PANCREAS ALERTS

Gastrointest Endosc 2011; 73:980-6.
(PMID: 21521566)

Acute pancreatitis after removal of retained prophylactic pancreatic stents.

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Prophylactic pancreatic stents (PPSs) are used to decrease the risk of post-ERCP pancreatitis (PEP) in high-risk patients. The risk associated with PPS removal is unknown. The authors aimed to describe the rate of PEP in patients undergoing PPS removal without pancreatogram or other manipulation of the major or minor papilla in a retrospective, cohort study carried out in a tertiary care academic center. This study involved 230 patients undergoing removal of PPSs from 1997 to 2010. Acute pancreatitis occurred after PPS removal in 7 of 230 (3.0%) cases. PEP was graded as mild, moderate, and severe in 2, 5, and 0 cases, respectively. Statistically significant risk factors of PEP after PPS removal include use of a 5F stent (P=0.001), use of a stent with an internal flange (P<0.01), and occurrence of PEP after the initial ERCP (P<0.01). Longer duration of stent within the pancreatic duct before removal was of borderline significance (P=0.06). Patient age; sex; indication for initial procedure; the presence of pancreas divisum, ansa loop, or chronic pancreatitis; and history of pancreatic or biliary sphincterotomy or orifice dilation were not significant risk factors for pancreatitis after PPS removal. Removal of retained PPSs may cause mild or moderate acute pancreatitis. This risk of acute pancreatitis may diminish the overall efficacy of PPS use by delaying the occurrence of PEP rather than eliminating it. This implies that PPSs should be used only in patients at high risk for PEP.

Postgrad Med J 2011; 87:379-81.
(PMID: 21515873)

Impact of a care pathway in acute pancreatitis.

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Previous studies have shown that accurate process of care predicts quality of care. Few examples currently exist for process of care for the acute surgical patient. A recent region wide audit had identified good outcomes for patients with acute pancreatitis at the authors' institution but aspects of care that could be improved. For this re-audit, a simple written care pathway for the management of those presenting with acute pancreatitis was introduced in the authors' institution from February to July 2009. The audit standards were set against the British Society of Gastroenterology (BSG) guidelines for management of acute pancreatitis and were compared with the previous region wide audit. Marked improvements were noted in the rates of abdominal imaging achieved within 24 h of diagnosis (35.2% *vs*. 47.7%), severity stratification within 48 h of diagnosis (28.7% *vs*. 75.0%), critical care admission for those classified as severe (39.3% *vs*. 63.6%) and definitive treatment during index admission (22.2% *vs*. 38.5%). Survival rates were 100% for this audit cycle and 95% for all patients within the region wide audit. Despite these improvements, care still does not reach the standards set out by BSG. In conclusion, predefined processes of care may help to recognise those developing or likely to develop severe pancreatitis, ensure accurate documentation of severity, expedite critical care review and/or admission, and help to encourage the timely management of those with a treatable underlying cause of their pancreatitis.

Inflamm Res 2011; Apr 21.
(PMID: 21509626)

Potential role of NADPH oxidase-mediated activation of Jak2/Stat3 and mitogen-activated protein kinases and expression of TGF-beta1 in the pathophysiology of acute pancreatitis.

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NADPH oxidase is potentially associated with acute pancreatitis by producing reactive oxygen species (ROS). The authors investigated whether NADPH oxidase mediates the activation of Janus kinase (Jak)2/signal transducers and activators of transcription (Stat)3 and mitogen-activated protein kinases (MAPKs) to induce the expression of transforming growth factor-beta1 (TGF-beta1) in cerulein-stimulated pancreatic acinar cells. AR42J cells were treated with an NADPH oxidase inhibitor diphenyleneiodonium (DPI) or a Jak2 inhibitor AG490. Other cells were transfected with antisense or sense oligonucleotides (AS or S ODNs) for NADPH oxidase subunit p22(phox) or p47(phox). TGF-beta1 was determined

by enzyme-linked immonosorbent assay. STAT3-DNA binding activity was measured by electrophoretic mobility shift assay. Levels of MAPKs as well as total and phospho-specific forms of Jak1/Stat3 were assessed by Western blot analysis. Cerulein induced increases in TGF-beta1, Stat3-DNA binding activity and the activation of MAPKs in AR42J cells. AG490 suppressed these cerulein-induced changes, similar to inhibition by DPI. Cerulein-induced activation of Jak2/Stat3 and increases in MAPKs and TGF-beta1 levels were inhibited in the cells transfected with AS ODN for p22(phox) and p47(phox) compared to S ODN controls. In conclusion, inhibition of NADPH oxidase may be beneficial for prevention and treatment of pancreatitis by suppressing Jak2/Stat3 and MAPKs and expression of TGF-beta1 in pancreatic acinar cells.

