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What Is a PCOE? Do You Need One?

By David C. Whitcomb, MD, PhD



UPMC has earned an international reputation for advanced pancreatic clinical care and groundbreaking pancreas research, especially related to genetics and technical procedures. An integration of translational research and technical advances, along with clinical expertise from multiple specialties into new clinical care models, occurs in UPMC's multidisciplinary Pancreas Center of Excellence (PCOE).

We share self-designated academic PCOE status with many other academic medical centers throughout the United States. However, standard minimum requirements for truly "qualified" centers of excellence remain unclear and undeveloped. PCOE programs, equipment, expertise, and the demonstration of quality care and excellent outcomes need further definition.

Patient advocacy groups such as the National Pancreas Foundation (NPF) and others can direct patients and families to qualified regional pancreas centers. These health nonprofits have recognized the need for qualified PCOEs to be assessed by independent and objective criteria.

Academic physician scientists at UPMC are working internally and with other colleagues to develop novel, automated patient assessment instruments, electronic medical record

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Robotic Cyst-Gastrostomy and Pancreatic Debridement for Walled-off Pancreatic Necrosis

By Amer H. Zureikat, MD, FACS

Walled-off pancreatic necrosis (WOPN) is an infrequent but serious sequela of acute necrotizing pancreatitis. This complication typically requires operative drainage into the stomach (cyst-gastrostomy) with debridement of the necrotic pancreatic tissue. The procedure is traditionally done via a laparotomy and associated with significant morbidity, but surgeons at UPMC are now using minimally invasive techniques to treat these collections in the hope of reducing blood loss, postoperative pain, morbidity, and length of hospital stay.

A 32-year-old male with no history of alcohol or cigarette abuse was referred with a WOPN following an attack of acute necrotizing pancreatitis in 2011. His past medical history was significant for systemic lupus erythematosus (SLE) (treated with chronic steroids), insulin-dependent diabetes mellitus (IDDM), and a cholecystectomy. The etiology of the pancreatitis was deemed to be secondary to SLE and/or chronic steroid use, because all other investigations (including genetic defects PRSS1, SPINK1, and CFTR) were negative. The collection measured 13 cm and was connected to another pelvic collection (12 cm) via a tract (Figures 1 and 2). This young patient was deemed a good candidate for a robotic-assisted operation, especially because he was at high risk for developing wound complications after a laparotomy.

The patient underwent a successful robotic cyst-gastrostomy, pancreatic cyst wall biopsy, pancreatic debridement (Figure 3), and drainage and debridement of the pelvic collection. Intraoperatively, the tract joining the pancreatic and pelvic

collections was identified, clipped, and severed. The operation was performed entirely in minimally invasive fashion in less than four hours with minimal blood loss (30 mL). Final pathology revealed a fibrotic cyst wall with no malignancy. The patient was discharged home six days postoperatively with no complications, and he was able to resume his daily physical activities within two weeks of discharge.

The robotic approach is being utilized increasingly in many pancreatic surgeries at UPMC, including Whipple procedures, central, distal, and total pancreatectomies, Frey and Puestow procedures, and pancreatic debridement and cyst-gastrostomies. This robotic approach allows complex pancreatic operations to be performed in a purely minimally invasive fashion while maintaining adherence to the principles of open pancreatic surgery.

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Zureikat AH, Moser AJ, Boone BA, Bartlett DL, Zenati M, Zeh HJ III. 250 Robotic Pancreatic Resections: Safety and Feasibility. *Ann Surg.* 2013 Oct;258(4): 554-62 PMID:24002300.



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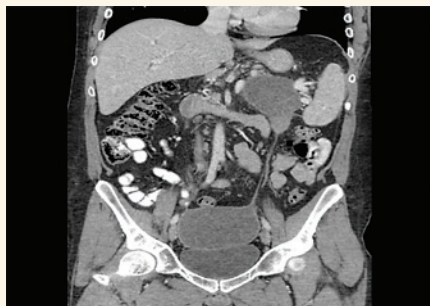


Figure 1. Walled-off pancreatic necrosis (WOPN) connected to a second pancreatic enzyme-rich collection in the pelvis. Note the connecting tract between the two collections.



Figure 2. Axial images showing the pancreatic collection with necrotic debris within it.

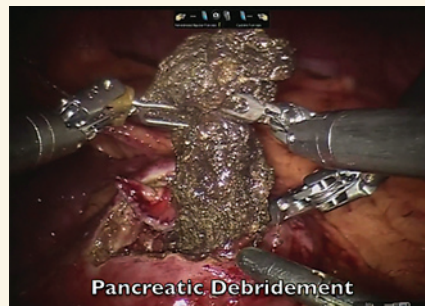


Figure 3. Robotic-assisted pancreatic debridement after the creation of the cyst-gastrostomy: the extraction of necrotic pancreatic debris from the WOPN using robotic graspers. The stereotactic vision and wristed instruments allow meticulous and comprehensive pancreatic debridement.

The Importance of Nutrition in Chronic Pancreatitis Patients

By Julia B. Greer, MD, MPH

Chronic pancreatitis is a progressive inflammatory disease characterized by irreversible structural changes and gradual fibrotic replacement of the pancreas. This parenchymal fibrosis leads to diminished exocrine and endocrine function of the gland. Not surprisingly, the majority of chronic pancreatitis patients will develop maldigestion and malabsorption of varying degrees due to the loss of exocrine function. Weight loss is also very common in these patients and has multiple contributing causes, including maldigestion, fear of eating due to pain (sitophobia), delayed gastric emptying, anorexia, nausea, and vomiting.

Levels of serum proteins, including albumin, prealbumin, and retinol-binding protein, are often significantly lower in chronic pancreatitis patients than in healthy individuals, reflecting protein-calorie malnutrition.^{1,2} Malabsorption frequently results in malnutrition and micronutrient deficiencies, and may elevate markers of oxidative stress and inflammation. Chronic pancreatitis patients may have diminished levels of nutrients such as glutathione, zinc, and selenium, as well as vitamins B12, C, D, and E. Micronutrient deficits compromise critical bodily enzymatic and immune functions, thereby compounding health issues. A recent systematic review demonstrated that most individuals with chronic pancreatitis have osteopathy, and one in four has osteoporosis.³

Pancreatic enzyme replacement therapy (PERT) is the most effective means of treating malabsorption in chronic pancreatitis patients.⁴ However, many clinicians do not prescribe PERT until overt symptoms, such as weight loss and steatorrhea (more than 15 g/day fecal fat), have developed. Many patients underdose or take enzymes before they begin eating, although PERT is most effective when taken in conjunction with a meal and right after eating.⁵ Some patients require larger doses of PERT than others, with or without gastric acid suppression, to achieve adequate nutrient absorption.⁵

