

## PANCREAS ALERTS

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### **Acute pancreatitis: models, markers, and mediators.**

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Acute pancreatitis has an incidence of approximately 40 cases per year per 100,000 adults. Although usually self-limiting, 10% to 20% of afflicted patients will progress to severe pancreatitis. The mortality rate among patients with severe pancreatitis may approach 30% when they progress to multisystem organ failure. The development of acute pancreatitis illustrates the requirement for understanding the basic mechanisms of disease progression to drive the exploration of therapeutic options. The pathogenesis of acute pancreatitis involves the interplay of local and systemic immune responses that are often difficult to characterize, particularly when results from animal models are used as a foundation for human trials. Experimental studies suggest that the prognosis for acute pancreatitis depends upon the degree of pancreatic necrosis and the intensity of multisystem organ failure generated by the systemic inflammatory response. This suggests an intricate balance between localized tissue damage with proinflammatory cytokine production and a systemic, anti-inflammatory response that restricts the inappropriate movement of proinflammatory agents into the circulation. The critical players of this interaction include the proinflammatory cytokines IL-1beta, TNF-alpha, IL-6, IL-8, and platelet activating factor (PAF). The anti-inflammatory cytokines IL-10, as well as TNF-soluble receptors and IL-1 receptor antagonist, have also been shown to be intimately involved in the inflammatory

response to acute pancreatitis. Other compounds implicated in disease pathogenesis in experimental models include complement, bradykinin, nitric oxide, reactive oxygen intermediates, substance P, and higher polyamines. Several of these mediators have been documented to be present at increased concentrations in the plasma of patients with severe, acute pancreatitis. Preclinical work has shown that some of these mediators are markers for disease activity, whereas other inflammatory components may actually drive the disease process as important mediators. Implication of such mediators suggests that interruption or blunting of an inappropriate immune response has the potential to improve outcome. Although the manipulations of specific mediators in animal models may be promising, they may not transition well to the human clinical setting. However, continued reliance on experimental animal models of acute pancreatitis may be necessary to determine the underlying causes of disease. Full understanding of these basic mechanisms involves determining not only which mediators are present, but also closely documenting the kinetics of their appearance. Measurement of the inflammatory response may also serve to identify diagnostic markers for the presence of acute pancreatitis and provide insight into prognosis. Understanding the models, documenting the markers, and deciphering the mediators have the potential to improve treatment of acute pancreatitis.

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### **The effect of CP96,345 on the expression of tachykinins and neurokinin receptors in acute pancreatitis.**

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Acute pancreatitis (AP) is a life-threatening condition that involves an acute inflammatory process in the pancreas. The involvement of tachykinins and neurokinin receptors in acute pancreatitis has been described only recently, despite their long-established role in inflammatory conditions. Among these, substance P (SP) is believed to play a central role in exacerbating the inflammatory process by acting through neurokinin-1 receptor (NK1R). Treatment with the NK1R antagonist, CP96,345, results in protection against caerulein-induced acute pancreatitis in mice. However, the mechanism by which NK1R and SP worsen the condition is still unclear. In the present study, the authors have investigated the effect of NK1R blockage on the expression of preprotachykinin genes and neurokinin receptors in acute pancreatitis. In the pancreas, CP96,345 treatment resulted in suppression of the elevation of SP concentration, preprotachykinin-A gene (PPT-A) mRNA expression, and NK1R mRNA and protein expression. In the lungs, the antagonist was found to suppress the increase in SP concentration, PPT-A mRNA expression and preprotachykinin-C gene (PPT-C) mRNA expression. However, the antagonist treatment further promoted the accumulation of pulmonary NK1R mRNA and protein expression. Neurokinin-2 receptor (NK2R) mRNA expression was not detected in normal pancreas. However, up-regulated expression of the mRNA for this receptor was observed during acute pancreatitis and treatment with CP96,345 further increased this expression. Pulmonary NK2R mRNA expression was found to be reduced during acute pancreatitis and CP96,345 treatment normalized this reduction. Neurokinin-3 receptor (NK3R) mRNA expression was absent in both pancreas and lung. These data have provided valuable information regarding the regulation of tachykinins and neurokinin receptors during acute pancreatitis.

