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POSTER SESSION

19 | Predictors of hospitalization for children with cyclic vomiting syndrome

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Background: Cyclic vomiting syndrome (CVS) involves acute episodes of intense nausea and vomiting lasting hours to days. Severe episodes can require emergency department (ED) care and hospitalization, leading to significant resource utilization and healthcare costs. Factors associated with an increased likelihood of hospitalization for CVS are poorly understood. Our aim is to evaluate for an association between patient, attack and ED care-related variables and hospitalization.

Methods: We retrospectively reviewed children with CVS seen at our institution between 2014-2018. We included patients who met the Rome IV diagnostic criteria for CVS. CVS-related ED visits that led to discharge were compared to those that led to hospitalization. We compared patient demographics and modifiable variables associated with pre-ED and ED care between the two groups, including use of prophylactic and abortive drugs, duration of symptoms prior to ED presentation, ED wait time before IV fluid and antiemetic administration and serum electrolyte levels.

Results: We included 142 patients with CVS (53% female, median age 11 years, range 4-17), of which 25% had presented to the ED for a CVS attack at least once. Of 149 ED visits during the time period studied, 93 (62.4%) led to hospitalization. Seventy-four percent of younger patients (<12 years) presenting to the ED were hospitalized compared to 40% of older patients (≥ 12 years) [OR 4.21, CI 2.04-8.66, *P*= <0.0001]. Overall, males were more likely to be hospitalized than females (78.3% vs. 51.7%, *P* = 0.001); however, this difference was no longer present when controlling for age. Forty-nine percent of patients presenting within 24 hours of symptom onset were hospitalized compared to 80.3% of patients presenting after 24 hours [OR 0.23, CI 0.11-0.499, *P* = <0.0001]. In patients presenting within 24 hours, ED wait time before IV fluids and antiemetic drug administration was similar between patients hospitalized and discharged. Serum electrolyte levels and use of prophylactic and pre-ED abortive drugs were similar between hospitalized and discharged patients.

Conclusions: In our sample, a quarter of all children with CVS had presented to the ED and nearly two thirds of these ED visits led to hospitalization. Hospitalization was more likely in younger patients and in patients with a delayed presentation to the ED. Further

investigation into modifiable variables that may mitigate the need for hospitalization and reduce the burden of CVS on both patients and the healthcare system is warranted.

20 | Trends and costs of hospitalization for children and adolescents with cyclic vomiting syndrome: 2015–2018

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Background: Although most patients with cyclic vomiting syndrome (CVS) are managed on an outpatient basis, patients with severe symptoms can require frequent hospitalization, leading to significant resource utilization and associated healthcare costs. Our aim is to evaluate both trends and costs of hospitalization for pediatric CVS between September 2015 to September 2018.

Methods: Using the Pediatric Health Information System, we selected hospitalizations with a diagnosis of CVS (ICD-10 G43.A0) from September 2015 to September 2018. We recorded dates of hospitalization, demographics, charges, costs and length of stay (LOS). Hospital costs were based upon each hospital's ratio of cost to charges and were adjusted for hospital location using the Centers for Medicare & Medicaid Services wage/price index.

Results: During the time period studied, 744 patients (61.6% female) were admitted a total of 1496 times for CVS. The total number of hospitalizations per year of study was 506 in 2015-2016 (Y1), 559 in 2016-2017 (Y2) and 431 in 2017-2018 (Y3). The proportion of repeat admissions decreased from 46.1% to 30.2% between Y1 and Y3 (P = <0.0001). Total cost of hospitalization was $5,615,385 in Y1, $6,003,047 in Y2 and $5,141,590 in Y3. Overall cost per hospitalization was similar across all years. Age and gender were not associated with the total cost of hospitalization. Mean cost per hospitalization in the South ($12,406) was 32.08% higher than in the West ($9,393), 23.85% higher than in the Northeast ($10,018) and 3.65% higher than in the Midwest ($11,969) ($P$ = 0.003).

Conclusion: Although the total number of hospitalizations for CVS remained stable between 2015 and 2018, the proportion of repeat admissions has steadily decreased. This may be secondary to an increase in new CVS diagnoses and improved outpatient management of patients with severe symptoms. We found significant regional differences in overall cost per hospitalization. Further evaluation of factors contributing to these differences may help reduce the overall financial burden of pediatric CVS.

21 | Altered lysophosphatidic acid receptor expression in chronic intestinal pseudo-obstruction

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Background: Chronic intestinal pseudo-obstruction (CIPO) is a gastrointestinal (GI) disorder characterized by colonic dysmotility in the absence of a mechanical blockade. While certain sub-types of CIPO arise secondary to neuronal, myopathic and mesenchymal dysfunction, many CIPO cases remain idiopathic. New data show that enteric glia regulate gut motility, but the potential role of enteric glia in the development of CIPO is completely unknown. Here, we tested the *hypothesis that altered glial function contributes to the pathogenesis of CIPO*, with a focus on the role of type I lysophosphatidic acid receptor (LPA_1R), which is known to modulate neuronal excitability and is abundantly expressed in enteric glia.

Methods: We used immunohistochemistry to study structural and morphological changes in the colonic myenteric plexus of healthy individuals and patients diagnosed with CIPO. Additionally, we conducted calcium imaging studies in *Wnt1Cre;CGaMP5 g-tdTomato* mice to assess enteric neural network activity.

Results: Expression levels of glial fibrillary acidic protein (GFAP), type III β-tubulin, PGP9.5 and LPA_1R were examined in a total of 28 myenteric ganglia from 6 CIPO patients and compared to 15 ganglia derived from 2 healthy controls. Our data show that myenteric ganglia from CIPO patients were 2.68-fold larger than those in healthy controls (P = 0.0002). CIPO ganglia exhibited a 0.43-fold reduction in PGP9.5 (P = 0.0067) and a 0.36-fold reduction in LPA_1R (P = 0.0004) expression levels. Pre-treatment of isolated mouse colonic myenteric ganglia with the LPA_1R agonist, 18:1 lysophosphatidic acid (LPA), altered electrical-field stimulation (EFS)-mediated calcium (Ca^{2+})-responses. Under control conditions, EFS evoked a robust increase in Ca^{2+} in myenteric ganglia ($\Delta F/F_0$=2.88 ± 0.142, n = 5). This response was attenuated by low concentrations of LPA (1 μM LPA: $\Delta F/F_0$=2.31 ± 0.146, n = 4) and augmented by high concentrations of LPA (100 μM: $\Delta F/F_0$=4.898 ± 0.35, n = 2).

Conclusions: Taken together, our findings highlight a novel role for LPA_1R signaling within the intact colon. Future studies will clarify the physiological role of LPA_1R and to determine its relevance to the onset/progression of functional GI diseases.

22 | Efficacy and safety of Dor fundoplication in patients with severe: Gastroparesis and refractory gastroesophageal reflux disease

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Background: Delayed gastric emptying in patients with severe gastroparesis (GP) worsens gastroesophageal reflux disease (GERD) symptoms, specifically nocturnal heartburn and regurgitation. While a Nissen fundoplication may be considered there are concerns related to inability to wretch and vomit post-op, increasing the risk of wrap rupture. Dor fundoplication (DF), a 180-200 degree anterior wrap, may improve sphincter competency and provide symptom relief while minimizing these concerns as well as avoiding vagal nerve damage.

Aim: To review symptom improvement and safety of DF in patients with refractory GERD in the setting of severe GP not responding to medical therapies.

Methods: 6 patients with refractory GERD and severe GP underwent a laparoscopic pyloroplasty (PP) and placement of gastric electrical stimulation (GES) system to improve gastric emptying and GP symptoms as well as an accompanying DF. An intraoperative EGD evaluated the wrap and confirmed location of 2 GES electrodes and the integrity of the pyloroplasty. PAGI-SYM was utilized to assess GP and GERD symptoms before surgery and at follow up visits.

Results: 6 patients, 1 diabetic, mean age of 49.9 (33-65) underwent simultaneous PP, GES and DF for drug refractory GP and GERD symptoms, from October 2015 to August 2018. The mean duration of postsurgical follow up was 19.7 (4-33) months. Patients rated their heartburn and regurgitation on a PAGI-SYM scale of 0-5 (0-none 5-very severe) before and after the surgery. The average nocturnal heartburn score of 3.4 and day time score of 2.6 were both significantly reduced post-surgery to 2.5 ($P < 0.05$). The mean regurgitation scores of 3.8 nocturnally and 3.6 upright improved to 2.2 and 2, respectively, post-surgery as did heartburn severity ($P < 0.01$). Based on their global assessment, all patients indicated a symptom improvement of > 50% post-op, with the dominant change being a reduction in nocturnal regurgitation. There was no complication either immediately post-op or upon long term follow up (up to 33 months), specifically no inability to belch or new onset dysphagia.

Conclusions: The Dor fundoplication performed for refractory GERD in the setting of severe GP significantly decreases regurgitation and heartburn, specifically nocturnally, without accompanying complications and therefore offers a major advance in managing refractory GERD in this clinical setting.

23 | Cesarean delivery and functional gastrointestinal disorders (FGID): Could an altered gut microbiome at birth increase the risk for FGID?

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Background: Functional gastrointestinal disorders (FGIDs) are a heterogeneous family of disorders. Their pathophysiology is not well understood. Alterations in the microbiome have been implicated in the development of FGIDs. The gut microbiome of infants born via Cesarean delivery is different from infants born via vaginal delivery as they do not have the same exposure to vaginal flora. Only one study has evaluated the relationship between mode of delivery and development of FGIDs in young adults, but none have assessed this association in children. Our study aimed to assess the association between mode of delivery and risk for development of FGIDs. We hypothesized that Cesarean delivery would be a risk factor for FGIDs in children.

Methodology: Questionnaires were mailed to families of school-aged children from 3 cities in Colombia. Parents completed information on mode of delivery, demographics, and the child's past medical history. School-children completed the Spanish version of the Questionnaire of Pediatric Gastrointestinal Symptoms Rome IV (QPGS-IV). Categorical data were analyzed using Fisher exact tests. Calculation of OR with 95% CI was performed between the variables of interest (age, group, sex, and education) and the effect variable (presence or absence of FGID). Approval was obtained by the Institutional Review Board.

Results: 1497 children/adolescents (535 preadolescents 10-12 years, 962 adolescents 13-18 years) participated. 22.7% (338/1497) of school-children had at least one FGID. The most common FGIDs were defecation disorders (13%), followed by abdominal pain disorders (5.8 %). For participants born via Cesarean delivery, there was no significant increase in prevalence of any of the Rome IV FGIDs.

Conclusions: We found no increased risk for development of FGIDs in those born via Cesarean delivery compared to vaginal delivery. This is the first study to examine the relationship between mode of delivery and FGIDs in Latin America. Our findings suggest that despite likely differences in the microbiome of those born via Cesarean delivery compared with vaginal delivery these differences may not have a role in the development of FGIDs in children and adolescents.

24 | Abnormal bolus reflux on impedance-ph monitoring independently predicts 3-year mortality in patients with idiopathic pulmonary fibrosis

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Background: Gastroesophageal reflux (GER) is prevalent among idiopathic pulmonary fibrosis (IPF) patients, but the role of GER in IPF remains debated as data on the effects of anti-reflux treatments on IPF outcomes are mixed. While abnormal reflux has been associated with increased 1-year IPF hospitalization, the predictive value of objective GER measures on long-term IPF disease progression remains unclear. Understanding the longitudinal relationships between GER and IPF outcomes may help define the role of GER in IPF pathogenesis and the utility of GER testing and anti-reflux therapy in clinical management. We aimed to assess the relationship between objective measures of GER on multichannel intraluminal impedance-pH testing (MII-pH) and mortality over 3 years in IPF patients.

Methods: 124 consecutive adults with IPF (62% male, mean age: 61.7) who underwent MII-pH off PPI at a tertiary center for routine pre-lung transplant evaluation were included. All patients were followed for 3 years from time of MII-pH to assess for death due to pulmonary causes. The association between abnormal GER on MII-pH and 3-year mortality was evaluated using Chi-square test (univariate) and logistic regression (multivariate). Time-to-event analyses were performed using Kaplan-Meier and Cox proportional hazard models, with censoring at date of anti-reflux surgery, lung transplant, or last follow-up.

Results: Patients with increased bolus exposure time (BET) on MII-pH had significantly higher 3-year mortality (40.6% vs 4.76%, P = 0.0038) and pulmonary hospitalization rate (52.9% vs 17.4%, P = 0.0068) than those with normal BET. On multivariate analysis controlling for age, sex, smoking history, BMI, PPI use, baseline pulmonary function, and anti-fibrotic therapy (pirfenidone) use, abnormal BET remained an independent predictor of 3-year mortality (OR 10.2, P = 0.04). Increased BET was also associated with decreased time to death in 3 years on Kaplan Meier analysis (log-ranked P = 0.03). On multivariate Cox regression, increased BET remained an independent predictor of early mortality (HR 6.30, P = 0.048).

Conclusion: Abnormal BET on MII-pH independently predicts 3-year mortality in IPF patients. BET may serve as a prognostic marker for pulmonary decline. These findings also support a pathogenic role for GER in IPF disease progression, suggesting the possible benefits of anti-reflux therapies in this challenging population. GER testing should be considered in the routine care of IPF patients to help optimize outcomes.

25 | Characterization of anorectal manometry of children with attention deficit hyperactivity disorder (ADHD)

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Introduction: Attention-deficit hyperactivity disorder (ADHD) is a neurologic disorder characterized by hyperactivity and/or inattentiveness. Adult patients report more flatulence and less frequent stools than those without ADHD. We analyzed the GI manifestations in our pediatric ADHD population focusing on symptomatology, associated diagnoses, and relationship to anorectal manometry characteristics.

Methods: This is a retrospective analysis of a prospective study of patients aged 6-19 years old seen at our institution for evaluation of refractory constipation and fecal incontinence with high resolution anorectal manometry (ARM) between 2016-2018. Patients sedated for the procedure or with anorectal malformations were excluded. Prior to the ARM, patients filled out questionnaires assessing presenting symptoms, sensory disorders, family confirmation of the ADHD diagnosis and identified sub-types of ADHD. Manometry was performed and interpreted by the same provider prior to review of questionnaire results.

Results: 62 patients (16 with ADHD, 46 without ADHD) (75 patients evaluated, 13 excluded) filled out questionnaires and had a non-sedated anorectal manometry. ADHD patients more often presented with fecal incontinence than those without (33%, 11% P = 0.049), had multiple stools per day (57%, 9% P =<0.0001) and an additional diagnosis of a sensory integration disorder (SID) (14%, 1.6% P = 0.02). ADHD patients more frequently reported sensitivities to food texture (38%, 13% P = 0.01), clothing texture (33%, 1% P = 0.001), and sounds (43%, 8% P = 0.0002). There was no difference in maximum resting or squeezing anal sphincter pressure between patients in these two groups nor each individual sub-type of ADHD. Sensation thresholds of the sub-types showed that patients with both inattentive and hyperactivity had a higher first sensation threshold than those without ADHD (184 mL, ADHD n = 5, 92.6 mL, nl, n = 87, P = 0.025). Although not statistically different, all ADHD patients had a smaller sensation differential between the first and urge sensations compared to normal patients (31 mL, 45.6 mL P = 0.25).

Discussion: This is the first study to characterize anorectal manometry findings in pediatric patients with ADHD. These patients present more frequently with fecal incontinence and those with the combined subtype may have an increased initial sensation threshold. The increased presence of SID and other sensitivities in ADHD patients suggest that issues with processing sensory input may be contributing.

26 | Clinical characteristics, trends and outcomes in inpatient pediatric cyclic vomiting syndrome in the USA

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Introduction: Cyclic Vomiting Syndrome (CVS) is an idiopathic disorder characterized by recurrent, stereotypical bouts of vomiting with intervening periods of normal health. However, the epidemiological impact in the inpatient pediatric setting has yet to be characterized. The Kid's Inpatient Database (KID), part of the Healthcare Cost and Utilization Project (HCUP), is a set of U.S. pediatric hospital inpatient databases where data is based on discharge billing abstracts created by hospitals. Using this database, we characterized the clinical and financial burden of this diagnosis in the inpatient pediatric population.

Methods: This is a cross-sectional analysis using the KID database where pediatric patients (between 1 and 18 years of age) between the years of 1997-2012 were identified as being hospitalized for CVS using the ICD-9 code 536.2. Using a multivariate logistic regression model, we analyzed patient demographics, costs, length of stay, as well as identifying trends of these CVS hospitalizations during this 15-year period.

Results: From 1997 to 2012, there were 9650 pediatric patients reported in KID who were admitted with the diagnosis of cyclic vomiting syndrome, 56.1% were female. The average cost per hospitalization increased from $7392.58 to $18358 ($P$ =<0.0001) and total yearly cost from $17,545,991 to $47,398,491 ($P$ =<0.0001). The frequency of CVS hospitalization per 10,000 patients has increased from 19.7 to 23.3 (P = 0.1253), and the average length of stay from 2.8 days to 3.0 days (P = 0.2088). Using adjusted odds ratios, females had increased odds of being admitted with CVS compared to males, aOR 1.31 (P =<0.0001), but there was no difference between age groups, ethnicities, insurance type, type of hospital (size and academic standing) or the geographical region of the hospital. Compared to healthy controls, CVS patients had increased odds of having additional diagnoses of gastroparesis (aOR 27.18, P =<0.0001), GERD (aOR 18.85, P =<0.0001), dysautonomia (aOR 9.83, P = 0.0006), migraines (aOR 6.48, P =<0.0001), Irritable Bowel Syndrome (aOR 6.28, P =<0.0001), anxiety (aOR 3.39, P =<0.0001), and use cannabis (aOR 1.85, P = 0.0009).

Discussion: This is the first study to characterize pediatric hospitalizations for cyclic vomiting syndrome in the USA. We also show the increasing financial burden of this population despite no statistical change in length of stay and hospital admission rates.

27 | Demographics and associated diagnoses of readmission of pediatric cyclic vomiting syndrome hospitalizations in the USA

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Introduction: Recurrent bouts of vomiting with intervening periods of normal health are characteristic of Cyclic Vomiting Syndrome (CVS). The National Readmission Database (NDS), part of the Healthcare Cost and Utilization Project (HCUP), is a US hospital database where data of discharged patients contain patient identifiers to track longitudinal care. We evaluated the trends and factors associated with pediatric inpatient readmissions for CVS within 1 and 3 months of the initial hospitalization.

Methods: Using the NDS, CVS hospitalizations were identified with the ICD-9 code 536.2 within the first nine months of each year between 2010-2014, allowing up to 3 month follow up. Factors associated with readmissions within 1 month and 3 months were analyzed with a multivariate logistic regression model.

Results: From January 1st to September 30th, in years 2010-2014, there were 3,017 pediatric patients (under 17 yo) who were hospitalized with CVS, 52% were female. The frequency of readmissions, length of stay, cost of each hospitalization and total cost of CVS readmissions had no statistical change between 2010 to 2014. Patients readmitted with a primary diagnosis of CVS within 1 and 3 months after their initial hospitalization more often came from large metropolitan areas (70.5% 1 mo, 69.4% 3 mo) and from the wealthiest income quartile (28.6% 1 mo, 27% 3 mo) compared to CVS patients who were readmitted with a different primary diagnosis (56.8% 1 mo, P =<0.0001, 55% 3 mo, P =<0.0001)(20.7% 1 mo P = 0.012, 20.1% 3 mo, P = 0.004). Patients readmitted with primary diagnosis of CVS more commonly had associated diagnoses of migraines (8.8% to 4% P = 0.04) and anxieties (12.5% to 8.6% P = 0.02) when admitted within 1 month and migraines (9% to 5.7% P = 0.006) and dysautonomia (0.8% to 0.2% P = 0.02) within 3 months of their initial hospitalization. Patients who were readmitted within both 1 or 3 months had increased odds of having the additional diagnosis of suicide (aOR 6.05 1 mo P = 0.02, aOR 4.53 3 mo P = 0.0438); however, there was no difference between age groups, insurance type, or the geographical region of hospitalization.

Discussion: This is the first study that analyzes factors for CVS readmissions in the pediatric population. We show associated diagnoses of migraines, dysautonomia and anxieties may be helpful to identify CVS patients at risk for readmission in the future and that this population is at higher odds to be suicidal. Further investigation is necessary to identify other predictors and interventions to prevent readmission.

28 | Does anorectal manometric parameters predict which patients expel a water-filled balloon using a commercial stool device following a failed balloon expulsion test?

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Background: Anorectal Manometry (ARM) and Balloon Expulsion Testing (BET) are used to evaluate anal sphincter and rectal pressure and function. Recently, a commercial device, Squatty Potty® (SP) has been marketed as a medical tool able to assist defecation in constipated patients. There are limited data on ARM metrics relative to chronically constipated (CC) patients (pts) failing a BET using this device to simulate defecation.

Objective: (i) Explore the likelihood of expelling a 50 cc water-filled balloon (WFB) with the assistance of the SP relative to ARM and BET metrics. (ii) Determine if DD sub-type predicts expelling a 50 cc WFB using the SP.

Methods: Retrospective analysis of CC pts who underwent ARM and BET at a tertiary care center, Oct 2017 – Feb 2019. ARM metrics included: anal sphincter relaxation vs. paradoxical contraction during simulated defecation (SD) and BET (abnormal = inability to pass a 50 ml WFB in < 60 second). DD was defined as an abnormal sphincter response during SD and an abnormal BET. Pts who failed BET were given another 60 seconds to expel the WFB while using assistance of the original (7-inch) SP. Pts with previous back and orthopedic surgeries were excluded. Non-parametric chi-square was performed to assess proportion of failed BET vs. expelled BET using the SP relative to ARM and BET metrics. A *P*-value of < 0.05 was considered statistically significant.

Results: 809 CC pts underwent an ARM and BET. 194 CC pts failed the BET (24.0%). Demographics included: 75% female, 74% Caucasian, mean age of 50.3 (SD = 17.1; Range 18-86), and mean BMI of 27.5 (SD = 6.5). 83% (*n* = 161) of CC pts failed the subsequent BET using the SP and 17% (*n* = 33) passed the BET using the SP (*P* = <0.001). 57.8% (*n* = 114) of CC pts depicted an abnormal SD response during an ARM: 56.7% Type 1, 4.4% Type 2, 29.2% Type 3, and 9.7% Type 4. DD subtypes were significant for a failed BET using SP: Type 1 (83%; *P* =<0.001); Type 2 (100%); Type 3 (88%; *P* = <0.001); Type 4 (100%). [Table 1] 63% (*n* = 63) of DD classified pts failed the BET using SP vs. 21% (*n* = 17) expelled the BET using SP (*P* =<0.001).

Conclusions: The Squatty Potty® provides assistance for expelling stool in subset of constipated pts. The data delineate as constipation increases in complexity including coordination discordance the Squatty Potty® may have limitations assisting with defecation.

Dyssynergic Defecation Sub-Type	Normal BET using the SP	Abnormal BET using the SP	*P*-value
Type 1	17%	83%	*P*=<0.001
Type 2	0%	100%	NA
Type 3	12%	88%	*P*=<0.001
Type 4	0%	100%	NA

29 | Physiological responses to sacral nerve stimulation in rodent colon

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One in five people suffer from functional gastrointestinal and motility disorders (FGIMD). Despite the prevalence and severity of FGIMD, pharmaceutical interventions are largely unsuccessful and even impede gut motility. Sacral nerve stimulation (SNS) is an alternative treatment for motility disorders. SNS received FDA approval to treat fecal incontinence in 2011, and it has also been shown to relieve the symptoms of constipation. However, the pathways and mechanisms mediating the effects of SNS are poorly understood. For example, the SNS parameters used to treat fecal incontinence are identical to the parameters used to treat constipation. (Figures 1 and 2)

Our objective is to resolve the paradoxical effects of SNS on colonic motility by measuring physiological changes in the colon during SNS, including myoelectric activity in rats and waves of calcium activity in transgenic mice. We developed a flexible, multi-electrode array to measure surface potentials from the serosal surface of the colon in awake rats and quantified the effects of SNS on colonic contractions by measuring myoelectric events. Second, we used transgenic mice with calcium indicators expressed in smooth muscle fibers to characterize spatiotemporal patterns of muscle activity during SNS. SNS generated an increase in the frequency of colon contractions in awake rats (Fig. 1), and this effect was occluded by injection of lidocaine into the sacrum. Similarly, in mice we observed spontaneous calcium waves and characterized them as propulsive or non-propulsive, and anterograde or retrograde (Fig. 2). SNS increased the contraction frequency and modulated the properties of contractions in rodents.

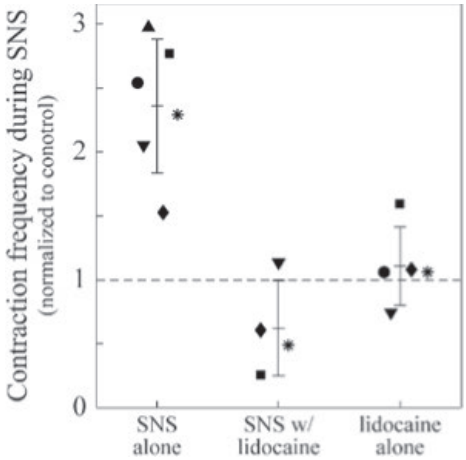

Fig. 1. Contraction frequency during SNS in awake rats (n ≥4).

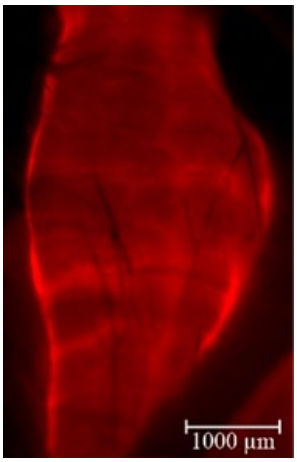

Fig. 2. Calcium waves in the mouse colon.

30 | A novel in vivo model of colonic aganglionosis using diphtheria toxin-mediated ablation of the enteric nervous system

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Hirschsprung disease (HSCR) is a congenital disorder characterized by incomplete colonization of the intestine by neural crest cells, leaving the distal colon aganglionic. Although surgical removal of the aganglionic bowel during early childhood is life-saving, at least 50% of children experience significant intestinal morbidity that persists into adulthood. Innovative cell-based or drug therapies are needed to treat HSCR. Testing new therapies has been significantly hampered by poor survival of existing mouse models of HSCR, which die within the first few weeks of life. An animal model of HSCR that can be utilized for long-term follow-up after experimental therapy is lacking.

We developed a novel model of colonic aganglionosis by crossing Wnt1-Cre mice with R26R-iDTR reporter mice, thus generating a Wnt1-iDTR transgenic line in which active Cre recombination renders Wnt1-expressing neural crest cells sensitive to diphtheria toxin (DT). Intraperitoneal injection of 40 µg/kg DT resulted in loss of myenteric neurons and enhanced expression of apoptotic marker, caspase-3, in the colon of Wnt1-iDTR mice but not control mice lacking DT receptor. Although we could ablate the ENS following i.p. DT administration, mice only survived an average of 2 days due to ubiquitous expression of *Wnt1* in all neural crest-derived cells. To limit neural crest cell injury to a focal region, we injected 4 µl of 1 ng/µl DT into the colon wall of these mice via laparotomy. This resulted in focal loss of ENS that was maintained up to 3 months, as confirmed by absence of neuronal markers, Hu and Tuj1, and glial marker, S100β, in the myenteric plexus, without any obvious loss of smooth muscle cells or interstitial cells of Cajal. Histological analysis revealed an increase in longitudinal muscle thickness by 111%, muscularis mucosa by 41% and villus height by 16% following focal ENS ablation. Moreover, focal loss of ENS did not alter solid or liquid gastrointestinal transit time or colonic contractility and did not produce a megacolon phenotype, resulting in markedly improved survival in this model of focal colonic aganglionosis as compared to other transgenic HSCR animal models. Thus, we have successfully generated a novel, non-lethal, and highly specific mouse model of colonic aganglionosis that can be utilized to assess therapeutic strategies for the treatment of neurointestinal disease.

31 | Abnormal enteric innervation and altered gut motility may contribute to post pull-through morbidity in Hirschsprung disease

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Purpose: Hirschsprung disease (HSCR), a congenital colorectal disorder which affects 1 in 5000 newborns, is characterized by failure of enteric neural crest-derived cells (ENCDCs) to colonize the entire GI tract. Surgical removal of aganglionic distal bowel is a life-saving treatment, however, GI motility disorders commonly persist postoperatively in at least 50% patients. The broad objective of this study was to test the hypothesis that abnormalities of the proximal ganglionated intestine contribute to continuing intestinal morbidity post pull-through surgery.

Methods: Using *Ednrb*$^{-/-}$ mice, a model of HSCR, immunohistochemical analysis was performed to evaluate myenteric neuronal density in stomach, small intestine, and proximal colon. Gastric emptying was measured *in vivo* and small and large bowel contractility was assessed by spatiotemporal mapping *ex vivo*. Ca^{2+} activity was evaluated in ENCDCs isolated from *Wnt1*^{GCaMP5tdTomato}; *Ednrb*$^{-/-}$ mice.

Results: Stomach preparations of HSCR mice had decreased neuronal fiber density and more densely packed neurons in the ganglia, along

with enhanced gastric emptying as compared to Ednrb$^{+/+}$ littermate controls. In the distal small intestine, a similar trend was observed in the neuronal fiber density and packing of neurons within the myenteric ganglia. Additionally, small intestine of HSCR mice had significantly smaller number of ganglia than controls. Interestingly, small intestinal ENCDCs of HSCR and control mice showed an equivalent calcium response to ACh, 5-HT, and ATP, and spatiotemporal mapping did not reveal any difference in the frequency and amplitude of contractions. In the proximal colon, there was a decrease in the density of neuronal cell bodies with no difference in neuronal fiber density in HSCR mice. Neuronal packing in the ganglia was similar between the two groups. HSCR mice had remarkably smaller ganglia in the proximal colon. In conjunction with these morphometric changes, spatiotemporal analysis of proximal colon of HSCR revealed significantly smaller number of colonic migrating motor complexes.

