



Pitt

Digest

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What Is This?

CENTERS OF EXCELLENCE:

- PANCREAS & BILIARY DISEASES
- INFLAMMATORY BOWEL DISEASE
- LIVER DISEASES
- NEUROGASTROENTEROLOGY & MOTILITY DISEASES
- INTESTINAL HEALTH & NUTRITION SUPPORT
- GASTROINTESTINAL CANCER PREVENTION & TREATMENT
- WOMEN'S DIGESTIVE HEALTH

Pitt Digest

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Strengthening Brain-Gut Connections:

An Integrated Behavioral-Medical Treatment Paradigm

by Eva M. Szigethy, MD, PhD

The gastrointestinal (GI) tract is one of the most innervated organ systems in the body and, as such, is influenced by psychosocial stress and psychopathology. This gut-brain connection plays an even larger role in patients with GI disorders who are also afflicted with psychological states such as anxiety, depression and the emotional stress often linked to physical disease onset and exacerbations. To date, treatment of most GI disorders has focused on medical and surgical management with little consistent emphasis on altering brain functioning pertaining to emotional regulation, pain processing and the management of stress. There is an increasingly under-served population of patients with co-morbid medical and psychological issues who do not respond optimally to medical/surgical treatments. These patients can over-utilize system resources without symptom improvements, costing the medical system dearly and resulting in low health quality of life for the patients.

The Medical Coping Clinic at Children's Hospital Pittsburgh (CHP) was designed to fill the niche of integrating behavioral health services into the delivery of comprehensive medical services to pediatric patients with GI disease. My CHP team provides comprehensive psychological assessments and treatment in the Gastroenterology Clinic with an integrated clinical research program for youth with inflammatory bowel disease (IBD). Crohn's disease and ulcerative colitis are chronic life-long conditions with primary symptoms of diarrhea, abdominal pain, fatigue and secondary symptoms of pubertal and growth



delay, joint and skin manifestations, and high rates of anxiety and depression.

Our team has developed a screening paradigm to detect emotional distress in youth with IBD and a cognitive behavioral therapy (CBT) treatment protocol to target coping with physical illness-related challenges and improving depression, anxiety, and pain. My research has identified the neurophysiological and neuro-anatomical underpinnings of depression in this population. With treatment, patients show improved functioning, and preliminary results demonstrate decreased depression as well as improvements in health-related quality of life, social functioning and medication adherence.

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This issue of *Digest* features some of the most challenging problems in clinical gastroenterology: functional disorders and abdominal pain syndromes. These conditions frustrate physicians, since either the mechanism of disease is unknown, treatments are ineffective, or both. Faculty within the Division of Gastroenterology, Hepatology and Nutrition at the University of Pittsburgh are working to solve these most difficult problems, with our major focus on visceral pain.

Faculty in the University of Pittsburgh's renowned Center for Pain Research (<http://pain.anes.pitt.edu>) are conducting innovative visceral pain research, which is sponsored by our Division and the University of Pittsburgh's Departments of Anesthesiology and Neuroscience. In our Division's clinical center, the Digestive Disorders Center (DDC), physician-scientists focus on pain in inflammatory diseases (e.g., IBD and chronic pancreatitis) as well as functional disorders.

A truly innovative program is the Visceral Inflammation and Pain (VIP) Center of Excellence directed by **Dr. Eva Szigethy** (see cover page), which focuses on coping with pain syndromes. Clinical trials exploring the treatment of pain are now in progress. Two functional GI disorders are highlighted in this issue as well. **Dr. Klaus Bielefeldt** discusses his novel view of gastroparesis, and **Dr. David Levinthal** zeros in on functional problems with mechanistic diagnoses. All of these physicians concentrate on supportive treatment strategies.

We trust that you will read and enjoy this issue of *Digest* and invite you to join us for more cutting edge post-graduate CME at the DDW 2011 AGA-Postgraduate Course, *Managing Digestive Diseases in the Next Decade*, in Chicago, IL, where both Dr. Szigethy and Dr. Bielefeldt will be featured speakers.



Sincerely,

David C. Whitcomb, MD, PhD

*Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition*

Something New for Gastroparesis



by **Klaus Bielefeldt, MD, PhD**

"I feel my stomach problems wasted everything I achieved." This is a young woman's description of her gastroparesis, as she continued to struggle with daily symptoms despite multiple treatment trials with dietary adjustments, various prokinetics and anti-emetics. Those of us who care for patients with gastroparesis have heard similar statements.

Varied Approaches to Treatment

Gastroparesis significantly impairs quality of life. Beyond providing us with "fuel," eating and drinking are part of many social interactions. Even if patients maintain weight by altering diet, they may still feel isolated from friends or family.

