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Abstracts
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1 Histological Evaluation of Chronic Pancreatitis by Endoscopic Ultrasound (EUS)–Guided Fine Needle Biopsy (FNB)

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Histopathological diagnosis of chronic pancreatitis has been classically limited to the study of surgical specimens. Since pancreatic biopsies are rarely done in the context of chronic pancreatitis, histological characteristics of different stages of the disease are unknown. Aim of the present study was to evaluate the histological characteristics of chronic pancreatitis in samples obtained by pancreatic EUS-FNB, and their relationship with EUS findings.

Patients and Methods: Eight consecutive patients (mean age 53 years, range 17–81, all male) who underwent EUS–FNB for the study of pancreatic masses in the context of chronic pancreatitis were included. EUS–FNB was performed under conscious sedation with a 22G needle guided by the lineal scanning Pentax FG-38UX echoendoscope. Parenchymal and ductal EUS criteria for chronic pancreatitis were evaluated. Following histological features were evaluated: presence of acini, ductal epithelium, fibrotic tissue (collagen) and inflammatory infiltration.

Results: Adequate sample for histological evaluation was obtained in all cases and all of them showed infiltration by inflammatory cells. Samples included pancreatic acini in only three cases (37.5%), in number of 2 to 13 acini each. In the remaining 5 cases (62.5%) the presence of ductal epithelium together with fibrotic tissue was observed. Biopsies including pancreatic acini were those obtained from patients with mild to moderate EUS changes of chronic pancreatitis (up to 5 EUS criteria). On the contrary, biopsy samples from more severe cases (8–10 EUS criteria) included only ductal epithelium with fibrotic component.

Conclusion: EUS–guided pancreatic biopsy allows evaluating histological changes of all stages of chronic pancreatitis. This may be an important advance for a better knowledge of the disease.

2 Calcium Activated Chloride Channels Can not Explain Forskolin-Stimulated Fluid Secretion in Pancreatic Ducts from Cystic Fibrosis Mice

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Cystic fibrosis (CF) produces in humans severe pancreatic alterations which do not appear in genetically modified CF mice. Pancreatic ducts from CF mice can secrete fluid, driven by both HCO₃⁻ and Cl⁻ transport, in response to forskolin and to carbachol. It has been suggested that calcium activated chloride channels (CACC) can take the role of CFTR and account for the fluid secretion in CF mice. Our aim was to check this hypothesis by analysing the effect produced by intracellular calcium chelation in the secretory response to forskolin and carbachol of pancreatic ducts from control and CFTR null mice. By measuring intracellular calcium by microfluorimetry in Fura-2 loaded pancreatic ducts we have confirmed that a preincubation with BAPTA-AM completely abolishes the increase of cytosolic calcium concentration after carbachol administration, and that forskolin does not increase calcium. Fluid secretion was studied in isolated pancreatic ducts fragments by measuring duct swelling using digital videomicroscopy. The secretory rate of control pancreatic ducts to forskolin was 244 ± 70 pl/min/mm² and it did not change in BAPTA loaded ducts (224 ± 57), but BAPTA completely abolished fluid secretion after carbachol stimulation (from 100 ± 26 to 19 ± 13). In ducts from CF mice the secretory response to forskolin attained 93 ± 13 and did not change significantly in the presence of BAPTA (62 ± 39). However the response to carbachol (100 ± 20) was completely inhibited by BAPTA (17 ± 25). Though the fluid secretion stimulated by carbachol might be driven by CACC, these channels can’t explain forskolin-stimulated fluid secretion in pancreatic ducts from CF mice; we can conclude that there are ion transport mechanisms in the luminal membrane of pancreatic duct cells from CF mice which are not CFTR nor CACC and can sustain a significant fluid and electrolyte secretion.
Abstracts

3

Role of IL-6, IL-8, IL-1 and IL-1 ra in the Relationship between Obesity and Severity of Acute Pancreatitis

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Background: The inflammatory response plays a fundamental role in the clinical course of acute pancreatitis (AP). The obesity favours the development of local and systemic complications in an AP, but the pathogenesis of this relationship remains unknown. Obese population may have a proinflammatory status which develops uncontrolled inflammatory cascade in patients with AP and obesity.

Aim: To assess the role of systemic inflammatory response in the relationship between obesity and severity of AP.

Patients and Methods: We collected prospectively patients admitted for AP in our Hospital between February 2003 and May 2004. Anthropometric parameters and serum levels of IL-6, IL-8, IL-1 and IL-1 ra were determined within 48 hours of the AP beginning. Sex, age and BMI matched healthy controls were also considered. Obesity was defined as BMI >30 kg/m².

Results: A total of 85 patients with acute AP and 40 healthy controls were collected. The AP causes were biliary 67%, alcoholic 5.8%, idiopathic 17.6% and others 9.4%. Clinical course was severe in 22 (25.9%) patients. In the AP group the obesity correlated with the severity of AP (p = 0.047) and serum level of IL-6, IL-8, IL-1 and IL-1 ra (p = 0.027; p = 0.026; p = 0.032; p = 0.008). We did not find differences in IL-6 and IL-8 between obese and non-obese healthy controls.

Conclusions: In obese patients, the increased incidence of severe AP is related to systemic inflammatory response.

4

The Agonist of PPAR-gamma (Peroxisome Proliferator-Activated Receptor-gamma) Reduces the Severity of Post-ERCP Acute Pancreatitis

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Introduction: Acute pancreatitis is a complication of endoscopic retrograde cholangiopancreatography (ERCP). Recently, it has been reported that PPAR-gamma agonists reduces the severity of acute pancreatitis induced by cerulein. The aim of this study was to evaluate the effects of prophylactic PPAR-gamma agonist application in an experimental model of post-ERCP acute pancreatitis.

Methods: ERCP-pancreatitis was induced by infusion of contrast medium into the pancreatic duct in male Wistar rats. In control group, pancreatic duct was cannulated without infusion. In additional groups, Rosiglitazone (a PPAR-gamma agonist) was administered in a single oral dose 1 h before the infusion of contrast medium. Vehicle was administered to control group. Three hour after the intervention, plasma and pancreas samples were obtained and levels of lipase, edema and myeloperoxidase were evaluated.