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## **Pathophysiology and treatment of acute pancreatitis: new therapeutic targets: a ray of hope?**

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Acute pancreatitis is a life-threatening disease with putatively high mortality rates, particularly in the setting of systemic inflammatory response and multiple organ failure when superinfection of necrosis occurs. Although the APACHE II and Ranson score are widely accepted as clinical scores to predict the prognosis, current medical treatment is still based upon state of the art intensive care treatment largely unrelated to the pathogenesis of the disease. The mechanisms by which premature enzyme activation and autodigestion of the pancreatic gland is triggered and maintained are still ill-defined. It is well known that activation of chemokines, cytokines and pancreatic enzymes characterize the cause of the disease, but disease-phase specific treatment attempts have thus far not resulted in successful molecular based medical treatments. The current summary describes the novel understanding in the pathophysiology of acute pancreatitis with special emphasis on specific disease phases. It outlines promising and novel experimental and medical therapeutic approaches which might become clinical targets and successful strategies to significantly reduce pancreatitis-associated mortality rates.

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**Comparison of early endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the management of acute biliary pancreatitis: a prospective randomized study.**

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The role and potential benefits of endoscopic ultrasonography (EUS) in the management of acute biliary pancreatitis have not been documented. The authors report a large prospective randomized study comparing early EUS and endoscopic retrograde cholangiopancreatography (ERCP) in the management of these patients. This prospective randomized study was performed on 140 patients with acute pancreatitis suspected to have a biliary cause. The patients were randomized to have EUS (n=70) or ERCP (n=70) within 24 hours from admission. In the EUS group, when EUS detected choledocholithiasis, therapeutic ERCP was performed during the same endoscopy session. In the ERCP group, diagnostic ERCP was performed, followed by therapeutic endoscopy when choledocholithiasis was detected. Examination of the biliary tree by EUS was successful in all patients in the EUS group, whereas cannulation of the common duct during ERCP was unsuccessful in 10 patients (14%) in the ERCP group (P=0.001). Combined percutaneous ultrasonography and ERCP missed detection of cholelithiasis in 6 patients in the ERCP group. The overall morbidity rate was 7% in the EUS group, and that in the ERCP group was 14% (P=0.172). The hospital stay and mortality rates were comparable in both groups. The authors concluded that in selected patients with acute biliary pancreatitis, EUS could safely replace diagnostic ERCP in the management for selecting patients with choledocholithiasis for therapeutic ERCP with a higher successful examination rate, a higher sensitivity in the detection of cholelithiasis, and a comparable morbidity rate.

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**Machine learning can improve prediction of severity in acute pancreatitis using admission values of APACHE II score and C-reactive protein.**

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Acute pancreatitis (AP) has a variable course. Accurate early prediction of severity is essential to direct clinical care. Current assessment tools are inaccurate, and unable to adapt to new parameters. None of the current systems uses C-reactive protein (CRP). Modern machine-learning tools can address these issues. Three hundred and seventy patients admitted with AP in a 5-year period were retrospectively assessed; after exclusions, 265 patients were studied. First recorded values for physical examination and blood tests, aetiology, severity and complications were recorded. A kernel logistic regression model was used to remove redundant features, and identify the relationships between relevant features and outcome. Bootstrapping was used to make the best use of data and obtain confidence estimates on the parameters of the model. A model containing 8 variables (age, CRP, respiratory rate, pO<sub>2</sub> on air, arterial pH, serum creatinine, white cell count and GCS) predicted a severe attack with an area under the receiver-operating characteristic curve (AUC) of 0.82 (SD 0.01). The optimum cut-off value for predicting severity gave sensitivity and specificity of 0.87 and 0.71 respectively. The predictions were significantly better (P=0.0036) than admission APACHE II scores in the same patients (AUC 0.74) and better than historical admission APACHE II data (AUC 0.68-0.75). The authors concluded that this system for the first time combines admission values of selected components of APACHE II and CRP for prediction of severe AP. The score is simple to use, and is more accurate than admission APACHE II alone. It is adaptable and would allow incorporation of new predictive factors.

