PANCREAS ALERTS

Eur Rev Med Pharmacol Sci 2012; 16(3):370-5.
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Pancreatic injury during AAA repair: a comparison between EVAR and open repair.

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Enzymatic pancreatic injury (EPI) in abdominal aortic aneurysm (AAA) treatment has been scarcely studied in the literature. Aim of this work was to compare perioperative EPI in AAA patients treated by endovascular repair (EVAR) or open repair (OR). Forty AAA patients consecutively treated with either EVAR (GI, 20 patients) or OR (GII, 20 patients) were prospectively evaluated in terms of epidemiology, comorbidities and technical details. Serum levels of amylase, lipase and pancreatic isoamylase were assessed before treatment (T0), before aortic clamping/endograft deployment (T1), 1, 2, and 6 hours after aortic declamping/endograft deployment (T2, T3, T4) and 24, 48, and 72 hours after the procedure (T5, T6, T7). GI and GII were compared by Mann Whitney test with significance set at $P<0.05$. GI patients were significantly older and with higher frequency of preoperative renal insufficiency than GII ones (P=0.001 and P=0.047 respectively). Other characteristics were not significantly different. Pancreatic enzymes values at T0 were within normal parameters in all patients. Total serum amylase was significantly greater in GII compared with GI at T4 (P=0.003), T5 (P=0.010), T6 (P=0.003), T7 (P=0.011) and isoamylase at T3 (P=0.052), T4 (P=0.037), T5 (P=0.016) and T6 (P=0.014). Amylase and isoamylase peak occurred 24 hours after the procedure. Lipase was significantly different in the two groups only in T4 (P=0.028). No acute pancreatitis occurred in the whole study group. EVAR significantly reduces EPI compared with OR in the AAA treatment.

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Treatment options for severe hypertriglyceridemia (SHTG): the role of apheresis.

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Hypertriglyceridemia is associated with a number of severe diseases such as acute pancreatitis and coronary artery disease. In severe hypertriglyceridemia (SHTG; triglycerides greater than 1,000 mg/dL), rapid lowering of plasma triglycerides (TG) has to be achieved. Treatment regimes include nutritional intervention, the use of antihyperlipidemic drugs, and therapeutic apheresis. Apheretic treatment is indicated in medical emergencies such as hypertriglyceridemic pancreatitis. Reviewing the current literature, plasmapheresis appears to be a safe and useful therapeutic tool in patients suffering from SHTG. Apheretic treatment is able to remove the causative agent for pancreatic inflammation. Data suggests that the use of apheresis should be performed as early as possible in order to achieve best results. The use of plasmapheresis, however, is limited due to the rather high costs and the limited availability of the procedure.

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Do genetic variants in the SPINK1 gene affect the level of serum PSTI?

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The serine protease inhibitor Kazal type 1 (SPINK1), also known as pancreatic secretory trypsin inhibitor (PSTI), is a peptide secreted by pancreatic acinar cells. Genetic studies have shown an association between SPINK1 gene variants and chronic pancreatitis or recurrent acute pancreatitis. The aim of this study was to clarify whether the SPINK1 variants affect the level of serum PSTI. One hundred sixty-three patients with chronic pancreatitis or recurrent acute pancreatitis and 73 healthy controls were recruited. Serum PSTI concentrations were determined with a commercial radioimmunoassay kit. Ten patients with the p.N34S variant, 7 with the IVS3+2T>C variant, two with both the p.N34S and the IVS3+2T>C variants, and one with the novel missense p.P45S variant in the SPINK1 gene were identified. The serum PSTI level in patients with no SPINK1 variants was 14.3±9.6 ng/mL (mean±SD), and that in healthy controls was 10.7±2.2 ng/mL. The PSTI level in patients carrying the IVS3+2T>C variant (5.1±3.4 ng/mL), but not in those with the p.N34S variant (8.9±3.5 ng/mL), was significantly lower than that in the patients without the SPINK1 variants and the healthy controls. The serum PSTI level in the patient with the p.P45S variant was 4.9 ng/mL. Low levels of serum PSTI (<6.0 ng/mL) showed sensitivity of 80%, specificity of 97%, and accuracy of 96% in the differentiation of IVS3+2T>C and p.P45S carriers

from non-carriers. Serum PSTI levels were decreased in patients with the IVS3+2T>C and p.P45S variants of the SPINK1 gene.

