
Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial.


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Infectious complications and associated mortality are a major concern in acute pancreatitis. Enteral administration of probiotics could prevent infectious complications, but convincing evidence is scarce. The aim was to assess the effects of probiotic prophylaxis in patients with predicted severe acute pancreatitis. In this multicentre randomized, double-blind, placebo-controlled trial, 298 patients with predicted severe acute pancreatitis (Acute Physiology and Chronic Health Evaluation (APACHE II) score equal to or greater than 8, Imrie score equal to or greater than 3, or C-reactive protein greater than 150 mg/L) were randomly assigned within 72 h of onset of symptoms to receive a multispecies probiotic preparation (n=153) or placebo (n=145), administered enterally twice daily for 28 days. The primary endpoint was the composite of infectious complications (ie, infected pancreatic necrosis, bacteremia, pneumonia, urosepsis, or infected ascites) during admission and 90-day follow-up. Analyses were by intention to treat. This study is registered, number ISRCTN38327949. One person in each group was excluded from analyses because of incorrect diagnoses of pancreatitis; thus, 152 individuals in the probiotics group and 144 in the placebo group were analysed. Groups were much the same at baseline in terms of patients' characteristics and disease severity. Infectious complications occurred in 46 (30%) patients in the probiotics group and 41 (28%) of those in the placebo group (relative risk 1.06, 95% CI 0.75-1.51). Twenty-four (16%) patients in the probiotics group died, compared with nine (6%) in the placebo group (relative risk 2.53, 95% CI 1.22-5.25). Nine patients in the probiotics group developed bowel ischemia (eight with fatal outcome), compared with none in the placebo group (P=0.004). In patients with predicted severe acute pancreatitis, probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotic prophylaxis should therefore not be administered in this category of patients.

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TGF-beta signaling preserves RECK expression in activated pancreatic stellate cells.


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Activated pancreatic stellate cells (PSCs) play a pivotal role in the pathogenesis of pancreatic fibrosis, but the detailed mechanism for dysregulated accumulation of extracellular matrix (ECM) remains unclear. Cultured rat PSCs become activated by profibrogenic mediators, but these mediators failed to alter the expression levels of matrix metalloproteinases (MMPs) to the endogenous tissue inhibitors of metalloproteinases (TIMPs). Here, the authors examined the expression of RECK, a novel membrane-anchored MMP inhibitor, in PSCs. Although RECK mRNA levels were largely unchanged, RECK protein expression was barely detected.
at 2, 5 days after plating PSCs, but appeared following continued in vitro culture and cell passage which result in PSC activation. When PSCs at 5 days after plating (PSCs-5d) were treated with pepstatin A, an aspartic protease inhibitor, or TGF-beta1, a profibrogenic mediator, RECK protein was detected in whole cell lysates. Conversely, Smad7 overexpression or suppression of Smad3 expression in PSCs after passage 2 (PSCs-P2) led to the loss of RECK protein expression. These findings suggest that RECK is post-translationally processed in pre-activated PSCs but protected from proteolytic degradation by TGF-beta signaling. Furthermore, collagenolytic activity of PSCs-5d was greatly reduced by TGF-beta1, whereas that of PSCs-P2 was increased by anti-RECK antibody. Increased RECK levels were also observed in cerulein-induced acute pancreatitis. Therefore, these results suggest for the first time proteolytic processing of RECK as a mechanism regulating RECK activity, and demonstrate that TGF-beta signaling in activated PSCs may promote ECM accumulation via a mechanism that preserves the protease inhibitory activity of RECK.

Blocking of monocyte chemoattractant protein-1 (MCP-1) activity attenuates the severity of acute pancreatitis in rats.