Conclusions: Abnormalities of neuronal density and motility are present in the ganglionated GI tract of mice with HSCR. These defects may contribute to the postoperative dysmotility observed following pull-through surgery in HSCR.

32 | Multichannel electrogastrography distinguishes gastric slow wave spatiotemporal parameter differences in pediatric chronic nausea

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Introduction: Functional nausea is a widespread chronic disease in adolescents that requires careful clinical assessment and individualized treatment plans. A quick, noninvasive method for characterizing gastric electrical dysrhythmias has the potential to provide quantitative assessments of chronic nausea. In this preliminary study, we hypothesize that spatiotemporal slow wave parameters in high resolution electrogastrograms (HR-EGG) discriminate symptomatic pediatric chronic nausea patients from healthy pediatric controls.

Methods: We studied ten pediatric patients (age 8-17 yrs) with chronic functional nausea using HR-EGG consisting of 25 electrode channels in a 5x5 square grid centered between the xiphoid and umbilicus. Patients were studied after obtaining their level of nausea on an adapted 10-point BARF (Baxter Retching Faces) scale in the postprandial phase. We compared results from patients with BARF scores between 2 and 8 with ten healthy pediatric controls. We used a Second Order Blind Identification (SOBI) algorithm to identify gastric sources and reduce signal artifact from confounding signals in their EGG. The reconstructed gastric SOBI-EGG components were used calculate dominant frequency and percentage power distribution, identify propagation patterns, and compute propagation velocity.

Results: We found a significant difference in postprandial dominant frequencies between pediatric chronic nausea patients and pediatric controls ($P < 0.05$). Patients had a lower percentage of normogastric frequencies (49 ± 2% vs 65 ± 2%, $P < 0.0001$) and higher brady- (25 ± 2% vs 17 ± 1%, $P < 0.01$) and tachygastric (26 ± 2% vs 18 ± 1%, $P < 0.001$) post-prandial frequency content, indicative of gastric uncoupling. Propagation patterns in healthy pediatric controls were mostly anterograde, with an average propagation velocity of 9.3 ± 1.3 mm/s. Chronic nausea patients exhibit a variety of abnormalities in the propagation maps. Though the predominant pattern observed was retrograde, we also observed static, circular and anterograde patterns in some subjects, with a significant difference in propagation velocity (P <0.0001).

Conclusion: Spatiotemporal gastric slow wave parameters obtained from high resolution EGG distinguish symptomatic chronic nausea patients from controls. Future studies should correlate the level of nausea with degree of slow wave spatiotemporal coupling in pediatric chronic nausea patients.

33 | Effect of secretin on gastric accommodation, emptying, and symptoms in health: A randomized, controlled, cross-over trial

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Objective: Functional dyspepsia is a common cause of morbidity and is estimated to affect over 30 million Americans annually. Previous studies found the pathophysiology of functional dyspepsia could partially be explained by altered gastric accommodation (GA) or gastric emptying (GE). Secretin is an upper gastrointestinal hormone secreted postprandially. The aim of our study was to determine the effects of secretin in human gastric motor functions and satiation.

Methods: We conducted a double-blind, randomized, placebo-controlled, cross-over trial in 10 healthy participants randomized to IV secretin or normal saline with a 1-4 week washout period. GA was measured by validated ^{99m}Tc-single photon emission computed tomography with standardized 300 mL Ensure® meal, radiolabeled with ^{111}In. GE was measured via scintigraphy of the radiolabeled meal. A nutrient drink test was performed to measure volume to fullness and maximum tolerated volume and symptoms on a 100 mm Visualized Analog Scale. Comparisons were by Wilcoxon Signed-Rank Test.

Results: Participants' median age was 45.0 years (IQR: 38.0, 49.0) and 80% were female. Baseline fasting gastric volume was not statistically different between treatment days ($P = 0.85$). Detailed results are shown in the table. Secretin delayed GE at 30 minutes ($P = 0.0039$) and reduced abdominal pain 30 minutes after maximum tolerated volume [10.5 mm (2.0, 18.0) vs. 19.5 mm (12.0, 38.0), $P = 0.0078$]. GA ratio (fed/fasting volumes), volume to fullness, maximum tolerated volume, nausea, fullness, and bloating were not statistically significant between secretin and placebo.

Conclusions: Secretin delayed gastric emptying and reduced abdominal pain after a maximum tolerated volume of Ensure® compared

with placebo in healthy volunteers. The reduced abdominal pain suggests that further studies are warranted in patients with functional dyspepsia.

Gastric Motor Testing and Nutrient Drink Test		Secretin	Placebo	*P*-value
Gastric Accommodation	*GA ratio (fed/fasting)*	3.4 [2.4, 3.6]	2.8 [2.1, 3.3]	0.7695
Gastric Emptying	*GE at 30 min. (%)*	10 [0, 10]	20 [20, 30]	0.0039
Nutrient Drink Test	*Volume to fullness (mL)*	892.5 [892.5, 1011.0]	951.8 [892.5, 1129.5]	0.2656
	Max. tolerated volume (mL)	1248.0 [1011.0, 1366.5]	1307.3 [1129.5, 1440.0]	0.1250

Median, [Q1, Q3], *P*-value calculated via Wilcoxon Signed-Rank Test; bolded *P*-value indicates statistical significance

34 | Abnormal reflux on combined hypopharyngeal-esophageal impedance-pH testing predicts poorer health-related quality of life in laryngopharyngeal reflux patients

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Background: Laryngopharyngeal reflux (LPR) symptoms are often more chronic and respond less robustly to treatment than typical esophageal symptoms. Health-related quality of life (HR-QOL) has been shown to be impaired in patients with suspected LPR symptoms. However, the relationship between patient-reported outcomes and objective measures of reflux in the LPR population remains unclear. We aimed to examine the association between objective reflux metrics on combined hypopharyngeal-esophageal impedance-pH testing (HEMII-pH) and (1) HR-QOL and (2) symptom severity in patients with suspected LPR symptoms.

Methods: Adults with suspected LPR referred for HEMII-pH at a tertiary care center from 4/2015 to 10/2018 were included. Validated symptom surveys were prospectively collected at time of HEMII-pH, including Gastroesophageal Reflux Disease Questionnaire (GERD-Q) and Short Form-12 (SF-12), for generation of physical (PCS) and mental (MCS) health composite scores for HR-QOL. Univariate and multivariate analyses were performed using Pearson correlation and general linear regression, respectively.

Results: 212 patients (35% male, mean age 56.5 years) were included. PCS significantly correlated with total reflux episodes (R^2=-0.46, P = 0.0020), proximal reflux episodes (R^2=-0.41, P = 0.0059), and pharyngeal reflux events (R^2=-0.33, P = 0.0326). The PCS was ~1.5 standard deviation lower in patients with abnormal pharyngeal reflux (>2 episodes) compared to those with normal pharyngeal reflux (57 vs 76.5, P = 0.05). On separate multivariate logistic regression models constructed adjusting for the same confounders (age, male gender, body mass index, smoking status, and presence of ineffective esophageal motility), PCS remained independently associated with total reflux episodes (β=-0.37, P = 0.023), proximal reflux episodes (β=-0.69, P = 0.04), and pharyngeal events (β=-1.80, P = 0.03). The GERD-Q regurgitation and medication use subscores significantly correlated with pharyngeal events (R^2=0.29, P = 0.047; R^2=0.34, P = 0.02 respectively), while the GERD-Q nausea subscore was associated with distal nocturnal baseline impedance (R^2=-0.35, P = 0.02) with a trend towards correlation with total reflux episodes (R^2=0.28, P = 0.06).

Conclusion: Increased pharyngeal reflux events as measured on HEMII-pH in patients with LPR symptoms are predictive of poor health-related quality of life and more severe symptoms. HEMII-pH should be considered in the evaluation of patients with suspected LPR symptoms to help guide management.

35 | Proton pump inhibitor therapy reduces risk of repeat ablation for atrial fibrillation in patients with gastroesophageal reflux disease

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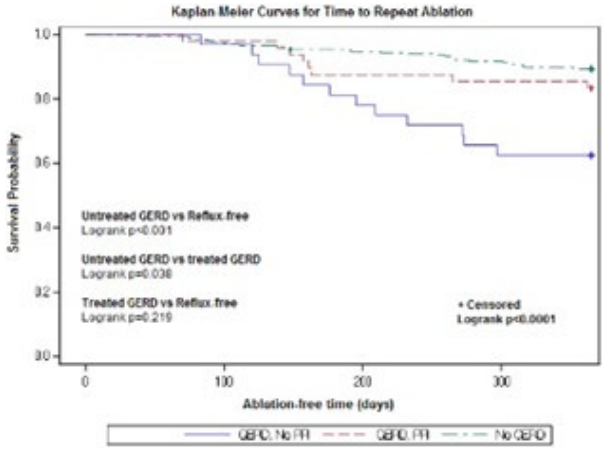
Background: GERD has been associated with atrial fibrillation (AF), likely due to vagally-mediated stimulation and anatomic proximity of the esophagus to left atrium. Prior studies suggest that patients with GERD may have higher AF recurrence after catheter ablation. The impact of PPI therapy for GERD on AF ablation outcomes remains unclear. We aimed to evaluate the risk for repeat AF catheter ablation within 1 year of initial therapy, stratified by GERD diagnosis and PPI treatment.

Methods: This was a retrospective study of paroxysmal or persistent AF patients who underwent initial catheter ablation at a tertiary center from 1/2011 to 9/2015. GERD was defined clinically or by reflux testing/endoscopy. GERD patients were further divided into untreated vs treated with PPI following ablation. Fisher's exact test was performed for univariate and logistic regression for multivariate analyses. Time-to-event analyses for repeat ablation were performed using Kaplan-Meier and Cox proportional hazards model, with censoring at last clinic follow-up. No deaths occurred within 1 year of initial ablation.

Results: 381 subjects (69% male, 61.2 years) were included, with 54 (14.2%) requiring repeat ablation within 1 year. Patients with GERD had higher 1-year repeat ablation rate than those without (25% vs 11.3%, $P = 0.0034$). When stratified by PPI therapy, untreated GERD subjects (37.5%) more likely required repeat ablation than reflux-free (11.3%, $P = 0.0003$) and treated GERD (16.7%, $P = 0.035$) subjects. On logistic regression, untreated GERD remained an independent predictor for repeat ablation (OR 4.11, $P = 0.03$), but not treated GERD. On time-to-event analyses, untreated GERD was associated with earlier repeat ablation versus no reflux (HR 4.1, $P < 0.0001$) and treated GERD (HR 2.53, $P = 0.04$) (Figure). On Cox regression, untreated GERD independently predicted early repeat ablation compared to no reflux (HR 3.76, $P = 0.0018$). No difference in repeat ablation risk was noted between reflux-free and treated GERD groups.



Conclusion: GERD was an independent risk factor for repeat catheter ablation for AF within 1 year of treatment. PPI therapy appeared to modulate this risk, as repeat ablation-free survival for treated GERD patients was non-inferior to reflux-free patients. These findings suggest that assessment for and aggressive therapy of GERD should be considered in the management of recurrent and refractory AF.

36 | Postreflux swallow-induced peristaltic wave index (PSPW) independently correlates with symptoms in laryngopharyngeal reflux patients

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Background: LPR is a challenging diagnosis due to its variable symptoms and lack of a well-validated diagnostic test. The role of PSPW index, a novel measure of esophageal chemical reflux clearance, in evaluating LPR is unclear. We aimed to assess the value of PSPW Index on combined hypopharyngeal-esophageal multichannel intraluminal impedance and pH testing (HEMII-pH) in predicting LPR symptoms.

Methods: 212 adults (35% male, 56.5 years) with suspected LPR referred for HEMII-pH at a tertiary center were included. Validated symptom surveys were prospectively collected at time of testing, including Voice Handicap Index (VHI), Reflux Symptom Index (RSI), Gastroesophageal Reflux Disease Questionnaire (GERD-Q), and reflux frequency and severity scores. PSPW was defined on HEMII-pH as a peristaltic swallow propagating the full length of the esophagus within 30 seconds of an impedance reflux event. PSPW index was the proportion of impedance reflux episodes associated with a PSPW (normal > 50%). Pearson correlation and student's t-test (univariate) and general linear regression (multivariate) were used.

Results: PSPW index inversely correlated with regurgitation frequency (R^2 -0.31, $P = 0.046$) and severity (R^2 -0.36, $P = 0.021$), GERD-Q regurgitation subscore (R^2 -0.38, $P = 0.009$), and RSI excess throat mucous subscore (R^2 -0.34, $P = 0.02$). When dichotomized, abnormal PSPW index was significantly associated with increased scores for regurgitation frequency and severity, and subscores for GERD-Q regurgitation, RSI excess throat mucous, and RSI heartburn. Regurgitation frequency (R^2 0.42, $P = 0.005$), severity (R^2 0.38, $P = 0.01$), and GERD-Q subscores (R^2 0.3, $P = 0.04$) were also positively correlated with excess throat mucous. Patients with abnormal PSPW index more likely had abnormal total GERD-Q (>8) (22.2% vs 0%, $P = 0.016$). On multivariate analysis, regurgitation frequency (β=-0.79, $P = 0.03$), severity (β=-1.04, $P = 0.009$), and GERD-Q subscores (β=-0.91, $P = 0.005$) remained associated with PSPW index after controlling for age, gender, smoking, pharyngeal reflux (HEMII-pH), and presence of ineffective esophageal motility.

Conclusion: PSPW Index independently predicts worse symptoms in LPR patients, particularly regurgitation and excess throat mucous. Poor esophageal chemical clearance may increase the chances of refluxate reaching the pharynx, resulting in extraesophageal symptoms, such as sensation of regurgitant or mucous reaching the throat. This novel metric may provide adjunctive diagnostic value in evaluating LPR.

37 | Tradipitant, a novel NK-1 receptor antagonist, significantly improved nausea and other symptoms of gastroparesis in a phase II trial

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Background: A phase II multicenter, randomized, double-blind, placebo-controlled trial with gastroparesis subjects demonstrating delayed gastric emptying and moderate to severe nausea were randomized to receive oral 85 mg tradipitant bid or placebo (1:1) for four weeks. Of the 152 patients, 60% of patients had idiopathic and 40% had diabetic gastroparesis.

Methods: The primary outcome was change in average nausea score from baseline, measured using the 5-point Gastroparesis Core Symptom Daily Diary (GCSDD). Overall gastroparesis symptoms were evaluated using the Gastroparesis Cardinal Symptom Index (GCSI), and Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM).

Results: A statistically significant and clinically meaningful improvement in nausea and overall gastroparesis symptoms was observed in patients on tradipitant. Subjects receiving tradipitant had a significant decrease in their average nausea score compared to placebo with LS mean difference (95% CI) of -0.53 (-0.92, -0.13, P = 0.0099) as well as a significant increase in nausea free days (28.8% increase on tradipitant compared to 15.0% increase on placebo, P = 0.0160). A clinically meaningful response of 1-point or more improvement on the GCSI total score was observed in 46.0% of patients on tradipitant compared to 24.2% of patients on placebo.

Conclusions: Tradipitant treatment resulted in statistically and clinically meaningful improvements in nausea and overall gastroparesis symptoms. Tradipitant was well tolerated with comparable rates of adverse events between tradipitant and placebo groups. These robust efficacy results suggest tradipitant has the potential to become a first line pharmacological treatment for gastroparesis.

38 | Tradipitant, a novel nk-1 receptor antagonist, significantly improved nausea in both diabetic and idiopathic gastroparesis

J. L. Carlin; M. S. Keefe; V. R. Lieberman; A. Dahal; C. Xiao; G. Birznieks; M. H. Polymeropoulos

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Background: A mixed population of gastroparesis patients was enrolled into a phase 2 multicenter, randomized, placebo-controlled trial. In this study, we hypothesized that tradipitant, a novel NK1-R antagonist, would effectively reduce nausea in patients with diabetic or idiopathic gastroparesis.

Methods: Diabetic and idiopathic gastroparesis subjects with delayed gastric emptying and moderate to severe nausea were randomized to oral 85 mg tradipitant bid or placebo (1:1) for four weeks. Change in nausea from Baseline to Day 28 was assessed using the 5-point Gastroparesis Core Symptom Daily Diary (GCSDD).

Results: Patients with diabetic gastroparesis (DG, n = 55/141, 39.1%) or patients with idiopathic gastroparesis (IG, n = 86/141, 60.9%) were randomized to tradipitant or placebo. The baseline nausea severity was similar between diabetic gastroparesis (3.0 + /- 0.77) and idiopathic gastroparesis (3.3 + /- 0.83) groups. The change in nausea severity score in patients with diabetic gastroparesis was -0.32 (-0.96, 0.31; P = 0.3084) between tradipitant and placebo. The change in nausea severity score in patients idiopathic gastroparesis was -0.61 (-1.14, -0.08; P = 0.0253).

Conclusions: Both idiopathic and diabetic gastroparesis patient populations improved their nausea score with tradipitant and had a similar placebo effect. Statistical significance was observed in the idiopathic gastroparesis group, which was the larger population. These robust efficacy results suggest tradipitant has the potential to become a first line pharmacological treatment for both diabetic and idiopathic gastroparesis.

39 | Clinical efficacy of per-oral endoscopic myotomy (POEM) for spastic esophageal disorders - a systematic review and meta-analysis

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Background: POEM has been successfully performed in patients with spastic esophageal disorders (SED), such as diffuse esophageal spasm, jackhammer esophagus & type 3 achalasia. We performed a systematic review and meta-analysis to evaluate its efficacy in these patients and if total average myotomy length and prior medical or endoscopic treatments affected clinical success.

Methods: PubMed, EMBASE, Google-Scholar, Scopus and Cochrane Review were searched for studies on POEM in SED from 2008 to September 2018. Clinical success was determined by Eckardt score (≤3) at follow up. Sub-group analysis was performed based on myotomy length and evaluate the effect of prior treatments on clinical success.

Results: 9 studies with 210 patients were included in the final analysis. We found that the pooled rate of clinical success for POEM was 89.6% (95% CI 83.5-93.1, 95% PI 83.4-93.7, I2 = 0%). In 3 studies (50 patients), where total myotomy length was < 10 cm, the pooled rate of clinical success was 91.1% (95% CI 79.5-96.4, I2 = 0%). In 6 studies (160 patients), the length was > 10 cms and the pooled rate of clinical success was 89.1% (95% CI 83.0-93.2, I2 = 0%). The difference between these results was not statistically significant (P = 0.69). Additionally, a meta-regression analysis showed that prior treatment status did not significantly affect the primary outcome (P = 0.43).

Conclusions: While it is well known that POEM is a safe and effective treatment for spastic esophageal disorders, we conclude that variation in total myotomy length and prior endoscopic or medical treatments did not have a significant effect on clinical success.

40 | Real-world evaluation of economic burden for diabetic gastroparesis in the US

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Objectives: Diabetic gastroparesis (DG) is characterized by poor glucose control, suboptimal nutritional and hydration status, greater risk of complications, and frequent need for hospitalization. However, economic burden of DG is not well understood. This study's objective was to quantify the economic burden associated with DG compared to diabetic (DM) patients without gastroparesis (GP) in the US.

Methods: A retrospective cohort study was conducted using a large claims database (Optum Research Database). The DG cohort included diabetic patients who had their first GP diagnosis during 2008-2016 (index period) with at least 2 separate GP diagnosis claims or 1 GP diagnosis claim after a scintigraphy test; aged 18 + years at index, continuously enrolled for at least 1 year before (baseline) and 1 year after the index, and with no GP claim at baseline. These DG patients were matched 1:1 to DM patients who did not have GP diagnosis (DM control cohort) via propensity scores based on baseline demographic (e.g. age, sex, region) and clinical (e.g. index year, comorbidities) characteristics. Healthcare resource utilization (HRU; i.e. encounters to hospital inpatient, emergency room [ER], outpatient/physician office [OP], pharmacy, and other settings) and associated costs were assessed. Average annual total costs (medical plus pharmacy) were compared between cohorts using t-tests. Costs are all-cause and in 2017 US dollars.

Results: Data from 31,610 patients (15,805 per cohort) were analyzed. The newly diagnosed DG patients were at a mean age of 62 years, 66% female, 59% insured by Medicare; at 1-year baseline, average (SD) Charlson Comorbidity Index score was 3.7 (2.4), and 47% had chronic diabetic complications (DM controls similar through matching). Compared to DM controls, DG patients had significantly higher annual costs across all HRU types: inpatient $22,679 vs. $9,992, ER $2,012 vs. $937, OP $25,078 vs. $16,156, pharmacy $8,473 vs. $5,907, other services (e.g. lab tests) $7,145 vs. $4,078 (all $P < 0.0001$). On average, incremental annual total costs per DG patient were $28,318 more than the matched DM control. Hospitalization accounted for major difference between the cohorts: 40.4% of DGs vs. 28.1% of DM controls had hospitalization in 1-year pre-index, and 50.7% vs. 22.3% in 1-year post-index.

Conclusions: This large database study found that, gastroparesis significantly increases the economic burden of diabetes. Onset of diabetic gastroparesis is associated with higher spending in all service categories, with the cost differences driven by hospitalizations.

41 | Enteric glial MHC II contributes to T-lymphocyte activation in LPS stimulation

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Introduction: Enteric glia contribute to the regulation of physiological gut reflexes and to neuroinflammation in disease. How glia contribute to gut inflammation through immune cells is poorly understood. Enteric glia express major histocompatibility class II (MHC II) during various forms of intestinal inflammation in mice and humans. Therefore, we hypothesize that antigen presentation by enteric glia contributes to a pro-inflammatory environment during inflammatory insult.

Methods: We tested our hypothesis by generating mice with a targeted ablation of MHC II in glia (Sox10CreERT2::IABfl/fl). Animals were injected (i.p.) with 1 µg interferon-gamma (IFNg) and 300 µg/kg lipopolysaccharide (LPS) or saline control and harvested 16 hours later. Glial MHC II expression was measured by gene expression and immunofluorescence. T-lymphocyte activation was assessed by flow cytometric measurement of CD69 expression on mesenteric lymph node isolated CD4 + cells. Glial specific changes to inflammatory stimuli were measured by microarray, and overall immune activation was assessed by bead-based multiplex quantification of serum and colonic tissue cytokine levels.

Results: By immunofluorescence, wild-type animals injected with IFNg and LPS have a 1-fold increase ($P < 0.05$; two-way ANOVA) in MHC II expression compared to controls, and this effect is eliminated by glial MHC II ablation. Similarly, serum levels of the pro-inflammatory cytokine IL-17 significantly increase ($P < 0.005$; two-way ANOVA) in wild-type animals injected with IFNg and LPS. Glial ablation of MHC II causes a 0.5-fold decrease in serum IL-17 levels, but does not reach statistical significance. CXCL9 cytokine levels increase by 2-fold ($P < 0.05$; two-way ANOVA) in the distal colon of wild-type animals injected with IFNg and LPS, but not in glial MHC II knockout animals. Flow cytometry data show that wild-type animals treated with IFNg and LPS demonstrate a 0.63-fold increase ($P < 0.05$; two-way ANOVA) in CD4 + CD69 + cells. Glial MHC II ablation causes a 0.36-fold decrease ($P < 0.05$; two-way ANOVA) in CD69 expression within CD4 + cells and returns expression to baseline control levels, suggesting T-lymphocyte activation as a potential cause in changes in tissue and serum cytokine levels.

Conclusion: Our results uncover an important mechanism of CD4 + T-lymphocyte activation regulated by enteric glial MHC II. These novel glial mechanisms of immune regulation could be important therapeutic targets for common GI diseases.

42 | Immunoreactivity for the Na^+/HCO_3^- cotransporter (NBCe1, Slc4a4) in pacemaker interstitial cells of cajal is selectively reduced by knocking down Slc4a4 gene expression using an ETV1-cre driver in mouse

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Background: Electrical slow wave activity, generated by interstitial cells of Cajal (ICC), is essential for efficient intestinal contractility. Normal electrical slow wave activity depends on the inclusion of bicarbonate (HCO_3^-) in the recording solutions. We previously reported that Na^+/ HCO_3^- cotransporter (NBCe1/Slc4a4) – immunoreactivity (IR) is enriched in pacemaker ICC of the small intestine (ICC-MY) and absent from ICC in the intestinal deep muscular plexus (ICC-DMP). Constitutive knockout of Slc4a4 is lethal to newborn mice. ETV1 (ETS-translocation variant 1) is a transcription factor specific for cells of the ICC lineage, Our **aim** was to target NBCe1 knockdown to ICC in the mouse gastrointestinal tract using ETV1 as Kit and Slc4a4 genes colocalize on mouse chromosome 5.

Methods: Slc4a4 fl/fl mice were bred with $ETV1^{CreERT2/-}$ mice to allow targeted, conditional knockout (KO) of Slc4a4 in ICC in response to tamoxifen treatment (130 mg/Kg). ICC were detected by labeling with a goat anti-Kit polyclonal antibody. The abundance of specific Slc4a4 transcripts was measured by immunolabeling for NBCe1-IR.

Results: As expected, NBCe1-IR was detected in the mucosal epithelium and mesothelial cells in the serosa in all regions of the GI tract as well as a subset of myenteric neurons. Strong labeling was also observed in Kit+ ICC responsible for generating electrical slow waves. NBCe1-IR was detected in ICC-MY but not ICC-IM of the gastric body and antrum, in ICC-MY but not ICC-DMP of the small intestine and in ICC-SMP but not ICC-MY of the colon. NBCe1-IR was significantly reduced in ICC-MY in small intestine of tamoxifen-treated $Slc4a4^{fl/fl}$,$ETV1^{CreERT2/+}$ mice. NBCe1-IR was not depleted in the mucosa or mesothelial cells of the intestinal serosa and unaffected in myenteric neurons of the proximal colon.

Conclusions: Slc4a4 is expressed in the subpopulation of ICC that generate electrical activity and ETV1 can be used to drive the targeted knockdown of Slc4a4 in intestinal ICC without affecting the expression of Slc4a4 in other cells that normally express this gene.

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43 | Upper gastrointestinal symptoms are related to the kind of alcoholic beverage

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Background: The relationship between Gastroesophageal Reflux Disease (GERD) and dyspeptic symptoms with alcohol consumption is well known; however, there is insufficient evidence of the association between specific symptoms according to the type of beverage ingested.

Methods: A prospective study was conducted in an open population from Mexicali, Mexico during 2017-2018. A face-to-face interview was performed capturing the prevalence of upper gastrointestinal symptoms according to ROMA IV criteria, graduating severity with a Likert scale. The analysis was performed using chi-squared test, as well as a logistic regression univariate and multivariate analysis.

Results: We evaluated 1504 subjects with the following demographics: Age 34 ± 5, male 56%; 63% reported active alcohol consumption, from which 67.5% had a mixed consumption pattern, 23.5% drink exclusively beer, 5.1% distilled beverages and 3.9% wine. Beer consumption was related to dysphagia OR = 0.326 (P = <0.001), regurgitation OR = 2.086 (P =<0.001), epigastric burning OR = 1.445 (P = 0.039), epigastric pain OR 0.190 (P = 0.002), early satiety OR = 1.420 (P = 0.025), empty stomach sensation OR = 1.651 (P = 0.004), postprandial fullness OR = 0.326 (P = 0.007), and bothersome hunger OR = 0.541 (P = 0.004). Distilled beverages consumption was related to early satiety OR 2.805 (P = 0.040) and postprandial fullness OR = 0.124 (P = 0.047). Wine consumption was related to regurgitation OR = 2.043 (P = <0.022) and epigastric pain OR = 2.145 (P =< 0.017)

Conclusion: Beer and wine consumers report a higher association with symptoms of visceral hypersensitivity and GERD. Postprandial distress syndrome has a strong relationship with consumption of distilled spirits suggesting an impact on gastric emptying. Further studies are needed to establish the relationship between these symptoms and the pathophysiological aspects in structural disease and brain-gut functional disorders.

44 | Characterization of esophageal motility in children with operated esophageal atresia using high resolution impedance manometry and pressure flow analysis

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Background: Esophageal dysmotility is common in patients with esophageal atresia (EA). High-resolution impedance manometry (HRIM) and Pressure Flow analysis (PFA) allow characterization of biomechanical bolus flow and swallow properties. The aim of this study was to characterize esophageal motility and bolus flow propulsion in children who underwent surgical EA repair.

Patients and methods: HRIM was used in 14 children with EA (type C, $n = 13$; type A, $n = 1$). Study was performed at a median (range) age of 11 years (5-17). The HRIM recordings were analyzed using conventional esophageal pressure topography and PFA (AIMplot software deployed via the open access Swallow Gateway application) and were compared with 13 patient controls (median age 14 years, range 5.75-17; P =NS vs patients) who underwent HRIM considered as normal according to Chicago classification and for whom the manometry results did not lead to treatment changes. Medical charts were reviewed for medical/surgical history and symptoms were assessed by standardized questionnaires.

Results: Esophageal peristaltic motor patterns were abnormal in all EA patients and were subdivided in 2 groups: Group A with presence of distal contraction in ≥ 50% of the swallows ($n = 6$) and Group B with presence of distal contractions in < 50% of the swallows ($n = 8$). IRP4s was similar in EA and controls. Bolus transport was impaired as shown by the higher impedance Ratio (IR) in EA than in controls (0.47 vs 0.22 $P < 0.001$). In Group A, proximal and distal contractile Integrals were lower than in controls ($P < 0.001$) and distal contractile velocity was shorter in EA ($P < 0.01$). IR was lower in Group A than in Group B ($P < 0.01$). In this sample, symptoms of dysphagia and presence of gastric metaplasia or esophagitis were not correlated with any of the measures determined.

Conclusions: Bolus transport as measured by impedance ratio is severely altered in EA patients but is not predictive of symptoms. The presence of residual distal contractions is associated with a more efficient bolus propulsion. Whether this is associated with a better outcome warrant further studies.

45 | Role of the endocannabinoid system in the regulation of intestinal barrier function: Effects of diet

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Introduction: The endocannabinoid system plays a role in regulating the neural control of ion transport and has been implicated in the control of intestinal barrier function. Increased endocannabinoid tone has been associated with a disruption in gut barrier function. However, whether the cannabinoid (CB)1 receptor is expressed on the intestinal epithelium and is involved in the acute regulation of intestinal barrier function has not been determined.

