Welcome to the first issue of Pitt Quarterly Digest, a quarterly publication of the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. Each issue will provide the latest in cutting edge gastroenterology and hepatology advancements for your practice.

The Division of Gastroenterology, Hepatology and Nutrition unites physicians and scientists for excellence in patient care, education and research, providing the best of tomorrow’s medicine today. The Division’s clinical arm – the UPMC Digestive Disorders Center (DDC) – encompasses six primary centers of excellence, each focusing on a specific gastroenterology category:

- **The Inflammatory Bowel Disease Center** treats people with ulcerative colitis and Crohn’s disease. This Center features one of the leading research programs in the world, investigating the genetic and immunological factors related to IBD.

- **The Pancreas & Biliary Center** offers expertise for simple and complex diseases of the pancreas and biliary tract and is world renowned for its discoveries related to the genetics of pancreas diseases. The Center’s research efforts focus on improved diagnosis for cholangiocarcinoma, idiopathic and familial pancreatitis and early detection and treatment for pancreatic cancer.

- **The Neurogastroenterology & Motility Center** is best known for its groundbreaking work on constipation, abdominal pain and pelvic floor disorders. This Center focuses on problems of intestinal function, including fecal incontinence and diarrhea, chronic constipation, swallowing disorders and gastroesophageal reflux.

- **The Center for Liver Diseases** provides expertise in the evaluation and management of a wide array of liver diseases. The majority of the center physicians are also trained as transplant hepatologists and partner with UPMC’s Thomas E. Starzl Transplantation Institute. A new and growing emphasis of this Center is living donor liver transplants.

- **The Gastrointestinal Cancer Prevention & Treatment Center** specializes in the diagnosis and treatment of cancers of the gastrointestinal tract, with highlighted advancements related to colon cancer and pancreatic cancer.

- **The Center for Intestinal Health & Nutrition Support** specializes in the evaluation and treatment of all conditions disrupting nutrient processing and offers advanced support for nutrition delivery, intestinal revitalization and intestinal transplant evaluation and support.

We consider you to be an integral part of this region’s “Digestive Health Network,” and we look forward to your interaction and feedback.

In good health,

David C. Whitcomb, MD, PhD
Professor of Medicine, Cell Biology & Physiology and Human Genetics
Chief, Division of Gastroenterology, Hepatology and Nutrition

P.S. All reading this newsletter are cordially invited to the University of Pittsburgh’s annual DDW Alumni Reception on Sunday, May 18 at the DDW meetings in Orlando. If you plan to attend DDW, please stop by the Peabody Orlando Hotel, Florida Ballroom II, between 6:00 and 8:00 pm.
Recurrent Melena in a Patient with Cirrhosis

by Neeraj Kaushik, MD
GI fellow, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh

This patient is a 63-year-old female with a past medical history significant for pulmonary fibrosis, diabetes mellitus and hypertension. Three months earlier, she had an episode of hematemesis; an upper endoscopy revealed grade 2 esophageal varices which were banded. She was diagnosed with cirrhosis secondary to nonalcoholic fatty liver disease (NAFLD) with a Child’s score of 6 and was started on nonselective β blockers. For the past three months she has had recurrent episodes of melena every 2–3 weeks and has become transfusion dependent receiving 21 units of PRBC over this period. Colonoscopy was negative and repeat EGD with push enteroscopy revealed small distal esophageal varices, prominent red spots with erythema in the body of the stomach, normal duodenum and jejunum and the above finding in the antrum of the stomach. (see Figure 1)

What is the etiology of recurrent melena in this patient? How would you proceed with further work up and treatment?

The two most likely explanations for recurrent melena given the endoscopic findings are diffuse gastric vascular ectasia (GVE) or severe portal hypertensive gastropathy (PHG). To differentiate between the two, antral biopsies were obtained (see Figures 2 and 3) showing vascular ectasia, fibrohyalinosis, spindle cells and microthrombi in the ectatic vessels confirming a diagnosis of diffuse GVE. With fibrohyalinosis and spindle cells on biopsy, GVE can be diagnosed with 86 percent accuracy. Thrombi seen in 50 percent of specimens with GVE are never seen on biopsy in PHG.

Our patient was treated with argon plasma coagulation (APC) and has shown endoscopic improvement with decreased transfusion requirements.