Within the last ten years, new treatments have come and gone. Botulinum toxin was supposed to improve gastric emptying and help symptoms. Early results looked encouraging, but two randomized controlled trials failed to show true efficacy. Gastric electrical stimulation excited many but, regrettably, was not superior to sham stimulation in two recent trials. Attempts to find a better motility agonist led to three large trials with two different agents, all showing similar outcomes: no difference compared to placebo. In the meantime, the only FDA approved drug for gastroparesis, metoclopramide, became the target of class-action lawsuits. We need new ideas for different approaches and better treatments.

Mind and Body Strategies

Physicians and patients will agree that gastroparesis exacts significant physical and emotional tolls. It is no surprise that depressive symptoms were identified as the most important predictor of poor quality of life in these patients in a recent prospective study. These findings stand in stark

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An Unusual Cause of Liver Failure



by **Amit Raina, MD**
Gastroenterology Fellow

Case Presentation

A 23-year-old pregnant female was admitted to an outside hospital after premature rupture of her membranes at 27 weeks gestation. She developed fevers, abdominal pain and an elevated white cell count, was diagnosed with chorioamnionitis, and required a Caesarean-section. Two days post operatively, she developed right upper quadrant (RUQ) pain, elevated transaminases (40 x upper limit of normal) and hypotension. She was intubated and required vasopressors. Dilatation and curettage was performed to evacuate suspected retained birth products, but the patient developed a full-blown disseminated intravascular coagulopathy with vaginal bleeding, epistaxis requiring balloon tamponade and surgical packing. She continued to deteriorate with increased INR of 6, AST of 6500 IU/L, ammonia of 90 μ Mol/L and mental status changes with worsening renal function. She was started on CVVHD and was transferred to UPMC.

There was no history of eclampsia or pre-eclampsia and no personal or family history of liver disease, intravenous drug use, blood transfusion, body piercing or tattoos. Additional history from her mother indicated that the patient's boyfriend was an active intravenous drug user. The patient was icteric but had no stigmata of chronic liver disease (spider angiomas, palmer erythema), and no skin rash. She was intubated and required vasopressors for hypotension. Admitting laboratory values were creatinine 1.6 mg/dl, albumin 2.1 gm/dl, total bilirubin 9.1 gm/dl, direct bilirubin 5.2 gm/dl, ALT 806 IU/L, AST 6696 IU/L, ALP 484 IU/L, ammonia 129 μ Mol/L, lactate 10.2 μ Mol/L, platelets

15000/ μ L, and INR 4.1. CT scan (Figure 1) of the abdomen revealed an enlarged and hypoattenuated liver, likely from edema. An acute liver disease work-up was negative including serological markers for acute hepatitis A, B, C or E, cytomegalovirus, Epstein-Barr, HIV (I&2) and herpes simplex (I&2). A working diagnosis of Hemolysis, Elevated Liver enzyme levels and a Low Platelet count (HELLP syndrome) with liver failure was considered.

The patient fulfilled criteria for acute liver failure (ALF), defined as any evidence of coagulation abnormality (INR >1.5), and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks duration. The liver transplant service was consulted, and she received a deceased donor liver transplant two weeks later. Pathology of the explanted liver was consistent with herpes simplex virus (HSV)-2 hepatitis with massive hepatocellular necrosis. She was started on IV acyclovir with clinical improvement and improved renal function.

Herpes virus infections rarely cause ALF, but both HSV-1 and HSV-2 have been implicated as etiologic agents. High risk populations include neonates, patients taking immunosuppressive medications, patients with cancer or myelodysplastic syndromes, patients with HIV and pregnant females. The usual presentation of HSV hepatitis is fulminant liver failure with associated high mortality (>80%) if untreated. Clinically, patients can have fever (82%), abdominal pain (33%), leukopenia (43%) and coagulopathy (20%). Typical oral and/or genital lesions are seen only in 30 percent of cases.

Diagnosis of HSV infection in patients with liver failure can be based on positive serology and/or liver biopsy with special stains (intranuclear inclusions and the presence of HSV antigens by immunofluorescence). Reported cases include patients with negative serologies and positive tissue cultures of HSV. Treatment should be initiated with acyclovir (high doses in pregnancy) for suspected or documented cases and may be life saving in some instances.

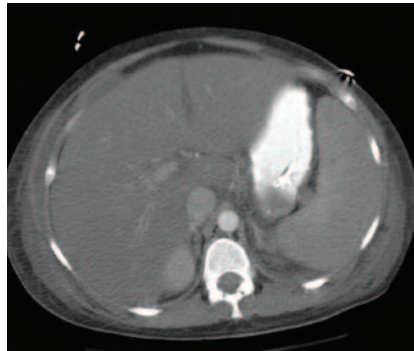


Figure 1. CT scan of abdomen with intravenous contrast: Hepatomegaly (approximately 24cm cranial-caudally) with hypoattenuated liver parenchyma likely secondary to edema. No evidence of cirrhosis.