Results: Infusion of contrast into the pancreatic duct results in increased lipase levels in plasma, and edema and myeloperoxidase activity in pancreas as well as an intense activation of nuclear factorkB (NFkB). Rosiglitazone partially reduces the increase in lipase and the level of edema and completely abolishes the increase in myeloperoxidase and in NFkB activation.

Conclusions: Prophylactic administration of PPAR-gamma agonists provides a protective effect in experimental post-ERCP pancreatitis. The mechanism of the protective effects of Rosiglitazone seems to be the inhibition of the NFkB-dependent inflammatory response.

5

Endoscopic Ultrasonography (EUS) vs. Magnetic Resonance Cholangiopancreatography (MRCP) in the Diagnosis of Pancreatobiliary Disturbances With and Without Dilated Biliary Tract: Definitive Results of a Prospective, Blinded and Comparative Study


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Aims: To prospectively and blindly compare the performance characteristics of EUS and MRCP 1) in the etiologic diagnosis of the dilated biliary tract and 2) in the diagnosis of choledocholithiasis in patients with non-dilated biliary tract.

Study Design and Methods: From March 2001 to June 2004, patients meeting one of the following inclusion criteria were prospectively enrolled: 1) Unexplained common bile duct dilation in transabdominal ultrasound (US) (Group I; n = 74) and 2) High suspicion of choledocholithiasis (fever, abdominal pain and hepatic tests impairment or acute pancreatitis of probable biliary origin) with a non-dilated biliary tract on US (Group II; n = 82). Patients with personal history of claustrophobia or gastroenteroaesthesia and peacemaker carriers were excluded. Radial EUS (Olympus GF UM20 and GF UM160) and MRCP with SSFSE technique were performed within a 24-hour period. The sequence of the two techniques was randomly assigned and the operators were blinded with respect to the results of the other procedure. Gold standard was endoscopic retrograde cholangiopancreatography (ERCP) (n = 86), surgery with intraoperative cholangiography when needed (n = 23) or clinical follow-up (n = 26).

Results: Of 156 patients (69 men, 87 women; mean age of 68 + 15) included, 21 were excluded for: lack of definitive diagnosis (n = 8), EUS (n = 6) or MRCP (n = 7). Therefore, a total of 63 and 72 patients were evaluated in Groups I and II respectively for the analysis. Mean time between EUS/MRCP and ERCP or surgery was 11 + 13 and 31 + 32 days respectively. Mean follow-up in patients whom this was considered as gold standard was 5.8 + 3.9 months. Final diagnosis was choledocholithiasis (Group I/II: n = 31/30),
cholelithiasis without choledocolithiasis (Group I/II: n = 2/5), pancreatic cancer (Group I/II: n = 17/2), cancer of the biliary tract (Group I/II: n = 5/3), others (Group I/II: n = 2/0) and lack of pathologic findings (Group I/II: 6/2). The agreement between the two techniques was 84% and 72% in Groups I and II respectively, as assessed by kappa statistics. There were no differences in the performance characteristics of EUS and MRCP in the two study groups (table):

<table>
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<th>Group I (%)</th>
<th>Group II (%)</th>
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<tr>
<td></td>
<td>Se</td>
<td>Sp</td>
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<tr>
<td>EUS</td>
<td>100</td>
<td>62</td>
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<tr>
<td>MRCP</td>
<td>93</td>
<td>87</td>
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</table>

Conclusions: EUS and MRCP are good techniques for the diagnosis of pancreatobiliary disturbances in patients with and without biliary tract dilation.

6
Endoscopic Sphincterotomy is the Preferred Option in Clinical Practice to Prevent Recurrences of Acute Biliary Pancreatitis (ABP)
H.N. Rodríguez, L.M. Román, M. Pérez-Miranda, F.P. Renedo, E.S. Serrador, F.G. Pajares, M.L. Goyeneche, A. Caro-Patón
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Background: The relative frequency with which the several options available to prevent recurrences of ABP are used in clinical practice remains largely unknown.

Aim: To define the approaches currently used in clinical practice to prevent ABP recurrences. To analyze the factors potentially affecting the decision-making process.

Patients and Methods: 103 clinical records of 110 consecutive patients admitted for ABP over a 12 month period from Dec 2003 were available for review. There were 35 non-biliary APs (15 alcohol; 12 idiopathic; 4 drugs/metabolic; 3 post-ERCP; 1 malignancy); and 68 ABPs (male/female: 33/45; mean age: 72 years; range: 21–97; diagnosis: abdominal US in 59 & altered LFTs alone in 9; 6 with prior choledocolithiasis). Out of 46 were not referred for or had CCx contraindicated (median age: 82.5 years; mean ASA score 3.2, p < 0.05); in these 5 patients, 4 ERCPs with ES and 1 CCx were performed. No treatment was carried out in 1 patient with a previous CCx. There were 3 admissions for cholecystitis/biliary colic, 2/13 in the non ES group and 1/45 in the ES group.

Conclusions: ES is currently the most widely used strategy in our institution to prevent recurrent ABP, chosen in 3/4 of cases. CCx is carried out in 1/4 of cases. 1/5 of patients with ABP does not receive any prophylactic treatment. This pattern is seen both in the first attack of ABP and in recurrences. Recurrences mostly occur in the untreated group, although a significant proportion is accounted for by initially missed alternative etiologies. Comparative data from other institutions are needed before our findings can be generalized.

7
Value of Endoscopic Ultrasound in Preoperative Staging of Malignant Tumours of Pancreas and Periampullary Area
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Endoscopic ultrasound (EUS) has become available in the diagnostic workup of pancreatic and periampullary tumors. The proximity of the transducer to the tumour, the adjacent major vessels, and the peritumoral lymph nodes may offer additional information.

Purpose: The purpose of the present study was to compare EUS findings with the pathological examination of specimens obtained after surgical resection.