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Monocyte chemoattractant protein-1 (MCP-1) has been shown to affect the progression of various inflammatory disorders, including pancreatitis. To investigate the role of MCP-1 in acute pancreatitis and to seek possible therapeutic means, the authors evaluated the effect of a plasmid expression vector containing a dominant-negative mutant MCP-1 gene (mMCP-1). Two rat models of acute pancreatitis were employed that used either cerulein (for mild pancreatitis) or a mixture of 5% taurocholic acid and trypsin (for severe pancreatitis). At 6 h after induction of acute pancreatitis with or without injection of mMCP-1, serum amylase levels and cytokine levels, as well as morphological evaluation of the pancreas, were determined. Survival rates were also evaluated. Severe pancreatitis was significantly reduced by mMCP-1 injection. mMCP-1 decreased serum levels of amylase, IL-6, IL-10, and LDH, and improved the survival rate 48 h after disease onset. Histopathological changes of pancreas and lungs were also improved by mMCP-1. MCP-1 appears to be involved in the progression of severe forms of acute pancreatitis. These data suggested that MCP-1 is a candidate as a therapeutic target to treat acute pancreatitis.

Changes in the expression and dynamics of SHP-1 and SHP-2 during cerulein-induced acute pancreatitis in rats.


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Protein tyrosine phosphatases (PTPs) are important regulators of cell functions but data on different PTP expression and dynamics in acute pancreatitis (AP) are very scarce. Additionally, both c-Jun N-terminal kinases (JNK) and extracellular signal-regulated kinases (ERK1/2), together with intracellular cAMP levels in inflammatory cells, play an essential role in AP. In this study the authors have detected an increase in PTP SHP-1 and SHP-2 in the pancreas at the level of both protein and mRNA as an early event during the development of Cerulein (Cer)-induced acute pancreatitis.
AP in rats. Nevertheless, while SHP-2 protein returned to baseline levels in the intermediate or later phases of AP, SHP-1 protein expression remained increased throughout the development of the disease. The increase in SHP-2 protein expression was associated with changes in its subcellular distribution, with higher percentages located in the fractions enriched in lysosomes+mitochondria or microsomes. Furthermore, while the increase in SHP-2 protein was also observed in sodium-taurocholate duct infusion or bile-pancreatic duct obstruction AP, that of SHP-1 was specific to the Cer-induced model. Neutrophil infiltration did not affect the increase in SHP-1 protein, but favoured the return of SHP-2 protein to control levels, as indicated when rats were rendered neutropenic by the administration of vinblastine sulfate. Inhibition of JNK and ERK1/2 with SP600125 pre-treatment further increased the expression of both SHP-1 and SHP-2 proteins in the early phase of Cer-induced AP, while the inhibition of type IV phosphodiesterase with rolipram only suppressed the increase in SHP-2 protein expression during the same phase. The results show that AP is associated with increases in the expression of SHP-1 and SHP-2 and changes in the dynamics of SHP-2 subcellular distribution in the early phase of Cer-induced AP. Finally, both JNK and ERK1/2 and intracellular cAMP levels are able to modulate the expression of these PTPs.

Bile and pancreatic juice exclusion activates acinar stress kinases and exacerbates gallstone pancreatitis.

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Bile and pancreatic juice exclusion from gut activates acinar stress kinases and exacerbates gallstone pancreatitis as evidenced by the ameliorating effects of replacement therapy in an experimental model of duct ligation-induced acute pancreatitis. In the early stages of gallstone pancreatitis, bile-pancreatic juice cannot enter the gut. Enteral exclusion worsens pancreatitis by causing feedback hyperstimulation of the exocrine pancreas that activates acinar cell stress kinases. Investigations using a unique surgical model, the Donor Rat Model, showed that duodenal replacement of bile-pancreatic juice in rats with duct ligation attenuates pancreatic stress kinase activation, reduces pancreatic cytokine production, and ameliorates pancreatic morphologic changes. These findings suggest that exclusion-induced acinar hyperstimulation, in the presence of duct obstruction, exacerbates acute pancreatitis via stress kinase activation. Although acinar hyperstimulation has often been implicated in the pathogenesis of acute pancreatitis, the lack of supporting evidence remains a conspicuous void. The proposed hypothesis draws on fresh evidence to present a new paradigm that reexamines the role of exocrine pancreatic hyperstimulation in gallstone pancreatitis pathogenesis.