Methods: We examined the expression and function of the CB1 receptor in the jejunum and ileum of mice fed standard chow or high-fat diet (45% Kcal, HFD) for 2 and 12 weeks. We used immunohistochemistry to assess the localization of the CB1 receptor on the gastrointestinal epithelium and Ussing chambers to assess intestinal barrier function using 4000 Da-FITC-Dextran (FITC-D) as a marker of intestinal permeability. We used two structurally distinct CB1 agonists (AM841 [1 μM] and CP55,940 [100 nm]) and two CB1 antagonists (AM251 [1 μM] and AM6545 [1 μM]).

Results: The CB1 receptor was expressed on the enteric nerves of the submucosal and myenteric plexus in the jejunum and ileum, but there was no epithelial expression in mice fed standard chow. However, following 2 weeks of HFD feeding, the CB1 receptor was expressed on the intestinal epithelium in the ileum, but the epithelial expression was no longer present after 12 weeks of HFD feeding. The CB1 agonist AM841 and antagonist AM251 had no effect on permeability to FITC-D in the jejunum and ileum of mice fed standard chow. In mice fed HFD for 2 weeks, the CB1 agonists AM841 and CP55,940 did not affect permeability in the jejunum, but CP55,940 decreased permeability to FITC-D in the ileum. In contrast, the CB1 antagonists AM251 and AM6545 both decreased permeability to FITC-D in the jejunum but not in the ileum. In mice fed HFD for 12 weeks, the CB1 agonist AM841 decreased permeability to FITC-D in the jejunum, whereas both CB1 agonists (AM841 and CP55,940) decreased permeability in the ileum. The CB1 antagonists AM251 and AM6545 had no effect on permeability in the jejunum or ileum.

Conclusions: Taken together, this study suggests that the endocannabinoid system may have a role in the acute modulation of intestinal permeability in conditions where baseline permeability is perturbed such as in high-fat diet feeding, but not under physiological conditions. *Supported by CIHR and NSERC*.

46 | The efficacy of celiac plexus block as a non-invasive procedure in treating median arcuate ligament syndrome (MALS) patients

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Introduction: The median arcuate ligament syndrome (MALS) is a rare condition characterized by chronic abdominal pain, nausea, vomiting, and weight loss. The pathophysiological origin can be explained by the compression of the celiac nerve plexus causing compression of the proximal celiac trunk by the median arcuate ligament. Standard diagnosis can be obtained through mesenteric ultrasounds by evaluating arterial velocities. Various procedures have shown to improve symptoms including celiac plexus blocks, decompression and revascularization. The purpose of this study is to determine the relationship between celiac velocity during the expiration phase and MALS symptoms after celiac plexus blocks.

Method: By reviewing the data collected from The Heartbeat Clinic's electronic medical records, we performed a retrospective study on 36 patients (pts) that had undergone the celiac plexus block procedure from June 2014 to February 2019. Only 28 out of the 36 patients, had a Mesenteric Ultrasound both pre- and post- procedure that were analyzed for changes in expiration celiac velocity. These 28 patients' records were also analyzed for patient reports of any subsequent symptomatic changes; and were then divided into 2 groups based on the duration of MALS Symptoms relief being short term (< 6 weeks) or long term (> 6 weeks). The patients were also categorized based on Celiac Expiration Velocity (cm/sec) following the procedure.

Results: Of the 28 patients, 5 were males (age 32.42 $\pm$ 4.92) & 23 were females (age 24.63 $\pm$ 5.24). 24 pts reported MALS Symptom relief being short term (< 6 weeks) and 4 pts had reported MALS Symptoms relief being long term (> 6 weeks). Of the 24 pts, 21 pts recorded a significant decrease in Celiac Artery Velocity with a mean decrease of 84 cm/s $\pm$ 9.3. Only 4 pts reported no relief in symptoms and showed no significant changes in Celiac Artery Velocity.

Conclusion: Celiac plexus block provided significant symptom relief for MALS pts. There was a trend in the decrease of Celiac Artery Velocities and improvements of MALS symptoms.

47 | Pharyngeal and upper esophageal sphincter motor dynamics during normal swallow

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Background: Pharyngeal muscle contractions and upper esophageal sphincter (UES) relaxation play a major role during the pharyngeal phase of swallowing. Pharyngeal and UES motor function have been evaluated by high-resolution esophageal manometry (HREM) in healthy adults and infants. There are currently no published data on this in the pediatric age group.

Objective: To determine normative values for pharyngeal and UES metrics during swallow in children.

Method: We reviewed electronic medical records and HREM of children aged ≤ 18 years who had a normal videofluoroscopic swallow study (VFSS). UES metrics (integrated relaxation pressure [IRP], resting pressure [URP], nadir pressure [UNP]), and peak pharyngeal pressure (velopharyngeal [VPP] and meso-hypopharyngeal [MPP]), were collected.

Results: We reviewed the UES metrics in 121 patients; age ranged from 11 months to 18 years (mean 11.4 years) and 47.1% were male. The indications included: dysphagia (59.5%), vomiting/regurgitation (25.6%), nausea (4.1%) and others (10.8%). The median [interquartile range, IQR] of IRP 0.2 s, 0.4 s, 0.6 s, 0.8 s, URP and UNP were 1.00 [-2.00, 8.00], 4.00 [0.00, 10.50], 10.50 [5.00, 16.50], 17.50 [11.50, 26.50], 54.00 [42.00, 75.00] and -1.00 [-4.50, 5.00] mmHg, respectively. HREM from 42 patients (of the total 121) included the entire pharyngeal region. Within this group, age ranged from 11 months to 18 years (mean 8.9 years) and 57.1% were male. Indications included: dysphagia (54.7%), vomiting/regurgitation (28.6%), nausea (2.4%) and others (11.9%) The median [IQR] of peak VPP and MPP were 252.25 [174.88, 319.00] and 196.25 [143.63, 222.50] mmHg, respectively.

Summary: This is the largest study reporting UES metrics and pharyngeal pressure changes with swallow in children with normal VFSS. UES-IRP values were less than adults (no data in neonates), URP values were greater than preterm infants and less than adults, and UNP values were less than neonates and adults. The peak pharyngeal pressures were higher than neonates and adults. Our data indicate that there are differences in the motor dynamics of swallowing from the newborn period to adulthood and may reflect a maturational process. This data can be used to enhance the interpretation of high-resolution pharyngeal manometry, and help guide management, in children presenting with dysphagia or feeding disorders.

48 | Efficacy of probiotic I3.1 symptomatic improvement in patients with lactose intolerance

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Background: The modification of the intestinal microbiota has been sought in order to create conducive to the degradation and absorption of lactose by taking probiotics in patients with lactose intolerance. The mechanism of improvement with the intake is that the modification of colonic bacteria increases the activity of intraintestinal lactose.

Objective: Evaluate the symptomatic improvement in patients with lactose intolerance after eight weeks of treatment with probiotic I3.1 (*Lactobacillus plantarun* CECT7484, *Lactobacillus plantarum* CECT7485, *Pediococcus acidilactici* CECT7483).

Methods: Randomized, single-blind study in patients with significant manifestations of lactose intolerance. Age, sex, BMI, symptom severity and lactose hydrogen breath test (LHBT) were included. A questionnaire of symptoms before and after the LHBT was applied, which was performed using 25 g of lactose and measurements 10 minutes before administration, after 60, 120 and 180 minutes. Two groups were assigned randomly, one group received placebo and the second Probiotic for 8 weeks. Term follow-up questionnaire before and after symptoms LHBT was performed again. The analysis of the results will be done using the statistical program IBM® SPSS® Statistics® version 22.0.

Results: We studied 25 patients, 18 (72%) in group A (probiotic I3.1) and 7 (28%) in group B (placebo). The mean age of the studied population was 45.4 ± 14.8 years, BMI 26 ± 4.2 kg/m^2, of which 10 patients (40%) are men and 15 (60%) women. In patients of group A, the mean severity of symptoms pretreatment was 10.38 ± 2.0 and after treatment it was 4.94 ± 2.7 (*P* 0.001). In patients of group B, the mean severity of symptoms pretreatment was 10.5 ± 2.5 and after treatment it was 8.5 ± 3.01 (*P* 0.093). In both groups improvement of each of the evaluated symptoms was observed, being significant in the symptom of flatulence in group A. Symptomatic overall improvement between the two groups was significant (*P* 0.016). The results of the lactose breath test before and after treatment showed no significant differences in both groups. No adverse effects were reported during the treatment.

Conclusion: The results of the present study allow us to conclude that the probiotic I3.1 is safe and showed significant improvement in the symptom of flatulence and the overall symptomatic perception after provocation test with lactose, in patients with severe symptoms.

49 | Retrograde gastroesophageal intussusception despite fundoplication

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Retrograde gastroesophageal intussusception (RGEI) is a rare and not well described gastrointestinal disorder in which a portion of the gastric wall protrudes through the lower esophageal sphincter and diaphragmatic crura into the esophageal lumen. It is infrequently encountered in the clinical setting, but can present with dysphagia, chest pain, vomiting and occasionally, hematemesis[1]. Risk factors identified in case reports include severe vomiting such as with "eating disorders or alcohol abuse, sudden sustained exertion, small-bowel obstruction, acid bile peptic disease, pregnancy" and poor fixation of the stomach due to loose or long mesenteric attachments[2]. Most recently, case studies suggest myotomy as an additional risk factor[3,4]. We present a rare case of RGEI which illustrates fundoplication after myotomy does not eradicate the risk of RGEI.

A 27 year old woman with a medical history significant for achalasia who underwent laparoscopic Heller myotomy and Dor fundoplication three years prior, presented with severe chest pain for three days. She reported persistent regurgitation of undigested food and occasional small volume hematemesis for the past year. She initially underwent esophagogastroduodenoscopy (EGD) which showed a large mass in the distal esophagus. Due to findings, a subsequent computed tomography (CT) of her chest and abdomen was performed. This showed herniation of a large portion of stomach and some mesenteric fat into the lower chest. Imaging suggested gastroesophageal intussusception with incarceration at the level of her Dor fundoplication. She was taken immediately to surgery, where upon air insufflation into the peritoneum, the stomach appeared to have spontaneously reduced. Re-examination with EGD intra-operatively revealed a marked delineation along the greater curvature of an area of beefy red induration, consistent with a gastric wall that had recently intussuscepted. The fundoplication was taken down and gastropexy was performed. The patient was safely discharged on post-operative day 2 with improvement of symptoms.

Patients who are treated with myotomy for achalasia have the potential to develop a patulous lower esophageal sphincter, thus placing them at higher risk of RGEI. Our case illustrates fundoplication after myotomy does not eradicate the risk of RGEI.

50 | Enteric GLIA express the cytosolic DNA sensor sting

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Functional gastrointestinal motility disorders (FGID) are characterized by microbial dysbiosis, immune activation, and altered enteric nervous system (ENS) function. Enteric glia are ideally positioned to transduce immune and microbial cues to changes in nervous system function, but the roles of enteric glia in FGID are poorly known. Other populations of neuroglia express the cytosolic DNA sensor stimulator of interferon genes (STING), which responds to bacterial cyclic dinucleotide messengers. Based on this data, we *hypothesized that enteric glia express STING and that glial STING signaling contributes to enteric neuroinflammation*. We assessed STING expression using immunohistochemistry, STING activation in response to the cyclic dinucleotide c-di-GMP with ELISA, intestinal permeability to c-di-GMP in Ussing chambers, and assessed colonic damage in response to c-di-GMP *in vivo*. We selectively ablated STING in enteric glia using *Sox10*::$^{CreERT2+/-}$/STING$^{f/f}$ mice and assessed STING pathway expression using *Sox10*::$^{CreERT2+/-}$/*Rpl22*$^{+/-}$ mice. Our results show that myenteric glia express STING (n = 3 animals). The activation of glial STING with 100 μM c-di-GMP evoked the release IFNβ *in vitro*

($P < 0.01$, $n = 3$ animals/group). C-di-GMP passes the mucosal barrier of the distal colon ($P < 0.001$, $n = 4$ animals). I*n vivo* administration of 20 μM c-di-GMP via drinking water did not cause colonic macroscopic damage or alter bowel movements ($P > 0.05$, $n = 4$ animals/group), but did reduce mucosal thickness in H&E staining ($P < 0.05$, $n = 4$ animals). Further experiments involving the more potent STING activator cGAMP and glial STING-KO mice will help define the role of glial STING activation. Our findings show that enteric glia express STING and that bacterial cyclic dinucleotides including C-di-GMP could influence gut function through effects on enteric glia.

51 | Ameliorating effects of sacral nerve stimulation for visceral hypersensitivity and mechanisms involving nerve growth factor and TRPV1 in rats with irritable bowel syndrome

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Background: Visceral hypersensitivity has been widely considered a biological marker of irritable bowel syndrome (IBS). Sacral nerve stimulation (SNS) has been widely used in bladder dysfunctions, fecal incontinence, and also been used in pelvic pain and anal pain. This study was designed to investigate the effects and mechanisms of SNS for visceral hypersensitivity in a rodent model of IBS.

Methods: Ten-days-old pups were randomly divided into IBS ($N = 14$) and control($N = 6$) groups. Pups intra-rectally treated with 0.2 ml of 0.5% acetic acid (AA) and 0.2 ml saline. After 8 weeks, all of rats were implanted a pair of electrodes on right sacral nerve (S3) and another pair in the external oblique muscles for recording electromyogram (EMG). Anti-NGF (16 μg/kg) and SB366791 (TRPV1 antagonist, 1 mg/kg) was intraperitoneally injected. The IBS rats were randomly divided into an SNS group ($n = 7$, 1 hr daily, optimized parameters) and a Sham SNS ($n = 7$, 0 mA) to receive 7-day SNS. At the end, colon and DRG (L6-S2) were collected.

Results: 1) Visceral hypersensitivity was noticed in AA-induced IBS rats. EMG responses on CRD at 20, 40, 60, 80 mmHg in AA-treated rats were significantly higher than in control group ($P < 0.01$ vs. control). 2) Acute SNS improved visceral hypersensitivity in the IBS rats ($P< 0.01$ vs. IBS model). 3) Seven-day SNS also significantly ameliorated visceral hypersensitivity ($P < 0.01$ vs. Sham SNS). 4) Anti-NGF significantly reduced EMG responses at CRD 20, 40, 60 and 80 mmHg in comparison with vehicle session ($P < 0.01$ vs. vehicle), and the decreased EMG response was close to that in the control rats. TRPV1 antagonist also significantly reduced EMG responses at CRD 20, 40, 60 and 80 mmHg in comparison with vehicle session ($P < 0.01$ vs. vehicle). SNS decreased the protein expressions of NGF (colon: 1.83 ± 0.85 vs. 6.84 ± 2.88, $P = 0.03$, vs. sham-SNS; DRG: 0.95 ± 0.39 vs. 4.09 ± 1.36, $P = 0.006$, vs. sham-SNS) and TRPV1 (colon:2.18 ± 1.09 vs. 8.83 ± 3.15, $P < 0.001$, vs. sham-SNS; DRG: 2.17 ± 0.55 vs. 7.23 ± 3.81, $P = 0.003$, vs. sham-SNS).

Conclusions: Bother acute and chronic SNS with optimized parameters improved visceral hypersensitivity in AA-induced IBS model rats. The analgesic effect of SNS is mediated via the NGF/TRPV1 mechanisms.

52 | Sub-serosal interstitial cells of Cajal contribute to nitrergic innervation and influence the excitability of longitudinal smooth muscle in the mouse proximal colon

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The colon is composed of an electrically coupled syncytium of cells in which the contractile behaviors of smooth muscle cells (SMCs) are modified by enteric neurons and various classes of interstitial cells of Cajal (ICC). A class of ICC exists at the sub-serosa (ICC-SS) of the proximal colon, where they run parallel to longitudinal SMC bundles. Virtually nothing is currently known about the functions of ICC-SS, although like all classes of ICC they express the Ca^{2+}-activated Cl^- channel, Ano1, suggesting that their physiological functions rely on Ca^{2+} signaling. We investigated possible roles of ICC-SS with *in situ* Ca^{2+} imaging, using a mouse model that expresses a genetically encoded Ca^{2+} indicator (GCaMP6f) exclusively in ICC (GCaMP6f activated by an ICC specific inducible Cre recombinase, *Kit*iCre). ICC-SS exhibited stochastic intracellular Ca^{2+} signaling *in situ*, firing hundreds of Ca^{2+} transients min^{-1} from multiple intracellular sites. ICC-SS showed variability in spatial and temporal kinetics of Ca^{2+} transients and events in ICC-SS were not entrained with adjacent cells. Ca^{2+} transients were abolished by the SERCA pump inhibitor CPA (10 μM) and reduced by the phospholipase C (PLC) inhibitor U73122. Ca^{2+} transients were voltage independent as they were unaffected by the K_{ATP} channel agonist pinacidil (10 μM) and the Cav1.2 channel inhibitor nicardipine (1 μM). Ca^{2+} influx played a major role in generating ICC-SS Ca^{2+} transients as they were inhibited after 2 min incubation in Ca^{2+} free medium and dose dependently blocked by a store-operated-Ca^{2+} entry (SOCE) blocker GSK 7975A (1-10 μM). Basal ICC-SS Ca^{2+} transients did not undergo tonic neural inhibition as they were unaffected by tetrodotoxin (1 μM) and the NO synthase inhibitor L-NNA (100 μM). Electrical field stimulation (EFS) of inhibitory nerves (in the presence of 1 μM atropine; 1,5,10 Hz, 10 sec) inhibited ICC-SS Ca^{2+} transients and this was blocked by L-NNA (100 μM) and a soluble guanylate cyclase (sGC) inhibitor ODQ (10 μM). Carbachol (1 μM) or EFS (10 Hz, 10sec) in the presence of L-NNA (100 μM) and MRS 2500 (1 μM) failed to evoke an excitatory Ca^{2+} response in ICC-SS. Contractions of longitudinally oriented strips of mouse colonic muscle were reduced by an Ano1 inhibitor (Ani9, 1 μM). Ca^{2+} signals in colonic longitudinal SMCs imaged *in situ* from a mouse expressing GCaMP6f in SMCs (smooth muscle heavy chain promoter for iCre) were blocked by Ani9 at a concentration that had no effect on ICC-SS Ca^{2+} transients (1 μM). In conclusion, ICC-SS are dynamically

active *in situ*, exhibiting stochastic, voltage independent Ca^{2+} transients arising from PLC/IP_3-dependent intracellular stores and SOCE. ICC-SS Ca^{2+} signaling activates Ano1 channels and increases the excitability of electrically coupled SMC. Ca^{2+} transients in ICC-SS and longitudinal muscle contractions can be suppressed by enteric inhibitory neurons via signaling through the NO-sGC pathway. (*Supported by R01 DK120759-01*)

53 | Frequency of manometry and esophagram abnormalities in jackhammer esophagus

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Background and Objective: Jackhammer esophagus named after its radiological appearance on esophagram and defined by distal contractile integral of > 8000 on high-resolution manometry (HREM). Here, we report frequency of additional esophageal motility abnormalities, clinical symptoms and esophagram abnormalities in patients meeting criteria for jackhammer esophagus on HREM.

Methods: All patients who underwent HREM and esophagram at our academic center for gastroesophageal symptoms were included. All manometries were reviewed by a staff physician, and blinded for clinical and esophagram findings. First, ten supine swallows were analyzed. Jackhammer esophagus was defined by distal contractile integral of > 8000 in at least 20% swallow. Symptoms of chest pain, dysphagia and regurgitation were recorded from a pre-manometry questionnaire routinely administered by two manometry nurses. Esophagram reports were reviewed to determine delay in liquid barium clearance and presence of esophageal dysmotility. Contingency analysis was performed using Fisher's exact test.

Results: Between January 2013 and May 2018, 474 patients underwent both esophagram and HRIM. Ten patients were excluded for whom the studies were incomplete or not interpretable. Of the 464 included patients, 41 cases (8.6%) met criteria for jackhammer esophagus, 6 of these were in post surgical patients, 5 met criteria for type II and 4 type III achalasia. Of remaining 26 patients, 11 (43%) had IRP > 15 mmHg (EGJOO). Amongst these 26 patients, esophagram abnormalities were noted in 13 (50%) patients, tertiary contractions 11 (42%) and bolus impairment in 6 (23%). Regurgitation 17 (65%) was most common symptom followed by dysphagia in 14 (54%) and chest pain in 10 (38%) patients. Symptoms and radiological abnormalities in patients with or without EGJOO were similar except higher proportion of patients with EGJOO had tertiary contraction, *P* 0.07).

Conclusion: Only half of the patients with jackhammer esophagus have abnormalities on esophagram. Over 40% patient had coexisting EGJOO, and likely associated with increasing frequency of tertiary contractions on esophagram. Study was limited by small sample size.

54 | Efficacy of nutrition intervention on key nutrients and fiber intake in patients with constipation and dyssynergic defecation

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Background: Chronic constipation affects 15% of the US population. Inadequate fiber intake and lifestyle issues may be major contributing factors. Dyssynergic defecation is one subtype with anorectal incoordination and difficulty with stool evacuation. Increased dietary fiber intake is often recommended as a treatment for constipation as soluble fiber absorbs water to become a gelatinous viscous substance that softens stool while insoluble fiber has a bulking action that decreases transit time through the lower GI. Reduced fat intake has been theorized to reduce gastric emptying and colonic transit times that may prevent constipation.

Aim: To evaluate the efficacy of nutrition counseling to increase total fiber and reduce total fat and sugar intake with participants diagnosed with dyssynergic constipation (≥ 1 year).

Methods: Thirty-five (*N* = 35) participated in a randomized controlled biofeedback therapy study. Food and beverage intake were recorded by the participants using a 3-day food diary at baseline and endpoint (completion of 12 weeks of treatment). Participants were individually counseled by a Registered Dietitian Nutritionist (RDN) to consume five servings of fruits and vegetables per day, gradually increase fiber intake to 25 g/day, and consume < 30% calories from fat. Macronutrients, fiber and energy intake were analyzed using Nutritionist Pro. Descriptive statistics was used to compile the data and paired t-test used to assess differences between pre and post intervention.

Results: Total carbohydrate, total fat, including saturated, monounsaturated, and polyunsaturated fats, total sugar consumption and total caloric intake significantly decreased ($P \leq 0.05$) post intervention. Importantly, there were significant increases ($P \leq 0.05$) in total fiber, soluble fiber, insoluble fiber, crude fiber, and trans-fat consumption.

Conclusion: The study provided supporting evidence that nutrition counseling was effective in increasing the fiber intake while decreasing the fat and sugar intake. Further analysis may determine whether these significant changes in diet also contributed to the improvement of symptoms in these patients. Constipated patients may benefit with nutrition counseling provided by a RDN along with other treatments.

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55 | Epigenetic factors in enteric nervous system development and disease

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Epigenetic modifications play an important role during development, but very little is known about their function in development of the enteric nervous system (ENS), which innervates the gut. One prominent type of epigenetic modification connected with development and disease of the enteric nervous system is methylation. Mutations in the cellular histone methylation machinery reduce ENS neuron density in mice and have been linked to Hirschsprung disease (HSCR), in which the distal gut is uninnervated. Decreased expression and potentially pathogenic missense mutations of the de novo DNA methyltransferase (Dnmt) have been found in HSCR patients. However, how epigenetic modifications such as DNA methylation affect ENS development and disease remains poorly understood. We found that functional loss of a DNA methylation machinery component, *ubiquitin-like protein containing PHD and RING finger domains 1 (uhrf1)*, leads to reduced enteric neuron number and changes in neuronal morphology. Interestingly, we also showed that *uhrf1* mutants have severe disruption of intestinal smooth muscle indicating that *uhrf1* affects both ENS neurogenesis as well as development of surrounding intestinal cells. Genetic chimeras revealed that Uhrf1 functions both cell-autonomously in enteric neuron progenitors and cell-non-autonomously in surrounding intestinal cells. Uhrf1 recruits the DNA methyltransferase Dnmt1 to unmethylated DNA during replication. Dnmt1 is also expressed in enteric neuron and smooth muscle progenitors. Mutants in *dnmt1* show a strong reduction in enteric neuron number and disrupted intestinal smooth muscle. Because *dnmt1*;*uhrf1* double mutants have a similar phenotype to *dnmt1* and *uhrf1* single mutants, Dnmt1 and Uhrf1 must function together during enteric neuron and intestinal muscle development. This work shows that genes controlling epigenetic modifications are important in coordinating intestinal tract development, provides the first demonstration that these genes are important in ENS development, and advances *uhrf1* and *dnmt1* as potential new Hirschsprung disease candidates.

56 | Transcutaneous vagal nerve stimulation improves symptoms, pain, and gastric emptying in patients with idiopathic gastroparesis

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Background: Gastroparesis, a chronic gastrointestinal motility disorder characterized by delayed gastric emptying, chronic abdominal pain, nausea, and vomiting, remains a largely unexplained disease, with a rising 3-fold incidence in hospitalizations and 10-fold associated healthcare costs. Medical therapy continues to be very limited. Vagal nerve stimulation (VNS) is an attractive therapeutic target for gastroparesis. Unfortunately, prior methods for VNS required invasive surgical placement of electrodes and electric stimulators. AIM: Open label pilot study to assess the impact of non-invasive VNS on symptoms and gastric emptying in patients with mild to moderate idiopathic gastroparesis.

Methods: Patients self-administered non-invasive cervical VNS twice daily for 4-6 weeks using the gammaCore hand-held vagal nerve stimulator (ElectroCore LLC). The gastroparesis cardinal symptom index daily diary (GCSI-DD) was assessed during a two week run-in period and during the 4-6 weeks of VNS. Gastric emptying breath test (GEBT) using Spirulina (Cairn Diagnostics) was performed before and after VNS therapy. The primary endpoint was change in the 1 week mean composite GCSI-DD before and at the end of VNS. Secondary endpoints included change in GCSI subscales and GEBT.

Results: Fourteen idiopathic gastroparesis patients (mean age = 39.4 years, range 23-59; 12 female) completed a median of 35 days of VNS (range: 28-46). Overall, there was improvement in the composite GCSI-DD (2.54 $\pm$ 0.72 to 1.92 $\pm$ 1.07; P = 0.008) and all of the CGSI-DD subscales. The greatest improvement was observed in the Fullness (3.2 $\pm$ 0.8 to 2.4 $\pm$ 1.3; P = 0.012) and Bloating (2.7 $\pm$ 1.2 to 2.1 $\pm$ 1.5; P = 0.016) subscales. Importantly, study subjects reported improvement in the Pain category (2.5 $\pm$ 1.3 to 2.0 $\pm$ 1.6; P = 0.032). Finally, a modest improvement was observed in the Nausea subscale (1.4 $\pm$ 0.8 to 1.0 $\pm$ 0.8; P = 0.011). VNS was associated with a significant reduction in gastric emptying ($T^{1/2}$ 149 min vs 123 min; P = 0.04, CI 1.4 to 49) (Figure 1).

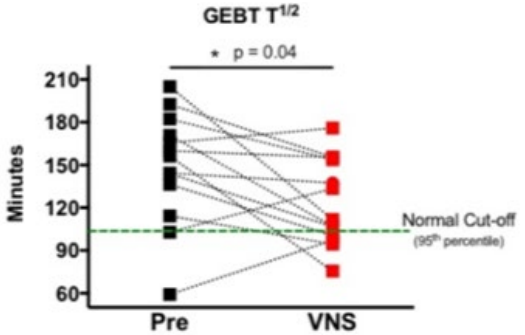

Figure 1. Effect of VNS on gastric emptying.

Conclusion: Short-term non-invasive VNS resulted in an improvement in gastroparesis symptoms, pain, and accelerated gastric emptying in patients with mild to moderate idiopathic gastroparesis. These findings will need to be evaluated in future larger randomized sham-controlled trials.

57 | Exploring the relationship between prematurity and functional gastrointestinal disorders in children

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Background: The pathogenesis of functional gastrointestinal disorders (FGIDs) remains unknown. Prematurity is one of the earliest factors that could influence the development of FGIDs. Prematurity affects multiple organ systems and is associated with increased exposure to antibiotics and stressors. These differences account for alterations in the gut microbiome and have also been associated with alterations in neuronal pain processing. Data from studies on the effect of prematurity on development of FGIDs are scarce and contradictory. This study assessed the relationship between length of gestation and FGIDs. We hypothesized that prematurity would be associated with an increased prevalence of FGIDs in children.

Methodology: Study information packets were mailed to children's families in the pacific region of Colombia. Parents provided demographic information, gestational age at time of delivery, and past medical history. School-children completed the Spanish version of the Questionnaire of Pediatric Gastrointestinal Symptoms Rome IV (QPGS-IV). Categorical data was analyzed using Fisher exact tests. Calculation of OR with 95% CI was performed between the variables of interest (age, group, sex, and education) and the effect variable (presence or absence of FGID). Approval was obtained by the Institutional Review Board.

Results: 22.7% (338/1497) of children/adolescents had at least one FGID. The most common diagnoses were functional constipation (FC) (13%), abdominal pain (5.8%) and nausea/vomiting (3.9%). There was a significant association between prematurity and FGIDs for those born between 28 and 32 weeks (P = 0.03). In this group, functional nausea was the only category of FGID to reach significance (P = 0.02). However, statistical significance was lost when gestational ages were grouped together with multivariate analysis.

Conclusions: Overall, our results suggest that prematurity cannot be considered a major risk factor for the development of FGIDs. Given prematurity's multifactorial nature, it is possible that unexplored factors could have acted as confounders in this study. Future studies evaluating neonatal exposure to antibiotics and neonatal stressors are warranted to better strengthen our understanding on the relationship between prematurity and FGIDs.

58 | Acute colitis following chronic traumatic brain injury in mice induces persistent neurobehavioral deficits

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Introduction: Disruptions in the bidirectional communications of the brain-gut axis are increasingly implicated in the onset and progression of a variety of disorders, diseases and injuries. We previously reported that following experimental traumatic brain injury (TBI) in mice (>28 days), pathogenic bacterial infection exacerbated the TBI-associated lesion volume and inflammation. The aim of this study was to determine the effects of acute experimental colitis on chronic neurological function following TBI.