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### **Galectin-1 induces chemokine production and proliferation in pancreatic stellate cells.**

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Galectin-1 is a beta-galactoside-binding lectin. Previous studies have shown that galectin-1 was expressed in fibroblasts of chronic pancreatitis and of desmoplastic reaction associated with pancreatic cancer. These fibroblasts are now recognized as activated pancreatic stellate cells (PSCs). The authors examined the role of galectin-1 in cell functions of PSCs. PSCs were isolated from rat pancreas tissue and used in their culture-activated phenotype unless otherwise stated. Expression of galectin-1 was assessed by Western blotting, reverse transcription-PCR, and immunofluorescent staining. The effects of recombinant galectin-1 on chemokine production and proliferation were evaluated. Activation of transcription factors was assessed by electrophoretic mobility shift assay. Activation of MAP kinases was examined by Western blotting using anti-phosphospecific antibodies. Galectin-1 was strongly expressed in culture-activated, but not freshly isolated, PSCs. Recombinant galectin-1 increased proliferation and production of monocyte chemoattractant protein-1 and cytokine-induced neutrophil chemoattractant-1. Galectin-1 activated ERK, JNK, activator protein-1, and NF-kappaB, but not p38 MAP kinase or Akt. Galectin-1 induced proliferation through ERK, and chemokine production mainly through the activation of NF-kappaB, and in part by JNK and ERK pathways. These effects of galectin-1 were abolished in the presence of thiodigalactoside, an inhibitor of beta-galactoside binding. In conclusion, these

results suggest a role of galectin-1 in chemokine production and proliferation through its beta-galactoside binding activity in activated PSCs.

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### **Natural history of endocrine failure in tropical chronic pancreatitis: a longitudinal follow-up study.**

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Diabetes in tropical chronic pancreatitis (TCP), also known as fibrocalculous pancreatic diabetes (FCPD), is frequently seen at diagnosis. The aim of the present study was to determine the natural history of endocrine failure in TCP subjects without diabetes at baseline. Of 73 TCP subjects without diabetes according to World Health Organization (WHO) criteria at baseline who were seen at an out-patient center, 54 (74.0%) underwent periodic oral glucose tolerance tests on follow up. Another 54 sex-matched, non-diabetic subjects without chronic pancreatitis served as controls. Baseline demographic and clinical characteristics were noted. RESULTS: After a median follow up of 5.0 years in TCP subjects and 7.0 years in controls, 27 of 54 TCP subjects (50%) developed diabetes compared with 14 of 54 controls (25.9%). Of the TCP subjects, those who developed diabetes on follow up were older ( $31 \pm 12$  vs  $23 \pm 11$  years;  $P=0.013$ ), had a higher body mass index ( $21.7 \pm 4.4$  vs  $18.2 \pm 3.5$  kg/m<sup>2</sup>;  $P=0.004$ ), higher 2 h post-load plasma glucose ( $8.8 \pm 1.9$  vs  $6.7 \pm 1.4$  mmol/L;  $P<0.001$ ) and lower fecal chymotrypsin ( $2.1 \pm 1.2$  vs  $4.3 \pm 2.5$  U/g;  $P<0.001$ ) at baseline compared with those who did not develop diabetes. The median time for the development of diabetes after diagnosis of TCP was 9.6 years (compared with 14.4 years

among controls). Only 2 of 13 TCP subjects (15.4%) who had undergone surgical interventions during the normal glucose tolerance phase developed diabetes during follow up. In conclusions, in TCP, there is progressive deterioration of endocrine pancreatic function, with development of diabetes in 50% of patients upon follow up, suggesting that FCPD is merely a later stage in the course of TCP. Early surgery may prevent the development of diabetes in TCP subjects.

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**Keratin 8 mutations are not associated with familial, sporadic and alcoholic pancreatitis in a population from the United States.**

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Genetic predispositions play a major role in the development of chronic pancreatitis. Recently, a mutation in the keratin 8 gene (G62C) was reported to be associated with chronic pancreatitis in Italy. The authors determined whether mutations in the keratin 8 gene are associated with familial, sporadic and alcoholic recurrent acute or chronic pancreatitis in a population from the United States. They investigated the relevant genomic region of the keratin 8 gene in 80 patients with familial pancreatitis without a cationic trypsinogen (PRSS1) gene mutation from 52 different families, 21 patients with familial hereditary pancreatitis and a PRSS1 mutation from 20 different families, 126 patients with sporadic pancreatitis without a PRSS1 mutation, 61 patients with alcoholic pancreatitis and 271 controls by direct DNA sequencing. The authors found the heterozygous G62C mutation in n=3/80 patients (n=2/52 patients from different families, 3.8%) with familial pancreatitis

