The No Endosonographic Detection of Tumor (NEST) Study: a case series of pancreatic cancers missed on endoscopic ultrasonography.


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The purpose of this study was to identify possible associated factors that may have contributed to failure to detect a pancreatic neoplasm during endoscopic ultrasound examinations by experienced endosonographers. A multicenter retrospective study was organized, and 20 cases of pancreatic neoplasms missed by nine experienced endosonographers were identified. Careful analysis of each case was carried out to identify the factors that might have led to the missed diagnosis on endoscopic ultrasound.

Twelve patients with a missed pancreatic neoplasm had endoscopic ultrasound features of chronic pancreatitis. Other factors that might have increased the likelihood of a false-negative endoscopic ultrasound examination included a diffusely infiltrating carcinoma (n=3), a prominent ventral/dorsal split (n=2), and a recent episode (within the previous 4 weeks) of acute pancreatitis (n=1). Five patients with a negative initial endoscopic ultrasound underwent a follow-up endoscopic ultrasound after 2-3 months, with a pancreatic mass being found in all cases. Three patients had a diffusely infiltrating pancreatic adenocarcinoma.

The authors concluded that endoscopic ultrasound is not a foolproof method of detecting a pancreatic neoplasm. Possible associated factors that may increase the likelihood of a false-negative endoscopic ultrasound examination include chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split and a recent episode (less than 4 weeks) of acute pancreatitis. If there is a high clinical suspicion of pancreatic neoplasm, if endoscopic ultrasound and other imaging methods are negative, and if the patient does not undergo surgery, this study suggests that a repeat endoscopic ultrasound after 2-3 months may be useful for detecting an occult pancreatic neoplasm.

Bloodstream infections after surgery for severe acute pancreatitis.

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To analyze the incidence and outcome of bloodstream infections in patients operated on for severe acute pancreatitis and to identify the source and associated risk factors. The authors retrospectively (1995-2001) analyzed 45 patients treated surgically for severe acute pancreatitis. Demographic characteristics, data on surgical and medical treatment and disease severity, the occurrence of bloodstream infections, microbiological data concerning the bloodstream infections and other infectious processes, the incidence of organ failure, and data on surgical and infectious complications were recorded. Fifteen episodes of bloodstream infection were found in 7 of 45 patients (15%), with 18 organisms involved. In all but 1 episode, the source of the bloodstream infection was pancreatic necrosis. Most of the organisms were gram positive (n=11); the others were gram negative (n=6) or fungi (n=1). Mortality was not statistically different in patients with
a bloodstream infection (57% vs. 35%). Multivariate analysis demonstrated that only the length of intensive care unit stay was associated with the occurrence of bloodstream infections (OR: 1.05; 95% CI: 1.02-1.09; P<0.01).

A bloodstream infection is not a rare finding after surgery for severe acute pancreatitis, especially in patients with a prolonged intensive care unit stay. The source is the infected necrosis in most of bloodstream infection episodes.


European survey of surgical strategies for the management of severe acute pancreatitis.

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This study is the first pan-European survey of surgical strategies for the management of severe acute pancreatitis. A questionnaire survey was undertaken of the 866 members of the European chapter of the International Hepato-Pancreato-Biliary Association. There were 329 replies from practicing clinicians giving a response rate of 38%. The modal case volume was 11-20 patients per year. Severity stratification was used by 324 (99%) respondents with the Ranson score being the most popular. Antibiotic prophylaxis was utilized by 239 (73%) with the median duration being 7 days (range 1-28). Fine needle aspiration of necrosis was undertaken by 174 (53%) and 131 would operate on a patient with a positive result. There was no consensus on optimum timing of surgery. The results of this first pan-European questionnaire demonstrate wide variations in care. Overall, the findings provide a unique insight into the current management of severe acute pancreatitis in Europe.


Different CFTR mutational spectrum in alcoholic and idiopathic chronic pancreatitis?


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Cystic fibrosis transmembrane conductance regulator (CFTR) mutations are responsible for cystic fibrosis and have been postulated as a predisposing risk factor to chronic pancreatitis, but controversial results demand additional support. Therefore, the role of the CFTR gene was investigated in a cohort of 68 chronic pancreatitis patients. The authors performed the CFTR gene analysis using 2 screening techniques. Fragments showing abnormal migration patterns were characterized by sequencing. Patients were classified in alcoholic (n=37) and idiopathic (n=31) chronic pancreatitis. Clinical features of chronic pancreatitis and cystic fibrosis were evaluated. Sixteen mutations/variants were identified in 27 patients (40%), most of them (35%) presenting a single CFTR mutant gene. The 1716G/A variant showed the highest frequency accounting for 22% in idiopathic chronic pancreatitis and 5% in alcoholic chronic pancreatitis, in contrast with other more common mutations such as F508del found in 8% of alcoholic chronic pancreatitis and the 5T variant identified in 7% of patients. Acute pancreatitis, abdominal pain, tobacco, pancreatic calcifications, and pancreatic pseudocysts showed significant higher values in alcoholic chronic pancreatitis than idiopathic chronic pancreatitis patients. No significant differences were found between patients with and without CFTR mutations.
Apart from reinforcing previous findings these data highlight the increased susceptibility of CFTR heterozygous to developing chronic pancreatitis. Heterozygosity, combined with other factors, places these individuals at greater risk.