Methods: Male C576Bl/6 mice were placed in either naïve (anesthetic), sham (craniotomy), or moderate-to-severe controlled cortical impact (CCI) groups. Twenty-eight days after injury, cohorts of mice in all groups were treated for 7 days with regular water or 3% DSS in the drinking water to induce colitis (injury) followed by replacement with regular water in all groups for an additional 28 days (recovery). Following induction of colitis, mice were tested on beam walk (BW), novel object recognition (NOR) and Morris water maze (MWM) to assess motor and cognitive function. Additionally, changes in social and anxiety-like behavior were assessed during the recovery stage using social approach (SA), light-dark box (LDB), marble burying (MB) and elevated plus maze (EPM).

Results: Acute DSS resulted in and exacerbated, respectively, deficits in spatial memory (MWM), declarative memory (NOR) and fine motor function in Sham+DSS and CCI+DSS mice two and four weeks following administration. Acute DSS administration also caused deficits in social behavior (SA) and increased anxiety-like behavior (LDB, MB, EMP) in Sham+DSS and CCI+DSS mice three and four weeks following administration. These changes were not observed in either Sham+H2O or Naïve+DSS groups.

Conclusion: This study shows that neither sham injury alone nor inflammation of colon alone (Naïve+DSS) are sufficient to induce neurobehavioral deficits. In contrast, acute colitis does persistently induce and exacerbate neurobehavioral deficits in sham and CCI injured mice. Sham-injury has been used widely as a control for TBI studies but is becoming increasingly recognized as an acute mild injury. Thus, these data demonstrate that even mild brain injury primes the brain for development of persistent neurological deficits in response to subsequent gut inflammation.

59 | Measurement of trans-esophagogastric junction (EGJ) pressure gradients during straight leg raise (SLR) maneuver can augment evaluation of the EGJ barrier during esophageal HRM

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Background: Straight leg raise (SLR) while supine increases intraabdominal pressure. We hypothesized that this elevation of intraabdominal pressure would transmit into the thoracic cavity if the EGJ was disrupted in GERD. We evaluated the intra-abdominal and intrathoracic pressure gradients at baseline and with SLR during HRM to determine if trans-EGJ gradients could predict EGJ barrier disruption.

Methods: Consecutive patients undergoing esophageal HRM from June 2018 through October 2018 were included if they had an adequate SLR maneuver. SLR was performed by hip flexion with knees extended for ≥ 5 sec while supine. EGJ morphology was subtyped according to the relationship between the intrinsic lower esophageal sphincter (LES) and the crural diaphragm (CD) (intact: LES and CD overlap; type 2: separation of < 3 cm; type 3: separation of ≥ 3 cm); HRM diagnoses were made according to Chicago Classification v3.0. pH studies were reviewed when available. Mean and peak intra-thoracic and abdominal pressures were measured at baseline and during SLR using on-screen software tools, and trans-EGJ gradients were compared. Trans EGJ pressure gradient < 1 mmHg denoted equalization of pressures.

Results: Of 430 patients, 248 (69.4% F, mean age 57.5 ± 0.9 yrs, mean BMI 30.5 ± 0.5 kg/m^2) successfully completed SLR. EGJ barrier was intact in 55 (22.2%) and disrupted in 101 (40.7%), with type 2 EGJ in 59 (23.8%) and type 3 EGJ in 42 (16.9%). When EGJ barrier was intact, neither the mean (baseline: 16.3 ± 1.2 mmHg vs post SLR:11.3 ± 3.2 mmHg, $P = 0.14$), nor peak (25.5 ± 3.6 mmHg vs 15.6 ± 5.9 mmHg respectively, $P = 0.14$) trans EGJ pressure gradient changed with SLR. In contrast, in type 3 EGJ, peak pressure gradient decreased significantly following SLR (4.0 ± 1.7 mmHg vs -8.1 ± 4.6 mmHg, $P < 0.02$). More type 3 EGJ patients equalized mean (50%) and peak (64%) pressures across EGJ compared to other EGJ subtypes (mean 21%, peak 27%, $P < 0.001$). Baseline esophageal pressures were lower, and the trans EGJ pressure gradient was higher with elevated supine and upright acid exposure ($P < 0.05$) compared to normal acid burden; both mean and peak intraabdominal and intrathoracic pressures increased following SLR ($P < 0.05$).

Conclusions: Evaluation of intraabdominal and intrathoracic pressures with SLR during esophageal HRM can provide evidence of significant disruption of the EGJ barrier, and can predict abnormal esophageal acid burden on ambulatory pH monitoring.

60 | Characterization of abdominal pain response to rifaximin in patients with irritable bowel syndrome with diarrhea (IBS-D), by baseline (BL) pain severity

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Introduction: Rifaximin is indicated for the treatment of IBS-D in adults. This post hoc analysis of a phase 3 trial evaluated response to 2 courses of rifaximin in patients subgrouped by BL abdominal pain severity.

Methods: Adults with IBS-D (mean daily abdominal pain score ≥ 3) received 2-weeks of rifaximin 550 mg three times daily. Abdominal pain was assessed daily (score range, 0-10). Patients who responded (during 4-week evaluation period) and then had symptom recurrence during an additional ≤ 18-week observation period (up to 22 weeks posttreatment) received a second 2-week rifaximin course and response was assessed for 4 additional weeks. Response was defined as a ≥ 30% decrease from BL in mean weekly abdominal pain score *and* ≥ 50% decrease from BL in days/week with Bristol Stool Scale type 6/7 stool (mushy/watery; composite endpoint) for ≥ 2 of the first 4 weeks posttreatment. Subgroups were defined by BL abdominal pain scores of < 5.0 (group A), ≥5.0-<8.0 (group B), and ≥ 8.0 (group C).

Results: 2579 patients received the first rifaximin course (68.2% female; mean age, 46.4 y; mean BL abdominal pain score, 5.5). In 2438 patients evaluable for efficacy (group A, $n = 962$; group B, $n = 1260$; group C, $n = 216$), response to rifaximin (composite endpoint) was observed in 40.4%, 47.0%, and 43.1% in groups A, B, and C, respectively. Response for the abdominal pain component was observed in 57.0%, 57.9%, and 49.5%, respectively. In 328 patients who experienced symptom recurrence and received repeat treatment with rifaximin (group A, $n = 114$; group B, $n = 178$; group C, $n = 36$), median BL abdominal pain score at repeat treatment BL was 4.4 (mean, 4.6), lower than observed at first-course BL. When subgrouped by repeat treatment BL pain score, response to repeat rifaximin treatment (composite endpoint) was reported in 38.6%, 34.8%, and 27.8% in groups A, B, and C, respectively. Response for abdominal pain was reported by 57.9%, 50.6%, and 50.0%, respectively.

Discussion: A high percentage of patients treated with rifaximin had clinically meaningful improvement in abdominal pain irrespective of BL abdominal pain severity category and treatment course (first vs repeat treatment). These data support rifaximin for improving IBS-related abdominal pain symptoms.

61 | Rifaximin for improving abdominal pain and bloating symptoms in patients with irritable bowel syndrome with diarrhea (IBS-D) using modified definitions of pain response

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Introduction: Rifaximin is a nonsystemic antibiotic indicated in the USA for adults with IBS-D. This post hoc analysis of a phase 3 trial evaluated repeat rifaximin treatment for abdominal pain and bloating symptoms in IBS-D.

Methods: Adults with IBS with an average abdominal pain score ≥ 3 (scale, 0-10) and ≥ 2 days/week with Bristol Stool Scale type 6/7 stool (mushy/watery) received 2 weeks of open-label (OL) rifaximin 550 mg TID. Patients with abdominal pain and bowel movement response with subsequent symptom recurrence during an 18-week observation period were randomized (double-blind [DB]) to a second 2-week course of rifaximin 500 mg TID or placebo. In a post hoc analysis, response was defined as simultaneously meeting weekly response criteria for abdominal pain (≥30%, ≥40%, or ≥ 50% improvement from baseline in the weekly average abdominal pain score) and bloating (≥1-point decrease from baseline in weekly average bloating score [scale range, 0-6]) during ≥ 2 weeks of the first 4 weeks posttreatment.

Results: 2579 patients received OL rifaximin (68.2% female; mean age, 46.4 y; mean baseline scores: abdominal pain, 5.5; bloating 4.1). Of 2438 evaluable OL patients, 47.7%, 43.6%, and 37.2% had a ≥ 30%, ≥40%, or ≥ 50% decrease from baseline in abdominal pain with ≥ 1-point decrease in bloating scores, respectively. In the DB phase, more patients in the rifaximin group (n = 328) vs the placebo group (n = 308) met the criteria of ≥ 30% decrease in abdominal pain plus ≥ 1-point decrease in bloating response (defined as criterion A: 40.5% vs 31.5%; P = 0.02) and ≥ 40% decrease in abdominal pain plus ≥ 1-point decrease in bloating score response (defined as criterion B: 35.4% vs 27.3%; P = 0.03). Durable response (10 weeks posttreatment) occurred more often with rifaximin vs placebo (criterion A: 26.5% vs 18.8%; P = 0.02; and criterion B: 22.6% vs 15.9% P = 0.04).

Discussion: Two-week courses of rifaximin 550 mg TID provided consistent (OL vs DB), significant, and durable improvement in abdominal pain and bloating symptoms vs placebo using modified definitions of IBS-D response.

62 | Decreased ileocecal junction pressure does not correlate with the presence of small intestinal bacterial overgrowth: A retrospective evaluation

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Background: Small intestinal bacterial overgrowth (SIBO) is a distressing multifactorial disorder that can cause unexplained GI symptoms. Its pathophysiology remains unclear with proposed mechanisms involving small bowel dysmotility, pH disturbance and more recently, ileocecal valve dysfunction.

Methods: Patients presenting to the Digestive Health Center of Augusta University with unexplained GI symptoms were evaluated. Patients underwent glucose breath test (GBT) or small bowel aspirate and culture during upper endoscopy to assess for SIBO. All patients also underwent wireless motility capsule. Ileocecal junction pressure (ICJP) was taken as the maximum pressure over a 5-minute window period before the distinctive drop in pH when the capsule enters the cecum. Symptoms were examined on 9-point Likert scale.

Results: A total of 162 patients were evaluated. Sixty-three or 38.9% (48 ± 16 years, M/F = 13/50) were positive for SIBO by glucose breath test and/or aspirate cultures. Patients with negative breath test and small bowel aspirate cultures were classified as non-SIBO (n = 34, 42 ± 14 years, M/F = 7/27). The small bowel transit time was prolonged in SIBO patients, but did not reach statistical significance when compared to non-SIBO patients (5.88 vs 4.74 h; P = 0.079). There were no significant differences in ICJP between SIBO and non-SIBO groups (48.6 vs 50.3 mmHg; P = 0.96). Similarly, when ICJ pressure was taken as mean over the 5-minute period, no difference was noticed between patients with SIBO and without SIBO (6.69 vs 6.46 mmHg; P = 0.60). Diarrhea was weakly positively correlated with ICJP (r = 0.23, P = 0.04). Bloating, abdominal pain, fullness, and gas were not significantly correlated with ICJP.

Conclusion: Our study demonstrates that decreased ICJP does not correlate with the presence of SIBO diagnosed by glucose breath testing and/or small bowel aspirates. Further studies should investigate whether decreased ICJP is associated with more distal and/or malabsorptive forms of SIBO.

63 | Nestin-expressing cells isolated from ganglionic region of mice with Hirschsprung disease can give rise to functioning neurons

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Purpose: Hirschsprung disease (HSCR) is a potentially lethal congenital disorder in which the enteric nervous system (ENS) is absent in the distal bowel. Cell therapy can offer the potential to replace the missing neurons and glial cells along the diseased intestine. We have previously shown that ENS progenitor cells (ENSPCs) can be isolated from small intestine of mice with HSCR; however, current isolation method needs to be optimized to maximize cell numbers. Furthermore, the ability of HSCR-derived ENSPCs to differentiate into functioning neurons need to be characterized.

Methods: ENSPCs were isolated from ganglionated small intestine of 2-3 week-old Nestin^{GFP};Ednrb$^{-/-}$ (Nestin^{GFP}HSCR) and Nestin^{GFP};Ednrb$^{+/+}$ (Nestin^{GFP}WT) mice in which enteric glia and ENS progenitor cells express GFP. To maximize the number of ENSPCs obtained, we established a new, optimized method to isolate cells from dissociated gut and culture them in non-adherent conditions for 10 days prior to fluorescent activated cell sorting (FACS). ENSPCs were characterized by immunohistochemistry and neuronal activity was measured using Ca^{2+} imaging following transduction of a Syn1-RCaMP Adeno-associated viral vector to ENSPCs.

Results: Using the "optimized" cell isolation strategy, we obtained significantly greater numbers of ENSPCs from each mouse intestine (74.8 ± 10.9 x 10^3 vs 418.4 ± 310.7 x 10^3 cells; n = 3, P < 0.001). ENSPCs isolated from Nestin^{GFP}HSCR mice demonstrated equivalent proliferation capacity to those from Nestin^{GFP}WT (141.6 ± 20.61 relative light units (RLUs) for ATP in HSCR vs 170.2 ± 10.59 RLUs in WT, P > 0.05). Immunostaining of neurospheres showed that the proportion of Hu+ neurons was lower in HSCR-ENSPCs (5.0 ± 0.8 % vs 12.6 ± 1.9 %, n = 6, P < 0.01), with fewer nNOS+ neurons (31.5 ± 4.3 % vs 63.6 ± 11.4 %, n = 3, NS) and more ChAT+ neurons (15.8 ± 4.0 % vs 9.6 ± 2.6 %, n = 3, NS). Ca^{2+} imaging demonstrated that both WT- and HSCR-ENSPCs gave rise to neurons that exhibited spontaneous neuronal firing with equivalent amplitude, time to peak, and length of response.

Conclusions: We have successfully optimized the isolation and culturing of ENSPCs from ganglionic regions of HSCR mice based on Nestin expression and demonstrated their ability to give rise to functioning neurons, albeit with altered neuronal subtype distribution. These findings will be beneficial to pursue the use of autologous-derived cells to treat HSCR and other neurointestinal disorders.

64 | Does etiology, prior therapy and operative time affect outcome of G-POEM in refractory gastroparesis? - A systematic review and meta-analysis

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Introduction: Gastric per-oral endoscopic myotomy (G-POEM) is an option for refractory gastroparesis. Literature on its efficacy when considering etiology of gastroparesis, prior therapies and total operative time is limited.

Aim: We performed a systematic review and meta-analysis to evaluate the clinical efficacy of G-POEM in patients with refractory gastroparesis and identify if there is any variation in outcome with operative time, prior therapies and etiology of gastroparesis.

Method: We conducted a search on PubMed, Embase, Scopus, Cochrane, Google Scholar to locate items pertaining to G-POEM in patients with refractory gastroparesis (January 2013 to February 2019). Random-effects model was used for analysis. Heterogeneity between study-specific estimates was calculated using Cochran Q statistical test, 95% confidence interval (CI) and I2 statistics. The outcomes assessed were the pooled rate of clinical success determined by total Gastroparesis Cardinal Symptom Index (t-GCSI) at follow up and improvement in the 4-hr Gastric Emptying Study (GES). Sub-group analysis was performed based on the total operative time. Meta-regression analysis was used to evaluate the effect of prior treatments on clinical success.

Results: Initial search yielded 67 results and 16 studies with 442 patients were included in the final analysis. Follow up t-GCSI and 4-hr GES data was available for 373 and 258 patients respectively. Overall pooled rate of clinical success was 75.9% based on t-GCSI and 84% based on improvement in 4-hr GES. Pooled rate of clinical success based on t-GCSI score with procedure time of < 50 min was 74.6% (8 studies, 214 patients) and 78.4% for > 50 min (8 studies, 159 patients), without statistical difference. Pooled rate of clinical success based on 4-hr GES was 76.5% for a procedure time < 50 min (6 studies, 126 patients) and 88.7% for > 50 min (8 studies, 132 patients), without statistical difference. The pooled rate of total adverse events was 13.4%, follow up time was 2-18 months and length of hospital stay was 1-6 days. Meta-regression analysis showed that prior treatment with botulinum toxin injection (P = 0.03) and gastric electrical stimulation (P = 0.03) could influence 4-hr GES success rate. Etiology (diabetes, idiopathic, post-surgical) and prior treatments did not affect the outcome based on t-GCSI score.

Conclusions: G-POEM is an effective and safe treatment modality for refractory gastroparesis without difference in the outcomes based on the etiology of gastroparesis or total operative time. However, prior treatment with botulinum toxin and gastric electrical stimulation could influence the success rate based on 4-hr gastric emptying.

65 | High stress level is associated with low motivation, confidence and rating of social support for weight management in participants in a clinical trial on pharmacologic management of obesity

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Background: Perceived stress has been shown to be associated with obesity. We aim to examine the relationship between baseline stress level, motivation to lose weight, confidence in ability to manage weight, and rating of social support in patients enrolling into a clinical trial on pharmacologic management of obesity.

Methods: This is an interim analysis of a sub-study of a clinical trial on the role of liraglutide in the management of obesity. We used a standardized questionnaire to collect baseline behavioral and psychological data from participants, including baseline levels of stress, motivation to manage weight, confidence in the ability to manage weight, and social support (using a scale from 0-10, 0 being "not at all" and 10 being "extremely"). Similar to studies of almost 14,000 employees (PMID: 27454399), participants were then categorized based on high vs non-high stress level (high stress level defined as a score ≥ 7). We used Wilcoxon rank sum test to compare the high stress group to the non-high stress group.

Results: High stress level was associated with significantly lower motivation score (P = 0.048), confidence in ability to manage weight (P = 0.049), and social support rating (P = 0.039) (table). Participants are completing monthly stress ratings. Preliminary analysis suggests baseline stress level is a significant predictor of adherence to obesity therapy and of weight reduction with pharmacologic treatment.

Conclusion: Participants with high baseline stress level, enrolling into a randomized controlled trial of a pharmacologic treatment of obesity, had significantly lower motivation to lose weight, confidence in their ability to lose weight, and social support rating, compared to participants with non-high baseline stress level. This is an important finding as all of these psychosocial factors are associated with poor outcomes from obesity treatment.

Group	Non-High Stress, n = 8	High Stress, n = 3	P-Value
Age (years)	34.5 (32, 41.8)	35 (23, 36)	NS
BMI (kg/m^2)	34.7 (32.4, 38.7)	41.9 (35.0, 49.6)	NS
Motivation	9 (8, 9.8)	6.5 (5, 8)	0.048
Confidence	7 (6.3, 8.4)	5 (4, 6)	0.049
Social Support	8 (7.3, 9.8)	5 (2.5, 7)	0.039

Data shown as Median (IQR); NS=nonsignificant; predominantly female sample

66 | Association of obesity class with gastric motor functions, appetite measures, gut hormones and body composition in individuals with obesity

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Background: Obesity is associated with alterations in gastric emptying (GE), satiety and satiation, and gastrointestinal (GI) hormones (PMID: 25486131). It is unclear whether these traits vary with degree of obesity. Our aim was to examine the association of BMI class with gastric motor functions, appetite measures, GI hormones and body composition in obesity.

Methods: Forty obese volunteers enrolled in a randomized controlled trial (RCT) on the effect of liraglutide in obesity (PMID: 28958851). For this sub-study, we compared in class I vs class II/III obesity the following baseline (prior to treatment) characteristics: GE $t_{1/2}$ of solids by scintigraphy, gastric accommodation (GA) by single photon emission computed tomography, plasma GLP-1 and PYY levels by immunoassay, satiation by nutrient drink test [volume to fullness (VTF) and Maximal Tolerated Volume (MTV)] using Ensure®, satiety by caloric consumption at an *ad libitum* meal, subjective measures of appetite (hunger, fullness, satiety and prospective food consumption) by visual analog scale, % regional body fat stores and lean body mass (LBM) by Dual-energy X-ray absorptiometry, and waist and hip circumferences. We used Wilcoxon rank sum test to compare groups.

Results: BMI ≥ 35 kg/m^2 was associated with significantly slower GE $t_{1/2}$ (P = 0.04), higher hunger score (P = 0.04), and a trend toward higher VTF (P = 0.08) denoting reduced satiation, compared to BMI < 35 kg/m^2 (table). As expected, BMI ≥ 35 group had higher % android, trunk, gynoid and total body fat, lower % LBM and higher waist and hip circumferences. No significant differences were observed in other appetite measures, GA, and GI hormones.

Conclusion: Individuals with class II/III obesity have slower GE $t_{1/2}$, increased hunger and reduced satiation, compared to class I obesity. These data suggest different gut patho-physiological mechanisms are associated with different classes of obesity, in addition to established differences between obesity and normal weight (PMID: 25486131).

Baseline Test	Obesity Class I, n = 17 (BMI = 30-34.9 kg/m^2)	Obesity Class II/III, n = 23 (BMI ≥ 35 kg/m^2)	P-value
% Lean body mass	50.9 (49.7, 55.3)	46.2 (45.3, 49.7)	<0.001
GE $T_{1/2}$ (min)	97 (87, 130.5)	124 (102, 145)	0.04
VTF (mL)	600 (510, 705)	660 (570, 870)	0.08
Hunger $AUC_{0\text{-}300\ min}$	17325 (9389, 20389)	20760 (13560, 23535)	0.04

Data shown as Median (IQR); Groups were controlled for age and gender; Predominantly female sample

67 | Gastric dysmotility and its relationship to upper gastrointestinal symptoms in patients with long-standing diabetes mellitus

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Background: Gastric dysmotility including delayed gastric emptying is reported in patients with diabetes mellitus (DM). These DM patients, some of them are diagnosed as diabetes gastroparesis, have several upper gastrointestinal (GI) symptoms such as nausea, vomiting, early satiety and bloating. However, the relationship between gastric dysmotility and GI symptoms has not been investigated well in Japanese patients with DM.

Aim: The aim of this study was to identify the relationship between gastric motility measures and upper GI symptoms in patients with long-standing Japanese DM.

Method: The subjects of this study were 15 healthy controls (female 9, male 6, aged 26-74) and 21 DM patients (female 13, male 9, aged 33-80). All DM patients were receiving insulin treatment, and at least one history of diabetes nephropathy, retinopathy or neuropathy. Gastric motility was evaluated with electrogastrography (EGG) and gastric emptying using 13C-octanoic acid breath test. All patients completed a self-administrated questionnaire including six symptoms (anorexia, nausea, vomiting, early satiety, abdominal pain and bloating) to assess subjective GI symptoms.

Results: Compared to healthy controls, long-standing DM patients showed a significant lower percentage of normogastria in both fasting and postprandial state with a lower power ration in EGG. Gastric emptying was significantly delayed in DM patients in overall analysis. Fifteen DM patients (68.2%) demonstrated abnormalities of either gastric myoelectrical activity or gastric emptying. The number of patients who had some GI symptoms was 13 in abnormal EGG or delayed gastric emptying versus 3 in normal gastric motility ($P = 0.032$). No significant correlation was observed between gastric emptying parameters and HbA1c values.

Conclusion: The patients with long-standing DM showed gastric dysmotility, including impaired gastric myoelectrical activity and delayed gastric emptying. Gastric dysmotility appear to be an important factor in the generation of upper GI symptoms in patients with long-standing DM.

68 | Effects of comprehensive self-management intervention on extraintestinal pain, fatigue, and sleep in adults with IBS

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Background: Irritable bowel syndrome (IBS) is a disorder characterized by abdominal pain and alterations in bowel habits. Although many patients with IBS report co-occurring extraintestinal symptoms such as pain, fatigue and sleep disturbances, the majority of self-management interventions focus on the improvement of gastrointestinal (GI) symptoms. Therefore, the purpose of this study was to determine the effects of a comprehensive self-management (CSM) intervention designed for IBS symptoms compared to usual care (UC) on extraintestinal symptoms of pain (backache, headache, muscle pain, joint pain), fatigue, and sleep in patients with IBS.

Methods: A secondary data analysis was conducted of two randomized controlled trials (RCTs) with follow-up at 3 and 6 months post randomization. The RCTs used similar recruitment strategies, and included participants aged 18-70 who met Rome-III criteria for IBS. Participants ($N = 243$) were randomized to CSM ($n = 148$) or UC ($n = 95$). The CSM intervention included 8 individual in-person or telephone visits with a research nurse. Participants completed a 28-day symptom diary at baseline, 3, and 6 months post randomization, reporting severity for 26 symptoms as not present to very severe. Daily symptoms were summarized across days as the percent of days with symptoms that were moderate to very severe. Regression was used to test the effects of CSM while controlling for symptom baseline.

Results: Study participants mean age was 43 years (SD = 14.7), 83% Caucasian, 88% female, 43.2% IBS-diarrhea, 17.7% IBS-constipation, 30.5% IBS-mixed, and 8.6% IBS-unclassified. Participants in CSM experienced a significant decrease in percentage of days with backache at 3 (B = -1.37, $P = 0.025$) and 6 months (B = -1.66, $P = 0.009$) and joint pain at 3 months (B = -1.37, $P = 0.036$) compared with UC. Muscle pain and headache were not statistically different between CSM and UC at 3 and 6 months. At 3 and 6 months post randomization, participants in the CSM intervention reported decreased percentage of days with moderate to very severe fatigue (B = -1.35, $P < 0.001$; B = -1.03, $P = 0.006$) and sleepiness during the day (B = -1.48, $P < 0.001$; B = -1.13, $P = 0.009$) compared to UC.

Discussion: This study found that a CSM intervention developed for IBS symptoms also diminished extraintestinal symptoms of backache, joint pain, fatigue, and sleepiness during the day. Even though the intervention was developed for IBS symptoms, the intervention strategies of cognitive restructuring, diet counseling, and relaxation may be beneficial for multiple chronic pain symptoms.

Future investigations evaluating the intersectionality of symptoms in patients with IBS, should thus consider the benefit of a CSM intervention.

69 | Real-world analysis of symptoms, diagnostic patterns, and provider perspective on acute hepatic porphyria

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Introduction: Acute hepatic porphyria (AHP) is a family of rare genetic diseases caused by mutations of enzymes involved in hepatic heme synthesis. The neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG), accumulate and can cause potentially life-threatening attacks and chronic debilitating symptoms. The study's objective was to understand physician experiences diagnosing AHP and to characterize the AHP patient population in a real-world setting.

Methods: Physicians (n = 175) from the US (29%), EU-5 (57%), Canada (9%), and Japan (6%) who actively managed or treated AHP patients (with and without recurrent attacks) in the year prior were recruited from 9/2017–10/2017 to complete an online survey collecting information on demographics, familiarity with AHP and diagnostic tests, perspective on symptoms important to diagnosis, referral patterns, and treatment preferences. Subsequently, physicians reviewed 1-4 of their AHP patients' charts (n = 546; 32% US), sharing data on anonymized patient demographics, medical history, number of porphyria attacks, and symptoms.

Results: Physicians had a mean of 18 years of experience, 51% worked in academic settings, and the most common specialty was gastroenterology (25%). Symptoms considered informative for AHP diagnosis included abdominal pain (88%), red/dark urine (75%), muscle weakness (63%), vomiting (62%), fatigue (59%), and nausea (57%). AHP diagnostic tests considered informative included ALA in urine (73%) and PBG in urine (68%); however, other nonspecific tests were also commonly considered informative. Among charts reviewed, patients' mean age was 40 years, 53% were female, and 82% had acute intermittent porphyria (AIP). Initially, 26% of patients were misdiagnosed and 31% were diagnosed correctly (43% did not know this information). Most common misdiagnoses were nonspecific abdominal pain (32%), irritable bowel syndrome (27%), depression (25%), and fibromyalgia (25%). Patients had a mean of 1.8 attacks and 1.1 hospitalizations in the past year. Most common chronic symptoms reported between attacks were abdominal pain (50%), fatigue (36%), and nausea (32%).

Discussion: This research revealed there may be underdiagnoses or misdiagnoses due to common symptomology associated with AHP and/or lack of understanding of appropriate laboratory and genetic testing procedures. Among patients diagnosed with AHP, both acute attacks as well as chronic symptoms were reported indicating AHP has both acute and chronic manifestations.

70 | The patient odyssey to confirmed acute hepatic porphyria diagnosis: clinical characteristics and healthcare utilization of patients preceding diagnosis of acute hepatic porphyria

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Introduction: Acute hepatic porphyria (AHP) is a family of rare genetic diseases caused by defects of specific enzymes involved in hepatic heme biosynthesis, with acute intermittent porphyria (AIP) being the most common subtype. Accumulation of neurotoxic heme intermediates can cause potentially life-threatening acute attacks and debilitating chronic symptoms, often requiring immediate medical attention. Patients with AHP commonly report nonspecific symptoms, leading to misdiagnosis, delays in diagnosis, and inappropriate therapy. The study's objective was to follow patients' healthcare journeys from first suspected symptom to AHP/AIP diagnosis.

Methods: IBM MarketScan Commercial Claims and Medicare Supplemental Databases were used to identify AHP/AIP patients between 1 January 2010 and 30 June 2010 using a previously defined claims algorithm: 1) ICD-9 277.1 porphyria diagnosis claim, symptoms, and AHP/AIP lab test, 2) ICD-9 277.1 porphyria diagnosis claim and hemin, or 3) ICD-10 E80.21 AIP claim. Patients were required to have 5 years of continuous enrollment prior to the index date, defined as the date of first AHP/AIP claim. The observation period (OP) was defined as the period between first AHP/AIP symptom(s) and index date. Healthcare resource utilization (HCRU), medications, symptoms, and diagnoses were analyzed during the OP.