Materials and Methods: A radial Olympus UM160 echoendoscope (frequency 5, 7.5, 12, and 20 MHz) was employed. Since no linear echoendoscope was available, EUS-guided biopsy was not obtained. Over the last 18-month period, 15 tumours were resected (pancreatic adenocarcinoma 10, ampuloma 3, cholangiocarcinoma 1, and duodenal adenocarcinoma 1). A cephalic duodenopancreaticoectomy was performed in all patients. The EUS data were blinded for the pathologist. Nine men, and 6 women, ranging from 35 to 83 years old were included. Tumour location and size, major venous vessel adherence or invasion, and the presence of lymph nodes was registered.

Results: Tumour was disclosed by EUS in 14 cases, and suspected in one case due to duodenal stenosis and bile duct dilatation. Mean large diameter of tumours was 24 mm [range 10–40] under EUS examination, and 30 mm [11–80] in the specimen. Major venous vessel adherence or invasion (yes, no, doubtful) was:

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>10</th>
<th>2</th>
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<tr>
<td>EUS Specimen</td>
<td>no</td>
<td>yes</td>
<td>doubtful</td>
<td>doubtful</td>
</tr>
</tbody>
</table>
| lymph nodes were detected by EUS in all cases; however, only one case was labeled as nodal invasion. By contrast, pathological examination revealed nodal invasion in 11 cases. Mean number of lymph nodes resected per case, 12 [range 6–21]; invaded, 2 [0–7].
Conclusions: EUS appears reliable in the evaluation of tumour size and major venous vessel involvement, and offers poor results in the diagnosis of lymph node invasion.

8 Expression of Transcription Factors Pdx-1, Hnf-1a and Ptf1a, and Cell Proliferation, are Inversely Regulated After Induction of Acute Experimental Pancreatitis

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During organogenesis, terminal differentiation of pancreatic cells is regulated by the sequential expression of a network of transcriptional regulators such as Pdx-1, Hnf-1a and Ptf1a. Their constitutive expression is needed to maintain the specific function of each cell type. In adult individuals regulation of these transcriptional factors may play a key role in tissue repair and regeneration after injury.

Aim: To analyze the expression of Pdx-1, Hnf-1a and Ptf1a in acute experimental pancreatitis from onset until full recovery.

Methods: Cerulein pancreatitis was induced in C57BL/6 mice. At timed intervals blood was obtained and pancreas processed for western-blot and immunohistochemistry. Cell proliferation was assessed by Ki67 immunohistochemistry and BrdU uptake.

Results: In normal pancreas Ptf1a is exclusively expressed in acinar cells. Pdx-1 is expressed at high levels in the islets and weakly in some acinar cells. Expression of Hnf-1a is high in the islets and, at a lesser degree, in most acinar cells. Early after pancreatitis nuclear expression of all three transcription factors is greatly diminished. Reexpression is initiated at days 2–4 and progressively increases throughout days 14–20. Fluctuations in Pdx-1 expression always heralds similar changes in Hnf-1a and Ptf1a, and it coincides with the rise and fall of interstitial cell proliferation. Noteeworthy, plasma glucose is elevated (245 +/− 22 mg/dl) when nuclear Pdx-1 is critically reduced. Expression of Pdx-1 is fully reestablished by day 2, whereas that of Hnf-1a begins at days 3–4 and progressively increases reaching baseline values at days 14–20. Acinar cell proliferation is weakly initiated at day 2, peaks at days 4–7 and decreases to baseline levels by day 14.

Conclusions: Following acute pancreatitis the expression of transcriptional regulators responsible for the terminal differentiation of pancreatic cells is tightly regulated. Their levels of expression are opposed to the reparative proliferation rates of interstitial and acinar cells.

9 Pancreatic and Periampullary Tumours: Morbidity, Mortality and Long-Term Survival

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Aim: To evaluate surgical morbidity, mortality and long-term survival of periampullar and pancreatic tumours.

Patients and Methods: 107 patients were prospectively included. Median age was 62.62 ± 12.74 years; 50.5% male and 49.5% female. The most frequent locations were head of pancreas (48.6%), papila of Vater (18.7%) and pancreatic body (17.8%). 81 resections were performed (55 proximal panreatoduodenectomy, 18 distal pancreatectomy, 3 central resections, 2 total panreatoduodenectomy and 3 ampullectomies) and 26 by-pass. Histological studies showed malignant lesions in 90.6% of cases.

Results: Overall morbidity was 40.2% (43/107 patients); 43.2% in resections (35/81 patients) and 30.8% in by-pass (8/26 patients) (p = 0.186). The most usual complications included intra-abdominal abscess (11.21%), wound infection (8.41%), delayed gastric emptying (5.6%), haemorrhage (4.67%) and pancreatic fistula (4.67%). Overall postoperative mortality was 6.5% (7/107); 4.9% after resections (4/81 patients) and 11.5% for by-pass (3/26 patients) (p = 0.224). 7 patients were re-operated (6.5%). The median postoperative hospital stay was 19.97 ± 11.63 days (median 18 d); 22.16 ± 11.90 days in resections and 13.15 ± 7.48 days in by-pass (p = 0.0001). According to the histology, 5 years survival was 100% for solid-cystic tumours, carcinoid or cystadenocarcinoma; 57% in ampuloma and 12% for adenocarcinoma. For resected pancreatic adenocarcinoma and papila tumours 5 years-survival was 28% (median 15 m) vs. 0% for those non-resected (median 6 m) (p = 0.0001). 5 years-survival for resected pancreatic adenocarcinoma was 24% (median 12 m) and 0% for non-resected (median 6 m) (p = 0.0117).

Conclusions: Despite of a high morbidity rates, pancreatic and periampullar tumours resections can achieve a long-term survival without an increased operative mortality, as other abdominal oncolo-gical procedures.
Utility of a Non Conventional Hospitalization Unit (UARH) in the Treatment of the Acute Pancreatitis
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Introduction and Aims: The need to improve the comfort of patients and families and the efficiency of the Social Health resources, added to the progress in technology and hospital accessibility has fostered the implementation of an unconventional hospitalization unit. The ap (acute pancreatitis) is a self-limited process with a minor evolution in 70% of the patients. This is our experience of the treatment of ap in an non conventional hospitalization unit.

