PANCREAS ALERTS

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Occurrence, clinical features and outcome of canine pancreatitis (80 cases).

Pápa K, Máthé A, Abonyi-Tóth Z, Sterczer A, Psáder R, Hetyey C, *et al.*

Szent István University Department and Clinic of Internal Medicine. Budapest Hungary.

Medical records of 80 dogs diagnosed with acute pancreatitis during a 4-year period were evaluated regarding history, breed predilection, clinical signs and additional examination findings. Cases were selected if compatible clinical symptoms, increased serum activity of amylase or lipase and morphologic evidence of pancreatitis by ultrasonography, laparotomy or necropsy were all present. Like in other studies, neutered dogs had an increased risk of developing acute pancreatitis. Although breed predilection was consistent with earlier reports, some notable differences were also observed. Apart from Dachshunds, Poodles, Cocker Spaniels and Fox Terriers, the sled dogs (Laikas, Alaskan Malamutes) also demonstrated a higher risk for pancreatitis according to the present results. Concurrent diseases occurred in 56 dogs (70%), diabetes mellitus (n=29, 36%) being the most common. Clinical signs of acute pancreatitis were similar to those observed in other studies. The study group represented a dog population with severe acute pancreatitis, having a relatively high mortality rate (40%) compared to data of the literature. Breed, age, gender, neutering and body condition had no significant association with the outcome. Hypothermia (P=0.0413) and metabolic acidosis (P=0.0063) correlated significantly with poor prognosis and may serve as valuable markers for severity assessment in canine acute pancreatitis.

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Genetic and pharmacological inhibition of the Ca^{2+} influx channel TRPC3 protects secretory epithelia from Ca^{2+}-dependent toxicity.

Kim MS, Lee KP, Yang D, Shin DM, Abramowitz J, Kiyonaka S, *et al.*

Epithelial Signaling and Transport Section, Molecular Physiology and Therapeutics Branch, NIDCR, NIH. Bethesda, MD, USA..

Excessive Ca^{2+} influx mediates many cytotoxic processes, including those associated with autoimmune inflammatory diseases such as acute pancreatitis and Sjögren's syndrome. TRPC3 is a major Ca^{2+} influx channel in pancreatic and salivary gland cells. The authors investigated whether genetic or pharmacological inhibition of TRPC3 protects pancreas and salivary glands from Ca^{2+}-dependent damage. The authors developed a Ca^{2+}-dependent model of cell damage for salivary gland acini. Acute pancreatitis was induced by injection of cerulein into wild-type and Trpc3-/- mice. Mice were also given the Trpc3-selective inhibitor pyrazole 3 (Pyr3). Salivary glands and pancreas of Trpc3-/- mice were protected from Ca^{2+}-mediated cell toxicity. Analysis of Ca^{2+} signaling in wild-type and Trpc3-/- acini showed that Pyr3 is highly specific inhibitor of Tprc3; it protected salivary glands and pancreas cells from Ca^{2+}-mediated toxicity by inhibiting the Trpc3-mediated component of Ca^{2+} influx. TRPC3-mediated Ca^{2+} influx mediates damage to pancreas and salivary glands. Pharmacological inhibition of TRPC3 with the highly selective TRPC3 inhibitor Pyr3 might be developed for treatment of patients with acute pancreatitis and Sjögren's syndrome.

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Mass spectrometry-based proteomics of endoscopically collected pancreatic fluid in chronic pancreatitis research.

Paulo JA, Lee LS, Wu B, Banks PA, Steen H, Conwell DL.

Center for Pancreatic Disease, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital and Department of Medicine, Harvard Medical School. Boston, MA, USA.

MS-based investigation of pancreatic fluid enables the high-throughput identification of proteins present in the pancreatic secretome. Pancreatic fluid is a complex admixture of digestive, inflammatory, and other proteins secreted by the pancreas into the duodenum, and thus is amenable to MS-based proteomic analysis. Recent advances in endoscopic techniques, in particular the endoscopic pancreatic function test (ePFT), have improved the collection methodology of pancreatic fluid for proteomic analysis. Here, the authors provide an overview of MS-based proteomic techniques as applied to the study of pancreatic fluid. The authors address sample collection, protein extraction, MS sample preparation and analysis, and bioinformatic approaches, and summarize current MS-based investigations of pancreatic fluid. The authors then examine the limitations and the future potential of

such technologies in the investigation of pancreatic disease. They conclude that pancreatic fluid represents a rich reservoir of potential biomarkers and that the study of the molecular mechanisms of chronic pancreatitis may benefit substantially from MS-based proteomics.