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Pancreatic perfusion CT in early stage of severe acute pancreatitis.

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Early intensive care for severe acute pancreatitis is essential for improving SAP mortality rates. However, intensive therapies for SAP are often delayed because there is no ideal way to accurately evaluate severity in the early stages. Currently, perfusion CT has been shown useful to predict prognosis of SAP in the early stage. In this presented paper, the authors would like to review the clinical usefulness and limitations of perfusion CT for evaluation of local and systemic complications in early stage of SAP.

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Meta-analysis: the placebo rate of abdominal pain remission in clinical trials of chronic pancreatitis.

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Treatment of the pain caused by chronic pancreatitis (CP) is not standardized. Knowledge of the response to placebo in this setting may aid the design of future trials. The authors aimed at investigating the placebo effect on abdominal pain remission rates in patients with CP. MEDLINE, EMBASE, and Scopus were searched, and randomized placebo-controlled trials in CP providing data on abdominal pain remission rates in placebo arms were included. Pooled estimates of the placebo rate were calculated using random-effects logistic regression analysis. Stratum-specific rates for different patients and study-level covariates were calculated to account for heterogeneity. Seven randomized controlled trials (202 placebo-treated patients) met the predefined criteria. The pooled estimate of the placebo rate for pain remission was 19.9% (95% confidence interval: 9-36%). There was a statistically significant heterogeneity among the studies (I=76%; P<0.001). A multicenter design, a run-in period of less than 2 weeks, and absence of a washout in crossover trials were all significant sources of heterogeneity associated with higher placebo responses. This meta-analysis identifies for the first time the efficacy of placebo for pain in CP and variables determining it. These data provide a sound basis for designing future placebo-controlled randomized clinical trials for the treatment of pain in CP.

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Diagnosis of pancreatic ductal adenocarcinoma and chronic pancreatitis by measurement of microRNA abundance in blood and tissue.

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A solid process for diagnosis could have a substantial impact on the successful treatment of pancreatic cancer, for which currently mortality is nearly identical to incidence. Variations in the abundance of all microRNA molecules from peripheral blood cells and pancreas tissues were analyzed on microarrays and in part validated by real-time PCR assays. In total, 245 samples from two clinical centers were studied that were obtained from patients with pancreatic ductal adenocarcinoma or chronic pancreatitis and from healthy donors. Utilizing the minimally invasive blood test, receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) analysis demonstrated very high sensitivity and specificity of a distinction between healthy people and patients with either cancer or chronic pancreatitis; respective AUC values of 0.973 and 0.950 were obtained. Confirmative and partly even more discriminative diagnosis could be performed on tissue samples with AUC values of 1.0 and 0.937, respectively. In addition, discrimination between cancer and chronic pancreatitis was achieved (AUC=0.875). Also, several miRNAs were identified that exhibited abundance variations in both tissue and blood samples. The results could have an immediate diagnostic value for the evaluation of tumor reoccurrence in patients who have undergone curative surgical resection, and for people with a familial risk of pancreatic cancer.

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Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies.