Results: A total of 126 unique patients with AHP/AIP were identified with a mean (SD) age of 47 years (18), 63% were female, and mean OP was 3.9 years (1.3). The most common first AHP-related symptoms identified were abdominal pain and hypertension (Table 1). Symptoms observed frequently throughout the OP were abdominal, chest, and back pain, nausea/vomiting, and malaise/fatigue (Table 1). During the OP, patients had a mean of 3 attacks (4.3); 1.6 attacks/year (2.9) among those with ≥ 1 attack. 51% had ≥ 1 hospitalization (mean, SD annualized: 1.2, 2.9), 73% had ≥ 1 emergency department (ED) visit (mean, SD annualized: 1.9, 3). The most commonly seen specialist was gastroenterologist (49% had ≥ 1 visit). The most commonly observed condition was acute abdomen, and the most commonly observed outpatient medications were opioid analgesics (86%).

Discussion: Prior to AHP/AIP diagnosis, patients exhibited symptoms commonly associated with AHP/AIP, high HCRU, including hospitalizations and ED visits, and were frequently treated with

opioid analgesics. Opportunity exists for earlier recognition of AHP/AIP based on patient history of neurovisceral and gastrointestinal symptoms and specific HCRU.

Table 1. Potential AHP/AIP Symptoms

	AHP/AIP Patients N = 126
First Identified AHP/AIP Related Symptom, N (%)	
Any abdominal pain	34 (27.0%)
Unspecified abdominal pain*	13 (38.2%)
Hypertension (benign essential and unspecified essential)	24 (19.0%)
Back pain	19 (15.1%)
Nausea/vomiting	18 (14.3%)
Chest pain	17 (13.5%)
Leg/arm pain	13 (10.3%)
Malaise/fatigue, other	11 (8.7%)
AHP/AIP Related Symptoms Anytime During Observation Period, N (%)	
Any abdominal pain	100 (79.4%)
Unspecified abdominal pain**	87 (87.0%)
Back pain	71 (56.3%)
Chest pain	73 (57.9%)
Malaise/fatigue, other	69 (54.8%)
Nausea/vomiting	77 (61.1%)

Common first AHP/AIP-related symptom(s) identified in claims and frequently reported symptoms throughout the OP, preceding AHP/AIP diagnosis. *Subset of *Any abdominal pain* (denominator: *n* = 34) **Subset of *Any abdominal pain* (denominator: *n* = 100).

71 | 'Non-pathological' reflux contributes to chronic cough

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Gastroesophageal reflux is among the most common etiologies of chronic cough. Part of the evaluation for patients with chronic cough of unknown cause is pH testing. This is especially important in patients with cough but without classic reflux symptoms. Our hypothesis is that patients with higher DeMeester scores will have more severe cough. The aim of this retrospective study was to evaluate 24 hour pH studies off PPI therapy and determine the relationship between DeMeester scores in patients with varying cough severities.

All patients referred to a tertiary care hospital for manometry in 2016 were included in the initial chart review. Of note, the sample initially used all patients referred for manometry as these patients completed a pre-manometry patient questionnaire that inquired about cough and cough severity. From the initial total 354 patients referred for manometry, 56 (21.4% Males, Mean Age 55.6 and 78.6% Females, Mean Age 51.5) patients were included in the final analyses because they also underwent 24-hour ambulatory pH study off PPI therapy. All others were excluded either because they did not endorse cough, did not specify cough severity, or did not undergo 24 hour ambulatory pH testing. Of the final 56 patients, 12 (21.4%) endorsed mild cough, 23 (41.1%) moderate cough, 10 (17.9%) severe cough, and 11 (19.6%) very severe cough. The average DeMeester score was 4.7 for mild cough, 7.9 for moderate, 9.6 for severe, and 14.8 for very severe. There was a statistically significant difference in DeMeester score between mild and severe cough ($P = 0.05$) and between mild and very severe cough ($P = 0.02$).

Although it is established that reflux is a common etiology for cough, there are many patients with chronic cough but without reflux symptoms who may nonetheless have asymptomatic reflux that may still be contributing to their cough. Our study provides evidence that reflux, regardless of whether classical symptoms are present, could be a factor contributing to cough, and that more esophageal acid exposure correlates with more severe cough, as demonstrated by higher DeMeester scores. Although multiple factors contribute to the presence of cough and its severity, this work suggests that degrees of reflux that are not typically considered to be pathological are a contributing factor as well.

72 | The association between BMI and cough severity in patients referred for esophageal manometry testing

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There exists a well-established association both between obesity and regurgitation as well as regurgitation and cough. The mechanism is thought to likely involve increased intra-abdominal pressure leading to loss of integrity of the esophageal sphincters and gastric contents regurgitation with resultant vocal cord irritation and cough. However, there is likely more than one mechanism whereby a high BMI contributes to cough. Other cough-inducing risk factors in patients with higher BMIs may include increased airway inflammation from adipose tissue surrounding the airway, obstructive sleep apnea, and asthma. The aim of this retrospective study was to compare BMIs amongst patients with varying cough severities to further elucidate if obesity may be playing a role in the cough experienced in our patient population of patients referred for esophageal manometry in the setting of chronic cough. All patients who endorsed cough and were referred for manometry testing in 2016 were included.

There were a total of 144 patients (21.5% Males, Avg Age 55.5 yo and 78.5% Females, Avg Age 57.4 yo) with cough who were referred for manometry testing in the year of 2016. Of these 144 patients, 46 (31.9%) endorsed mild cough, 48 (33.3%) moderate cough, 35 (24.3%) severe cough, and 15 (10.4%) very severe cough, on pre-manometry patient questionnaire. The average BMIs for patients with

mild, moderate, severe, and very severe cough were 30.3, 29.1, 28.8, and 30.0, respectively.

Overall, our results did not show that patients with higher BMIs had endorsed more severe cough. There were no appreciable trends or differences in the BMI based on cough severity. This could partially be attributed to the patient sample source, which included only those referred for manometry, thus already increasing the likelihood of contributing factors to cough other than obesity, such as dysphagia and dysmotility-induced reflux. However, it is interesting to note, that on average, all patients with cough referred for manometry had BMIs in the overweight or obese category. Future studies will look at BMI in patients without cough compared to those with cough, as well as compare endorsement of regurgitation in our patients.

73 | The association between esophageal dysmotility and cough

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Gastroesophageal reflux is often considered the culprit for chronic cough; however, other GI issues such as weak esophageal peristalsis has not been looked at. The aim of this retrospective study was to determine the prevalence of a diagnosis of "ineffective esophageal motility" and/or "fragmented esophageal motility" (as determined by manometry testing) amongst patients with varying degrees of cough (as reported on patient questionnaire).

All patients referred to a tertiary care hospital for manometry testing in the year of 2016 were analyzed. Of a total of 355 patients referred for manometry, 156 endorsed symptoms of cough on their pre-manometry patient questionnaire and 199 did not. Amongst the 156 who endorsed cough, they further rated their cough severity as follows: 47 reported mild cough, 55 moderate cough, 37 severe cough, and 17 very severe cough. The percentages of patients with a diagnosis of weak peristalsis in each cough group (i.e. no cough, mild, mod, severe, very severe cough) was calculated. There was no statistically significant difference in the prevalence of weak peristalsis amongst patients with and without cough or amongst patients with varying severities of cough. However, overall ~59% of patients without cough carried the diagnosis of weak esophageal peristalsis compared to ~10% of patients with cough.

Past literature shows that there exists a key relationship between esophageal-laryngopharyngeal interactions (i.e. GERD-induced cough), however here we found that patients who carry a diagnosis of ineffective or fragmented esophageal motility are less likely to experience cough. Reflux-associated cough is believed to be due to two pathways: reflux-induced aspiration and a vagally-mediated esophago-bronchial reflex. The vagus nerve provides the sensory pathways for esophageal peristalsis and the vagal esophago-bronchial reflex; so potentially anything that affects the vagus nerve will effect both peristalsis and the cough reflex. Thus, patients with intact peristalsis and presumed intact vagal function, are more likely to experience cough, whereas patients with ineffective motility report less cough. It would be beneficial for future work to look at the pH studies of patients with weak peristalsis and note the actual distal and proximal acid exposure in these patients compared to those without esophageal dysmotility.

74 | Lower basal esophagogastric junction pressures associated with regurgitation severity

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It is thought that regurgitation is brought on by changes in esophageal pressure ultimately causing a transient relaxation in the lower esophageal sphincter (LES) with resultant regurgitation. However, it is unknown if the severity of regurgitation symptoms experienced by a patient are related to the basal LES pressure. Our hypothesis is that patients with more severe regurgitation symptoms have lower basal LES pressures. The aim of this retrospective study was to compare the basal LES pressures, as measured by impedance enhanced esophageal manometry, between patients with varying degrees of regurgitation severity, as reported on pre-manometry patient questionnaire.

All patients referred to a tertiary care hospital for manometry testing in 2016 were initially included. Of the 354 patients referred for manometry, 167 patients (41 males, mean age 54.6; 126 females, mean age 55.6) endorsed regurgitation. Of those 167 patients, 62 reported their symptoms as "mild", 61 as "moderate", 29 as "severe", and 15 as "very severe". The average LES pressure was 33.22 mmHg for those with mild regurgitation, 27.98 for moderate, 23.94 for severe, and 19.02 for very severe ($P = 0.03$). There was also a statistically significant difference in LES pressures between mild and severe regurgitation ($P = 0.03$) and mild and very severe regurgitation ($P = 0.01$).

Overall, it is known that transient relaxations in LES pressure lead to regurgitation. However, we aimed to assess if there is a difference in basal LES pressures amongst patients who experience regurgitation symptoms, as perhaps a lower basal pressure makes a patient more prone to experiencing more severe regurgitation. There was a statistically significant difference in basal LES pressures amongst patients with varying severities of regurgitation. Future studies should look at pH testing to note if there is an actual increase in proximal acid exposure in patients with lower basal LES pressures and more severe regurgitation.

75 | GC-C agonism with linaclotide attenuates chronic stress-induced colonic hypersensitivity independently of elevated crf expression in the central nucleus of the amygdala

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Background: Psychological stress is a risk factor for irritable bowel syndrome (IBS), a functional pain disorder exhibiting a female predominance. Linaclotide, a peripherally restricted guanylate cyclase-C (GC-C) agonist, relieves IBS with constipation and exhibits antinociceptive activity in a rodent model of post-inflammatory visceral hypersensitivity. Here, we test the hypothesis that GC-C agonism attenuates stress-induced colonic hypersensitivity through normalization of amygdala CRF expression.

Methods: Adult female Long Evans rats were exposed to water avoidance stress (WAS) or sham WAS (1 hr. /day) for 10 days and fecal pellet output was recorded as a measurement of autonomic outflow. On day 28, colonic sensitivity was assessed via a visceromotor response (VMR) to graded pressures (20–60 mmHg) of isobaric colorectal distension (CRD). In a separate cohort following WAS or sham WAS animals were euthanized on day 28 and the central nucleus of the amygdala (CeA) was isolated for CRF expression via RT-qPCR. In another series of experiments, the effect of linaclotide (3 µg/kg p.o. for 7 days prior to outcome assessment) on WAS-induced colonic hypersensitivity or amygdala CRF expression was investigated.

Results: During the stressor rats exhibited an elevated fecal pellet output (WAS = 9.9 ± 0.3 vs. sham WAS = 3.9 ± 0.3 pellets/hr.). Animals also exhibited colonic hypersensitivity on day 28 (60 mmHg = 43.0.0 ± 4.0 vs. 19.6 ± 2.7 abdominal contractions/10 min., $P < 0.0001$). Linaclotide significantly reduced colonic hypersensitivity (60 mmHg = 25.6 ± 1.5 abdominal contractions/10 min) to levels resembling vehicle controls (60 mmHg = 24.3 ± 1.5 abdominal contractions/10 min $P < 0.0001$). Post WAS, RT-qPCR analysis revealed significantly elevated amygdala CRF mRNA compared to sham WAS (Fold Change = 4.3 ± 0.7 ($2^{-\Delta\Delta C(T)}$), $P < 0.001$). Linaclotide had no inhibitory effect on the WAS-induced increase in CeA CRF expression.

Summary: Stress induces persistent colonic hypersensitivity and elevated CRF expression in the CeA in female rats. Following treatment with linaclotide there was an inhibition of stress-induced colonic hypersensitivity without any reduction in elevated amygdala CRF expression.

Conclusion: Stress-induced visceral nociception can be effectively managed with linaclotide, a peripherally restricted GC-C agonist.

76 | Inter-observer reliability for stool consistency between the Bristol stool scale and the Brussels Infant and Toddler Stool Scale (BITSS) when using Rome IV criteria in younger children

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Introduction: One of the criteria for functional constipation in Rome IV criteria is the presence of hard or painful bowel movements. In adults and children, the Rome IV criteria recommends the use of the Bristol stool scale (BSS). The BSS uses photographs of different types of stool in order to assess its consistency. There has been poor validation of BSS in older children, and this scale is thought not to be appropriate for evaluation of stool consistency in young children and infants. Recently, the Brussels Infant and Toddler Stool Scale (BITSS) was developed as a visual stool form scale for infants and younger children wearing diapers. The only study to date on BITSS was aimed to assess inter-evaluator agreement. There are no prior studies comparing BITSS with BSS. Our main aim was to compare parental assessment for stool consistency using the Rome IV questionnaire against BITSS and BSS. In addition, we also correlated parental assessment of stool consistency between BITSS and BSS.

Methods: Surveys were provided to parents of participants that attended their well child visit in two cities from Colombia. Questions included demographics, Rome IV validated questionnaire and assessment of participant's stool consistency using pictures for BSS and BITSS. Inter-observer reliability was measures using the kappa (κ) statistic.

Results: 815 children were recruited. Mean age was 17.6 months (range 1 to 48 months). 173 patients (21.2%) fulfilled criteria for FGIDs using the Rome IV questionnaire and 78 children (9.6%) had functional constipation. There was overall slight to fair inter-rater agreement between Rome IV versus BSS and BITSS. Inter-rater reliability between BSS and BITSS was overall fair (κ0.28) and moderate when used in infants up to one year of life (κ0.42). Stratification of patients by presence/absence of FGIDs or functional constipation did not elicit any significant improvement on κ values.

Conclusion: There is no adequate parental inter-observer reliability between Rome IV and stool consistency assessment with either BSS or BITSS. Moreover, BITSS does not have good parental reliability when compared to BSS. Stool consistency evaluation remains to be challenging in younger pediatric populations.

77 | Baseline impedance on high-resolution esophageal impedance-manometry correlates with impedance parameters of reflux in lung transplantation

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Background: Bolus and acid reflux have been associated with poor lung transplant outcomes, leading to the use of impedance-pH testing (MII-pH) in transplant evaluation. MII-pH can be time-consuming and poorly tolerated in this high-risk population. Mean nocturnal baseline impedance (MNBI) is a metric of mucosal integrity on MII-pH that has been associated with acid reflux. Baseline impedance measured on high-resolution esophageal impedance-manometry (HRIM-BI) may provide useful data on reflux burden to stratify transplant risk. We aim to assess the relationship between HRIM-BI and reflux metrics on MII-pH.

Methods: This was a retrospective cohort study of lung transplant recipients who underwent pre-transplant HRIM and MII-pH off PPI at a tertiary care center. HRIM-BI was extracted from the distal-most pair of impedance electrodes (3–5 cm above high-pressure zone), measured across 15 seconds at the start of HRIM. On MII-pH, both traditional and advanced reflux metrics including postreflux swallow-induced peristaltic wave (PSPW) and MNBI were recorded. PSPW was an antegrade peristaltic swallow propagating the length of the esophagus within 30 seconds of an impedance reflux event. PSPW index is the proportion of all impedance reflux events associated with a PSPW. Distal MNBI was recorded from the distal-most pairs of impedance electrodes (5 & 3 cm above LES) measured across 10 minutes over three stable periods at 12am, 1am, and 2am while recumbent. Correlations were assessed using Pearson correlation coefficients.

	Mean Value	R^2 *vs* HRIM-BI	*P*
PSPW index	31.1% (SD 11.6%)	0.40	0.02
Distal MNBI	1769 Ω (SD 1150)	0.31	0.04
Acid exposure time	2.84% (SD 4.04)	−0.08	0.54
Total bolus episodes	55.6 (SD 35.7)	−0.26	0.05

Results: 133 subjects (59% men, 56 yrs) were included. Overall, lung transplant subjects demonstrated low HRIM-BI (1023 Ω, SD 668), low PSPW index, and low distal MNBI. The mean MNBI values were below the published cutoff of 2292 ohms for esophageal reflux (Frazzoni 2016). HRIM-BI values significantly correlated with MII-pH reflux parameters.

Conclusion: HRIM-BI was low in lung transplant recipients, and significantly correlated with other advanced impedance metrics associated with mechanisms of post-reflux clearance and reflux-mediated injury. HRIM-BI also correlated with total bolus episodes on MII-pH, likely reflecting the consequences of acid and non-acid reflux. HRIM-BI derived solely from esophageal manometry may be a useful proxy for reflux severity in pre-lung transplantation evaluation without the need for additional, prolonged testing.

78 | Gastroesophageal reflux is associated with chronic rejection after lung transplantation independent of underlying pulmonary physiology

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Background: Gastroesophageal reflux (GER) has been associated with bronchiolitis obliterans syndrome (BOS) as a reflection of chronic rejection after lung transplantation. Prior studies demonstrated that restrictive pulmonary physiology, as seen in interstitial lung disease (ILD), may have greater association with GER than obstructive physiology, such as chronic obstructive pulmonary disease (COPD). Despite these findings, the impact of pulmonary physiology on transplant outcomes remains controversial, and the mechanistic relationship between GER and pulmonary physiology, in association with transplant outcomes, is poorly understood. We aimed to assess the relationship between objective GER measures, FEV1/FVC ratio on pulmonary function test (PFT), and development of BOS after lung transplantation.

Methods: 108 lung transplant recipients (58% men, mean age: 57, mean follow-up: 2.65 years) at a tertiary center who underwent pre-transplant 24-hr impedance-pH testing off PPI were included. Patients with pre-transplant antireflux surgery were excluded. PFT results within 3 months prior to lung transplantation were recorded. FEV1/FVC > 70% was used to define a restrictive versus obstructive pulmonary process. Primary outcome was BOS as a reflection of chronic rejection, defined clinically/histologically per ISHLT criteria. Time-to-event analysis using Cox proportional hazards model was applied. Subjects not meeting the outcome were censored at death, last clinical reflux, or post-transplant antireflux surgery.

Covariate	Cox Univariate Analysis HR (95% CI)	p-value
AET	1.10 (1.01-1.19)	0.03
AET >4.2%	2.76 (1.14-6.71)	0.02
FEV1/FVC	13.9 (1.48-130.5)	0.02
FEV1/FVC >70%	3.58 (1.28-10.0)	0.01
Age at transplant	1.01 (0.97-1.05)	0.58
Body Mass Index	0.99 (0.90-1.08)	0.77
Male gender	1.30 (0.91-1.86)	0.15
Covariate	**Cox Multivariate Analysis HR (95% CI)**	**p-value**
AET >4.2%	2.88 (1.09-7.58)	0.03
FEV1/FVC >70%	6.06 (1.68-21.9)	0.006
Age at transplant	1.00 (0.96-1.04)	0.92
Body-Mass Index	0.93 (0.83-1.04)	0.20
Male gender	1.31 (0.50-3.41)	0.58

Results: Univariate analyses demonstrated associations between BOS and acid exposure time (AET), elevated AET, FEV1/FVC, and restrictive FEV1/FVC (Table 1a). On multivariate analysis,

increased acid exposure (HR 2.88, $P = 0.03$) and restrictive pulmonary physiology (HR 6.06, $P = 0.006$) remained independent risk factors for BOS, after controlling for age at transplant, BMI, and sex (Table 1b).

Conclusion: Increased GER and restrictive pulmonary physiology on pre-transplant testing independently correlated with higher risk of BOS. These findings suggest that the effect of GER on lung transplantation outcome is independent of underlying pulmonary mechanics. Routine evaluation for GER in all transplant candidates regardless of pulmonary diagnosis should be considered.

79 | Obesity is independently associated with increased risk of fecal incontinence and rectal hyposensitivity

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Introduction: Hindgut symptoms in obesity are poorly understood, even though they may worsen patients' social isolation and quality of life. While there is an association between obesity and diarrhea, the relationship between fecal incontinence (FI) and obesity is less clear. We aimed to evaluate the relationship between obesity and FI, and physiological changes in anorectal function.

Methods: Consecutive adults undergoing high-resolution anorectal manometry (HRAM) at a tertiary center for anorectal symptoms were included. Patient demographics, clinical history, surgical and obstetric history, medications and HRAM findings were reviewed. Included subjects were classified by obesity class: normal (BMI < 25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), Class I (30–34.9 kg/m^2), and Class II+III (>35 kg/m^2). Fisher exact test, student t-test, and Pearson's correlation were performed for univariate analyses, while logistic regression and general linear regression were used for multivariate analyses.

Results: 552 adult patients (83.7% female, 53.7 years) were included. Mean BMI was significantly higher among patients with FI compared to those without (27.5 kg/m^2 vs 25.9, $P = 0.013$). FI was more prevalent in class II+III obese patients vs non-obese patients (31.7% vs 14.7%, $P = 0.006$). On multivariate analysis controlling for potential confounders (age, gender, IBS, pelvic or anorectal surgery, and squeeze and resting pressures on HRAM), class II+III obesity (OR 3.05, $P = 0.018$), but not overweight or class I obesity, remained an independent risk factor for FI. On HRAM, BMI had significant positive correlation with first rectal sensation volume ($R = 0.117$, $P = 0.0067$) and mild negative correlations with anal sphincter squeeze pressure ($R = -0.087$, $P = 0.04$) and resting pressure ($R = -0.079$, $P = 0.06$). On general linear regression controlling for age, gender, IBS, and surgical history, BMI remained significantly associated with increased first rectal sensation volume (β-coefficient 0.634, $P = 0.004$). When grouping patients into obesity classes, class II +III obesity remained an independent risk factor for rectal hyposensitivity (OR 12.98, $P = 0.007$). No association between anal sphincter pressures and BMI or obesity class was noted on multivariate analyses.

Conclusions: Class II+III obesity (BMI > 35 kg/m^2) was an independent risk factor for FI. Rectal hyposensitivity on balloon distention testing correlated with increasing BMI and obesity. Decrease in rectal sensation may play an important role in the pathophysiology of FI in this population. Anorectal physiology testing should be considered in the management of obese patients with FI to help guide therapy.

80 | Clinical phenotypes of GERD patients non-responder to double doses of PPIs: a prevalence study based on esophageal pH monitoring results

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Background: GERD symptoms persist in a significant portion of patients treated for GERD with appropriate acid suppression. Defining whether treatment failure is due to persistent acid reflux, or due to a functional condition is crucial for the clinical management. The aim of the study was to determine the prevalence of clinical phenotypes of patients with GERD whose symptoms persist despite treatment with double doses of proton pump inhibitors (PPI).

Methods: Patients with GERD under treatment with double doses of PPI for at least 8 weeks, with esophageal symptoms such as heartburn, regurgitation, and/or chest pain were selected. Atypical symptoms were also recorded. All patients underwent dual pH-multichannel intraluminal impedance (pH-MII) monitoring. Symptoms were considered associated with reflux if occurring within 5 min after a reflux event. Patients were classified into three groups: persistent acid reflux (acid esophageal exposure [AET] >4.5% of time), reflux hypersensitivity (AET < 4,5%, symptom index [SI]≥50% and symptom association probability [SAP] >95%), and functional symptoms (AET < 4.5%, SI < 50% and SAP < 95%).

Results: We included 296 patients. The most prevalent phenotype was functional reflux, followed by reflux hypersensitivity and persistent acid reflux (59%, 30% and 11%, respectively). The patients with functional symptoms had more extraesophageal symptoms than patients with reflux hypersensitivity and persistent acid reflux (61%, 30% and 8%, respectively). The body mass index no was different among groups.

Conclusion: The majority of patients with GERD whose symptoms persist despite to PPI therapy have functional symptoms or other causes not related to reflux. Thus, the treatment of PPI non-responders should focus on mechanisms beyond reflux, such as visceral hypersensitivity and hypervigilance.

81 | Influence of high fat diet on the enteric nervous system during pregnancy

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The enteric nervous system (ENS) retains plasticity throughout life span. As diet is known to influence the enteric nervous system (ENS), we tested the hypothesis that a high fat diet during pregnancy may influence the maternal ENS and structure within the colon. Five-week old female C57BL/6J mice were fed a control (n = 9) or a high fat (60% kcal from fat; n = 6) diet for 6 weeks prior to and throughout gestation. At 18.5 days gestation, maternal colon tissue was fixed in Carnoy's solution, processed, embedded in paraffin and cross-sectioned at 5 µm, one section per sample. Enteric neurons within the myenteric plexus were visualized by immunolabeling with antibodies against protein gene product 9.5, images were captured using a microscope and computer image analysis was performed using the Volocity image analysis system. Enteric neurons within the myenteric plexus were quantified as a proportion of the total myenteric area. Five fields of view per section at 20x magnification were analyzed. Crypt depth was also measured to assess structural changes within the colon. No significant differences were found in PGP9.5 density between control and high fat fed mice. No significant differences were found in crypt depth between control and high fat fed mice. Further research will be needed to determine whether any adaptations occur to the myenteric plexus throughout the gestational period. This will require analyzing more samples from different time points during pregnancy, such as 10 days gestation.

82 | Distribution of transient receptor potential vanilloid type 2 channel in rat gastrointestinal tract: alteration in TNBS-induced colitis

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Transient receptor potential vanilloid (TRPV) 1 and TRPV2 are two TRP channels originally described as heat-sensitive. TRPV1 is activated by heat > 43 °C and protons. TRPV2 has a much higher thermal activation threshold (> 52°C). In rat dorsal root ganglion (DRG), TRPV1 neurons are small to medium-sized whereas TRPV2 have medium-sized to large cell bodies. However, little is known about the distribution of TRPV2 in gastrointestinal tract. In this study, we investigated the expression of TRPV2 in rat enteric and DRG/nodose ganglion (NG) innervating distal colon, and their alteration under TNBS-induced colitis compared with TRPV1. Abundant TRPV2 immunoreactivities were detected in the mucosa and muscle layer of the rat distal colon. TRPV2 immunopositive cell bodies were co-localized with intrinsic primary afferent neuronal marker NeuN-(67.0%) and inhibitory motor neuronal marker nNOS-(32.0%) positive cells in the myenteric plexus. TRPV2 cells were colocalized with macrophage marker ED2-positive cells in mucosa. On the other hand, TRPV1 cell bodies were not detected in myenteric plexus. Subtypes of TRPV2-and TRPV1-immunopositive L6/S1 DRG were labeled with the A-fiber marker NF200 and the C-fiber marker IB4, respectively. Subtypes of TRPV2-and TRPV1-immunopositive NG neurons were labeled with both NF200 and IB4. To determine the tissue-specific neuronal distribution of TRPV1 and TRPV2, we counted the co-expression of TRPV1 and TRPV2 immunoreactivity in retrograde fluorescent tracer fluorogold labeling neurons that innervate the distal colon. TRPV2-immunoreactive cell bodies in DRG (23.0%) and NG (65.1%) were double-labeled with fluorogold. TRPV1-immunoreactive cell bodies in DRG (40.0%) and NG (45.7%) were double-labeled with fluorogold. Expression of TRPV2 and TRPV1 in the distal colon, DRG, and NG neuron was significantly increased in a trinitrobenzene sulfonic acid-induced colitis model compared with normal rat. In conclusion, TRPV2 are expressed in enteric macrophages, intrinsic primary afferent neuron and inhibitory motor neuron in the enteric nervous system. TRPV2 are also expressed in spinal and vagal primary afferent neurons innervating distal colon. TRPV1 are expressed in spinal and vagal primary afferent neurons innervating distal colon, but not in intrinsic neuron. The alteration of TRPV2 in TNBS-induced colitis model may contribute to various functions under intestinal inflammation.

83 | Mechanotransduction in enteric glia may cause direct presynaptic facilitation of non-cholinergic neuromuscular contractions

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Introduction: Mechanical stimulation of enteric glia (EGC) in animals and man triggers a glial Ca^{2+} wave that is altered by inflammation. Ca^{2+} signals in enteric glia modulate motility and are implicated in GI Diseases (Gastroenterology, 2018).

Aim: Therefore, we sought to further investigate glial mechanosensory signaling in mouse and man and explore its putative physiological role.

Methods: A 1 sec light touch mechanical stimulus (MS) used to trigger a Ca^{2+} wave is applied with a fire-polished glass pipette (3.5–4.5 µm tip) using a joystick Piezo micromanipulator programmed to deliver the stimulus. Ca^{2+} wave analysis was done in networks of myenteric glia in culture (hEGC) or isolated networks of myenteric ganglia from human colon surgical specimens (N = 20; IRB 2017H0441), and glia in intact myenteric plexus-preparations of NestinCre-GCAMP-tdT^{+}Ca^{2+} reporter mice. Atropine and nicardipine limits muscle contractions. Spatio-temporal-imaging was done to study fluid-induced peristalsis of the colon (or ileum) in response to gliotoxin fluoroacetate.

Results: In hEGC, touch in 358 of 358 trials caused a Ca^{2+} wave in 18 ± 1 glia/field (32% of $DAPI^{+}$/s100β^{+} glia/field, *n* = 23 trials). The gap junction inhibitor carbenoxolone (0.2 mM) reduced the response by 63% (*P* < 0.0001). The touch response is reduced in 0 Ca^{2+}+EGTA from 35% to 23% cells/field (*P* = 0.04, *n* = 6–7). In networks of human myenteric ganglia (*n* = 4 networks) touch evoked a glial response in 3.89 ± 0.54 glia/touch in 80% of trials (*n* = 50 trials; glia respond to ADP/ SaTx). Touch caused V_m-depolarization in hEGC or networks (14 ± 9 mV, *n* = 7). In Ca^{2+} reporter mice, a single touch onto a ganglion (not outside) caused a Ca^{2+} wave in 140/140 trials, 9.23 ± 0.66 glia/ganglion and < 0.5 HuC/D^{+} neurons/ganglion, and TTX had no effect (55% versus 52% of glia/ganglion respond; *P* > 0.05, *n* = 20 ganglia). Touch caused muscle contraction in either direction subsequent to the Ca^{2+} wave that was inhibited by TTX from 64% to 15% of touch-responses (*P* = 0.0036). Zero Ca^{2+} buffer partially inhibited Ca^{2+} transients (*P* = 0.0048); but glia responding were the same (*P* = 0.92, *n* = 11 ganglia). Zero Ca^{2+} did not inhibit contractions (*n* = 10, *P* > 0.99). Gliotoxin disrupted fluid distension-induced contractions or peristaltic waves (*P* < 0.01, *n* = 3–5 each), or reversed direction of peristalsis.

