

What's Up with the Pancreas?

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Dr. Anderson completed her internal medicine residency and gastroenterology fellowship at the University of Michigan, Ann Arbor where she trained in advanced endoscopy including endoscopic ultrasound and ERCP. Following fellowship training, she joined the faculty at Michigan where she studied genetic mutations associated with chronic pancreatitis and pancreatic cancer under a Fellow to Faculty Transition Award from the American Gastroenterological Association. In 2005, she received a Masters' of Science degree in clinical research design and statistical analysis from the School of Public Health at the University of Michigan. Dr. Anderson's clinical focus is on diseases of the pancreas and biliary system with a special emphasis on chronic pancreatitis, pancreatic cancer and therapeutic EUS and ERCP as they relate to these diseases. Currently, she is investigating biomarkers for the early diagnosis of pancreatic cancer under a career development award from the American Society of Gastrointestinal Endoscopy. This is translational research using EUS and ERCP derived specimens and molecular technology to study expression levels of various genes in pancreatic cancer and chronic pancreatitis. She continues to perform EUS and ERCP in clinical practice as well as in teaching forums both nationally and internationally.

I am Michelle Anderson from the University of Michigan. We are going to discuss ten abstracts today. There are ten additional abstracts that were interesting but didn't make the top ten list, that can be read on your own.

The first set of abstracts are related to autoimmune pancreatitis. A lot of this literature is from Korea, in part because as recently as five years ago we just did not "see" autoimmune pancreatitis that often in the United States. At least we thought we didn't. I think in the United States we just didn't know that we were looking at it. I think we looked at pathology specimens on patients that have had suspected malignancy and had gone to the OR, which turned out to be read as chronic pancreatitis, but a percentage of them were autoimmune pancreatitis. There is a male to female predominance, in a ratio of about 2-5:1. In an abstract this year from Korea male/female was quite high at 15:1. This is generally an elderly population (mean age 59 to 74 years). They frequently present with painless jaundice (35%), non-specific abdominal pain (35%), weight loss (65%) and about half will have glucose intolerance and in some cases diabetes. The problem with all of those symptoms is they sound like pancreatic cancer. So, the symptoms do not discriminate.

Radiographically, autoimmune pancreatitis often is described as diffuse enlargement of the pancreas and it has been called a "sausage" or "sausage-like" appearance on CT scanning if you have ever seen it. During the arterial phase on CT scanning, there is delayed enhancement and this is thought to be due to infiltration from the lymphoplasma site and secondary fibrosis.

Going back to the comments about pancreatic cancer and similar presentation, the CT picture raises the radiologists' suspicion for cancer. On ERCP, patients typically have diffuse or segmental narrowing of the pancreatic duct and the changes can be focal in one area. This also leads people to be suspicious that there is a cancer there. I've seen these patients, and remarkably when they are focal they're very much like a cancer stricture, which can be scary. Patients also can have biliary stenosis, which can be extra hepatic from the inflammation in the pancreatic head causing bile duct obstruction and can also be intrahepatic. Also, there is sort of a sister disease with autoimmune pancreatitis and sclerosing cholangitis. They seem to go hand in hand and that is what causes the intrahepatic stricturing. MRI and MRCP are insensitive for looking for changes in the pancreatic duct in patients with autoimmune pancreatitis. If you get a patient

with the right clinical scenario and something makes you think it is not a cancer, MRI and MRCP may not be the way to go. This may be the case where you might benefit from doing diagnostic ERCP because that is going to pick up the more subtle changes that you see in patients with autoimmune pancreatitis. It is very uncommon to see stones, calcifications or pseudocysts in patients that have autoimmune pancreatitis. There has been a lot of interest in serologic marker research and there are several abstracts at this year's meeting that look at serologic markers in autoimmune pancreatitis. Patients with this disease will have elevated total IgG and IgG4. The original literature from Korea and Japan focused on total IgG but as time has gone by and more research has been done, it seems like IgG4 is more sensitive and perhaps more specific for autoimmune pancreatitis. The patients can also have positive autoantibodies including ANA and rheumatoid factor. They frequently will have an elevated sedimentation rate. It is actually uncommon to see amylase and lipase elevations in these patients and interestingly about 40 to 50% of patients will have elevations in the cancer markers CA 19-9, again clouding that issue as to whether this is cancer. It is not elevated in the tens of thousands but in the several hundred range, which is why CA 19-9 is a pretty problematic biomarker for pancreatic cancer and that is actually exactly what my research is on; looking for better biomarkers.

There is the Japanese Pancreas Society Criteria for Autoimmune Pancreatitis. These are three fold; radiographic, laboratory based and then histopathology. The Society says that all patients should have the radiographic changes including diffuse enlargement of the gland and/or irregular narrowing of the pancreatic duct.

They really feel that all patients should have diffuse enlargement of the gland so that you don't include a shrunken down pancreas. When I evaluate patients that I think may have autoimmune pancreatitis I send all my labs and then I let the data dictate to me my level of suspicion and whether I am going to do a biopsy in that patient. Is it enough that I am going to treat that patient with steroids? For me, at least in clinical practice, it's a collection of all those findings that makes me decide how to go forward with their treatment, even if they have a focal mass. I am treating two patients right now with steroids who presented with focal mass in the head of the pancreas, bile duct obstruction and jaundice.

Clearly, there is the risk that you might miss a cancer in these cases. But the Japanese Criteria don't insist upon the histopathology, so there are times we treat with radiographic and then either laboratory or histopathology.

I do think, however, that there are plenty of patients that go to the OR for suspected pancreatic cancer because we are not comfortable saying that it is autoimmune pancreatitis.

Treatment is generally oral prednisone in a dose of 30 to 40 mg a day. When I treat patients, I typically will keep them on that moderate dose for a period of six to eight weeks and then start tapering down by about 5 mg every two to four weeks. There really isn't a lot of data out there on maintenance, how long you need to do the taper, or on immunosuppressants like Imuran or Methotrexate. Additionally, there is not much known in what happens to the patient's labs if you follow the IgG, IgG4, ANA and the sed rate. Do those normalize with steroid treatment or do they stay elevated?

That actually leads us to the first abstract:

Abstract 226023: "Utility of total immunoglobulin and IgG4 levels in the diagnosis and management of autoimmune pancreatitis"

This abstract is from the Mayo group. They looked at IgG, total IgG and IgG4 levels in 154 patients, 28 of whom had autoimmune pancreatitis and 126 who had other diseases including pancreatic cancer, acute

pancreatitis from other etiologies, chronic pancreatitis from other etiologies and then normal patients with no pancreatic disease - patients that had their IgG4 or their total IgG checked for some other reason. They found that patients with autoimmune pancreatitis were more likely to have elevated IgG4 than the total IgG - 82% versus 57%. As I said earlier, maybe the IgG4 is more sensitive for making that diagnosis. Nine out of 126 patients without autoimmune pancreatitis though, had elevated total IgG and 14 of them had an elevated IgG4. There is going to be a group of patients that are going to have elevations of these that don't have autoimmune pancreatitis. The reason that I selected this abstract was the next two points, and that is that the IgG4 level decreased or normalized in all the patients that they treated with steroids, and the reduction in the IgG4 levels did not correlate with radiographic improvement with therapy. This makes it even harder to see how these patients are going to do and what we can do with therapy.

Should we consider this IgG4 level as a screen? In my group that is what we do. I will send an ANA, sed rate, total IgG and then IgG4.

Is IgG4 a readily available test? It is, yes. We do it at our place. The way that we order is called quantitative gamma globulins with subclasses because there are four classes (1,2,3,4) and it's the fourth subclass that is specific for the autoimmune pancreatitis.

One key question is how high of an ANA or IgG4 you need. Is an abnormal IgG4 alone sufficient or is it the combination? In the patients that I have seen they will have one or the other and not both. However, the general cut off for IgG4 is 140. It is going to vary by your lab since they set the normal range. The people that I have seen with autoimmune pancreatitis, that I have treated and responded, had elevations in the 600 to 700 range. One of them normalized completely with treatment and one of them decreased to just above the normal range. The two guys I have on therapy right now have both normalized. One of my patients with autoimmune pancreatitis actually went to laparotomy and they thought he was unresectable because the inflammatory process was so encasing the portal vein that they thought he was unresectable, and it was autoimmune pancreatitis.

Question: In terms of follow up, do you do a CT scan every six months?

Answer: In patients that I treat with steroids I usually do eight weeks of moderate dose steroids (40 mg a day) and then at the eight week mark I repeat their IgG4 level and an imaging study (usually CT).

Question: Do you also include that with a CA 19-9?

Answer: Almost all of those patients have had CA 19-9 drawn anyway because you suspect pancreas cancer to begin with. So I don't follow it. It is an interesting question. Would it go down with treatment? That is not known.

Most people won't do a CT-guided fine needle aspiration (FNA) in a patient with pancreatic cancer unless they are already unresectable, because you can seed the tract. Most of the centers I know would do EUS.

Let's move on to the next abstract.