Materials and Methods: The High Resolution Hospitalization Unit (UARH) was created to treat predetermined and protocolled processes during the first 72 hours; after this time patients are sent home under outpatient care depending on their clinical or social circumstances, or they are admitted to hospital in conventional conditions or home hospitalization. A protocol was designed and applied to 56 ap patients in the UARH in 2002 and 2003. Those patients, who after 72 hours had less than 3 prognosis criteria of Imrie, PCR < 150mg/L, no organic failure, no pain and oral tolerance, were sent home given they had adequate social and family conditions, and if they were less than one hour’s drive from hospital.

Results: 26 of the 56 patients were admitted to hospital under conventional conditions, 28 patients (50%) were sent home and 2 needed clinical Home Care. The average stay in UARH was 3.43 ± 1.62 days, as opposed to 18.93 ± 13.68 days of conventional hospitalization (p = 0.000005). Six patients of those sent home (28) were readmitted to hospital, 2 of them suffering from their biliary pathology. Only one of those kept in hospital (26) was readmitted to hospital (p = 0.05). None of those sent home died.

Conclusion: The implementation of new ways of hospitalization may lead to a good and efficient attention of ap.

Lack of Association between Chronic Pancreatitis and Liver Cirrhosis in Chronic Alcoholism. Clinical, Functional and Morphological Study
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1Servicios de Hepatología, 2Cirugía General del Hospital Clínico Universitario de Valencia, 3Departamento de Fisiología de la Universidad de Valencia, Valencia, 4Unidad de Psiquiatría Ser, Valenciano de Salud, Valencia

Chronic pancreatitis (CP) and liver cirrhosis (LC) coexist with a variable and uncertain frequency in patients with chronic alcoholism, in spite of sharing similar risk factors.

Aim: To study the possible association between CP and LC of alcoholic etiology.

Patients and Methods: 142 consecutive patients divided into four groups: a) alcoholic CP: 53 cases, 52 ± 10 years-old, alcohol consumption 127 ± 48 g/day for 21 ± 7 years; b) idiopathic CP: 20 cases, 62 ± 18 years-old; c) alcoholic LC: 57 cases, 56 ± 10 years-old, alcohol consumption 125 ± 35 g/day for 25 ± 9 years; d) asymptomatic alcoholism (AA): 22 cases, 50 ± 8 years-old, alcohol consumption 153 ± 75 g/day for 19 ± 8 years. In all cases the clinical manifestations of CP and LC, Child-Pugh (Child-P) index, hepatic clearance of indocianine green (R15), upper digestive haemorrhage (Hd), ascitis (Asc), hepatic encephalopathy (Ep), diabetes mellitus (DMID), chronic diarrhoea/steatorrhoea (D/Est), foecal pancreatic elastase (E1), pancreatic calcifications (Cp), pseudopcynts (Pq) or alterations of the main pancreatic duct (DW) were assessed.

Results: Only one patient exhibited alcoholic CP and previous history of HD, Child-P of 6, but normal R15. Among patients with alcoholic LC, four exhibited mild alterations of E1, without clinical manifestations or morphological features of CP. Among AA subjects, three exhibited mild functional alterations (E1 and R15), without clinical previous history or morphological findings. (See Table 1.)

Conclusions: CP and LC of alcoholic etiology occur simultaneously with a very low frequency. The pancreatic functional alterations in patients with cirrhosis, or vice versa, have been very mild and without clinical or morphological correlation. These results indicate that ethanol does not have a parallel action on pancreas or liver, suggesting the existence of other different risk factors.

Table 1 for Abstract 11

<table>
<thead>
<tr>
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<th>D/Est</th>
<th>Cp/Pq/DW</th>
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<th>E1 &lt; 100</th>
<th>Asc/Hd/Ep</th>
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<td>66*</td>
<td>55*</td>
<td>92.5*</td>
<td>94*</td>
<td>85*</td>
<td>1.9</td>
<td>5.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Idiopathic CP (n = 20), %</td>
<td>65</td>
<td>55</td>
<td>65</td>
<td>55</td>
<td>95</td>
<td>80</td>
<td>5</td>
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<td>0</td>
<td>7</td>
<td>0</td>
<td>89.5*</td>
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</tr>
<tr>
<td>AA (n = 22), %</td>
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<td>13.6</td>
<td>0</td>
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</tr>
</tbody>
</table>

*p < 0.05.
12 PRSS1, SPINK1 and Alfa1-Antitrypsin Mutations in Chronic Pancreatitis

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1Servicios de Patología Digestiva, 2de Bioquímica, Hospital de la Santa Creu i Sant Pau, Barcelona

Introduction: Genetic alterations may be involved in the pathogenesis of chronic pancreatitis (CP), both when the etiology is alcoholic, in which case alcohol would participate as a co-factor, and when it is idiopathic.

Aims: To analyze the presence of PRSS1, SPINK1 and AAT mutations in a series of chronic pancreatitis.

Material and Methods: A total of 99 patients with CP were included (78 males; 21 females). Based on their etiology, 74 were alcoholic (ACP), 16 idiopathic (ICP), 3 had familial aggregation (PCH) and 6 had other etiologies. Following leukocitary DNA extraction, R122H and N29I mutations of the PRSS1 gene, the N34S mutation of the SPINK gene and the S and Z alleles of the AAT gene were sequenced. All subjects were specifically interviewed for tobacco or alcohol consumption and for family and personal history of pancreatic or neoplastic diseases. During a 24–42 month follow up the following parameters were analyzed: need for surgical interventions, exocrine and endocrine insufficiency, and cancer development.

Results: We have not detected any mutations in the PRSS1 gene. SPINK1 gene mutations or polymorphisms were detected in 12.5% of patients with ACP, 20% of patients with ICP and in 2.8% of healthy subjects. N34S (in association with the IVS1–37T > C polymorphism) was the most common mutation found (6.25% in ACP and 10% in ICP). CFTR gene mutations were present in 17/48 (35%) of the patients with ACP, in 5/30 (16.6%) of the patients with ICP and in 11/35 (31.4%) of healthy subjects. Most common detected mutations were 1716G/A in 5/48 (10.4%) and G576A + R668C in 4/48 (8.3%) of ACP, 5T −11TG in 2/30 (7%) of ICP, and delF508 and 1716G/A in 2/35 (5.7%) healthy subjects. Combined CFTR and SPINK1 mutations were found only in 3 patients (2 ACP and 1 ICP). Overall, 44% of patients with ACP had mutations in either CFTR or SPINK1, 96% were smokers, 44% had surgery, 38% had exocrine pancreatic insufficiency and 48% had diabetes. 33% of the ICP patients had CFTR or SPINK1 mutations, 43% were smokers, 32% had required surgery, 17% had exocrine insufficiency, 27% had diabetes and 3.3% developed cancer. None of these parameters changed significantly when patients were grouped according to CFTR or SPINK1 gene mutation profile.

