NewYork-Presbyterian

2018 • Issue 1

ADVANCES IN GASTROENTEROLOGY AND GI SURGERY

Marc Bessler, MD
Chief, Minimal Access/
Bariatric Surgery
NewYork-Presbyterian/
Columbia University Medical Center
mb28@cumc.columbia.edu

David E. Cohen, MD, PhD
Chief, Gastroenterology
and Hepatology
NewYork-Presbyterian/
Weill Cornell Medical Center
dcohen@med.cornell.edu

Jeffrey W. Milsom, MD
Chief, Colon and Rectal Surgery
NewYork-Presbyterian/
Weill Cornell Medical Center
mim2035@med.cornell.edu

Timothy C. Wang, MD
Chief, Digestive and Liver Diseases
NewYork-Presbyterian/
Columbia University Medical Center
tcw21@cumc.columbia.edu

Pancreatic Cysts: When Is There a Cause for Concern?

With the use of advanced abdominal imaging techniques, the incidental identification of pancreatic cysts is becoming increasingly more common. "Pancreatic cysts are the most readily identifiable precancerous lesions for pancreatic cancer," says **Tamas A. Gonda, MD**, Director of Endoscopic Research in the Division of Digestive and Liver Diseases at NewYork-Presbyterian/Columbia University Irving Medical Center, and a member of Columbia's Pancreatic Cyst Surveillance Program. "As such, they represent an opportunity for us to identify patients who are at risk for developing pancreatic cancer so that hopefully we can intervene at a time when we can prevent a progression to invasive disease."

While cysts represent precancerous lesions, they are also very common, with estimates between five and 20 percent of people in the United States having pancreatic cysts. "Obviously, that's a huge number, and pancreatic cancers are nowhere near that high," says Dr. Gonda. "That means that the majority of patients who develop pancreatic cysts will never progress to cancer. You don't want to put patients through interventions or any kind of procedure, or for that matter, surgery, if it is not going to benefit them. Our Pancreatic Cyst Surveillance Program focuses on risk stratification to enable us to identify those patients with pancreatic cysts who are at risk for developing cancer and those who are not."

Dr. Tamas A. Gonda

Although the majority of pancreatic cysts are benign, mucinous cysts represent at least a third of all cysts and are capable of malignant transformation. Mucinous cysts include mucinous cystic neoplasms and intraductal papillary mucinous neoplasms.

(continued on page 2)

Fecal Microbiota Transplant: An Old Remedy Made New

The first recorded use of fecal material as a medical remedy dates back to 4th-century China when it was administered orally to a patient with severe diarrhea. The historical trace then goes dark regarding the healing properties of fecal matter until its use in veterinary medicine in the 1700s. 1958 marked the first use of fecal material administered to humans delivered via enema to treat antibiotic-associated pseudomembranous colitis. Fecal matter was again utilized in 1981 to treat this colitis now known to be caused by the bacteria, *Clostridium difficile* or "*C. diff*" for short. However, its application as a healing remedy did not broaden. More recently, when called into action to successfully halt multiple recurrences of this disease within *C. diff* epidemics, fecal transplant is now being seen as a possible treatment for a host of disorders, including chronic diseases in and out of the digestive tract.

"Fecal transplant, or fecal microbiota transplant [FMT], is a therapy we started using more frequently after 2005 in order to control multiple relapses of *Clostridium difficile* infections," says **Carl V. Crawford, MD**, a gastroenterologist in the Division of Gastroenterology and Hepatology,

(continued on page 3)

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL GASTROENTEROLOGY & GI SURGERY 2017-18

Pancreatic Cysts: When Is There a Cause for Concern? *(continued from page 1)*

Understanding the Variables in Risk Stratification

"Much of our work is focused on understanding when a patient walks through the door if he or she is likely to be more of a high-risk person versus a low-risk person," says Dr. Gonda. This requires an integrated and truly multidisciplinary approach with active participation of surgeons, radiologists, and gastroenterologists. **Beth A. Schrope, MD, PhD**, Surgical Director of the Pancreatic Cyst Surveillance Program in the Pancreas Center at Columbia, and Dr. Gonda work closely in pursuing aggressive investigations on how to best stratify an individual's risk of developing pancreatic cancer. The first step is to examine demographics and patient characteristics. Patients undergo a comprehensive protocol that enables the physicians to capture as many variables as possible to better understand the risks of cancer and counsel them regarding the possible treatment options, including surgery.