There are few published investigations of malnutrition in chronic pancreatitis,⁶ and most studies are small in size and are of limited statistical significance.¹ Currently, our group at UPMC is conducting a large-scale, adequately powered study to measure serum levels of micronutrients and markers of oxidative stress in 300 chronic pancreatitis patients and 300 individuals without pancreatic disease. Study participants are derived from the North American Pancreatitis Studies (NAPS). Our initial goal is to show that micronutrient deficiencies exist in a significantly greater proportion of the chronic pancreatitis patients than controls. Secondarily, we will assess how disease duration and comorbidities, such as diabetes mellitus and alcoholism, may affect these same measures of nutritional status and oxidative stress. Finally, it will be possible to correlate deficiencies with quality of life variables, such as degree of pain. This data will

Table 1. Nutrition in Chronic Pancreatitis

Biomarker	What Blood Levels Indicate
Pre-albumin	Protein-calorie malnutrition
Retinol Binding Protein	Protein-calorie malnutrition
Vitamin D (25-hydroxy vitamin D3)	Fat malabsorption, bone mineral density
Vitamin E (α -tocopherol)	Fat malabsorption, potential oxidative stress
Vitamin B12 (cobalamin)	Malabsorption, potential nervous system dysfunction
Tumor Necrosis Factor Alpha (TNF- α)	Inflammation
Interleukin-6	Inflammation
C-Reactive Protein	Inflammation
Apolipoprotein-CII	Fat malabsorption
Glutathione	Protein-calorie malnutrition, immune function
Zinc	Mineral malabsorption, immune function
Osteocalcin	Bone mineral density

enable us to design an interventional study of PERT in specific subsets of chronic pancreatitis patients, such as those whose primary etiologic factor is heavy alcohol consumption. The variables that we are evaluating are listed in Table 1.

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PRSS1 Hereditary Pancreatitis: Lessons From Pathology

By Aatur D. Singhi, MD, PhD

Hereditary pancreatitis is a rare, heritable form of chronic pancreatitis. It is an autosomal dominant disorder with an 80 percent penetrance and variable expressivity. Patients with hereditary pancreatitis suffer from recurrent episodes of acute pancreatitis, and the majority progress to having chronic pancreatitis. The disease usually begins in early childhood, but onset can vary from infancy to the sixth decade of life.

By microsatellite linkage analysis, David Whitcomb, MD, PhD, and colleagues discerned the gene responsible for 80 percent of hereditary pancreatitis families on the long arm of chromosome 7 (7q35).¹ Subsequently, mutations within the cationic trypsinogen gene, also referred to as serine protease 1 (PRSS1), were identified as the underlying defect by candidate gene approach.² Several mutations within both the coding sequence and introns of PRSS1 have been described, but the R122H and N29I mutations are the most prevalent. The discovery of PRSS1 mutations has allowed for the development of genetic testing and, consequently, better classification of the etiology of chronic pancreatitis within a subset of patients and their families. Further, a major motivation for identifying patients with hereditary pancreatitis is the increased risk of developing pancreatic cancer. Recent studies have found a lifetime risk of pancreatic cancer of approximately 40 percent at 70 years of age.

Data on the histopathologic findings of PRSS1 hereditary pancreatitis have been limited. Practical difficulties in obtaining biopsies from the pancreas have prevented research during the early stages of the disease. In addition, studies obtaining specimens at later disease stages from patients undergoing surgery or from autopsies are lacking, although a report of two young adults with PRSS1 hereditary pancreatitis describes

histologic findings as indistinguishable from those seen in the setting of nonhereditary forms of chronic pancreatitis (e.g., pancreatic atrophy and prominent fibrosis).³

A review of pancreatic pathology from PRSS1 patients seen at UPMC argues the contrary.⁴ Patients with PRSS1 mutations develop a clinicopathologic form of pancreatitis that involves progressive pancreatic lipomatous atrophy. In children, most often the pancreas is grossly normal, but microscopically, there is variation in pancreatic lobular size and shape (Figure 1A). While the central portions of the pancreas display parenchymal loss and are accompanied by loose fibrosis, the periphery of the pancreas is remarkable for replacement by mature adipose tissue. These changes are more developed in younger adults, where fatty replacement seems to extend from the periphery to the central portion of the pancreas (Figure 1B). With older

patients, the pancreas shows marked atrophy and extensive replacement by mature adipose tissue with scattered islets of Langerhans and rare acinar epithelium (Figure 1C). In one patient, the extensive fatty replacement mimicked a mass lesion within the head of the pancreas.

While lipomatous atrophy of the pancreas is a frequent occurrence in the general population and is seen with increasing age, it typically presents focally and not as extensively as in PRSS1 patients.⁵ Other conditions associated with fatty replacement of the pancreas include Cushing's syndrome, steroid therapy, malnutrition, and viral infections. Genetic syndromes, such as Shwachman-Diamond, Johanson-Blizzard, and cystic fibrosis, are also associated with lipomatous atrophy. Of note, the most common etiology of pancreatitis in children is cystic fibrosis, an autosomal recessive disorder caused by CFTR. CFTR mutations result in thick inspissated secretions and mucus plugs within the pancreatic ducts, and ductal obstruction has been postulated to be responsible for lipomatous atrophy. However, how a similar phenomenon could be envisioned in PRSS1 patients is not entirely clear.

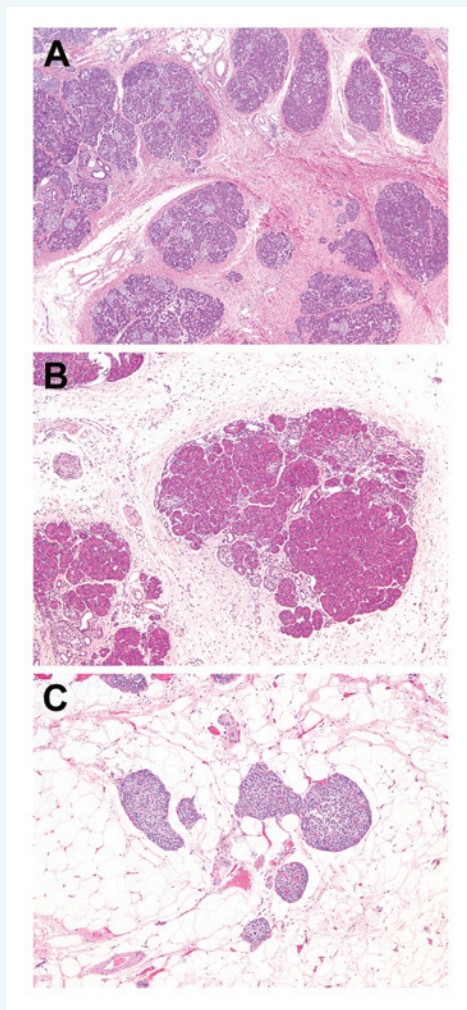


Figure 1. (A) Microscopic variation in pancreatic lobular size and shape in children. (B) Fatty replacement extending from periphery to central portion of the pancreas in a young adult. (C) Marked atrophy and extensive replacement by mature adipose tissue with scattered islets of Langerhans and acinar epithelium in older adults.