Discussion: PHG is common in the setting of cirrhosis occurring in 65 percent of patients. Endoscopically, PHG appears as red point lesions, cherry red spots, or black brown spots on a background of a mosaic-like mucosal pattern. Although PHG may cause chronic anemia or melena, transfusion dependence is uncommon. PHG is thought to occur due to changes in gastric mucosal blood flow, increased mucosal susceptibility to NSAID-induced damage, increased nitric oxide levels and increased expression of tumor necrosis factor α (TNFα), tumor growth factor α (TGFα) and epidermal growth factor (EGF) receptors. Nonselective β blockers decrease bleeding and prevent rebleeding in PHG. There are many reports showing effectiveness of octreotide, somatostatin, estrogen/progesterone combinations and rebapimide in treating PHG. Transjugular intrahepatic portosystemic shunts (TIPS) cause a dramatic decrease in PHG with resolution in a majority of patients with mild PHG. Surgical portocaval shunts are effective but are not commonly performed because of complications. Liver transplantation reverses PHG.

Classically, gastric vascular ectasia occurs in middle age females with autoimmune diseases, and 30 percent of patients with GVE have cirrhosis. Non-cirrhotic patients typically have “watermelon stomach” limited to the antrum, whereas cirrhotic patients usually have diffuse disease. These patients frequently have melena and often become transfusion dependent. GVE is an acquired ectasia thought to occur due to mechanical stress on the mucosa, abnormal antral motility in cirrhotics and altered metabolism of vasoactive substances such as vasoactive intestinal peptide (VIP) and 5-hydroxytryptamine (5HT). β blockers are ineffective in treating GVE. There are case reports showing effectiveness of octreotide and estrogen/progesterone combinations in treating GVE whereas TIPS and surgical portocaval shunts are ineffective in GVE and frequently lead to serious complications. Antrectomy and gastrectomy are effective treatments but carry an increased risk in cirrhotics. Argon plasma coagulation is effective in treating GVE and decreases transfusion requirements. Liver transplantation in cirrhotics cures GVE.

continued on page three
Recurrent Melena continued from page 2

Summary
PHG and GVE are distinct entities in the setting of cirrhosis and may be difficult to differentiate based on clinical and endoscopic findings. Differentiation between PHG and GVE is usually possible by histology and is important, since treatment options are different for the two conditions.

References


Upper GI Bleeding With a Twist

by Mehul Lalani, MD
*GI Fellow, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh*

A 40-year-old white male with no significant past medical history was transferred from an outside hospital for further management of upper gastrointestinal bleeding. He presented originally to an outside facility with a one-week history of melena, and underwent an upper endoscopy which was reportedly normal. The patient was subsequently discharged home but continued to have melena and had one episode of bright red hematemesis. He was readmitted, and a repeat endoscopy reportedly showed a Dieulafoy’s vessel in the gastric fundus which was injected with epinephrine. A third endoscopy was performed and revealed a possible gastric varix. He received a total of six units of blood at the outside hospital and was transferred for further management. Physical examination was normal without signs of liver disease. Laboratory data on presentation to the University of Pittsburgh Medical Center included the following: hemoglobin 9, MCV 91, RDW 16, BUN 17, and creatinine 0.7.

What would be your next step in management?
In our experience, endoscopic ultrasound has been helpful in delineating vascular lesions. An endoscopic ultrasound was performed revealing an anechoic submucosal area in the gastric fundus consistent with a vascular lesion (see Figure 4). An arteriogram confirmed two left gastric arteries: one normal artery off the celiac trunk and an anomalous artery arising directly from the aorta. The anomalous left gastric artery formed an abnormal tangle of arterial vessels in the fundus of the stomach consistent with the findings on endoscopic ultrasound (see Figure 5). The patient was taken to the operating room for an exploratory laparoscopy where the aberrant left gastric artery was visualized and ligated, and gastric devascularization was performed. The patient had no further bleeding and his blood counts remained stable.

Discussion: Common causes of upper gastrointestinal bleeding include peptic ulcer disease, varices, arteriovenous malformations, and Mallory-Weiss tears. In this patient, we report a very rare cause of upper gastrointestinal bleeding. The incidence of an anomalous left gastric artery originating directly from the aorta is between 0.5 percent and 15 percent. This artery is important, because it supplies blood to the area of gastric bleeding in over 50 percent of patients. However, this case is unusually rare in that the patient had two left gastric arteries. Upon review of the English literature, we were unable to find a similar case.

