PANCREAS ALERTS

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Early hemoconcentration is associated with pancreatic necrosis only among transferred patients.

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Studies evaluating hemoconcentration as a marker of necrosis in acute pancreatitis have reached different conclusions. The aim of this study was to determine the impact of transfer status on the accuracy of hemoconcentration for the prediction of pancreatic necrosis. The authors prospectively enrolled 339 patients in an observational cohort study from June 2005 to December 2007. Univariate and multivariate logistic regression analyses were used to evaluate the impact of transfer status on the relationship between hemoconcentration and necrosis. Accuracy for prediction of necrosis was measured by the area under the receiver operating characteristic curve. Hemo-concentration was associated with increased risk of necrosis only among transferred patients (odds ratio: 3.6; 95% confidence limits: 1.2, 10.8). The area under the receiver operating characteristic curve for admission hematocrit for prediction of necrosis was 0.78 among the transferred patients versus 0.55 among those with primary admissions (chi, P<0.0001). Transferred patients had greater initial severity (median bedside index of severity in acute pancreatitis, 2 *vs*. 1; P<0.0001), were more likely to have hemo-concentration (44% *vs*. 18%; chi, P<0.0001), and experienced increased necrosis (37.5% *vs*. 3.6%; chi, P<0.0001) compared with primary admissions. After adjusting for sex, disease severity, fluid resuscitation, and transfer status, hemoconcentration was not associated with necrosis (Wald chi, P=0.14). Transfer status is a confounder in the relationship between hemoconcentration and pancreatic necrosis.

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Alcohol-induced acute pancreatitis: the 'critical mass' concept.

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The association of alcohol consumption and acute pancreatitis (AP) has been well documented. Extensive research in the field of alcohol-induced AP has allowed scientists to understand the different aspects by which ethanol may alter pancreatic cellular function. However, despite the recognition and understanding of these proposed mechanisms, the basic question that remains unanswered is that although alcohol is consumed the world over, why is it that only some people develop AP? Epidemiologic data indicates a higher frequency of alcohol-induced AP in geographical locations where surrogate/home-brewed alcoholic beverages are freely available. These surrogate/home-brewed alcoholic beverages contain in addition to ethanol, higher alcohols (e.g. propanol and butanol) and other by-products/contaminants (e.g. acids, aldehydes and esters), the potential of which to induce pancreatic damage has been incompletely studied. Mutations in genes that metabolise alcohol as well as those that protect the acinar cells and the extra-acinar milieu from prematurely activated digestive enzymes (e.g. genetic mutations in *SPINK1* or *PRSS1* genes) have also been noted in these geographical locations. Based on the available epidemiologic, clinical and basic research data available at the present time, the authors propose a unifying hypothesis presenting for the first time the 'critical mass' concept. The authors hypothesise that it is the achievement of a 'critical mass' of damaged acinar cells that is required to trigger off the inflammatory cascade leading to a clinically recognised attack of AP. The consequence of a critical mass of damaged acinar cells is the generation of sufficient mediators to result in clinical AP. While the consumption of alcohol does damage acinar cells, the number of damaged acinar cells does not necessarily reach the 'critical mass' with every binge. Co-factors such a high fat or protein meals are required to sensitize the acinar cells by raising the metabolic state to a high level which compromises the viability of the cells. In addition, the existence of genetic mutations and/or the consumption of surrogate alcoholic beverages, by facilitating acinar cell damage, directly or indirectly, potentially hasten the achievement of the 'critical mass', leading to an attack of AP.

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Current trends in the management of infected necrotizing pancreatitis.

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Severe acute pancreatitis is a potentially life-threatening disease. Pancreatic necrosis is associated with an aggravated prognosis, while superimposed infection is almost always lethal without surgery. Bacterial translocation mainly from the gut is the most widely accepted mechanism in the pathogenesis of infected pancreatic necrosis. Infected pancreatic necrosis should be suspected in the presence of the usual markers of systemic inflammation (i.e., fever and leukocytosis), organ failure, or a protracted severe clinical course. The diagnostic method of choice to confirm the diagnosis of pancreatic necrosis is contrast-enhanced computed tomography, where necrotic areas are evidenced as regions without enhancement. The presence of pancreatic necrotic infection should be based on a combination of clinical manifestations, results of laboratory investigation (mainly increased levels of CRP and/or procalcitonin), and can be confirmed by image-guided fine-needle aspiration and gram stain/culture of the aspirates. Surgery remains the treatment of choice for the management of infected pancreatic necrosis and involves open necrosectomy (debridement) and wide drainage of the peripancreatic areas, often in association with continuous irrigation. Planned reoperations may be required to achieve complete removal of the necrotic/infected material. The timing of surgery is of paramount importance; ideally, surgery should be performed after 2 or 3 weeks from the onset of pancreatitis. Recently, various minimally invasive approaches have been described, but they have not been compared in prospective trials with the classical open surgery. Antibiotic therapy is routinely used in patients with infected necrotizing pancreatitis, in conjunction with surgical debridement; its role, however, in the management of patients with sterile necrosis is recently questioned. Nutritional support should be taken into consideration in these patients; enteral nutrition should be preferred over total parenteral nutrition to improve the anatomical and functional integrity of the gut mucosa, thereby preventing bacterial translocation.