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Genetic basis of chronic pancreatitis in Asia Pacific region.

Reddy DN, Prasad SS.

Asian Healthcare Foundation, Asian Institute of Gastroenterology, Somajiguda. Hyderabad, Andhra Pradesh, India.

Chronic pancreatitis (CP) is a disease characterized by irreversible destruction and fibrosis of the parenchyma, leading to pancreatic exocrine insufficiency. In developed countries, the etiology for 60% to 70% of CP amongst male patients is alcohol and 25% are classified as idiopathic chronic pancreatitis (ICP). The genetic predisposition to CP could be an inappropriate activation of trypsinogen in the pancreas. Two common haplotypes, c.101A>G (p.N34S) and c.-215G>A, and four intronic alterations of the serine protease inhibitor Kazal type 1 (SPINK1) gene have been found to increase the risk for CP in the Asia Pacific region. Hence, SPINK1 is thought to be a candidate gene for pancreatitis. A loss-of-function alteration in chymotrypsinogen C (CTRC) gene has been shown to be associated with tropical calcific pancreatitis (TCP). Cathepsin B (CTSB) is also found to be associated with TCP. However, mutations in cationic and anionic trypsinogen gene do not play an important role in causing CP in Asia Pacific region.

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Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep®), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis.

Toskes PP, Secci A, Thieroff-Ekerdt R, for the Zenpep® Study Group.

Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Florida. Gainesville, FL, USA.

EUR-1008 (Zenpep®: pancrelipase delayed-release capsules) is a novel, enteric-coated, porcine-derived pancreatic enzyme product. This study evaluated the efficacy and safety of two doses of Zenpep® in patients with chronic pancreatitis (CP) and exocrine pancreatic insufficiency (EPI). The effect of Zenpep® on the coefficient of fat absorption (CFA) was investigated in a randomized, double-blind, dose-response, crossover study with placebo run-in (7-9 days) and two treatment periods (9-11 days) composed of a high dose (7×20,000 lipase units per day) and a low dose (7×5,000 lipase units per day). Mean CFA was significantly higher with low- (88.9%) and high-dose (89.9%) Zenpep® *versus* placebo run-in (82%; P<0.001; n=72) with no difference between doses (P=0.228, primary end point). In patients with baseline CFA less than 90% (n=33), the high dose was significantly more effective (CFA: 84.1%) than the low dose (CFA: 81.1%; P<0.001). Post hoc analysis revealed an increase in treatment effect with more severe EPI. Coefficient of nitrogen absorption (P<0.001), body weight (P≤0.021), and body mass index (P≤0.020) also increased significantly with both doses compared with baseline. Percentage of days with EPI symptoms decreased with both doses. These findings suggest that CP patients with EPI benefit from a low dose of Zenpep®, whereas the high dose might be needed for patients with more severe EPI.

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Differential expression of ERCC1 in pancreas adenocarcinoma: high tumor expression is associated with earlier recurrence and shortened survival after resection.

Maithel SK, Coban I, Kneuertz PJ, Kooby DA, El-Rayes BF, Kauh JS, *et al.*

Department of Surgery, Division of Surgical Oncology, Winship Cancer Institute, Emory University. Atlanta, GA, USA.

Increased tumor expression of excision repair cross-complementing gene-1 (ERCC1) is associated with decreased survival in patients with various cancers. Its effect in pancreatic adenocarcinoma (PAC) is not defined. Ninety-five patients were selected from a prospective database of all patients (n=220) who underwent pancreaticoduodenectomy for PAC between January 2000 and October 2008. Tumor was isolated to perform immunohistochemistry for ERCC1 expression and was graded by a single pathologist. Main outcomes were recurrence-free survival (RFS) and overall survival (OS). Median age was 63 years; 50 patients (53%) were male and 73 (77%) received adjuvant chemotherapy. Median follow-up was 25 months. Median RFS and OS were 9 and 16 months, respectively. Median tumor size was 3 cm; 26% had a positive resection margin, 34% had poorly differentiated tumors, 61% had positive lymph nodes, 88% had perineural invasion, and 45% had lymphovascular invasion. Tumors exhibited differential ERCC1 expression in terms of intensity staining (none-weak: 61%; moderate-strong: 39%), percentage

