



Pitt

Digest



Fall/Winter 2011

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

Pitt Digest

is a publication of the
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Hepatology and Nutrition

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Marked Increase in Pediatric Acute Pancreatitis Inspires National Collaboration

by Mark E. Lowe, MD, PhD

In 1991, no cases of acute pancreatitis were diagnosed in a child admitted to the Children's Hospital of Pittsburgh. Since then, the number of cases has increased every year. Over the last ten years 90 to 150 children were admitted annually with the diagnoses of acute or chronic pancreatitis. About 90 percent of these admissions are for a new diagnosis of pancreatitis, and the other ten percent are for recurrent or chronic pancreatitis. Similar increases in pediatric pancreatitis have been reported at other children's hospitals in the U.S., Australia and Mexico. It is clear that the diagnosis of childhood pancreatitis is increasing – but why?

Theories include an increase in systemic illness diagnoses and a change in referral patterns with children going to tertiary care

centers rather than local hospitals. Our Pittsburgh data show a strong correlation between the number of amylase and lipase tests ordered and the rising incidence of disease. This increased testing can account for almost 90 percent of increased admissions for pancreatitis, suggesting a new recognition that pancreatitis can occur in children.

Because more children are diagnosed with pancreatitis, it has become easier to assemble larger numbers of patients for retrospective observational studies of childhood pancreatitis. Consequently, a number of papers on the subject have been published during the last ten years, and several trends have emerged from these studies. The etiology of acute pancreatitis in childhood is quite diverse, and idiopathic pancreatitis still comprises a sizeable fraction in most studies. The importance of pancreatitis in systemic disease is clear from recent studies. In children, pancreatitis

is more often a result of severe systemic illness rather than the cause. Importantly, biliary disease, mostly gallstone disease, once thought uncommon in childhood is a sizable fraction in most reports, even the leading diagnosis in some.

The glaring common message from these retrospective reports is that solid data about the etiologies and outcomes in childhood pancreatitis are unavailable. Children can have complicated pancreatitis with necrosis,

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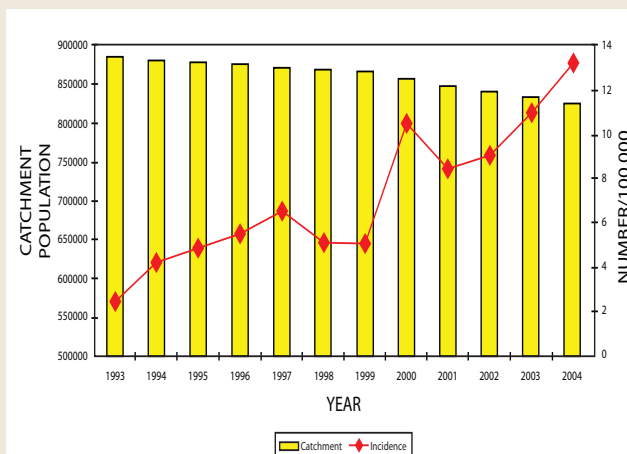


Figure 1: Catchment population of Children's Hospital of Pittsburgh of UPMC and number of admissions for pancreatitis/100,000 children from 1993 to 2004. Since 2004, the catchment population and incidence have remained relatively stable.

This issue of *Digest* highlights the leadership role of **Dr. Mark Lowe**, Chief of Pediatric Gastroenterology, Hepatology and Nutrition for the Children's Hospital of Pittsburgh (CHP) of UPMC. In his cover article, Dr. Lowe highlights the increasing incidence of acute pancreatitis diagnoses in children and discusses progress to address this concerning trend. Dr. Lowe is a prominent physician-scientist who has concentrated on lipid digestion by pancreatic enzymes as well as more complex pancreatitis models. He also serves on the National Pancreas Foundation Board of Directors and is a national expert on pancreatic diseases in children.