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Elevated serum neutrophil gelatinase-associated lipocalin is an early predictor of severity and outcome in acute pancreatitis.

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About 210,000 new cases of acute pancreatitis (AP) involving reversible inflammation of the pancreas are reported in the United States every year. About one-fourth of all patients with AP go on to develop severe acute pancreatitis (SAP), which, unlike uncomplicated or mild acute pancreatitis (MAP, usually a self-limiting disease), constitutes a life-threatening condition with systemic complications, chiefly multiorgan dysfunction. An early prediction of the severity and outcome of patients with acute pancreatitis (AP) can lead to better treatment regimens for patients with SAP. There is currently no established biomarker for the early diagnosis of SAP. In this study, the authors investigated the potential of serum neutrophil gelatinase-associated lipocalin (NGAL) as an early marker to distinguish severe (SAP) from MAP and examine its ability to predict the prognosis of patients with SAP. To check the time kinetics of rise in NGAL during AP, the authors quantified NGAL levels in sera from mice with MAP or SAP at various time points (6, 12, 24 and 48 h) using sandwich enzyme-linked immunosorbent assay. NGAL levels were also quantified in serum from 28 MAP and 16 SAP cases and compared with 28 chronic pancreatitis and 30 healthy control samples. Samples collected within 5 days from onset of symptoms were included. The relationship of NGAL levels with survival and multiorgan failure (MOF) in SAP was also examined. Although NGAL levels were significantly higher in mice with both MAP and SAP 6 h after induction (compared to control animals), only mice with SAP exhibited a significant increase in NGAL levels at 24 h (P=0.003). NGAL levels declined at 48 h after induction in animals with both MAP and SAP but did not reach baseline levels. Among patients, mean (±SE) serum NGAL level was significantly higher in SAP (634±139 ng/mL) compared to MAP (84.7±7 ng/mL, P=0.0001). On subanalysis, the difference between MAP and SAP cases was significant in the first 48 h but not at 72, 96, or 120 h. NGAL was 100%, 96%, 97%, and 84% specific and 100%, 87.5%, 92%, and 94% sensitive in distinguishing SAP from MAP at 48, 72, 96, and 120 h, respectively, after the onset of symptoms. NGAL levels were significantly higher in SAP cases complicated by MOF (P=0.004), and high NGAL levels in SAP appeared to correlate with a fatal outcome. These data provide the first evidence for the potential of serum NGAL as an early marker to distinguish MAP from SAP. Further, high NGAL levels predict MOF and fatal outcome in patients with SAP. This study provides sufficient evidence for multi-institutional randomized trials for estimating the potential of NGAL as early biomarker for SAP.

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Acute pancreatitis in patients operated on for intraductal papillary mucinous neoplasms of the pancreas: requency, severity, and clinicopathologic correlations.

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Acute pancreatitis (AP) may reveal intraductal papillary mucinous neoplasms of the pancreas (IPMN). The aims were to describe the characteristics of AP associated with IPMN and to compare patients with AP with those without AP. All patients who underwent surgery for IPMN between 1995 and 2006 were retrospectively studied. Clinical, imaging, and histological data were collected. The clinical and radiological severity of AP, the number of episodes, and recurrence after surgery were assessed. One hundred eighty-five patients were included. Sixty-four (34.6%) had at least 1 AP (median, 2; range, 1-10). The median Balthazar score was 1 (0-6). Imaging analysis showed no difference between the two groups except for the presence of a mass. Branch duct IPMNs were more frequent in the AP group (74.4% *vs.* 45.3%, P=0.001), whereas combined IPMNs were more frequent in the non-AP group (45.3% *vs.* 21.5%, P=0.001). There was no difference in the grade of dysplasia between AP and non-AP groups: carcinoma, 45.3% *versus* 56.2%; benign IPMN, 54.7% versus 43.8% (P NS), respectively. Acute pancreatitis occurs in 34.6% of patients with IPMNs. Acute pancreatitis is not severe and often recurs. Histology showed no difference between the two groups.