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Acute pancreatitis severity is exacerbated by intestinal ischemia-reperfusion conditioned mesenteric lymph.


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To determine the effect of intestinal ischemia-reperfusion (IIR) on acute pancreatitis (AP) and the role of mesenteric lymph. Intestinal ischemia is an early feature of AP and is related to the severity of disease. It is not known whether this contributes to the severity of AP or is a consequence. Two experiments are reported here using intravital microscopy...
and a rodent model of mild acute pancreatitis (intraductal 2.5% sodium taurocholate). In the first, rats had an episode of IIR during AP that was produced by temporary occlusion of the superior mesenteric artery (30 min or 3x10 min) followed by 2 h reperfusion. In a second study rats with AP had an intravenous infusion of mesenteric lymph collected from donor rats that had been subjected to IIR. In both experiments the pancreatic erythrocyte velocity (EV), functional capillary density (FCD), leukocyte adherence (LA), histology and edema index were measured. The addition of IIR to AP caused a decline in the pancreatic microcirculation greater than that of AP alone (EV 42% of baseline vs. 73% of baseline AP alone, FCD 43% vs. 72%, LA 7 fold increase vs. 4 fold increase). This caused an increased severity of AP as evidenced by 1.4-1.8 fold increase of pancreatic edema index and histologic injury respectively. A very similar exacerbation of microvascular failure and increased pancreatitis severity was then demonstrated by the intravenous infusion of IIR conditioned mesenteric lymph from donor animals. Unidentified factors released into the mesenteric lymph following IIR injury are capable of exacerbating AP. This highlights an important role for the intestine in the pathophysiology of AP pathogenesis and identifies mesenteric lymph as a potential therapeutic target.


Activation of Wnt signalling in stroma from pancreatic cancer identified by gene expression profiling.


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Pancreatic ductal adenocarcinoma is characterized by an abundant desmoplastic stroma. Interactions between cancer and stromal cells play a critical role in tumour invasion, metastasis and chemoresistance. Therefore, the authors hypothesised that gene expression profile of the stromal components of pancreatic carcinoma is different from chronic pancreatitis and reflects the interaction with the tumour. The authors investigated the gene expression of eleven stromal tissues from pancreatic ductal adenocarcinoma, nine from chronic pancreatitis and cell lines of stromal origin using the Affymetrix U133 GeneChip set. The tissue samples were microdissected, the RNA was extracted, amplified, and labelled using a repetitive in vitro transcription protocol. Differentially expressed genes were identified and validated using quantitative RT-PCR and immunohistochemistry. The authors found 255 genes to be over-expressed and 61 genes to be under-expressed within the stroma of pancreatic carcinoma compared to the stroma of chronic pancreatitis. Analysis of the involved signal transduction pathways revealed a number of genes associated with the Wnt pathway of which the differential expression of SFRP1 and WNT5a was confirmed using immunohistochemistry. Moreover, the authors could demonstrate that WNT5a expression was induced in fibroblasts during co-cultivation with a pancreatic carcinoma cell line. The identified differences in the expression profile of stroma cells derived from tumour compared to cells of inflammatory origin suggest a specific response of the tissue surrounding malignant cells. The over-expression of WNT5a, a gene involved in the non canonical Wnt signalling and chondrocyte development might contribute to the strong desmoplastic reaction seen in pancreatic cancer.


A prospective crossover study comparing secretin-stimulated endoscopic and Dreiling tube pancreatic function testing in patients evaluated for chronic pancreatitis.