Semin Respir Crit Care Med 2011; 32:174-80.
(PMID: 21506053)

Rational use of antimicrobials in patients with severe acute pancreatitis.

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Infectious complications in severe acute pancreatitis are associated with considerable morbidity and mortality. The course of the disease is often protracted, and patients often stay in the hospital for several weeks. Diagnosis of infected pancreatic necrosis is difficult, and the treatment consists of source control and antibiotic treatment. Antibiotic use should be rational in terms of a rational indication, a rational spectrum, and a rational duration. Prophylactic antibiotics are not effective in reducing the incidence of (peri)-pancreatic infection in patients with severe disease (or even documented necrotizing pancreatitis). The only rational indication for antibiotics is documented infection. The spectrum of empirical antibiotics should include both aerobic and anaerobic gram-negative and gram-positive microorganisms. Also, fungal infections are often present in these patients, and antifungal coverage or even prophylaxis should be considered, especially if multiple risk factors for invasive candidiasis are present. Although initiation of antibiotics may be a difficult decision, stopping antibiotic therapy often proves to be even more difficult. Currently, no tools are available to guide antimicrobial treatment. Antibiotic use is only effective if proper source control has been established.

Gastrointest Endosc 2011; 73:987-93.
(PMID: 21521567)

A prospective evaluation of fatty pancreas by using EUS.

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Fatty liver is associated with obesity, diabetes, hyperlipidemia, and the metabolic syndrome. The pathophysiology of fatty pancreas is poorly understood, but it may be closely related to fatty liver. The aim of this study was to determine the prevalence of fatty pancreas and risk factors associated with its development. This is a prospective, single center study carried out in a tertiary-care academic medical center. The study involved 250 consecutive patients referred for EUS examination. All patients undergoing EUS were prospectively identified. Information regarding demographics, tobacco use, alcohol use, blood test results, and comorbidities were collected before EUS. Pancreatic echogenicity was graded in comparison to the spleen at the time of EUS by using an a priori specified grading scheme. The authors evaluated the prevalence of fatty pancreas and factors associated with its development. During the study period, 250 consecutive patients were prospectively enrolled. The prevalence of fatty pancreas was 27.8% (95% CI, 22.1-34.1%). Fatty liver was seen in 22.6% of patients. Factors associated with fatty pancreas on univariate analysis were increasing body mass index (BMI) (P=0.004), fatty liver (P<0.0001), hyperlipidemia (P=0.04), and the metabolic syndrome (odds ratio [OR] 3.13, P=0.004). The presence of any metabolic syndrome components, that is, BMI equal to, or greater than, 30 kg/m^2, hyperlipidemia, diabetes, or hypertension, increased the prevalence of fatty pancreas by 37% (OR 1.37, P=0.01). Factors independently associated with fatty pancreas on multivariate analysis were increasing BMI (OR 1.05, P=0.03) and fatty liver (OR 3.61, P<0.001). The authors found no association between fatty pancreas and chronic pancreatitis or adenocarcinoma of the pancreas. In conclusion, the authors found a strong association between fatty pancreas and the metabolic syndrome.

Hum Mutat 2011; Apr 21.
(PMID: 21520337)

Common CFTR haplotypes and susceptibility to chronic pancreatitis and congenital bilateral absence of the vas deferens.

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CFTR mutations enhance susceptibility for idiopathic chronic pancreatitis (ICP) and congenital bilateral

absence of the vas deferens (CBAVD), however, it is unknown why CFTR heterozygotes are at increased disease risk. The authors recently showed that common CFTR variants are associated with aberrantly spliced transcripts. Here, the authors genotyped for common CFTR variants and tested for associations in two ICP (ICP-A: 126 patients, 319 controls; ICP-B: 666 patients, 1,181 controls) and a CBAVD population (305 patients, 319 controls). Haplotype H10 (TG11-T7-470V) conferred protection (ICP-A: OR 0.19, P<0.0001; ICP-B: OR 0.78, P=0.06; CBAVD: OR 0.08, P<0.001), while haplotype H3 (TG10-T7-470M) increased disease risk (ICP-A: OR 8.34, P=0.003; ICP-B: OR 1.88, P=0.007; CBAVD: OR 5.67, P=0.01). The risk of heterozygous CFTR mutations carriers for ICP (OR 2.44, P<0.001) and CBAVD (OR 14.73, P<0.001) was fully abrogated by the H10/H10 genotype. Similarly, ICP risk of heterozygous p.Asn34Ser SPINK1 mutation carriers (OR 10.34, P<0.001) was compensated by H10/H10. Thus, common CFTR haplotypes modulate ICP and CBAVD susceptibility alone and in heterozygous CFTR and p.Asn34Ser mutation carriers. Determination of these haplotypes helps to stratify carriers into high- and low-risk subjects, providing helpful information for genetic counselling.