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Dietary carbohydrates, glycemic load and glycemic index have been hypothesized to influence pancreatic cancer risk, but epidemiological studies have been inconsistent. The authors conducted a systematic review and meta-analysis of prospective studies to clarify these results. PubMed and several other databases were searched for prospective studies of intake of carbohydrates, glycemic index and glycemic load and pancreatic cancer up to September 2011. Summary relative risks were estimated using a random effects model. Ten cohort studies (13 publications) were included in the meta-analysis. The summary relative risk (RR) per 10 glycemic index units was 1.02 (95% confidence interval (CI): 0.93-1.12, I^2=0%), per 50 glycemic load units was 1.03 (95% CI: 0.93-1.14, I^2=10%), per 100 g/day of total carbohydrates was 0.97 (95% CI: 0.81-1.16, I^2=35%), and per 25 g/day of sucrose intake was 1.05 (95% CI: 0.85-1.23, I^2=53%). A positive association was observed with fructose intake, summary RR=1.22 (95% CI: 1.08-1.37, I^2=0%) per 25 g/day. This meta-analysis does not support an association between diets high in glycemic index, glycemic load, total carbohydrates or sucrose and pancreatic cancer risk. The finding of an increased risk with fructose intake warrants further investigation in studies with better adjustment for confounding and in non-American populations.

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Identification of the lymphatic drainage pathways from the pancreatic head guided by indocyanine green fluorescence imaging during pancreatico-duodenectomy.

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The authors identified the lymphatic drainage pathways from the pancreatic head guided by indocyanine green (ICG) fluorescence imaging to analyze optimal lymphadectomy for pancreatic cancer. The lymphatic pathways in 20 patients undergoing pancreatico-duodenectomy were analyzed. The authors injected ICG into the parenchyma in the anterior (n=10) or posterior surface (n=10) of the pancreas head and observed the intraoperative lymphatic flows by ICG fluorescence imaging. The seven main lymphatic drainage pathways were identified: (1) along the anterior or posterior pancreaticoduodenal arcade, (2) running obliquely down behind the superior mesenteric vein (SMV), (3) reaching the left side of the superior mesenteric artery (SMA), (4) running longitudinally upward between the SMV and SMA, (5) along the middle colic artery toward the transverse colon, (6) reaching the paraaortic (PA) region, and (7) reaching the hepatoduodenal ligament. The lymphatic pathway reaching the left side of the SMA was observed in 4 patients (20%), while that reaching the PA region in 17 patients (85%). The mean time to reach around the SMA was longer than that to reach the PA region. The authors found that several lymphatic drainage routes were observed from the pancreatic head, suggesting that a lymphadectomy around the SMA might have a similar oncological impact as that of the PA region.

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Nicotine, IFN-gamma and retinoic acid mediated induction of MUC4 in pancreatic cancer requires E2F1 and STAT-1 transcription factors and utilize different signaling cascades.

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The membrane-bound mucins are thought to play an important biological role in cell-cell and cell-matrix interactions, in cell signaling and in modulating biological properties of cancer cell. MUC4, a transmembrane mucin is overexpressed in pancreatic tumors, while remaining undetectable in the normal pancreas, thus indicating a potential role in pancreatic cancer pathogenesis. The molecular mechanisms involved in the regulation of MUC4 gene are not yet fully understood. Smoking is strongly correlated with pancreatic cancer and in the present study; the authors elucidate the molecular mechanisms by which nicotine as well as agents like retinoic acid (RA) and interferon-gamma (IFN-gamma) induce the expression of MUC4 in pancreatic cancer cell lines CD18, CAPAN2, AsPC1 and BxPC3. Chromatin immunoprecipitation assays and real-time PCR showed that transcription factors E2F1 and STAT1 can positively regulate MUC4 expression at the transcriptional level. IFN-gamma and RA could collaborate with nicotine in elevating the expression of MUC4, utilizing E2F1 and STAT1 transcription factors. Depletion of STAT1 or E2F1 abrogated the induction of MUC4; nicotine-mediated induction of MUC4 appeared to require alpha7-nicotinic acetylcholine receptor subunit. Further, Src and ERK family kinases also mediated the induction of MUC4, since inhibiting these signaling molecules prevented the induction of MUC4. MUC4 was also found to be necessary for the nicotine-mediated invasion of pancreatic cancer cells, suggesting that induction of MUC4 by nicotine and other agents might contribute to the genesis and progression of pancreatic cancer. The studies show that agents that can promote the growth and invasion of pancreatic cancer cells induce the MUC4 gene through multiple pathways and this induction requires the transcriptional activity of

E2F1 and STAT1. Further, the Src as well as ERK signaling pathways appear to be involved in the induction of this gene. It appears that targeting these signaling pathways might inhibit the expression of MUC4 and prevent the proliferation and invasion of pancreatic cancer cells.