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Autoimmune Pancreatitis: A Great Masquerader

By Rawad Mounzer, MD

A 75-year-old male with past medical history of COPD, coronary artery disease, nephrolithiasis, and a new onset of diabetes presented to clinic for the evaluation of a 10-month history of diarrhea and weight loss. He reported having three to four greasy stools per day with nocturnal symptoms, and he had lost 40 pounds since symptom onset. He denied taking any new medications and has made several dietary modifications with no significant improvement. He denied any recent travel history. He reported no sick contacts but did endorse drinking well water at home.

The patient had undergone an upper endoscopy and colonoscopy at an outside facility, and biopsies taken during those procedures showed no abnormalities. Normal blood work at presentation was ascertained from a CBC, TSH, ESR, and CRP in addition to a CEA and CA 19-9. However, the patient's serum IgG4 level was highly elevated. Stool studies for infectious etiologies of diarrhea were unrevealing, and he tested positive on a fecal fat screen. A CT scan of the abdomen and pelvis revealed no significant abnormalities.

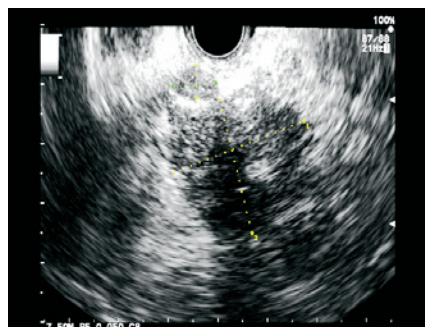


Figure 1. Pancreatic mass and abnormal peri-pancreatic lymph node on EUS.

EUS was performed, which showed diffuse parenchymal abnormalities, including echogenicity and hyperechoic foci throughout the pancreas with a vague mass-like appearance measuring 3 cm in the head of the pancreas plus

several abnormal peri-pancreatic lymph nodes (Figure 1). FNA of the mass was negative for malignant cells and revealed a polymorphous lymphoid cell population. The patient was diagnosed with type 1 autoimmune pancreatitis (AIP) and was started on pancreatic enzyme replacement in addition to a prednisone taper, resulting in almost complete resolution of his diarrhea.

AIP is divided into two subtypes, which differ in both clinical presentation and histologic findings. Type 1 has a male predominance, and the majority of patients are more than 50 years of age. The classic presentation of type 1 is obstructive jaundice with a mass-like lesion noted on abdominal imaging, resembling pancreatic cancer. New onset of diabetes and weight loss may also present, which raises concern for malignancy. Serum IgG4 levels

are elevated in these patients, and histologic evaluation of the pancreas shows lymphoplasmacytic sclerosing pancreatitis. AIP is thought to be a part of a IgG4-related systemic disease, which may involve other organs, including the biliary tree, salivary glands, kidneys, and retroperitoneum.

Type 2 disease usually presents in a younger age group and has a fairly equal gender distribution. Type 2 also can present as an obstructive pancreatic mass or as acute pancreatitis in approximately one-third of patients. Serologic evaluation is usually negative for IgG4, with histology revealing granulocytic epithelial lesions. Despite the absence of other organ involvement, this subtype is associated with inflammatory bowel disease in nearly one-third of patients.¹ The main diagnostic criteria of AIP are divided into five categories, known as the HISORT criteria:

- Histology (H)
- Imaging (I)
- Serology (S)
- Other organ involvement (OOI)
- Response to steroids therapy (Rt)²

Treatment of AIP consists primarily of corticosteroids, which may alleviate the need for biliary stenting in patients with obstructive jaundice and can help to restore pancreatic exocrine function. Moreover, response to corticosteroid therapy aids in confirming an AIP diagnosis.³ Disease relapse rates range from 30 to 50 percent in type 1, with most relapses occurring within the first few years of diagnosis. Relapse in type 2 disease is rare.²

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Lifestyle Choices That Impact the Pancreas

By Dhiraj Yadav, MD, MPH

Many common gastrointestinal diseases are associated with particular lifestyle factors. For some, such as gastroesophageal reflux disease and constipation, lifestyle modification is an important component of management. The lifestyle factor typically associated with pancreatic disease is *heavy* alcohol consumption. Moreover, physicians often believe that after initial presentation with alcohol-related pancreatitis, patients will inevitably continue to drink and have progressive disease. Research in the past few years has identified several lifestyle factors other than alcohol that impact pancreatic disease.

Alcohol is the second-most common cause of acute pancreatitis and the most common risk factor for chronic pancreatitis. The attributable risk of alcohol to the burden of chronic pancreatitis in the United States is about 40 percent. Contrary to what was formerly taught, research has shown that in patients with alcohol-related pancreatitis abstinence can substantially reduce the

risk of abdominal pain, recurrences, hospitalizations, and progression to chronic pancreatitis. Alcohol also can modify the risk and progression of pancreatitis of any etiology. Therefore, all patients with recurrent acute or chronic pancreatitis should be

...a critical component of management is patient education.

counseled (repeatedly, if necessary) to avoid all alcohol consumption. Even without data support, social drinking may be appropriate for patients who have had only one episode of mild acute pancreatitis from a cause that can be eliminated (e.g., gallstones, medications, etc.).

Smoking is now recognized as a strong risk factor for all forms of pancreatitis, as well as pancreatic cancer. Patients who drink alcohol are more likely to be smokers. While physicians may routinely counsel pancreatitis patients to quit drinking, they may neglect counseling for smoking cessation. Tobacco use is responsible for 25 percent of all cases of chronic pancreatitis and pancreatic cancer each, making smoking cessation the best option available currently to reduce the risk of pancreatic cancer. Therefore, smoking cessation counseling also should be included in the management of pancreatitis patients.

