that cannabis may interfere with inhibitory signals and could thus lead to esophageal motility abnormalities characterized by impaired inhibition. To our knowledge, no studies have evaluated the effect of cannabis use on esophageal motor function through high-resolution esophageal manometry (HRM).

Aims: Compare the prevalence of esophageal motility abnormalities in cannabis users and control patients not on cannabis who completed HRM at our center.

Patients and Methods: Retrospective review of cannabis users (N = 27) and consecutive patients not on cannabis (N = 48) who...
underwent HRM. Cannabis use (inhaled or ingested) was documented through motility database and chart review. Patients with prior gastroesophageal surgery, pneumatic dilation, esophageal botulinum toxin injection within 6 months of HRM, esophageal stricture, and current opioid use were excluded. Demographics, clinical information, and manometry diagnosis by Chicago classification v3.0 were obtained from a prospectively maintained motility database.

Esophageal motility abnormalities were classified as (a) disorders of impaired inhibition (achalasia, EGJOO, DES, Jackhammer esophagus), or (b) disorders of impaired contractility (absent contractility, ineffective esophageal motility, fragmented peristalsis, scleroderma-like esophagus). Fisher’s exact test was used to compare prevalence of these motility disorder groups among cannabis users and controls.

Results: Disorders of impaired inhibition were present in 4 cannabis users (2 achalasia, 2 EGJOO) but not seen in controls. Disorders of impaired inhibition were significantly more prevalent in cannabis users versus controls (15% vs 0%, \( p = 0.01 \)). The prevalence of disorders of impaired contractility was similar for cannabis users and controls (37% vs 21%, \( p = 0.18 \)).

Discussion: Compared with controls, patients using cannabis were significantly more likely to have esophageal motility disorders characterized by impaired inhibition including achalasia and EGJOO. This study suggests that cannabis may interfere with inhibitory signals in the esophagus, which is consistent with prior evidence of cannabis decreasing TLESRs. A larger sample size and additional studies are needed to confirm these findings and to elucidate the underlying mechanisms.

## Clinical and demographic variables among patients with ineffective esophageal motility using Chicago classification v4.0

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Background: The Chicago Classification v4.0 (CCv4.0) of ineffective esophageal motility (IEM) requires ineffective contractions following > 70% of swallows or failed contractions following ≥50% of swallows on esophageal high resolution manometry (HRM) and is more stringent than the CCv3.0 definition. IEM is a heterogeneous disorder with an unclear and likely multifactorial pathophysiology. Studies have suggested that various systemic or esophageal disorders are linked to IEM. Medications can also affect esophageal function, possibly resulting in IEM.

Aim: Our study examines the prevalence of clinical and demographic variables among patients diagnosed with IEM at the Milton S. Hershey Medical Center (HMC) between 2011 and 2019 in patients who meet the more stringent CCv4.0 criteria of IEM.

Methods: We retrospectively studied 183 adults diagnosed with IEM on HRM based on CCv3.0 at HMC between 2011 to 2019. Charts were reviewed for demographics, symptoms, comorbidities, medications, manometric data, and findings on additional studies. Means are presented with standard deviations (mean ± SD).

Results: Based on CCv4.0, 133 patients met criteria for IEM. Mean age was 53 ± 17 years. Seventy percent were female and 88% were white. Body mass index was: underweight (3%), normal (23%), overweight (33%), and obese/morbidly obese (40%). Dysphagia was the primary indication for manometry in 53% of patients; other prevalent symptoms were reflux in 50% and heartburn in 35%. Common comorbidities included digestive system (93%), endocrine (57%), and mood (56%) disorders; 57% of patients have a history of alcohol use and 36% have a history of smoking. Common medications were: proton pump inhibitor (84%), selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor (35%), and non-steroidal anti-inflammatory drug (32%). On manometry, the mean percent of weak contractions was 41 ± 29% and failed contractions was 46 ± 25%, totaling a mean 87 ± 12% ineffective contractions. The mean lower esophageal sphincter pressure was 20 ± 13 mmHg. The mean integral relaxation pressure (IRP) was 5 ± 7 mmHg, and 6 patients had an elevated IRP (>15 mmHg). The mean percent of swallows with cleared bolus was 13 ± 21%. On upper endoscopy, 22% of patients had esophagitis and 36% had a hiatal hernia.

Conclusion: This study builds on our understanding of the clinical characteristics and manometric and endoscopic findings in patients meeting CCv4.0 criteria for IEM.

## Implications of esophageal contractility in post-lung transplant patients

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Introduction: Gastroesophageal reflux disease (GERD) is a risk factor for chronic lung allograft dysfunction (CLAD), a feared complication after lung transplant (LTx). A proposed hypothesis suggests that altered esophageal motility in post-LTx recipients inhibits clearance of gastric refluxate, thus promoting aspiration injury to the lung allograft. The purpose of this study is to assess the relationship between esophageal contractile vigor using high-resolution esophageal manometry (HRM), reflux using 24-hour pH impedance and allograft rejection following LTx.

Methods: A retrospective review of medical records was performed for patients who received a LTx at our institution between January 1, 2017 and July 23, 2019. All HRM and 24-hour pH impedance studies were read in a blinded manner after randomization. Covariates, reflux parameters and acute lung rejection rates were compared using nonparametric univariate analyses (Mann-Whitney and Fisher’s exact) in patients with and without increased distal contractile integral (DCI) following LTx.

Results: Of the 35 patients (mean age 60 +/- 6, 46% female) who underwent LTx, mean DCI increased significantly post-LTx (2435 vs 3500, \( p < 0.001 \)). Patients with increased DCI post-LTx had
lower distal acid exposure times (2.2 vs 9.4, \(p = 0.073\)) and higher mean nocturnal baseline impedance (2393.7 vs 1671.8, \(p = 0.059\)). Additionally, mean DCI post-LTx was inversely associated with post-transplant distal esophagus acid exposure time (Spearman’s \(\rho = -0.348, \ p = 0.041\)). The present study did not find an association between increased DCI and acute allograft rejection.

**Conclusion:** Our study demonstrates that increased esophageal contractile vigor post-LTx could have a potential protective effect against acid reflux. Further studies are needed to elucidate the pathophysiology leading to GERD post-LTx and its role in aspiration and CLAD.

**62 | Early life factors in eosinophilic esophagitis: A systematic review and meta-analysis**

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**Objectives:** The rising incidence of Eosinophilic esophagitis (EoE) has led to increased interest in etiologic factors in the development of this disease. EoE has been linked to various exposures in the perinatal period and infancy. A systematic review and meta-analysis was conducted to assess the association of antibiotic exposure, preterm delivery, breastfeeding, and cesarean section on the development of EoE.

**Methods:** Pubmed, Embase, Web of Science, and Cochrane Central were searched from inception to June 2020. A systematic literature search was conducted for published manuscripts and major conference abstracts identifying case-control studies of EoE that examined the above exposures. Fixed and random effects models were used to develop pooled OR and \(I^2\) values. Primary outcome was expressed as a pooled odds ratios for EoE with 95% confidence intervals for each exposure of interest.

**Results:** Ultimately, eight studies were eligible for inclusion, comprising a total of 8,239 subjects with 2,311 EoE cases. Seven studies reported data for early antibiotics exposure, with pooled odds ratio \(OR = 1.90\) (95% CI 1.21–2.99, \(p = 0.005\)). Five studies reported data for breastfeeding, with a pooled odds ratio \(OR = 1.24\) (95% CI 0.85–1.81, \(p = 0.26\)). Five studies reported data for Cesarean section, with a pooled odds ratio \(OR = 1.66\) (95% CI 1.17–2.36, \(p = 0.004\)). Four studies reported data for preterm delivery, with a pooled odds \(OR = 1.91\) (95% CI 1.55–2.35, \(p = 0.0001\)).

**Conclusions:** Early exposure to antibiotics, preterm delivery, and Cesarean section were associated with increased odds of EoE, while breastfeeding was not found to be protective. Greater understanding of the interplay between these factors and EoE can potentially allow for the development of predictive tools and models for risk stratification.

**63 | Proximal reflux on impedance-pH, not patient-reported symptoms, predicts worse pulmonary function in interstitial lung disease**

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**Background:** Gastroesophageal reflux disease (GERD) has been associated with interstitial lung disease (ILD) and poorer pulmonary function, potentially due to gastric refluxate-induced lung damage. Identifying those at risk for reflux-related lung injury may affect management of ILD, but the optimal strategy to assess GERD and esophageal measures most associated with clinical severity remain unclear.

**Aim:** To assess the association between reflux measures on multichannel intraluminal impedance pH (MII-pH) and ILD severity on pulmonary function testing (PFT), compared with patient-reported symptoms.

**Methods:** 56 consecutive ILD patients (39.3% male, age = 59.8 ± 10.6 years) undergoing routine pre-lung transplant MII-pH at a tertiary center were enrolled. Validated symptom surveys were collected prospectively, including GERDQ, reflux symptom index (RSI), dominant esophageal symptom intensity (DSI), and global symptom severity (GSS). ILD severity was quantified by diffusion capacity for carbon monoxide (DLCO) on PFT performed at the time of MII-pH. MII-pH parameters obtained included distal and proximal acid exposure time (AET), bolus reflux episodes, and mean nocturnal baseline impedance (MNBI), calculated by averaging baseline impedance at three 10-minute time intervals. Univariate (Spearman’s correlation) and multivariable (general linear regression) analyses were performed.

**Results:** Proximal AET inversely correlated with DLCO (\(R = -0.313, \ p = 0.019\)) and %predicted DLCO (\(R = -0.274, \ p = 0.041\)). Lower proximal MNBI was associated with worse DLCO (\(R = 0.375, \ p = 0.019\)) and %predicted DLCO (\(R = 0.409, \ p = 0.0098\)). A similar trend was observed for distal MNBI and DLCO that did not reach statistical significance (\(R = 0.294, \ p = 0.06\)). No significant association was found between distal AET, distal or proximal bolus reflux episodes, or distal MNBI with DLCO. On multivariable models adjusting for age, sex, smoking, and BMI, proximal MNBI remained independently predictive of lower %predicted DLCO (\(\beta = 0.0010, \ p = 0.034\)). No symptom scores correlated with MII-pH or PFT measures.

**Conclusion:** Proximal reflux metrics were associated with more severe lung disease on PFT, strengthening the proposed physiologic mechanism of refluxate traveling through the upper esophagus to induce lung injury. Patient-reported symptoms did not correlate significantly with objective reflux or PFT measures, suggesting a role for routine objective reflux testing in ILD management.

Gastric physiology, pathophysiology, and clinical disorders
64  |  Nutritional deficiencies and predictors of mortality in gastroparesis patients

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Background: Gastroparesis is a debilitating condition that may impact morbidity and mortality. There is lack of long-term studies examining morbidity and mortality. The aim of this study is to determine the predictors of mortality in gastroparesis and to determine the nutritional deficiencies.

Patients and Methods: Between September 30, 2009 and January 31st, 2020, we identified 320 patients (mean age 47.5 years ± 5.3, 70% women, 71.3% Whites, 39.7% had diabetes mellitus) with gastroparesis. 99mTc sulfur labeled food was used to diagnose gastroparesis. Cox proportional hazard regression was used to compute the association of mortality predictors.

Results: Of the 320 patients, 46 (14.4%) died during the study period. Among diabetics, age (HR:1.06, 95%CI: 1.03–1.10, p=0.001), chronic kidney disease (CKD) (HR: 4.69, 95% CI 1.62–13.59, p = 0.004), and malnutrition (HR: 10.95 95% CI 3.23–37.17, p < 0.001) were associated with higher mortality whereas in non-diabetics age (HR:1.05, 95% CI 1.01–1.09, p = 0.04), CKD (HR: 10.2, 95% CI: 2.48–41.99, p = 0.001), chronic obstructive pulmonary disease (COPD) (HR: 7.5, 95% CI 2.11–26.82, p = 0.002), coronary artery disease (CAD) (HR: 9.7, 95% CI 1.8–52.21, p = 0.008) and malnutrition (HR: 3.83, 95% CI 1.14–29.07, p = 0.03) were associated with mortality. Overall, 48.8% had vitamin D, 18.2% had vitamin B12 and 50.8% had iron deficiencies. Only 19.4% of the whole cohort was evaluated by nutritionist.

Conclusion: Gastroparesis is a debilitating condition that may impact patient’s quality of life. There is lack of long-term studies examining predictors of clinical outcomes. The aim of this study is to determine the predicting factors of failure of clinical improvement.

Patients and Methods: Between September 30, 2009 and January 31st, 2020, we identified gastroparesis patients based on 99 mTc sulfur labeled gastric emptying test. Nausea, vomiting, abdominal pain, bloating, early satiety, post prandial fullness, constipation, diarrhea, and weight loss were common presenting complaints in these patients. Patients without partial or complete symptom improvement at 4- and 12-weeks were labeled failure to improve patients. Logistic regression was used to compute the association between different factors and clinical outcomes.

Results: We identified 320 patients (mean age 47.5 years ± 5.3, 70% women, 71.3% Whites, 39.7% had diabetes mellitus). Failure of clinical improvement was seen in 34.7% patients at week 4 and 27.5% at week 12 of gastroparesis diagnosis. At week 4, history of bariatric surgery (OR:2.36 95% CI: 1.03–5.38, p = 0.04) and renal failure (OR: 3.14, 95% CI: 1.56–6.3, p = 0.001) were associated with lack of improvement whereas type 2 diabetes mellitus was associated with better clinical outcomes (OR: 0.49, 95% CI: 0.24–0.97, p = 0.04).

Conclusion: In gastroparesis patients, the history of bariatric surgery and renal failure was associated with worse clinical improvement. The patients with type 2 diabetes mellitus had significant symptom improvement.

65  |  Clinical predictors of failure of symptom improvement in gastroparesis

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Background: Gastroparesis is a debilitating condition that may impact patient’s quality of life. There is lack of long-term studies}

66  |  Tradipitant, a novel neuropeptide-1 receptor antagonist, showed continued improvement in nausea and other symptoms associated with gastroparesis in an open-label extension of a phase II clinical trial

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Background: Tradipitant is a novel NK-1 receptor antagonist that has previously showed efficacy in diabetic and idiopathic gastroparesis in reducing nausea, vomiting and overall gastropaesthetic symptoms in a phase 2 study compared to placebo. After completing the 4-week randomized, double-blind, placebo-controlled phase, patients were invited to enter an open-label extension phase where they received 85 mg tradipitant BID for an additional 8 weeks. Here we report the results of the 8 week open-label extension (OLE) portion of the phase 2 study that assessed the symptoms of gastroparesis.

Methods: Idiopathic and diabetic gastroparesis patients with moderate to severe nausea, who completed the 4-week double-blind
phase received 85 mg tradipitant BID open label for 8 weeks (n = 93). Clinical symptoms were measured by the Gastroparesis Core Symptom Daily Diary (GCSDD) and the Gastroparesis Cardinal Symptom Index (GCSI) questionnaire. Symptom improvements are presented as change from original baseline and change from OLE baseline as measured by the daily diary and GCSI. Symptom improvement was also compared between respective active and placebo groups from the double blind phase.