Conclusions: 1 – Combined mutations in CFTR and SPINK1 genes are rare in our cohort of patients with chronic pancreatitis. 2– The outcome of the disease appears to be unrelated to the presence of SPINK1 or CFTR gene mutations.

13 Impact of SPINK1 and CFTR Gene Mutations in the Outcome of Both, Alcoholic and Idiopathic Chronic Pancreatitis

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It has been suggested that combined mutations affecting to both the Serine Protease Inhibitor Kazal type 1 (SPINK1) and the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) genes may predispose to the development of chronic pancreatitis. However, the impact of such a combination in the outcome of the disease is unknown.

Aim: To determine if patients with chronic pancreatitis present different patterns of disease progression according to SPINK1 and/or CFTR gene mutation status.

14 Role of Map Kinases in Taurocholate-Induced Glutathione Depletion in Acinar Cells and Its Relationship with Death by Necrosis and Apoptosis

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Pancreatic glutathione is depleted in pancreas during acute pancreatitis, however the mechanism responsible for this depletion has not been elucidated yet. On the other hand, the type of cell death has been correlated with the severity of the disease. Our aim was to investigate the mechanism of glutathione depletion and its relationship with the apoptosis and necrosis induced by taurocholate. Our in vivo
model was acute pancreatitis induced by taurocholate 3.5% perfusion into the biliopancreatic duct. Reduced glutathione (GSH) levels and oxidized glutathione levels have been determined in pancreas, and gamma-glutamyl cysteine synthetase (GCS) heavy and light subunit expression was also measured in pancreas by RT-PCR. Taurocholate-induced glutathione depletion was investigated in pancreatic acini and AR42J cells using specific MAP kinase and protease inhibitors. Confocal microscopy was performed using specific probes to detect apoptosis, necrosis and glutathione levels in AR42J cells. In the in vivo experiments, we observed fast and early GSH depletion without glutathione oxidation in pancreas. All three major families of MAP kinases were activated at 30 minutes after pancreatitis induction. However, up-regulation of GCS expression was mild and occurred only late in the course of acute pancreatitis. In the in vitro experiments, ERK inhibition prevented taurocholate-induced glutathione depletion in acinar cells and in AR42J cells. AEBSF, an inhibitor of serin proteases, prevented glutathione depletion in AR42J as well. This prevention caused less necrosis and more apoptosis in these cells. In conclusion, glutathione is depleted in pancreas via ERK activation and serin protease activity. Ineffective up-regulation of GCS hinders the restoration of GSH levels. By preventing glutathione depletion, necrosis decreases whereas apoptosis increases, and the latter type of cell death has been related with a minor severity of the disease.

15
Prophylactic Antibiotic Treatment Prevents Pancreatic Infection in Severe Acute Pancreatitis? Presentation of a Prospective Double-Blind, Placebo-Controlled Randomized Trial
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Objective: Pancreatic infection is the main cause of mortality after severe acute pancreatitis (SAP). The use of prophylactic antibiotic in SAP remains controversial. We study the effect of prophylactic antibiotic on pancreatic infection and mortality after SAP.

Methods: Between 1999 and 2003, 795 patients were recovered after acute pancreatitis, 28.7% were SAP (228/795). During this period a prospective double-blind, placebo-controlled randomized trial was conducted. Ev ciprofloxacin (CIP) (300mg/12h)-that provides therapeutical levels in pancreatic tissue- vs. control group, with- out antibiotic (PLA) in patient with SAP. Inclusion criteria in the study were pancreatic necrosis in CT scan without previous antibiotic therapy and no documented allergy to ciprofloxacin. Forty-two patients were included. Mean age was 65 years (31–84). We mainly study pancreatic infection and mortality.

Results: Twenty two patients received CIP, and 20 PLA. Thirty 32% of CIP group developed pancreatic infection compared to 35% of placebo group (p = 0.827). Mortality rate were 18% in CIP group vs. 20% in PLA group (p = 0.881). There were no differences between surgical rate and infection in both groups. Mean hospital stay was 17.5 + 55.7 days in CIP group vs. 17 + 53.3 days in PLA group.

Conclusions: There were no benefits after prophylactic antibiot- ic treatment with ciprofloxacin to prevent surgery or infection in SAP. Mortality and evidence of other infection was not minor in the antibiotic group.

16
Regulation of the Expression of Genes Involved in the Development of Acute Pancreatitis by the Chromatin Immunoprecipitation Assay (CHIP)
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Despite the use of therapeutic strategies, severe acute pancreatitis (PA) exhibits a relatively high mortality rate due to multiorganic failure. Many efforts have been invested in this area of research, however, the molecular mechanisms that trigger the pathology are not yet well established.

Objective: The objective of this work was the analysis of the regulation of genes implicated in this disease by using the chromatin immunoprecipitation technique (ChiP) in rat pancreas and in acinar cells AR42J treated with taurocholate. In addition, we studied the action of pentoxifylline, an inhibitor of TNF-α production, on the expression of those target genes.

Results: The results, obtained from quantitative RT-PCR screening of potential genes implicated in PA, allowed us to distribute the pro-inflammatory genes, according to temporary expression criteria and regulation models, in three classes: the immediate-early gene group (1–3 hours after PA induction with taurocholate, direct target genes), as for instance EGR1, the early gene group (1–3 hours after PA induction, secondary targets), as NOS2. The ChiP assay showed that gene expression is dependent on the binding of specific transcription factors (SP1, EGR1, NF-κB, among others) and histone modifications (specific lysine acetylations and methylations) on the promoters of these genes. On the other hand, the administration of pentoxifylline during the early phase of PA reduced drastically the expression of those target genes in contrast that of constitutive genes. These results support the use of pentoxifylline as a therapeutic agent in the initial phases of PA by acting as a regulator of the expression of acute pancreatitis target genes.
17 Magnetic Resonance Cholangiopancreatography Fisrt of Cholecystectomy in Acute Gallstone Pancreatitis
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**Aim:** To assess a diagnostic-therapeutic guideline in gallstone pancreatitis with performance of a preoperative magnetic resonance cholangiopancreatography (C-RM).

