Antibiotic prophylaxis in patients with severe acute pancreatitis.

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The prophylactic use of antibiotics in patients with severe acute pancreatitis remains contentious. The authors reviewed the current studies on antibiotic prophylaxis in patients with severe acute pancreatitis. All papers found by a Medline search were relevant to human trials of antibiotic prophylaxis in patients with severe acute pancreatitis. In the 1970s, three small randomized studies of prophylactic ampicillin in the treatment of acute pancreatitis showed no effect on mortality or morbidity, but the inclusion of patients at low risk for infection and the use of an ineffective antibiotic were insufficient to detect any differences. From 1993 to 2001, eight prospective clinical trials of antibiotic prophylaxis were conducted in patients with severe acute pancreatitis. Seven of the eight trials showed significant effect of the prophylaxis in prevention of pancreatic infections, and one showed significant improvement of clinical course documented by the Acute Physiology and Chronic Health Evaluation II scores. Only two trials did demonstrate the significance of the prophylaxis in lowering the mortality rate. Despite variations in drug agents, study size and patient selection, duration of treatment, and methodology (none of the studies was double-blinded), a meta-analysis showed the positive effect of antibiotics in reducing the mortality. The authors suggested that antibiotic prophylaxis with proven efficacy in necrotic pancreatic tissues should be given to all patients with acute necrotizing pancreatitis. In recent years, however, the first double-blind, placebo-controlled multicenter study from Germany detected no benefit of antibiotic prophylaxis with respect to the risk of developing infected pancreatic necrosis. The authors concluded that prophylactic antibiotics for severe acute pancreatitis is still a matter of discussion and further studies are required to provide adequate data to answer many questions and to define the role of antibiotic prophylaxis in patients with severe acute pancreatitis.
prescription for proton-pump inhibitors and/or amoxicillin, macrolides or tetracycline within 30, 31-180, or 181-365 days before hospitalization, or index date among controls, adjusted odds ratios were 8.3 (95% CI: 2.6-26.4), 2.7 (95% CI: 1.4-5.5), and 1.7 (95% CI: 0.6-4.8), respectively. In conclusion, metronidazole may increase the risk of acute pancreatitis. However, the risk seems mainly to increase when metronidazole is used in combination with other drugs used for Helicobacter pylori eradication.


99mTc-hexamethylpropylene amineoxime leukocyte scintigraphy in acute pancreatitis: an alternative to contrast-enhanced computed tomography?

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Contrast-enhanced computed tomography is the most efficient imaging technique for the diagnosis and staging of acute pancreatitis; its use, however, may be unfeasible in some patients as a consequence of the drawbacks of intravenous contrast material. The authors aimed to investigate the utility of labeled leukocyte scintigraphy as an alternative imaging technique to contrast-enhanced computed tomography for the staging of acute pancreatitis. Sixty-six patients with acute pancreatitis were prospectively studied. All patients underwent contrast-enhanced computed tomography and pancreatic labeled leukocyte scintigraphy using (99m)Tc-hexamethylpropylene amineoxime as leukocyte label within a time interval of 2 days, in the early phase of acute pancreatitis. In addition, all patients had their serum C-reactive protein concentration measured within 48-72 h after admission. Contrast-enhanced computed tomography images were analyzed for Balthazar's grade of pancreatitis and for the presence or absence of pancreatic necrosis. Scintigraphic activity of 3-4 h planar images was scored on a 0-2 scale in relation to physiological liver uptake. Labeled leukocyte scintigraphy score was significantly related (p < 0.001) to both components of contrast-enhanced computed tomography (grade of pancreatitis and pancreatic necrosis). Labeled leukocyte scintigraphy and serum C-reactive protein showed similar results for detecting the most severe pancreatic damage as showed by their respective receiver operating characteristic curves. Sensitivities and specificities of labeled leukocyte scintigraphy score of 2 were, respectively, 62% and 96% for the detection of grade D-E pancreatitis and 90% and 89% for the detection of pancreatic necrosis. Scintigraphic score of 2 increased the likelihood of grade D-E pancreatitis from 32% (pretest probability) to 87% (posttest probability) (likelihood ratio: 13.9) and that of pancreatic necrosis from 16% to 60% (likelihood ratio: 8.4). Results show that leukocytes are related to the severity of local pancreatic damage in acute pancreatitis. Thus, labeled leukocyte scintigraphy is a potential alternative technique to contrast-enhanced computed tomography for staging acute pancreatitis.