Results: The combined mean (SD) change in average daily nausea from baseline to week 8 of OLE was −1.74 (1.263, p < 0.0001). The mean (SD) change in average daily nausea from baseline to week 8 of OLE was −1.78 (1.116) for patients who originally received tradipitant and was similar to −1.71 (1.389) in patients who originally received placebo (p = 0.2872). The mean percentage (SD) of nausea free days improved in patients originally assigned tradipitant or placebo by 48.13% (36.5%) and 40.24% (41.61%) respectively (p = 0.364).

Conclusions: Treatment with tradipitant continued to be effective in improving nausea and overall symptoms in patients with gastroparesis and was safe and well tolerated during the OLE of the study.

67 | Withdrawn

68 | Can gastric half emptying time (T1/2) in gastric emptying scintigraphy replace conventional retention values for evaluating gastroparesis?

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Background: Gastric emptying scintigraphy (GES) reports % retention at 1 h for rapid GE, 2 and 4 h for delayed GE. T1/2 (time to empty half the meal) is not often used as it does not reflect differences in 2 and 4 h retention which represent early (fundal) vs. late (antral) phase delays. This study aims to compare the performance of GES T1/2 to current 2 and 4 h recommendations across three methods for determining T1/2.

Methods: Patients undergoing GES 3/2016–1/2021 were retrospectively reviewed. Rapid, normal, delayed gastric emptying (GE) was determined according to consensus values for retention at 1, 2, 4 h. T1/2 was determined using 3 methods: (1) curve-fitting T1/2 by Xeleris™ software; (2) linear interpolation using 0, 0.5, 1, 2, 3, 4 h data; (3) linear interpolation using only 0, 1, 2, 4 h data (“Tougas” times). For linear calculations, adjacent measurements before and after 50% empty were used. Spearman’s rho was used for correlations.

Results: 495 patients (46.0 ± 16.0 years; 80% F) were studied. 265 had normal GE, 4 had rapid GE (<30% retention at 1 h), 228 had delayed GE: 17 were delayed only at 2 h (>60% ret.); 94 were delayed only at 4 h (>10% ret.); and 115 were delayed at both. Strong correlations were seen between each T1/2 method and 1, 2, 3, 4 h %-empty values: curve-fit T1/2 (r = −0.851, −0.942, −0.864, −0.744; p < 0.01), exact-time linear T1/2 (r = −0.848, −0.972, −0.878, −0.763; p < 0.01), and Tougas-time linear T1/2 (r = −0.853, −0.974, −0.868, −0.760; p < 0.01). Strong correlations were seen between curve fit T1/2 and both exact (r = 0.969, p < 0.01) and Tougas-time (r = 0.968, p < 0.01) T1/2, as well as between exact and Tougas-time T1/2 (r = 0.997, p < 0.01). Patients were grouped by result: rapid, normal, delayed at 2 h only, delayed at 4 h only, delayed at both. Within groups, GE was categorized as normal or delayed using the T1/2 cutoff of 132 min proposed by Tougas et al. Depending on which T1/2 method is used, the 132 min cutoff captures 99.1% to 100% of patients with delayed GE at both 2 and 4 h and 76.5% to 94.1% of those delayed at 2 h only, but only 36.7% to 39.4% of those delayed at 4 h only. 3.5% to 11.3% of patients with normal GE were misclassified as delayed. No one T1/2 method performed best across groups.

Conclusions: GES T1/2 correlates more strongly with retention at 2 and 3 h than at 4 h; this was seen for each of the three T1/2 methods. T1/2 alone may misclassify patients, particularly those with only late phase delayed GE, reducing its diagnostic utility for gastroparesis.

69 | Systematic assessment of the quality of smartphone applications for gastroesophageal reflux disease

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Background: Gastroesophageal reflux disease (GERD) has a prevalence of ~20% in North America. Numerous smartphone applications aimed at providing education about GERD and tracking GERD-related symptoms exist. These have been downloaded more than 100,000 times yet no systematic assessment of their quality has been completed. The objective of this study was to assess the quality of patient-directed smartphone applications for GERD.

Methods: The Apple App Store and Google Play Store were systematically searched for relevant applications. Two independent reviewers performed an application screening and eligibility assessment. Included applications were graded by both reviewers using the validated Mobile Application Rating Scale which encompasses four sub-scores (engagement, functionality, aesthetics and information) as well as an overall App Quality Mean Score. Applications were also assessed for the inclusion of clear end-user safety guidelines. Means, standard deviations and inter-rater reliability were calculated for each score.

Results: The initial search identified 4867 unique applications. 46 applications met inclusion criteria (App Store = 5, Google Play = 37, Both = 4). The overall App Quality Mean Score was 3.02 ± 0.40 out of 5. Applications scored highest for aesthetics and functionality and lowest for information and engagement. Symptoms tracking applications were of significantly higher quality than education-focused applications (3.59 versus 2.88, p < 0.001). There was no significant correlation between graded quality and either App...
Store rating or number of downloads. 19/46 applications were accompanied by clear end-user safety guidelines. The application with the highest overall quality was My GiHealth GI Symptom Tracker.

**Conclusions:** While many smartphone applications exist for GERD, their quality is variable, and applications aimed at patient education are of particularly low quality. Application quality was not correlated with metrics patients often consider when selecting an application to download such as overall number of downloads or App Store ratings. Clinicians can use this information to recommend applications which are of higher quality to their patients. This study also highlights the need for higher quality evidence-informed applications aimed at GERD patient education.

### 70 | Meal eating characteristics of patients with gastroparesis

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**Background:** Patients with gastroparesis often consume only small meals due to early satiety. Dietary modifications are also suggested to reduce symptoms and help caloric intake. This study aims to: (1) Describe meal eating characteristics of patients with gastroparesis; (2) Relate meal eating characteristics to symptoms, gastric emptying (GE), and body weight.

**Methods:** Patients with gastroparesis filled out questionnaires including demographic data, Patient Assessment of Upper GI Symptoms (PAGI-SYM), and a questionnaire about meal habits and body weight. Patients underwent 4-hour gastric emptying scintigraphy.

**Results:** Of 192 gastroparesis patients, 93% endorsed early satiety (ES) with average severity of 3.7 ± 1.5 (scored from 0–5) and 93% endorsed postprandial fullness (PPF) with average severity of 3.9 ± 1.3. Time spent consuming meals averaged 13.6 ± 17.7 minutes; main reasons patients stopped eating were fullness (61%), nausea (48%), and abdominal pain (31%). Time spent eating correlated inversely with PPF (r = −0.23, p < 0.05), stomach fullness (r = −0.21, p < 0.01), PPF (r = −0.23, p < 0.01), and loss of appetite (r = −0.34, p < 0.01). Postprandial fullness lasted for 316 ± 344 minutes. Duration of PPF correlated with nausea (r = 0.30, p < 0.01), retching (r = 0.29, p < 0.01), vomiting (r = 0.28, p < 0.01), stomach fullness (r = 0.33, p < 0.01), loss of appetite (r = 0.35, p < 0.01), and constipation (r = 0.27, p < 0.01). Underweight patients had increased inability to finish a normal meal (p < 0.01), loss of appetite (p < 0.01), and lower abdominal pain/discomfort (p < 0.05). Patients had lost an average of 3.06 ± 10.60 kgs from their baseline weight. Weight loss correlated with nausea (r = 0.26, p < 0.01), ES (r = 0.30, p < 0.01), and loss of appetite (r = 0.28, p < 0.01).

**Conclusions:** This study evaluated meal eating characteristics of patients with gastroparesis. Early satiety and postprandial fullness were common with high severity. The main reasons for meal cessation were early satiety, nausea, and abdominal pain. Body weight and change in body weight were associated with symptoms of gastroparesis.

### 71 | Frequency of GLP-1 analogs use in diabetic patients with delayed gastric emptying (GE): A retrospective study

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Gastroparesis (GP) is a syndrome characterized by postprandial nausea, vomiting, abdominal pain, and fullness in the absence of a mechanical obstruction. GP has a prevalence of approximately 10 million in the US and > 70% of patients are females. Prevalence of GP amongst diabetics is predicted to range between 28%–65% of patients. Prolonged diabetes mellitus (DM) (> 5 years) can result in GP primarily due to irreversible neuronal damage from prolonged poor glycemic control. GLP-1 analogs are used to treat DM with the convenience of weekly subcutaneous dosing and their favorable weight loss side effect. They bind to incretin receptors, which results in insulin release and suppression of glucagon secretion. GLP-1 analogs also inhibit antral and duodenal motility and increases pyloric pressure which slows GE. Due to the high prevalence of diabetic GP and the growing use of GLP-1 analogs, we started a retrospective examination of all the patients who underwent a gastric emptying study (GES) from January 2019–January 2021 in our tertiary care hospital. Our goal was to identify patients who underwent a GES while on GLP-1 analogs and hence determine the potential for GP overdiagnosis due to likely iatrogenic GP. We reviewed 236 patient records, of which 33% had evidence of delayed GE and 64% of whom had diabetes and were diagnosed with diabetic GP. 30% of patients diagnosed with diabetic GP were on a GLP-1 analog prior to the GES which showed delayed GE. We also noted that 2 patients had interval worsening in GE after initiating a GLP-1 analog and 4 instances where patients had GLP-1 analogs stopped after being diagnosed with GP and the GES normalized. In conclusion: 1) 30% of diabetic patients with delayed GE were on GLP-1 analogs; 2) This knowledge is crucial in interpreting the implications of a GE result, since true diabetic GP is thought to be irreversible while iatrogenic GP could be reversible.
ABSTRACT

Subtypes of gastroparesis (GP) and functional dyspepsia (FD) based on gastric myoelectrical activity (GMA) in response to the water load satiety test (WLST)

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Introduction: Symptoms associated with FD and GP are similar and are often unrelated to the rate of gastric emptying. On the other hand, patients with FD and GP have gastric dysrhythmias and loss of normal 3 cpm GMA.

Aims: To compare GMA and symptoms in patients with GP and FD in response to the WLST.

Methods: Patients with symptoms associated with GP were studied. GP was defined by > 60% meal retained at 2 hrs. and/or > 10% at 4 hrs. by scintigraphy. GMA was recorded with cutaneous electrogastrography with the WLST during which patients ingested water until completely full over a 5-minute period. The % GMA activity in 4 frequency ranges (normal 2.5–3.7 cpm; bradygastria, 1.0–2.5 cpm; tachygastria, 3.7–10.0 cpm; duodenal-respiration, 10–15 cpm) was determined and compared with controls. Symptoms were assessed using a 100 mm visual analog scale. Ingestion of less than 238 ml of water in 5 min was considered abnormal.

Results: 284 patients with GP and 113 patients with FD (symptoms associated with GP but normal emptying) were studied. GP and FD patients ingested similar volumes of water (mean ± SD: 378 ± 218 ml and 402 ± 226 ml; p = 0.15) and reported similar increases in postprandial fullness, nausea, bloating, and abdominal discomfort. 26% of GP and 19% of FD patients ingested < 238 ml water (p = 0.05). Gastric dysrhythmias were recorded in 66% and 65% of patients with GP and FD, respectively; normal 3 cpm GMA was recorded in 34% and 35% of patients with GP and FD, respectively. Although overall % of gastric dysrhythmias and normal GMA were similar in the two groups, there were differences in the classifications of specific diagnoses (p = 0.02) (Table 1).

Conclusions: 1. Nearly 2/3 of the patients with GP and FD have dysrhythmic GMA and 1/3 have normal 3 cpm GMA, identifying subtypes of GP and FD based on GMA; 2. Patients with GP and FD also had similarities in water volume ingested and symptoms induced and 3. These findings suggest overlapping pathophysiological characteristics in patients with GP and FD which link the disorders on the spectrum of gastric neuromuscular disorders.

Table 1 GMA Responses in GP and FD

| Gastroparesis (n = 284) | Functional dyspepsia (n = 113) |
|------------------------|-------------------------------|
| Dysrhythmic GMA response |
| Tachygastria            | 87 (31%)                      | 35 (31%)                     |
| Bradygastria            | 50 (18%)                      | 23 (20%)                     |
| Mixed dysrhythmia       | 25 (9%)                       | 1 (1%)                       |
| Hypnormal 3 cpm GMA    | 26 (9%)                       | 14 (13%)                     |
| Normal 3 cpm GMA response |
| Normal 3 cpm GMA        | 44 (15%)                      | 21 (19%)                     |
| Hypernormal 3 cpm GMA   | 14 (6%)                       | 10 (9%)                      |
| Normal 3 cpm with dysrhythmia | 38 (13%)     | 9 (8%)                       |

p = 0.02 (Fisher’s exact test)

A new antibody assay may help identify abnormalities in patients with the symptoms of gastroparesis

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Introduction: Autoimmune activation has been reported to play a role in patients with symptoms (Sx) of gastroparesis(Gp). We hypothesized that autoimmune markers, detected by more sensitive testing might be detected in consecutive patients with Gp Sx using a novel immunoassay for the qualitative detection of serum antinuclear antibodies.

Methods: 43 consecutive patients [15 M, 28 F, mean age 46.3 yrs; 23 diabetes mellitus (DM), 20 idiopathic Gpi(Gp)] were studied. Samples were drawn at baseline, time of temporary gastric electric stimulator (TGES) placement and after permanent (PGES) placement [NGM, 2019; 31(3)]. Specimens were tested for presence of connective tissue disease (CTD)-related autoantibodies including: dsDNA, Sm/RNP, Ro52, Ro60, SSB, Scl-70, Centromere, Mi-2, Ku, Th/To, RNA Pol III, Pm/Scl, PCNA, Jo-1, Ribosomal-P using a chemiluminescent assay (QUANTA Flash® CTD Screen Plus, Inova Diagnostics, USA) run on the BIO-FLASH instrument (Biokit, Barcelona). CTD results (in CU units) were compared with Valsalva ratio, heart rate, BP, mucosal nerve length, volume; fibrosis; mast cells, serosal amplitude and frequency/amplitude ratio; leptin and glucagon. Spearman correlation analysis evaluated associations between CU levels and the above measures.

Results: At a 20 CU cutoff, 9/43(20.4%) of patients were interpreted as positive. Multiple significant correlations existed between CTD
levels and physiologic, anatomic and serologic factors. At baseline, a correlation was noted between fibrosis \((r = 0.41, p = 0.01)\) and serum glucagon levels \((r = -0.38, p = 0.01)\) in total population and serum glucagon levels in DM \((r = -0.46, p = 0.03)\), with mucosal nerve length \((r = 0.51, p = 0.02)\) and mast cell count in myenteric plexus (MY) \((r = -0.05, p = 0.03)\) in iGp pts. At TGES placement, DM pts had correlations with standing diastolic BP \((r = -0.48, p = 0.03)\) and serosal frequency amplitude ratio \((r = 0.51, p = 0.04)\), while iGp pts had positive correlations with mucosal nerve length \((r = 0.58, p = 0.01)\) and volume \((r = 0.45, p = 0.05)\) and a negative correlation with mast cell counts \((r = -0.48, p = 0.04)\). Other correlations with CTD related autoantibodies existed after permanent GES between Valsalva ratio, fibrosis, serum leptin, serum glucagon, mucosal nerve length, mast cell count in myenteric plexus, and serosal electrophysiology.

**Conclusion:** Screening for CTD-related autoantibodies may help identify underlying autoimmunity in some patients with Gp symptoms. In a group of DM and non-DM patients, the assay appears to correlate with several physiologic, anatomic and serologic measures. Further work with chemiluminescent testing in patients with upper GI motility disorders appears warranted.