**Methods:** Prospective study of patients with moderate gallstone pancreatitis (PAB) (Atlanta classification) admitted in our hospital, from January 2004 to March 2005. A C-RM was performed after the acute episode to the whole of the patients. If a common bile duct stone was diagnosed (LVB) a ERCP was performed before surgery was undertaken. All patients followed cholecystectomy when LVB were excluded or treated.

**Results:** 27 patients were included, mean age of 66.4 ± 18 years, 78% women. The mean interval time from acute pancreatitis to cholangiopancreatography (C-RM) was 2 ± 1.4 months. Two patients (7.4%) had relapse acute pancreatitis in one month while waiting for cholecystectomy. Four patients (14.8%) had LVB in C-RM. ERCP was successful in 3 patients. One patient was unable to stone extraction due to cystic lodgement.

**Outcome:** One patient with LVB treated by ERCP suffered from acute pancreatitis after surgery and a new C-RM confirmed LVB. Another patient with a negative preoperative C-RM also had postoperative acute pancreatitis with positive postoperative C-RM.

**Comments:** C-RM is an accurate tool for common bile duct stone. The inclusion of C-RM before surgery in acute pancreatitis is not efficient. A negative C-RM is not confident for exclusion of LVB in the time of surgery.

18 Acute Pancreatitis Post-ERCP
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**Introduction:** Acute pancreatitis post endoscopic retrograde cholangiopancreatography (ERCP) with diagnostic intention and/or therapy is a complication that appears between 1% and 40% of the occasions, being in most of the series of around 5%. Most of the pancreatitis post-ERCP are light and don’t require a hospital stay superior to 2–3 days.

**Material and Methods:** From January 1st 2002 to 31st December 2004 were carried out a total of 517 ERCP in our service following the established protocol. After the ERCP we registred vital signs (temperature, blood pressure and diuresis) in regime of hospital entrance. 6 and 17 hours after the realization of the technique basic biochemistry, hemograma, serum amylase level and amylase concentration in urine was a determined. Was pancreatitis acute defined post-ERCP as the appearance of abdominal pain that required analgesia and that remained at least 18 hours together with serum amylase level elevation and/or amylase concentration in urine 3 times the basal value. We defined as patients with high risk to develop acute pancreatitis post-ERCP those with suspicion of dysfunction of the sphincter of Oddi, previous history of acute pancreatitis post-ERCP or in the event of young patients, gender woman and with normal levels of bilirubin.

**Results:** Of the 517 ERCP practiced 5.2% (27 patients) presented acute complication pancreatitis, being 25 mild (92.6%), 2 moderate and any one severe. The mean age of patients with acute pancreatitis post-ERCP was of 70 years, being 76.9% women and 23.1% men. The acute pancreatitis could be detected in the first 6 hours after the technique in 25 patients (92.6%); the other two patients with abdominal pain presented hyperamylasemia at the 6 hours posttechnique smaller than 3 times the basal value although later on level rose above this. The percentage of defined patients as of previous risk was of 4.6% (24/517), only developing pancreatitis 2 of these patients – 8.3% – (2/24) and appearing this in the first 6 hours in both cases.

**Conclusion:** Acute pancreatitis post-ERCP in our series appears in a similar percentage to that published in the literature. Acute pancreatitis post-ERCP can be detected previously based on clinical and analytic data in the first 6 hours. This suppose a rapid discharge (short hospitalization time) with security. High risk patients of acute pancreatitis post-ERCP can be managed in ambulatory regimen.

19 Impact of Endoscopic Ultrasound–Guided Fine Needle Biopsy (EUS–FNB) in the Histological Diagnosis of Pancreatic Masses
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EUS–guided fine needle aspiration (FNA) has markedly improved the diagnostic approach to pancreatic lesions. The efficacy of the method is limited by the obtention of material only for cytological study. We modified the method of processing FNA samples to obtain a core specimen for histological study (FNB). The impact of this new method on the diagnostic efficacy of pancreatic masses is evaluated.

**Patients and Methods:** 34 consecutive patients (mean age 59 years, range 47–74, 19 male) who underwent a EUS–FNB of pancreatic masses were prospectively included. EUS–FNB was performed under conscious sedation with a 22G needle guided by the linear scanning Pentax FG-38UX echoendoscope. The material obtained with the first puncture was recovered by expelling it on a microscope slide using the needle stylet and injection of air through the needle and processed for cytological study. The material of the second and third punctures was recovered into a tube containing a 10% formol solution by injecting saline solution through the needle, and processed for histological study. The percentage of cases in which obtention of adequate samples was achieved and the diagnostic accuracy were evaluated.


**Results:** Adequate samples for histological and cytological study was obtained in 32 (94.1%) and 20 (58.8%) cases respectively (p < 0.001). In these cases with adequate sample, the diagnostic sensitivity was 85.0% (95% CI 64.0–94.8%) for cytology and 87.5% (95% CI 71.9–95.0%) for histology (n.s.). If all included patients are considered, diagnostic sensitivity was 50.0% (95% CI 34.1–65.9%) for cytology and 82.4% (95% CI 66.5–91.7%) for histology (p < 0.01). Histology also showed a significantly higher sensitivity than cytology for detection of malignancy 76.2% (95% CI 54.9–89.4%) vs. 38.1% (95% CI 20.8–59.1%) (p < 0.05). There was just one complication (acute pancreatitis) related with the technique (morbidity 2.9%), with no mortality.

**Conclusions:** EUS–guided FNB of the pancreas allows obtaining adequate sample for histological study, which lead to a significant improvement of the sensitivity for the diagnosis of pancreatic masses.