Dr. Beth A. Schrope

"Columbia is now participating in several international multicenter studies that are focused on collecting data on a large number of patients with a very large number of variables," says Dr. Gonda. "This is to help us identify what the real risk is for a patient to develop any kind of worrisome cyst. We ask if there is a personal history of other types of cancers, or the presence of associated pancreatitis, and gather detailed information about their family history of cancer. We are also beginning to recognize that metabolic parameters, such as diabetes, may be a potential marker of somewhat elevated risk."

The next phase in the risk stratification algorithm involves radiologic imaging, an area that Dr. Gonda and his colleagues have researched at length. "Patient characteristics combined with our expertise in the radiographic characterization of pancreatic lesions provide us with a decent sense of the type of cyst we are facing."

Patients in the Pancreatic Cyst Surveillance Program are given an informed evaluation of their risk and recommended next steps based upon the physicians' findings. "Twenty to 40 percent of patients will require further investigation and more invasive studies," says Dr. Gonda. "First we perform an endoscopic ultrasound with detailed imaging to evaluate the cystic lesion. Several new methodologies allow us to image the cysts in greater detail than ever before possible. Endoscopic ultrasound with confocal laser endomicroscopy enables us to obtain images from the cyst wall. The newest innovation is an endoscopic ultrasound-guided direct biopsy of the cyst wall letting us, for the first time, to obtain tissue from these cystic lesions."

"The most precise, personalized imaging technologies will rely on highly specific molecular markers that can be used for imaging targets," says Dr. Gonda. "We are still at the stage of using non-individualized imaging modalities to stratify risk. Then we obtain biopsy-based information to identify the one or two highly specific markers that can then be specifically imaged. But taking a biopsy of a pancreatic cyst is more challenging than your typical biopsy because what you usually access in pancreatic cysts is fluid, not cells. That is why we need to turn to complex molecular analysis of the tissue to help us distinguish the risk potential of a lesion. If you can identify a molecular marker that can be detected, then you have an amazing imaging tool to scan the cyst and determine whether or not a particular molecular abnormality exists. We are coming full circle on personalizing this approach, but we are not there yet."

Dr. Gonda stresses that a high-volume, specialized center such as the Pancreatic Cyst Surveillance Program at Columbia allows for the expertise and input from every member of the team. "Our radiologists are highly in tune to identifying and utilizing the newest imaging technologies. Our pathologists are highly in tune to the nuances of the questions we are asking of tissue samples. And our expertise as endoscopists in cutting-edge imaging and biopsy technology allows us to minimize the number of procedures and interventions that patients undergo. Our hope is to be able to identify the relatively small subset of patients who can be saved by a preventive intervention."

To this day, the most impactful intervention to prevent pancreatic cancer from developing in pancreatic cysts is surgical resection. Surgical innovation over the last one to two decades has revolutionized pancreatic surgery. According to Dr. Beth Schrope and **John A. Chabot, MD**, Executive Director of the Pancreas Center, "Our surgeries are much safer and our outcomes are better than before. We are using increasingly less invasive approaches, including laparoscopic and robotic surgery, for the majority of patients with cystic neoplasms. These procedures allow greater oncologic precision and faster recovery. Nonetheless, the goal is to develop diagnostic and nonsurgical techniques to minimize the need for resection in the majority of patients."