### 74 | Patient treatment pathway patterns at an academic tertiary motility referral center

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**Introduction:** Treatment strategies for motility often revolve around a one-size-fits-all approach. Stratifying pts into disease subtypes, demographics, clinical features may allow the benefit of more targeted treatments. We aimed to assess patient demographics and treatment strategies for consecutive pts seen at a tertiary referral center by tracking symptoms over time.

**Methods:** Information regarding consecutive pts with a first visit from 2/2016-4/2016, and subsequent follow up visits, seen at an academic motility referral center, were gathered including reason for referral, procedures, medications, and subsequent interventions. All pts had GI symptom (Sx) scoring at each visit by an FDA compliant (Trad) PRO scoring system for foregut (GI) and hind gut (GI / GU) Sx (scaled 0-4).

**Results:** 70 consecutive pts (83% women, median 51.5 yrs [IQR 40.3-59.8]) were followed over a median of 3 yrs (0.7-3.6). The most common dx was gastroparesis (40%). During this time period pts received a median of 3 meds (IQR 2-4). Pts. were stratified by at least 1-point improvement in total upper and total lower symptom scores (Table 1). 47% of pts with upper GI Sx and 41% with lower GI Sx improved by at least 1 point. Approximately 21% pts had score improvement in both upper and lower total symptom scores. In pts with improved upper GI Sx, improvement was noted in all Sx. In pts with improved lower Sx, improvement was noted in GI but not GU sx. There was no change noted in number of meds given or procedures performed between improved and non-improved groups. Sx change variability, assessed using interquartile ranges for individual Sx showed upper GI Sx scores were driven by nausea, bloating, reflux and lower scores were driven by constipation and diarrhea.

**Conclusion:** Pts seen in an academic motility center had > 40% improvement in 1pt for either upper or lower GI Sx at 3 year follow-up and 20% improved in both upper and lower Sx. Nausea is a predominant feature that could be used as a target to optimize outcomes. Pts with anorexia predominant symptoms appear to be a high yield target for future symptom score improvement. Based on this assessment, sx tracking could be an important tool to further characterize the best treatment approaches in GI motility pts.

### 75 | Longer acidification time on wireless motility capsule (Smartpill™) correlates with gastroesophageal reflux disease

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**Introduction:** Wireless motility capsule (WMC) uses pH data to determine gastric transit time but has not been used in the evaluation of gastroesophageal reflux disease (GERD). A prior study found that motility capsule pH measurements correlate with gastric acid output. We hypothesized that nadir post prandial pH and acidification time may correlate with esophageal acid exposure on ambulatory reflux testing, providing supportive evidence for GERD using WMC.

**Methods:** This was a retrospective study of 28 patients who had undergone both WMC and reflux testing via wireless pH capsule or pH/impedance. Acidification time (the time from capsule ingestion to pH<2) and nadir post-prandial pH (lowest pH prior to small bowel entry) were manually determined from the WMC capsule proprietary software. Spearman’s correlation was used to compare these metrics with gastric transit time, percent esophageal acid exposure, and DeMeester score. The median acidification time and pH nadir were compared in patients with positive and negative reflux testing using the Mann Whitney U test. The rates of abnormal reflux testing were compared in patients with below vs. above median acidification time and pH nadir using Fisher exact test.

**Results:** Acidification time moderately correlated with gastric transit time, \(R = 0.44, p = 0.02\), but not nadir pH, percent esophageal acid exposure, or DeMeester score. However, patients with an abnormal reflux test had a significantly longer median acidification time (135.5 minutes vs. 78.5 minutes, \(p = 0.021\)). There was no difference...
in nadir pH between patients who had a positive vs. negative reflux test (median 0.875 vs. 0.75 respectively, \( p = 0.69 \)). After stratifying by patients with normal vs. delayed gastric transit time, there was still a trend towards longer acidification time in patients with positive reflux testing in both groups, but this was not statistically significant.

**Conclusions:** Patients with a prolonged acidification time on wireless motility capsule tests were more likely to have GERD on ambulatory testing. Longer acidification time could be a result of prolonged gastric retention of a buffered meal in the initial phase of digestion, which may also induce reflux. Larger studies comparing acidification time metrics with esophageal reflux may demonstrate a clearer correlation and could allow wireless motility capsule tests to provide supporting evidence for GERD.

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**78 | Pyloric diameter and distensibility profiles of patients unresponsive to G-POEM who sought further botulinum toxin injection after myotomy.**

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**Background:** Gastric per-oral endoscopic myotomy (G-POEM) increases pyloric diameter and distensibility measured by EndoFLIP, yet many patients report persistent symptoms after G-POEM and seek further pyloric botulinum toxin (BTx) therapy. It is unknown if pyloric function fails to improve after G-POEM in these patients or if it worsens over time due to scarring. We aimed to (i) assess if these patients show typical improvements in pyloric function after G-POEM, (ii) test if pyloric function worsens after G-POEM to the time of BTx injection, and (iii) define factors relating to pursuit of additional BTx therapy.

**Methods:** 6 patients underwent pyloric BTx injection a mean of 520 days (range 207–869 days) after G-POEM. EndoFLIP values were compared before and after G-POEM and before BTx. Symptoms and quality of life (QOL) were quantified by GCSI and SF-36 surveys before and 3 months after G-POEM.

**Results:** Pyloric diameter at 50 mL inflation increased 2.1+2.2 mm and distensibility increased 1.2±0.7 mm²/mmHg after G-POEM in these 6 patients similar to diameter (2.4±2.1 mm, \( p = 0.77 \)) and distensibility (1.3±2.5 mm²/mmHg, \( p = 0.96 \)) increases in G-POEM patients who did not seek additional BTx. However, absolute distensibility values post-G-POEM were lower in the 6 patients vs. those not pursuing further BTx (4.9±1.0 vs. 6.8±3.5 mm²/mmHg, \( p = 0.02 \)). Distensibility did not deteriorate in the time between G-POEM and BTx (4.8±2.5 mm²/mmHg, \( p = 0.79 \)). Diameter did not worsen in the time between G-POEM and BTx (16.0±6.2 vs. 15.1±2.0 mm, \( p = 0.99 \)). GCSI (3.0±0.7 vs. 2.6±1.6, \( p = 0.60 \)) and SF-36 (27.9±13.1 vs. 36.3±17.3, \( p = 0.20 \)) scores did not improve from baseline to 3 months after G-POEM. Gastric emptying did not normalize in the 4 patients who had follow-up scintigraphy after G-POEM (range 18%–32% 4 hr retention). 5 of 27 (18%) of patients that had single myotomy G-POEM sought additional BTx vs. 1 of 13 (8%) who had double myotomy.

**Conclusions:** Patients with prior G-POEM who sought follow-up botulinum toxin injection showed sustained increases in pyloric diameter and distensibility after myotomy lasting ~18 months. However, these patients showed no initial symptom or QOL benefits of G-POEM, exhibited less pyloric distensibility than G-POEM responders, had persistent gastric emptying impairment, and mostly had undergone single myotomies. These findings identify several possible factors related to pyloric dysfunction unrelated to pyloric physiology that warrant further study in larger cohorts.

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**79 | Performance characteristics of scintigraphic measurement of gastric emptying of solids in diabetes with gastroduodenal symptoms or gastroparesis.**

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**Background:** A recent study from the NIH Gastroparesis Consortium has documented the overlap of symptoms in patients with gastroparesis and functional dyspepsia as well as the variation in results of gastric emptying (GE) measurements (PMID: 33548234).

**Aim:** Our aim was to assess inter-subject coefficients of variation (COV\(_{\text{inter}}\)) of scintigraphic GE measurements in 10 patients with type 1 and 10 with type 2 diabetes (DM) and gastroduodenal (GD) symptoms (PMID 23639598; 22961573) and COV\(_{\text{intra}}\) in patients with proven idiopathic (\( n = 7 \)) or diabetic (\( n = 3 \)) gastroparesis (GP) by comparing results at baseline and after treatment for 4 weeks with placebo (PMID: 33711180).

**Methods:** Data from scintigraphic measurements of GE of solids using a standard 320 kcal egg meal (30% fat) were analyzed. Data were previously published for patients on placebo treatment. Primary endpoints were GE T\(_{1/2}\) and GE % at 1, 2, and 4 hours. Bland–Altman plot was constructed for the intra-subject comparison for GP on placebo.

**Results:** The patient cohort consisted of 30 patients (10 DM1, 10 DM2 with one GE measurement each, and 3 DM and 7 idiopathic GP with two GE measurement each 28 days apart). Bland–Altman plot (figure) in GP showed difference (\( \Delta \)) GE T\(_{1/2}\) similarly distributed (4 weeks apart) across mean GE T\(_{1/2}\) 120–240 min, except for one patient with severe GP. The GE T\(_{1/2}\) in gastroparesis demonstrated an average 9.4% change relative to mean GE T\(_{1/2}\) 202.4 min with the COV\(_{\text{intra}}\) 11.1%.

**Conclusions:** Inter-subject variations (COV\(_{\text{inter}}\)) in scintigraphic GE results in diabetics with GD symptoms were lowest for GE 4 h%. Within subject measurements of GE T\(_{1/2}\) (4 weeks apart) in gastroparesis were also reproducible over time, with average change of 9.4% and COV\(_{\text{intra}}\) 11.1%.
ABSTRACT

Table shows data (% emptied or T 1/2) mean ± SEM

| Group                  | N  | GE 1 h % | GE 2 h % | GE 4 h % | T 1/2, min |
|------------------------|----|----------|----------|----------|------------|
| DM1 + GD symptoms      | 10 | 36.1 ± 4.7 | 62.2 ± 7.5 | 82.6 ± 7.8 | 119 ± 27   |
| DM2 + GD symptoms      | 10 | 31.5 ± 3.6 | 51.7 ± 5.3 | 83.8 ± 4.5 | 128 ± 19   |
| COVinter DM1 and 2     | 20 | 37%       | 36.3%     | 23.6%     | 57.6%      |
| Gastroparesis baseline | 10 | 10.0 ± 2.5 | 21.7 ± 3.4 | 68.3 ± 5.4 | 206 ± 22   |
| Gastroparesis placebo  | 9.0 ± 0.8 | 26.8 ± 3.0 | 69.3 ± 4.5 | 198 ± 12   |

Background: Disorders of gut brain interaction (DGBIs) may develop as sequelae to acute inflammatory processes in the abdomen such as infectious gastroenteritis, inflammatory bowel disease, etc. Abdominal trauma can result in acute GI inflammation.

Objectives: To assess whether children with abdominal trauma are more likely to develop DGBIs in long-term follow-up than controls.

Methods: Families of children, between ages 4 and 18 years, seen in the ER for abdominal trauma from 2015 to 2020 were contacted at least 3 months after the ER visit. Parents completed a validated questionnaire to diagnose functional gastrointestinal disorders according to Rome IV criteria for the patient and a sibling (without trauma).

Results: Fifty-one subjects (32 males and 19 females) with a mean age of 11.9 and 26 controls (19 males and 7 females) with a mean age of 11.5 were recruited. Of the patients, 41% had gastrointestinal symptoms at the time of study ($p = 0.29$). Of the patients who reported gastrointestinal symptoms and completed survey, only 21% met Rome IV criteria for diagnosis of DGBI. Of the controls, 19% met criteria for DGBIs.

Conclusions: Patients with a history of abdominal trauma are not at an increased risk to develop DGBIs. More participants and further analysis are needed to strengthen our conclusions.

80 | Abdominal trauma in children and the incidence of disorders of gut brain interaction

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Background: Abdominal trauma in children and adolescents

82 | A case report: Gut directed hypnotherapy in resolution of refractory IBS in a pediatric patient

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Background: IBS is a functional gastrointestinal disorder characterized by abdominal pain associated with altered bowel habits in the absence of an underlying organic cause. Although the exact etiology of IBS is not fully understood, one theory postulates a pathology within the Brain-Gut Axis that leads to an overall increase in gastrointestinal sensitivity and pejorative changes in gastrointestinal motility. Studies have shown GDH has a beneficial clinical role in improving Mind-Gut control and comorbid conditions such as anxiety, abdominal pain, constipation, and diarrhea.

Aim: We present a 17-year-old male with underlying anxiety and two-year history of IBS—Constipation Predominant Subtype (IBS-C), who has demonstrated improvement of symptoms following GDH treatment initially refractory to medications including bisacodyl, senna, docusate, magnesium citrate, lubiprostone, and linaclotide.

Method: The patient was referred to a licensed clinical psychologist specializing in clinical hypnosis and CBT who implemented "The Standardized Hypnosis Protocol for IBS" developed by Dr. Olafur S. Palsson, Psy.D at the UNC, Chapel Hill. The hypnotherapy protocol consisted of seven weekly 45-minute sessions supplemented with a 20-minute audio recording to be listened to once daily. Outcome variables included the GAD-7, PHQ-9, and the CDI-2, as well as self-ratings (ranging from 0–10) for pain (or intensity and frequency), emotional distress about IBS symptoms, and overall emotional distress. All variables were measured at intake prior to administration of the hypnosis protocol and at the conclusion of the hypnosis treatment. A retrospective IBS Questionnaire (IBS Severity Scoring
System) was also completed at the conclusion of the GDH treatment for pre- and post-test ratings of clinical symptoms.

Results: The patient showed improvement in all outcome variables and self-ratings including abdominal pain intensity, frequency of abdominal pain episodes, emotional distress relating to gut issues, depression, and anxiety. The IBS Questionnaire showed a significant improvement from an initial severity score of 400 (severe) followed by 55 (complete resolution) at four months after the last GDH session. IBS Questionnaire subsets that showed a significant score improvement were abdominal pain intensity, days of pain experienced per 10 days, satisfaction with bowel habits, and overall interference of life affected by IBS symptoms.

Conclusion: This case supports the existing research literature that GDH can have a significant therapeutic role in symptoms and the quality of life in patients with refractory IBS. The IBS Questionnaire data reflects a patient with severe IBS with failed response to medications that underwent full and sustained resolution after GDH, supporting the possibility of GDH as a future mainstay and first line treatment option in IBS.

Results: Fifteen patients and parents (14 females, 1 male, mean age 16 years) completed the questionnaires. Quality of life and general well-being average scores on the parent and patient report increased after the 4th PENFS placement. In the patient report, statistical significance was observed in the physical functioning scale from baseline to week 8 and week 4 to week 8 (p = 0.01, p = 0.02 respectively). The patient report total generic core scale also significantly improved from baseline to week 8 (p = 0.03). There was an observed statistical significance (p = 0.04) in the parent report general well-being scale from week 4 to week 8.

Conclusions: Patient and parental report demonstrated an increase of quality of life after a four-week PENFS therapy. Patients experienced a significant improvement in their physical functioning. A parent-proxy discrepancy exists as parents perceive their child to have a higher quality of life after PENFS therapy compared to what the patient reports. Ongoing recruitment of more participants will likely strengthen our conclusions.
was 6.126 (+/− 0.64). Eight studies (N = 451) reported the primary outcome of interest. In 6/8 studies, a significant placebo response was found. The weighted mean placebo response rate across these trials was 32.4% (95%CI = 17.8–47.1%, p < 0.001) with substantial heterogeneity (I² = 92.2%). Several studies included a cleanout at study outset which could play a role in the placebo effect. An analysis of the 3 studies without a cleanout (N = 208) found a placebo response rate of 25.2% (95%CI = 16.0–45.4%, p < 0.001) with substantially reduced heterogeneity across these trials (I² = 45.4%).