Clinical significance of increased lipase levels on admission to the ICU.

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The authors examined the incidence, risk factors, and sequelae associated with asymptomatic hyperlipasemia in the ICU. Two hundred forty-five adult critically ill patients admitted to an ICU for >72 h with a diagnosis other than pancreatitis were studied prospectively. Serum amylase and lipase were measured on ICU admission and every third
day until normalized. Clinical parameters including the incidence of ileus, the ability to tolerate enteral feeds, and the results of radiologic studies were also recorded. Hyperlipasemia was present in 40% of patients. Increased multiple-organ dysfunction scores, hypotension, anemia, mechanical ventilation, bacteremia, elevated liver function test results, and elevated creatinine and triglyceride levels were all associated with increased lipase levels. In multivariate analysis, hypotension, anemia, elevated serum bilirubin, and mechanical ventilation were independently associated with higher lipase levels. Although mortality was not different, ICU length of stay and the duration of mechanical ventilation were significantly greater in patients with increased lipase levels (p < 0.05). Fifty patients underwent imaging studies. Pancreatitis was confirmed in 11 patients. The mean peak lipase value was significantly increased in patients with a positive study finding as compared to those with negative findings (p < 0.01). Enteral feedings, when initiated, were tolerated in 94% of patients with increased lipase levels and 97% of patients with normal lipase levels. Elevated serum lipase levels are frequently encountered in critically ill patients. In the majority of these patients, enteral feedings are well tolerated and there are minimal clinical sequelae. Extremely high lipase levels may be associated with radiologic evidence of pancreatitis. Hypoperfusion and inflammatory processes associated with multiple-organ failure appear to be contribute to these increases.

Intraductal neoplasms of the pancreas are generally referred to as intraductal papillary mucin-producing neoplasms (IPMNs), according to the WHO classification system. Herein, the authors report that morphologic and immunohistochemical features of intraductal tubular carcinoma (ITC) are quite different from those of intraductal papillary mucinous carcinoma (IPMC). The authors analyzed histogenesis and differentiation of ITC by light microscopy and immunohistochemistry. Histologically, ITC was characterized as an intraductal nodular appearances with a monotonous tubular growth pattern without papillary projection. ITC showed de novo-like appearance without sequential progression usually observed in IPMC, suggesting that ITC is a homogeneous neoplasm. Cuboidal tumor cells in ITC resembled normal pancreatic duct epithelia, and the characteristic growth pattern of ITC replaced that of normal pancreatic duct epithelium. Immunohistochemically, ITC cells were positive for MUC-1 on the apical side of the cell membrane. In contrast to ITC cells, IPMC cells were negative for MUC-1, and ductal adenocarcinoma cells were strongly positive for MUC-1, as was the stroma around the cancer. The immunohistochemical staining pattern of DUPAN-2 resembled that of MUC-1. Interestingly, localization of MUC-1 and DUPAN-2 staining in ITC cells was similar to that in normal pancreatic ductules. ITC cells were negative for MUC-2 and MUC-5AC. In contrast, most IPMC cells were positive for MUC-2 and MUC-5AC. Based on histologic and immunohistochemical findings, the intraductal pancreatic neoplasm (IPN) can be classified into 2 groups: IPN with gastrointestinal differentiation and IPN with pancreatic duct differentiation. Present data indicated that ITC cells may arise directly from duct epithelia without progression and possessed pancreatic duct differentiation. On the basis of our data, we suggest that classification of pancreatic neoplasms in the WHO and The Armed Forces Institute of Pathology (AFIP) systems should be reconsidered.