A healthy diet and regular exercise also may reduce the risk of pancreatitis. A high-fat diet and lack of exercise are associated with metabolic syndrome. Abdominal (central) obesity, elevated

fasting blood sugar levels, and high serum triglycerides are important components of metabolic syndrome. Although not a direct cause of acute pancreatitis, obesity increases the risk of gallstone formation, which in turn is the most common cause of acute pancreatitis. Therefore, the rising rate of obesity in the United States is believed to be an important contributor to the increasing incidence of acute pancreatitis observed within the past two to three decades. Obesity is a strong determinant of experiencing more severe disease for acute pancreatitis patients, and obesity also increases the risk of diabetes. In recent studies, diabetes was shown to independently increase the risk of acute pancreatitis by two to threefold. Appropriate management of diabetes can reduce pancreatitis risk.

Severe hypertriglyceridemia (i.e., serum triglyceride levels of 1000 mg/dl or higher) is an uncommon, under-recognized cause of acute and recurrent acute pancreatitis. In genetically predisposed subjects (conditions not too uncommon in the general population, such as familial combined hyperlipidemia, which has a prevalence of 1:200, and familial hypertriglyceridemia, which has a prevalence of 1:500), serum triglyceride levels typically range between 250 and 1000 mg/dl. In these subjects, poorly controlled diabetes and alcohol consumption can precipitate severe hypertriglyceridemia and can increase the risk of pancreatitis. Many of these patients require frequent hospitalizations, often due to poor control of these secondary risk factors. Therefore, a critical component of management is patient education. Dietary and lifestyle modifications (i.e., strictly following a low-fat diet and avoidance of alcohol and tobacco), tight control of diabetes, and when needed, medications, can be used to control triglyceride levels and may virtually eliminate the risk of future pancreatitis episodes.

Awareness among physicians and the general public about the role of lifestyle factors that impact the pancreas is therefore very important for prevention and treatment of pancreatic diseases.

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Yadav D, Lowenfels AB. The Epidemiology of Pancreatitis and Pancreatic Cancer. *Gastroenterology*. 2013;144:1252-61. PMID: 23622135.



Dr. Yadav is associate professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition.

Role of Imaging in Necrotizing Pancreatitis

By Anil K. Dasyam, MD

Acute pancreatitis has a varied prognosis, ranging from complete recovery to death. Associated morbidity and mortality are higher in the presence of pancreatic and/or peripancreatic necrosis, especially if the pancreas is infected.

Contrast-enhanced CT scan (CECT) supports the diagnosis of acute pancreatitis (Figure 1). After the first week, CECT is a vital tool to assess for complications such as pancreatic/peripancreatic necrosis, peripancreatic fluid collections (PFC), vascular thrombosis, and pseudoaneurysms. Based on the revised Atlanta classification criteria, CECT accurately characterizes PFCs as acute peripancreatic fluid collection, pseudocyst, acute necrotic collection, or walled-off necrosis.

MRI with or without contrast is comparable to a CT in diagnosing pancreatitis and its complications. MRI is superior to CECT for the identification of choledocholithiasis, non-liquefied components in PFCs, and the presence of pancreatic duct disruption early in the course of disease.

The presence of gas in pancreatic or peripancreatic necrosis is a strong suggestion of infection. In the settings of a new onset of sepsis, systemic inflammatory response syndrome, or organ failure, presumed infected pancreatic necrosis may be confirmed with image-guided percutaneous tissue sampling.

Prompt surgical debridement has been the historical mainstay of treatment of infected pancreatic necrosis. More recently, disease treatment has dramatically shifted toward conservative management and minimally invasive procedures, such as image-guided percutaneous catheter drainage (PCD), endoscopic drainage, and minimally invasive surgical procedures (e.g., video-assisted retroperitoneal drainage) to delay or avoid open surgical necrosectomy.

PCD is performed with ultrasound or CT guidance and is indicated for infected necrotic collections in a septic, unstable patient. Ideally, PCD should be delayed until the collections are walled off. PCD is not needed for sterile necrotic collections, except when they are associated with intractable abdominal pain or mechanical obstruction of the bowel or biliary tract. PCD is a safe procedure with a high technical success rate and is associated with improved clinical outcomes.

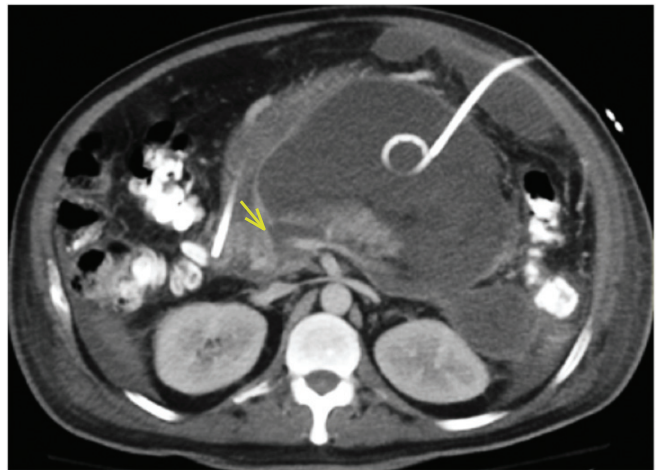


Figure 1. Axial contrast-enhanced CT scan image showing a percutaneous pigtail drainage catheter within a heterogeneous infected pancreatic necrotic collection. Note the nonenhancing necrotic parenchyma in the pancreatic neck (arrow).

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Nutritional Support in Acute Pancreatitis: Pancreatic Rest and How to Avoid TPN

By Stephen J.D. O'Keefe, MD, MSc

The nutritional management of patients with severe acute pancreatitis is one of the most complex situations encountered in medicine, consuming an enormous amount of health care costs. The reasons are threefold:

- Acute pancreatitis (AP) is one of the most catabolic diseases in the ICU. Consequently, the rate of the body's nutrient loss is higher than in the majority of other acute conditions, making patients "nutritionally at risk."
- Feeding can stimulate the pancreas and thus exacerbate the disease process.
- The function of the upper GI tract is impaired by extrinsic compression from the pancreatic inflammatory mass or from fluid collections, leading to gut failure with obstruction and vomiting, thereby increasing aspiration risk.