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Remission and relapse of autoimmune pancreatitis: focusing on corticosteroid treatment.

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Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by swelling of the pancreas, narrowing of the main pancreatic duct, elevation of serum immunoglobulin G or G4 level or presence of several autoantibodies, or lymphoplasmacytic infiltration and fibrosis in the pancreas. However, the pathogenesis of AIP remains unclear, and the natural history and long-term prognosis of AIP are little known. Oral corticosteroid therapy for AIP is recommended. The absolute indications for steroid therapy for AIP are bile duct stenosis and accompanying systemic disease such as retroperitoneal fibrosis and diabetes mellitus. The dosage for remission induction is 30 to 40 mg/d for 1 to 2 months. The remission maintenance is needed to prevent relapse, and 5 to 10 mg/d for at least 6 months is recommended in patients who do not have complete remission. When relapse occurs, the dose used at remission induction can be readministered. Herein, the authors discuss remission and relapse of AIP, focusing on corticosteroid treatment to help clinicians care for patients with AIP and to help make an ideal treatment protocol of AIP through a review of published data. The authors also tried to define remission and relapse of AIP to help investigate the natural course of AIP.

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Epidemiological study of pancreatic diabetes in Japan in 2005: a nationwide study.

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There have been few epidemiological studies on pancreatic diabetes. In this study, the authors determined the incidence and pathology of pancreatic diabetes in Japan. The authors examined the epidemiology of pancreatic diabetes in Japan in 2005 by using a nationwide stratified random-sampling method. Especially, the authors focused on newly developed diabetes in association with the occurrence of pancreatic disease (true pancreatic diabetes). A total of 19,500 individuals received treatment for true pancreatic diabetes, accounting for 0.8% of patients with diabetes. Prevalence was estimated to be 15.2 per 100,000 with an annual onset incidence of 1.1 per 100,000. With regard to the complications in true pancreatic diabetes, the incidence of retinopathy was lower than that in types 1 and 2 diabetes. Among true pancreatic diabetes with chronic pancreatitis, alcoholic pancreatitis was found in the largest sector. Furthermore, as many as 53.7% were continuous drinkers, and 66.7% received insulin therapy. The frequency of hypoglycemia was high in regular drinkers treated with insulin. Hypoglycemia was a major cause of death in patients who were on insulin and continuous drinkers. The authors clarified the epidemiology of pancreatic diabetes in Japan. Patients with chronic pancreatitis-associated pancreatic diabetes should receive lifestyle guidance focused on drinking cessation.

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Single-pattern convergence of K-*ras* mutation correlates with surgical indication of intraductal papillary mucinous neoplasms.

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One or more patterns of 6 K-*ras* mutations are detected in cells from the pancreatic juice of patients with

intraductal papillary mucinous neoplasms (IPMNs). The authors investigated whether these mutations are associated with malignant progression. Between January 2002 and December 2007, 53 patients with IPMN were subjected to collection of pure pancreatic juice to evaluate K-*ras* mutation. According to the histological and radiological findings, the IPMNs were classified into 4 groups: carcinoma group, adenoma group, high-risk group, and low-risk group. The authors retrospectively investigated the mutation with these groups. In patients with a positive K-*ras* mutation, a single pattern of K-*ras* mutation was observed in 80% (8/10) of the carcinoma group, in 71% (5/7) of the adenoma group, in 40% (2/5) of the high-risk group, and in 38% (8/21) of the low-risk group. The rate of a single pattern of K-*ras* mutation decreased in a stepwise order (P=0.017). The incidence of a single pattern of K-*ras* mutation was significantly higher in the patients who received surgical therapy (75%, 12/16) than in those who did not (38%, 10/26; P=0.033). The present study suggests that the single-clonal convergence of K-*ras* mutation is associated with the malignant progression of IPMNs.

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The global impact of endoscopic ultrasound (EUS) regarding the survival of a pancreatic adenocarcinoma in a tertiary hospital.