Exocrine pancreatic function after alcoholic or biliary acute pancreatitis.

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There have been various studies of exocrine pancreatic function after acute pancreatitis, but few have examined the relationship between this function and the etiology of the pancreatitis. The aim of this work was to study pancreatic function in patients who had had acute alcoholic or acute biliary pancreatitis.

Seventy-five patients who had had a single attack of acute pancreatitis were studied. The etiology was alcohol in 36 and cholelithiasis in 39. Pancreatic function was studied between 4 and 18 months after pancreatitis by duodenal intubation in 18 patients (8 alcohol, 10 lithiasis) and by the amino acid consumption test in the remaining 57 (28 alcohol, 29 lithiasis). For those who underwent amino acid consumption test, the test was repeated 1 year after the first examination.

Among the 36 patients with alcoholic pancreatitis, most had impaired pancreatic function at both duodenal intubation (8/8, 100%) and at amino acid consumption test (22/28, 78.6%); at the second test, the amino acid consumption test remained pathological (18/23, 82.1%). Of the 39 patients with biliary pancreatitis, only 4 of the 10 (40%) who underwent duodenal intubation and only 5 of the 29 (17.2%) who performed amino acid consumption test had pancreatic insufficiency; at the second test, only 4 of the 26 (15.4%) who repeated the amino acid consumption test were pathological. The differences in the frequency and degree of pancreatic insufficiency between patients with alcoholic and those with biliary pancreatitis were statistically significant.

The results show that after alcoholic acute pancreatitis, the pancreatic insufficiency was significantly more frequent and more severe than after biliary pancreatitis. These findings together with the fact that the insufficiency was also more persistent suggest that acute alcoholic pancreatitis may occur in a pancreas that already has chronic lesions.


Comprehensive analysis of matrix metalloproteinase and tissue inhibitor expression in pancreatic cancer: increased expression of matrix metalloproteinase-7 predicts poor survival.

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To enable the design of improved inhibitors of matrix metalloproteinases (MMPs) for the treatment of pancreatic cancer, the expression profiles of a range of MMPs and tissue inhibitors of MMPs (TIMPs) were determined.

Nine MMPs (MMPs 1-3, 7-9, 11, 12, and 14) and three TIMPs (TIMPs 1-3) were examined in up to 75 pancreatic ductal adenocarcinomas and 10 normal pancreata by immunohistochemistry. Eighteen additional pancreatic ductal adenocarcinomas and an additional eight normal pancreata were also analyzed by real-time reverse transcription-PCR and additionally for MMP-15.

There was increased expression by immunohistochemistry for MMPs 7, 8, 9, and 11 and TIMP-3 in pancreatic cancer compared with normal pancreas (P<0.0001, 0.04, 0.0009, 0.005, and 0.0001,
respectively). Real-time reverse transcription-PCR showed a significant increase in mRNA levels for MMP-11 in tumor tissue compared with normal pancreatic tissue (P=0.0005) and also significantly reduced levels of MMP-15 (P=0.0026). Univariate analysis revealed that survival was reduced by lymph node involvement (P=0.0007) and increased expression of MMP-7 (P=0.005) and (for the first time) MMP-11 (P=0.02) but not reduced by tumor grade, tumor diameter, positive resection margins, adjuvant treatment, or expression of the remaining MMPs and TIMPs. On multivariate analysis, only MMP-7 predicted shortened survival (P<0.05); however, increased MMP-11 expression was strongly associated with lymph node involvement (P=0.0073).

The authors propose that the principle specificity for effective inhibitors of MMPs in pancreatic cancer should be for MMP-7 with secondary specificity against MMP-11. Moreover, these studies indicate that MMP-7 expression is a powerful independent prognostic indicator and potentially of considerable clinical value.

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**Dietary advice for treatment of type 2 diabetes mellitus in adults.**


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While initial dietary management immediately after formal diagnosis is an 'accepted' cornerstone of treatment of type 2 diabetes mellitus, a formal and systematic overview of its efficacy and method of delivery is not currently available. Aim of this study was to assess the effect of type and frequency of different types of dietary advice to all adults with type 2 diabetes on weight, measures of diabetic control, morbidity, total mortality and quality of life.