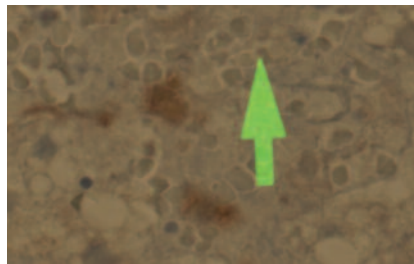


Figure 2. Liver allograft biopsy with positive staining (faint brown staining of nucleus) for HSV (immunofluorescence).

Brain-Gut Connections *continued from page 1*

I have expanded this clinical service and research through the implementation of the Visceral Inflammation and Pain Center (VIP), a parallel integrated center for adults with GI disorders at UPMC Presbyterian Hospital. The VIP Center will offer comprehensive psychological evaluation and treatment for adult patients with IBD. Patient management will target associated depression, anxiety, sleep disturbances and functional pain. Using a similar treatment algorithm to our successful pediatric model, patients will first see a therapist to learn CBT coping skills, stress management techniques and medical hypnosis. Psychopharmacology management will follow as needed.

Future plans include expansion of the VIP Center to include all GI patients. Strengthening brain-gut connections and the development of more adaptive coping strategies can help patients to lessen the psychosocial burden of chronic GI diseases. Such comprehensive and integrated psychosocial care to patients with GI conditions promises to decrease suffering and distress, enhance societal productivity, and save on unnecessary medical costs.



Dr. Szigethy is an associate professor of psychiatry and pediatrics in the University of Pittsburgh Division of Pediatric Gastroenterology and also directs the Visceral Inflammation and Pain Center (VIP) within the Division of Gastroenterology, Hepatology and Nutrition.

Physicians and patients will agree that gastroparesis exacts significant physical and emotional tolls.

Gastroparesis *continued from page 2*

contrast to results from gastric emptying studies. Gastric emptying measures, though critical to define disease, do not correlate with symptom severity or quality of life.

Our University of Pittsburgh research group interpreted these findings as a call to shift treatment from conventional approaches emphasizing acceleration of gastric emptying with prokinetics to alternative strategies focusing more on mind and body. In collaboration with team members **Dr. Ronald Glick** and **Dr. Eva Szigethy**, trials examining the effects of hypnotherapy or acupuncture have been designed and implemented. Encouraged by promising empirical results from the use of psychological therapeutics in other functional illnesses, we hope to implement more comprehensive strategies to help patients with this frustrating illness. Though still in an early phase of the trial, we are actively enrolling patients. Initial results may become available within a year. We will keep you posted!

Dr. Bielefeldt is an associate professor of medicine with the Division of Gastroenterology, Hepatology and Nutrition. His clinical and bench research addresses the care of patients with functional bowel disease and gastrointestinal pain.



What Is This? by Su Min Cho, MD, Gastroenterology Fellow. References upon request.

Twenty to 40 percent of patients with inflammatory bowel disease have extra-intestinal disease manifestations affecting the joints, eyes, skin and hepatobiliary system. Orocutaneous manifestations in IBD patients include aphthous ulcers (affecting approximately 10%), mucosal cobblestoning and, less commonly, orofacial granulomatosis in Crohn's disease. Our patient was diagnosed with pyostomatitis vegetans which is associated with ulcerative colitis. Patients develop millary pustules, superficial erosions and plaques on buccal and gingival mucosa. Ninety percent of affected patients experience peripheral esinophilia. Treatments focus on the underlying disease, using topical and systemic steroids, azathioprine, methotrexate and anti-TNF agents.

What Is This?

Novel Approaches to Gastroparesis Management



by **David Levinthal, MD, PhD**
Gastroenterology Fellow

Case Presentation

A 33-year-old woman presented with a four-month history of persistent nausea and vomiting. Although healthy until her late teenage years, the patient subsequently developed a complex array of medical disorders including neurocardiogenic syncope, chronic migraines, epilepsy, painful peripheral neuropathy and chronic fatigue. A progressive, proximal muscle weakness required eventual use of a wheelchair for ambulation outside of the home. She was maintained on a complex medication regimen including multiple anti-epileptic medications and other centrally acting agents.

Her nausea and vomiting developed rapidly without an obvious cause. While at its worst in the morning, nausea was persistent throughout the day and worsened with eating.

She often vomited following larger meals, particularly after consuming a meal containing fried or fatty foods or pasta. She described early satiety, post-prandial fullness and bloating with mild abdominal discomfort. There was no associated change in bowel movements, dysphagia or odynophagia. She had no associated fevers, chills, night sweats, skin rashes, visual changes, oral ulcers or arthralgias. She had restricted her diet to less than 1000 kcal/day over the past month and lost ten pounds, with 30 total pounds lost since symptom onset. She denied any recent travel, acute illnesses, or major changes in her medications.