Abstract 218376: "Outcome of autoimmune pancreatitis without corticosteroid treatment"

I selected this because there are times that patients may present without symptoms. In other words they have a coincidental CT finding that looks like autoimmune pancreatitis. Should we treat those people? What do we do with that group of patients? What about patients who don't want therapy and what happens to them? That is really the focus of this abstract. This is a study of 35 patients (17 of whom were

male) with a median age of 67 years. All of them had no symptoms and none of them were treated. They were then followed up over a period of 12 to 152 months (mean 54 months). Among those 35 patients, 12 of them ended up developing symptoms. Symptom occurrence had no correlation with the age, gender, or IgG4 level of the patient. In other words you couldn't use those things ahead of time to help you determine who is going to go on and have symptoms. All 12 of them were treated with steroids and all of them responded. I think this is yet another issue that is going to need further investigation as we learn about the natural history of this disease.

Question: Would you treat somebody who does not present with symptoms?

Answer: In my practice I probably would not treat somebody without symptoms. I might follow them more closely than I would an average person and treat them if they developed symptoms. I have patients that I try to wean off of prednisone with autoimmune pancreatitis and they re-flare. In those cases I have used immunosuppressants such as azathioprine.

The next set of abstracts looks at acute pancreatitis and treatment. In reviewing the literature you can see there have been a number of drugs studied for acute pancreatitis. Gabexate and aprotinin are both protease inhibitors. Allopurinol, acetylcysteine (also known as Mucomyst[®]), and octreotide have been examined and of course prednisone has been looked at as well. All of these drugs were studied in randomized controlled trials, usually placebo controlled, and none of them reduced mortality or length of stay associated with pancreatitis. That is why this next abstract was interesting because it is still searching for a way to intervene in patients with acute pancreatitis.

Abstract 219140: "Randomized, double-blind, placebo-controlled, trial of high-dose intravenous anti-oxidant therapy in severe acute pancreatitis"

In this study there were three treatment arms. That will be pertinent when we discuss the findings. A portion of the patients were treated with n-acetylcysteine, a portion were treated with selenium and a portion were treated with vitamin C or ascorbic acid. The primary end point for this study was organ dysfunction score on a daily basis. I think that was their equivalent of the Apache score. When they designed the trial they estimated that they needed 120 patients to have 85% power to show a 25% improvement in organ function score. They stopped the study early because they had low recruitment. They actually had criteria where if they didn't enroll enough patients by a certain period of time they would stop the study and analyze the data, so in fact they prepared for that. Even though they conclude that there is no beneficial effect from this line of therapy, based on this provided sample size calculation, the risk of type II error was high. In other words, the chance of concluding there was no effect when one truly existed was quite high.

This is an interesting study, but the problem is it is in hospitalized patients with acute pancreatitis. This is the first randomized trial, so it is a very important trial but there are other things like chronic pancreatitis, acute, recurrent acute pancreatitis (which may be a chronic condition) that may benefit from anti-oxidants. Some do better, some don't but it is not going to hurt them. Patients can get antioxidants at any drugstore or go to a Web site and get them. Antox[®] is the name of the drug. I think there are more studies being done with this supplement.

The next abstract looks at diet in patients with acute pancreatitis. Patients that have mild acute pancreatitis are admitted to the hospital and are normally given IV fluids, but don't have a prolonged NPO status. If they are going to have prolonged NPO status there is this huge issue about how to give them nutrition. Do we give them TPN or do we give them enteral nutrition. There have been several studies of feeding methods in acute pancreatitis including three randomized control trials that looked at TPN versus

enteral nutrition in acute pancreatitis. Even though there is not a reduction in mortality for acute pancreatitis, there is reduction in morbidity, including infections, line sepsis and things like that, and there is a lower cost to treat these patients enterally. So typically we feed patients enterally, but beyond the ligament of Treitz.

This next abstract looks at an interesting question – “What we do without any evidence?” Most of us who take care of patients with mild acute pancreatitis when they start to eat again will give them a clear liquid diet. It is one of those things in medicine that we do that is not based on evidence. It is just what you were taught. That is where this next study comes from. This is a start toward where we need to go in pancreatic disease research.

Abstract 217114: “A prospective, randomized, controlled trial of clear liquids vs. low-fat solid diet as the initial meal after mild pancreatitis”

This study looked at what we should do in terms of re-feeding patients when they are getting better from their mild acute pancreatitis. This was a study of 121 patients, all of whom had mild disease according to the Atlanta Criteria. They were randomized to receive either clear liquids or a low-fat solid diet and the primary outcome of this study was the length of stay after the re-feed. They measured how many more days the patients were in the hospital once they started to eat again. When they looked at the calories the patients in each of the groups consumed, patients on the low-fat solid diet had a significantly higher number of calories that they were able to consume. That makes intuitive sense. Similarly they had higher amounts of fat if they were in the low-fat solid diet, but there was no difference in symptoms. No difference in pain, nausea, or vomiting between the two groups and there was no significant difference in the length of stay. They are almost identical; 1.7 days versus 1.9 +/-2.

They concluded that the low-fat solid diet was well tolerated and did not increase or decrease the length of stay. For most of us, that is the critical issue because we advance their food intake and when you get to solids you send the patient home. Their question was, “If we put you on solids to begin with, will we get you out the door sooner?” That didn’t happen but it also suggested that the patients tolerated solids fine. We probably don’t need to give them liquids. I think the take-home message here is that we should let the patients determine what they feel they can tolerate. That actually may end up decreasing length of stay – letting the patients have a choice.

We are going to move ahead to chronic pancreatitis. The next abstract looks at pain. You all know that there are multiple mechanisms for pain in chronic pancreatitis and multiple ways to treat it. Most of us use narcotic medications in patients with severe pain with chronic pancreatitis although as we mentioned earlier we also use anti-inflammatories. This abstract looked at radiation treatment for chronic pancreatitis. I did a review of the literature because it was so surprising to me to see the abstract. I found two studies that would be relevant to this. The first one was a canine study published in 1979 with 12 dogs that had bile trypsin-induced pancreatitis in which the authors randomized the dogs to receive either radiation therapy 400 rads or just general supportive care. They found a 13-fold increase in survival time in the dogs that had radiation. There was a single case report from Germany in 1998 where they treated a patient with severe pain that was resistant to even narcotic medication and that patient received 7 Gy and had pain relief after one week that persisted for up to three years of follow up. To my knowledge this abstract is the first actual study of radiation therapy for chronic pancreatitis that has been done.

Abstract 220748: “Novel radiotherapeutic management of painful flare ups in chronic pancreatitis”

This is a study of 12 patients, seven of whom had alcohol induced chronic pancreatitis, four that were idiopathic and one that had cystic fibrosis. The patients had to meet one of two criteria to be entered in

this study. They either had to have at least two flares over the six months preceding their enrollment or they had to have continuous pain for at least a three-month period. All the patients enrolled had at least two flares in the six-month period and two also had continuous pain for three months. In this study they gave 8 Gy of radiation which I thought was fairly close to the single case report that I found when I researched the literature myself prior to our meeting today, and I wonder if that was where they got it. They found that 10 out of the 12 patients had no further flares during their four-year follow up period. One patient had a repeat attack, was re-treated with a second dose of radiation therapy and had no symptoms for the follow-up period of 26 months. One patient did not respond. It was interesting that the patients that responded not only had improvement in their pain but they had weight gain; a median weight gain of 6 Kg or over 12 pounds. They used quality of life measure and they had statistically significant improvement in quality of life scores. I thought that this was really novel. In a way it makes intuitive sense that this should help. Think about the other inflammatory conditions (e.g., cancers) that you treat with radiation and patients have improvement.

The next abstract looks at cigarette smoking in chronic pancreatitis. This is in follow-up to the studies that have been done previously. There was a study in Gut published in 2005 looking at the age of presentation, risk for calcification, and diabetes in smokers versus non-smokers. The study showed that smokers usually present at a younger age, about five years younger, than their non-smoking counterparts with chronic pancreatitis and they are more likely to develop calcification and diabetes.

Abstract 215386: “Stopping smoking at the clinical onset of chronic pancreatitis reduces the risk of developing pancreatic calcifications”

The authors looked at 360 patients (88% male) who had known tobacco use, at least six years of follow-up, and did not have calcifications in their pancreas at the time of initial enrollment. Alcohol was the etiology in 255/360. Median follow up was 19 years in these patients. Compared to non-smokers, ex-smokers had similar odds ratio of developing calcifications. They found that patients who were current smokers regardless of whether they smoked 1 to 10 cigarettes per day, 11 to 20 per day, or more than 20 per day were more likely to develop calcification than their non-smoking counterparts. The message is if we can get our patients to stop smoking when they are diagnosed with chronic pancreatitis we may prevent disease progression.

Issues with this study: First, if you stop smoking is it going to decrease your cancer risk? Second, it is not clear that they controlled for alcohol to the level that they needed to. That always has been a confounder. Capturing data on alcohol and tobacco use accurately in these patients is really difficult.