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Direct pancreatic function tests (PFT) are conventionally performed with use of double-lumen "Dreiling" collection tubes. The authors have developed an endoscopic collection method (ePFT) that eases the performance of these tests. The aim was to compare the bicarbonate results obtained from the secretin ePFT and Dreiling PFT methods in patients evaluated for chronic pancreatitis. A prospective crossover design was used to compare the PFT methods. Twenty-four patients undergoing an evaluation for chronic pancreatitis underwent the secretin-stimulated ePFT and Dreiling PFT methods on separate days. Duodenal fluid bicarbonate concentrations and estimated bicarbonate outputs were compared. The mean difference in peak bicarbonate concentration (Dreiling PFT minus ePFT) was 7 mEq/L (SD 20) and not statistically significant (P=0.11). A good correlation in peak bicarbonate concentrations ($r=0.74$, $95\%$ CI, $0.48-0.88$) and estimated bicarbonate output ($r=0.78$, $95\%$ CI, $0.54-0.90$) was observed between the two PFT methods. The sensitivities and specificities of the secretin ePFT and Dreiling PFT could not be compared because of the lack of a histologic gold standard. The secretin ePFT yields results similar to those of the Dreiling PFT in patients evaluated for chronic pancreatitis.

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Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm?


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Benign biliary strictures (BBS) are usually managed with plastic stents, whereas placement of uncovered metallic stents has been associated with failure related to mucosal hyperplasia. The authors analyzed the efficacy and safety of temporary placement of a covered self-expanding metal stent (CSEMS) in BBS. Patients with BBS received temporary placement of CSEMSs until adequate drainage was achieved; confirmed by resolution of symptoms, normalization of liver function tests, and imaging. Seventy-nine patients with BBS secondary to chronic pancreatitis (32), calculi (24), liver transplant (16), postoperative biliary repair (3), autoimmune pancreatitis (3), and primary sclerosing cholangitis (1). Intervention: ERCP with temporary CSEMS placement. Removal of CSEMSs was performed with a snare or a rat-tooth forceps. Main outcome measurements: End points were efficacy, morbidity, and clinical response. CSEMSs were removed from 65 patients. Resolution of the BBS was confirmed in 59 of 65 patients (90\%) after a median follow-up of 12 months after removal (range 3-26 months). If patients who were lost to follow-up, developed cancer, or expired were considered failures, then an intent-to-treat global success rate of 59 of 79 (75\%) was obtained. Complications associated with placement included 3 post-ERCP pancreatitis (4\%), 1 post sphincterotomy bleed (1\%), and 2 pain that required CSEMS removal (2\%). In 11 patients (14\%), the CSEMS migrated. In 1 patient, CSEMS removal was complicated by a bile leak that was successfully managed with plastic stents. Temporary CSEMS placement in patients with BBS offers a potential alternative to surgery.


The clinical impact and cost implication of endoscopic ultrasound on use of endoscopic retrograde cholangiopancreatography in a Canadian university hospital.

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Endoscopic ultrasound (EUS) is a safe alternative to endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic biliary imaging in choledocholithiasis. Evidence linking a decline in diagnostic ERCP with the introduction of EUS in clinical practice is limited. The authors assess the clinical impact and cost implications of a new EUS program on diagnostic ERCP at a tertiary referral centre. A retrospective review was performed of data collected during the first year of EUS at the University of Alberta Hospital (Edmonton, Alberta). Patients were referred for ERCP because of suspicion of choledocholithiasis based on clinical, biochemical and/or radiological parameters. If they were assessed to have an intermediate probability of choledocholithiasis, EUS was performed first. ERCP was performed if EUS suggested choledocholithiasis, whereas patients were clinically followed for six months if their EUS was normal. Cost data were assessed from a third-party payer perspective, and cost savings were expressed in terms of ERCP procedures avoided. Over 12 months, 90 patients (63 female, mean age 58 years) underwent EUS for suspected biliary tract abnormalities. EUS suggested choledocholithiasis in 20 patients (22%), and this was confirmed by ERCP in 17 of the 20 patients. EUS was normal in 69 patients, and none underwent a subsequent ERCP during a six-month follow-up period. One patient had pancreatic cancer and did not undergo ERCP. The sensitivity and specificity of EUS for choledocholithiasis were 100% and 96%, respectively. A total of 440 ERCP procedures were performed over the same 12-month period, suggesting that EUS resulted in a 14% reduction in ERCP procedures (70 of 510). There were no complications of EUS. The cost of 90 EUS procedures was $42,840, compared with $108,854 for 70 ERCP procedures. The cost savings for the first year were $66,014. EUS appears to be accurate, safe and cost effective in diagnostic biliary imaging for suspected choledocholithiasis. The impact of EUS is the avoidance of ERCP in selected cases, thereby preventing the risk of complications. Diagnostic ERCP should not be performed in centres and regions with physicians trained in EUS.