Reference Articles

Gausman V, Kandel P, Van Riet, PA, Kayal M, Do C, Poneros JM, Sethi A, Gress FG, Schrope BA Luk L, Hecht E, Jovani M, Bruno MJ, Cahen D, Wallace MJ, Gonda TA. Predictors of progression among low-risk intraductal papillary mucinous neoplasms in a multicenter surveillance cohort. *Pancreas*. 2018. [In press]

Xu MM, Yin S, Siddiqui AA, Salem RR, Schrope B, Sethi A, Poneros JM, Gress FG, Genkinger JM, Do C, Brooks CA, Chabot JA, Kluger MD, Kowalski T, Loren DE, Aslanian H, Farrell JJ, Gonda TA. Comparison of the diagnostic accuracy of three current guidelines for the evaluation of asymptomatic pancreatic cystic neoplasms. *Medicine* (Baltimore). 2017 Sep;96(35):e7900.

Kayal M, Luk L, Hecht EM, Do C, Schrope BA, Chabot JA, Gonda TA. Long-term surveillance and timeline of progression of presumed low-risk intraductal papillary mucinous neoplasms. *American Journal of Roentgenology*. 2017 Jun 7:1-7.

For More Information

Dr. Tamas A. Gonda • tg2214@cumc.columbia.edu
Dr. Beth A. Schrope • bs170@cumc.columbia.edu

Fecal Microbiota Transplant: An Old Remedy Made New *(continued from page 1)*

Dr. Carl V. Crawford

NewYork-Presbyterian/Weill Cornell Medical Center. "This infection had been around for decades, and it had always been associated with antibiotic exposure in the inpatient setting and now in the outpatient setting."

The revival of FMT for *C. diff* came in the midst of a drug-resistant *C. diff* epidemic that started in Canada and spread to U.S. inpatient settings. Upon examination, the epidemic appears to be a consequence of using powerful antibiotics. "Unfortunately, the advent of newer antibiotics to cover more organisms allowed for development of resistant strains of *C. diff*. These are very hyper-virulent, toxic strains," says Dr. Crawford. "So, this one novel strain, which was selected for broad-spectrum and widespread antibiotic use, actually became more dominant."

The epidemic, based ironically on remarkable medical advancements, caused researchers to look more closely at *C. diff*. "When people started to investigate this infection," Dr. Crawford says, "they saw that this hypervirulent organism was producing 16 times more toxin A and 23 times more toxin B, the proteins that attack the colon and cause diarrhea and colitis – and death – than other traditional strains."

According to the National Hospital Discharge Survey, the incidence of *C. diff.* doubled from 31 to 61 per 100,000, between 1996 and 2003. The rate of colectomy and mortality also increased dramatically. In 2010, there were an estimated 500,000 cases of *C. diff* with a mortality of 15,000 to 20,000.

C. diff infections had been mostly an inpatient phenomenon, but now with an astonishing rate of recurrence it is being seen more in the community. "A susceptible host pretty much rules in everyone in the hospital, especially anyone on antibiotics or whose immune system is compromised in some way," says Dr. Crawford. Once a patient develops the *C. diff* infection, there is at least a 20 percent chance of getting it again, then a 40 percent chance of relapse or reinfection. After that, the chance of further manifestations rises to over 60 percent.

"Fecal transplant is an old therapy made new for *C. diff*, restoring the good bacteria in the gastrointestinal tract in a heartbeat," says Dr. Crawford. In fact, the success rate with FMT is a remarkable 90 percent for those deemed good candidates, yet no one can say exactly how it works. The healing and destructive properties of the microbiome are now being explored in many studies, and Dr. Crawford acknowledges the unique challenges in researching human gut flora. "When we do a fecal transplant, every single donor solution we use is uniquely different from the next donor. In each sample there are hundreds of different kinds of bacteria and strains."

While FMT has been shown to have a tremendous effect in patients with *Clostridium difficile* infection, Dr. Crawford notes that in other causes of disease, it is not as effective, yet there is still some effect. "In order to understand that effect we need to look at the genetics of the bacteria of the patients and correlate the clinical outcomes after the fecal transplant," says Dr. Crawford. "Inside the gastrointestinal tract, these are not just random bacteria; they serve a very specific niche or function. If we can break down the functions of these bacteria, isolating whether they metabolize amino acids, carbohydrates, proteins, etc, and look at their specific ecosystems, we may be able to determine, in certain diseases, what's lacking. Once we find easy ways to identify those communities of bacteria, we can easily imagine just putting those communities back."