Abstract 219567: “Glucidic homeostasis improvement after endoscopic ductal drainage in chronic pancreatitis”

We often will drain ducts in patients with pain in chronic pancreatitis because we think that the decompression of the duct causes less pain, duct stimulation and we see improvement. What I have also seen with drainage in patients that have dilated ducts is improvement in their exocrine function. Patients have decreased steatorrhea or malabsorption when you drain that duct. These authors are looking at whether duct drainage improves endocrine function. This is a study of 34 patients with chronic pancreatitis. They say that they had symptoms requiring drainage, but you are not told what that is in a specific breakdown. For some patients it was pain, for some it was dilation and for some it was pseudocyst, but they don't tell you what the breakdown was. I suspect that a big portion of the patients were actually drained for pain, but we don't have that information in the abstract. Seventy-three percent had calcified disease at the time of drainage. If we think that calcification is a marker for advanced disease, these were patients with advanced disease. In fact, 35% of the patients had diabetes when they

underwent drainage. The primary outcome for this study was glycosylated hemoglobin levels and the HOMA test (before decompression and 1-and 3 months after decompression). The HOMA test is homeostasis model assessment of insulin sensitivity. It is actually a test of beta cell reserve. How well can their beta cells kick out insulin if they need to? Eighty-one percent of the patients were successfully drained. They found that in the group that had non-calcified chronic pancreatitis, their HOMA test improved (76% versus 101%, $p < 0.05$) post drainage. In diabetic patients the glycosylated hemoglobin improved (7.1% prior to drainage and 6.1% after drainage; $p < 0.05$). They concluded that drainage before the patient develops calcification improves glucose control. That makes sense. If you are waiting until the patient has calcified disease, it may be too late to show improvement.

The last three abstracts are looking at pancreatic cancer.

Abstract 222925: “Angiotensin converting enzyme inhibitors reduce the incidence of pancreatic cancer: A study of half a million U.S. Veterans”

This is from Khurana and colleagues. He presented an abstract at last year’s meeting that used the same database and looked at statins for lowering risk of pancreatic cancer. He also looked at esophageal cancer and colon cancer with the same thing. Using the same database they looked at ACE inhibitors. What they found in this case controlled study was that ACE inhibitors actually lowered risk for the development of pancreatic cancer by about 50%. Patients that were on an ACE inhibitor had an odds ratio of 0.48. The problem with this study and any study like it is that it is an association study. You can’t show causation. Moreover, this was an almost all male cohort because it was a Veteran’s hospital database. The other problem was that they didn’t control for dose, duration, or type of ACE inhibitor that was used. We don’t know how long you have to be on an ACE inhibitor to actually get a beneficial effect. Last year, I selected the one looking at statins because there have been no studies that have shown any benefit from any chemopreventative agent in pancreatic cancer. Now here comes this second drug that might be beneficial as well.

As the years have gone by, we have been tracking more data on these higher risk groups. There are several multicenter studies going on right now that are looking at high-risk patient populations and they’re tracking the medication use. Obviously we are not going to go out and put everybody in the United States on an ACE inhibitor or statin to prevent pancreatic cancer. There are only 33,000 cases a year so it would be a huge cost, right? In a high-risk population it would make sense if you could really show benefit.

Maybe we can hone in on the people with the family history or people with hereditary pancreatitis. Most people that study pancreatic cancer think that is the place where we are going to make an intervention that can be meaningful. Most of the EUS studies looking at screening possibilities are looking at high-risk populations.

The next abstract looks at stenting in patients with malignant biliary obstructions. Generally the issue that comes up is whether we should place plastic or metal stents and in which patient. This abstract looks at that.

Abstract 213199: “Endoscopic biliary stenting for pancreatic cancer and biliary obstruction: Predictive factors of stent patency and patient survival”

These authors looked at 136 patients who were undergoing stent placement. In all, 151 stents were placed, 111 were plastic and 40 were the self-expanding metal stents. They compared the patency of metal versus plastic and patency was 50% in the metal group versus 12% in the plastic stent at six months. The factors that were significant for patient survival were absence of metastasis (6.2 months versus 4 months) in

patients that had metastatic disease. Patients that were undergoing adjuvant chemotherapy had an average survival of 13 months compared to a survival of only 4 months in those who did not have adjuvant chemotherapy. They concluded that in unresectable pancreatic cancer patients presenting with obstruction, the best patients to put a metal stent in are those that don't have mets at the time of their presentation and/or are going to undergo chemotherapy. This is important because it is giving us evidence and data that we can use in everyday clinical practice.

Let's just finish up with the last abstract.

Abstract 214844: "Prognostic factors for survival in pancreatic cancer: A population-based study"

This is from Eloubeidi's group at the University of Alabama. It is a multicenter trial and the premise for doing this study was that there is not a lot of data about prognostic factors in minorities. The University of Alabama has a fairly large proportion of African Americans in their patient group so they wanted to look at things specific to that group that might differ from Caucasians in terms of prognosis. The study was of 2,230 patients, 73% of whom were Caucasian and 27% were African American, and African Americans were significantly more likely to refuse therapy across all treatment types. They found that survival was not dependent on race when controlling for the stage of disease and type of therapy. Overall, survival was longer when the patient received treatment whether surgery, chemotherapy, or radiation. African Americans were less likely to receive treatment than whites. They were also more likely to refuse chemotherapy, radiation therapy and more likely to refuse surgical intervention, which raises the question of why? What are we doing? What are we missing as medical professionals that this group of patients doesn't want care? Maybe there is a communication barrier. I think that there is a good follow-up study that is going to come out of this.

Thank you.

Abstracts Discussed

226023: Utility of Total Immunoglobulin and Igg4 Levels in the Diagnosis and Management of Autoimmune Pancreatitis. *Suresh T Chari, Thomas C Smyrk, Amaar H Ghazale, Michael Levy, Mark Topazian, Naoki Takahashi, Jonathon Clain, Randall Pearson, Bret Petersen¹ Santhi Swaroop Vege, Michael Farnell*

Background: Autoimmune pancreatitis (AIP) remains a diagnostic challenge. Presence of serologic abnormalities (elevation in titers of gammaglobulin and a variety of antibodies) are an important adjunct to diagnosis of AIP. Elevation of levels of the IgG4 subclass of IgG has been reported to be highly sensitive and specific for the diagnosis of AIP. Its usefulness in monitoring patients on steroid therapy remains unknown. Aims: Our aims were to a) assess the diagnostic accuracy of elevated levels of total IgG and IgG4 for AIP and b) determine the response of serum IgG4 levels to steroid therapy in AIP and its correlation with activity of the disease assessed radiologically. Methods: Total IgG levels (normal 600-1500 mg/dl) and IgG4 (normal 8.0-140 mg/dl) levels were measured in 154 patients including 28 with AIP, 44 with pancreatic cancer, 36 with acute/chronic pancreatitis and 32 without pancreatic disease. Follow-up IgG4 levels were noted in the 15 AIP patients that had IgG4 measurement during and/or after completion of steroid treatment. Results: For diagnosis of AIP, elevation of IgG4 levels had better sensitivity compared to total IgG (23/28 (82%) vs 16/28 (57%), $p=0.04$). All 16 AIP patients who had elevated total IgG also had IgG4 elevation. Of the 5 patients with AIP and normal IgG4 levels, one had the measurement after steroid therapy and another after pancreatic resection. Frequency of total IgG and IgG4 elevation was similar in patients that did not meet criteria for AIP (9/126 vs 14/126, $p = 0.1$). Of the 14 patients with IgG4 elevation (range 146-366 mg/dl) that did not meet criteria for AIP, 4 had biopsy-proven pancreatic cancer (range 168-330 mg/dl), 3 had idiopathic pancreatitis, one had type 1b diabetes and pancreatic steatorrhea, 3 had idiopathic pancreatic steatorrhea and 3 had no detectable pancreatic abnormality or any known extra-pancreatic manifestation of AIP. During steroid therapy IgG4 levels decreased or normalized in all patients studied. IgG4 were normal in all patients studied after completion of therapy. However, IgG4 levels did not correlate with intra-abdominal radiologic abnormalities. Conclusions: IgG4 elevation is more sensitive for diagnosis of AIP than total IgG. However, IgG4 elevation is characteristic but not diagnostic of AIP. In AIP patients on steroid therapy IgG4 levels normalize with treatment, but IgG4 levels do not appear to correlate with radiologic evidence of disease activity.