Clin Cancer Res 2011; Apr 28.
(PMID: 21527562)

Treatment of advanced pancreatic carcinoma with 90Y-clivatuzumab tetraxetan: A Phase I single-dose escalation trial.

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Humanized antibody hPAM4 specifically binds a mucin glycoprotein expressed in pancreatic adenocarcinomas. This phase I study evaluated a single dose of ^{90}Y-clivatuzumab tetraxetan (^{90}Y-labeled hPAM4) in patients with advanced pancreatic cancer. Twenty-one patients (4 stage III, 17 stage IV) received ^{111}In-hPAM4 for imaging and serum sampling before ^{90}Y-hPAM4. Study procedures evaluated adverse events, safety laboratories, CT scans, biomarkers, pharmacokinetics, radiation dosimetry, and immunogenicity (HAHA). ^{111}In-hPAM4 showed normal biodistribution with radiation dose estimates to red marrow and solid organs acceptable for radioimmunotherapy and with tumor targeting in 12 patients. One patient withdrew before ^{90}Y-hPAM4; otherwise, 20 patients received ^{90}Y doses of 15 (n=7), 20 (n=9), and 25 mCi/m^2 (n=4). Treatment was well tolerated; the only significant drug-related toxicities were (NCI CTC v.3) grade 3-4 neutropenia and thrombocytopenia increasing with ^{90}Y dose. There were no bleeding events or serious infections, and most cytopenias recovered to grade 1 within 12 weeks. Three patients at 25 mCi/m^2 encountered dose-limiting toxicity with grade 4 cytopenias more than 7 days, establishing 20 mCi/m^2 as the maximal tolerated ^{90}Y dose. Two patients developed HAHA of uncertain clinical significance. Most patients progressed rapidly and with CA 19-9 levels increasing within one month of therapy, but 7 remained progression-free by CT for 1.5-5.6 months, including 3 achieving transient partial responses (32-52% tumor diameter shrinkage). In conclusion, ^{90}Y-clivatuzumab tetraxetan was well tolerated with manageable hematological toxicity at the maximal tolerated ^{90}Y dose, and is a potential new therapeutic for advanced pancreatic cancer.

Invest New Drugs 2011; Apr 28.
(PMID: 21526355)

A phase II study of the halichondrin B analog eribulin mesylate in gemcitabine refractory advanced pancreatic cancer.

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Eribulin mesylate is a halichondrin B analog that inhibits microtubule dynamics. Pre-clinical studies have suggested anti-tumor activity in pancreatic cancer. This phase II study of eribulin in patients with advanced pancreatic cancer previously treated with gemcitabine was conducted by the Princess Margaret Hospital Phase II consortium. Eligibility criteria included locally advanced or metastatic pancreatic adenocarcinoma and previous treatment with gemcitabine. The study was a single arm phase II trial using a Simon 2-stage design. The primary endpoint was response rate, secondary endpoints included time to progression and overall survival. Fifteen patients were enrolled, 14 received treatment, and 12 were evaluable for response. The median age was 61 years, and the majority of patients were ECOG performance status 1. Grade 3 or greater adverse events included neutropenia (29%), fatigue (14%), peripheral neuropathy (7%) and thrombosis (7%). There were no complete or partial responses and therefore the study was closed after the first stage. The best response was stable disease in 5/12 (42%) of patients. Of these five patients, three had stable disease for 9 months or greater. Median time to progression was 1.4 months, and median overall survival was 6.1 months. Eribulin was well tolerated but did not result in any objective responses in gemcitabine refractory pancreatic cancer. However, several patients had prolonged stable disease, suggesting that further studies of eribulin in pancreatic cancer may be warranted.

Cancer Chemother Pharmacol 2011; Apr 28.
(PMID: 21526352)

Erufosine, an alkylphosphocholine, with differential toxicity to human cancer cells and bone marrow cells.