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**Acute Biliary Pancreatitis and Cholelithiasis. Are There Differences in the Rate of Choledocholithiasis?**


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**Background:** During the episodes of acute biliary pancreatitis (ABP) there seems to be a high rate of choledocholithiasis, decreasing throughout the following days. Nowadays, the incidence of choledocholithiasis at the time of elective surgery after mild ABP is still controversial.

**Aims:** 1) To investigate whether the incidence of choledocholithiasis in mild ABP is higher than in patients with symptomatic cholelithiasis (SC). 2) To evaluate the usefulness of intraoperative cholangiography (IOC) during ABP surgery.

**Patients and Methods:** Prospective study including 130 patients undergoing elective laparoscopic surgery for biliary diseases during a period of 24 months. Patients were classified into two groups: mild acute biliary pancreatitis (ABP, n = 44) and symptomatic choledolithiasis (SC, n = 86). The diagnosis of choledocholithiasis has been performed by IOC, endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance imaging (MRI).

**Results:** Both groups were homogeneous regarding age and sex. 19 MRI (9 in SC vs. 10 in ABP) and 11 ERCP (8 in SC vs. 3 in ABP) were performed preoperatively identifying choledocholithiasis in 5 patients in SC and 2 in ABP (5.81 % vs. 4.54%; p = 0.472). In 117 cases (90%) IOC was successfully performed (90.7% in SC vs. 88.6% in ABP; p = 0.465) identifying choledocholithiasis in 5 patients of SC group and 3 in the group of ABP (5.81 % vs. 6.81%; p = 0.492). The total number of patients with choledocholithiasis in the whole series was 15 (11.5%), 10 in the SC group and 5 in the ABP group (11.6% vs. 11.4%; p = 0.605). After a follow-up of 418 ± 207 days, residual choledocholithiasis has not been found in any case.

**Conclusions:** The rate of choledocholithiasis was not significantly different between the groups of patients with mild ABP and SC. IOC identifies unsuspected choledocholithiasis in 6.81% of patients with mild ABP.

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**New Pancreatic Cancer Preclinical Models of Great Utility for Combined Therapy Studies**

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In spite of its low incidence, the aggressiveness of human pancreatic adenocarcinoma and the few successes of current therapies makes it the fourth cause of cancer deaths in occidental countries. Better knowledge of resistance mechanisms to current therapies in pancreatic cancer is essential to design new therapies. Besides, the possible multifactorial origin of this resistance points towards combination of several drugs with different mechanisms of action as the therapy of choice. Nonetheless, clinical studies in pancreatic cancer, due to intrinsic features related to the disease itself, are difficult to perform. The orthotopic model in athymic mice is the most close to clinical reality. This model, that consists in the implantation of a small surgical human tumor fragment in the pancreas of athymic mice, allows us to obtain viable and vascularized tumours with spontaneous metastatic behaviour that reproduces the original dissemination patterns. In such perpetuated and amplified tumoral samples one can perform multiple therapeutic combinations. In the present work, several orthotopic models have been generated. Tumoral growth kinetics in the successive passages, as well as their dissemination patterns have been determined. Histological analysis has showed that the tumours grown in the pancreas of the athymic mice maintain the original structure of the primary tumor. The expression of several growth factor receptors and transcription factors has been characterized by immunohistochemistry. Treatment with different therapeutic agents has allowed us to validate this model and to underline its utility to planify clinical assays with targeted therapies based on the alteration patterns of each tumor.
cause of death from cancer in the world. A better knowledge of prognostic factors related to this neoplasia might help to improve the survival of these patients.

Aim: To evaluate the prognostic significance of different factors in both overall survival and tumor recurrence in patients with PDA who had undergone pancreatic resection.

Methods: All patients with PDA submitted to surgical resection in our Unit from January 1995 to February 2005 were evaluated. Epidemiological, clinical, analytical, histological and therapeutic variables were analyzed. Univariate (Kaplan-Meier, log-rank test) and multivariate (Cox regression) analyses were performed to select independent prognostic factors.

Results: Ninety seven patients have been evaluated. The average of age was 63 years and 52% were women. The average time of overall survival was 24 ± 3 months, being the probability of overall survival at 1, 3 and 5 years of 63%, 18% and 8%, respectively. Univariate analysis identified degree of differentiation, ratio of involved to resected lymph nodes, pathological N and TNM stages, and adjuvant treatment as variables associated with overall survival. With respect to tumor recurrence, the average free time of recurrence was 23 ± 4 months, being the probability at 1, 3 and 5 years of 48%, 17% and 9%, respectively. Predictive variables of recurrence were preoperative N and TNM stages, postoperative serum CA 19.9 concentration, degree of differentiation, ratio of involved to resected lymph nodes, and pN and pTNM stages. Multivariate analysis identified degree of differentiation and pathological N stage as independent predictive factors of both overall survival and tumor recurrence.

Conclusions: The degree of differentiation and pathological N stage predict the prognosis of patients with PDA after surgical resection.

23 PAP/Reg Inhibits Inflammation through STAT3 Activation and IkappaB Upregulation in Pancreatic Epithelial Cells

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Introduction: PAP/Reg protein has been recently described as an endogenous mechanism involved in the regulation of inflammation. In the present study we show, for the first time, some of the molecular mechanisms involved in the intracellular signaling pathways activated by PAP/Reg in a pancreatic acinar cell line. Knowing that PAP/Reg and IL-10 responses share several features, we looked whether both could reciprocally regulate their expressions and the role of Jak/STAT3 and NF-kappaB signaling pathways in PAP/Reg-mediated suppression of inflammation.

Methods: AR42J cells were seeded at subconfluent levels and treated with immunopurified rat PAP/Reg or with IL-10. Total RNA was obtained 15, 30, 60, 120 and 240 min after treatment and the expression of PAP/Reg, IL-10, IkappaB and SOCS3 were examined by RT-PCR. In addition, STAT3 activation was measured by immunofluorescence in cells activated with PAP/Reg. Western Blot analysis was used to determine the effect of PAP/Reg on STAT3 protein activation, SOCS3 and IkappaB expression.

Results: We observed a strong induction of PAP/Reg gene in response to IL-10 and in response to PAP itself. PAP/Reg treatment induced phosphorylation and nuclear translocation of STAT3 while inhibited NF-kappaB signaling by overexpressing IkappaB. Finally, PAP/Reg exerts its effect through induction of the Suppressor Of Cytokine Signaling (SOCS) 3.