218376: Outcome of Autoimmune Pancreatitis without Corticosteroid Treatment. *Kenji Hirano, Saburo Matsubara, Osamu Togawa, Toshihiko Arizumi, Takeshi Sasaki, Natsuyo Yamamoto, Yousuke Nakai, Takeshi Tsujino, Naoki Sasahira, Hiroyuki Isayama, Minoru Tada, Nobuo Toda, Takao Kawabe, Kazumi Tagawa, Tetsuo Katamoto, Ryo Nakata, Tateo Kawase, Masao Omata*

Aim: Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by irregular narrowing of pancreatic duct, swelling of parenchyma, lymphoplasmacytic infiltration and fibrosis, and a favorable response to corticosteroid treatment (CST). Since little is known about the outcome of AIP patients without CST, we attempted to clarify their clinical course. Patients and Methods: Diagnosis of AIP was based on imaging findings such as pancreas swelling and narrowing of main pancreatic duct and pathological features such as fibrosis with infiltration of lymphocytes and plasmacytes. Among 35 patients with AIP we experienced, 21 patients were followed up without CST at first because they were asymptomatic or became asymptomatic after biliary drainage. Their clinical features were retrospectively reviewed. Results: The patients without CST consisted of 17 males and 4 females and their average age was 67 years (range 41 to 80). Nine patients received biliary drainage before observation without CST. During follow-up of 54 months in mean (12 to 152 months), 12 patients developed symptoms including pancreatitis in 3 and bile duct involvement (sclerosing cholangitis) in 9. In analysis of risk factors for developing symptoms, severe bile duct stricture was identified. All the patients with late occurrence of sclerosing cholangitis had severe bile duct stricture at the diagnosis of AIP. Age, gender, serum IgG4, or abdominal pain was not related. The patients with developing symptoms were managed with CST and had favorable response. Conclusion: Patients with AIP tend to suffer from recrudescence without CST. Particularly in patients accompanied with severe bile duct stricture, CST is indispensable.

219140: Randomized, Double-Blind, Placebo-Controlled, Trial of High-Dose Intravenous Anti-Oxidant Therapy In Severe Acute Pancreatitis. *Ajith K Siriwardena, James M Mason, Srinivasan Balachandra, Anil Bagul, Simon Galloway, Laura Formela, Jonathon Hardman, Saurabh Jamdar, David Schofield, Pauline Kay, Ioannis T Virlos*

Introduction: Oxygen free-radicals (oxidative stress) mediate acinar injury in acute pancreatitis (AP). In clinical AP, inhibitors of oxidative stress (anti-oxidants) are depleted with extent corresponding to severity. Small studies suggest that anti-oxidant supplementation ameliorates AP but there is no substantive evidence. This study undertakes the first randomised, double-blind, placebo-controlled trial of anti-oxidant therapy in human severe AP. Methods: Patients with a clinical diagnosis of AP were eligible if their admission APACHE II score was >8 . Principal inclusion criteria were: ability to give informed consent, disease duration <72 hours and not on anti-oxidants. Patients were randomised to receive intravenous n-acetylcysteine, selenium and ascorbic acid or three equivalent-volume placebos. All complications were characterized by Atlanta conference criteria. Principal end-point was daily organ dysfunction scores during the first 7 days. A study population of 110 was predicted as sufficient to detect a 25% improvement in primary end-point at 85% power. Hospital pharmacy allocated arm by random

number generation. Independent monitoring of recruitment/complications was undertaken and stopping criteria were met in 2005 (under-recruitment). Results: 44 patients were randomized (23 anti-oxidants vs 21 placebo). Groups were statistically similar in terms of age, gender, etiology, APACHE and organ dysfunction score. Duration of anti-oxidant therapy was median 4 days in both. Anti-oxidant levels fell from admission in placebo but not in the treatment group. Analysis of primary endpoint showed 7 patients to have triggered organ dysfunction during the first 7 days in the anti-oxidant group (7/22 [31%]) compared to 4 of 21 (19%) in placebo. This difference was not statistically significant ($P=0.49$ Fisher's exact 2-sided). There was no difference in the incidence of individual organ dysfunction, complications or mortality. Overall 4 patients died (all in the anti-oxidant group) [$P=0.11$; Fisher's]. Although underpowered to detect change: with 43 patients the original power calculation has a 60% risk of type II error, further recruitment is unjustified as the probability of detection of any major effect of therapy is exceedingly low. Conclusion: This is the first study to examine the effect of anti-oxidant therapy in a well-characterized population of severe AP using contemporary disease descriptors in a double-blind, placebo-controlled fashion. The results show no evidence of benefit from treatment. Although underpowered, the final analysis suggests that there is unlikely even to be a trend towards benefit from treatment.

217114: A Prospective, Randomized, Controlled Trial of Clear Liquids vs. Low-fat Solid Diet as the Initial Meal After Mild Pancreatitis. *Brian C Jacobson, Martha B Vandervliet, Michael Hughes, Rie Maurer, Katherine D McManus, Peter A Banks*

Background: Patients recovering from mild acute pancreatitis typically receive a clear liquid diet (CLD) when ready to initiate oral nutrition. The timing of patient discharge frequently depends upon successful advancement to solid food. We hypothesized that initiating feeding with a low-fat solid diet (LFSD) after mild pancreatitis would be well tolerated and would result in a shorter hospital length of stay (LOS). Methods: A sample size of 120 subjects was calculated to have 90% power to detect a one day difference in LOS between two study arms. Exclusion criteria included narcotic use within 6 hours prior to refeeding, an underlying condition that could itself cause poor oral intake or prolonged LOS, inability to monitor the patient post-discharge, pregnancy, and supervision of a patient's care by a study team member. Patients with mild pancreatitis, defined in accordance with the Atlanta symposium, were randomized to receive either a CLD or a LFSD when the responsible medical team determined refeeding was appropriate. The decision to advance a patient's diet and the timing of discharge were determined by the medical team. Patients were monitored daily for dietary intake, recurrence of pain, need to stop feeding, post-refeeding LOS, and for a total of 28 days post-refeeding to capture symptoms or readmission. Post-refeeding LOS (primary outcome) was compared using a t test and need to stop feeding (secondary outcome) was compared with Fisher's Exact test. Results: We randomized 121 patients: 66 to CLD, 55 to LFSD. Baseline characteristics including age, gender, and cause of pancreatitis were similar in both groups. The number of patients requiring cessation of feeding because of pain, nausea or vomiting was similar in both groups (5% for CLD and 9% for LFSD; $p=0.47$). There was no difference in 28 day re-admission rates between the two arms. By intention-to-treat, the mean LOS after refeeding was similar in both groups (1.7 1.9 days for CLD and 1.7 2.0 days for LFSD; $p=0.94$). Calorie counts for the first meal consumed were available for 69% of patients and showed significantly lower calories and grams of fat consumed in the CLD arm than in the LFSD arm (mean 177 106 cal vs 394 250 cal; 2 4 gm fat vs 8 7 gm fat; $p<0.001$ for both comparisons). Per-protocol analyses and analyses restricted to those with calorie counts provided similar results for both diet tolerability and post-refeeding LOS. Conclusions: Initiating feeding with a LFSD was as well tolerated as a CLD, but did not result in a shorter LOS.

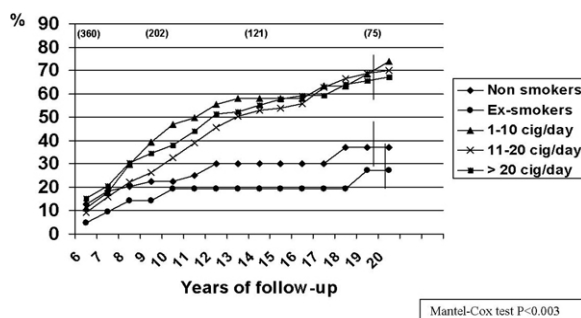
220748: Novel Radiotherapeutic Management of Painful Flare Ups in Chronic Pancreatitis. *Luisa Guarner, Xavier Molero, Begona Navalpotro, Jordi Giralt, Juan-Ramon Malagelada*

Patients with chronic pancreatitis may present repeated painful flare-ups of pancreatitis and even unrelenting pain. Current management options are limited to analgesics and surgery, in selected cases. We reasoned that anti-inflammatory radiotherapy, which appears to be effective in other inflammation based painful disorders of the body, might prove valuable to severely symptomatic patients with chronic pancreatitis. PATIENTS AND METHODS: We studied prospectively over a 4-year period till Nov. 05, the efficacy of single dose anti-inflammatory radiotherapy in 12 consecutive patients with chronic pancreatitis (ethanol related in 7, idiopathic in 4 and cystic fibrosis in one) who fulfilled the following criteria: either 2 flare ups of pancreatitis in the previous 6 months (all 12 patients) and/or continuous pain for more than 3 months (2 of the 12). Median age was 41 years (range 32-80), there were 9 males and 3 females; diagnosis of chronic pancreatitis (6 months to 16 years, median 5 years) and number of prior attacks (2 to >15, median 6). Treatment consisted in a single dose of radiation of 8 Gy. Before and after radiation we assessed: exocrine function by fecal elastase, endocrine function by c peptide, quality of life (EuroQol) and clinical outcomes. Response was defined as no further pain or flare-ups of pancreatitis. RESULTS: During follow up (median 33 months, range 1 to 48 months) 10/12 patients had no further pain or flare-ups. One patient required a second radiation dose after 1 year and has been well since (26 months), 1 patient did not respond and had a pancreaticojejunostomy at 1 month. Before radiation 4 patients had exocrine (fecal elastase<100 $\mu\text{g/g}$) and 2 endocrine (c peptide<0.50 ng/ml) dysfunction. Post treatment 1 additional patient developed exocrine (at 25 months) and endocrine (at 13 months) insufficiency. The responder group (11/12) gained 4 to 20 Kg in weight during follow up (median 6 Kg) and EuroQol improved significantly from 0.572

before till 0.817 after treatment ($p < 0.01$). CONCLUSION: Radiation treatment of severely symptomatic chronic pancreatitis is effective and could potentially substitute or delay surgery.