The authors carried out a comprehensive search of The Cochrane Library (The Cochrane Library Issue 3, 2003), MEDLINE (1966 to October Week 1, 2003), EMBASE (1980 to Week 40, 2003), CINAHL (1982 to October Week 1, 2003), AMED (1985 to October 2003), bibliographies and contacted relevant experts. All randomised controlled trials, of six months or longer, in which dietary advice was the main intervention in adults with type 2 diabetes mellitus were selected. The lead investigator performed all data extraction and quality scoring with duplication being carried out by one of the other six investigators independently with discrepancies resolved by discussion and consensus. Authors were contacted for missing data. For continuous outcomes, endpoint data were preferred to change data. Thirty-six articles reporting a total of eighteen trials following 1,467 participants were included. Dietary approaches assessed in this review were low-fat/high-carbohydrate diets, high-fat/low-carbohydrate diets, low-calorie (1,000 kcal per day) and very-low-calorie (500 kcal per day) diets and modified fat diets. Two trials compared the American Diabetes Association exchange diet with a standard reduced fat diet and five studies assessed low-fat diets versus moderate fat or low-carbohydrate diets. Two studies assessed the effect of a very-low-calorie diet versus a low-calorie diet. Six studies compared dietary advice with dietary advice plus exercise and three other studies assessed dietary advice versus dietary advice plus behavioral approaches. The studies all measured weight and measures of glycemic control although not all studies reported these in the articles published. Other outcomes which were measured in these studies included mortality, blood pressure, serum cholesterol (including LDL and HDL cholesterol), serum triglycerides, maximal exercise capacity and compliance. The results suggest that adoption of regular exercise is a good way to promote better glycemic control in type 2 diabetic
patients, however all of these studies were at high risk of bias.

The reviewers concluded that there are no high quality data on the efficacy of the dietary treatment of type 2 diabetes, however the data available indicate that the adoption of exercise appears to improve glycated hemoglobin at six and twelve months in people with type 2 diabetes. There is an urgent need for well-designed studies which examine a range of interventions, at various points during follow-up, although there is a promising study currently underway.


Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus.


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In short acting insulin analogues the dissociation of hexamers is facilitated, achieving peak plasma concentrations about twice as high and within approximately half the time compared to regular human insulin. According to these properties this profile resembles the shape of non-diabetic patients more than that of regular human insulins. Despite this theoretical superiority of short acting insulin analogues over regular human insulin, the risk-benefit ratio of short acting insulin analogues in the treatment of diabetic patients is still unclear. The aim of this study was to assess the effect of treatment with short acting insulin analogues versus regular human insulin.

A highly sensitive search for randomised controlled trials combined with key terms for identifying studies on short acting insulin analogues versus regular human insulin was performed using the Cochrane Library (issue 1, 2003), MEDLINE and EMBASE. Date of last search was December 2003. The authors included randomized controlled trials with diabetic patients of all ages that compared short acting insulin analogues to regular human insulin. Intervention duration had to be at least 4 weeks. Trial selection, as well as evaluation of study quality, was done by two independent reviewers. The quality of reporting of each trial was assessed according to a modification of the quality criteria as specified by Schulz and Jadad. Altogether 7,933 participants took part in 42 randomized controlled studies. Most studies were of poor methodological quality. In patients with type 1 diabetes, the weighted mean difference (WMD) of HbA1c was estimated to be -0.1% (95% CI: -0.2% to -0.1%) in favor of insulin analogue, whereas in patients with type 2 diabetes the WMD was estimated to be 0.0% (95% CI: -0.1% to 0.1%). In subgroup analyses of different types of interventions in type 1 diabetic patients, the WMD in HbA1c was -0.2% (95% CI: -0.3% to -0.1%) in favor of insulin analogue in studies using continuous subcutaneous insulin injections whereas for conventional intensified insulin therapy studies the WMD in HbA1c was -0.1% (95% CI: -0.2% to -0.0%). The WMD of the overall mean hypoglycemic episodes per patient per month was -0.2 (95% CI: -1.2 to 0.9) and -0.2 (95% CI: -0.5 to 0.1) for analogues in comparison to regular insulin in patients with type 1 diabetes and type 2 diabetes, respectively. For studies in type 1 diabetic patients the incidence of severe hypoglycemia ranged from 0 to 247.3 (median 20.3) episodes per 100 person-years for insulin analogues and from 0 to 544 (median 37.2) for regular insulin, in type 2 the incidence ranged from 0 to 30.3 (median 0.6) episodes per 100 person-years for insulin analogues and from 0 to 50.4 (median 2.8) for regular insulin. No study was designed to investigate possible long term effects (e.g. mortality, diabetic complications), in particular in patients with diabetes related complications.

The reviewers concluded that this analysis suggests only a minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term
efficacy and safety data are available, a cautious response to the vigorous promotion of insulin analogues may be suggested. Due to fears of potentially carcinogenic and proliferative effects, most studies to date have excluded patients with advanced diabetic complications. For safety purposes, a long-term follow-up of large numbers of patients who use short acting insulin analogues is needed. Furthermore, well designed studies in pregnant women to determine the safety profile for both the mother and the unborn child are also needed.