Conclusions: A considerable placebo response rate exists in RCTs for the treatment of pediatric constipation. Investigators must take this finding into consideration when designing future studies in this field. This data will also help inform clinicians’ expectations when treating constipation in children. Moving forward, a better understanding of the factors that promote this placebo response will be important to delineate.

86 | Behavioral factors and gastric electrical stimulation in children with nausea and vomiting

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Background: Gastric electrical stimulation (GES) can be an effective treatment for children with chronic nausea and vomiting, but little is known about predictors of response. Our objective is to evaluate whether behavioral factors affect GES outcomes in children with chronic nausea and vomiting.

Methods: We performed a prospective cohort study and survey. We included patients < 21 years of age with chronic nausea and vomiting treated with GES from 2009–2018. Demographics, medical history, and past treatment were recorded. Patients completed a Symptom Monitor Worksheet (SMW) and recorded GI medications and route of nutrition at baseline and follow up visits. We contacted patients in 2019–2020 to repeat a SMW and administer the Connor Davidson Resilience Scale-10 (CD-RISC-10), Life Orientation Test-Revised (LOT-R), and a mental health and school/activity survey. We evaluated whether behavioral factors were associated with improvement in SMW or ability to stop supplemental nutrition.

Results: We included 34 patients (median age 14 years, range 2–19; 70.6% F). At baseline, 23 (67.6%) needed supplemental nutrition (22 tube feeding and 5 parenteral nutrition, PN), 13 (38.2%) had anxiety disorder, and 10 (29.4%) had depression. 16 patients (47.1%) were enrolled in school full time but the majority (58.8%) were missing school most or all of the time. Most patients (61.8%) had an Individualized Education Plan (IEP). Nearly all (97%) reported missing activities some of the time or more. We contacted patients at a median of 5.2 years after starting GES. Patients attending school full time had better SMW scores (average 30.5) than those with partial or no attendance (41.3 and 40.0 respectively). Higher LOT-R scores, indicating a more optimistic outlook, were associated with better SMW as well (correlation coefficient −0.60). After 1 year of GES, SMW scores improved by 14.7 ± 15.8 and 13 of 23 patients (57%) no longer needed supplemental nutrition. Older age and not having an IEP were associated with improvement in SMW (p = 0.02, 0.06 respectively). Anxiety, depression, and CD-RISC-10 were not associated with improvement in SMW or no longer needing supplemental nutrition.

Conclusions: In our cohort, older age, optimism, school attendance, and not needing an IEP were associated with symptom improvement.

87 | ERK1/2 activation preserves gastric pacemaker stem cells in aging

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Background & Aims: Impaired gastric accommodation and compliance in the elderly may cause reduced food intake leading to frailty, sarcopenia and increased mortality. We previously found that reduced nitrergic relaxation and compliance of gastric muscles were mainly due to depletion of interstitial cells of Cajal (ICC) in progeric klotho and naturally aged mice (PMIDs: 20581042, 32771388); and these changes were associated with reduced food intake in the klotho model. ICC loss was preceded by a robust decline in ICC stem cells (ICC-SC), which were the primary target of overactive Wnt signaling-induced cell cycle arrest. Downstream of Wnt, our results implicated transformation-related protein 53 (Trp53)-induced suppression of extracellular signaling-regulated protein kinase (ERK) 1/2 signaling in the ICC-SC cell cycle arrest. Here, we investigated whether stimulation of ERK1/2 signaling with the nutrient-sensing hormone insulin-like growth factor-1 (IGF-1) (PMID: 24116170), which is invariably reduced with age, could mitigate ICC-SC/ICC loss and gastric dysfunctions in klotho mice. Methods: Progeric klotho mice were treated with the stable IGF-1 analog LONG R3 recombinant human (rh) IGF-1 (150 μg/kg i.p. BID for 3 weeks starting at 4 weeks of age). Gastric ICC and ICC-SC were enumerated by flow cytometry and ICC were assessed by KIT western blotting (WB). ERK activation was studied by detecting phosphorylated ERK1/2 by WB. Trp53 was induced with the MDM2 antagonist nutlin 3a (30 μM) with the inactive enantiomer nutlin 3b (30 μM) serving as a control. ERK1/2 signaling was activated by rhIGF-1 (100 ng/ml for 72 h) in the ICC-SC line D2211B. Cell viability was assessed by MTS assay. Results: In klotho mice, LONG R3 rhIGF-1 treatment prevented the age-associated reduction in ERK1/2 phosphorylation, gastric KIT protein levels, and both ICC-SC and ICC numbers. LONG R3 rhIGF-1 treatment also mitigated the reduced food intake and impaired body weight gain characteristic of klotho mice, suggesting improved gastric functions, which remain to be verified experimentally. In D2211B ICC-SC, rhIGF-1 treatment mitigated nutlin 3a-induced reduced ERK1/2 phosphorylation and cell viability, indicating that IGF-1 was able to counter Trp53-induced ICC-SC cell cycle arrest. Conclusions:
IGF-1 treatment can mitigate age-related ICC/ICC-SC loss by activating ERK1/2 signaling leading to improved food intake and body weight gain in klotho mice. *Grant support: NIH R01 DK121766, P30 DK084567, AGA-Allergan Foundation.*

88 | Prevalence of gastrointestinal symptoms in cystic fibrosis: Results of a prospective multicenter study-GALAXY

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**Background:** People with cystic fibrosis (PwCF) suffer from overlapping gastrointestinal (GI) symptoms which affect their quality of life (QOL). No large US-based multicenter studies have been done using patient-reported outcomes measures (PROMs) to evaluate the prevalence and severity of these GI symptoms among PwCF.

**Methods:** PwCF who were ≥2 years of age and able to complete PROMs electronically outside-of-clinic were eligible for the GALAXY study. Validated PROMs on constipation symptoms (PAC-SYM), GI symptoms (PAGI-SYM), and constipation-related QOL (PAC-QOL), as well as stool-specific questionnaire were administered prospectively over a period of 4 weeks. Total and domain scores of PROMs were evaluated overall and by age group using linear regressions. The period-prevalence of constipation, defined as any occurrence between baseline and week 4, was also compared by age group.

**Results:** 402 participants were enrolled in GALAXY, N = 169 (42%) were < 18 years old and 41.3% were on laxatives. For all participants, the mean (95% confidence interval (CI)) total score was 0.52 (0.47, 0.57) for PAC-SYM, 0.63 (0.57, 0.69) for PAGI-SYM, and 0.67 (0.62, 0.73) for PAC-QOL. Overall, the mean (95% CI) scores for treatment dissatisfaction recorded by PAC-QOL was 1.39 (1.30, 1.47). Aggregated over 4 weeks, the prevalence of moderate to very severe symptoms captured by individual questions were reported for all participants: straining to pass bowel movements (BM) (20.3%), fullness (18.3%), incomplete BM (17.1%), bloating (16.4%), distension (16.4%), upper (5.15%) and lower (7.5%) abdominal pain. Higher prevalence of symptoms was observed in age group ≥18 compared to < 18, e.g. bloating (63.7% versus 27.3%), lower abdominal pain (39.8% vs. 26.2%), stomach fullness (75.6% vs. 56.2%), and abdominal distension (60.2% vs. 34.9%). The estimated period-prevalence (95% CI) of protocol-defined constipation (<3 BMs in the previous week) was estimated to be 21.5% (16.9%, 27.1%) in all participants, 18.9% (12.3%, 28.0%) for those < 18, and 23.2% (17.2%, 30.5%) for those ≥18.

**Conclusions:** GI symptoms are common in PwCF with the highest prevalent symptoms reported being bloating, distension, lower abdominal pain and stomach fullness. The high period-prevalence of constipation and the high percentage of participants with symptoms such as straining or incomplete defecation, while being managed in pulmonary clinics and already on laxatives, suggest an unmet need in the treatment of PwCF.

89 | Schwann cell precursors in the aganglionic segment of Hirschsprung disease have a capacity to generate neurons in the gut

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**Background:** Cell therapy offers the potential to replace missing neurons in the distal bowel of Hirschsprung disease (HSCR) by transplanting neural progenitor cells to restore gut function. Schwann cell precursors (SCPs) have recently been shown to possess a capacity to generate neurons in the intestine. However, it is unknown if SCPs can be isolated from the aganglionic segment of HSCR and whether they can be used for cell-based therapy.

**Methods:** Aganglionic bowel was obtained from human HSCR and Ednrb⁻/⁻ mice. SCPs were isolated from the hypertrophic nerve bundles in the aganglionic segment. SCPs were transplanted into the aganglionic mouse colon ex vivo and in vivo. Immunohistochemistry was used to demonstrate engraftment, survival, and neuroglial differentiation of SCPs following transplantation. Live cell imaging was used to determine neuronal calcium activity.

**Results:** Hypertrophic nerve bundle-derived SCPs are capable of forming neurospheres in culture and possess neurogenic potential. In differentiation condition, SCPs give rise to TuJ1 expressing neurons that exhibit spontaneous and electrically stimulated calcium activity. Following transplantation into aganglionic mouse colon, SCPs engraft, migrate extensively, and differentiate into enteric neurons and glia.

**Conclusion:** SCPs from the aganglionic segment of HSCR demonstrate the capacity to regenerate functioning neurons in vitro. They can be transplanted into the aganglionic colon where they survive, migrate, and differentiate into appropriate phenotypes. SCPs therefore represent a potential autologous source of neural progenitor cells. Current studies are aimed at determining whether these cells restore colorectal function, an essential step in establishing cell-based therapies as a viable treatment for HSCR.

90 | Motility in Parkinson's disease: Is a multidisciplinary approach the best move?

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**Introduction:** Gastrointestinal (GI) symptoms are common in Parkinson’s Disease (PD) including dysphagia, early satiety, fullness, weight loss, bloating, and constipation impacting quality of life. Often, these symptoms are overlooked by providers. Limited data is
available pertaining to community gastroenterologists (CG) versus academic gastroenterologists (AG) related to PD symptom work-up.

**Objectives**: (i) Compare GI symptom presentations of PD patients seen by academic versus community gastroenterologists (ii) Assess differences between CG vs. AG related to diagnostic workup of PD patients.

**Methods**: Retrospective analysis of 32 adult patients with PD who were referred to either a CG or AG. Collected data included demographics, GI presenting symptoms, urological symptoms, and diagnostic testing ordered (endoscopic, radiological, and physiology). Statistical analyses included chi-square test and independent t-tests. p-values < 0.05 were considered statistically significant.

**Results**: 32 subjects were included in the analysis: mean age of 73.6 ± 9.7; Range: 46–88, mean BMI 24.9 ± 8.2. No demographic differences between CC or AC centers were seen. Statistically significant differences were seen between the CC and AC for symptoms of fecal incontinence and for urological symptoms only. Statistically significant differences were seen between the CC and AC for diagnostic testing included: Modified Barium Swallow Studies, EndoFLIP™ Impedance Planimetry, Gastric Emptying Study, Anorectal manometry and biofeedback therapy. Statistically significant mean total of physiological lab tests between AC and CC: 1.9 ± 1.3 AG and .32 ± .568 CG, p-value < .001. Radiological testing was also statistically significant with mean .80 ± .632 for AG and .36 ± .492 for CG, p-value .042. Total number of diagnostic tests were similar between the groups: Mean 2.8 ± 1.1 AG and 2.7 ± 1.2 CG. Total number of endoscopic evaluations were also similar with mean 1.3 ± .68 for AG and 1.2 ± 1.2 for CG.

**Conclusion**: Patients with PD are referred to academic multidisciplinary centers more commonly for symptom presentations of fecal incontinence and urinary issues. AG were more likely to proceed with ordering radiological and physiology tests. This preliminary data will be used to evaluate the benefit to PD patients of a multidisciplinary approach to care including assessing the benefit of increased diagnostic testing to guide targeted therapies to improve patient’s QOL.

**93 | Withdrawn**

**94 | Efficacy of transcutaneous posterior tibial nerve stimulation in children with functional constipation**

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**Introduction**: Most children with functional constipation (FC) improve with conventional treatments. However, a proportion of children have poor treatment outcomes. Management of intractable FC may include botulinum toxin injections, transanal irrigation, antegrade enemas, colonic resections, and in some cases sacral nerve stimulation (SNS). SNS is surgically placed, not readily available and expensive. Posterior tibial nerve stimulation (PTNS) allows transmission of electronic impulses and retrograde stimulation to the sacral nerve plexus in a portable, simple and non-invasive fashion.

**Objectives**: To assess the efficacy and safety of transcutaneous PTNS for the treatment of FC in children.

**Methods**: Single-center, prospective interventional study. Children 4–14 years with Rome IV diagnosis of FC received 10 daily PTNS (30 min/day) sessions. Electrodes were placed over the ankle. Strength of the stimulus was below pain threshold. Outcomes were assessed during treatment and 7 days after.

**Results**: 23 subjects enrolled. Two children excluded (acute gastroenteritis, COVID-19 contact). 20 completed the study (4–14 years), (8.4 ± 3.2 years, 71.4% female). There was 91.3% improvement in incomplete BMs, 86.3% improvement in abdominal pain. We found significant improvement consistency of Bowel Movements (BM) (p = 0.005), Fecal Incontinence (FI) (p = 0.005) blood in stools (p = 0.0059) and presence (p ≤ 0.001), and intensity of abdominal pain (p = 0.005). 96.7% reported treatment satisfaction. Only one child required rescue therapy.

**Conclusion**: We found significant improvement in stool consistency, FI, abdominal pain and hematochezia. This suggests that transcutaneous PTNS could be a promising noninvasive treatment for FC in children. Large studies are needed.

**95 | Jejunostomy tubes in patients with gastroparesis does not protect against readmission for lower respiratory infection**

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**Introduction**: Previous small studies have noted that in jejunostomy tubes have not decreased risk of future lower respiratory tract infections (LRTI). However, either due to paucity of evidence or due to patient or consultant demands, jejunostomies for the purposes of preventing aspiration events continue to be performed. Specifically, in patients with gastroparesis, relationship between jejunostomy tubes on future LRTI has not been evaluated. After adjusting for multiple risk factors, we compare long-term (180-day) readmission rates for LRTI in patients with gastroparesis who did and did not receive jejunostomy at index admission.

**Methods**: We used the Nationwide Readmission Database, an all-payer claims archive, to identify patients with gastroparesis admitted between 2010–2014. Only patients who had index admission between January & June of each year were evaluated to allow for observation period of 180-days. Chi-square analysis was used to evaluate differences in readmission rates (for LRTI) in patients with and without jejunostomy placement at index admission. Logistic multivariable analysis was used to highlight the odds of readmission for LRTI after placement of jejunostomy.
Results: N = 163,645 index admissions were identified in patients with gastroparesis (mean age 51, 65% female). Jejunostomy was placed in 697 patients. 180-day readmission (for LRTI) rate for patients who had a jejunostomy tube placement was 41%. In patients who did not undergo jejunostomy tube placement, the 180-day readmission rate for LRTI was 25% (p < 0.001). After adjusting for age, sex, diabetes, heart failure, obstructive lung disease, cerebrovascular disease, nutritional deficiency, and total number of chronic comorbidities, presence of jejunostomy tube resulted in increased odds of readmission for LRTI [odds ratio, 1.46, (95% confidence interval, 1.22, 1.73)].

Conclusions: Jejunostomy tube placement despite adjusting for common variables has not resulted in reduced readmissions for lower-respiratory tract infections. Future prospective analysis can help further evaluate this association.