215386: Stopping Smoking at the Clinical Onset of Chronic Pancreatitis Reduces the Risk of Developing Pancreatic Calcifications. *G. Talamini, Massimo Falconi, Nora Sartori, Marina Mastrotauro, Claudio Bassi, Paolo Pederzoli, Italo Vantini*

Cigarette smoking is associated with a higher risk of developing chronic pancreatitis and increases the likelihood of developing pancreatic calcifications. It is not known whether stopping smoking is capable of modifying the course of this disease. Methods. We reviewed 701 chronic pancreatitis patients with well known smoking and drinking habits and selected a subgroup of patients with follow-up longer than 6 years and with no calcifications by the end of the 5th year. A total of 360 patients with the above-mentioned characteristics were identified. Three groups of patients were studied: smokers, non-smokers and patients who stopped smoking within 5 years of onset of symptoms of chronic pancreatitis. In the actuarial analysis the 6th year from onset of symptoms was taken as time 0. Results. The 360 patients selected comprised 43 females (11.9%) and 317 males (88.1%) with a mean age of 38.7 years (SD 11.4). The median follow-up was 19.0 years (25th percentile 13.0; 75th percentile 24.0). The chronic pancreatitis was alcohol-associated in 255 patients, familial in 10, obstructive in 54, and idiopathic in 41. At the end of follow-up 212 patients (59.8%) developed calcifications. Thirty-seven patients stopped smoking. Smokers were 317 (88.1%) with a mean total of 23.4 cigarettes smoked daily. Drinkers drank a mean amount of 147 grams of alcohol daily. As regards the risk of calcifications, non-smokers and ex-smokers had similar actuarial survival curves and these were significantly different from the curve for smokers ($p < 0.003$). Cox multivariate actuarial analysis supported these data. Considering non-smokers as the reference class, ex-smokers had an Odds Ratio (OR) of 0.56 (0.2-1.4; $p = ns$), patients smoking 1-10 cig/day an OR of 1.95 (1.1-3.4; $p < 0.019$), patients smoking 11-20 cig/day an OR of 1.76 (1.1-2.8; $p < 0.018$), and those smoking > 20 cig/day an OR of 1.79 (1.1-2.9; $p < 0.019$). Conclusion. Stopping smoking within 5 years of clinical onset of chronic pancreatitis reduces the subsequent risk of developing pancreatic calcifications.



219567: Glucidic Homeostasis Improvement after Endoscopic Ductal Drainage in Chronic Pancreatitis. *Pierre Deprez, Helene Devroye, Jean-Paul Thissen, Yves Horsmans, Jean-Francois Gigot, Michel Hermans*

Chronic pancreatitis is characterized by progressive parenchymal fibrosis, ductal obstruction and calcification of the pancreas. One of the common complications of the disease is the onset of “secondary” diabetes, which is the result of the progressive destruction of the Langerhans islets. The influence of medical, endoscopic and surgical therapy in chronic pancreatitis on endocrine function has received little attention in clinical research. The aim of our study was to evaluate the impact of endoscopic drainage on endocrine function in chronic pancreatitis. Our hypothesis was that an efficient drainage of the obstructed ducts might improve endocrine pancreatic insufficiency and/or secondary diabetes of these patients. Patients and methods: prospective study including patients with chronic pancreatitis (CT-EUS-MRI or ERCP proven) and an indication for endoscopic drainage (pain, duct dilation, pseudocyst). Endocrine function was evaluated by glycosylated hemoglobin levels and HOMA test before and after (1 and 3 months) ductal decompression. Inflammatory (WBC and CRP) and nutritional (weight, BMI, fat mass, IGF-1, prealbumin, Cu, Zn, Se levels) parameters were recorded. Results: 34 pts were included between, mean age $54 \text{ y} \pm 12$; mean BMI was $21.2 \pm 3.1 \text{ kg/m}^2$. Etiology was alcohol in 19 and obstructive or genetic or idiopathic in 15. Smoking was present in 56%, calcifying pancreatitis in 73.5%, exocrine insufficiency in 65% and diabetes in 35%. At the first visit, we observed a significantly worse endocrine function in patients with pancreatitis caused by alcohol and smoking, with calcifying pancreatitis and when exocrine insufficiency was present ($P < 0.01$). After endoscopic drainage (successful in 81% of pts), increase in the β cell function was significant in the group of patients with less severe (non calcifying) pancreatitis (76% before vs. 101.2% after drainage, $P < 0.05$) and reduction in glycosylated hemoglobin was significant in the diabetic subgroup (7.1% before vs. 6.1% after drainage, $P < 0.05$) Conclusion: patients with non calcifying pancreatitis appear to be the favorite candidates for endoscopic drainage which seems to be more efficient on endocrine functional recovery when it is carried out early in the course of the ductal obstruction. However, glucidic homeostasis was also improved in the more severe pancreatitis group with a reduction in glycosylated hemoglobin levels, suggesting that endoscopic drainage might also be a valuable option.

222925: Angiotensin Converting Enzyme Inhibitors Reduce the Incidence of Pancreatic Cancer: A Study of Half A Million US Veterans. *Vikas Khurana, Ankur Sheth, Gloria Caldito, Jamie S Barkin*

AIM: To investigate the effect of Angiotensin Converting Enzyme (ACE) Inhibitors use in reducing the incidence of pancreatic cancer in the US veteran population. BACKGROUND: ACE Inhibitors are commonly used antihypertensive and nephroprotective agents. Vascular Endothelial Growth Factor (VEGF) is believed to play a major role in angiogenesis in human tumors. Blocking the VEGF inhibits angiogenesis and suppresses tumor growth. ACE inhibitors cause suppression of VEGF in experimental models, leading to their anticancer effect. ACE Inhibitors have been noted to suppress tumor growth by inhibiting tumor angiogenesis in several animal and experimental models. DESIGN: The VISN 16 database contains clinical and demographic information about all veterans (>1.4 million patients) cared for in the South Central VA Health Care Network (eight states in south central United States). The data was queried from Oct 1998 to June 2004, using a retrospective case control design. Statistical analysis was performed using SAS software version 9.0 (Chicago, IL). Multiple logistic regression analysis was used with calculation of odds ratios and 95% confidence intervals. The data was adjusted for age, race, gender, BMI, smoking, alcohol use, diabetes and statin use. Patients were placed in the ACE inhibitor user group if they were using ACE inhibitors prior to the diagnosis of pancreatic cancer. RESULTS: A total of 483,733 patients were included in the analysis. 185,852 (38.43%) of those were using ACE inhibitors. Pancreatic cancer (ICD-9 code 157) was seen in 475 (0.1%). ACE inhibitor users were 48% less likely to develop pancreatic cancer (Odds ratio 0.484; 95% CI 0.386-0.607, p <0.01). The protective effect of ACE inhibitors was independent of statin use. Other significant covariates include age (OR 1.020, 95% CI for OR 1.012, 1.027, p <0.01); prior statin use (OR 0.458, 95% CI for OR 0.363, 0.580, p<0.01) and diabetes (OR 3.837, 95% CI for OR 3.089, 4.767, p<0.01). CONCLUSION: ACE inhibitors are associated with a 48% reduced incidence of pancreatic cancer after controlling for age, race, gender, BMI, smoking, alcohol use, diabetes and statin use. The limitations of our data are the VA population, the database and the fact that this is a case control study. The dose, duration and type of ACE inhibitor used were not factored into the analysis.