With 18 faculty members, the pediatric GI division at CHP provides world-class patient care with special expertise in diseases of the pancreas, inflammatory bowel disease, liver diseases, gastroesophageal reflux disease and esophagitis, and motility disorders. In collaboration with the Thomas E. Starzl Transplantation Institute, they also support outstanding programs in pediatric small intestine transplantation, liver transplantation and islet autotransplantation.

In addition to clinical expertise, the pediatric GI program is a major research center with study expertise in liver and pancreatic diseases. For example, **David H. Perlmutter MD**, Physician-in-Chief and Scientific Director for Children's Hospital and Chair of the Department of Pediatrics, recently reported major breakthroughs in alpha-1-antitrypsin deficiency (ATT) biology that could lead to new medical treatments (see *Science*, PMID: 20522742 and *JCI*, PMID: 21505264). **Dr. Wednesday Sevilla**, pediatric GI fellow, presents a case of ATT in this issue. **Dr. Dale King** who trained in Pittsburgh and **Dr. Andrew Chu** from the Children's Hospital of Philadelphia were recruited this year and will contribute to CHP's AAT research efforts. The CHP pancreas research group welcomed **Dr. Sohail Husain** this year, who is an NIH-funded physician-scientist from Yale University.

This issue of *Digest* welcomes the new academic year with additional teaching cases from two of our Division's excellent adult GI fellows, **Drs. Bridger Clarke** and **Jeffery Easler**.



In good health,

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*

Pediatric Acute Pancreatitis

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fluid collections and pleural effusions, but the incidence of these complications is not known. There is scant data on recurrent acute pancreatitis transitioning into chronic pancreatitis. As with adults, there is no therapy to prevent recurrent episodes or progression to chronic pancreatitis. Most studies suggest that death from pancreatitis is much lower in children than adults.

To address these large knowledge gaps, a group of pediatric gastroenterologists have organized **INSPPIRE (International Study Group of Pediatric Pancreatitis In Search of a Cure)**, which is a multicenter study group focused on pediatric recurrent acute pancreatitis and chronic pancreatitis. An INSPPIRE survey of participants from 19 separate institutions revealed that pancreatitis admissions ranged from less than 10 to more than 100 each year. The number of patients with recurrent or chronic pancreatitis followed at each institution ranged from less than 5 to more than 50.

While patients with acute pancreatitis may be managed by various hospital services, most of the children with recurrent or chronic pancreatitis are managed by pediatric gastroenterologists. Even so, the evaluation of these patients differs markedly among centers. INSPPIRE is developing a database comprised of children with recurrent acute pancreatitis and chronic pancreatitis and will work to identify basic information about these diseases in children. Hypothesis driven trials of therapies will be realized in the near future.



Dr. Lowe is a Professor of Pediatrics and is the Chief of the Division of Pediatric Gastroenterology, Hepatology and Nutrition with the Children's Hospital of Pittsburgh (CHP) of UPMC.

Dr. Lowe also serves as the Vice Chair for Postgraduate Education at CHP.

Fever, Jaundice & Anemia in a Young Man



by **Bridger Clarke, MD**
Gastroenterology Fellow

Case Presentation

A 29-year-old male presented with one week of progressive jaundice, fatigue and abdominal pain. One week prior to presentation, while in the hospital for the birth of his son, he began to feel tired and weak. Shortly thereafter, he noticed yellowing of his sclera. He reported vague upper abdominal pain that was constant and not exacerbated by eating or position change. He was mildly nauseated but not vomiting. Ten days prior to admission, he completed a one-week course of azithromycin for bronchitis but took no other medications.

The patient lived with his wife and newborn son and worked at a shipyard. He had no significant medical history, and family history was unremarkable. He denied significant tobacco or alcohol use.

Vital signs were normal with the exception of a low grade fever of 37.9. Exam revealed scleral icterus and jaundice. Palpation revealed mild tenderness across the right upper quadrant without rebound or guarding. No stigmata of chronic liver disease were evident. Initial bloodwork demonstrated AST 195, ALT 326, Alk Phos 214, and INR 1.1. *Table 1* shows bloodwork progression over the first three days as an inpatient.