Summary
Standard endoscopic evaluation is considered in the management of upper gastrointestinal bleeding. This rare case illustrates the importance of angiography in enigmatic patients.

References


Inhaled Carbon Monoxide Suppresses the Development of Postoperative Ileus in the Small Intestine

by Anthony J. Bauer, PhD and Beverley A. Moore, PhD

Postoperative ileus is a major clinical problem after abdominal surgery, extending the length of hospital stay and often contributing to medical complications during recovery. We have recently shown in humans that the degree of intestinal manipulation occurring during routine abdominal surgical procedures initiates an inflammatory cascade within the intestines that is characterized by the release of pro-inflammatory agents. The intestine then takes an extended period of time to resume appropriate function, resulting in lost time and money for caregiver and patient alike.

Nearly all patients experience some degree of post-operative ileus. For approximately ten to 15 percent of these patients, post-operative ileus can linger for weeks with the patient being unable to eat regular food, putting the patient at risk for the development of bacterial overgrowth and sepsis. Treatment and extended hospital stays due to postoperative ileus account for over $10 billion in health care costs each year.

In research supported by the National Institutes of Health, the Bauer Lab consisting of Drs. Jörg Kalff, Nicolas Schwarz, Andreas Türler, Beverley Moore and Anthony Bauer has documented that the patient’s body sees the surgeon’s intrusion as a major insult, and that an inflammatory cascade develops in the intestinal wall temporarily shutting down the organ. A key step in this process involves a network of sentinel cells called macrophages that lie stealthily within the muscle layer. These resident leukocytes sense the intrusion, become activated and play a key role in orchestrating an intense local inflammatory response within the muscular wall of the intestine.

Through research on animal models and confirmatory studies in humans, we found that ileus is substantially caused by the release of nitric oxide via iNOS and prostaglandins via COX-2, potent inflammatory mediators that suppress the activity of gastrointestinal smooth muscle and modulate the nervous system of the gastrointestinal tract. A very limited number of medications currently used for the medical management of ileus are only marginally effective.

For example, prokinetics carry the potential for serious cardiovascular complications. Our new approach taps into the body’s natural anti-inflammatory armory for a possible therapeutic treatment. One such anti-inflammatory pathway that is evoked is heme oxygenase-1, which endogenously generates biliverdin and carbon monoxide (CO). Our group’s research turned to CO, when our collaborators, Drs. Leo Otterbein and Augustine Choi, discovered that low concentrations of exogenous CO (<500ppm) in air displayed significant anti-inflammatory properties by themselves.

In a February 2003 research article published in Gastroenterology, we examined the effects of low-dose inhaled CO on the development of postoperative ileus in mice. Our data demonstrated that protective effects of CO inhalation occur by targeting the down regulation of selective pro-inflammatory pathways and upregulating potent anti-inflammatory pathways within the intestinal muscularis. This resulted in decreased nitric oxide and prostaglandin production, and, thus, prevention of postoperative ileus. The results of this study provide important information necessary for the identification of molecular signaling pathways and their interactions that underlie the anti-inflammatory effects of inhaled CO. An increased understanding of these processes will provide the basis for assessing the further potential clinical use of CO in the operating room. The incorporation of low concentrations of CO into anesthetics gases during preoperative and postoperative periods has the potential to provide a minimally invasive technique that would reduce ileus in susceptible patients, hasten postoperative recovery and shorten hospital stays. These insights have applications in other inflammatory conditions including sepsis, hemorrhagic injuries resulting from automobile or industrial accidents and small bowel transplantation.
Cutting Edge IMID Treatment for IBD
by Scott E. Plevy, MD