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TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study.

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Both the European Neuroendocrine Tumor Society (ENETS) and the International Union for Cancer Control/American Joint Cancer Committee/World Health Organization (UICC/AJCC/WHO) have proposed TNM staging systems for pancreatic neuroendocrine neoplasms. This study aims to identify the most accurate and useful TNM system for pancreatic neuroendocrine neoplasms. The study included 1,072 patients who had undergone previous surgery for their cancer and for which at least 2 years of follow-up from 1990 to 2007 was available. Data on 28 variables were collected, and the performance of the two TNM staging systems was compared by Cox regression analysis and multivariable analyses. All statistical tests were two-sided. Differences in distribution of sex and age were observed for the ENETS TNM staging system. At Cox regression analysis, only the ENETS TNM staging system perfectly allocated patients into four statistically significantly different and equally populated risk groups (with stage I as the reference; stage II hazard ratio (HR) of death equal to 16.23, 95% confidence interval (CI): 2.14 to 123, P=0.007; stage III HR of death equal to 51.81, 95% CI: 7.11 to 377, P<0.001; and stage IV HR of death equal to 160, 95% CI: 22.30 to 1143, P<0.001). However, the UICC/AJCC/WHO 2010 TNM staging system compressed the disease into three differently populated classes, with most patients in stage I, and with the patients being equally distributed into stages II-III (statistically similar) and IV (with stage I as the reference; stage II HR of death equal to 9.57, 95% CI: 4.62 to 19.88, P<0.001; stage III HR of death equal to 9.32, 95% CI: 3.69 to 23.53, P<0.001[a]; and stage IV HR of death equal to 30.84, 95% CI: 15.62 to 60.87, P<0.001). Multivariable modeling indicated curative surgery, TNM staging, and grading were effective predictors of death, and grading was the second most effective independent predictor of survival in the absence of staging information. Though both TNM staging systems were independent predictors of survival, the UICC/AJCC/WHO 2010 TNM stages showed very large 95% confidence intervals for each stage, indicating an inaccurate predictive ability. These data suggest the ENETS TNM staging system is superior to the UICC/AJCC/WHO 2010 TNM staging system and supports its use in clinical practice.

[a]P=0.94 was erroneously reported in the abstract of the published paper. The correct value is shown in Table 3 (JOP note).

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Treatment of liver metastases in patients with neuroendocrine tumors of gastroesophageal and pancreatic origin.

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Well-to-moderately differentiated neuroendocrine tumors of gastroesophageal and pancreatic origin (GEP-NETs) with liver metastasis are a heterogeneous group of malignancies for which a range of therapeutic options have been employed. Surgical resection of hepatic metastases or hepatic artery embolization may be beneficial in patients with hepatic-predominant metastatic disease. Patients with ”carcinoid” syndrome and syndromes associated with functional pancreatic NET (PNET) can be effectively treated with somatostatin analogs. On the other hand, the efficacy of systemic chemotherapy for these patients is limited. A placebo-controlled, double-blind, prospective, and randomized study showed that octreotide LAR improves progression-free survival in patients with advanced midgut functional ”carcinoids”. In patients with advanced pancreatic NET, randomized, placebo-controlled studies have recently demonstrated that treatment with the tyrosine kinase inhibitor sunitinib or with mTOR inhibitor everolimus is associated with improved progression-free survival. Based on these studies, octreotide LAR, sunitinib, or everolimus are now considered as first-line therapeutic options in patients with advanced NET. Future studies will likely further define the role of these agents in patients with carcinoid liver metastasis and pancreatic NET liver metastasis.