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Inducing apoptosis and enhancing chemosensitivity to gemcitabine via RNA interference targeting Mcl-1 gene in pancreatic carcinoma cell.


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Resistance to chemotherapy is a major cause of treatment failure and poor prognosis in pancreatic carcinoma. Myeloid cell leukemia-1 (Mcl-1) is highly up-regulated in pancreatic carcinoma and is associated with the anti-apoptosis and the resistance to chemotherapy drugs. Suppression of Mcl-1 would be an approach to induce apoptosis and enhance the chemosensitivity. In this study, three pancreatic cancer cell lines (PANC-1, BxPC-3 and SW1900) stably expressing shRNAs targeting Mcl-1 gene were established and gene expression inhibition was assessed by Real-Time QPCR and Western blotting. The effects of Mcl-1 downregulation mediated by RNAi were explored in vitro and in vivo. The authors showed that the specific down-regulation of Mcl-1 strikingly inhibited cell growth, colony formation, cell cycle arrest and induced apoptosis in pancreatic cancer cells in vitro, and markedly decreased the tumorigenicity in a mouse xenograft model. Moreover, knockdown of Mcl-1 significantly increased the chemosensitivity to gemcitabine in pancreatic carcinoma cells. These data suggests that the specific downregulation of Mcl-1 by RNAi is a promising approach to induce apoptosis and enhance the chemosensitivity for pancreatic carcinoma gene therapy.
Functional MRI evaluation of tumor response in patients with neuroendocrine hepatic metastasis treated with transcatheter arterial chemoembolization.

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The purpose of this study was to evaluate contrast-enhanced and diffusion-weighted MRI changes in neuroendocrine tumors treated with transcatheter arterial chemoembolization (TACE). Sixty-six targeted lesions in 26 patients (18 men, eight women; mean age, 57 years) with hepatic metastasis of neuroendocrine tumors treated with TACE were retrospectively analyzed. MRI studies were performed before and after TACE. Imaging features included tumor size, percentage of enhancement in the arterial and portal venous phases, and diffusion-weighted imaging apparent diffusion coefficients (ADCs) of the tumor, liver, and spleen. Tumor response to treatment was recorded according to World Health Organization criteria and Response Evaluation Criteria in Solid Tumors. Liver function tests were performed, and clinical performance was assessed before and after treatment. Statistical analysis included paired Student's t tests and Kaplan-Meier survival curves. Mean tumor size and percentage enhancement in the arterial and portal venous phases decreased significantly after treatment (P<0.001). The tumor ADC increased from 1.51x10^{-3} mm^2/s before treatment to 1.79x10^{-3} mm^2/s after treatment (P<0.001), but the ADCs for the liver and spleen remained unchanged. Despite the change in tumor size, no patient in this cohort achieved complete response according to World Health Organization criteria and Response Evaluation Criteria in Solid Tumors. Partial response was achieved in only 27% and 23% of the patients according to the respective criteria. Results of liver function tests and performance status also remained unchanged. The mean survival period for all patients was 78 months. Contrast-enhanced and diffusion-weighted imaging showed significant changes after TACE of neuroendocrine tumors and can be used to assess response of targeted tumors.