Conclusions: Mechanotransduction in glia is a putative physiological mechanism of motility in mouse and man. Touch triggers a glial Ca^{2+} wave resulting in presynaptic facilitation of non-cholinergic neuromuscular contractions. *(NIH DK113943).*

84 | Neuroanatomical and connectivity abnormalities identified by brain MRI analysis in CVS patients with and without marijuana use

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Introduction: Adult Cyclic Vomiting Syndrome (CVS) is a disorder characterized by abrupt episodes of nausea, vomiting, and abdominal pain separated by intervals of relative wellbeing lasting days to months. A dysregulation of central nervous system is the proposed underlying theory in pathophysiology. Recent literature has pointed to marijuana use (MU) as a major etiological factor of CVS and an entity termed Cannabinoid Hyperemesis Syndrome (CHS) has been coined as a separate identity from "standard" CVS. However, little is known about brain structural and functional connectivity (CN) in both the non-marijuana (non-MU) and MU CVS subgroups.

Methods: 23 CVS subjects (13 non-MU, 10 MU) and 20 healthy controls (HC); age and gender matched were enrolled in an IRB approved study. Criteria for CVS-MU patients was > 3 years of daily MU. All CVS patients completed MRI scans during a symptomatic episode. Image analysis of subcortical (SC) volume (V); SC segmentation was carried out using FreeSurfer which runs on automated segmentation of 40 brain regions. Resting state functional CN analysis group differences were evaluated with Independent component analysis and MANCOVA statistical model.

Results: Structurally, anatomical analysis revealed significant (Sig.) differences in SC grey matter (GM) V among the study groups. Specifically, non-MU CVS group had Sig. reductions in GM compared to MU-CVS who are similar to HC (Hippocampus *P* < 0.01; L Amygdala *P* < .05. Also, CVS non-MU subjects had sig. higher CN than HC and CVS MU subjects within the insula and temporal component network. This CN data is clinically relevant since abnormal functional alterations of the insula have been found in other GI disorders associated with nausea and vomiting.

Conclusion: 1. Based on brain MRI analysis we concluded that non-MU CVS had sig. reductions in GM compared to MU CVS patients, who were similar to HC- Suggesting MU may have a positive influence on stress and pain, such that SC V had less reduction. 2. The sig. reductions in GM were in regions associated with emotion, stress and pain-the amygdala & hippocampus as well as regions related to dopaminergic innervation. 3. The greater CN data in non-MU CVS is a new observation providing insights for future therapeutic approach in CVS.

85 | Evidence for the abnormal anchoring between the lower esophageal sphincter and crural diaphragm in patients with achalasia esophagus

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Background: The LES and crural diaphragm (CD) are anchored together by the phrenoesophageal ligament and move together with inspiration and expiration. However, with swallow the LES moves in an oral direction. Contraction deceleration point (CDP) during peristalsis is an important landmark at which velocity of peristalsis decreases. Studies show that bolus propulsion beyond the CDP is related to the descent of an ascended esophagus or LES back into its resting location. Impedance transition line (ITL) at the lower edge of LES in the resting state and with swallow, moves in the cranial direction, close to CDP and returns back after peristalsis.

Goal: Determine the relationship between lower edge of LES, ITL, CDP, and inspiration related CD impression (CDI) on the HRMZ recordings in normal subjects and patients with achalasia esophagus.

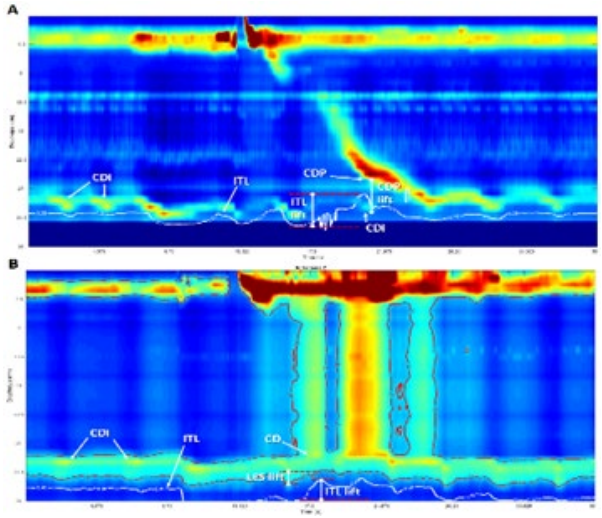

Fig 1. Location of CDP, ITL and CDI in (A) normal subject, (B) Achalasia patient

Methods: 14 healthy subjects and 14 patients with achalasia II were studied. Impedance isocontour that represented the lower edge of LES was used to track the movements of LES with swallow. The CDP location in relationship to lower edge of LES before swallow, and movement of CDI with swallow were measured from HRMZ recording.

Results: In normals, the CDP is located 4.29 ± 0.6 cm from the lower edge of LES. Isocontour line at the lower edge of LES also moved 3.59 ± 0.4 cm with swallow. At rest the LES and CDI are superimposed on each other, and its location did not change with swallow suggesting the CDP is located above the CDI, before as well as during swallow. In patients, the CDP is not identifiable. Before swallow, the LES and CD are located together (similar to normals). During swallows even though the LES lifts (1.29 ± 0.3 cm) (as seen by HRM), and ITL there is no separation between the CDI and LES.

Conclusion: Swallow related axial shortening of the esophagus results in anatomical separation between the LES and CD, which is not the case in achalasia esophagus. Lack of sliding between the LES and CD may play an important role in impaired LES relaxation in the achalasia esophagus.

86 | Electrophysiological and mechanical characteristics of rectal compliance and role of enteric nervous system and interstitial cells in gastrointestinal smooth muscle

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Rectal compliance is a unique characteristic, differentiated from the colonic propulsive movement, with contributing to fecal storage. The rectal smooth muscle can be relaxed with the fecal volume increasing without pressure increasing. Abnormal rectal compliance can be presented in many gastrointestinal (GI) motility disorders, such as irritable bowel syndrome, constipation and fecal incontinence. This study aimed to explore the electromechanical characteristics of rectal compliance in the murine rectal smooth muscle and investigate the contribution of intrinsic inhibitory neurotransmission and interstitial cells, such as interstitial cells of Cajal (ICC) and Platelet-derived growth factor receptor α-positive (PDGFRα$^+$) cells, on rectal compliance.

Male C57BL/6 mice, aged 8 weeks or more were used for recording rectal compliance, in vivo and ex vivo. Electrophysiological microelectrode recordings for membrane potential changes and mechanical tension recordings for contractions were performed. Confocal microscopic imaging was used to record calcium activities in the smooth muscle cells or interstitial cells in the mice expressing genetically encoded calcium indicator (GCaMP).

The rectal compliance significantly decreased after injection of L-NNA or apamin, intraperitoneally, in vivo (P = 0.002, 0.005). The compliance, ex vivo, also decreased after L-NNA or apamin (P = 0.016, 0.015). The colonic migrating motor complex (CMMC) did not develop in the rectum. The area under the curve (AUC) (mNxmin) was significantly different between the colon and rectum (49.72 ± 21.43 vs 8.79 ± 3.45, P = 0.001). When the L-NNA or apamin were administrated, contractions were increased and propagated from the distal colon (6.19 ± 3.98 vs 20.35 ± 15.78, P = 0.031, 7.20 ± 3.32 vs 29.12 ± 20.75, P = 0.046). Inhibitory junction potential (mV) significantly increased after L-NNA or apamin (17 ± 2.9 vs 16 ± 1.6, P = 0.04, 24 ± 2.5 vs 13 ± 3.6, P = 0.02). The AUC of calcium transient in the rectum was smaller than colon (9.36 ± 4.57 vs 3.49 ± 2.58, P = 0.03), similar to CMMC. The AUC increased after L-NNA or apamin (3.79 ± 1.93 vs 9.71 ± 4.52, P = 0.001 3.26 ± 1.92 vs 8.31 ± 4.12, p = 0.021). The calcium transient (IUxmin) significantly increased after L-NNA in the ICC (7.39 ± 2.52 vs 10.98 ± 3.71, P = 0.012).

Large compliance, different from the colonic CMMC, were identified in the murine rectum. Enteric inhibitory neurotransmissions associated with nitric oxide or purine were related to the rectal compliance and ICC or PDGFRα$^+$ cells can control the rectal smooth muscle activities. These electrophysiological and mechanical characteristics of rectal compliance can be used for further studies of GI motility disorders.

87 | Importance of cgrp-mediated mechanisms in visceral organ cross sensitization

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Background: Irritable bowel syndrome (IBS) and bladder pain syndrome/interstitial cystitis (BPS/IC) are highly comorbid chronic pain

disorders with unknown etiology, limited treatment options and purported to involve visceral organ cross sensitization. Calcitonin gene-related peptide (CGRP) is a major mediator of nociceptive processing. Here we investigate the hypothesis that visceral organ crosstalk is mediated by sensitization of CGRP-containing peripheral afferents. Methods

To induce visceral organ crosstalk, adult female Sprague Dawley rats received a single transurethral infusion of protamine sulfate (PS, 1 mg/mL) into the urinary bladder. Colonic and bladder sensitivity was assessed 24-hr or 5 days post-PS. Colonic sensitivity via a visceromotor response (VMR) to grade pressures (0–60 mmHg) of isobaric colorectal distension (CRD) quantified as the number of abdominal contractions and bladder sensitivity via the frequency of withdrawal responses to von Frey hairs (0.16–15 g) applied to the suprapubic region. In a separate group of female rats, PS-induced colonic and bladder permeability was investigated *in vitro* via measurements of transepithelial electrical resistance (TEER) at 24-hr and 5 days post-PS. To investigate the importance of peripheral CGRP-mediated mechanisms in colon-bladder cross-sensitization, a peripherally restricted anti-CGRP $F(ab')_2$ (30 mg/kg i.p.) or isotype control $F(ab')_2$ were administered 24-hr prior to outcomes assessment. Sham controls (catheter inserted but no bladder infusion) were also included in the study.

Results: As shown in Table 1 adult female rats that received a PS infusion into the bladder exhibited colonic hypersensitivity as measured via an increase in the VMR to CRD at both 24-hr and 5 days post PS compared to sham controls ($P < 0.0001$). The same rats also demonstrated bladder hyperalgesia, with a greater number of withdrawal responses provoked by suprapubic pressure compared to sham controls ($P < 0.001$). In a separate cohort of rats PS-into the bladder induced an increase in colonic and bladder permeability quantified as a decrease in TEER ($Ohm.cm^2$) 24-hr. and 5 days after PS administration. PS infused rats treated with anti-CGRP $F(ab')_2$ exhibited significantly reduced bladder and colonic hypersensitivity at 24-hr. and 5 days. Anti-CGRP $F(ab')_2$ also normalized both colonic and bladder TEER on day 5.

Summary: Visceral pain is difficult to manage and poorly understood, here we show that CGRP-mediated mechanisms play a key role in colon-bladder cross organ sensitization through an attenuation of visceral hypersensitivity and epithelial hyperpermeability.

Conclusion: Our findings suggest that anti-CGRP antibody treatment may serve as a novel approach to treat pain caused by visceral organ cross sensitization

Table 1:

	Outcome assessment			
	Sensitivity		Permeability	
Treatment	24-hr	Day 5	24-hr	Day 5
COLON	60 mmHg (VMR to CRD)		TEER ($Ohm.cm^2$)	
PS + Vehicle	25.6 ± 1.6††††	24.5 ± 0.9†††	173.7 ± 8.7†	184.4 ± 6.8†
PS + Anti-CGRP	19.1 ± 1.9$^{**, \#}$	17.3 ± 1.6$^{**, \#\#\#\#}$	231.7 ± 10.2$^{**, \#\#\#\#}$	243.8 ± 10.8$^{**, \#\#\#\#}$
PS + Isotype	23.6 ± 1.1	26.4 ± 1.1	156.1 ± 7.4	167.51 ± 9.4
Sham	18.0 ± 1.2	18.0 ± 1.2	223 ± 16.7	223 ± 16.7
BLADDER	15 g (Gram Force)		TEER ($Ohm.cm^2$)	
PS + Vehicle	6.1 ± 0.4††††	5.5 ± 0.6†††	1578 ± 99.0††	1605 ± 80.4††
PS + Anti-CGRP	4.3 ± 0.5$^{**, \#\#\#\#}$	3.5 ± 0.7$^{*, \#\#\#\#}$	1538 ± 44.8	2345 ± 202.7$^{*, \#\#}$
PS + Isotype	6.2 ± 0.3	6.8 ± 0.4	1472 ± 103.5	1496 ± 143.7
Sham	2.4 ± 0.5	2.4 ± 0.5	2524 ± 422.1	2524 ± 422.1

$^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$, $^{\dagger\dagger\dagger\dagger}P < 0.0001$ anti-CGRP $F(ab')_2$ compared to Vehicle
$^{*}P < 0.01$, $^{**}P < 0.001$, $^{***}P < 0.0001$ anti-CGRP $F(ab')_2$ compared to Vehicle
$^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#\#}P < 0.0001$ anti-CGRP $F(ab')_2$ compared to Isotype control $F(ab')_2$
One or Two-Way ANOVA w/ Bonferroni's or Tukey's multi-comparison post-test.

88 | Long-term symptom improvements after recommending gastroparesis diets in patients with suspected gastroparesis in relation to gastric emptying on wireless motility capsule testing

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Background: The longitudinal impact of diet changes on overall and individual upper GI symptoms of patients with suspected gastric emptying time (GET) delay by wireless motility capsule (WMC) testing is unknown. Low particle size diets reduce symptoms in diabetic gastroparesis but benefits of gastroparesis diets with normal gastric emptying are untested. We hypothesized gastroparesis diets reduce overall and individual gastroparesis symptoms more on long-term follow-up in patients with delayed vs. non-delayed GET by WMC.

Methods: Patients with suspected gastroparesis at 10 sites underwent gastric emptying testing by concurrent scintigraphy and WMCs. Investigators recommended treatment changes (including diet) based on gastric emptying rates. Gastroparesis diets (low fat, fiber, or residue and/or liquid and/or frequent, small meals) were recommended for 21 patients with non-delayed GET and 26 patients with delayed GET. For this analysis, overall GCSI and individual symptom scores from PAGI-SYM surveys (0 = none, 5 = very severe) at baseline and 6 month follow-up on diet were related to the presence or absence of delayed GET (>5 hr) by WMC.

Results: Gastroparesis diet recommendations were associated with overall GCSI reductions from 2.7 ± 1.0 to 2.2 ± 1.2 over 6 months in the whole group (P = 0.003). Overall GCSI scores improved in patients with delayed GET (from 3.0 ± 0.9 to 2.3 ± 1.1, P = 0.004) but not non-delayed GET (from 2.4 ± 1.2 to 2.1 ± 1.4, P = 0.22). In those with delayed GET, individual symptoms of nausea/vomiting (from 2.4 ± 1.3 to 1.6 ± 1.4, P = 0.02), fullness/early satiety (from 3.4 ± 1.2 to 2.7 ± 1.3, P = 0.005), bloating/distention (from 3.2 ± 1.5 to 2.6 ± 1.4, P = 0.04), and upper abdominal pain (from 2.8 ± 1.7 to 2.0 ± 1.8, P = 0.009) improved. For those with non-delayed GET, pain decreased (from 2.8 ± 1.5 to 2.1 ± 1.7, P = 0.04) and bloating/distention trended better (from 3.1 ± 1.7 to 2.4 ± 1.9, P = 0.07) while nausea/vomiting (from 1.3 ± 1.4 to 1.6 ± 1.2, P = 0.56) and fullness/early satiety (from 2.7 ± 1.3 to 2.3 ± 1.6 P = 0.14) did not improve.

Conclusions: This observational study found a positive impact of gastroparesis diet recommendations on overall and individual symptoms in patients with suspected gastroparesis who exhibit gastric emptying delays, whereas those with non-delayed gastric emptying noted minimal benefits over 6 months. These findings suggest that gastric emptying may have some capability to predict responders vs. non-responders on gastroparesis diet therapy based on gastric emptying times.

89 | Initial experience with abdominal massage during pediatric colonic manometry

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Introduction: Constipation is one of the most prevalent pediatric conditions encountered. Adherence to medical therapy, and parental misconceptions about it, often encumber optimal management. Abdominal massage for treatment of constipation has been described as early as the 19th century and is thought to stimulate peristalsis as well as increase rectal fecal loading. Our goal is to evaluate the effects of abdominal massage on colonic motility in patients receiving colonic manometry testing for various indications.

Method: Patients undergoing colonic manometry were enrolled to receive a standardized 5-minute abdominal massage prior to the medication provocation phase of the study, followed by 1 hour monitoring. Three pediatric gastroenterologists independently reviewed manometric tracings for objectively defined motility patterns: low amplitude propagating contractions (LAPC, amplitude < 50 - 60 mmHg, duration > 10 seconds and propagating distance > 30 cm), high amplitude propagating contractions (HAPC; amplitude > 80 mmHg, duration > 10 seconds and propagating distance > 30 cm) and non-propagative colonic motor activity (segmental contractions). Subjective findings such as cramping, passage of flatus or stool, were also documented by the bedside nurse.

Results: Eight patients were enrolled, 63% female, average age 8.63 years (Table 1). Inter-rater reliability between all three reviewers was 83%. Six out of 8 patients (75%) had one or more motility patterns present after the intervention (Table 2). Four patients demonstrated segmental contractions after the massage, LAPCs were observed in three patients and HAPCs were noted in two patients. As expected, patients with subjective symptoms (abdominal cramping, flatus or stool) also demonstrated colonic motility patterns. Inversely, many patients with identifiable colonic motility patterns did not have associated subjective symptoms present.

Discussion: Our small and diverse cohort had promising findings with 75% (6 out of 8 patients) exhibiting manometric evidence of colonic motor activity after receiving a standardized abdominal massage. This may suggest that previously observed clinical benefits of abdominal massage in treatment of constipation relate to increased colonic motor activity following manual stimulation of the abdomen.

90 | Clinical phenotypic presentation of rectal prolapse varies with age

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Background: Rectal prolapse (RP) is a debilitating condition that affects patients of all ages. Its diverse symptom profile can be difficult to recognize, especially in patients with intermittent or internal prolapse. We aimed to identify age-specific features of RP as a means of facilitating early recognition and treatment of this heterogeneous population.

Methods: An IRB-approved, prospectively-maintained database of patients with RP was analyzed. Clinical features, Cleveland Clinic Fecal Incontinence Scores (CCFIS), and Obstructed Defecation Scores (ODS) were collected and compared between patients of three age groups: younger than 50, between 50 and 70, and older than 70 years old (YO).

Results: Of the 99 consecutive patients (93 women) analyzed, 46 patients were > 70 YO (80.9 ± 7); 36 patients, 50–70 YO (60.8 ± 6); and 17 patients, <50 YO (36.7 ± 13). The most common symptom amongst all age groups was mucus discharge, as seen in 76% of patients > 70 YO, 71% of patients 50–70 YO, and 53% of patients < 50 YO. There were no significant differences in the prevalence of mucus discharge or fecal incontinence (FI); however, FI was reported as the most bothersome symptom by patients 50–70 YO. The severity of FI was highest in older patients ($P = 0.30$), whereas patients < 50 YO were the least likely to be bothered by FI ($P = 0.03$). Both patients < 50 YO and > 70 YO reported pain as their most bothersome RP symptom ($P = 0.03$). ODS scores were significantly higher in patients < 50 YO compared to those > 70 YO (9.3 vs 6.9, $P = 0.02$), consistent with the higher prevalence of history of constipation in patients < 50 YO than those > 70 YO (47% vs 24%, $P = 0.03$). No patients < 50 YO reported prolapse at rest, compared to 17% of patients 50–70 YO and 32% of those > 70 YO ($P = 0.03$). Neither the prevalence of concomitant vaginal prolapse nor concurrent urinary incontinence was significant between the three age groups. Likewise, BMI, duration of RP, rate of prior rectal surgery, opioid use, and the prevalence of chronic medical conditions such as diabetes, neuropsychiatric disorders, and connective tissue diseases were comparable among all groups.

Conclusion: Age-specific differences exist in the clinical presentation of RP. Mucus discharge is the most commonly reported symptom across age groups and should raise suspicion for RP. Although constipation is more common in younger patients and FI in older ones, pain is most bothersome to these patients seeking evaluation. The presence of concurrent urinary symptoms and vaginal prolapse, independent of age, favors a multidisciplinary pelvic floor approach.

Table 1. Patient and prolapse characteristics by patient age

	<50 YO (*n* = 17)	50–70 YO (*n* = 36)	>70 YO (*n* = 46)
Age (±SD),Y	36.7 ± 13	60.8 ± 6	80.9 ± 7
BMI (±SD), kg/m^2	23 ± 0.51	24 ± 0.45	23 ± 0.43
Mucus Discharge, *n* (%)	9 (53)	25 (70)	35 (76)
Fecal incontinence, *n* (%)	7 (41)	13 (36)	20 (43)
RP pain, *n* (%)*	15 (88)	16 (44)	27 (59)
History of constipation, *n* (%)	8 (47)	10 (28)	11 (24)
History of prior PR surgery, *n* (%)	17 (17)	36 (13)	46 (19)
Prolapse at rest, *n* (%)*	0 (0)	6 (17)	15 (33)
Duration of prolapse < 1 year, *n* (%)	6 (35)	9 (25)	20 (43)
Duration of prolapse 1–5 years, *n* (%)	9 (53)	20 (56)	17 (37)
Duration of prolapse > 5 years, *n* (%)	2 (12)	7 (19)	9 (20)
ODS	9.4	8.5	7
CCFIS	8.5	12.2	13.5
Urinary incontinence, *n* (%)	7 (41)	19 (53)	18 (39)
Vaginal prolapse, *n* (%)	1 (6)	4 (11)	10 (22)

*$P < 0.05$

91 | Symptom severity predicts short-term response to gastric electrical stimulation in children with refractory nausea and vomiting

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Background: Gastric electrical stimulation (GES) can improve symptoms and decrease dependence on supplemental nutrition in children with nausea and vomiting refractory to conventional treatment. Our aim was to identify patient factors associated with treatment response amongst children undergoing GES.

Methods: Using a prospective patient registry, we identified patients < 21 years treated with GES at our institution between 2009 and 2018. We reviewed baseline characteristics and follow-up symptom severity (Symptom Monitor Worksheet, SMW) and need for supplemental enteral/parenteral nutrition at 1 month, 12 months, and the most recent follow-up. Successful response was defined as (1) a > 1-point improvement in a patient's average SMW score or (2) the ability to stop supplemental nutrition.

Results: 85 patients (68% female, median age 15 years) were treated with GES. 13 had postural orthostatic tachycardia syndrome (POTS). Gastric emptying was delayed in 29/36 and antroduodenal manometry was abnormal in 27/40. Successful response based on SMW

was seen in 20/32 at 1 month, 19/38 at 12 months, and 30/60 at the most recent follow-up (all $P < 0.001$). Response at 1 month was associated with higher baseline nausea and vomiting severity scores ($P = 0.04$, $P = 0.003$). Out of the 60 children who required supplemental nutrition at baseline, 27 had stopped supplemental nutrition by 1 month and 33 by the most recent follow-up (all $P < 0.001$). Response at 1 month was associated with higher baseline vomiting severity scores ($P = 0.049$). Response based on SMW or the ability to stop supplemental nutrition was not associated with age, sex, abdominal pain severity or frequency, prior diagnosis of POTS, delayed gastric emptying or manometry findings, or prior abdominal surgery.

Conclusion: More severe baseline vomiting and nausea were associated with short-term response to GES, but likelihood of long-term response remained similar. Other baseline factors did not predict response. Further research is needed for a better understanding of the role of baseline factors in patient improvement.

92 | Resilience in irritable bowel syndrome is lower compared to the general population and other chronic gastrointestinal conditions

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Introduction: Resilience is the ability to recover and thrive in response to adversity. In select patient samples, lower resilience has been found in irritable bowel syndrome (IBS) vs healthy controls and is associated with worse symptom severity and quality of life. The aims of this study were to compare: 1) resilience and its determinants between IBS and non-IBS subjects in the general US population and 2) resilience between IBS and other chronic gastrointestinal (GI) conditions with similar symptoms.

Methods: Participants from the general US population were recruited by Cint USA to complete an online questionnaire. Demographics and self-reported physician diagnosis of IBS, celiac, inflammatory bowel disease and microscopic colitis were collected. Three questionnaires measured the components of resilience: the Connor-Davidson Resilience Scale (CD-RISC), adaptive resilience and the Brief Resilience Score (BRS). GI symptoms, early life adversity, and neuroticism were collected. For Aim 1, IBS was defined as those with a diagnosis of IBS and/or who met Rome criteria without co-morbid GI disease; non-IBS were all others in the sample. For Aim 2, the other chronic GI conditions group included those with the GI conditions listed above matched with IBS subjects by age, sex and neuroticism. Linear regression determined the association between resilience and early life adversity in IBS and non-IBS adjusting for demographics and neuroticism. The Kruskal-Wallis test was used to determine if resilience differed between IBS and other chronic GI conditions.

Results: 820 IBS (mean age 45.1 yrs, 85% F) and 1026 non-IBS (mean age 40.4 yrs, 67% F) were included. Resilience was lower in IBS compared to non-IBS (P's<0.05, all 3 measures). Demographic determinants of resilience were mostly similar in IBS and non-IBS. However, early life adversity was associated with increased resilience in non-IBS but not in IBS (CD-RISC, $P = 0.027$). IBS had significantly lower resilience vs other chronic GI conditions ($n = 95$ per group; CD-RISC and adaptive resilience, $P < 0.001$). BRS scores was similar in IBS and other GI conditions.

Conclusion: Individuals with IBS have lower resilience compared to non-IBS and other GI conditions in the general US population. Low resilience may serve as the link between early life adversity and the increased risk of having IBS. Resilience may be a novel, clinically relevant therapeutic target in IBS.

93 | Post-fundoplication gastroparesis: similarities and differences to idiopathic and diabetic gastroparesis

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NIH Gastroparesis Consortium

Post-fundoplication gastroparesis (PFGp) is being seen more frequently and represents an important form of gastroparesis.

Aims: (1) Describe clinical characteristics of patients with PFGp. 2) Compare clinical characteristics of patients with PFGp to patients with idiopathic (IGp) and diabetic (DGp) gastroparesis.

Methods: Patients with gastroparesis based on 4 hour gastric emptying scintigraphy and negative endoscopy underwent H&P, questionnaires assessing symptoms (Patient Assessment of Upper GI Symptoms [PAGI-SYM] which includes Gastroparesis Cardinal Symptom Index [GCSI]), quality of life (SF36v2), measures of depression (Beck Depression Index, BDI) and anxiety (State Trait Inventory, STI). Prior surgeries and present and past treatments for gastroparesis were determined.

Results: 28 patients with PFGp from Nissen fundoplication enrolled in NIDDK GpCRC registries: 79% female, age 55.6 ± 14.9 years, BMI 28.3 ± 7.1, with 46.3 ± 24.0% gastric retention at 4 hours. Compared to patients with IGp (473 patients), PFGp were older at the start of gastroparesis symptoms (48 ± 15 vs 36 ± 14 years; $P < 0.001$), had more severe gastric retention at 4 hours (46 ± 24 vs 28 ± 18%; $P < 0.001$). PFGp were less likely to use analgesic (nonnarcotic) medications (43 vs 63%; $P < 0.05$), but more likely to have received pyloric Botox injection (25% vs 11%; $P = 0.065$). Compared to patients with DGp (249 patients), PFGp were also older at start of gastroparesis symptoms (48 ± 15 vs 40 ± 13 years; $P = 0.003$), had similar gastric retention at 4 hours (46 ± 24 vs 40 ± 25%). Patients with PFGp has less severe vomiting (1.5 ± 1.9 vs 2.5 ± 1.8; $P = 0.013$). PFGp were less likely to be taking neuropathic pain medications (14% vs 33%;

P = 0.05) and more likely to have used complementary and alternative medicines (CAM) (46 vs 22%; P = 0.009). PFGp patients had significantly lower BDI scores, STI scores, and higher mental component of SF36 QOL than IGp and DGp (ps < 0.05).

Conclusions: Patients with PFGp have similarities and differences to IGp and DGp; symptom differences were associated with treatment differences. Overall, PFGp patients have: 1) More gastric retention on scintigraphy testing; 2) Vomit less due to restrictions of fundoplication; 3) Diagnosis relies on association of onset of Gp symptoms after fundoplication surgery.

94 | Economic burden of idiopathic gastroparesis in the United States

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Objectives: While often associated with diabetes mellitus, more cases of gastroparesis (GP) are idiopathic (IG) in etiology. There has been a gap in real world evidence quantifying the economic burden of IG. The objective of this study was to evaluate the economic burden associated with IG in the US.

Methods: This was a retrospective cohort study using a large claims database (Optum Research Database) for IG patients initially diagnosed in 2008–2016 (index period). The IG cohort included patients who were: with 2 + separate GP diagnosis claims or only 1 GP diagnosis claim but after a scintigraphy test (first GP diagnosis was the index), aged 18 + years at index, continuously enrolled for at least 1 year before (baseline) and 1 year after the index, no presence of diabetes or Parkinson disease or gastric surgery, and no GP claim at baseline. IG patients were matched 1:1 using a nearest-neighbor matching to people who had no GP diagnosis in database (Control cohort) via propensity scores based on baseline demographic (e.g. age, sex, region) and clinical (e.g. index year, comorbidities) characteristics. All-cause healthcare resource use (HRU; encounters to hospital inpatient, emergency room [ER], outpatient/ physician office [OP], pharmacy, and other settings) and associated costs were analyzed. Average annual total costs (medical plus pharmacy) were compared between IGs and controls. Costs are in 2017 US dollars.