96 | Significant temporal association of esophageal air events (supragastric belches, gastric belches, and air swallows) with hiccups: A case study in an adolescent.

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Background: We previously reported our ability to objectively test the temporal association of gastroesophageal reflux disease (GERD) symptoms with esophageal air events (EAEs) that include air-swallows, gastric belching and supragastric belching. We recently evaluated a teenage female presenting with symptoms of recurrent hiccups. We report here the results of a comprehensive 24-hr examination using multichannel intraluminal impedance and pH monitoring (MII-pH).

Methods: Four copies of the MII-pH tracing (Laborie/MMS, Amsterdam, The Netherlands) were generated and each was analyzed either for episodes of gastroesophageal reflux (GER), air-swallowing, gastric belching or supragastric belching, and corresponding symptom association probability (SAP) values were generated. SAP values > 95% were considered significant. Mean lag time durations prior to a hiccup episode for each esophageal disturbance were calculated and compared using a student t test with significance set at α < 0.05.

Results: Recorded during the study were 34 hiccup episodes, 26 GER episodes, 25 supragastric belches, 12 gastric belches and 114 air swallows. Two of the hiccup episodes occurred during feeding and were thus ignored. Hiccups were significantly associated with GER (SAP = 100%), air-swallows (SAP = 99.7%), supragastric belches (SAP = 100%), and gastric belches (SAP = 100%). All but 4 hiccup episodes (87.5%) occurring during fasting or post-prandial periods were preceded by one or more esophageal disturbance. The data show that remarkably more hiccup episodes were preceded by supragastric belches (17 [60.7%]) when compared to air swallows (11 [39.3%]), gastric belches (8 [28.6%]) and GER (11 [39.3%]). The mean time (± SD) delay for an air-swallow (60.5 ± 39.2 seconds) prior to a hiccup was significantly longer compared to GER (10.3 ± 4.0 seconds, p = 0.001), gastric belches (9.1 ± 5.9 seconds, p = 0.001) and supragastric belches (10.1 ± 18.2 seconds, p = 0.0001).

Discussion and Conclusion: While the pathophysiology of hiccups is unclear, studies have suggested distension of the proximal esophagus for playing role. Our study, using a novel application of the MII-pH technology, reveals objective data that support a temporal relationship between hiccups and EAEs (including supragastric belches, gastric belches and air swallows). Additional studies are needed to further explain our observations.

97 | Should all asymptomatic infants under the age of 12 months undergoing impedance testing be assessed for aerophagia?

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Background: Gastroesophageal reflux (GER) and air swallowing are both common in infants. While the association of GER with symptoms in infants has been well studied, the association of air swallows with similar symptoms has not. We recently showed that a novel application of multichannel intraluminal impedance and pH monitoring (MII-pH) can be used to objectively assess the temporal relationship between air swallows and GER-like symptoms.

Aim: The purpose of this investigation was to assess the role of air swallowing in infants presenting with symptoms suggestive of GER as an etiology.

Methods: We searched our MMS data base for infants (≤12 months) who had been tested using MII-pH from 2014 to 2020. Tracings were excluded if there were significant technical defects or if recording time during non-feeding periods was < 15 hours. Two copies were made of each tracing; the first copy was used to manually tag GER events and the second copy was used to manually tag air swallows. For both tracings, temporal association was tested using the symptom association probability (SAP) index with a positive association set at > 95%.

Results: Forty-five infants were enrolled (21 F). Age (median [IQR]) was 6.9 [4.8–9.3] months, acid reflux index was 2.1 [0.6–3.9]%, and percent bolus exposure was 0.98 [0.55–1.39] %. Forty infants (87%) were on anti-reflux medications that included PPI (30; 65%), histamine-2 receptor antagonist (11; 24%), erythromycin (2; 4%) and baclofen (1; 2%). Air swallowing occurred in all subjects with a median [IQR] number/hr. of 7.6 [3.4–11.3] (total), 0.32 [0.17–0.66] (acidified esophagus), and 7.0 [3.4–11.1] (non-acidified esophagus). Significantly more air swallows occurred when the esophagus was...
not acidified (92.2% vs 7.8%, p < 0.0001). In 8 (17.8%) infants, symptoms were significantly associated with only GER. In 38 (84.4%) infants, symptoms were significantly associated with either GER or air swallows. In 14 (36.8%) infants, symptoms were significantly associated with only air swallows.

**Discussion:** The data show that air swallows are indeed common in infants. In a study involving a moderately-sized cohort, the data also show that in the absence of MII-pH analyses that includes air swallowing more than a third of infants may not receive a diagnosis.

### 98 Increased occurrence of high amplitude propagating contractions on next day colon manometry for refractory pediatric constipation

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**Background:** Per ANMS-NASPGHAN guidelines, detecting a gastrocolonic response to a meal plus high amplitude propagating contractions (HAPC) after a meal or bisacodyl defines normal colon manometry in children with constipation. Others report more prevalent HAPCs and fuller propagation on manometry done the day after catheter placement. Using high resolution colon manometry, we (i) compared HAPC presence and propagation characteristics on same vs. next day testing and (ii) assessed impact of procedural anesthesia on same vs. next day HAPCs.

**Methods:** 5 children with refractory constipation (age 9–17 year) underwent colonoscopic placement of high resolution catheters with 36 pressure ports at 1.5 cm intervals to the right colon under monitored anesthesia in the implementation of a colon manometry program at our center. Same day 4 hr fasting recording was followed by 2 hr fed recording (1 failed fed tracing). After awakening, next day tests included 4 hr fasting and 2 hr fed recording then 1 hr recording after bisacodyl (10 mg). HAPC criteria included > 75 mmHg amplitude, > 10 sec duration, and propagation distance > 30 cm.

**Results:** Manometry indications included helping plan surgery for refractory constipation (2 cases), assessing if a diverted colon could be reconnected, distinguishing functional constipation from dysmotility, and assessing persistent symptoms after Hirschsprung’s surgery. One child had fasting HAPCs and 2 had fed HAPCs on same day testing; 4 children had both fasting and fed HAPCs on the next day. HAPC amplitude (117±43 vs. 99±16 mmHg, p = 0.32), duration (14 vs. 23±16 sec, p = 0.38), and propagation distance (47±6 vs. 50±8 cm, p = 0.60) were similar on same vs. next day testing. Propagation velocity was greater on same vs. next day testing (2.8±1.0 vs. 1.5±0.4 cm/sec, p = 0.01) but numbers were small. Propofol was used for all tube placements, midazolam was given for 2 cases, and ondansetron was given in 3 cases. One child received fentanyl > 2 hr before fasting testing but showed no difference in same vs. next day HAPCs.

**Conclusion:** In a small pediatric series undergoing colon manometry for diverse indications, HAPCs were more often seen the day after catheter placement vs. on same day testing. HAPC propagation characteristics on high resolution analyses were similar (except propagation velocity) on next vs. same day recording. HAPC findings were not related to procedure anesthesia. Based on this initial experience, we have adopted next day recordings for colon manometry interpretation while accumulating ongoing data.

### 99 Intestinal electrical stimulation synchronized with intestinal slow wave ameliorates glucagon-induced hyperglycemia in rats

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**Background:** Type 2 Diabetes remission after bariatric surgery is believed to be largely attributed to the increased release of incretin hormones glucagon-like peptide-1 (GLP-1) arising from rapid nutrient delivery to the distal gut. GLP-1 strongly potentiates the secretion of insulin from pancreatic β cells in response to the rising plasma glucose concentration. Intestinal electrical stimulation (IES) was reported to reduce body weight and improve glucose tolerance in animal studies and therefore is proposed as a potential treatment for type 2 diabetes. IES delivered in synchronization with the intrinsic slow wave of small intestine (SIES) was previously reported to be more potent in accelerating small intestinal transit than IES delivered at fixed frequency and phase. We hypothesized that SIES is more potent in suppressing postprandial blood glucose by enhancing the release of GLP-1 and then insulin due to its more potential prokinetic effect on intestinal transit.

**Methods:** 12 male Sprague-Dawley rats were chronically implanted with two pairs of electrodes at the duodenum for the detection of slow waves and delivery of stimulation. Hyperglycemia induced by glucagon during an oral glucose tolerance test (OGTT) was used to compare the suppressive effects of IES and SIES on blood glucose. Blood samples were collected from tail vein at baseline, 15, 30 and 60 minutes after oral glucose ingestion for the measurement of plasma GLP-1 and insulin concentrations.

**Results:** (1) An algorithm for the real-time detection of intestinal slow wave peaks and delivery of IES in synchronization with the slow wave peaks was developed and validated with an accuracy above 90%. (2) Compared to sham (no stimulation), both IES and
SIES significantly reduced postprandial blood glucose at 30 min by 17% and 20%, respectively. SIES showed a further inhibitory effect at 60 min (147 vs. 171 mg/dl, p = 0.001, vs. sham). (3) Compared to sham (137 pg/ml), GLP-1 at 30 min was increased in both IES (157 pg/ml) and SIES (169 pg/ml) and GLP-1 level was still high at 60 min in rats with SIES while those in sham and IES groups returned to the basal level. (4) At 30 min, the plasma insulin level was 18.8 μU/ml with SIES, which was significantly higher than that with sham (7.1 μU/ml, p = 0.001) and that with IES (13.2 μU/ml, p = 0.046).

Conclusions: Compared to IES, synchronized IES is more effective in reducing postprandial blood glucose in rats with glucagon-induced acute hyperglycemia by enhancing the release of GLP-1 and insulin. (This study was supported by a grant from NIH (R01DK107754))

100  |  Efficacy of gastric electrical stimulation in gastroparesis: a systematic review and meta-analysis

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Background/AIM: Gastroparesis (GP) represents a chronic syndrome characterized by delayed gastric emptying with no evidence of mechanical obstruction. GPs have different etiologies. These include Diabetic GP (DGP), Idiopathic GP (IGP), and post-surgical gastroparesis; with other minor etiologies. It produces a variety of upper abdominal manifestations; including nausea and vomiting as a major manifestation in addition to early satiety, postprandial fullness bloating, and upper abdominal pain. Gastric Electrical stimulation (GES) represents the new management approach for GP. It depends on delivering a high-frequency electrical impulse to stimulate the gastric wall; controlling its pacemaker activity. This study aims to evaluate the efficacy of GES in diabetic gastroparesis patients compared with Idiopathic gastroparesis regarding symptoms relief.

Methods: We searched four databases: Web of Science, SCOPUS, Cochrane CENTRAL, and PubMed, from inception until October 2020. We followed this search strategy with no restriction on time or languages: [gastric electric stimulation] AND [idiopathic gastroparesis OR diabetic gastroparesis OR vomiting OR emesis]. The risk of bias assessment was performed using Cochrane’s risk of bias tool. We included the following Outcomes: Total symptoms score (TSS), vomiting, and nausea as primary outcomes. Early satiety, bloating, postprandial fullness, and epigastric pain as the secondary outcomes.

We analyzed continuous data using mean difference (MD) with relative 95% confidence interval (CI).

Results: We included six clinical trials. We found that the Diabetic GP group show a significant difference from the Idiopathic GP group regarding the following outcomes: vomiting (MD = −0.64 [−0.82, −0.46]) (p = 0.16); and nausea (MD = −0.66 [−0.83, −0.48]) (p = 0.51). On the other hand, other outcomes show no significant difference between both subgroups; TSS (MD = −1.71 [−3.55, 0.12]) (p = 0.13). Bloating (MD = −0.29 [−0.79, 0.22]) (p = 0.71), Early satiety (MD = −0.63 [−1.23, −0.03]) (p = 0.04), Post prandial fullness (MD = −0.38 [−0.90, 0.13]) (p = 0.29), and Epigastric pain (MD = −0.01 [−0.19, 0.18]) (p = 0.94).

Conclusion: GES significantly reduced the symptoms of GP but with no significant difference between diabetic GP and Idiopathic GP subgroups.

101  |  Response of bioelectric therapy for abdominal pain may be related to gastric tissue cell counts

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Introduction: Abdominal pain remains a difficult aspect of gastroparesis (Gp) to treat. Bioelectric therapies such as gastric electrical stimulation (GES) have had variable effects on abdominal pain (AP). Full thickness gastric biopsies (FTGBx), done at the time of permanent GES implantation, offer information that may correlate with outcome of GES. We recently reported (Tirumanisetty, P. et al. GE 158:6;S‑619‑620) that medium energy GES can be effective for AP in up to 50% of patients treated, but the mechanism of improvement is unknown. We aimed to see if energy delivered, as well as FTGBx cell counts, might play a role in response for medium energy GES for abdominal pain.

Methods: 252 patients [48 M, 204 F, mean age 44 years, DM Gp 81, non‑DM 171] with the symptoms (Sx) of Gp were evaluated at baseline and after 12 months follow up with medium energy (cycled at much higher than nominal settings) GES. Patients’ pain scores were evaluated by a standardized PRO as recently described (NGM, 2019;31(3)e13534). Patients were divided into improved (n = 116) or non‑improved (n = 136) at 12 months from baseline. Full thickness gastric biopsy data was analyzed for CD‑177/Cajal and S‑100/neural fiber cells/per HPF. Energy delivered was calculated from GES settings at last adjustment using standard engineering formulas as:
charge/pulse (micro-coulombs), energy/pulse (micro-joules), power/pulse (milli-watts) and average power (milliwatts). These energy calculations were then adjusted by total cell counts (CD-177 & S-100) and the results were compared by non-parametric analyses and reported as median and intra quartiles.

**Results:** The average power for patients who improved was lower than non-improved patients for all energy values but especially significant for average power (25.9 milli-watts for improved Vs. 51.4 milli-watts for non-improved; \( p = 0.005 \)). When corrected by number of gastric cells (CD117&S100 HPF) the average power/cell was also significantly lower, 1.831 milli-watts for improved vs. 3.150 milliwatts for non-improved; \( p = 0.047 \).

**Discussion:** Some patients with the symptoms of gastroparesis and abdominal pain improved with medium energy GES and that group had significantly lower overall energy and less power per cell as present on full thickness biopsies. These energy related findings may help explain the mechanisms of improvement in abdominal pain with medium energy GES and may lead to new approaches for bioelectric stimulation for abdominal pain in for some patients with gastroparesis and perhaps other disorders.

Microbiome and probiotics in GI health and disease

**102 | Compositional and functional characterization of gut microbiome in slow transit constipation patients**

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Slow transit constipation (STC) is a major type of functional constipation characterized by extended colon transit time as a result of dysfunction of smooth muscle activity in the colon. Alteration of gut microbiome may be related to the pathophysiology of STC, but no clear evidence has been identified. This study aims to investigate compositional and functional characterization of gut microbiome in STC patients and to gain an insight into potential role of microbiome in the regulation of gastrointestinal motility. We analyzed the microbiome of fecal samples from 27 STC patients (Female = 25, Male = 2; mean age ± SD = 54.19 ± 10.31) and 27 age- and sex-matched healthy controls (HC) using shotgun metagenomic sequencing. Distinct compositional and functional features were identified using multivariable regression analysis. We tested for the association between microbial species versus STC diagnosis adjusting for frequency of laxative use as a potential confounder. The abundance of Alistipes finegoldii was high in STC patients, whereas the abundance of Eubacterium ramulus was low compared to HC (A). The abundance of Haemophilus parainfluenzae, Blautia producta, an unclassified specie of Coprobacillus (q value = 0.123) and Clostridium hathewayi (q value = 0.185) was higher in subjects taking laxatives (B). In analyses of functional profiling, the pathways L-methionine biosynthesis III (q value = 0.073) and inosine-5-phosphate biosynthesis III (q value = 0.095) were increased in STC patients compared with HC. We found significant compositional and functional pathways associated with STC. Our results also show that laxative use may be an important confounder in the microbiome analysis in STC patients.