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Pancreatic ductal adenocarcinoma is a type of neoplasm with a high mortality rate. There are a number of different procedures that may be followed in the study of the pancreas; one such procedure is endoscopic ultrasonography (EUS). This study aimed to retrospectively evaluate the impact on patient survival of a biliopancreatic EUS performed 2 months prior to the first treatment session of the pancreatic ductal adenocarcinoma. The authors carried out a retrospective evaluation of the medical case histories of patients who had been diagnosed with pancreatic ductal adenocarcinoma over a period of 10 years (1 Jan 1999-31 Dec 2008), combining the computer archives of Pathological Anatomy (biopsy and cytology) Dept. and those of the Digestive Department's Endoscopic Ultrasonography Unit in order to exclude any pancreatic neoplasms derived from other origins. Information regarding the patients' age, sex, tumor location, and various diagnostic tests (EUS, EUS-fine-needle aspiration (FNA), helical computed tomography (CT), multidetector-row CT (MDCT)) were recorded, along with the different treatments that had been followed in each case. When the survival rates of patients diagnosed with and without EUS were compared, evaluating the average survival rate and the survival rate after 1, 3, and 5 years, respectively, the differences in the results proved to be statistically significant (P=0.014) in favor of the diagnosis with EUS. However, no significant differences were found when using other diagnostic imaging methods, such as EUS-FNA (P=0.271), helical CT (P=0.843), or MDCT (P=0.738). To evaluate other influencing survival factors, a study was undertaken to record data depending on the sex of the patients. Results showed a higher survival rate in the female patients with a median of 6.57 months compared to that of the male patients with a median of 4.7 months (P=0.014). Variables, which had resulted significant prior to treatment, were included in a multivariate Cox regression model, after which only the sex and EUS remained significant. A biliopancreatic EUS carried out during the 2 months prior to the start of the treatment of the pancreatic ductal adenocarcinoma has a statistically significant impact on the patient survival rate. The authors believe that this is due to the possibility of a very-early-stage diagnosis of the adenocarcinoma permitted by the use of this technique.

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Biobanking of human pancreas cancer tissue: impact of *ex-vivo* procurement times on RNA quality.

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Tissue banking has become a major initiative at many oncology centers. The influence of warm *ex-vivo* ischemia times, storage times, and biobanking protocols on RNA integrity and subsequent microarray data is not well documented. A prospective institutional review board-approved protocol for the banking of abdominal neoplasms was initiated at Memorial Sloan-Kettering Cancer Center in 2001. Sixty-four representative pancreas cancer specimens snap-frozen at various *ex-vivo* procurement times (less than, or equal to 10 min, 11-30 min, 31-60 min, more than 1 h) and banked during three time periods (2001-2004, 2004-2006, 2006-2008) were processed. RNA integrity was determined by microcapillary electrophoresis using the RNA integrity number (RIN) algorithm and by results of laser-capture microdissection (LCM). Overall, 42% of human pancreas cancer specimens banked under a dedicated protocol yielded RNA with a RIN equal to, or greater than 7. Limited warm *ex-vivo* ischemia times did not negatively impact RNA quality (percentage of tissue

with total RNA with RIN equal to, or greater than 7 for 10 min or less, 42%; 11-30 min, 58%; 31-60 min, 33%; more than 60 min, 42%), and long-term storage of banked pancreas cancer biospecimens did not negatively influence RNA quality (total RNA with RIN equal to, or greater than 7 banked 2001-2004, 44%; 2004-2006, 38%; 2006-2008, 50%). RNA retrieved from pancreatic cancer samples with RIN equal to, or greater than 7 subject to LCM yielded RNA suitable for further downstream applications. Fresh-frozen pancreas tissue banked within a standardized research protocol yields high-quality RNA in approximately 50% of specimens and can be used for enrichment by LCM. Quality of tissues of the biobank were not adversely impacted by limited variations of warm ischemia times or different storage periods. This study shows the challenges and investments required to initiate and maintain high-quality tissue repositories.

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S100P is a novel marker to identify intraductal papillary mucinous neoplasms.