Total parenteral nutrition (TPN) seemed to be a clear solution to these problems. Previous studies from our group examined the relative stimulatory effects of enteral and parenteral feeding in healthy volunteers and showed that TPN was the best way to provide feeding while maintaining pancreatic rest (Figure 1).¹

In the 1980s and 1990s, TPN became a universal management therapy for any form of mild or severe AP, while patient outcomes became increasingly impaired by "TPN complications," most notably catheter-related septicemia and hyperglycemia. A key early study performed by Sax et al. showed that the use of TPN in patients

admitted to the hospital with mild to moderate AP had impaired outcomes compared with those who received no nutrition (Table 1).²

Several larger RCT studies of enteral vs. parenteral feeding followed, such as our own, which included patients with severe necrotizing disease. A meta-analysis showed that TPN was more expensive than enteral feeding and was associated with a significantly greater number of infectious complications (Table 2).³

Table 1

TPN Can Worsen Outcomes in Acute Pancreatitis

- *Controlled Study: TPN vs. IV fluids:*²
 - 54 patients with mild disease (average Ranson's score 1)
 - TPN group did worse
 - Catheter sepsis 11% vs. 2%, $p < 0.01$
 - Length of hospital stay 16 vs. 10 days
 - TPN arm more expensive



Finally, the study from Russia reported by Petrov et al. put the final nail in the coffin for TPN, because it found that mortality was higher in those study patients randomized to TPN.³

In all of these studies, enteral feeding had taken the form of semi-elemental formula infused into the jejunum in an attempt to minimize pancreatic stimulation. However, two studies, one from Scotland and a second from India, questioned whether pancreatic rest was needed, as they randomized patients to feeding either into the stomach (NG) or the jejunum (NJ) and found no difference in outcomes. Based on these results, they concluded that NG feeding was the best approach to nutritional support, because it was easier to start earlier, and evidence indicated that early feeding improved disease resolution.⁴ Our group criticized this conclusion, since we knew from our physiologic studies,¹ and from those of the Dutch,⁵ that their form of "jejunal" feeding, which was at best given into the proximal jejunum, remained stimulatory to the pancreas. In order to avoid pancreatic stimulation, feedings need to be delivered at least 40 to 60 cm past the ligament of Treitz. Consequently, these two studies had used "stimulatory" feeding in both of their arms, and the question of the importance of pancreatic rest remained unanswered.

In an attempt to evaluate this question, we designed a multicenter, randomized comparative trial between NG and distal jejunal feeding called the Study of Nutrition in Acute Pancreatitis (SNAP).

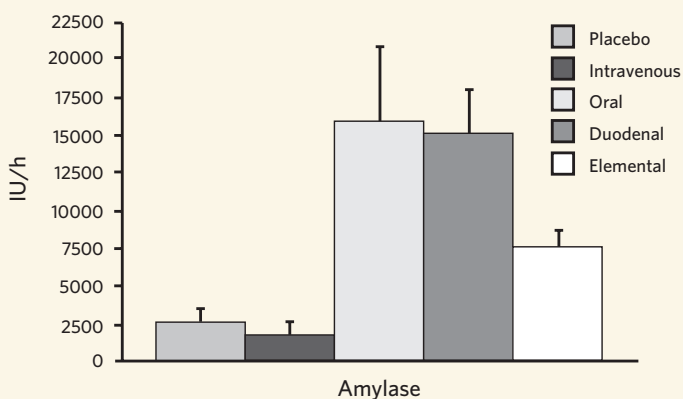


Figure 1. Amylase secretion in response to enteral and parenteral nutrition. Relative amylase secretory responses to enteral and parenteral feeding, illustrating no difference between oral and duodenal feeding of a complex diet, an intermediate response to duodenal elemental diet feeding, and no stimulatory effect of intravenous feeding compared with placebo saline.¹

continued from Page 8

To start, we designed a form of enteral feeding that avoided pancreatic stimulation. Recognizing that there had to be a “null point” somewhere between the duodenum and ileum where feeding was no longer stimulatory (note: feeding into the ileum actually inhibits pancreatic secretion), we fed volunteers at progressive distances past the ligament of Treitz, namely 20, 40, 80, 105, and 120 cm. The pattern of the secretory responses during 360 minutes of feeding demonstrates no significant secretory response to mid-distal jejunal feeding, because secretion rates were no different from those measured during fasting or IV feeding (Figure 2).⁶ Examination of gut peptide responses supported the suggestion that pancreatic secretion might have been suppressed by induction of the ileal brake, with substantial increases in plasma glucagon like peptide-1 and peptide YY, but not cholecystokinin. Our results were consistent with those of Vu et al., who established that the infusion of a mixed polymeric liquid diet at normal tube feeding rates (i.e., 1.6 kcal/min) into the proximal jejunum stimulated basal trypsin secretion four-fold, whereas infusion 60 cm below the ligament of Treitz had no stimulatory effect over three hours.⁶ Based on the results of our study, we now had a form of enteral feeding, termed distal jejunal feeding or DJ, that avoided pancreatic stimulation and could be used in our proposed NG vs. DJ feeding study.

Only 26 patients completed the SNAP study, and the study was closed before total recruitment was achieved due to slow enrollment. With such a small number of participants, the question of pancreatic rest could not be addressed. That is, we needed to show exacerbation of the disease, which was very difficult in a patient who was already critically ill and on a ventilator. However, our analysis revealed important information about best practice feeding techniques such as “feeding failure,” defined as failure to achieve a feeding rate of more than 10 percent of goal for a 48-hour period, which occurred in 0/14 DJ feeding patients and in 6/11 NG patients. Feeding failure in the NG group was primarily due to nausea, vomiting, or gastric residual volumes of more than 500 ml/4h, which is an indication of gastric outlet obstruction that necessitated a crossover to DJ feeding. As a result, the quantity of feed delivered was significantly higher in DJ patients, leading to greater success for enteral feeding via this route. It is now our standard of practice to place double-lumen feeding tubes by transnasal endoscopy as early in the disease as possible. These tubes feed 40 cm past the ligament of Treitz and decompress the stomach proximally.

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Table 2

Random Effects Model of Relative Risk (95% confidence interval) of Infections Associated With Enteral Feeding Compared With Parenteral Nutrition

Study	Enteral	Total Parenteral	Relative Risk (95% CI random)	Weight %	Relative Risk (95% CI random)
Abou-Assi	1/26	9/27		7.7	0.12 (0.02 to 0.85)
Gupta	0/8	2/9		3.7	0.22 (0.01 to 4.04)
Kalfarentzos	5/18	10/20		41.2	0.56 (0.23 to 1.32)
McClave	2/16	2/16		9.2	1.00 (0.16 to 6.26)
Olah	5/41	13/48		34.6	0.45 (0.18 to 1.16)
Windsor	0/16	3/16		3.7	0.16 (0.01 to 2.87)
Total (95% CI)	13/125	39/138		100.0	0.45 (0.26 to 0.78)

Test for heterogeneity: $\chi^2 = 3.71$, $df=5$, $P=0.59$
 Test for overall effect: $z=2.85$, $P=0.004$