staining (0: 39%; 1-10: 29%; 11-50: 20%; 51-100: 12%), and overall expression (low: 84%; high: 16%). High ERCC1 expression was associated with reduced RFS (6 *vs*. 10 months; P=0.03) and decreased OS (9 *vs*. 18 months; P=0.019). After accounting for adverse tumor factors, high ERCC1 expression persisted as a negative prognostic factor on multivariate Cox regression for both RFS and OS (hazards ratio (HR), 2.1; 95% confidence interval (CI), 1.1-3.9; P=0.02; HR, 3; 95% CI, 1.6-6; P=0.001, respectively). A subset analysis of only those 73 patients who received adjuvant therapy revealed the same negative effect of high ERCC1 expression on RFS (4 *vs*. 15 months; P=0.001) and OS (9 *vs*. 20 months; P<0.001). Pancreas cancer exhibits differential expression of ERCC1. High ERCC1 expression is associated with both reduced RFS and OS after resection. ERCC1 expression levels may help to predict patient outcome with adjuvant chemotherapy.

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Patterns of pancreatic resection differ between patients with familial and sporadic pancreatic cancer.

Barton JG, Schnelldorfer T, Lohse CM, Bamlet WR, Rabe KG, Petersen GM, *et al.*

Division of GI and General Surgery, Mayo Clinic. Rochester, MN, USA.

Although the increased risk of developing pancreatic cancer (PC) in families with a strong history of the disease is well known, characteristics and outcomes of patients with familial PC is not described well. This study aims to evaluate outcomes following resection in patients with familial PC. The authors studied 208 patients who underwent resection of PC from 2000 to 2007 and had prospectively completed family history questionnaires for the Biospecimen Resource for Pancreas Research at the authors institution. They compared clinical characteristics and outcomes of familial and sporadic PC patients. Familial (n=15) and sporadic PC patients (n=193) did not have significantly different demographics, pre-operative CA 19-9, pre-operative weight loss, R0 status, or T-staging (all P≥0.05). Familial PC patients had lower pre-operative total serum bilirubin concentrations (P=0.03) and lesions outside of the pancreatic head more frequently (P=0.02) than sporadic PC patients. There was no difference in survival at 2 years between familial and sporadic PC patients (P=0.52). Familial PC patients appear to develop tumors outside of the pancreatic head more frequently than sporadic PC patients. This difference in tumor distribution may be due to a broader area of cancer susceptibility within the pancreas for familial PC patients.

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Real-world impact of availability of adjuvant therapy on outcomes in patients with resected pancreatic adenocarcinoma: a Canadian Cancer Agency experience.

Kim C, Owen D, Gill S.

Department of Medical Oncology, Cross Cancer Institute. Edmonton, Alberta, Canada.

Patients with resected pancreatic cancer (PC) have a poor prognosis. In 2004, European Study Group for Pancreatic Cancer 1 (ESPAC1) showed that the use of adjuvant therapy (AT) with 5-fluorouracil (5-FU) improves overall survival (OS). Subsequently, the British Columbia Cancer Agency (BCCA) introduced guidelines to offer AT as the standard of care for patients with resected PC. This study reviews the OS and disease-free survival (DFS) in a pre-AT era (2000 to 2004) to the AT era (2005 to 2008) at the BCCA. Using pathology records, all PC resections at Vancouver General Hospital from 2000 to 2008 were identified. Patients referred to the BCCA and their treatment records were obtained from the Cancer Agency Information System and BCCA pharmacy database. Charts were reviewed to abstract patient and tumor characteristics, DFS, and OS. Outcomes were compared by log-rank comparison. In the pre-AT era, 53 resections were recorded, with 64% referred to the BCCA. Median age was 65 years; poorly differentiated 59% and margin positive 38%. About 24% of patients received AT: all 5-FU. In the AT era, 64 resections were recorded, with 86% referred. Median age was 65 years, poorly differentiated 34% and margin positive 34%. Sixty-nine percent of patients received AT: 61% 5FU and 39% gemcitabine. Major reasons for no AT: delayed referral or metastases at time of referral 45% and poor performance status 35%. Pre-AT DFS 13 months *versus* 15 months AT era (P=0.55). Pre-AT OS 19 months *versus* 18 months AT era (P=0.59). Since the guideline for AT, there was an increase in the proportion of patients referred and treated, however, over 30% still do not receive or complete AT. In this single-institution series, there was no difference in survival outcomes between the pre-AT and AT eras. Strategies to improve rate and timeliness of referral should be explored.