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Intraductal papillary mucinous neoplasms of the pancreas are subclassified based on morphological features, and different immunohistochemical profiles have been identified in association with the subtypes. The authors previously reported that S100P was an early developmental marker of pancreatic carcinogenesis and that there was higher S100P expression in intraductal papillary mucinous neoplasms than in normal pancreatic ductal epithelium. However, there have been no reports on novel diagnostic markers to distinguish intraductal papillary mucinous neoplasm from nonneoplastic lesions. Surgical specimens of intraductal papillary mucinous neoplasm obtained from 105 patients were investigated using immunohisto-chemistry. S100P expression was not detected in normal pancreatic ductal epithelium but was detected in all intraductal papillary mucinous neoplasm cells (100%) with diffuse nuclear or nuclear/cytoplasmic staining. MUC5AC was also expressed in most of the intraductal papillary mucinous neoplasms (102/105; 97%). Furthermore, S100P was clearly expressed in the invasive component of intraductal papillary mucinous neoplasms (32/32; 100%), including perineural and lymphatic and minimal invasion. On the other hand, MUC5AC was expressed in only 23 cases of 32 invasive components (P<0.01). These data suggest that the S100P antibody may be a useful marker for detecting all types of intraductal papillary mucinous neoplasms.

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Serum gamma-glutamyltransferase levels are related to insulin sensitivity and secretion in subjects with abnormal glucose regulation.

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The authors aimed to test the association between gamma-glutamyltransferase level and glucose regulation. They performed a cross-sectional analysis of 500 subjects (199 men, 301 women; age 47±11 years, body mass index (BMI) 28.6±5.5 kg/m^2) referred to Diabetes Clinics because of potential risk of type 2 diabetes mellitus (T2DM). The prevalence of all glucose intolerance categories was higher in the top quartile of gamma-glutamyltransferase than in the first. Subjects with normal glucose tolerance showed lower gamma-glutamyltransferase levels compared with those with impaired glucose tolerance (IGT), impaired fasting glucose (IFG)+IGT and T2DM (ANOVA, P<0.0001), but not those with IFG. Homeostasis model assessment-insulin resistance (HOMA-IR) increased with increasing levels of gamma-glutamyltransferase, while the insulinogenic index/HOMA-IR ratio decreased. In an age- and sex-adjusted analysis, the top gamma-glutamyltransferase quartile was independently associated with IFG+IGT (odds ratio (OR): 2.41; 95% confidence interval (CI): 1.13-5.15) and T2DM (OR: 2.77; 95% CI: 1.47-5.22). After further adjustment for BMI, alcohol intake, family history of diabetes, cigarette smoking and physical activity, the top quartile of gamma-glutamyltransferase remained an independent predictor of IFG+IGT (OR: 2.62; 95% CI: 1.13-6.07) and T2DM (OR: 2.39; 95% CI: 1.20-4.76). Only when transaminases and HOMA-IR have been added to the model, the top quartile of gamma-glutamyltransferase resulted no more independently associated to IFG+IGT or T2DM. Gamma-glutamyltransferase is closely related to insulin resistance, reduced beta-cell function and deterioration of glucose tolerance.

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Interleukin-18 contributes more closely to the progression of diabetic nephropathy than other diabetic complications.

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Diabetic complication is comprised of a wide variety of pathophysiological factors involving proinflammatory

cytokines, adipokines, and oxidative stress, among others. Each of these complications differs in their incidence and the stage of their occurrence. The authors examined cytokines and stress markers in 48 patients with type 2 diabetes mellitus and compared the difference of their contribution to pathogenesis between nephropathy and other diabetic complications. Hemoglobin A1c correlated with the level of low-density lipoprotein-cholesterol, and significantly elevated in the severe macroangiopathy group. Cystatin C increased in the severe microangiopathy groups but did not increase in the macroangiopathy group. The levels of interleukin 18 (IL-18), high-sensitive CRP (H-CRP), liver-type fatty acid binding protein, and 8-hydroxy-2-deoxyguanosine increased in the severe microangiopathy group. These data suggest the participation of proinflammatory signaling and oxidative stress in the progression of microangiopathy. In particular, IL-18 and H-CRP were significantly elevated only in the severe nephropathy group but did not significantly elevate in other complications. These data suggest another effect of IL-18 on glomerulus in addition to its proinflammatory effect. In conclusion, the authors propose that IL18 has a specific role that contributes more closely to the progression of diabetic nephropathy than other diabetic complications.

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Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications.

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Cardiovascular disease is a major complication of diabetes mellitus, and improved strategies for prevention and treatment are needed. Endothelial dysfunction contributes to the pathogenesis and clinical expression of atherosclerosis in diabetes mellitus. This article reviews the evidence linking endothelial dysfunction to human diabetes mellitus and experimental studies that investigated the responsible mechanisms. The authors then discuss the implications of these studies for current management and for new approaches for the prevention and treatment of cardiovascular disease in patients with diabetes mellitus.

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