The Immune Mediated Inflammatory Disease (IMID) Treatment Center located at the Magee-Womens Hospital in the Oakland section of Pittsburgh offers one of the only dedicated biologic infusion treatment centers in the western PA region. Advances in molecular medicine over the past decade have shown that inflammatory bowel disease (IBD) and many ostensibly unrelated diseases such as rheumatoid arthritis, psoriasis, and multiple sclerosis, share a common pathophysiology: immune-mediated inflammation. These immune-mediated inflammatory disorders, or IMIDs, trigger chronic inflammatory injury involving an inappropriate immune response that is associated with dysregulation of the normal cytokine milieu. Therefore, recognizing the shared underlying pathology allows for the possibility that the most effective treatment for many of these conditions may be a single drug or group of drugs. For patients with IBD, the newly increased appreciation of disease pathogenesis and the advent of anti-tumor necrosis factor (TNF) treatment strategies have signaled the onset of an era of specialized immunotherapy. Perhaps for the first time, clinicians caring for IBD patients now need a basic understanding of immunologic mechanisms to fully appreciate the efficacy and potential for side effects of new biologic therapies. The team of specialists at Magee is an immunotherapy resource for referring physicians and their patients with Crohn’s disease, rheumatoid arthritis and other immune-mediated diseases. The Magee IMID Treatment Center team treats all aspects of these challenging disorders within one comprehensive, state-of-the-art center.

Supported by IBD specialists from the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition, the IMID Treatment Center is one of only 19 academic institutions on the Federation of Clinical Immunology Societies (FOCIS) Academic Platform, which works collaboratively to study the diagnosis and treatment of immune disorders.

Mainstays of drug treatment for Crohn’s disease continued on page six
The University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition is pleased to announce the following new GI Fellow recruits. These candidates are slated to begin their work with the Division in the summer of 2004.

**NAME/MEDICAL SCHOOL RESIDENCY**

<table>
<thead>
<tr>
<th>Name</th>
<th>Medical School</th>
<th>Residency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen Banegura, MD</td>
<td>University of Michigan</td>
<td>University of Michigan</td>
</tr>
<tr>
<td>Kenneth Fasanella, MD</td>
<td>University of Virginia</td>
<td>Duke University</td>
</tr>
<tr>
<td>Rachelle Johns, MD</td>
<td>UPMC Health System</td>
<td>University of Pittsburgh</td>
</tr>
<tr>
<td>Daniel Mullady, MD</td>
<td>Boston Medical Center</td>
<td>University of Connecticut</td>
</tr>
<tr>
<td>Benjamin Siemanowski, MD</td>
<td>University of Utah</td>
<td>Jefferson Medical College</td>
</tr>
</tbody>
</table>

Current chief fellow, **David Sass, MD**, was recently awarded the 2003 AASLD/Schering Advanced Hepatology Fellowship. This fellowship will provide salary and benefit support for his fourth year of training. Dr. Sass will focus on clinical research and patient care in adult hepatology. His research project, *The Genetic Basis for Primary Biliary Cirrhosis (PBC)*, is designed to identify and define the role of inherited genes in the MHC susceptibility locus in the development of PBC. The study will recruit patients with PBC, identify whether any of their relatives have PBC or other related non-liver auto-immune diseases and will then perform basic genotype-phenotype correlations. The study is exploratory in design and will serve as a feasibility study for later in-depth genetic linkage studies, perhaps adopting a more genome-wide approach. Dr. Sass will be co-mentored by Division faculty David C. Whitcomb, MD, PhD and Brian Berk, MD.

Cutting Edge IMID Treatment

**continued from page five**

previously included corticosteroids and immunosuppressants such as azathioprine, methotrexate and cyclosporine. These medications dampen the body’s entire immune system in an effort to control the overactive immune response of the gastrointestinal tract. Clearly, there is much room for improvement upon the safety and efficacy of these traditional agents. With this in mind, biological therapies in the form of monoclonal antibodies (MAb) have been developed to target specific proteins involved in disease progression. The staff of the IMID Treatment Center is internationally recognized for its expertise in the use of current biological therapies such as infliximab (Remicade) and is a leading force in the development of new biological therapies.

There is still no single magic bullet to cure IBD or other IMIDs. However the clinical and research advancements of the IMID Treatment Center offer a whole arsenal of magic bullets to better treat patients today.

The IMID Treatment Center at Magee-Womens Hospital offers clinical excellence for adults suffering from Crohn’s disease and other IMIDs in a professional and comfortable environment. For more information or to schedule a patient appointment, call the IMID Treatment Center at 412-641-2144.

**Dr. Plevy is Associate Professor of Medicine, Co-Director, Inflammatory Bowel Disease Center, Director, IMID Treatment Center**

What Is This?

A 77-year-old male with h/o CAD and dementia presents after a 2-day history of nausea and vomiting. EGD reveals this finding in the third portion of the duodenum. *Compare your answer to Dr. Chandrupatla’s answer on page four.*