213199: Endoscopic Biliary Stenting for Pancreatic Cancer and Biliary Obstruction: Predictive Factors of Stent Patency and Patient Survival. *Cristina Gomez, Carlos Guarner, Candid Villanueva, Xavi Cusso, Antonio Farre, Joaquin Balanzo*

Endoscopic biliary stenting is a well established palliation treatment for patients with biliary stricture caused by nonresectable pancreatic cancer. Stent clogging is the predominant late complication, occurring more frequently with plastic stents. The use of self-expanding metallic stent (SEMS) however is not current practice due to their high cost. It would be important to select patients in our area with a better predicted survival, who could benefit from a SEMS, in order to be more cost-effective. OBJECTIVES: To evaluate the efficacy and complications of palliative endoscopic treatment for biliary obstruction caused by pancreatic cancer, and to investigate predictive factors of stent patency and patient survival. PATIENTS AND METHODS: Prospective, non-randomized trial in patients with nonresectable pancreatic cancer and biliary obstruction treated with endoscopic plastic or SEMS between January 2000 and May 2005. RESULTS: One hundred and twenty-six patients with nonresectable pancreatic cancer and biliary obstruction were treated with 151 endoscopic stents (plastic= 111, SEMS= 40). Technical success was 90%. Early complications were observed in 17% of cases (cholangitis 6%, early stent obstruction 6.5%, haemorrhage 2.5% and migration 2.7%). The most common late complication was stent clogging (25.7%). Median stent patency (period between stent placement insertion and obstruction or death) was 4 months. The type of stent (plastic vs. SEMS) was identified in a multivariate analysis as the only independent predictive factor of patency. Comparing plastic versus SEMS, the actuarial probability of patency at 6 months was the 12% and 50.1% (p<0.05) respectively. In a multivariate analysis, the absence of metastases (median survival=6.2 months versus 4 months with metastatic disease) and adjuvant chemotherapy (median survival= 13 months versus 4 months without chemotherapy) were independent predictive factors of better prognosis for survival (>4 months). CONCLUSION: Patients with nonresectable pancreatic cancer and biliary obstruction without metastases are the ideal candidates for self-expanding metallic biliary stent insertion.

214844: Prognostic Factors for Survival in Pancreatic Cancer: A Population-Based Study. *Mohamad Eloubeidi, Renee Desmond, Charles M Wilcox, Reda Wilson, Pavan Manchikalapti, Mona Fouad, Isam Eltoun, Selwyn Vickers*

Background: There is currently no population-based study from the Deep South of the United States (with >25% African American residents) evaluating survival of patients with pancreatic cancer. Our aims were to 1) analyze prognostic factors influencing pancreatic cancer survival using the population-based Alabama Statewide Cancer Registry (ASCR) 2) to determine whether race/ethnicity is an independent determinant of outcomes in patients with pancreatic cancer. Methods: Eligible cases included all persons diagnosed with pancreatic cancer from 1996-2000 and reported to the ASCR. Survival time was calculated from time of diagnosis to death for pancreatic cancer deaths or to date of last contact or death from other causes for censored cases. Risk factors associated with survival were assessed with the Kaplan-Meier survival method and the log-rank test. Demographic, tumor and treatment variables were assessed using Cox proportional hazards model. Results: Of 2,230 patients, the median age at diagnosis was 71 years and the male to female ratio was approximately 1:1. Seventy-three percent of patients

were White, and 27% of patients were Black. The distribution by stage was 12.5% localized disease, 29.6% regional, 35.3% distant and 22.6% unstaged. The median survival for all cases was 0.39 (SD 0.01) years. Patients that underwent surgical treatment were less likely to die from pancreatic cancer (HR 0.48 95% CI, 0.41-0.56). Similarly, patients that underwent either chemotherapy or radiation therapy had improved survival (HR 0.62 95% CI, 0.53-0.73). Across all stages, Black patients were significantly less likely to receive chemotherapy compared to White patients (27.8% vs. 32.7%, $p=0.03$) and were significantly less likely to receive surgical intervention (15.2% vs. 18.9%, $p=0.049$). When examining patients who were offered the therapy of choice but refused, we found across all stages that a greater proportion of Black patients refused therapies vs. Whites (4.3% vs. 2.1% ($p=0.02$) for chemotherapy; 2.1% vs. 0.8% ($p=0.05$) for radiation and 3.3% vs. 1.4% ($p=0.01$) for surgery). Cox proportional hazard model showed no effect of race on overall survival while controlling for stage at presentation, type of therapy received, age at diagnosis and site of primary tumor. Conclusion: Survival in patients with pancreatic cancer remains dismal. Tumor characteristics and treatment factors are directly related to survival in patients with pancreatic cancer. Black patients were less likely to receive therapy but were also more likely to refuse indicated therapy. Factors leading to racial disparity in treatment of pancreatic cancer warrant further investigation.

Additional Reading: What's Up With the Pancreas?

218401: Corticosteroids Are Efficacious in Patients With Lymphoplasmacytic Sclerosing Pancreatitis (LSP) but Relapses Are Frequent. *Pascal Hammel, Vinciens Rebours, Dermot O'Toole, Marie-Pierre Vullierme, Karine Nahon-Uzan, Frederique Maire, Philippe Ponsot, Alain Aubert, Annie Sibert, Laurent Palazzo, Philippe Levy, Philippe Ruszniewski*

Clinical, biological and morphological features of LSP (either "autoimmune": AIP or eosinophilic [EP]) are currently better characterized; however the effects of medical treatment to date has been poorly evaluated. Aim: To assess therapeutic management (indications, treatment modalities and results) of patients with LSP in a monocentric series. Patients (pts) and methods: Prospective inclusion of all pts with LSP between 01-2002 and 08-2005. The diagnosis of LSP was made in view of clinical biochemical and imaging according to Yoshida's criteria (1). Symptomatic pts received oral corticosteroids in the absence of untreated biliary stenosis or sepsis. Results: 29 pts (21 M, 8 F, median age 39 years (17-73), 25 with LSP, 4 with EP) were included with a median follow-up of 14 months (1-55). Median age at symptom onset was 39 years (16-69). The first symptom was abdominal pain, acute pancreatitis, weight loss, and jaundice in 35 %, 24 %, 21 % and 17 % of pts, respectively (fortuitous diagnosis in one symptom-free pt). Associated auto-immune or inflammatory bowel diseases were present in 6 (21%) and 4 (14%) pts, respectively. Pathological data obtained from EUS-guided biopsy were available in 12 (41%) pts, showing typical features of LSP in 11 and fibrosis alone in 1. Prednisolone (1 mg/kg day for 1 month with progressive tapering over 3 months) was given to the 13 pts (45%) with pain or jaundice. Biliary drainage was necessary in 3. Symptoms improved in 12 of the 13 pts (92%), and radiological improvement was observed in 58 % of cases. In one patient, septicaemia led to treatment withdrawal. Pancreatic (n=3) or biliary (n=5) symptoms relapsed in 8 pts (67%) at time of treatment withdrawal, 3 of whom had ≥ 2 symptomatic relapses. A second course of prednisolone was given in 7 pts (2 of whom also required biliary stenting), and biliary stenting alone was performed in 1 pt. Azathioprine or imatinib were prescribed in 2 and 1 pt experiencing at least two relapses, respectively, with no further recurrence after 9-11 months. Conclusion: Corticosteroid treatment of pancreatitis was necessary in 45% of pts, occasionally associated with biliary drainage. Treatment efficacy concerning symptoms was high (> 90 %) but relapses were frequent (2 out of 3 pts). Immunosuppressive therapy can be envisaged for steroid-dependent pts.

223397: The Natural Course of Acute Idiopathic Pancreatitis. *Paul G Lankisch, Nils Breuer, Anja Bruns, Bettina Weber-Dany, Patrick Maisonneuve, Albert B Lowenfels*

The natural course of acute idiopathic pancreatitis is unknown. The aim of our study was to determine the incidence of relapses and to identify any factors associated with these recurrences. Patients and Methods: We identified 106 patients with a first attack of acute idiopathic pancreatitis admitted to our hospital from 1987 - 2004. Alcohol consumption was less than 40 g of pure alcohol/day in all patients, and in none of them could biliary disease or other causes of acute pancreatitis be identified as the underlying etiology. All living patients were interviewed by telephone and questionnaire to obtain information on their health status, lifestyle, and family health history. For patients who died after the first acute pancreatitis the cause of death was obtained from their general practitioners. Results: 1. Diagnosis: The etiology proved to be different than originally thought (idiopathic) in two patients in whom a pancreatic carcinoma diagnosed during follow-up was responsible for the first attack. 2. Mortality: 38 (37%) patients died, 9 (9%) during the first attack and 29 (28%) from unrelated causes. None of the latter group experienced any relapse. 3. Follow-up: Of the 66 living patients 64 could be contacted, and 8 of these had had recurrent attacks (4 patients: 1 attack, 3 patients: 2 attacks, 1 patient: 3 attacks). The etiology of these relapses was again unknown with the exception of one attack which occurred following alcohol abuse. In none of the patients did relapsing pancreatitis progress to chronic pancreatitis. One patient developed pancreatic cancer 15 years after a single attack of acute pancreatitis. 4. Recurrence risk: Among living patients, recurrence was more frequent in those with a family history of pancreatic disease (acute pancreatitis, pancreatic cancer, or diabetes mellitus; $p=0.047$) and in smokers, although the latter association was not

statistically significant ($p=0.17$). However, 3 of the 4 patients, who had multiple relapses, were smokers. Neither the APACHE II score on admission for the first attack, nor the Imrie and Ranson score after 72 hours, nor the result of a contrast-enhanced computed tomography (Balthazar score) correlated with the recurrence rate. Conclusion: The relapse rate in patients with acute idiopathic pancreatitis is low. In the case of recurrence, a change of etiology is very unlikely. There is no progression from acute to chronic pancreatitis in this etiological subgroup. Patients who have experienced acute idiopathic pancreatitis are advised to stop smoking and to undergo appropriate imaging procedures 3 months after the attack in order to identify the eventual presence of a pancreatic carcinoma.