**104 | Diagnostic yield and microbial characteristics of duodenal aspirate and culture for SIBO or SIFO**

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**Introduction:** Small intestinal bacterial (SIBO) or fungal overgrowth (SIFO) is characterized by excessive bacteria or fungus in small bowel and abdominal symptoms. Small bowel aspiration/culture is considered the gold standard for diagnosis, but its clinical usefulness is unclear because of small studies and variable methodology. **Aim:** To determine the diagnostic yield, risk factors and microbial content of duodenal aspirates in a consecutive series of patients over 7 years. **Methods:** Adults with unexplained abdominal pain, distention, bloating, and gas (duration>1 yr.) and suspected SIBO/SIFO underwent endoscopy with duodenal aspirates and aerobic, anaerobic, and fungal cultures using a 3 mm Liguory catheter under aseptic conditions. Colony count > 10^3 CFU/mL was considered diagnostic for SIBO or
SIFO. Symptom characteristics were compared, and diagnostic yield and microbiology assessed.

**Results:** We evaluated 776 (m/f = 170/606) patients; 462 (60%) had positive culture for SIBO or SIFO; 295 (38%) had SIBO only, and 32 (4.2%) had SIFO only and 135 (17.3%) had both SIBO and SIFO. Significantly more patients with positive culture used PPI compared to negative culture, 45% vs 29% (p < 0.0001), and had small intestinal or colon surgery (25% vs 17%, p = 0.01). Abdominal pain (85.8%), bloating (84.6%), fullness (80.2%) and gas (83.8%) were commonly reported in the positive aspirate group but their prevalence was similar to negative group. In patients with positive SIBO culture, 239 (55.6%) had > 10³ CFU/mL and 191 (44.4%) had > 10⁵ CFU/mL. In patients with positive SIFO culture, 129 (77.2%) had > 10³ CFU/mL and 38 (22.8%) had > 10⁵ CFU/mL. The predominant organisms were Streptococcus, Haemophilus, Klebsiella, E. coli, Neisseria, multiple anaerobes, (<3 species), Bacterioides, Veillonella, Fusobacterium, Candida albicans, and Candida glabrata and Candida Dubliensis.

**Conclusion:** In this large study, duodenal culture had a high yield (60%) for diagnosis of SIBO and/or SIFO. Majority of organisms were aerobes (69%), 16% were anaerobes and 15% were fungi. PPI and intestinal surgery were predisposing risk factors, but symptoms were poor predictors of diagnosis. Duodenal aspirate/culture has high diagnostic yield, can characterize bacterial count, organisms, and antibiotic susceptibility, and aids accurate diagnosis and treatment of patients with suspected SIBO/SIFO.

**Neuroimmune modulation of secretomotor, vasomotor, pain and barrier functions in health and disease**

**105 | Impact of neuromodulators for treatment of spastic chest pain after heller myotomy for achalasia**

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**Background:** Chest pain (CP) affects 50%–70% patients with achalasia and is often refractory to treatment. Previous studies have reported persistent and even worsening of CP in patients undergoing Heller myotomy (HM) in 60%–70% cases. Up to 1/3rd of patients with CP after HM have spastic CP. The exact etiology of spastic CP in an aperistaltic esophagus after HM is unknown. Neuromodulators such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have previously been demonstrated to treat spastic chest pain and esophageal hypersensitivity in subjects without achalasia. We hypothesized that treatment with neuromodulators to be effective in treating spastic CP in patients with achalasia after HM.

**Methods:** This was an Institutional Review Board approved retrospective single center study conducted from 2016–2021. Patients with achalasia who were prescribed a neuromodulator (TCAs/SSRIs) for spastic chest pain after HM were included. Pain was assessed per the Eckardt score ranging from 0–3 where 0 = no pain, 1 = occasional pain, 2 = daily pain and 3 = pain with each meal. Response to treatment at first follow up after starting psychotropic drug was recorded using numeric modified Likert scale from 1 to 5, where 1 = much worse, 2 = slightly worse, 3 = no change, 4 = slightly better, and 5 = much better.

**Results:** Five patients (4 females and 1 male) with a median age of 22 (range 16–47) years were included. Spastic CP was reported at a median time interval of 44 months (range 1–96) after HM. SSRIs and TCAs were started in two and three patients respectively. All five patients reported improvement in spastic CP with three patients (60%) having complete resolution after a median follow up of 144 (103–428) days. All included patients opted to continue treatment with the neuromodulators and were doing well at last follow up. Patient no. 2 (47 year female) reported dry mouth with amitriptyline and was switched to escitalopram with maintained response.

**Conclusion:** Neuromodulators were found to be a safe and effective for treatment of spastic CP persisting after HM in patients with achalasia. Complete resolution of pain was seen in 60% of patients. Neuromodulators offer a treatment modality for a challenging and distressing condition. Prospective randomized control trials should be considered for further evaluation.

**106 | Catechol-O-methyltransferase drives cell-specific nociceptive signaling via the enteric MIR-155-155/TFN-α axis**

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**Background & aims:** Irritable bowel syndrome (IBS) is characterized by persistent abdominal pain and altered bowel habits (diarrhea and/or constipation) and treatments are nonideal. We sought to identify mechanisms underlying different IBS phenotypes to guide new treatment development.

**Methods:** Translational datasets that included in vitro models (cell cultures), in vivo models (COMT−/−mice), and human studies (laser capture microscopy [LCM] of IBS patient cells) were used in this study.

**Results:** In post-infectious, diarrhea-predominant IBS (PI-IBS-D), COMT expression was reduced 3-fold, which potentiated GI symptoms and visceral pain through up-regulation of TNF-α/miR-155 signaling. MIR-155 increased TNF-α expression via down-regulation of COMT expression. TNF-α, via an integrated-feedback circuit, suppressed COMT expression even further. Anti-TNF-α therapy
reversed visceral hypersensitivity via upregulated COMT expression which further suppressed TNF-α expression through a feedback loop mechanism. These feedback loops help explain differing phenotypic expression and chronic gastrointestinal symptoms in IBS patients. The COMT/miR-155/TNF-α axis exhibited different physiological and phenotypic expressions in IBS patients with different etiologies and phenotypes (e.g., PI-IBS-D vs. fibromyalgia-associated IBS [FM-IBS-D]).

Conclusions: Our findings suggest that distinctive etiologic mechanisms/phenotypes are driven by different cell types in IBS patients. In PI-IBS-D patients, colonic neuronal and epithelial cells along with macrophages are key drivers of phenotypic mechanisms. However, in FM-IBS-D patients, colonic enteric neurons appear to be a major driver, but not epithelial cells and macrophages. These are important findings as they may lead to new paradigms for both phenotyping IBS mechanisms and directing treatment strategies leading to more targeted personalized medicine approaches.

Keywords: Irritable Bowel Syndrome; Catechol-O-Methyltransferase; Visceral Hypersensitivity

New methods and approaches to understanding neurogastroenterology and motility

107 | Healthy vs Hirschsprung: Bringing clarity to visualizing the enteric nervous system in children

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Background: In contrast to animal models, human enteric nervous system (ENS) structure and function remain under-investigated, especially in children. This makes it difficult to define mechanisms and predict outcomes in bowel motility disorders. For example, in Hirschsprung disease (HSCR), a birth defect in which ENS is missing from distal bowel, removal of bowel that lacks neurons is theoretically curative. However, post-operative outcomes are highly variable. We hypothesize that adverse outcomes after HSCR surgery are linked to structural defects in residual ENS after pull through surgery and that these could be more readily visualized via threedimensional imaging and tissue clearing.

Aims: To visualize and analyze structure and composition of the ENS of healthy pediatric colon as compared to pediatric HSCR colon and adult colon.

Methods: We utilize tissue clearing, immunohistochemistry, and confocal imaging to visualize human ENS in full-thickness bowel. We compare segments of descending colon obtained from two pediatric organ donors – ages 3 days old and 5 years old – to five HSCR pull-through resections and four segments from adult colon. Quantitative analyses of images are performed to define ENS anatomy.

Results: The density of human colon myenteric plexus decreases during childhood, as measured by proportion of bowel wall containing myenteric plexus (infant 37.9%, five-year-old 33.0%, adult 25.3%). The area occupied by ganglion cells similarly decreases with age (infant 27.0%; five-year-old 16.2%; adult 9.7%). The proportion of myenteric plexus comprised by ganglia is also greater in infant (71.2%) compared to five-year-old (49.1%) and adult colon (38.5%). Furthermore, the percentage of nitrergic neurons in the myenteric plexus increases with age. For HSCR pull-through resections, ENS structure varies greatly in the transition zone from ganglionic to aganglionic bowel. In some cases, submucosal ganglia are abundant distal to the termination of myenteric ganglia, while in other samples, the opposite is seen.

Conclusions: The pediatric ENS appears distinct in organization compared to human adult ENS. Defining normal human ENS structure in children and ENS organization in the HSCR transition zone may provide new insight into HSCR and other bowel motility disorders.

108 | Unbiased detection and analysis of interstitial cell of Cajal classes by single-cell chromatin assay

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Background & Aims: Interstitial cells of Cajal (ICC) display considerable heterogeneity in their distribution across GI organs and tissues, light microscopic and ultrastructural morphology, development, function, and gene expression (PMIDs: 31183821, 17895395). However, systematic analysis of ICC classes has been limited by the paucity of approaches suitable for their selective labeling and isolation. Here, we performed single-nucleus analysis of transposase-accessible chromatin by sequencing (snATAC), which detects active/poised promoters and enhancers, to identify ICC subsets in an unbiased manner.

Methods: KIT+ cells lacking hematopoietic markers were sorted by FACS from gastric, small intestinal, and colonic muscles of C57BL/6 mice (14, 4 and 4 per sort, respectively) to obtain KIT+ ICC, KIT+ precursors and dedifferentiated ICC, and some KIT- non-ICC for reference. 6 batches of 2,000–12,000 nuclei harvested in 2 sorts/organ were processed for snATAC or snATAC+snRNA-seq using the 10x Genomics Chromium platform. Paired-end sequencing to 50 (ATAC) or 100 bases (RNA) was performed using Illumina HiSeq 4000 or NovaSeq 6000 (S1) instruments. The 10x Genomics Cell Ranger ATAC pipeline and Loupe Browser were used for the initial bioinformatic analysis of the snATAC data discussed herein.
**Results:** We sorted $6 \times 270,000$–$350,000$ cells with a median KIT$^{low}$ enrichment of 76%. 843–4,265 cells including 318–2,583 ICC were covered by > 29,000 read pairs. In striking concordance with the previously identified ICC classes, by t-SNE analysis we detected 2, 3, and 5 ICC clusters in the small intestines, stomach, and colon, respectively. Non-ICC included smooth muscle and "fibroblast-like" cells, glia, pericytes, endothelial and mesothelial cells. ICC clusters had strong ATAC signal in the cis-regulatory elements of key ICC marker genes (Kit, Ano1, etc.), which were enriched in binding motifs for ICC lineage-specific transcription factors (TFs) ETV1 and LRIG1. We also detected differential enrichment in accessible TF binding motifs and in regulatory elements of genes previously linked to electrical pacemaking and mediation of neuromuscular control. All gastric and small intestinal ICC clusters and 2 of the 5 colonic ICC clusters included minor subsets with low accessibility (activity) of the Kit promoter. In the colon, ICC-like cells with low ATAC signal near the main ICC marker genes also formed a separate cluster.

**Conclusion:** Single-cell epigenomic profiling is suitable for the label-free analysis of ICC classes. *Grants: NIH R01 DK58185, P30 DK084567.

### 109 | Improved Fecobionics test for anorectal function assessment

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Fecobionics is a novel simulated feces test of anorectal function and was developed due to the well-known disagreement between current anorectal tests. Data until now have been obtained using a wired Fecobionics device that measured pressures during device evacuation in normal subjects and patients with fecal incontinence (CGH 2020). Here we present data with a greatly improved wireless device that measured pressure, bending angle (a proxy of the anorectal angle) and shape from impedance planimetric recordings.

Studies have been done in 12 normal subjects aged 40 ± 5 years. The new Fecobionics device is 10 cm-long and 10 mm diameter with a bag mounted. The shape and deformability mimic feces (Bristol stool scale type 4). Data were transmitted wireless to an external data recorder. After insertion in rectum, the subjects did the following procedures: coughs, anal squeezes, straining and push before the bag was distended to urge-to-defecate level. At this point, the filling tube was detached and the subjects were allowed to evacuate the device in privacy. The figure shows the graphical user interface (GUI) with topography plots of diameters, pressures, orientation and bending (left) as well as the shape (right) from a typical experiment lasting 20 min. The three arrows point to the insertion, start of procedures and evacuation, respectively. The anal resting and squeeze pressures measured by the front sensor were 32 ± 6 and 89 ± 22 cm H$_2$O. The bending was 115 ± 11° and 147 ± 7° before and after bag filling. The urge volume was 87 ± 5 ml. The maximum delta pressure (rectoanal pressure gradient) during evacuation was 86 ± 11 cm H$_2$O and the expulsion duration was 21 ± 4 s. Fecobionics obtained highly integrated data of anorectal function in a single test. Usually such data are acquired by four tests, i.e. anorectal manometry, BET, defecography and EndoFLIP.

### 110 | First case report using anal irrigation system to treat constipation in a visually impaired patient

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Neurogenic and myopathic bowel disorders (NMBD) are multifactorial disorders effecting a wide population of patients including those with severe spinal injuries, connective tissue diseases, Parkinson's disease, spina bifida, cerebral palsy and others who often suffer from severe constipation, incomplete defecation, fecal impactions and fecal incontinence which impacts quality of life (QOL). Since neurogenic bowel is refractory to oral laxative therapy, an anal irrigation system (AIS) can be used as a bowel management device to aid with defecation. We report here the first case reported of a patient with NMBD and visual impairment and how we trained patient on use of the AIS for relief of their constipation symptoms.

**Case Description:** A 47-year-old female with a past medical history of undifferentiated connective tissue disease, unknown etiology of blindness, papillary thyroid cancer status post resection, fibromyalgia, depression, inflammatory arthritis, lumbar spine fusion and severe constipation was referred to our clinic. Reported progressive worsening of constipation for years with incomplete bowel movements (BMs) twice a week. BMs described as hard, large, and painful. Patient reported pushing, straining, abdominal pain, decreased sensation and urgency with BMs. Colonic transit study using radiopaque markers while on laxatives revealed 21 markers retained from right colon to rectum concerning for slow transit constipation even while on laxative therapy. Anorectal manometry (ARM) revealed abnormal pattern of rectal coordination with abnormal balloon expulsion testing (BET) consistent with dyssynergic defecation and rectal
Development and implementation of a novel hybrid model for neurogastroenterology and motility fellowship

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Background: Adult neurogastroenterology and motility (NGM) training often lacks elements focused on knowledge, skills, attitudes, and values needed to address pediatric-to-adult transitions of care. We share our experience with a novel, cross-institutional, hybrid NGM Advanced Training Fellowship. In addition to rigorous adult NGM training, the pediatric-based modules aim to furnish the trainee with expertise in the diagnosis and management of NGM disorders as they affect adolescents and young adults, in the service of streamlining the care of pediatric patients with NGM disorders continuing into adulthood.