Expanding the Application of FMT

"Originally, the FDA had only acknowledged the use of FMT for *C. diff* infections," continues Dr. Crawford. "But the very successful *C. diff* results have made widely expanded studies possible, including using FMT in the inflammatory bowel disease population, whether or not *C. diff* infection is present."

Research of the microbiome has led to recognition of its connection to other disorders, including Crohn's disease and ulcerative colitis. In a recent pilot study, Dr. Crawford and his co-investigators **Randy Longman, MD, PhD**, **Vinita E. Jacob, MD**, and their colleagues in the Jill Roberts Institute for Research in IBD at Weill Cornell, looked at an FMT preparation (FMP) created from a healthy two-donor resource in order to increase the microbial diversity of the donor material to treat patients with active ulcerative colitis. Building on reports of trials that suggested FMT with repeated enemas and high-diversity FMT donors is a promising treatment to induce remission in ulcerative colitis, the Weill Cornell

This is the first study to evaluate the clinical, microbiological, and immunological impact of a two-donor fecal microbiota preparation (FMP) for active ulcerative colitis.

Clinical Outcomes at Week 4 Post-Fecal Microbiota Transplant

Outcome	Number of Patients	Percent
Clinical Response	7	35%
Clinical Remission	3	15%
Mucosal Healing	2	10%
Escalation of Therapy	3	15%
Colectomy	1	5%
Medical	2	10%

Source: *Inflammatory Bowel Disease,* June 2017

(continued on page 4)

NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10065
www.nyp.org

AMAZING ADVANCES IN RESEARCH, TECHNOLOGY, AND PATIENT CARE

NewYork-Presbyterian's new clinical innovations site for professionals

nyp.org/amazingadvances

Fecal Microbiota Transplant: An Old Remedy Made New *(continued from page 3)*

researchers pursued a preliminary investigation of microbial engraftment of a single fecal micobiota preparation delivered by colonoscopy.

Among other areas, the study explored the RNA composition of the recipient microbiome and the engrafted material. The use of genetic analysis of the donor preparation and the recipient's digestive bacteria before and after implant was key to the study's design. Results, which were published in *Inflammatory Bowel Disease* in June 2017, showed that of the 20 patients enrolled in the study, 7 patients (35%) achieved a clinical response by week four; 3 patients (15%) were in remission at week four; and 2 of these patients (10%) achieved mucosal healing. Three patients (15%) required escalation of care.

According to the researchers, the data support the short-term efficacy of single colonic delivery in achieving microbial engraftment. The 7 patients who had a response at week 4 maintained improvements in clinical scores at week 12. However, they note that "longer follow-up is needed to evaluate the efficacy of less-intensive therapy, which may ultimately be more practical for patient care, and larger placebo-controlled trials are needed to evaluate durable FMT or FMP strategies in both biological naïve and refractory patients."

"This is definitely an exciting time in our field," says Dr. Crawford. "Because of *C. diff*, we were forced to develop a greater understanding of the role of gut bacteria and microorganisms in health and disease. In addition to FMT for *C. diff*, we will be looking at new avenues of investigation, such as the effects of restoration of the biodiversity inside the gastrointestinal tract for treatment of non-gastrointestinal diseases. This has really opened the door to a whole, new realm of biotherapeutics for the treatment of many other human diseases that we never would have traced back to the bacteria that live in us and that outnumber us. To be honest, it is like a whole new beginning."

Reference Article

Jacob V, Crawford C, Cohen-Mekelburg S, Viladomiu M, Putzel GG, Schneider Y, Chabouni F, O'Neil S, Bosworth B, Woo V, Ajami NJ, Petrosino JF, Gerardin Y, Kassam Z, Smith M, Iliev ID, Sonnenberg GF, Artis D, Scherl E, Longman RS. Single delivery of high-diversity fecal microbiota preparation by colonoscopy is safe and effective in increasing microbial diversity in active ulcerative colitis. *Inflammatory Bowel Disease*. 2017 Jun;23(6):903-11.

For More Information

Dr. Carl V. Crawford • cvc9002@med.cornell.edu