0.01 0.1 1 10 100
 Favors enteral nutrition Favors total parenteral nutrition

Influence of Feed Complexity and Feeding Position on Trypsin Secretory Response

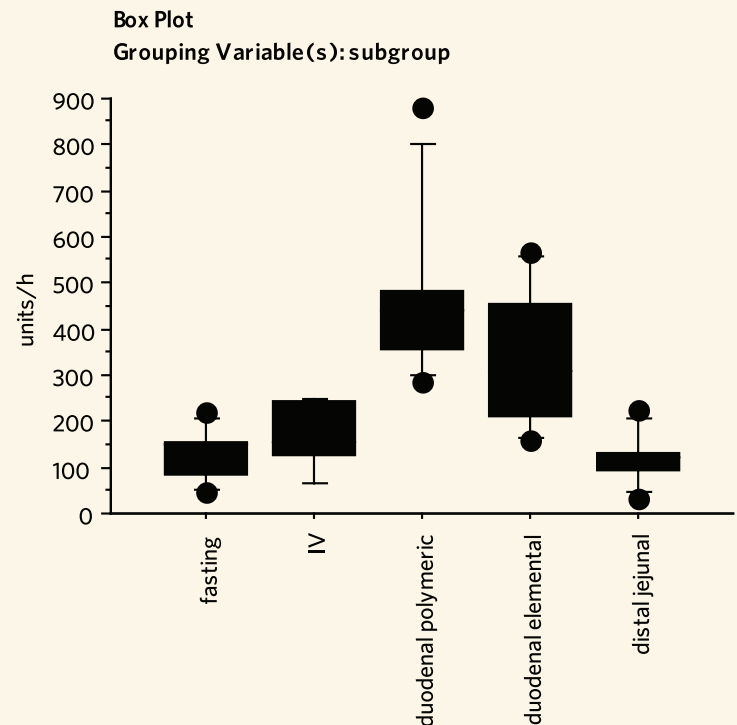


Figure 2. The relative pancreatic stimulatory effects of enteral and parenteral (IV) feeding on pancreatic secretion in normal healthy volunteers showing that distal jejunal (>40 cm past the ligament of Treitz) feeding had no stimulatory response.⁶

What Is a PCOE? *continued from Page 1*

interfaces, information management systems, and analytical tools, all complemented by quality indicators to address questions of qualifications and competency. Initial challenges for our group will focus on chronic pancreatitis, because this illness requires a true

...PCOEs will provide assurance that high-quality, cutting-edge, evidence-based care linked to quality indicators and known outcomes is available to guide patient choices.

multidisciplinary approach to achieve optimal care for patients. The PCOE process for UPMC, as well as other models, was reviewed this summer at *PancreasFest 2014*, at which academic physician leaders from across the U.S. discussed PCOE objectives and process implementation during a dedicated, half-day program. Physicians from more than 20 well-established academic

pancreas centers participated in this PCOE discussion to identify unanticipated problems and opportunities. This process was observed by representatives from the NPF and other groups, who functioned as independent monitors.

The goal for academic PCOE programs is to provide every medical center and practice with guidelines to develop and maintain the best possible care for patients with pancreatic diseases. PCOEs are not intended to be exclusive or elitist organizations. Instead, PCOEs will provide assurance that high-quality, cutting-edge, evidence-based care linked to quality indicators and known outcomes is available to guide patient choices. In addition to offering standard high-quality care to patients, academic PCOEs provide a classroom for advanced education; a research laboratory for translational research; a testing ground for new medications, instruments, and treatments; and a last resort for the most complex and challenging of patients. Such critically important functions may be seen as “money losers,” so system financial margins may threaten the existence of academic PCOEs in the future. The time for better models of care is now.

Rapid and dynamic changes have magnified our understanding of chronic pancreatitis etiologies, complications, outcomes, and treatments. We need to implement and measure treatment advancements to provide better guidance to all physicians. Our understanding of the role of susceptibility genes, modifier genes, smoking, alcohol, pain subtypes, type 3c diabetes mellitus, nutrition, and cancer risk have changed dramatically over the past 20 years. Different approaches and measures of disease progression are

needed.^{1,2} The acceptance of total pancreatectomy with islet autotransplantation (TP-IAT) is also growing, from implementation at only two major U.S. centers only a few years ago to at least 18 centers performing these procedures today. A workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was held immediately before *PancreasFest 2014* to address gaps in knowledge and methods for TP-IAT patient evaluation, and TP-IAT guidelines were developed at *PancreasFest 2014*.³

The key to a successful academic PCOE program includes acceptance and continued evaluation of new recommendations, a collaborative process among major centers, and demonstration of superb outcomes. Support of such centers also requires an economic model in which stakeholders (i.e., patients, patient advocacy groups, educational institutions, government, industry, and philanthropy) understand the value of an academic PCOE to address unique and unmet needs, and to provide appropriate levels of support.

The annual *PancreasFest* conference has become a venue to advance these ideas due to its robust history of major academic pancreas programs working collaboratively on multicenter studies. *PancreasFest* also provides an opportunity for subspecialty programs and leaders to partner with colleagues and contribute efforts to markedly improve patient care.

If you or your colleagues would like to participate in the PCOE, please contact me or PCOE co-coordinator, Darwin Conwell, MD, MS, Ohio State University. PCOE meetings will occur throughout the year, and we welcome your input.

Dr. Whitcomb is the Giant Eagle Foundation Professor of Cancer Genetics and serves as chief for the Division of Gastroenterology, Hepatology, and Nutrition. He co-chairs PancreasFest, an international subspecialty pancreas symposium for physicians and scientists.

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Managing Chronic Pancreatitis: Our Multidisciplinary Case-by-Case Approach

By Georgios I. Papachristou, MD

Physicians at the UPMC Pancreas Center of Excellence (PCOE) manage a large number of patients with chronic pancreatitis (CP) in both outpatient and inpatient settings. CP is a progressive inflammatory disease of the pancreas characterized by destruction and subsequent fibrosis. CP patients are a heterogeneous population with a broad range of clinical symptoms and morphologic features. Such patients typically present with chronic unrelenting abdominal pain, as well as pancreatic exocrine and/or endocrine insufficiency.

Abdominal pain is a prominent symptom of CP. The patient's discomfort may range from mild postprandial discomfort to severe, debilitating pain. This pain can be intermittent, episodic with flares, or constant. The first steps for pain management involve confirmation of the CP diagnosis, etiology identification, treatment of the underlying etiology when feasible, and elimination of risk factors for disease progression, such as alcohol use and cigarette smoking.