Results: 13,478 patient pairs were matched (total of 26,956 patients). Baseline characteristics of IG patients (similar to the controls through matching) were mean age 54 years at diagnosis, 75% female, 65% insured by commercial plans; average (SD) baseline Charlson Comorbidity Index score was 1.3 (1.8), with chronic pulmonary disease (26.8%) and fibromyalgia (14.3%) more often reported. Compared to controls, IG patients had significantly higher annual costs across all HRU categories: inpatient $12,311 vs. $4,421, ER $1,024 vs. $442, OP $15,010 vs. $7,303, pharmacy $5,118 vs. $2,977, and other services $3,883 vs. $1,903 (all P < 0.0001). On average, IG patients incurred more than two times of the annual total costs compared to their matched controls, $37,346 vs. $17,046.

Conclusions: This large real-world database study indicated that, idiopathic gastroparesis imposes substantial economic burden on healthcare systems, primarily from hospitalizations and outpatient physician visits. Understanding the roles of symptoms and associated morbidity on the economic burden, as well as the impact of poor disease awareness and delayed diagnosis is needed.

95 | Psychometric evaluation of the ANMS GCSI-DD in patients with idiopathic or diabetic gastroparesis

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Objectives: The ANMS GCSI-DD was developed to meet the FDA recommendations for use as a patient reported outcome (PRO) measure to support symptom-based clinical trial endpoints in idiopathic (IG) or diabetic gastroparesis (DG). The instrument measures the core symptoms of gastroparesis based on a daily diary. The purpose of this analysis was to further evaluate the psychometric measurement properties of the ANMS GCSI-DD.

Methods: Patients were recruited in the US for a randomized, double-blind, phase 2a trial, consisting of visits at Screening, Pre-dose Day 1, and Days 1–9. Patients completed the ANMS GCSI-DD daily during Screening period and Days 1–9. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity scale from none (0) to very severe (4) and the number of vomiting episodes during the past 24 hours. The endpoint composite score is the average of the four symptom severity scores and the core symptom score is the average of all five items (capping vomiting episodes at 4). Statistical analyses using SAS included internal consistency reliability on a random day at Screening and concurrent and known groups validity at Baseline (evening) and Day 9.

Results: 51 patients were analyzed, 34 DG and 17 IG. Mean age was 53 (SD = 13) with 78% women and 82% white. Internal consistency (Cronbach's alpha) was 0.83 and 0.82 for the ANMS GCI-DD composite endpoint and core symptom score, respectively. Convergent validity was supported by strong correlations for the composite endpoint score with the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (r = 0.57–0.78) and Clinical Symptom Severity Rating (CSSR) (0.52–0.63). The core symptom score showed comparable correlations. Mean ANMS GCSI-DD composite endpoint and core symptom scores differed between groups of patients by CSSR-defined severity groups (P < 0.001), supporting known groups validity.

Conclusions: This study provided additional data to indicate that the ANMS GCSI-DD has good reliability and validity as a composite

and total symptom score for gastroparesis symptoms. These results provide further support for the use of ANMS GCSI-DD as a PRO in therapeutic clinical trials for IG or DG patients.

96 | Early postnatal malnutrition causes gastrointestinal dysmotility that is sexually dimorphic

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Background: Slow gastrointestinal (GI) transit is observed in states of undernutrition including anorexia nervosa, severe acute malnutrition, and small-for-gestational-age neonates. Mechanisms underlying malnutrition-associated dysmotility are unknown, in part due to lack of animal models. We sought to characterize dysmotility in multiple mouse models of early-life malnutrition.

Methods: Neonatal mice were malnourished by timed separation from lactating dams starting at five days of life. Alternatively, low-protein, low-fat chow was administered to dams, with malnourished neonates tested at two weeks or weaned to the same chow and tested at two months (as young adults). We assessed total GI transit time by carmine red gavage, colonic motility by rectal bead latency, and both gastric emptying and small bowel motility by calculating the distribution of fluorescein isothiocyanate (FITC)- dextran. Mucosa and muscularis thickness was determined from H&E-stained sections.

Results: Both models of neonatal malnutrition and young adult malnourished males exhibit moderate weight loss, stunting, and strikingly abnormal stomachs on gross inspection. Young adult females are minimally affected by malnutrition in terms of weight loss, stunting, and gastric morphology. Both neonatal models of malnutrition exhibit significantly decreased mean geometric center of FITC progression, whereas gastric emptying is impaired only in maternally separated pups and in malnourished young adult females. Pups malnourished by maternal separation had markedly dilated stomachs with thinning of the mucosa (mean 52.4 vs 110.4 μm, $P < 0.01$) and muscularis externa (mean 16.9 vs 30.4 μm, $P < 0.01$).

Conclusions: Malnutrition delays upper GI transit in a sex-specific manner. In maternally separated pups, gastroparesis is associated with muscularis and mucosal atrophy. Ongoing studies will use these models to identify mechanisms underlying malnutrition-induced dysmotility and sex-specific regulatory mechanisms.

97 | Clinical utility of advanced impedance metrics of reflux in the pre-lung transplant population

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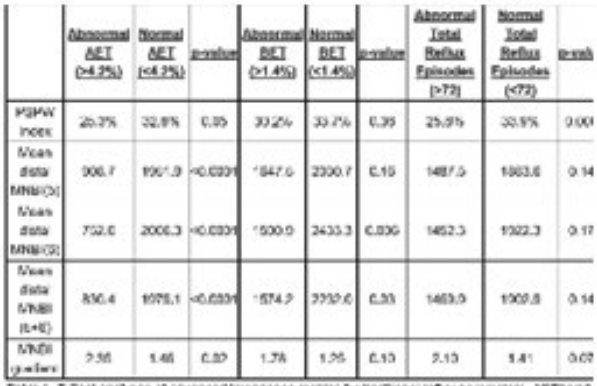
Background: GERD is prevalent in advanced lung disease patients and a predictor of poor outcomes. Postreflux swallow induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI) are novel measures of esophageal reflux clearance and mucosal integrity on impedance-pH testing (MII-pH). Their association with traditional reflux parameters in advanced lung disease patients is unclear. We aimed to assess the relationship between PSPW Index, MNBI, and established reflux parameters acid exposure time (AET), bolus exposure time (BET), and total reflux episodes on MII-pH.

Methods: 133 adults (59% male, 56 years) who underwent routine pre-transplant MII-pH at a tertiary center were included. PSPW was defined as a peristaltic swallow propagating the full length of the esophagus within 30 seconds of an impedance reflux event. PSPW index was calculated as the number of PSPW divided by total impedance reflux events. Distal MNBI was the average of electrode pairs at 3, 5, 7, and 9 cm above the LES across three stable 10-minute periods at 12am, 1am, and 2am while recumbent. We proposed a new metric MNBI gradient calculated as the ratio of proximal to distal MNBI values, with a higher gradient (more differential between proximal and distal MNBI) suggesting more reflux.



	Abnormal AET (>4.2%)	Normal AET (<4.2%)	p-value	Abnormal BET (>1.4%)	Normal BET (<1.4%)	p-value	Abnormal Total Reflux Episodes (>72)	Normal Total Reflux Episodes (<72)	p-val
PSPW index	26.7%	32.8%	0.35	33.2%	33.7%	0.39	25.9%	33.5%	0.00
Mean data MNBI(D)	906.7	1061.9	<0.0001	1047.6	2300.7	0.15	1487.5	1883.6	0.14
Mean data MNBI(P)	732.6	2006.3	<0.0001	1500.9	2433.3	0.036	1462.3	1922.3	0.17
Mean data MNBI (D+P)	830.4	1678.1	<0.0001	1374.2	2310.6	0.33	1483.9	1909.8	0.14
MNBI gradient	2.56	1.46	0.02	1.76	1.25	0.13	2.13	1.41	0.07

Table 1. T Test analysis of advanced impedance metrics by traditional reflux parameters. AET=acid exposure time; BET=bolus exposure time; PSPW=post reflux swallow induced peristaltic wave; MNBI=mean nocturnal baseline impedance and (X) refers to the channel(s) from which the data was obtained. SD=standard deviation.

	Mean Value	R² Pearson correlation with AET	R² Pearson correlation with BET	R² Pearson correlation with Total Reflux Episodes
PSPW Index	31.1% (SD 11.6%)	0.37 p=0.008	0.21 p=0.14	0.38 p=0.01
Mean distal MNBI(c)	1761 Ω (SD 900)	-0.40 p=0.0004	-0.16 p=0.17	-0.15 p=0.20
Mean distal MNBI(c)	1777 Ω (SD 1306)	-0.41 p=0.0003	-0.22 p=0.05	-0.23 p=0.05
Mean distal MNBI(c-c)	1769 Ω (SD 1150)	-0.43 p=0.0002	-0.21 p=0.08	-0.20 p=0.09
MNBI gradient	1.63 (SD 1.24)	0.40 p=0.0005	0.15 p=0.22	0.27 p=0.02

Table 2. Correlation of advanced impedance metrics with traditional reflux parameters. AET=acid exposure time; BET=bolus exposure time; PSPW=post-reflux swallow-induced peristaltic wave; MNBI=mean nocturnal baseline impedance and (#) refers to the channel(s) from which the data was obtained; SD=standard deviation.

Results: Overall mean PSPW index was 31%, with mean distal MNBI of 1769 Ω and MNBI gradient of 1.63. Abnormal AET correlated with lower PSPW index, lower distal MNBI, and higher MNBI gradient compared to normal AET, while abnormal BET was associated with lower distal MNBI (Table 1). Excellent correlation was observed between AET and all advanced metrics, as well as with total bolus episodes (Table 2).

Conclusion: Established advanced metrics (PSPW Index and distal MNBI) significantly correlated with traditional reflux parameters (AET, BET, total bolus episodes) on MII-pH in a lung transplant population. We introduced a new metric (MNBI gradient) that may show promise in evaluating reflux. These novel measures of GERD may have added utility in patients with extraesophageal GERD, as bolus exposure is known to be an important parameter in these patients.

98 | A new treatment regimen achieves effective outcomes in rumination syndrome: a single-center experience

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Background: Rumination syndrome (RS) is an under-recognized gastrointestinal functional disorder characterized by effortless regurgitation of food and/or liquids that starts within 5 to 30 minutes of eating; usually preceded by belching and accompanied by epigastric abdominal wall pain, as well as gastric visceral hypersensitivity. Almost invariably, the onset of symptoms is preceded by a major psychological stressor (MPS). The mainstay of treatment is cognitive behavioral therapy (CBT) with diaphragmatic breathing/relaxation techniques (DB/RT). In the background of stress and gastric hypersensitivity, we report a single-center treatment experience combining a Tricyclic Antidepressant (TCA) with DB/RT.

Methods: Patients referred to an academic motility center for vomiting of unknown origin and who met Rome IV criteria for RS were identified from 2016 to 2018. All received an electronic file with instructions on how to perform DB/RT, as well as on-site coaching, and started pharmacotherapy with a TCA (nortriptyline in escalating doses from 10 to 50 mg qHS). Patients who completed a minimum of 3 months of therapy were interviewed and asked to complete a symptoms questionnaire.

Results: A total of 37 patients, 29 women; mean age 39.7 [range 20–71] met criteria for RS, followed the treatment protocol, and completed a follow-up questionnaire. Mean time from reported onset of symptoms to diagnosis was 36.9 months [range 6–180]. Epigastric abdominal wall pain was the commonest (91.9%) accompanying symptom. 64.9% had a history of either anxiety or depression, and 62.2% reported the onset of symptoms correlated with an MPS event in their life. Five patients had a jejunostomy feeding tube (J-tube), and one was receiving TPN. After completing a minimum 3 months of therapy; average follow up of 8.2 months [range 3–23], 88% of patients reported improvement in their symptoms from baseline, mean subjective improvement was 55.4%, and specifically, 43.2% of patients reported ≥ 70% improvement. Mean time to notice any improvement was 5.5 weeks [range 1–12]. All 5 patients with a J-tube were successfully weaned off, and the patient on TPN was transitioned to a J-tube.

Conclusions: 1) RS is an under-recognized and misdiagnosed entity, 2) to our knowledge, we report the largest case series treating RS with a new regimen, combining a TCA with DB/RT, improving symptoms in 88% of patients and essentially achieving resolution in 43.2% of patients.

99 | 4D MRI allows for dynamic estimation of gastric motility in humans

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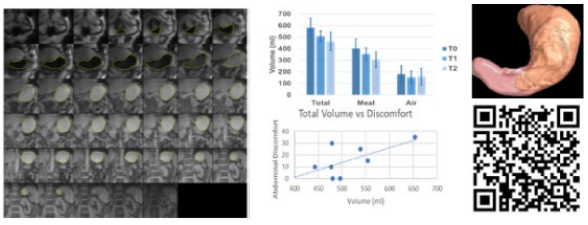
Gastric volumetric measures in real time may allow assessment of the complex dynamics of contractility and volumes within the stomach to investigate gastric accommodation and emptying. Our MRI technique introduces a novel approach offering 4D image data with excellent soft tissue contrast and without the risks of MRI contrast agents such as gadolinium. 8 healthy subjects (4F, 31.1 ± 8.9 years) underwent stomach imaging immediately after the ingestion of a food-based MR contrast test meal, a commercially available vanilla pudding infused with blended pineapple (for high manganese content). Gastric MRI at 3T used a 4D cine sequence not requiring breath holding (3D stack of stars GRE FLASH, temporal resolution = 7s, 40 slices, 2.1x2.1 mm in-plane resolution, 3.5 mm slice thickness, 40 volumes). Data were acquired at time 0, 30 and 60 minutes post-meal (T0, T1 and T2). Semi-automated gastric segmentation was implemented on all volumes and timepoints, and total, meal and air volumes and rates of change (slope of the linear interpolant) were evaluated. Volumetric measures showed a significant reduction from T0 for total volume (T0: 581.6 ± 80.6 ml; T1: 506.6 ± 82.4 ml;

T2: 464.5 ± 73.2 ml) and meal volume (T0: 401.7 ± 49.6 ml; T1: 353.4 ± 55.6 ml; T2: 305.6 ± 54.5 ml), but no significant change in air volume (T0: 179.9 ± 77.8 ml; T1: 153.2 ± 65.8 ml; T2: 158.9 ± 72.3 ml). For 3 subjects reporting abdominal discomfort (0–100 rating scale), discomfort intensity significantly correlated with total volume (Pearson's r: 0.69, *P*-val = 0.04). Trending significance was also found for correlation between discomfort intensity and meal volume change rate (r: −0.58, *P*-val = 0.1) and air volume change rate (r: 0.62, *P*-val = 0.1). Thus, greater abdominal discomfort was linked with greater total stomach volume, increased meal volume reduction, and greater air volume increase over time. These preliminary results suggest the importance of dynamic volumetric measures for gastric function characterization.

(QR code to access 4D gastric MRI movie)



(QR code to access 4D gastric MRI movie)

100 | Patient perspectives on short-course pharmacotherapy: barriers and facilitators to rifaximin adherence

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Background: Medication non-adherence is a global health issue that contributes to poor health outcomes and overall healthcare costs. Much research has focused on chronic long-term medication adherence; however, little is known about short-term medication adherence. This qualitative study examined the patient perspective on adherence and factors that influence adherence to short-term pharmacotherapy for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D).

Methods: Determinants of Adherence was a descriptive study designed to identify the level of adherence to thrice daily 14-day rifaximin treatment for IBS-D. A subset of participants were interviewed regarding their perceptions of barriers and facilitators to their rifaximin adherence. This analysis was limited to those 19 interviewees. Self-report demographic data and pre- and post-treatment symptom severity, in addition to objective measurement of adherence using the Medication Event Monitoring System®, were obtained. Interviews were audiotaped, transcribed verbatim and analyzed by inductive content analysis.

Results: Participants were primarily female (89%), ages 18–65. Sixty-eight percent of interviewees were identified as "low-adherers" or the percent of days with correct daily dosing of rifaximin was < 80% in the 14 day prescription. The mean adherence rate was 73%. Participants missed the midday dose most frequently; averaging 3 missed midday doses within the 14 day prescription (range: 0 – 8 missed midday doses). On average, it took participants 18 days to complete the 14-day prescription. Low-adherers identified higher levels of pain post treatment ($P \geq 0.0001$). The final coding framework identified factors that influenced adherence at the individual level (forgetfulness, knowledge & beliefs regarding adherence, business of daily life, inconvenient dosing), provider level (relationship with provider, medication education), and socioeconomic level (family support, medication expense).

Discussion: Patient responses highlight diverse factors that influence adherence and the need for tailored interventions that address these multiple components. Future research that focuses on implementing a patient-focused paradigm for behavior change by collaborating with a broad set of stakeholders has the potential to result in improved patient outcomes.

102 | Opioids interfere with deglutitive inhibition assessed by response to multiple rapid swallows during high-resolution esophageal manometry

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Introduction: Data regarding opioid effects on esophageal function are limited. Opioids appear to interfere with inhibitory pathways. Assessment of response to multiple rapid swallows (MRS) during high-resolution esophageal manometry (HRM) enables detection of impaired inhibition during MRS, as well as post-MRS contraction vigor. Healthy subjects show deglutitive inhibition during the MRS, followed by an augmented contraction with higher vigor compared to single swallows. We hypothesize that opioids may interfere with deglutitive inhibition during MRS. Our aim was to compare response to MRS in opioid users to non-users.

Methods: This was a retrospective review of 99 chronic opioid users (≥3 months) and 99 controls not on opioids who underwent HRM with MRS 2014–2018. Excluded patients with gastroesophageal surgery, pneumatic dilation, esophageal botulinum toxin injection within 6 months before HRM, achalasia type I or II, and scleroderma. Demographic and manometric data were extracted from a prospectively maintained database. Response to MRS was evaluated for complete versus incomplete inhibition (contractility with DCI > 100 mmHg-sec-cm during MRS), and presence of post MRS contraction augmentation (DCI post MRS greater than mean DCI for single swallows). Categorical variables were analyzed by chi square.

Results: Incomplete inhibition during MRS was significantly more frequent in chronic opioid users compared to controls (25% vs 11%

P = 0.016). There was a significant difference in the rate of incomplete MRS inhibition for patients on oxycodone, hydrocodone, and tramadol (27% vs 34% vs 22% P = 0.001). Augmentation post MRS was similar for opioid users compared to controls (46% vs 57%, P = 0.201).

Discussion: Impaired inhibition during MRS was significantly more frequent among opioid users compared to controls, and was more common with stronger opioids (oxycodone and hydrocodone), compared to tramadol. These findings support our hypothesis that opioids interfere with inhibitory signals in the esophagus.

103 | Effects of esophageal provocation on aerodigestive reflexes in infants following gastrostomy tube placement

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Background: Feeding difficulties in convalescing NICU infants pose a significant challenge to providers in that the indication, timing, or the appropriateness of gastrostomy tube (G-tube) placement and/or fundo-plication, is not clear. Our aims were to examine the effects of esophageal provocation on aerodigestive reflexes in infants following G-tube placement.

Methods: Data from 17 infants who underwent esophageal motility evaluation pre- and post G-tube (Time 1 and Time 2, respectively) at 43 (39–44) and 49 (46–52) weeks post menstrual age (PMA) were compared with that of orally-fed control infants at comparable time points of 42 (39–43) and 48 (45–49) weeks PMA. Esophageal motility testing was performed and pressure recordings from the pharynx, upper esophageal sphincter (UES), proximal-, middle-, distal- esophagus, lower esophageal sphincter (LES), stomach, and middle-esophageal infusion port were obtained. Mechano, osmo-, and chemo- receptor stimulation was induced using graded volumes of air, water, and apple juice.

Results: Effects of 2,145 esophageal provocations were analyzed and compared between control and G-tube patients. The frequency of UES contractile response (53% vs 32%, Time 1 vs Time 2, P < 0.01) and LES relaxation response (59% vs 42%, Time 1 vs Time 2, P 0.02) significantly decreased in control patients. UES resting pressure increased in control (13 ± 2 vs 17 ± 2 mmHg, Time 1 vs Time 2, P < 0.01) and G-tube patients (15 ± 3 vs 22 ± 3 mmHg, Time 1 vs Time 2, P < 0.01). Similarly, LES resting pressure increased in both control (21 ± 3 vs 25 ± 3 mmHg, Time 1 vs Time 2, P < 0.01) and G-tube patients (21 ± 3 vs 24 ± 3 mmHg, Time 1 vs Time 2, P < 0.01).

Discussion: The presence of a G-tube does not result in distinct differences in esophageal sensory-motor characteristics of peristalsis, UES or LES reflexes. As the resting LES pressure increased significantly in both populations, we speculate that G-tubes do not increase the risk for inadequate clearance reflexes or sphincteric hypotonicity. Careful evaluation of aerodigestive reflexes may obviate the need for unnecessary procedures such as fundoplication.

104 | Patients with irritable bowel syndrome (IBS) consume a considerably healthier diet than the general US population

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Introduction: The role of diet in IBS is of interest to medical professionals and patients. While physiological mechanisms of diet continue to be assessed, many patients modify their diet, often on their own. The Healthy Eating Index (HEI) provides evidence-based assessment of diet quality and adherence with U.S. Dietary Guidelines. To date, no study assesses HEI in IBS patients nor compares HEI dietary patterns to the general population (GP).

Methods: Adults with Rome-III IBS recruited from 2 university-based gastroenterology clinics and online via Researchmatch.org completed the National Cancer Institute's Dietary History Questionnaire used to calculate HEI with 13 previously defined components scored on a density basis per 1000 kcal of intake, demographic and disease data, including diet treatment. Values for HEI items were adjusted based on individual caloric intake prior to computing the components. Welch's unequal variances t-Tests and Cohen's d effect size determined group differences. Pearson's correlation evaluated HEI and symptom severity.

Results: 80 subjects: 75% IBS-D, 91% female, 90% non-Hispanic White with mean±SD age of 42.7 ± 13.9 years. 81% were using a diet treatment (48% self-directed elimination (SDE), 16% low-FODMAP). Mean IBS symptom severity was 221.7 ± 73.3 (Range: 97 – 375). More symptomatic patients ate less dairy (r = −0.37, P = 0.02). IBS patients scored higher in diet quality than GP (Table) by eating more nutrient dense foods (total fruit, total vegetables, dark greens, seafood and plant based proteins), less refined grains and added sugars, and having a better unsaturated-saturated fatty acid ratio. While patients consumed more total fruit, they ate less whole fruit. IBS patients consume less dairy, specifically less cheese (P = .05) versus milk (P = .76) or yogurt (P = .54), and equal amounts of whole grains as the GP. Analysis by diet type reveals patients on SDE ate less whole grains (P = .027) while those using low-FODMAP ate less dairy (P = .046) and less saturated fat (P = .008).

Conclusions: IBS patients eat a considerably healthier diet than the GP especially plant based foods, healthy fats, dark green vegetables and total fruit. Common IBS diets seem to have little impact on diet quality. IBS patients may consume more fruit juices and less whole grains, especially those using SDE or low-FODMAP diets. Implications of higher diet quality on HRQOL, IBS severity and cardiometabolic risk factors deserves further study.

Table

	Max Score	IBS, *N* = 80	Adults 18 + , 2015 Norms*N* = 7,935	*P*	d
Total HEI Score	100	69.01 ± 9.7	56.6 (0.53)	<.0001	11.3
Total Fruits	5	3.76 ± 1.5	2.9 (0.07)	<.0001	5.2
Whole Fruits	5	2.52 ± 1.7	3.1 (0.10)	.003	3.0
Total Vegetables	5	4.00 ± 1.3	3.1 (0.03)	<.0001	6.8
Greens and Beans	5	3.66 ± 1.7	2.5 (0.09)	<.0001	6.1
Whole Grains	10	2.65 ± 2.1	3.0 (0.10)	.14	1.5
Dairy	10	5.20 ± 2.9	6.5 (0.08)	.0001	4.4
Total Protein Foods	5	4.91 ± 0.5	4.6 (0.04)	<.0001	4.9
Seafood & Plant Proteins	5	4.02 ± 1.4	3.6 (0.09)	.009	2.5
Fatty Acid Ratio	10	9.48 ± 1.4	4.6 (0.10)	<.0001	31.2
Refined Grains	10	8.22 ± 2.4	5.9 (0.08)	<.0001	9.2
Sodium	10	4.92 ± 3.0	4.3 (0.06)	.07	2.0
Added Sugars	10	7.52 ± 3.0	6.3 (0.09)	<.001	3.9
Saturated Fats	10	8.15 ± 3.4	6.1 (0.15)	<.0001	5.6

Higher scores = better diet.

105 | Feasibility and acceptability of health coaching for patients with irritable bowel syndrome

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Background: There is a robust body of evidence demonstrating the effectiveness of psychological interventions for patients with gastrointestinal (GI) conditions. Yet, these interventions require independent use of behavioral skills, which is challenging for some individuals. Health coaching has been deployed to improve patient management of health conditions. Patients report benefits including increased access to care, understanding the link between behaviors and condition, and motivation for healthy behaviors. There has been no research to date exploring health coaching for patients with GI conditions. This pilot study aims to evaluate the feasibility and acceptability of health coaching to augment psychological intervention for patients with irritable bowel syndrome (IBS).

Methods: GI Psychologists within an integrated academic gastroenterology program invited patients with IBS who completed at least one session of brain-gut psychotherapy to participate in a study about health coaching in their final session. Participants were offered up to 12 sessions of health coaching provided via phone or messaging over the course of 6 months. Qualitative data was collected regarding reasons for participating in or declining coaching, perceived benefits, and suggestions for improvement. Health coaching participants completed a 1-item measure to assess satisfaction.

Results: Twelve participants have completed the study. Participants are primarily female (83.3%), Caucasian (100%), ranging in age from 22 to 50 (*M* = 30). Ten participants agreed to coaching but two never responded to outreach; thus, 8 (66%) participated in coaching. Average number of coaching sessions was 4 (*M* = 4.13, range: 2–8). Satisfaction (0 = not at all, 7 = completely) ranged from 3 to 7 (*M* = 5.14). Reasons for declining coaching included lack of time. Reasons for participating included desire for additional behavioral treatment, accountability, curiosity, and health. Benefits included easier transition to using skills independently, accountability, improved goal-setting, and symptom improvement. Suggestions included an easier scheduling tool, in person or video sessions, and online check in forms to assess progress. Two participants found the coaching style difficult, desiring more straightforward instructions for how to change their health.

Conclusion: Preliminary data from this pilot study suggests that many patients with IBS are interested in participating in health coaching to support use of behavioral skills to manage their digestive health. Integration of health coaching into gastroenterology programs may benefit a subset of patients. Further studies are warranted.

106 | Environmental parkinsonism induces stressless response in neurons of the dorsal motor nucleus of the vagus

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The majority of Parkinson's disease patients experience gastrointestinal (GI) dysfunctions such as reduced gastric motility, dysphagia, and severe constipation. In recent years an interesting theory

hypothesizes that α-synucleinopathy and idiopathic PD could be triggered by the absorption of environmental pathogens in the GI tract. The α-synucleinopathy reaches the central nervous system via retrograde transport through the vagus, and spreads to the substantia nigra pars compacta (SNpc) via a nigro-vagal pathway to ultimately induce the SNpc degeneration. We have developed a novel model of environmental parkinsonism, in which subthreshold doses of a combination of neurotoxicants induce misfolding of α-synuclein in the enteric and central nervous system, SNpc degeneration and motor deficits, and GI dysfunctions.

The aim of the present study is to investigate i) the changes in the membrane properties and ii) pharmacological responsiveness to dopamine (DA) of dorsal motor nucleus of the vagus (DMV) neurons.

Male Sprague Dawley rats received daily oral gavages for 7 consecutive days of vehicle (CTL group), 1 mg/kg paraquat (1P), or 1 mg/kg paraquat + 0.05% lectins (P+L). Two weeks after the end of the treatment rats were sacrificed for whole-cell patch clamp experiments.

DMV neurons from 1P or P+L groups exhibited basic neuronal properties similar to those of CTL rats. Specifically, there were no alterations in the duration of the action potential, in the amplitude and decay kinetics of the after hyperpolarization, nor in the IA, IH, or IKIR currents ($P > 0.05$; $N = 22$, 15–19, and 36–38 for CTL, 1P and P+L respectively).

In 40%, 20% and 37.5% of neurons from CTL, 1P and P+L groups, perfusion with DA (30 μM) induced a concentration-dependent variation in DMV neuronal firing rate. Blockade of the excitatory DA1-like receptors with SCH 23,390 (10 μM) decreased their firing rate, while neurons from the P+L group responded with an increase in firing rate. Conversely, the majority (66%) of neurons from the 1P group responded to blockade of the inhibitory DA2-like receptor with L-741,626 (10 μM) with an increase in firing rate, while neurons from the P+L group exhibited a bimodal response.

These data indicate that the response to DA inputs is significantly altered in a model of environmental PD despite no changes are observed in the membrane properties of DMV neurons. This suggests that the GI dysfunctions observed in PD may be determined by impairment of the synaptic connectivity, possibly of the nigro-vagal pathway.

107 | Wireless motility capsule demonstrates changes in colon contractility during fiber administration compared to placebo

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Background: Fiber is thought to have multiple but poorly defined effects on the gastrointestinal (GI) tract, including possibly altering contractility. It can be an important component of the management of constipation. An experimental fiber-hydrogel and carboxymethylcellulose (CMC) fiber were compared to placebo using a wireless motility capsule (WMC) that was deployed pre- and post-study drug ingestion. The impact of CMC on gastrointestinal contractility (contractions per hour) was examined.

Methods: Post-hoc analysis was performed of a single center, randomized, double-blind, parallel-group, placebo-controlled pilot study evaluating 20 participants randomized in a 1:1 fashion who received 3 capsules with either CMC (total of 2 g) or placebo. Mixed between subject and within subject repeated measures analysis of covariance (ANCOVA) was performed. Employing ANCOVA where the between subject factors were treatment group, gender, and age, and the within subject factor was time, we assessed the effects of treatment on measures of contractility frequency throughout the GI tract.