	Day 1	Day 3
WBC	13.9	19.3
Hgb	11.0	6.4
Bilirubin	26	42
Direct bili	18	20
Platelet	161	64

Table 1: Bloodwork progression during days 1 and 3 of hospitalization

CT imaging of the abdomen and MRCP were unremarkable. Initial workup revealed negative hepatitis serologies (A, B, and C) and normal ANA, ASMA, AMA, ceruloplasmin, and alpha-1 antitrypsin. Ferritin was >15,000 with an otherwise

normal iron panel. Heterophile antibody (Monospot) and Epstein-Barr virus (EBV) antibody were both positive.

Packed red blood cells were transfused to counteract falling hemoglobin. There were no signs of clinical blood loss, and bloodwork for hemolysis was positive. A hematology consult diagnosed a cold-agglutinin hemolytic anemia.

Given the progression of lab abnormalities (*Table 1*), a liver biopsy was performed which demonstrated moderate acute portal inflammation and multiple granulomas (*Image 1*). Further staining revealed the presence of fibrin-ring granulomas (*Image 2*) and scattered EBV-positive lymphocytes, consistent with EBV hepatitis. His serum EBV PCR returned positive with 120,000 viral copies.

Hematology recommended plasmapheresis for the hemolytic anemia. After several days of treatment, the patient's blood work began to improve. He was discharged home after two weeks of hospitalization. His transaminases remained

mildly elevated for several months after the episode but returned to normal by the one-year follow-up appointment.

Infectious mononucleosis (IM) is classically described by the triad of fever, tonsillar pharyngitis and lymphadenopathy. IM is caused by EBV, which is transmitted through the passage of saliva and

infects B cells in the oropharynx. Infected B cells induce antibodies directed against viral antigens. These "heterophile antibodies" are detected with the Monospot test.

Clinical manifestations of IM can include splenomegaly, fever, maculopapular rash and jaundice. Hematologic findings include an atypical lymphocytosis and thrombocytopenia. Classically, anemia occurs due to a cold-agglutinin hemolytic process. Hepatic involvement is common and, typically, manifests as a mixed hepatocellular/cholestatic picture. Less commonly, it may progress to fulminant liver failure. Usually, liver biopsy shows acute hepatitis with cholestasis. Fibrin ring granulomas are rare and may be seen with Q fever (*Coxiella burnetii*), EBV infections or atypical drug reactions. The presence of EBV positive lymphocytes is diagnostic in an immunocompetent patient. Treatment is supportive unless major complications occur, in which case steroids may be considered.

References upon request.

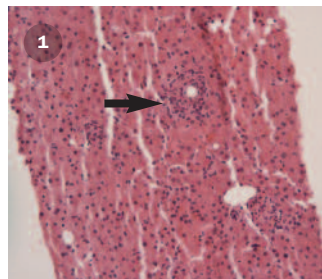


Image 1: Liver biopsy showing inflammation and granulomas (arrow).

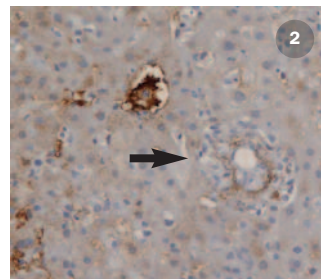


Image 2: Immunohistochemical staining for fibrin highlights fibrin-ring granulomas (arrow).

Infant with CNS Hemorrhage



by **Wednesday A. Sevilla, MD, MPH**
Pediatric Gastroenterology Fellow

Case Presentation

A five-week-old Amish male presented with sleepiness, poor feeding and unequal pupils. One week prior, he developed jaundice and intermittent epistaxis. He was born at term via spontaneous vaginal delivery at home. Parenteral vitamin K was not administered during the newborn period. When circumcised at one week of age, he had more bleeding than usual, but the bleeding resolved without intervention. In the referring emergency room, the infant was unresponsive and pale. Initial physical examination showed a full anterior fontanelle, anisocoria and ecchymosis of the right scrotal sac. No obvious signs of head trauma were noted.