without PRSS1 mutation and in n=3/126 patients (2.4%) with sporadic pancreatitis. They detected an adjacent heterozygous I63V mutation in n=2/80 patients (n=2/52 patients from different families, 3.8%) with familial pancreatitis without PRSS1 mutation and in n=1/61 patients (1.6%) with alcoholic pancreatitis. The authors found the G62C mutation in n=2/271 controls (0.7%) and the I63V mutation in n=2/271 controls (0.7%). There were no statistically significant differences in the genotype frequencies between patients and controls (P>0.05). Screening of additional available family members revealed that these variants did not segregate with the disease phenotype. There was no statistically significant difference in the frequency of these keratin 8 variants between patients with chronic pancreatitis and controls (P>0.05). In conclusion, these keratin 8 variants are not associated with familial, sporadic or alcoholic pancreatitis.

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**A selective COX-2 inhibitor suppresses chronic pancreatitis in an animal model (WBN/Kob rats): significant reduction of macrophage infiltration and fibrosis.**

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Therapeutic strategies to treat chronic pancreatitis (CP) are very limited. Other chronic inflammatory diseases can be successfully suppressed by selective cyclooxygenase-2 (COX-2) inhibitors. Since COX-2 is elevated in CP the authors tried to inhibit COX-2 activity in an animal model of CP (WBN/Kob rat). They then analyzed the effect of COX-2 inhibition on macrophages, important mediators of chronic inflammation. Male WBN/Kob rats were continuously fed the COX-2 inhibitor Rofecoxib, starting at the age of 7 weeks. Animals were sacrificed 2, 5, 9, 17, 29 weeks later. In some animals,

treatment was discontinued after 17 weeks, and the animals were observed for another 24 weeks. Compared to the spontaneous development of inflammatory injury and fibrosis in WBN/Kob control rats, animals treated with Rofecoxib exhibited a significant reduction and delay ( $P < 0.0001$ ) of inflammation. Collagen and TGF- $\beta$  synthesis was significantly reduced. Similarly, PGE<sub>2</sub>-levels were markedly lower, indicating a strong inhibition of COX-2 activity ( $P < 0.003$ ). If treatment was discontinued at 24 weeks of age, all parameters of inflammation strongly increased comparable to that in untreated rats. The correlation of initial infiltration with subsequent fibrosis led us to determine the effect of Rofecoxib on macrophage migration. In chemotaxis experiments, macrophages turned insensitive to the chemoattractant fMLP in the presence of Rofecoxib. The authors concluded that in the WBN/Kob rat, chronic inflammatory changes and subsequent fibrosis can be inhibited by Rofecoxib. Initial events include infiltration of macrophages. Cell culture experiments indicate that migration of macrophages is COX-2 dependent.

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**Impact of etiology on the painful early stage of chronic pancreatitis: a long-term prospective study.**

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This prospective study was aimed to investigate the impact of etiology on the pain profile in relation to alterations of function and morphology from early to advanced chronic pancreatitis (CP). The mixed medico-surgical cohort comprised 265 patients with alcoholic (ACP), 21 with idiopathic "juvenile" (IJCP), 46 with idiopathic "senile" (ISCP) and 11 with hereditary CP (HPCP). The patients were followed regularly from onset of disease according to the protocol published previously. Males predominated in ACP, IJCP, ISCP (>71%) but not in HP (46%). Age at onset (median) was 10, 23, 36 and 62 years in HP, IJCP, ACP and ISCP, respectively. Follow-up from disease onset ranged from 14 to 36 years. The progression to late-stage CP, documented by exocrine insufficiency (86-100%) and calcification (80-91%) lasted 2 to 5-fold longer in HP/IJCP compared to ACP. Early stage CP, characterized by recurrent pancreatitis prevailed in  $\geq 90\%$  of patients, except for those with ISCP (48%), and lasted up to 5-fold longer in HP/IJCP compared to ACP. Surgery for severe pain was required for ACP/IJCP in 57% of the patients compared to <27% in HP/ISCP. Permanent pain relief regularly occurred in late-stage CP irrespective of etiology and surgery. The authors concluded that the clinical profile of the 4 "etiological" subgroups is predictably different in the painful early (precalcific) CP stage.