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Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.

Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, *et al.*

Service Inter-Hospitalier de Cancérologie et Service de Gastroenteropancréatologie, Hôpital Beaujon. Clichy, France.

The multitargeted tyrosine kinase inhibitor sunitinib has shown activity against pancreatic neuroendocrine tumors in preclinical models and phase 1 and 2 trials. The authors conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors-defined disease progression documented within 12 months before baseline. A total of 171 patients were randomly assigned (in a 1:1 ratio) to receive best supportive care with either sunitinib at a dose of 37.5 mg per day or placebo. The primary end point was progression-free survival; secondary end points included the objective response rate, overall survival, and safety. The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42; 95% confidence interval (CI), 0.26 to 0.66; P<0.001). A Cox proportional-hazards analysis of progression-free survival according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) *versus* 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% CI, 0.19 to 0.89; P=0.02). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue. Continuous daily administration of sunitinib at a dose of 37.5 mg improved progression-free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors.

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Everolimus for advanced pancreatic neuro-endocrine tumors.

Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, *et al.*

University of Texas M.D. Anderson Cancer Center. Houston, TX, USA.

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. The authors evaluated the agent in a prospective, randomized, phase 3 study. They randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients), or placebo (203 patients), both in conjunction with best supportive care. The primary end point was progression-free survival in an intention-to-treat analysis. In the case of patients in whom radiologic progression occurred during the study, the treatment assignments could be revealed, and patients who had been randomly assigned to placebo were offered open-label everolimus. The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval (CI), 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group *vs*. 17% in the placebo group), rash (49% *vs*. 10%), diarrhea (34% *vs*. 10%), fatigue (31% *vs*. 14%), and infections (23% *vs*. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% *vs*. 0%) and hyperglycemia (5% *vs*. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks *vs*. 16 weeks). Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events.

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Gene expression profiling in ethnic Malays with type 2 diabetes mellitus, with and without diabetic nephropathy.

Lokman FE, Seman NA, Ismail AA, Yaacob NA, Mustafa N, Khir AS, *et al.*

Cardiovascular, Diabetes and Nutrition Research Centre, Institute for Medical Research. Kuala Lumpur, Malaysia.

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) among type 2 diabetes mellitus patients (DM) in Malaysia. This study used microarray analysis to determine the gene expression profiling in ethnic Malay patients with type 2 DM. A total of 312 patients were recruited; 25 were on dialysis due to ESRD, 128 were classified as

normoalbuminuric, 93 as microalbuminuric and 66 as macroalbuminuric, based on urine albumin to creatinine ratio of <3.5, between 3.5, and 35 and ≥35 mg/mmol, respectively. Microalbuminuria was associated with up- and down-regulation of 2,694 and 2,538 genes, respectively, while macroalbuminuria was associated with up-regulation of 2,520 genes and down-regulation of 2,920 genes. There was significant up-regulation of 1,135 genes and down-regulation of 908 genes in the ESRD samples. Thirty-seven significantly up-regulated genes and 40 down-regulated genes were commonly expressed in all 3 groups of patients with worsening of renal functions. Up-regulated genes included major histocompatibility complex (HLA-C), complement component 3a receptor 1 (C3AR1), solute carrier family 16, member 3 (SLC16A3) and solute carrier family 9 (sodium/hydrogen exchanger) (SLC9A8). Consistently down-regulated genes included were bone morphogenetic phosphatase kinase (BMP2K), solute carrier family 12, member 1 (SLC12A1), solute carrier family 7 (SLC7A2), paternally expressed 10 (PEG10) and protein phosphatase 1 regulatory (inhibitor unit) (PPP1R1C). This study has identified several genes of interest, such as HLA-C, SLC16A3, SLC9A8, SLC12A1 and SLC7A2, that require verification of their roles as susceptibility genes for diabetic nephropathy in ethnic Malays with type 2 DM.

URL http://www.serena.unina.it/index.php/jop/article/view/3358/3605