Hemoglobin was 6 grams/dl, and a head CT showed bilateral subdural hematomas with a midline shift. The patient received packed red blood cells, fresh frozen plasma and mannitol prior to transfer.

Upon arrival at Children's Hospital of Pittsburgh of UPMC, physician examination revealed tachycardia, mild hyperreflexia in the lower extremities and no response to pain. Stool was noted to be acholic. At admission, labs revealed hemoglobin 6.4 gm/dl, platelets $397 \times 10^9/L$, INR 4.6, albumin 2.3 gm/dl, total bilirubin 4.8 mg/dl, conjugated bilirubin 2.0 mg/dl, ALT 51 IU/L, AST 85 IU/L, alkaline phosphatase 399 IU/L and GGTP 721 IU/L. Fresh frozen plasma, packed red blood cells and parenteral vitamin K were administered. Surgical evacuation of the subdural hematomas was performed. INR corrected within 24 hours, and there was progressive neurologic recovery with no evidence of residual injury.

While initial diagnosis was late-onset hemorrhagic disease of the newborn, the persistence of cholestasis, total bilirubin of 9.2 gm/dl with conjugated bilirubin of 7.0 gm/dl, and hypoalbuminemia prompted an evaluation for primary liver disease. A fasting abdominal US showed no focal hepatic lesions and a contracted gallbladder. A hepatobiliary iminodiacetic (HIDA) scan showed no excretion. Therefore, biliary atresia could not be excluded. The alpha-1 antitrypsin

phenotype for the patient was determined to be ZZ, which is associated with increased risk for neonatal jaundice, cirrhosis and emphysema. Because of the abnormal HIDA scan, stool color, sonographic findings and the patient's age, biliary atresia still had to be ruled out surgically. An intraoperative cholangiogram showed a patent biliary tree. The liver biopsy showed preservation of lobular architecture with increased cellularity in the portal area, and the alpha-1-antitrypsin stain showed intense granular cytoplasmic staining in the periportal hepatocytes.

Alpha-1-antitrypsin (AAT) deficiency is an inherited disorder which affects the lung and liver. AAT is an inhibitor of protease elastase. Whereas lung injury in AAT deficiency is caused by unimpeded action of elastase, liver disease is caused by intrahepatocyte accumulation of mutant AAT. Hepatocyte inclusions are seen on periodic acid-Schiff staining, with multiple alleles associated with AAT deficiency. Diagnosis of AAT deficiency relies upon the AAT genotype of the four possible phenotypes: normal, deficient, null or dysfunctional. Screening may be done with an AAT serum

level, however results should be correlated clinically, since circulating levels of the enzymes are affected by blood transfusions and the acute phase reaction. The prognosis of AAT deficiency varies from the development of cirrhosis as early as the first decade of life to anicteric hepatitis with no clinical

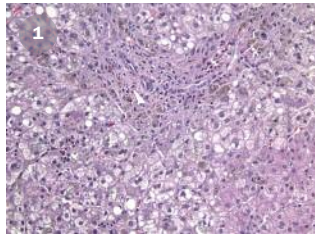
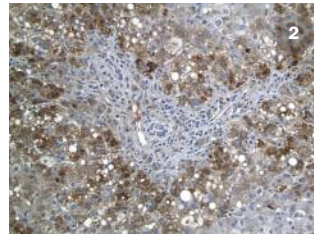


Image 1: Liver biopsy H&E stain showing increased cellularity in portal area.
Image 2: Alpha-1-antitrypsin staining with immunoperoxidase showing intense cytoplasmic staining.



evidence of liver disease. ZZ liver disease phenotype variability may relate to the unevenness in response to misfolded proteins. Breastfed infants with cholestasis are at risk for development of vitamin K deficiency, particularly in the setting of AAT deficiency. A population study completed in the Netherlands in 2009 showed that 75 percent of breastfed infants with AAT deficiency presented with a vitamin K deficiency and bleeding. To date, treatment of liver disease from AAT deficiency is supportive. End-stage liver disease is treated by organ transplantation.