A stepwise approach is the best way to manage abdominal pain.¹ Use of analgesics should be judicious. We frequently start by prescribing low doses of tricyclic antidepressants, such as nortriptyline, aiming to block neuropathic pathways. Short courses of opiates with or without hospitalization are often needed to break the pain cycle. Chronic opioid analgesia is still required for many patients. We prefer to utilize long-acting agents under the guidance of pain management specialists. Pregabalin, an anticonvulsant agent, has shown promising results recently as an adjuvant therapy to opioids.²

Endoscopic therapy (ET) has an important role in the management of CP patients. ET is not applicable for all, but can be effective in a select subset of CP patients. ET aims to relieve pancreatic duct (PD) obstruction from strictures or stones and to address local complications, such as biliary obstruction or large pancreatic fluid collections. Utilization of ET is based on the hypothesis that intraductal hypertension leads to worsening pain. Our group recently published on the long-term outcomes of 150 CP patients from the North American Pancreatitis Study.³ Medical therapy alone was used in one-third of patients, and resulted in clinical improvement in 30 percent. ET was performed

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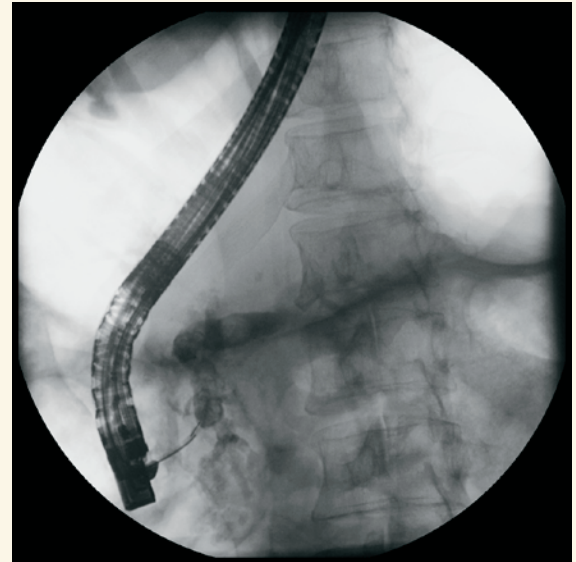


Figure 1. CT scan showing chronic calcific pancreatitis.



Figure 2. ERCP showing a dilated PD with filling defect consistent with PD stones.

Managing Chronic Pancreatitis *continued from Page 11*

... CP is a disabling disease that significantly affects a patient's quality of life. Its numerous management challenges require a multidisciplinary team approach.

in almost 60 percent of patients. Patients selected for ET had more severe symptoms and more complex pancreatic morphology on imaging than patients who were medically managed. The ET

for this study included pancreatic therapy (sphincterotomy, balloon dilation, stone extraction, stent placement), biliary therapy, and/or transenteral pseudocyst drainage. ET was safe and had a high rate (85 percent) of technical success in our expert hands. Long-term clinical success was achieved in 50 percent of patients. Older patients who had shorter disease duration

and required fewer narcotics showed higher rates of ET responsiveness. Among patients with persistent symptoms existing beyond ET procedures, surgery was performed with the aim to either decompress the PD (Frey and Puestow), or to resect the affected pancreas (Whipple), showing clinical improvement in 50 percent of the remaining patients. Overall, long-term clinical success of ET and surgery was observed in two-thirds of patients.

UPMC Presbyterian is one of a few specialized centers in the United States offering extracorporeal shock wave lithotripsy (ESWL) for the treatment of large obstructive PD stones. ESWL works by concentrating shock waves (SW) on stones via a water cushion. Patients are placed under general anesthesia, PD stones are localized using fluoroscopy, and hundreds of SWs are applied to a focal area, resulting in gradual fragmentation of the stones. Subsequently, usually in the same session, an ERCP is performed to remove stone fragments from the PD. ESWL has high efficacy (up to two-thirds of patients) and a low complication rate.⁴

In summary, CP is a disabling disease that significantly affects a patient's quality of life. Its numerous management challenges require a multidisciplinary team approach. At the UPMC Pancreas Center of Excellence, experts from different fields, including pancreatologists, advanced endoscopists, and pancreaticobiliary surgeons, work together to manage patients with judicious utilization of interventions. Challenging cases are presented in weekly meetings for consensus decisions in treatment plans. Our approach is stepwise, starting with medical therapy. Symptomatic patients with complex morphologic features undergo endoscopic therapy early in the disease course, including ESWL for large obstructive PD stones. A subset of patients subsequently requires surgical intervention. As described above, our multidisciplinary approach is tailored on a case-by-case, individualized basis, and aims to provide safe, effective, and long-lasting improvement of symptoms.

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Dr. Papachristou is associate professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition. He also serves as a co-director for pancreatitis research with the UPMC Liver Pancreas Institute.

The Complex Nature (and Nurture) of Recurrent Acute Pancreatitis

By Anthony Razzak, MD

Gastroenterology Fellow, Year III



A 27-year-old medical student of Pakistani descent was referred to clinic for evaluation of recurrent acute pancreatitis of unclear etiology. She experienced her first episode one year prior, and described severe epigastric pain associated with nausea and vomiting.

She denied alcohol use and was not taking any medications or supplements. Acute

pancreatitis was diagnosed with a lipase of greater than 10,000 U/L. Her liver function tests were normal. An abdominal ultrasound was negative for gallbladder pathology or biliary ductal dilation. A CT scan with IV contrast revealed acute interstitial pancreatitis without evidence of chronic inflammatory changes. Metabolic parameters, calcium, and triglycerides were within normal limits. She was managed conservatively and recovered without complications.

Six months later, she experienced a second, similar episode of radiating abdominal pain with vomiting that required hospitalization. Her admission lipase was again noted to be markedly elevated (greater than 22,000 U/L) with normal liver function tests. Acute pancreatic interstitial inflammation was noted on a contrast-enhanced CT, and she was diagnosed with recurrent acute pancreatitis (RAP). A magnetic resonance cholangiopancreatography (MRCP) was performed and suggested findings consistent with pancreas divisum, a congenital anomaly that can contribute to recurrent acute pancreatic injury.¹ She recovered without difficulties and was referred to UPMC for outpatient endoscopic retrograde pancreatography (ERP) with possible intervention.

During the ERP, her dorsal pancreatic duct appeared to communicate with the ventral duct, discounting the presence of divisum. Fluoroscopically, her pancreatic duct appeared prominent and contained noncalcified stones in the pancreatic head, which precluded passage of a wire to facilitate stone removal.