Design and Implementation: An inaugural fellow was selected by application and a program structure was outlined, tailored in part to the fellow’s individualized clinical and research interests. Advanced training at the University of Pennsylvania included mentored rotations through ambulatory consultation-based practices in esophagology and NGM; elective experiences in colorectal surgery, psychiatry, radiology and pelvic floor physical therapy; performance and interpretation of core physiology studies according to previously published minimum competency standards; didactic initiatives with general gastroenterology fellows and medical students; longitudinal conference series; and mentored original research. Synchronously, clinical rotations were pursued through the Children’s Hospital of Philadelphia in an interdisciplinary dysautonomia clinic; a biopsychosocial model-based pediatric Irritable Bowel Syndrome clinic; pediatric physiology laboratory with unique technologies missing in the adult context (i.e. antroduodenal and colonic manometry).

Conclusion: This fellowship curriculum utilizes existing and hitherto separate educational resources in order to hybridize adult and pediatric neurogastroenterology and motility training experiences. We aim to build on this model in future iterations, graduating a larger cohort of subspecialist colleagues with unique expertise in NGM disorders that straddle an often fraught demographic divide.

112 Chronic intestinal pseudo-obstruction is associated with methane overproduction

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Background: Chronic intestinal pseudo-obstruction (CIP) is a rare motility disorder and a common cause of intestinal failure. The disease pathogenesis, and presentation commonly overlaps with small intestinal bacterial overgrowth (SIBO). In recent times, intestinal methanogen overgrowth (IMO) has shown a bidirectional relationship; as both the cause and effect, of decreased intestinal motility and stasis. To study an association between CIP and IMO we conducted a retrospective analysis that aims to identify the positivity rate of methane on a glucose breath test(GBT) in patients with CIP at a tertiary care center.

Methods: Chart review was conducted for 110 patients with who underwent GBT between September 2017 and September 2020. An increase in hydrogen concentrations of > 20 ppm and a concentration of > 10 ppm of methane at any time during the test was considered positive for hydrogen and methane, respectively. GBT results were combined into two levels: ‘positive (IMO+)’ with original level ‘Methane’, and ‘negative (IMO-)’ with original levels ‘Hydrogen’ and ‘Negative’. Furthermore, the search term “chronic intestinal pseudo-obstruction” was used to review patients with CIP who had undergone GBT. We also reviewed demographic data, including age, gender, body mass index, tobacco and alcohol history, medical comorbidities, use of proton pump inhibitors and history of colectomy.

Results: Among 110 patients, 21 (19.1%) were IMO+. The mean age of IMO+ patients was 52.1 years (OR:1.011, 0.982–1.041, p > 0.05). The mean BMI in IMO+ patients was 24.3 kg/m² (OR: 0.936, 0.867–1.011, p > 0.05). 26 out of 110 patients had CIP. There was significant association between patients with CIP and methane positivity,
with 13/21 (61.9%, OR: 9.497, 95% CI: 3.294–27.385, \( p < 0.001 \)) IMO+ patients having CIP. The overall positivity rate of methane was higher in CIP (13/26, 50%, \( p < 0.05 \)) compared to patients without CIP (8/84, 9.5%). Univariate analysis after adjusting for CIP revealed male gender (OR: 3.991, CI: 1.177–13.518, \( p < 0.05 \)) to be positively associated with IMO while patients who had a history of colectomy (OR: 0.183, CI: 0.034–0.969, \( p < 0.05 \)) had lower odds of being methane positive.

**Conclusion:** We conclude that there is a significant association between CIP and IMO. To our knowledge, this is a novel study that solidifies the association of CIP and methanogen overgrowth. Furthermore, it provides a potential avenue of medically treating gastrointestinal symptoms in CIP.

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**113 | MoPill: Noninvasive assessment of gastric emptying and gastric motility**

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**Introduction:** Based on studies utilizing a wireless motility capsule (SmartPill), the passage of this nondigestible capsule from the stomach into the duodenum takes place with the onset of a migrating motor complex during the interdigestive phase. MoPill is a novel system where every second a capsule, wirelessly transmits radiofrequency signals of its location. Our goal was to investigate the timing of when postprandial gastric contractions end and the expulsion of the MoPill capsule into the duodenum signaling that gastric emptying has occurred, signaling when gastric emptying is complete.

**Methods:** The MoPill system consists of a capsule, color-coded adhesive sensors (4 applied to the abdomen and 4 to the back), cables carrying the signals to a recorder and the software. After an overnight fast, 9 subjects ingested a 250-calorie protein bar and 17 oz. of water, followed by swallowing of the activated capsule. No further caloric contents were allowed for at least 5 hours. At 1 and 5 hours, AP and lateral abdominal x-rays were obtained. Analysis of MoPill data was conducted to capture the postprandial changes in the stomach, specifically measuring contraction frequency and identifying when the contractions end and when the MoPill capsule leaves the stomach.

**Results:** The frequency of gastric contractions ranged from 2.6 to 4.4 contractions/min, with a mean of 3.4 contractions/min (Figure 1). The time between the end of contractions and the passage of MoPill into the duodenum signaling that gastric emptying has occurred is shown in Figure 2. The difference between the two endpoints in this pilot study ranged from 1 to 53 minutes with a mean value of 18 minutes.

**Conclusion:** (1) MoPill is able to record gastric contractions as well as the exit of the capsule signaling gastric emptying. (2) This data in normal subjects sets the stage for studies in gastroparesis and functional dyspepsia patients where abnormalities in gastric motor function and delayed gastric emptying can be quantified. (3) MoPill; "the GPS of the gut", is a major advance in diagnosing gastric motility disorders as well as having the potential to document dysmotility in the small bowel and colon.

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**114 | Accelerated contrast-enhanced gastrointestinal MRI captures whole-stomach motor events in rats**

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**Purpose:** Dynamic contrast-enhanced gastrointestinal magnetic resonance imaging (GI-MRI) is a non-invasive method to potentially image and characterize gastric motor events, including gastric accommodation, tonic and peristaltic contractions. To support these goals, GI-MRI needs to be fast enough to capture motility ranging from 4 to 8 cycles per minute, and be robust against motion artifacts due to respiration. Specifically for rats, it is desirable to image the entire stomach at sub-millimeter resolution within one or maximally two consecutive respiration cycles. In our prior work, fully sampled Fast Low Angle Shot MRI sequences (FLASH) were used to acquire only a few slices covering a portion of the stomach. In the present work, we aimed to capture gastric motor events across all stomach compartments, such as time-resolved peristalsis over distal corpus and antrum, the opening and closing of the pylorus, and tonic contractions over the fundus. Such GI-MRI images with high temporal resolution and full coverage of the stomach will enable the characterization of normal gastric dynamics and differentiation from those associated with gastric-related disorders.

**Method:** We used KT-Generalized Autocalibrating Partially Parallel Acquisitions (KT-GRAPPA), a parallel imaging technique exploiting spatiotemporal redundancies to reduce acquisition time and obtain full coverage of the stomach at high spatiotemporal resolution.
as required to capture peristaltic dynamics. We customized the respiration-triggered FLASH sequence to minimize the respiratory artifacts and maximize SNR. A partially sampled scheme in k-space is implemented to speed up the acquisition with a reduction factor of three. It employed between 8 and 16 autocalibration phase encodings (ACS) in the center of the k-space combined with an interleaved acquisition of the peripheral phase encodings. An in-house KT-GRAPPA reconstruction algorithm was also developed for predicting missing phase encodings and reconstructing the images at full resolution.

**Results:** We implemented our method on pre-clinical 7T Agilent MRI. Compared to earlier work, we extended partial spatial coverage of the stomach from 4 slices to full coverage with 12–20 slices per 1.5 s, with TE/TR = 1.4 ms/9.9 ms, at a resolution of 0.5 mm × 0.5 mm and a slice thickness of 1.5 mm. Frame rates were well above the Nyquist frequency for proper capture of peristaltic dynamics. Our work enables future comprehensive and automatic analysis and integration of gastric motor events, such as antral peristalsis, fundic tonic contractions, and antrum-pylorus-duodenum coordination. Furthermore, our pilot data suggests the possibility of capturing even faster dynamics of the duodenum.

**Pharmacotherapy and pharmacogenomics**

**ABSTRACT**

**115 | Treatment satisfaction and improvement in quality of life with plecanatide among patients with chronic idiopathic constipation and irritable bowel syndrome with constipation: analyses from four phase 3 trials**

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**Introduction:** Chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) impact quality of life (QOL). We analyzed four phase 3 trials (2 in CIC; 2 in IBS-C) assessing plecanatide treatment satisfaction and QOL among CIC/IBS-C patients with the lowest QOL at baseline (i.e., patients experiencing the greatest impact of CIC/IBS-C on their QOL and therefore the most to gain from effective treatment).

**Methods:** Rome III CIC or IBS-C patients were randomized to plecanatide 3 mg (PLE) or placebo (PBO) once daily for 12 weeks. Treatment satisfaction was evaluated at Weeks 4, 8, and 12 using a scale of 1 (not at all satisfied) to 5 (very satisfied). Patient assessment of constipation (PAC-QOL) (a 28-item questionnaire administered to CIC patients) uses a scale of 0 (not at all) to 4 (extremely/all the time). IBS-QOL (a 34-item questionnaire administered to IBS-C patients) uses a scale of 1 (not at all) to 5 (extremely/a great deal). Higher scores indicate lower QOL. This analysis focused on the quintile of patients with the lowest QOL at baseline.

**Results:** The lowest QOL subgroup included 269 out of 1762 total patients with CIC (PLE, n = 146; PBO, n = 123) and 271 out of 1453 total patients with IBS-C (PLE, n = 144; PBO, n = 127). Significantly more plecanatide-treated patients achieved a treatment satisfaction score of 4 or 5 across 12 weeks (CIC: PLE = 62.3%, PBO = 47.2%; p < 0.05; IBS-C: PLE = 63.2%, PBO = 45.7%; p < 0.05); significant differences were observed by Week 4. Significantly more plecanatide-treated patients met established clinically meaningful improvements in PAC-QOL (≥1-point reduction; PLE = 58.2%; PBO = 51.2%; p < 0.05) and in IBS-QOL (≥14-point reduction; PLE = 70.8%; PBO = 55.9%; p < 0.01).

**Conclusion:** Across four phase 3 CIC and IBS-C trials, PLE led to statistically significant and clinically meaningful improvements in treatment satisfaction and QOL compared to PBO among patients with the lowest QOL at baseline. Plecanatide appears effective in improving patient-centric factors in a population of individuals with severe self-reported CIC and IBS-C.

**116 | Plecanatide is effective in severely constipated patients with chronic idiopathic constipation and irritable bowel syndrome with constipation**

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**Introduction:** Chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) are characterized by infrequent, hard, and difficult-to-pass bowel movements as well as varying degrees of abdominal symptoms. Plecanatide is FDA approved to treat CIC and IBS-C; however, its efficacy in severe constipation is unclear. The aim of this analysis of four phase 3 studies is to evaluate the impact of plecanatide in severely constipated patients with CIC and IBS-C.

| Endpoint          | CIC     | IBS-C    | Endpoint          | CIC     | IBS-C    |
|-------------------|---------|----------|-------------------|---------|----------|
| CSBMs/week        | 2.23, 1.27*** | 1.01, 0.37*** | Straining         | -1.50, -1.07*** | -2.75, -1.85*** |
| SBMs/week         | 2.67, 1.48**  | 1.40, 0.25*** | Pain              | -0.84, -0.62**  | -1.99, -1.36**  |
| BSFS              | 1.87, 1.10*** | 1.43, 0.98**  | Bloating          | -0.92, -0.65**  | -1.91, -1.20**  |
Methods: Patients from two CIC studies and two IBS-C studies were randomized to receive plecanatide 3 mg (PLE) or placebo (PBO) once daily for 12 weeks. Severe constipation was defined as having no complete spontaneous bowel movements (CSBMs) and an average scoring of ≥3 (CIC; 5-point scale) or ≥8 (IBS-C; 11-point scale) over the 2-week baseline period. Endpoints included CSBMs/week, spontaneous bowel movements (SBMs/week), stool consistency (Bristol Stool Form Scale), straining, abdominal pain, and bloating. In CIC and IBS-C studies, straining, abdominal pain, and bloating were rated on a Likert scale (0–4) and numeric rating scale (0–10), respectively.

Results: 433/1762 (24.6%) patients with CIC (PLE, n = 220; PBO, n = 213) and 356/1453 (24.5%) patients with IBS-C (PLE, n = 188; PBO, n = 168) met criteria for being severely constipated. Across 12 weeks, significant improvements in PLE-treated patients were observed. Least square mean changes from baseline are reported (PLE, PBO). **p < 0.01, ***p ≤0.001 vs PBO.

Conclusion: Nearly 25% of patients enrolled in the trials were severely constipated at baseline. Both abdominal and bowel symptoms improved significantly in severely constipated CIC and IBS-C patients treated with PLE when compared to PBO.

117 | Chronic colonic and bladder hypersensitivity induced by pelvic irradiation is attenuated by guanylate cyclase-c agonist IW-3300

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Background: Radiotherapy for pelvic cancers can lead to radiation-induced visceral organ injuries that frequently develop into persistent chronic radiation proctitis, colitis, and cystitis. One key symptom associated with both of these conditions is pain associated with the affected organ. Currently, no recommended guidelines for the treatment of visceral pain associated with radiotherapy exist, making the management of these conditions extremely challenging. Here, we test the hypothesis that guanylate cyclase-c (GC-C) engagement via GC-C agonist IW-3300 relieves pain in a rat model of pelvic radiation injury.

Methods: Adult male Lewis rats received a fractionated dose of radiation (FR: 48 Gy total over 8 days), a single high dose of radiation (HR: 25 Gy), or sham irradiation. On day 42 colonic sensitivity was assessed via a visceromotor response (VMR) to graded pressures of isobaric colorectal distension (CRD, 20–60 mmHg) and bladder sensitivity was assessed via quantification of suprapubic withdrawal reflex to von Frey filaments (SWR). Rats exposed to fractionated radiation then received intracolonic IW-3300 (3 µg/kg) or vehicle on days 56–72 and rats exposed to a single high dose of radiation received IW-3300 or vehicle on days 42–72. Colonic and bladder sensitivity was reassessed in both groups on days 56 and 72.

Results: On day 42, rats in both radiation groups exhibited an increased VMR to CRD (p < 0.0001; 60 mmHg) and suprapubic withdrawal reflex (p < 0.0001; 15 g) that persisted until day 72. IW-3300 decreased the VMR to CRD and SWR (VMR 60 mmHg = 14.6 ± 1.1 vs. 23.3 ± 0.58 contractions; SWR 15 g = 4.2 ± 0.5 vs. 7.2 ± 0.8 withdrawal frequency) of FR rats on day 72 compared to vehicle. Similarly, HR rats that received IW-3300 demonstrated a significantly attenuated VMR to CRD and SWR on days 56 (VMR 60 mmHg = 14.0 ± 0.6 vs. 23.8 ± 1.2 contractions; SWR 15 g = 4.2 ± 0.3 vs. 7.8 ± 0.3 withdrawal frequency) and 72 (VMR 60 mmHg = 13.8 ± 0.5 vs. 23.6 ± 0.5 contractions; SWR 15 g = 4.3 ± 0.3 vs. 7.2 ± 0.3 withdrawal frequency).