Intraductal tubular neoplasms of the pancreas: histogenesis and differentiation.


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Clinical testing for multiple endocrine neoplasia type 1 in a DNA diagnostic laboratory.

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Based on results of diagnostic MEN1 testing, the authors have attempted to further define the mutational spectrum of the MEN1 gene and the clinical features most frequently associated with MEN1 mutations. Mutation testing was performed on blood samples by PCR amplification and sequencing of exons 2 to 10 of the MEN1 gene and the corresponding intron-exon junctions. Pedigree phenotypic information was obtained by written questionnaire. Among 288 presumably unrelated pedigrees, 73 independent mutations were found in 89 families. Five mutations were found in 2 pedigrees, and 4 mutations were seen in more than 2 pedigrees. There were 17 nonsense mutations (23.3%), 2 in-frame deletions (2.7%), 18 frameshift-deletion mutations (24.7%), 10 frameshift-insertion or -duplication mutations (13.7%), 13 splice-site mutations (17.8%), and 13 presumptive missense mutations (17.8%). Thirty-nine of 56 pedigrees with parathyroid and pancreatic islet neoplasia tested positive, compared with 4/24 and 8/32 pedigrees affected with hyperparathyroidism or hyperparathyroidism and pituitary tumors. MEN1 mutations were found in 6/20 sporadic patients, all of whom had both parathyroid and pancreatic neoplasms. Of 14 mutation-negative sporadic patients, 10 exhibited hyperparathyroidism and pituitary tumors without islet cell neoplasia. Somatic mosaicism was detected in 1 sporadic patient. Patients from pedigrees with hyperparathyroidism and pancreatic islet tumors are most likely to test positive for MEN1 mutations. Mutations are less often detected in patients from pedigrees with hyperparathyroidism alone or in combination with pituitary tumors without pancreatic islet neoplasia. Sporadic cases are less likely to test positive than familial cases, in part due to somatic mosaicism.
that show loss of Dpc4 protein in 55% of cases, loss of Dpc4 expression is absent in pancreatic nonductal neoplasms. Expression of 14-3-3 sigma is frequently seen in both pancreatic nonductal neoplasms (25-100%) and ductal adenocarcinomas (89%). Aberrant nuclear expression of beta-catenin is common in pancreatic nonductal neoplasms, specifically in solid pseudopapillary tumors (88%) and pancreatoblastomas (100%) but is rarely seen in pancreatic ductal adenocarcinomas (<5%). Expression of topoisoisomerase II alpha is not seen in solid pseudopapillary tumors and undifferentiated carcinomas with osteoclastic-like giant cells but is focally seen in pancreatoblastomas (50%) and acinar cell carcinomas (85%). Expression of PSCA and mesothelin was observed in pancreatic non ductal neoplasms but their expression was seen less frequently (0-50%) and weaker than that in pancreatic ductal adenocarcinomas (60-100%). CK19, a marker of pancreatic ductal adenocarcinomas, is not expressed in pancreatic non ductal neoplasms. Expression of gamma-synuclein as well as stromal markers (fascin, hsp47 and fibronectin) is frequently seen in both. These findings indicate pancreatic non ductal neoplasms have distinctive patterns of protein expression relative to pancreatic ductal adenocarcinomas and suggest that pancreatic non ductal neoplasms have different genetic pathways from the more common pancreatic ductal adenocarcinomas.

Large cell carcinoma with calcitonin and vasoactive intestinal polypeptide-associated Verner-Morrison syndrome.