217569: Predictors of Length of Hospitalization for Acute Biliary Pancreatitis in a Tertiary Medical Center. Sameer Barkatullah, Aziz Aadam, Garth Swanson, Ami Shah, Sri Komanduri

BACKGROUND: Several factors in the management of acute biliary pancreatitis (ABP) have been studied for their value in predicting morbidity and mortality. In addition to these outcomes, factors that provide insight into expected length of hospitalization (LOH) merit evaluation. We retrospectively reviewed the management of ABP, with attention to the predictive value of various standard practices on the LOH at a large urban teaching center. **METHODS:** Patients with ABP were identified by evidence of epigastric pain, elevated lipase and liver function tests (LFT), and abnormal transabdominal ultrasound demonstrating cholelithiasis or choledocholithiasis with or without ductal dilatation. A total of 75 admissions for ABP were reviewed between January 1, 2002 and December 31, 2004. APACHE II scores and percent change in lipase, alkaline phosphatase (AP), total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values were calculated at admission, 48, and 72 hours. Time to ERCP, cholangiogram findings, and empiric antibiotic usage were also recorded. **RESULTS:** The mean age was 56 years, with female preponderance (65%), and a mean LOH of 6.8 days. 51 patients underwent ERCP. Those who had ERCP within 72 hours had a significantly shorter LOH compared to those undergoing ERCP after 72 hours (5.8 vs. 9.9 days) ($p < 0.05$). In addition, those who had filling defects within the biliary tree on ERCP had higher APACHE II scores than those without filling defects at 72 hours (5.38 vs. 3.44) ($p < 0.05$). Fluid balance, changes in lipase or LFTs did not reliably predict LOH at any time interval. Patients receiving empiric antibiotics had a greater mean LOH than those on no antibiotic therapy (8.4 vs. 6.5 days). This difference approached statistical significance. **CONCLUSION:** Our data suggests that early ERCP (<72 hours) in select patients with ABP decreases length of hospitalization. This is in accordance with previous data suggesting improved outcome with early ERCP in this cohort. Interestingly, patients with a filling defect on cholangiogram had significantly worse pancreatitis at 72 hours than those with a negative cholangiogram. This supports the concept of performing ERCP in ABP to prevent ongoing pancreatic injury due to biliary obstruction. We found no correlation between trends in serum lipase or liver function tests, or empiric antibiotic usage and length of hospital stay. Our data suggests that early ERCP, when appropriate, significantly decreases LOH in ABP. The practice of drawing daily labs and administering empiric antibiotics, however, does not change length of stay, and should be reassessed.

222453: Management of Acute Pancreatitis: A Survey of Internal Medicine Residents. Sameer Barkatullah, Ami Shah, Aziz Aadam, Sri Komanduri

PURPOSE: We conducted a survey to evaluate the current understanding of the management of acute pancreatitis (AP) among internal medicine residents. The survey was conducted to assess the efficacy of current teaching patterns and to improve overall patient care at a large urban teaching center. **METHODS:** We administered a 23-question survey to 58 Internal Medicine residents. The questions were multiple choice and centered on basic aspects of management of AP. These included appropriate use of laboratory testing and radiologic imaging, assessment of severity, use of antibiotics, nutrition, and indications for surgical intervention. **RESULTS:** Approximately 50% of the surveys collected were completed by first year residents and the other 50% by senior residents. Though 38% could not identify the initial appropriate laboratory testing, an even greater proportion, 62% of residents, did not recognize Hematocrit as the most important predictor of severity on admission. About 25% felt that administration of empiric antibiotics for all cases of AP were the standard of care. Furthermore, 21% felt the diagnosis of AP was made by identifying inflammation on CT scan. In the setting of acute biliary pancreatitis, only 66% identified RUQ ultrasound as the preferred initial imaging modality, and only 59% could identify the appropriate timing and utility of ERCP. A larger gap of knowledge was seen in identification and management of severe pancreatitis. The majority of residents (81%) underestimated the incidence of pancreatic necrosis in the setting of severe pancreatitis. As for early feeding, only 36% of residents felt that it decreased morbidity and mortality in necrotizing pancreatitis; 31% preferred total parenteral nutrition to enteral feeding. Perhaps most surprising, only 55% correlated necrotizing pancreatitis with Systemic Inflammatory Response Syndrome (SIRS). Finally, 66% of all residents could not recognize appropriate indications for surgical intervention in AP. As for the use of prognostic indices, only about two-thirds used Ranson's criteria occasionally, while 52% reported never using the APACHE II score to assess severity. Overall only 21% of residents felt very confident in managing acute pancreatitis. **CONCLUSION:** The morbidity and mortality of AP continues to be a problem. In addition, there continues to be a large amount of resources utilized for this cohort of patients. The lack of understanding and inconsistent management of severe pancreatitis is alarming. A dedicated educational effort is needed at the resident level in order to begin to decrease the morbidity of AP as well as to curtail ineffective use of costly resources.

221924: Image Registered Gastroscopic Ultrasound (IRGUS): 3D Registration of Endoscopic Ultrasound and CT Improves Efficiency and Structure Identification over Standard Endoscopic Ultrasound. *Christopher C Thompson, Nicholas Stylopoulos, Raul San-Jose Estepar, Eigil Samset, Randy Ellis, William Brugge, Kirby G Vosburgh*

INTRODUCTION Although Endoscopic Ultrasound (EUS) is a useful tool for the diagnosis and staging of abdominal and thoracic diseases, it has not been maximally adopted by gastroenterologists. This is due in part to the long learning curve and the lack of confidence in ultrasound interpretation. To overcome these hurdles, we have designed and implemented IRGUS, a novel system that links preprocedure CT with real-time EUS imaging. **MATERIAL AND METHODS** IRGUS aligns preprocedure CT images with real time EUS imaging so that the CT image corresponds to the oblique EUS plane. The operators are also provided with a novel 3D display and important spatial cues that show them how the plane of the EUS is oriented relative to the patient's anatomy. In this study, novice and expert gastroenterologists were asked to perform an in vivo EUS examination of anesthetized pigs, identifying 8 key anatomic structures in a 5-minute period using traditional EUS and IRGUS. A sensor that was mounted on the echoendoscope allowed the tracking and recording of the motion of the scope during the task. These recordings were then used to calculate the efficiency of performing the exam, which is based on a set of kinematic parameters that we have used and validated in previous studies. At the conclusion of the tasks, participants completed a questionnaire. **RESULTS** Using conventional EUS, novices identified 29% of the structures and experts 50%, within the allotted time. Using IRGUS these rates increased significantly to 71% and 80% respectively ($P < 0.0001$). IRGUS had the largest impact on the localization and identification of the right lobe of the liver and the right kidney. IRGUS also had a statistically significant benefit in assisting novices to identify the pancreatic body and tail. In the questionnaire, all participants rated IRGUS as superior to EUS. The analysis of kinematic data showed that IRGUS increased efficiency of conventional EUS by improving the economy of movements (path length), the smoothness of motion and the response orientation of the operator. **CONCLUSIONS** IRGUS is superior to conventional EUS in the localization and identification of anatomic structures and in various kinematic measures. It enhances procedural efficiency of both experts and novices and allows direct CT confirmation of structures and lesions. This novel technology has the capability of expanding the applications of conventional EUS and may allow for broader adoption beyond its current use. Portions of this work are sponsored by the US Department of the Army. The information does not necessarily reflect the position of the government and no official endorsement should be inferred.

226347: Spectral Markers of the Duodenum Can Detect Pancreatic Cancer. *Randall Brand, Yang Liu, Young Kim, Alexy Kromine, Hemant Roy, Nahla Hasabou, Dhiren Shah, Vadim Backman*

Introduction: Due to limitations in pancreatic imaging modalities and lack of good tumor markers, it is not possible to diagnose individuals with pancreatic adenocarcinoma (PC) at an early stage. Our group has developed a novel optics technology, four-dimensional elastic light-scattering fingerprinting (4D-ELF), which allows quantitative assessment of the nanoscale cellular architecture. We have demonstrated that 4D-ELF has unprecedented sensitivity for assessment of the genetic/epigenetic changes of the field effect field of colon carcinogenesis, whereby, uninvolved mucosa accurately predicted the presence of colonic neoplasia. Assessment of the duodenal mucosa by 4D-ELF represents an attractive approach given the profound genetic/epigenetic alterations in the histologically normal duodenal mucosa of PC patients(pts) (*Clin Cancer Res* 2005;11:573). We, therefore, investigated in this pilot study whether 4D-ELF derived spectral markers from normal appearing duodenal mucosa could detect the presence of PC. **Methods:** Periapillary biopsies from 28 control pts obtained by endoscopy and 19 PC pts, obtained by pancreatic resection(7) or endoscopy(12), were analyzed for the 4D-ELF derived markers of spectral slope and fractal dimension. The spectral slope evaluates size distribution of intracellular components ranging from macromolecules to small organelles. The fractal dimension reflects the tissue organization at larger length scale, ranging from large organelles to groups of cells. **Results:** The median age of PC pts and controls were 74(51-87) and 57(27-84), respectively. 26% of PC pts and 25% controls were male. PC stage was I-2, II-8, III-2, and IV-7. There were statistically significant differences in the spectral slope ($p=0.02$) and the fractal dimension ($p=0.003$) between the controls and PC pts. Diagnostic accuracies are shown in Table. **Conclusions:** We demonstrate for the first time that 4D-ELF of periapillary biopsies can identify PC. This study provides compelling data to further investigate 4D-ELF's ability to discriminate PC from not only normal pts but pts with other pancreatic diseases. The use of additional spectral markers may increase both our sensitivity and specificity. A probe is currently under development, which would alleviate the need to obtain biopsies, and thereby, allow for an even less invasive manner to predict the presence of PC.