Summary: Irradiation of the pelvic region induces persistent colonic and bladder hypersensitivity in adult male rats that is inhibited by GC-C agonist IW-3300.

Conclusion: These results demonstrate the potential of GC-C agonism to help manage radiation-induced visceral hypersensitivity and support the further evaluation of IW-3300 in humans for this indication.

118 | Patterns of IBS-D medication use in patients with IBD

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Introduction: Abdominal pain and diarrhea are hallmark symptoms in active IBD, but often persist after resolution of acute inflammation. Despite the burden of these IBS-D-like symptoms, there is limited information about symptom-based therapies for these patients. Coupling IBS-D medication use with specific IBD therapy may result in improved quality of life. To clarify this issue, we determined the prevalence of IBS-D medication use and clinical characteristics of users in a large cohort of IBD patients.

Methods: Using a large, prospective IBD natural history registry, we identified a study cohort of patients with either Crohn’s disease (CD) or ulcerative colitis (UC) who had at least 2 years of enrollment in the registry. Patients prescribed the following categories of IBS-D therapies were included for analysis: anti-diarrheals, bile acid sequestrants, antibiotics (Rifaximin), 5-HT3 antagonists, mu-opiate receptor agonists, and anti-spasmodics. IBD specific outcomes included frequency of elevated CRP, Harvey-Bradshaw Index (HBI), Ulcerative Colitis Activity Index (UCAI), and quality of life (Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

Results: Out of 3,299 IBD patients, 47.0% (n = 1,549; 68.8% CD, 27.8% UC; 3.4% unspecified) received a prescription for at least one IBS-D category therapy. Using logistic regression, we found that males were more likely than females to receive IBS-D medications (OR 1.8 for CD, p < 0.0001; OR 1.56 for UC, p < 0.002). An increased elevated CRP was observed in 67.4% of the IBS-D medication group (no difference between CD and UC), with 63.0% of the group receiving an immunomodulator and 58.9% receiving a biologic (CD significantly higher rates of both medications than UC). There was no...
significant difference in median SIBDQ or median HBI-UCAI scores between CD and UC patients in the IBS-D medication group, indicating similar degrees of disease activity and multiyear severity.

**Conclusion:** Nearly half of IBD patients are prescribed adjuvant IBS-D medications—predominantly for patients with CD. The majority of IBD patients using IBS-D medications also used IBD-specific medications. Further studies would clarify which IBD patients would benefit the most from early, concerted use of IBS-D medications in improving long term symptom scores and quality of life.

**119 | Patterns of IBS-C medication use in patients with IBD**

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**Introduction:** While irritable bowel syndrome with diarrhea in IBD patients is frequently described, IBD patients with constipation has not been well described. We aimed to determine prevalence of constipation in IBD patients and their treatment strategies.

**Methods:** Consented patients enrolled in a prospective IBD natural history registry at a tertiary referral center formed the study population. Patients with either Crohn’s disease (CD) or ulcerative colitis (UC) followed for a minimum of 2 years were included. Patients specifically prescribed the following IBS-C categories of therapy for constipation-related symptoms were included in the study cohort: general constipation, bulk forming laxatives, stimulant laxatives, osmotic laxatives, suppositories, stool softeners, and medications targeting opioid-induced constipation. IBD specific outcomes included frequency of elevated CRP, Harvey-Bradshaw Index (HBI), Ulcerative Colitis Activity Index (UCAI)), and quality of life (Short Inflammatory Bowel Disease Questionnaire (SIBDQ).

**Results:** Out of 3,299 IBD patients, only 2.9% (n = 97) received a prescription for at least one IBS-C category therapy (53.5% with Crohn’s, 46.5% with UC). More women were noted in the IBS-C medication group (57.0% women vs 43.0% men (p = 0.016)). With an overall elevated CRP of 57.7%, there was no significant difference in elevated CRP between those with Crohn’s or those with UC. In terms of disease activity/severity, there was no statistically significant difference in median SIBDQ or HBI-UCAI scores between the two disease types. For both Crohn’s and UC, increase in age was associated with likelihood to need IBS-C medication (p < 0.004 for Crohn’s and p < 0.001 for UC).

**Conclusion:** In our registry, ~3% of IBD patients required constipation medications during the study period. Patients with Crohn’s disease have a slightly higher prevalence of constipation compared to those with UC. Elevated inflammatory markers suggest that the mechanism for constipation in these patients may be driven by an inflammatory-fibrosis type mechanism. Further studies into treatment strategies for constipation in IBD patients may yield improved patient outcomes in this group.

**120 | Eighteen-month interim analysis of efficacy and safety of givosiran, an RNAi therapeutic for acute hepatic porphyria, in the ENVISION open label extension**

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**Background and Aims:** Acute hepatic porphyria (AHP) is a family of rare genetic diseases due to enzyme defects in hepatic heme biosynthesis. Induction of 5-aminolevulinic acid synthase 1 (ALAS1), leads to accumulation of heme intermediates, 5-aminolevulinic acid and porphobilinogen that may result in neurovisceral attacks. ENVISION is an ongoing study evaluating efficacy and safety of givosiran in symptomatic AHP patients in a 6-month double blind (DB) period and a 30-month open label extension (OLE) period. Here, the effects through Month 18 of the OLE are reported.

**Methods:** ENVISION (NCT03338816) is a Phase 3 global, randomized, placebo-controlled study. Exploratory efficacy outcome measures included composite porphyria attacks (i.e. those requiring hospitalization, urgent care, or IV-hemin at home). Analyses were descriptive and represent the timepoint where patients completed at least their 18-month visit.

**Results:** As of January 10, 2020, 93/94 patients entered the OLE (placebo/givosiran = 46; givosiran/givosiran = 47) with mean exposure to givosiran 12.97 [SD = 3.6] months and 18.86 [3.6] months, respectively, and maximum exposure of 25.1 months. Continued treatment in givosiran/givosiran patients led to a median annualized attack rate (AAR) of 0.58 (range: 0–16.2) through Month 18. Patients in the placebo/givosiran group had an AAR of 1.62 (range: 0–11.8) after receiving givosiran for ≥12 months during the OLE, compared with 10.65 (range: 0–51.6) during the DB period. Average number of attacks declined for both groups. There were no new safety concerns.

**Conclusions:** In an ongoing Phase 3 study, givosiran demonstrated maintenance of clinical efficacy and an acceptable safety profile consistent with that previously observed.

**Keywords:** porphyria, pain, RNAi.
Background: We evaluated whether baseline osmotic agents (eg, milk of magnesia, polyethylene glycol, lactulose, sorbitol) stimulants (eg, senna, bisacodyl), or stool softeners (eg, docusate sodium) affect the efficacy and safety of methylnaltrexone (MNTX) in opioid-induced constipation (OIC) patients with advanced illness.

Methods: Two multicenter, randomized, double-blind, PBO-controlled studies in adults with OIC and advanced illness were pooled. Study 302 compared SC MNTX 0.15 mg/kg vs PBO and study 4000 compared body weight-based SC MNTX 8 mg (38–<62 kg) or 12 mg (≥62 kg) vs PBO. Patients who received baseline osmotic agents, stimulants, and/or stool softeners, which were permitted to continue during the studies, were identified. Efficacy endpoints included rescue-free laxation (RFL) within 4 or 24 hours after the first dose (ie, a spontaneous bowel movement without requiring rescue laxatives) and pain intensity. Safety endpoints included TEAEs.

Results: The pooled analysis yielded 363 patients with advanced illness. Of those, 286, 167, or 123 patients were using a laxative regimen at baseline that contained a stimulant, osmotic agent, or stool softener, respectively (patients were permitted to use more than 1 type of laxative). A greater proportion of patients who received MNTX (63%–66%) had RFL within 4 hours compared with PBO (14%–21%) regardless of the type of laxative used at baseline (p < 0.0001). Similar findings were observed for those with RFL response within 24 hours of MNTX treatment (72%–77%) vs PBO (43%–46%, p < 0.005). There were no significant differences between MNTX or PBO in the change from baseline pain scores after 1 day or 7 days regardless of the type of laxative used at baseline. The most commonly reported TEAE was abdominal pain.

Conclusions: MNTX use in patients with advanced illness significantly increased the proportion of patients with RFL response within 4 and 24 hours of treatment in patients refractory to baseline laxative use. MNTX did not reduce the analgesic effects of opioid treatment and did not induce unexpected AEs.

Psychogastroenterology and behavioral interventions

122 | Environmental enrichment prevents stress-induced epigenetic changes in gene expression at the central nucleus of the amygdala to inhibit visceral hypersensitivity

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Introduction: Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder, typically exacerbated by stress. Previously, we showed that exposure to psychological stress induces viscerosomatic hyperalgesia in a rodent model via amygdala-(CeA) mediated mechanisms. Exposing rodents to an enriched environment (EE) before and during the stressor prevents viscerosomatic hypersensitivity, but the effects of EE on stress-induced changes in the CeA epigenome and spinal nociception were left unexplored. We hypothesize that exposure to EE prevents stress-induced epigenetic changes at glucocorticoid receptors in the CeA and inhibits enhanced spinal nociception to attenuate viscerosomatic hypersensitivity.

Methods: Female rats (8/group) underwent 1 h/day for 7 days water avoidance stress (WAS) to induce viscerosomatic hypersensitivity. Rats were exposed to EE (larger cage, additional cage-mates, and toys) 1 week before and during WAS. Control rats were kept in standard housing (SH). Somatic sensitivity was measured using an electronic von Frey on the hind paw and visceral sensitivity was assessed by measuring the number of abdominal contractions to isobaric colorectal distensions (20, 40 and 60 mmHg) in freely moving rats on day 8. All rats were then put in SH for 3 weeks and viscerosomatic sensitivity assessed again on day 28 before the spinal cords were collected to quantify pERK expression as a measure of neuronal activation. Another cohort was euthanized on day 8 and the CeA collected to measure epigenetic changes at the glucocorticoid (GR) and corticotropin releasing hormone (CRH) promoter regions. Results were analyzed using 1-or 2-way ANOVA.

Results: Exposure to EE prevented WAS-induced visceral hypersensitivity (p < 0.01) and somatic allodynia (p < 0.001) and these effects were persistent up to day 28. EE also prevented stress-induced increase in H3K9 acetylation at the CRH promoter (p < 0.001), decreased H3k9 acetylation at the GR promoter (p < 0.001) and decreased GR-CRH interaction (p < 0.01) in the CeA and blocked stress-induced increase in pERK expression at the dorsal horn (p < 0.0001).

Conclusions: Exposure to EE before and during WAS prevented the stress-induced changes at the epigenome of GR and CRH in the CeA, prevents enhanced spinal nociception and as a result, persistently attenuates psychological stress induced viscerosomatic hypersensitivity. This study reveals potential mechanisms underlying the positive role of behavioral therapies in IBS.
Sex differences in neurogastroenterology and motility

124 | Stress-induced visceral pain in female rats is associated with epigenetic remodeling in the central nucleus of the amygdala

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Background: Chronic abdominal pain is a common complaint of patients with irritable bowel syndrome (IBS). Chronic stress often triggers or exacerbates visceral pain in these patients. We have previously shown in male animals that water avoidance stress (WAS) can recapitulate stress-induced visceral hypersensitivity. Stress caused visceral hypersensitivity through epigenetic and gene expression changes of glucocorticoid receptor (GR) and corticotrophin-releasing hormone (CRH) in the central nucleus of the amygdala (CeA). Whether stress dysregulates the epigenome of the CeA of female rats is unknown. Following WAS exposure, we evaluated histone acetylation at the GR and CRH promoters in the CeA of female rats. Furthermore, we investigated whether inhibition of histone deacetylases (HDAC) in the CeA could ameliorate WAS-induced visceral hypersensitivity.

Methods: The first group of female rats were exposed daily to 1 hour of WAS or SHAM for 7 consecutive days. The second group underwent stereotaxic implantation of indwelling cannulas directly above the CeA, before being exposed to 1 hour of WAS for 7 consecutive days. Each WAS session was followed by infusion of the HDAC inhibitor TSA (100 ng/μl) or vehicle (VEH) in the CeA. Twenty-four hours after the final stressor/infusion, visceral sensitivity was assessed in freely moving rats by quantifying the number of abdominal contractions induced by colorectal distension at isobaric pressures (20, 40 and 60 mmHg). In another cohort, the CeA was isolated following graded pressure (0–60 mmHg) of isobaric distension. Microglial morphology, microglia-mediated synaptic engulfment and the expression of synaptic pruning-related signals complement C1q and CR3 receptor were measured using immunofluorescence and RNAscope assay.

Results: We show that elevated CORT in the CeA induced i) visceral hypersensitivity (p = 0.0001) and 2) microglial activation (p = 0.001) with an increased expression of synaptic pruning-related signals (C1q p < 0.0001; CR3 p = 0.0002). Housing rats in EE cages for 14 days attenuated visceral hypersensitivity as compared to SH controls following CORT implantations (40 mmHg p = 0.0029; 60 mmHg p = 0.0002). EE also reduced microglial activity (p < 0.005) and microglia-mediated synaptic remodeling in the CeA (p < 0.005).

Conclusion: In female rats, chronic stress signals are integrated into the epigenome of the amygdala. These epigenetic mechanisms regulating GR and CRH expression contribute to stress-induced visceral hypersensitivity.

125 | MoPill: A noninvasive measure of small bowel segmentation and the role of gender

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Introduction: As food interacts with the lining of the small intestine (SI), nutrients are extracted. The more sustained interaction, the potential for greater extraction. The SI is known to undergo “segmentation” where a section closes and mixes contents back and forth. Little is known about the role of “segmentation” in conditions where nutrient absorption is deficient despite apparently adequate caloric food intake. Segmentation may also play a role in obesity as it has been shown that weight gain is not solely dependent on caloric intake (Dutch Hunger Winter Study https://www.pnas.org/centnt/107/39/16757). MoPill is a novel electronic capsule that transmits information on its position to sensors worn on the abdomen
and back, providing location every second. Though the capsule only measures position, if the distance the pill travels while in the small intestine is greater than the length of the small intestine (approximately 7 meters) that could suggest retrograde motion and segmentation. If the total distance that the capsule travels in the SI is divided by 7, it provides a multiple of the SI travel and could serve as a segmentation index.

**Methods:** In a pilot study 9 normal subjects (4 Female; mean BMI 25; and 5 Male mean BMI 23) were given a 250 calorie protein bar and water after an overnight fast and ingested activated MoPill capsule at the same time. The distance the capsule traveled while in the small intestine was divided by 7 to calculate a segmentation index.

**Results:** The results of the segmental index for all subjects are presented in Figure 1 based on gender (in descending order), while Figure 2 shows the average (11.3 vs. 6.1), and range (25.7 vs. 6.9) of the Segmental Index which was higher in female than male participants.

**Conclusion:** Though this is a very small study, it appears that females have more segmentation in their small intestine than do males which may lead to greater extraction of nutrients and more weight gain in females than males for similar caloric ingestion. These results need to be verified with a larger study. MoPill is new technology that may be an objective diagnostic tool for assessing the degree of small bowel segmentation as well as transit abnormalities.