The patient presented with no problems or complaints during her follow-up clinic visit. She denied any family history of pancreatitis or cystic fibrosis. She did not endorse any clinical manifestations of pancreatic exocrine or endocrine insufficiency. A thorough

serologic evaluation to investigate her recurrent acute and suspected early chronic pancreatitis (CP) was initiated. She was found to be homozygous for the N34S variant of the serine protease inhibitor Kazal type 1 (SPINK1) gene, a well-known contributor to RAP and CP.^{2,3}

RAP/CP syndrome is thought to be a complex multifactorial disorder, involving genetic susceptibility with environmental stress and stimuli, which appears largely related to pathologic intra-pancreatic trypsin activation and subsequent pancreatic injury.⁴⁻⁶ The list and mechanisms leading to RAP/CP continue to grow.⁷

Genetic tests are available for SPINK1, cationic trypsinogen gene (PRSS1), and some CFTR mutations, but these tests may identify only a fraction of the susceptibilities associated with RAP/CP. The cost of testing is high, and the medical, personal, and ethical implications of testing should invite discussion with a genetic counselor.²



SPINK1 encodes a secretory trypsin inhibitor that protects against prematurely activated intra-pancreatic trypsin.^{5,8} When mutated, its pathologic role in pancreatitis is not direct but related to an impaired defense against trypsin activation from a variety of other pancreatitis susceptibility factors. It has been implicated in tropical pancreatitis, a syndromic pancreas-related process afflicting populations in Asia and Africa.⁹ The South Asian ancestral history of this patient and lack of family history are consistent

with the complex genetic risk inheritance patterns for SPINK1-associated pancreatitis.

Current management options available for RAP/CP are limited. Scant evidence suggests that antioxidant therapy (vitamins A, C, E, and selenium) may help to prevent oxidative parenchymal injury and pain.¹⁰ The role of total pancreatectomy with islet autotransplantation (TP-IAT) is unclear but may lessen the insulin requirements and narcotic needs of younger patients.^{11,12} For most patients, pancreatic enzyme replacement, insulin, and opiate-based analgesia remain mainstay therapies for disease-related complications.

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What Is This?

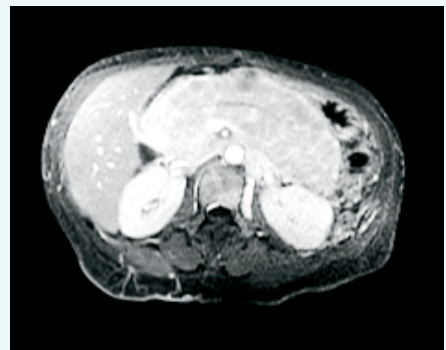
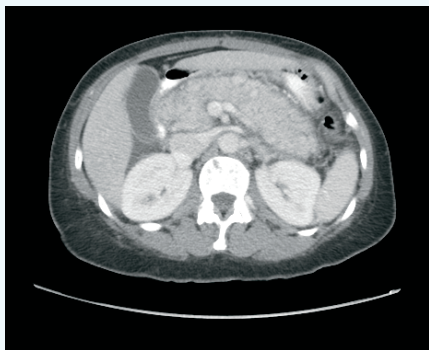
Elizabeth J. Blaney, MD

Clinical Assistant Professor of Medicine
Division of Gastroenterology, Hepatology, and Nutrition



A 51-year-old African-American female with a history of multiple myeloma has recurrent admissions for abdominal pain consistent with pancreatitis. Pancreatic enzymes are normal, and a CT was normal one year ago. Sequential images over the three months since symptoms began are shown below.

Compare your answer to Dr. Blaney's on Page 15.



Recurrent Acute Pancreatitis *continued from Page 13*

The remainder of our patient's evaluation was negative, including CFTR and PRSS1 mutation analyses. She did not drink or smoke, and was without any obvious environmental exposures. Our finding of homozygous SPINK1 risk alleles provided an etiologic diagnosis and facilitated discussion regarding clinical expectations, prognosis, and management options. To date, she has not endorsed evidence of exocrine or endocrine insufficiency, and thus remains a candidate for TP-IAT evaluation at UPMC.¹²

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Welcoming New Faculty

The Division of Gastroenterology, Hepatology, and Nutrition is proud to welcome the following new faculty members:



Elizabeth J. Blaney, MD

Clinical Assistant Professor of Medicine
Practicing gastroenterology at the Magee-Womens Hospital of UPMC



Naudia N. Jonassaint, MD, MHS

Assistant Professor of Medicine
Practicing hepatology at the UPMC Center for Liver Diseases



Vinod K. Rustgi, MD, MBA

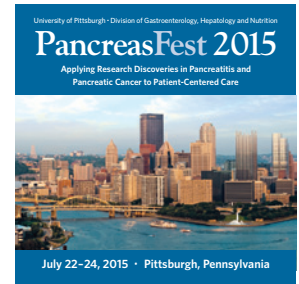
Professor of Medicine
Clinical Director of Hepatology
Medical Director for Liver Transplantation

Save the Date

PancreasFest 2015

July 22-24, 2015

Pittsburgh, Pennsylvania



PancreasFest is an annual research and clinical conference designed for gastroenterologists, surgeons, researchers, other physicians, and interested medical professionals. Lectures, discussion groups, and investigative research meetings will further participants' multidisciplinary understanding of the treatment of pancreatic diseases.

David Whitcomb, MD, PhD, Named "Gastroenterologist to Know"



David C. Whitcomb, MD, PhD, has been named to the 2014 listing of "160 Gastroenterologists to Know," an honor designated by *Becker's ASC Review*. Dr. Whitcomb was recognized for his leadership, research, and business development as a division chief and pancreas genetics subspecialist.

Pancreatic plasmacytoma is a rare condition, with approximately 26 cases reported in the literature, and should be considered in the differential diagnosis of pancreatic mass in patients with multiple myeloma. Patients typically present with jaundice and abdominal pain. Radiographic characteristics include homogeneous enhancement of a solid mass or diffuse enlargement, though findings are nonspecific and mimic other pancreatic neoplasms. Endoscopic ultrasound with biopsy is often the diagnostic modality of choice. Anaplastic myeloma is an aggressive variant of myeloma, which is associated with extensive extramedullary disease, portending a poor prognosis as seen in this case.

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What Is This? continued from Page 14

Nutritional Support in Acute Pancreatitis *continued from Page 9*

This process maintains gut function, prevents ileus and bacterial overgrowth, and decompresses the obstructed proximal gut, decreasing aspiration risk.⁷

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Dr. O'Keefe is professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition. He treats patients within UPMC's Clinical Nutrition Support Service.

PRSS1 Hereditary Pancreatitis *continued from Page 4*

Furthermore, how the histopathologic findings contribute to chronic pain in PRSS1 patients remains enigmatic. As genetic testing for hereditary pancreatitis becomes more widespread, future studies should provide greater insight into the pathophysiology of this debilitating disease.



Dr. Singhi is assistant professor of pathology in the Division of Anatomical Pathology at UPMC.

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