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Verner-Morrison syndrome, characterized by diarrhea, hypokalemia, and hypochlorhydria, is caused most commonly by vasoactive intestinal polypeptide-secreting islet cell tumors of the pancreas. Verner-Morrison syndrome has not been described as a paraneoplastic syndrome in non-small cell lung cancer. We describe a 38-year-old man with metastatic non-small cell lung cancer of large cell carcinoma with neuroendocrine differentiation who presented with bone metastasis and intractable secretory diarrhea that was unresponsive to pharmacological treatment, including octreotide. Laboratory evaluation indicated elevated serum calcitonin and vasoactive intestinal polypeptide levels. Chemotherapy resulted in a transient response in the patient's diarrhea and neuroendocrine markers. The patient did not respond to further therapy and died 5 months after onset of back pain. To knowledge of the authors, this is the first published case of large cell carcinoma with neuroendocrine differentiation associated with treatment-responsive paraneoplastic Verner-Morrison syndrome.

Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer.


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The authors analyzed the effects of a treatment program of intraoperative electron beam radiation therapy (IOERT) and external beam radiation therapy and chemotherapy on the outcome of patients with unresectable or locally advanced pancreatic cancer. From 1978 to 2001, the authors studied 150 patients with unresectable and nonmetastatic pancreatic cancer received IOERT combined with external beam radiation therapy and 5-fluorouracil-based chemotherapy for

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definitive treatment. The 1-, 2-, and 3-year actuarial survival rates of all 150 patients were 54%, 15%, and 7%, respectively. Median and mean survival rates were 13 and 17 months, respectively. Long-term survival has been observed in 8 patients. Five patients have survived beyond 5 years and 3 more between 3 and 4 years. There was a statistically significant correlation of survival to the diameter of treatment applicator (a surrogate for tumor size) used during IOERT. For 26 patients treated with a small-diameter applicator (5 cm or 6 cm), the 2- and 3-year actuarial survival rates were 27% and 17%, respectively. In contrast, none of the 11 patients treated with a 9-cm-diameter applicator survived beyond 18 months. Intermediate survival rates were seen for patients treated with a 7- or 8-cm-diameter applicator. Operative mortality was 0.6%, and postoperative and late complications were 20% and 15%, respectively. In conclusion, a treatment strategy employing IOERT has resulted in long-term survival in 8 of 150 patients with unresectable pancreatic cancer. Survival benefit was limited to patients with small tumors. Enrollment of selected patients with small tumors into innovative protocols employing this treatment approach is appropriate.


CEACAM6 is a novel biomarker in pancreatic adenocarcinoma and PanIN lesions.


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The purpose of this study was to test the hypothesis that CEACAM6 expression is an indicator of adverse pathologic features and clinical outcome in pancreatic adenocarcinoma. Previously, the authors have demonstrated carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) to be an oncoprotein that plays an important role in the biology of pancreatic adenocarcinoma. Suppression of CEACAM6 expression reduces tumorigenesis and metastasis in vivo. A tissue microarray was constructed using tumor specimens obtained from 89 consecutive patients who had undergone pancreatic resection for pancreatic adenocarcinoma with curative intent. A second microarray containing 54 pancreatic intraepithelial neoplasia (PanIN) lesions was constructed using tissues from a separate cohort of 44 patients. Both arrays were immunostained using a specific anti-CEACAM6 monoclonal antibody. Tumoral CEACAM6 expression was dichotomized into negative and positive immunoreactivity groups. The log-rank test was used to evaluate univariate associations of CEACAM6 expression with prognosis. Survival curves were derived using the Kaplan-Meier method. Tumoral CEACAM6 expression was detected in 82 (92%) pancreatic adenocarcinoma specimens. CEACAM6 expression was more prevalent in high-grade than in low-grade PanIN lesions (P = 0.0002). Negative tumoral CEACAM6 expression was associated with absence of lymph node metastases (P=0.012), lower disease stage (P=0.008), and longer postoperative survival (P=0.047). CEACAM6 is a novel biomarker for pancreatic adenocarcinoma. CEACAM6 warrants further evaluation as both a prognostic factor and a therapeutic target in pancreatic cancer.