	Sens	Spec	PPV	NPV
Spectral slope	53%	57%	64%	45%
Fractal Dimension	53%	89%	77%	74%
Combined	68%	79%	79%	68%

220570: Predicting Success of Endoscopic Aspiration for Suspected Pancreatic Cystic Neoplasms. *Richard M Walsh, Gregory Zuccaro, John Vargo, John Dumot, Nancy Brown*

The analysis of cyst fluid contents can play a valuable role in the management of patients with suspected pancreatic cystic neoplasms. It has an increasing role in evaluating small incidental cysts when observation is being considered. We reviewed our experience with cyst aspiration of suspected pancreatic cystic neoplasms to determine the size and location of cysts which resulted in a successful cyst fluid analysis. Over a five-year period ending December 2004, 235 patients enrolled in a prospective protocol for evaluation of suspected pancreatic cystic neoplasms. The route for all cyst aspirations was by endoscopic ultrasound (EUS). A successful aspiration analysis was defined by the ability to determine up to three variables: cytology including qualitative assessment of extracellular mucin, CEA and amylase. The distribution of cystic lesions was: 87 (37%) in the head, 77 (33%) tail, 42 (18%) body, 22 (9%) uncinata, and 7 patients with multiple cysts. EUS was performed in 210 patients (89%) for cysts with a mean size of 3.4 cm. An aspirate was obtained in 194 patients (92%) with a mean volume of 10 cc. There was a significant correlation between cyst size and volume aspirated (Spearman correlation of 0.60, $p < 0.0001$). The ability to achieve a complete aspirate analysis (all three variables) significantly correlated with cyst size (Spearman correlation of 0.31, $p < 0.0001$). All three variables were successfully obtained in 67 patients (35%) with a mean cyst size of 4.3 cm, two or more variables in 81 patients (42%) with a mean size of 4.3 cm, and one or more variables in 149 patients (77%) with a mean size of 3.8 cm. Logistic regression curves predict the likelihood of success based on cyst size, e.g. aspiration of a 2 cm cyst will be successful in 73% to determine one variable, 33% for two variables, and 26% for three variables. There was no significant difference between location of a cyst and successful aspiration ($p = 0.14$), although there was a trend towards an unsuccessful aspiration and fewer cysts with a complete aspirate analysis for uncinata cysts when compared to all other locations (44% versus 20% and 18% versus 37%, respectively). Twenty-five patients did not undergo EUS and their cysts averaged 1.9 cm, and 16 (8%) had an unsuccessful attempt at EUS aspiration with cysts that averaged 2.4 cm. There was one EUS complication of a duodenal perforation in a patient with a serous cystadenoma who survived emergent surgical repair. In summary, there are a predictable number of variables that can be obtained from an EUS aspiration from a pancreatic cyst based on cyst size which is independent of location.

219316: Prospective Comparison of Routine Cytology (RC), Digital Image Analysis (DIA), and Fluorescence in Situ Hybridization (FISH) in Patients Undergoing Endoscopic Ultrasound Guided Fine Needle Aspiration (EUS FNA). *Michael J Levy, Jonathan E Clain, Amy C Clayton, Kevin C Halling, Gavin C Harewood, Benjamin R Kipp, Elizabeth Rajan, Lewis R Roberts, Thomas J Sebo, Mark D Topazian, Kenneth K Wang, Maurits J Wiersema, Gregory J Gores*

Background: Prior studies indicate enhanced diagnostic accuracy for DIA and FISH versus RC when evaluating biliary strictures. These tumor markers have never been applied to EUS FNA specimens. We hypothesize that these molecular markers incorporate generic targets capable of identifying a broad spectrum of malignancy. **Aim:** To compare the diagnostic accuracy of DIA and FISH to RC for a broad spectrum of pathologies sampled during EUS FNA. **Methods:** We prospectively evaluated pts with known or suspected malignancy by RC, DIA, and FISH. For clinical purposes, presence of malignancy by either DIA or FISH (DIA/FISH) was considered diagnostic. However for study purposes separate confirmation of malignancy was required for diagnosis. Pts with benign disease were followed at least 12 months and charts were reviewed to determine the accuracy. **Results:** 39 pts were enrolled and each diagnostic test performed upon samples collected from 42 sites to evaluate lymphadenopathy ($n=19$), solid pancreatic mass ($n=12$), cystic pancreatic lesion ($n=7$), esophageal or gastric wall mass ($n=3$), and thyroid mass ($n=1$). Malignancy was detected in 30/42 pts, including esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, pancreatic mucinous cystic neoplasia, intraductal papillary mucinous neoplasia, metastatic forearm sarcoma, small cell lung cancer, non small cell lung cancer, thyroid follicular carcinoma, malignant gastrointestinal stromal tumor, melanoma, adenocarcinoma of unknown primary, and lymphoma. The sensitivity, specificity, and accuracy of DIA/FISH versus RC for detection of malignancy were 97%, 100%, 98% versus 87%, 100%, 90% respectively. (Table 1) No false positive results occurred for DIA or FISH. The one failed diagnosis for DIA/FISH was in a patient with a malignant gastrointestinal stromal tumor. DIA/FISH correctly identified dysplasia or malignancy in 5 pts with cytology interpreted as benign, atypical, or suspicious. The final diagnosis in these pts was pancreatic adenocarcinoma ($n=3$), esophageal squamous cell carcinoma ($n=1$), and IPMN ($n=1$). No complications were identified. **Conclusion:** Our findings suggest that in pts undergoing EUS FNA that DIA and FISH have a higher diagnostic accuracy than RC. These data suggest that these tumor markers incorporate generic targets as suggested by the high diagnostic sensitivity in this cohort of pts with diverse pathologies.

Table 1:

	DIA/FISH	RC
Sensitivity	97%	87%
Specificity	100%	100%
Accuracy	98%	90%

226897: Resectability of Pre-Symptomatic Pancreatic Cancer and Its Relationship to Onset of Diabetes: A Retrospective Review of CT Scans And Fasting Glucose Values Prior to Diagnosis. *Mario Pelaez-Luna, Naoki Takahashi, Joel G Fletcher, Suresh T Chari*

Background/Aim: Pancreatic cancer (PaC) is frequently unresectable at diagnosis. The timeline of progression of PaC from resectable to unresectable disease is unknown. Glucose intolerance and diabetes (DM) occur in up to 80% of PaC and new-onset DM may be a marker of early PaC. Our purpose was to determine the resectability of PaC on CTs done prior to clinical diagnosis and correlate resectability with onset of DM. Methods: 20 PaC patients with DM who had ≥ 1 abdominal CT scans prior to diagnosis of PaC (total 45 CT scans) were included in the study. Most CTs were performed for non specific abdominal pain or for other reasons different from PaC related symptoms. CTs were reviewed by one radiologist and pancreatic changes characterized as negative for pancreatic mass, pancreatic ductal changes (dilatation, abrupt termination), resectable, relative unresectable or unresectable PaC. Fasting blood glucose (FBG) values obtained at and prior to diagnosis were available in 14 patients. Date of onset of DM was defined as date of first FBG ≥ 126 mg/dl with a prior normal FBG. Interval between onset of DM and diagnosis of PaC was noted. Results: At diagnosis of PaC, 8 (57%) patients were deemed resectable; however, successful surgical resection was possible only in 3 (21%) cases. 23 CTs in 20 patients were done >6 months prior to diagnosis; 18 were normal and 5 had pancreatic ductal changes or resectable mass. At the onset of DM, 7 patients had normal pancreas, 5 had resectable and 2 had unresectable PaC. By the time of PaC diagnosis 3/7 cases with previous normal pancreas had unresectable disease after a median interval of 13 months. Among those with resectable PaC on previous scans, 4 were still resectable at diagnosis of PaC and 1 was unresectable. Conclusions: Resectability of PaC can be significantly improved if detected >6 months prior to clinical diagnosis. Onset of PaCDM predates clinical diagnosis of PaC by >12 months. Detecting asymptomatic PaC in subjects with new onset diabetes can lead to improved resectability.