References upon request.

The following Children's Hospital of Pittsburgh of UPMC faculty members contributed to this case discussion: Mark E. Lowe, MD, PhD, Professor of Pediatrics, Chief, Division of Pediatric Gastroenterology, Hepatology & Nutrition, & Vice Chair for Postgraduate Education; Sarangarajan Ranganathan, MD, Director of Anatomic Pathology, Division of Pediatric Pathology; Benjamin L. Shneider, MD, Director, Pediatric Hepatology, Division of Pediatric Gastroenterology, Hepatology & Nutrition.

Fellowship Updates . . .

The UPMC Gastroenterology, Hepatology and Nutrition Fellowship Program enjoys a complement of 18 fellows.

In June 2011, the program graduated six fellows and welcomed them as gastroenterologist colleagues:

- **David Brokl, MD** moved to the Mayo Clinical Health System, Southwest Minnesota Region.
- **Su Min Cho, MD** joined Gastroenterology Associates in Pittsburgh, PA.
- **Kofi Clarke, MD** is a gastroenterologist with the Allegheny Center for Digestive Health in Pittsburgh, PA.
- **Julie Holinga, MD** and **Priya Roy, MD** joined the Ohio Gastroenterology Group in Columbus, OH.
- **Ari Wiesen, MD** is completing an Advanced Endoscopy Fellowship and is a Visiting Instructor of Medicine with the University of Maryland Division of Gastroenterology and Hepatology.

Faculty Updates . . . **Dr. Brand to Receive Hirshberg Foundation Award**



Randall Brand, MD, familial pancreatic cancer specialist and UPMC faculty member, will receive the inaugural Moore Memorial Award for Exceptional Dedication to Pancreatic Cancer Research from the Hirshberg Foundation for Pancreatic Cancer Research. This award will be presented on November 19, 2011 in Wintersville, Ohio.

Dr. Brand is a Professor of Medicine with the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition. He serves as the Academic Director for the UPMC Shadyside GI group and is the Director of UPMC's GI Malignancy Early Detection, Diagnosis and Prevention Program. Dr. Brand is recognized internationally as an expert on familial pancreatic cancer, pancreaticobiliary disorders and GI malignancies. He specializes in the care of patients at high risk for the development of pancreatic cancer.

The Hirshberg Foundation for Pancreatic Cancer Research seeks to find a cure for pancreatic cancer through patient support, research funding and enhanced patient care. Dr. Brand's 2011 award will be given in memory of Ken Moore on the one-year anniversary of his passing.

"We are incredibly proud to acknowledge the distinguished work of Dr. Brand, in memory of foundation friend, Ken Moore," said President and Founder Agi Hirshberg. "Ron Hirshberg and Ken Moore fought every day to win the battle with pancreatic cancer. Now we must carry on in this fight, to unravel the unknown."

Joshua Novak, MD joined the Division as a nutrition support subspecialist with special interests in short gut and intestinal rehabilitation.

Jennifer Chennat, MD will join the Division in November 2011 as Director of Therapeutic Endoscopy, specializing in the diagnosis and treatment of disorders of the gastrointestinal luminal and pancreaticobiliary tracts.

Toby O. Graham, MD received the Division's 2011 Teaching & Mentorship Award. This honor is awarded by Division GI Fellows. Dr. Graham is an Associate Professor of Medicine and directs the Division's Nutrition Support team.

Brian Davis, PhD was selected to serve as the Division's Associate Chief for Research. Dr. Davis will lead translational and basic science research initiatives for the Division and will coordinate multidisciplinary and trainee research contributions.

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The patient's CT demonstrated mild infiltration of the fat involving the mid-portion of the descending duodenum extending into the pancreatic duodenal groove, but the remaining pancreatic fat was not inflamed. Endoscopy showed a peri-ampullary diverticulum and non-specific duodenitis. Ultimately, an evaluation with a side viewing duodenoscopy revealed a moderate size, edematous-appearing duodenal diverticulum involving the ampulla.