Results: There was a significant treatment x day interaction for the 1st quarter of the colon ($P = 0.008$) where contractions per hour decreased by −0.46 ± 0.16 ($P = 0.007$ with Tukey-Kramer adjustment), and a marginally significant treatment x day interaction for the 4th quarter of the colon ($P = 0.098$) where contractions per hour increased by + 0.47 ± 0.19 ($P = 0.02$ with Tukey-Kramer adjustment). Notably, this impact was magnified in women ($P < 0.0001$ in the proximal colon, and $P = 0.03$ in the distal colon) independent of age ($P = 0.93$).

Conclusions: CMC decreases proximal colon contractility but likely also increases distal colon contractility especially in women. Fiber may provoke increased distal contractility in preparation for expulsion. This is one of the first studies directly measuring fiber's impact on contractility using WMC. It suggests that different types of fiber may ultimately be needed to resolve constipation in different populations.

108 | 'First in man' routine patch clamp recordings in neurons and glia in isolated networks of human myenteric ganglia–a model of the human little brain

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Introduction: Emerging evidence suggests neuroinflammation and abnormal neural-glial communication in ENS are involved in GI diseases and disorders. To what extend this knowledge is translatable to man is not known. Voltage-sensitive dyes or electrophysiology with sharp tip microelectrodes in intact surgical tissues are used to study cell excitability in human gut. The latter is far from routine practice and low yield hampers analysis.

Aim: This is a pilot/feasibility study to determine whether routine patch-clamp recordings of neurons or glia are possible in isolated networks of human myenteric ganglia (devoid of muscle) as done for other peripheral ganglia in mice.

Methods: Patch-clamp recordings were done using a Scientifica-Rig in intact networks of isolated myenteric ganglia pinned-down by

metal pressure feet. Cell shapes were identified by 5,6,carboxyfluorescein or neurobiotin–labeling and 3-D reconstruction using Olympus FV3000 LSCM / IMARIS software-analysis. Studies were done in 27 GI non-inflamed surgical specimens (IRB2017H0441).

Results: Stable recordings from 33 neurons and 52 glia, lasted for 0.5 to 3 hr. Neurons were S/Dogiel Type I with TTX-sensitive spikes, and occasional spontaneous slow EPSPs or spikes. Neurons had lamellar dendrites, simple shapes, or were small neurons with a single long axon/varicose fiber. CGRP/ChaT is expressed, and we identified 1 AH/Dogiel Type II neuron. 'V_m oscillator neurons' with extensive axon collaterals, displayed rhythmic spontaneous V_m-oscillations with recurrent bursts of A.P.'s, responding to ACh and forskolin. A slow EPSP-like response (or inhibitory response) was evoked by ATP (16/20), ACh (20/20), forskolin (9/13), sarafotoxin (6/9), UTP (4/5) or adenosine (5/9). Gut biopsy supernatants from CD-inflamed patients or mouse postoperative ileus caused slow EPSP-like responses (7/7 cells). Glia were dye-coupled and responded to touch/pressure (4/7 glia), ATP (26/28), SaTX (13/13) and ACh (7/7). ATP caused a 24 ± 5 mV depolarization or −20 ± 7 mV hyperpolarization; SaTX had similar effects. Pressure-puff on an adjacent glial cell to release gliotransmitter increased excitability of the recorded neuron.

Conclusions: Our pilot study established feasibility of 'first in man' patch-clamp recording from neurons or glia in intact networks of human myenteric ganglia for routine analysis. Further development opens the exciting possibility for in-depth study of glia, neurons and channels in GI Diseases or disorders in surgical tissue or mucosal biopsy *(DK113943/NCI P30LA16058).*

109 | Aquaporin channel expression in normal human colon and terminal ileum mucosa and preliminary measurements in patients with IBS

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Background: Water moves across gastrointestinal epithelia following osmotic gradients and hydrostatic forces. Water flux occurs partially through the aquaporins (AQP): small, integral membrane proteins that function as water channels throughout the human body. Studies largely in animals show that AQP1, 3, 4, 5, 7, 8, 9, and 10 are expressed in the gastrointestinal epithelium. However, human expression of these channels in normal and disease states of water imbalance (diarrhea, constipation) are still largely unknown. APQ8 may be associated with inflammation in IBD and APQ10 in the terminal ileum (TI) is increased in infectious diarrhea. We previously showed that IBS with normal or high bile acid excretion diarrhea is associated with increased expression of AQP7, 8 and decreased AQP3 in rectosigmoid mucosa. We aimed to further characterize the mRNA expression of APQ channels in-vivo in mucosa from healthy human TI, ascending and sigmoid colonic mucosa. We also obtained preliminary data from patients with IBS-D and IBS-C.

Methods: Mucosal biopsies were obtained from the rectosigmoid, ascending colon, and TI in healthy volunteers and patients with IBS D or C via colonoscopy. Samples were analyzed using RT-PCR based measurement of expression of APQ-1, 3, 7, 8, and house-keeper gene GADPH as control. RNA quality was assessed on the Agilent Bioanalyzer (RIN > 7) and was reverse transcribed using RT^2 First Strand Kit (Qiagen), and samples were analyzed for expression by RT^2 PCR Assays.

Results: Our study includes 23 healthy volunteers (52% men, average age 43), 8 female IBS-C patients (average age 47), and 7 IBS-D patients (29% men, average age 43). In healthy controls, there were differences in APQ expression between the TI and rectosigmoid mucosa, and between ascending colon and rectosigmoid mucosa. In the TI, compared to the rectosigmoid, AQP1, 3 and 7 showed higher and AQP 8 decreased expression ($P < 0.001$). AQP1 (but not AQP 3, 7, and 8) expression was lower in ascending colon compared to rectosigmoid mucosa. In the preliminary analysis of mucosa from 15 patients with IBS, there are differences in AQP1 expression in ascending colon relative to sigmoid biopsies in IBS-C compared to healthy controls.

Conclusions: In healthy humans there is reduced expression of AQP8 in the terminal ileum mucosa compared to rectosigmoid mucosa, but increased expression of other AQPs. This may reflect the differences in absorptive capacity of ileal and colonic mucosa in health. Further studies are underway to appraise AQP expression in ileal and colonic mucosa in IBS-D and IBS-C patients.

110 | Descending perineum syndrome causes ~10% of constipation in 297 adults in referral center

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Introduction: Outlet obstruction constipation accounts for 30% of chronic constipation cases in a referral practice. In women, outlet obstruction can be secondary to descending perineum syndrome (DPS). We describe a cohort of patients diagnosed with DPS by a single gastroenterologist and compared their clinical and radiological features and risk factors to patients with constipation without DPS in the same practice.

Methods: A retrospective review was conducted on 297 consecutive patients seen for constipation from 2007–2018. Medical, surgical, and obstetrics history, rectal exam, anorectal manometry, and proctography if available were extracted. Diagnosis of DPS was made either by proctogram (anorectal junction [ARJ] descent of > 3 cm past the pubococcygeal plane during strain) or on clinical evaluation by history supported by estimated excessive (>3 cm) perineal descent on rectal exam. Characteristics were compared between the DPS and non-DPS patients. Logistic regression with univariate and multivariate analysis was used to identify risk factors for DPS.

Results: 26 (8.75%, all female) of the 297 patients had DPS by either proctogram or clinical features; 80.4% (n = 218) of the non-DPS patients were female. BMI was similar but the DPS group was older (mean age 50.8 yrs vs. 41.7 yrs in non-DPS, P = 0.012). Among 17 DPS patients who underwent proctogram compared to 10 non-DPS patients, mean ARJ descent at maximal strain was 6.4 ± 1.8 cm in the DPS group, and 87.5% (n = 14) had a rectocele compared to 28.6% of non-DPS patients (P = 0.005). Enteroceles and cystoceles were rare and similar in both groups. DPS patients had more vaginal deliveries (85.7% vs. 30.8%, P < 0.001), more traumatic deliveries (episiotomy, tears, forceps or vacuum-use (33.3% vs. 11.1%, P = 0.0043), more births (mean 2.17 ± 1.47 vs. 0.93 ± 1.17, P = 0.0006) and more hysterectomies (47.6% vs. 15.67%, P = 0.0005) compared to non-DPS group. Anorectal manometry showed lower anal sphincter pressure at both rest (81.1 ± 24.9 mmHg vs. 94.7 ± 31.4 mmHg P = 0.024) and squeeze (139.4 ± 29.1 mmHg vs. 173.7 ± 74.5 mmHg P = 0.001), as well as higher average volume to discomfort on balloon distension (154.2 ± 89.5 mmHg vs. 111.4 ± 71.3 mmHg, P = 0.055) in DPS. On univariate analysis, predictors of DPS were history of vaginal delivery or traumatic delivery. Traumatic delivery was a significant predictor of DPS on multivariate analysis adjusted for age and rectal sensation.
Conclusion: Descending perineum syndrome accounts for almost 10% of referral constipation patients and is associated with lower anal sphincter pressures, older age, more pregnancies, and more vaginal deliveries, especially those associated with trauma.

111 | Enriched environment housing alleviates post-colitis pain and visceral hypersensitivity in male and female rats

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Adverse psychosocial events contribute significantly to the relative risk of developing post-infectious irritable bowel syndrome. Clinical studies support the hypothesis that chronic pain is maintained in part by maladaptive changes in the mesolimbic pathway. Our objectives in this study are to evaluate the effects of differential housing conditions on development of visceral hypersensitivity (VHS) and pain during recovery from colitis in male and female rats, and to define the role of brain derived neurotrophic factor (BDNF) expression in the nucleus accumbens (NAc).
Methods: Ten-day old neonatal rats received colon infusion of trinitrobenzene sulfonic acid. Controls received saline and were conventionally housed after weaning. Enriched environment (EH) rats were housed in a ferret cage, 14 per cage, containing of a variety of toys that were changed daily from weaning until experiments were begun. Remaining rats were single housed (SH). Eight weeks-old rats received colonic infusion of TNBS. Behavior experiments were begun two weeks later. The visceromotor response to graded colorectal distention was recorded. The conditioned place preference (CPP) test was used to measure the magnitude of analgesic-induced relief (intracolonic 2% Lidocaine) from ongoing pain.
Results: With respect to visceral hypersensitivity: Females were significantly more sensitive than males in all three experimental conditions Within females, single housed rats were significantly more sensitive compared to control P < 0.001, and to enriched environment housed rats, P = 0.01. Within males, single housed rats were significantly more sensitive compared to control, P < 0.001 and to enriched environment housed rats, P = 0.003. In the CPP test, both male P < 0.001 and female P < 0.001 SH rats displayed significantly greater changes in preference for the lidocaine-paired chamber compared to control rats. EH significantly reduced change in preference in both male P = 0.035 and female rats, P = 0.001 compared to SH rats. We found significant increases in BDNF protein expression in both male and female SH rats in the NAc compared to their respective controls and EH housed rats. Knockdown of BDNF expression in the NAc significantly reduced CPP in post colitis single housed males and female.
Conclusions: Single housed rats displayed evidence of an aversive state, in addition to hypersensitivity to colorectal distension following recovery from colitis. These conditions were significantly ameliorated by enriched environment housing or by knockdown of BDNF expression in the NAc.

112 | The relationship between esophageal acid exposure and ineffective esophageal motility

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Background: Ineffective esophageal motility (IEM) is gaining attention as the most common functional esophageal disorder seen in High-resolution esophageal manometry (HREM). The attention has focused on the relationship between the pathology of IEM and GERD. However, the connection remains unclear
Aim: The aim of this study was to compare and investigate the background factors, HERM findings, esophagogastroduodenoscopy (EGD) findings, esophageal pH-monitoring, health related quality of life (HRQOL), and psychological factors of two groups of patients who underwent HREM with esophageal symptoms including dysphagia, with a diagnosis of IEM or normal esophageal motility (NEM), in order to clarify the relationship between clinical characteristics of IEM and esophageal acid exposure.
Methods: HREM was performed in 103 patients who presented to our department with esophageal symptoms between February 2015 and May 2018. Of these patients, 22.3% (n = 23) and 31.1% (n = 32) were diagnosed with IEM and NEM. The two groups were compared and investigated for background, HREM findings (LESP; LES pressure, LES residual pressure, IRP; Integrated relaxation pressure,

DCI; Distal contractile integral), EGD findings, pH < 4 holding time (pH < 4 HT), DeMeester score, HRQOL, and psychological factors.

Results: No significant differences were seen in the two groups for LESP or LES residual pressure, but DCI was significantly lower in the IEM group than in the NEM group (265.2 ± 229.5 vs. 1754.1 ± 1165.0 mmHg·s·cm, $P < 0.0001$). IRP was also significantly lower in the IEM group than in the NEM group (13.0 ± 4.6 vs. 16.4 ± 4.74 mmHg, $P = 0.02$). Comparison of EGD findings between the two groups revealed that the IEM group had a significantly larger number of concomitant cases of esophageal hiatal hernia (56.5% vs. 25.0%, $P = 0.03$) and esophageal mucosal injury (34.8% vs. 6.3%, $P = 0.01$) than the NEM group. Furthermore, pH-monitoring revealed no significant differences between the two groups for pH < 4 HT or DeMeester score. HRQOL and psychological factors also did not differ significantly between the two groups.

Conclusions: No significant differences were seen in the IEM and NEM groups for esophageal acid exposure, HRQOL, or psychological factors. However, low IRP and concomitant cases of esophageal hiatal hernia and esophageal mucosal injury were significantly more common in the IEM group, suggesting that these conditions could influence esophageal motility.

113 | Digital rectal examination in the evaluation of neuropathy in patients with anorectal disorders

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Background: Digital rectal examination (DRE) is helpful in evaluating patients with anorectal disorders. An impaired or absent ano-cutaneous reflex suggests neuronal injury. Recently, translumbosacral anorectal magnetic stimulation (TAMS) test was found to be useful for detecting anorectal neuropathy. Our aim is to examine the clinical utility of ano-cutaneous reflex on DRE in assessing neuropathy detected by TAMS.

Methods: Ninety (F/M = 69/21, 58 ± 16.1 years old) patients with suspected fecal incontinence (FI) ($n = 34$), mixed FI/constipation ($n = 35$) and levator ani syndrome (LAS) ($n = 21$) underwent both DRE and TAMS. TAMS was performed by applying a magnetic coil to bilateral lumbar and sacral regions and measuring anal motor evoked potentials (MEPs). Neuropathy is defined by weak or absent anocutaneous reflex on DRE or MEP latency ≥ 2 SD of healthy population on TAMS. The diagnostic yield and agreement for neuropathy between DRE and TAMS were evaluated.

Results: In FI subjects, 30 (88.2%) were found to have neuropathy on TAMS, 18 (47.1%) had neuropathy on DRE ($P = 0.001$), 16 had neuropathy on both, and 2 did not have neuropathy on either. Fourteen FI subjects with normal DRE were found to have neuropathy on TAMS. In subjects with mixed FI/constipation, 28 (80.0%) were found to have neuropathy on TAMS vs 19 (54.3%) on DRE ($P = 0.022$), and 15 had neuropathy on both. Thirteen mixed FI/constipation subjects with normal DRE were found to have neuropathy on TAMS. In LAS subjects, 16 (76.2%) were found to have neuropathy on TAMS vs 12 (57.1%) on DRE ($P = 0.190$), and 8 had neuropathy on both. Eight LAS subjects with normal DRE were found to have neuropathy on TAMS. The overall agreement between DRE and TAMS in patients with FI, mixed FI/constipation and LAS was 52.9%, 51.4% and 42.9 %, respectively.

Conclusion: Our findings suggest that DRE is a useful, readily available clinical tool for detecting pelvic neuropathy in patients with anorectal disorders. However, normal DRE does not reliably exclude neuropathy. TAMS is superior and more sensitive than DRE in revealing neuropathy in these subjects.

114 | Enteric neuronal aggregation of α-synuclein causes colonic dysmotility

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Parkinson's disease (PD) is characterized by abnormal accumulation of α-synuclein (α-syn) in substantia nigra dopamine neurons and fibers causing eventual neuronal death and resulting in parkinsonian motor symptoms. Similar pathology occurs in the enteric nervous system (ENS) and may explain gastrointestinal (GI) dysfunction experienced by PD patients with constipation being the most common GI symptom. To date, there is no information elucidating the role of α-syn aggregation on colonic dysfunction nor are there effective pharmacotherapies for patients experiencing these symptoms. We hypothesize that α-syn aggregation in murine myenteric neurons impairs ENS neuromuscular transmission causing abnormal colonic propulsion. To study the role of α-syn on PD-induced constipation, we used a novel gene therapy method whereby recombinant adeno-associated virus-mediated (rAAV9-α-syn or GFP as control) transduction was targeted to myenteric neurons in the mouse colon and we investigated colonic function through fecal pellet output and colonic migrating motor complex (CMMC) analysis combined with electrophysiological recordings of proximal colon preparations. We found a modest decrease in CMMC frequency in α-syn mice without any changes in dry stool weight or circular smooth muscle inhibitory junction potentials between control and α-syn mice. This suggests that a possible deficit in colonic propulsion may not be a result of impaired inhibitory neuromuscular transmission. Future studies will investigate excitatory neuromuscular transmission. Overall, this work will help us understand the neuronal pathology underlying α-syn mediated impairment of colonic propulsion and help us identify novel drug targets that treat constipation in PD.

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115 | Comparison between direct vagal nerve stimulation and noninvasive auricular vagal nerve stimulation for opioid-induced constipation

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Introduction: Constipation affects a huge population; the opioid epidemic lead to opioid-induced constipation (OIC) is another major problem. However, treatment options for constipation are limited. Aims of this study were to investigate whether vagal nerve stimulation (VNS) and a noninvasive method of auricular VNS (aVNS) could treat constipation and to compare the performance between the two methods.

Methods: In acute study, 10 rats implanted with electrodes at vagal nerve as VNS/sham-VNS group and another 10 rats with electrodes at auricular brunch of vagal nerve as aVNS group. All rats implanted with a polyethylene catheter in the proximal colon for assessing whole colon transit by collecting marker at the anus for 100 minutes (min). For chronic studies, 28 rats were induced OIC then treated with sham-stimulation (N = 10, 0 mA), VNS (N = 10, one hour daily) and aVNS (N = 8, one hour daily) with previously optimized parameter for one week. Feces were analyzed daily, distal colon transit time (dCTT) and whole gut transit time (WGTT) were measured before and after the stimulation. Heart rate variability derived was analyzed to evaluate autonomic functions. Colon tissues were collected. The protein expressions of ChAT, nNOS, GDNF, p-Akt were assessed by western blot.

Results: 1) Both VNS and aVNS accelerated the whole colon transit. 2) One-week VNS increased the total number of fecal pellets (261 vs. 219, $P < 0.01$, vs. sham-VNS) and water content in feces (23.2 ± 5.8% vs. 16.5 ± 5.2%, $P < 0.02$). aVNS showed similar effects. 3) Both chronic VNS and aVNS shortened WGTT and dCTT. VNS was more potent than aVNS for dCTT but not WGTT. 4) Both VNS and aVNS decreased sympathovagal ratio (64.6%, $P < 0.05$ and 49.2%, $P < 0.05$ vs. sham-VNS), increased vagal activity (54.5%, $P < 0.05$ and 47.8%, $P < 0.05$ vs. sham-VNS). 5) VNS increased the protein expression of ChAT by 21.7% ($P < 0.02$, vs sham-VNS) and GDNF by 50.6% ($P < 0.01$) but decreased the protein expression and p-Akt by 31.6% ($P = 0.08$). Both VNS and aVNS decreased the protein expression of nNOS (75%, $P < 0.05$ and 66%, $P < 0.1$ vs. sham-VNS).

Discussion: VNS and aVNS can both improve constipation. The aVNS seems to be a more attractive therapy for constipation since it has similar effects on OIC as VNS but can be implemented noninvasively.

Objective: 1) To assess the effect of VNS and noninvasive VNS in treating constipation. 2) To analyze the mechanism of VNS and aVNS in both acute and chronic status. 3) To compare the performance of the noninvasive aVNS with direct invasive VNS.

Conclusions: Both VNS and aVNS improve constipation by enhancing colon motility mediated by balancing autonomic functions.

116 | The role of Na^+/HCO_3^- Co-transporter activity in electrical slow waves of the mouse intestine

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Interstitial cells of Cajal (ICC) generate electrical slow waves and are important in gastrointestinal motility. In small intestine, ICC located in myenteric region are pacemaker cells but ICC in the deep muscular do not generate slow waves. The electrogenic, Na^+/HCO_3^- co-transporter (Slc4a4/NBCe1) is expressed in pacemaker ICC suggesting that NBCe1 regulates electrical activity in ICC-MY as reported for other excitable tissues. The contribution of Slc4a4/NBCe1 to the function of pacemaker ICC has not been investigated.

Aim: To determine how Slc4a4 contributes to the effects of HCO_3^- on electrical slow waves in mouse intestine.

Methods: Sharp electrodes filled with 3M KCl were used to record slow waves from circular muscle at 37°C. HCO_3^- concentrations were 15.5 mM (in 97% O_2, 3% CO_2), 0 mM (in 100% O_2) and 100 mM (in 80% O_2, 20% CO_2). NaCl was replaced with LiCl, gassed with 97% O_2, 3% CO_2. 15.5 mM HEPES was included to buffer pH to 7.4 at 37°C. Slc4a4 $^{fl/fl}$ mice were bred with ETV1$^{CreERT2/+}$ mice to allow knockdown of Slc4a4 in ICC in response to tamoxifen (130 mg/Kg). Statistical differences were tested by repeated measures ANOVA.

Results: Removal of HCO_3^- caused a reversible and reproducible depolarization of the membrane potential by 4.11 ± 2.4 mV and reduced slow wave amplitude by 4.71 ± 3.6 mV and frequency by 0.09 ± 0.06 Hz. 100 mM HCO_3^- caused a reversible and significant hyper-polarization of 6.03 ± 2.3 mV, increased peak amplitude by 4.54 ± 2.9 mV and shortened the events by 149.27 ± 93.8 ms. Li^+ containing solutions, to prevent Na^+/HCO_3^- co-transport (as NBCe1 does not transport Li^+), also caused a reversible and reproducible depolarization by 7.96 ± 4.1 mV and reduced slow wave amplitude by 9.86 ± 7 mV) and frequency 0.11 ± 0.08 Hz, and lengthened the events by 419 ± 383 ms. Knockdown of Slc4a4 in ICC significantly reduced the effect of removing HCO_3^- on smooth muscle membrane potential.

Conclusions: The presence of extracellular HCO_3^- and Na^+ and Slc4a4/NBCe1 co-transporter activity are important for regular slow wave activity. Therefore regulation of intracellular pH homeostasis

contributes to normal pacemaker activity in mouse small intestine and alterations in Slc4a4/ NBCe1 activity may contribute to gastrointestinal motility disorders. *Supported by DK57061*.

117 | Type II achalasia is increasing in incidence

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Background: The Chicago Classification describes three subtypes of achalasia: Type I (aperistalsis), II (pan-pressurization), and III (spastic). Since the widespread use of high-resolution manometry (HRM), the evolving incidence of these subtypes has not been elucidated. We aim to determine the incidence of each subtype at a major academic medical center a decade after the adoption of the Chicago Classification.

Methods: This is a retrospective cohort analysis of patients diagnosed with achalasia on HRM at an academic medical center between 2015–2018. Patients were excluded if they had prior esophageal motility disorders, treatment for achalasia, or foregut surgery. Demographic data, manometric subtype, esophageal dilatation grade on endoscopy (0 = normal, 2 = most severe), and esophageal width on barium esophagram were obtained. Incidence of achalasia subtypes, demographics, and dilatation grade were compared with a published historical control population (2004–2007).

Results: Of 52 patients at our institution and 99 in the historical control, the incidence of Type I achalasia was 6% vs. 21%, Type II 69% vs. 50%, and Type III 25% vs. 29%, respectively (overall Fisher's $P = 0.02$). The mean age in our population was 59 years, compared to 57 in the historical control, and the proportion of men 38% vs. 47%, respectively. At our institution, 31% of patients had esophageal dilatation grade 1 or 2 on endoscopy, including 67% of Type I patients, 26% of Type II, and 8% of Type III. Mean dilatation grade was 1.3 for Type I patients, 0.6 for Type II, and 0.2 for Type III (ANOVA $P = 0.05$), compared with 1.5, 0.6, and 0.4, respectively. Overall mean dilatation grade was 0.57 in our cohort vs. 0.73 (t-test $P = 0.22$). Median esophageal width on barium esophagram was 2.5 cm for Type I patients (interquartile range (IQR) 2.5–2.9), 2.9 cm for Type II (IQR 2.4–4.7), and 2.3 cm for Type III (IQR 2.2–3.4).

Conclusion: The incidence of Type II achalasia was significantly greater and incidence of Type I significantly less in our patient population compared to our predefined historical control. Other characteristics such as age and sex were similar between the two cohorts, which suggests that these variables are less likely to account for this difference. Histopathological evidence has suggested that Type II achalasia may be an earlier form of Type I; thus the increased incidence of Type II achalasia may be related to earlier detection of the disease. The adoption of HRM and widespread use of the Chicago Classification in the past decade may be contributing to these changes in epidemiology.

118 | On the use of pressure-CSA loop analysis in the assessment of anal sphincter muscle dysfunction in patients with fecal incontinence

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Background: Cardiac loops have been used extensively for many decades to study the cardiac pump function during a cardiac cycle. With cardiac pump/myocardial failure these loops are shifted to the right. Functional luminal imaging probe (FLIP) recordings lend themselves for loop analysis.

Goal: To study anal sphincter function in normal subjects and patients with fecal incontinence (FI) using pressure-CSA (PCSA) loops.

Methods: 14 healthy nulliparous subjects, and 14 FI by FISI and Wexner questionnaires were recruited. A custom designed FLIP bag (30 mm diameter) was placed first in the vagina, and then in the anal canal and distended in 20 ml steps (from 30 to 90 ml). At each volume, subject was asked to perform maximal voluntary squeezes 3 times. Pressure-CSA loops were generated for each squeeze cycle.

Results: With increase in the bag volume, the loops shifted to the right and upwards in normal subjects (both anal and vaginal), which represents the length-tension function of the muscle. Similar to normal, the CSA pressure loops also shifted to the right with the increase in bag volume in FI patients, however, the shift to right was greater and upwards movement was less in FI patients as compared to normal subjects. The difference in the location of pressure CSA loops was statistically significant at volumes of 50 ml, 70 ml and 90 ml, ($P < 0.05$). Trend similar to the above was also found in the vaginal-CSA loops. Bag pressure at rest was not different between the groups ($P = 0.32$), but there was a trend for lower pressure in patients at squeeze ($P = 0.08$). The CSA was significantly greater in patients for both the anal and vaginal canals, apart from vaginal baseline distension, that was also trending ($P = 0.056$).

Discussion: We propose PCSA loops as a novel way to study anal sphincter muscle function and dysfunction and may be a better way to determine the degree of anal sphincter and puborectalis muscle dysfunction in FI patients.

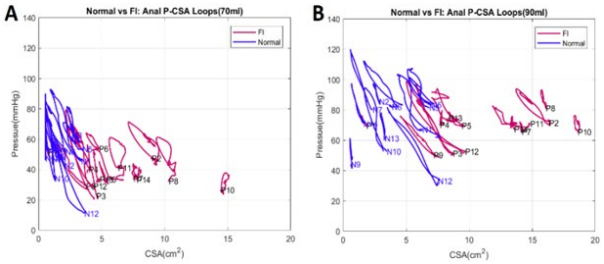

Fig. 1 Anal P-CSA loops in normal and FI patients (70 ml–90 ml).

119 | Swallow-induced esophageal distension patterns during peristalsis in patients with functional dysphagia: an unsupervised analysis

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Background: Initial inhibition followed by contraction occurring sequentially along the length of the esophagus constitute normal peristalsis. Luminal distension is a surrogate of the initial inhibition that can be measured by multi-channel intraluminal impedance (MII) recordings. Functional dysphagia (FD) is characterized by normal esophageal contraction.

Goal: Evaluate esophageal distension patterns via an objective unsupervised segmentation of the distension topographs, derived from the MII recording in FD patients.

Methods: 14 patients with FD (>3-month, BEDS ≥ 7), and 14 normal volunteers were studied. HRMZ recordings were obtained in the Trendelenburg position (−20 degrees), 5 swallows of 10 ml each, 0.5N saline. Distension topographs were built from the impedance measurements. An unsupervised isocontour based segmentation was used to segment the distension topographs to distinct regions, using solutions of probability-based optimization problem, with the volume evolution of distension isocontour starting from the top and gradually growing, as decreasing altitude level of the isocontour, thus creating local islands. Next, morphometric parameters were extracted.

Results: Amplitude of peak distension and number of distension peaks are lower in FD patients compared to normal, (Median 56.3(IQR 33.3)) and (32.3(9.3)), ($P < 0.01$), alongside, their respective spatial location (more distal in FD subjects). The overall intra-group, inter-distance of the peaks was different between two groups (smaller in the normal, $P < 0.01$). The spread of areas of segmented regions was smaller in normal (45(91) pixels compared to FD patients (59(226.75)) pixels), $P < 0.01$.

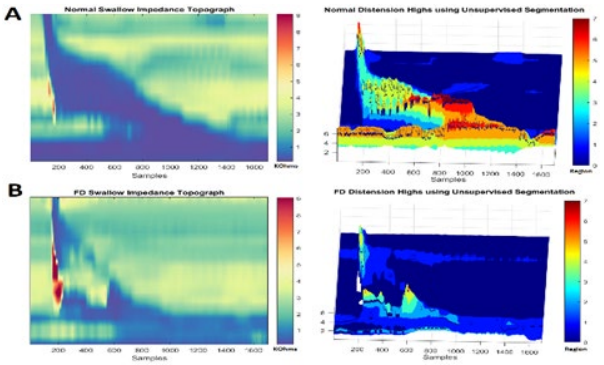

Fig 1. Detected peak islands shown as superimposed black contours on the topographs, (A)Normal (B) FD.

Conclusion: Patients with FD have smaller esophageal distension and more interrupted flow during bolus transit along the length of the esophagus suggesting abnormality in the inhibitory phase of peristalsis.