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The authors aimed to investigate the activity and myeloprotective properties of erufosine, a novel alkylphosphocholine (APC), on human malignant cells and normal bone marrow cells. Human or mouse bone marrow cells were exposed to erufosine, miltefosine, perifosine, or edelfosine in CFU-GM assays. Human MDA-MB-231 breast carcinoma, Panc-1 pancreatic carcinoma, and RPMI8226 multiple myeloma cells were exposed to erufosine in colony formation assays. Colony formation of Panc-1 tumor cells and mouse bone marrow cells *ex vivo* were quantified following intravenous administration of erufosine to tumor-bearing mice. Western blotting methods were applied to human U87 glioblastoma cells exposed to erufosine to investigate Akt inhibition. Erufosine was less toxic to human and mouse bone marrow cells than perifosine, miltefosine, and edelfosine and was equally toxic to human and mouse CFU-GM. The human cancer cells MDA-MB-231 breast, Panc-1 pancreatic, and RPMI8226 MM cells were more sensitive to erufosine in a colony formation assay than were human bone marrow cells generating an approximately tenfold differential in IC(90) values. Erufosine injected intravenously significantly reduced Panc-1 tumor cell colony formation *ex vivo* but not mouse bone marrow CFU-GM. Erufosine inhibited Akt phosphorylation in human U87 glioblastoma cells. Erufosine offers potential as a novel therapeutic for cancer with a reduced toxicity profile to bone marrow cells compared with other agents in this class. Human cancer cells were more sensitive to erufosine than human or mouse bone marrow cells indicating a favorable therapeutic window for erufosine.

Clin Endocrinol (Oxf) 2011; 74:593-8.
(PMID: 21470282)

Glucagonoma and the glucagonoma syndrome - cumulative experience with an elusive endocrine tumour.

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Glucagonoma is a pancreatic neuroendocrine tumour that arises from alpha cells in the pancreas and is often accompanied by a characteristic clinical syndrome. In this report, the authors present the cumulative experience and clinical characteristics of six patients diagnosed with glucagonoma and the glucagonoma syndrome and treated at the authors' centre during the past 25 years. Although the course of the disease was variable, some features were similar. The median age at diagnosis was 53.5 years; the median time from onset of symptoms to diagnosis was 39 months. Presenting symptoms were as follows: weight loss 5/6 (83%), necrotizing migratory erythema (NME) 5/6 (83%), diabetes mellitus 4/6 (66%) and diarrhoea, weakness and thrombosis 2/6 (33%). Plasma glucagon was elevated in all patients upon diagnosis (range 200-10.000 pm; N<50). Skin biopsy was diagnostic only in 1/6 specimens obtained, even after revision. Metastatic disease developed in all patients; 4/6 initially presented with hepatic metastasis. All patient symptoms responded to somatostatin analogue therapy. In 4/6, the NME responded to amino acid solutions. Other modes of therapy were as follows: surgery in 3/6 patients, peptide receptor radioligand therapy with ^{90}Y-DOTATOC (PRRT) in 3/6 patients (two responses) and chemotherapy in three patients (two responded). Four out of six patients died of the disease, and median survival time was 6.25 years (range 2-11 years) from diagnosis and 8 years (range 8-16 years) from initial symptoms. Five-year survival was 66%. These data indicate that somatostatin analogues and an aggressive surgical approach offer symptom relief and tumour control. Among other available treatment modalities, PRRT seems to hold the most promise.

ACS Nano 2011; 5:2770-8.
(PMID: 21452804)

Influence of hydrophobicity on the surface-catalyzed assembly of the islet amyloid polypeptide.

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The islet amyloid polypeptide (IAPP) is a hormonal factor secreted by the beta-cells in the pancreas. Aggregation of misfolded IAPP molecules and subsequent assembly of amyloid nanofibrils are critical for the development of type 2 diabetes mellitus. In the physiological environment, amyloid aggregation is affected by the presence of interfaces such as cell membranes. The physicochemical properties of the interface dictates the interaction of the peptide with the surface, i.e., electrostatic and hydrophobic interactions on hydrophilic and hydrophobic surfaces, respectively.

The authors have studied the influence of hydrophobicity on the surface-catalyzed assembly of IAPP on ultrasmooth hydrocarbon films grown on ion-beam-modified mica surfaces by atomic force microscopy. The contact angle theta of these surfaces can be tuned continuously in the range from less, or equal to, 20° to about 90° by aging the samples without significant changes of the chemical composition or the topography of the surface. On hydrophilic surfaces with a theta of about 20°, electrostatic interactions induce the assembly of IAPP nanofibrils, whereas aggregation of large (about 2.6 nm) oligomers is observed at hydrophobic surfaces with a theta of about 90°. At intermediate contact angles, the interplay between electrostatic and hydrophobic substrate interactions dictates the pathway of aggregation with fibrillation getting continuously delayed when the contact angle is increased. In addition, the morphology of the formed protofibrils and mature fibrils at intermediate contact angles differs from those observed at more hydrophilic surfaces. These results might contribute to the understanding of the surface-catalyzed assembly of different amyloid aggregates and may also have implications for the technologically relevant controlled synthesis of amyloid nanofibrils of desired morphology.

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