The patient failed to respond to conservative therapy and NPO status. He did respond to IV antibiotics and was discharged on a course of oral antibiotics, ciprofloxacin and metronidazole. The patient's symptoms resolved, and follow-up outpatient imaging demonstrated interval resolution of his regional inflammation.

The incidence of duodenal diverticula (DD) in autopsy series has been reported as high as > 20 percent. Most DD occur within segment 2 of the duodenum and are juxta-papillary. Only five percent of patients with DD will experience symptoms.

DD is a rare and challenging diagnosis with a non-specific clinical presentation. Imaging can demonstrate regional inflammation which can be mistaken for diseases such as pancreatitis. This patient's presentation, loco-regional inflammation, edematous DD on duodenoscopy, and prompt response to antibiotic therapy were all critical to establishing the diagnosis.

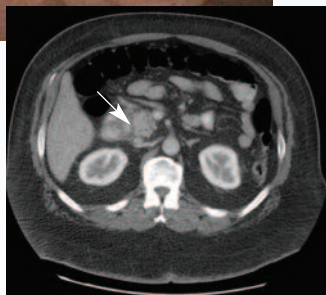
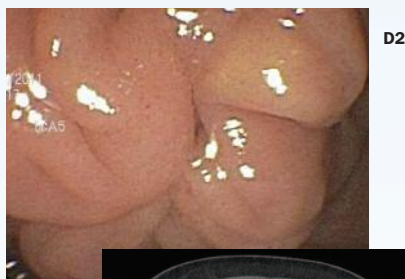
What Is This? by Jeffrey Easter, MD, Gastroenterology Fellow. References upon request.

Information concerning **Pitt Digest** or requests for additional newsletter copies may be directed to
Joy Jenko Merusi at joj2@pitt.edu. Visit our website at www.dom.pitt.edu/gi

What Is This?

A 61-year-old male with a past medical history of acute pancreatitis, diabetes mellitus and GERD presented with a month of intermittent epigastric pain. Symptoms worsened with eating, and he was nauseated with 15 pounds of weight loss since onset. The patient denied significant alcohol or substance abuse. On admission, liver function tests, amylase and lipase levels were normal. An upper endoscopy and a CT scan of the abdomen and pelvis with IV contrast were performed.

Compare your answer to Dr. Easler's on page 5.



Faculty Updates *continued from page 5*

Miguel Regueiro, MD will chair the Professional Education committee for the Crohn's & Colitis Foundation of America's National CCFA Medical and Science Advisory Board. Dr. Regueiro serves as the Co-Director & Clinical Head of UPMC's Inflammatory Bowel Disease Center.

David C. Whitcomb, MD, PhD has been named one of the Top 20 Great Pennsylvania Physicians by *Becker's ASCReview*. Dr. Whitcomb serves as chief of the Division of Gastroenterology, Hepatology and Nutrition with the University of Pittsburgh Department of Medicine. He is a world leader in pancreatic disease research and education with contributions at the clinical, translational and basic science levels. His laboratory group discovered the hereditary pancreatitis gene, and he is involved currently in studies of complex genetics of pancreatic diseases.

PHYSICIAN EDUCATION OPPORTUNITIES



Webinar . . .

**Postoperative Crohn's Disease:
Pittsburgh's Treatment Trial
A Model for Understanding IBD**

Wednesday, November 9, 2011, 6 p.m.

A free continuing medical education webinar presented by **Miguel D. Regueiro, MD**, Clinical Head & Co-Director, UPMC IBD Center. To participate in this broadcast, visit orlive.com/ibd.



PancreasFest 2012 . . .

The annual Pittsburgh **PancreasFest 2012** (PF12) conference will be held on **July 27 & 28, 2012**. Pancreatic cancer detection, diagnosis of early lesions and novel treatments will be the program's 2012 focus. PF12 will continue to welcome collaborative working groups studying all aspects of pancreas disease research. For more conference information, call **412-578-9518**.