Her physical examination was normal except for mild tenderness to deep palpation in the epigastrium and right

upper quadrant and moderately impaired proximal muscle strength in the lower extremities. Laboratory tests obtained prior to her visit revealed normal electrolytes, BUN and creatinine, liver function tests, TSH, T4 and cortisol, complete blood count and inflammatory markers including ESR, C₃ and C₄. An EGD performed prior to her visit showed a normal appearing esophagus, stomach and duodenum with biopsies from all regions revealing normal mucosa.

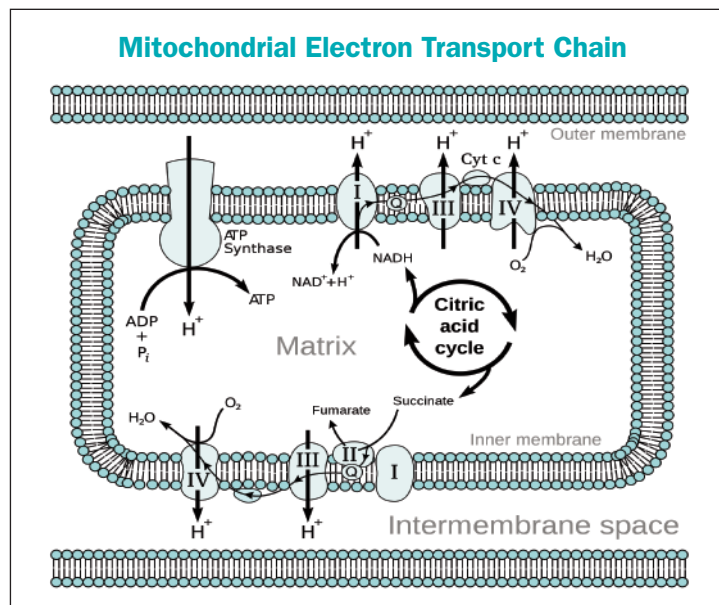
The differential diagnosis for a patient presenting with nausea and vomiting is broad, but given this patient's unremarkable prior work up including negative laboratory and endoscopic exams, gastroparesis or functional dyspepsia was thought to best account for her symptoms. Importantly, this patient had a strong history of multiple neurologic conditions with an associated proximal muscle

weakness, suggestive of an underlying mitochondrial disorder. Thus we prescribed Coenzyme Q-10 100 mg PO BID and Phenergan 25 mg PO every four hours as needed for the nausea. Additional bloodwork obtained during the visit showed an elevated resting pyruvate level, confirming a primary defect somewhere within the oxidative phosphorylation cascade.

At four-week follow up, the patient had made remarkable gains

in functional status, with increased energy, ability to stand and walk, and, importantly, improved nausea requiring only occasional Phenergan use. She was no longer vomiting, and her food intake increased to near baseline. The patient recalled that she had been tested for a putative mitochondrial disorder years ago, and she brought in old records that showed a markedly elevated pyruvate level and severe lactic acidosis obtained only after three minutes of moderate exercise. Together, these results are highly suspicious for mitochondrial dysfunction. Our final diagnosis was gastroparesis secondary to an underlying mitochondrial disorder.

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What Is This?

A 60-year-old female presented with a longstanding history of ulcerative colitis and several months of painful mouth ulcers. On examination, she had gingival and buccal mucosal aphthous ulcerations with white plaques with a normal tongue and palate. She had a peripheral eosinophilia (12%) with normal ESR, CRP, zinc level and folate level. Biopsy of an ulcer showed superficial perivascular and interstitial infiltrate with no viral/fungal effects.



Compare your answer to Dr. Cho's on page 4.

Novel Approaches *continued from page 5*

Mitochondrial dysfunction is an often under recognized yet prevalent mechanism that can be associated with disorders involving highly metabolically active tissue such as the peripheral and central nervous system, the heart, and striated muscle. Gastrointestinal manifestations are common and include bloating, dysphagia, recurrent nausea and vomiting, and colonic motility derangements ranging from chronic diarrhea to pseudo-obstruction. Treatment of mitochondrial disorders involves supplementation of nutrients to support oxidative phosphorylation, with Coenzyme Q-10, B vitamins, and L-carnitine being the most frequently used agents. This case demonstrates that Coenzyme Q-10 supplementation may be used effectively to treat gastroparesis attributable to mitochondrial dysfunction. Given that this therapy is inexpensive with little to no risk of side effects, a trial of "Co-Q 10" is reasonable for patients presenting with gastroparesis and a history of neurologic or muscle disorders.