Conclusions: These findings suggest that PAP/Reg inhibits the inflammatory response through, at least two mechanisms, one dependent on STAT3 activation, the other targeting NF-kappaB. Important functional similarities with the anti-inflammatory cytokine IL-10 suggests that PAP/Reg could be an IL-10 counterpart in epithelial cells.

24 Detection of Pancreatic Necrosis in Acute Pancreatitis (AP) Using 99mTc-Hexamethylpropylene Amineoxime (99mTc-HMPAO) Labelled Leukocyte Scintigraphy (LLS)

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Aim: Pancreatic necrosis is the main local complication in the initial evolution of AP. Contrast-enhanced computed tomography (CECT) has become the cornerstone of diagnosis of necrotizing pancreatitis. However, contrast medium may exacerbate the necrotizing process and renal dysfunction. Pancreatic leukocyte infiltration is an important event in the pathogenesis of AP suggesting that LLS with 99mTc-HMPAO might be useful in the prognosis assessment of patients with AP. The purpose of this study was to assess the accuracy of LLS with 99mTc-HMPAO in order to predict pancreatic necrosis emergence in patients with AP. Then, the results were compared to those attained using an alternative method [that is, measurement of plasmatic levels of C-reactive protein (CRP)].

Methods: We examined 84 patients with AP (54 men, 30 women; average age: 59 years, rank: 20–96 years). The aetiology was: biliary litihasis in 38 (45.2%), alcohol consumption in 21 (25.0%), idiopathic in 14 (16.7%) and other causes in 11 cases (13.2%). CECT was performed in order to evaluate pancreatic necrosis after 72 hours of clinical evolution. Plasmatic levels of CRP were obtained within 48–72 h after admission. All patients underwent LLS with 99mTc-HMPAO taking planar abdominal and SPECT images (30 min and 3 h after injection of the leukocytes). The activity of pancreatic infiltration was quantified by a visual gradation (score 0–3 in relation to the physiological bone marrow, liver and spleen uptake). Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and area under ROC (CI 95%) curve were calculated.

Results: Necrotizing pancreatitis was present in 11 (13.1%) patients and oedematous pancreatitis in 73 (86.9%) patients. LLS was positive in 38 patients (45.2%). The values of Sn, Sp, PPV and NPV of each parameter were: CRP (≥150 mg/DL), 81.8%, 76.7%, 34.6%
and 96.5%; and LLS (≥2 points), 90.9%, 87.7%, 52.6% and 98.5%. The area under ROC curve (CI 95%) of each parameter was: PCR, 0.851 (0.733–0.968); and LLS, 0.926 (0.866–0.986).

**Conclusion:** In patients with AP, LLS with 99mTc-HMPAO predicts pancreatic necrosis with an acceptable level of confidence. Therefore, LLS with 99mTc-HMPAO could be an alternative technique to CECT in diagnosing pancreatic necrosis.

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**25**

**Early Enteral Nutrition vs. Parenteral Nutrition in Severe Acute Pancreatitis**

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**Introduction:** Severe acute pancreatitis (SAP) is an hypermetabolic and hyperdynamic process that can promote a systemic inflammatory response and, in its evolution, a state of nutritional deterioration. Total parenteral nutrition (TPN) has been commonly used in SAP patients in order to improve their nutritional status in spite of the increased risk of infections and metabolic disorders. On the other hand, maintenance of the intestinal mucous barrier with early enteral nutrition (EEN) would favor the immune response and prevent the bacterial translocation possibly implicated in SAP septic complications.

**Aims:** To compare the effectiveness of EEN vs. TPN in the evolution of clinical severity in patients with SAP and in the rate of local and systemic complications and mortality.

**Material and Methods:** A total of 22 patients with clinical criteria of SAP (Apache II score ≥ 8, CT scan: grade D–E according to the Balthazar criteria and/or C reactive protein [CRP] ≥150 U) were included and randomized. Eleven patients received TPN and 11 EET. Endpoints were: serial measurement of inflammatory response markers (CRP, TNF-α, IL-6), nutritional status (pre-albumin, albumin), complications (sepsis) and mortality.

**Results:** Serum concentrations of PCR, TNF-α and IL-6 did not differ significantly between patients receiving EEN or TPN. Neither did pre-albumin or albumin levels show significant differences. In the TPN group, there were 3 exitus vs. none in the EET group. A larger trend, without statistical significance, was observed in the appearance of complications in the TPN group (7 patients) as compared to the EET group (4 patients).

**Conclusions:** 1. EEN is an excellent alternative in SAP patients. 2. A larger number of patients is needed to confirm the theoretical advantages of EEN observed in the present study.

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**26 Clinical Outcomes of ERCP as a First Line Approach in the Management of Post-OLT Biliary Complications**

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**Background:** ERCP-based therapies are increasingly replacing percutaneous or surgical intervention in the management of post-OLT biliary complications.

**Aim:** To assess short and mid-term safety and efficacy of ERCP as a first line therapeutic approach in the management of post-OLT biliary complications.

**Patients and Methods:** Between Nov 2001 and June 2005, 94 OLTs were carried out in 92 patients (male/female: 64/28; age range: 19–69 years). Of these, 27 (male/female: 20/7; age range: 22–68 years) developed post-OLT leaks or strictures (31.1%), excluding 4 with ischemic biliary complications. Mean time from OLT to the index ERCP was 30 days (range: 2–927). Endoscopic findings, diagnostic & therapeutic success, and clinical outcomes were retrospectively reviewed.

**Results:** Index ERCP & sphincterotomy was successful in all but 1 patient. 22 patients had biliary strictures (81.5%), 5 leaks (18.5%), 4 strictures & leaks (14.8%), 2 common bile duct stones (7.4%) and 3 biliary sludge (11.1%). All biliary strictures were anastomotic. 24 patients underwent biliary stent placement of 1–2 plastic stents, 9 had balloon dilatations, 2 stone removal and 1 nasobiliary drain placement. Overall success was 96.3% (26/27). Initial treatment response was good (with resolution of jaundice/abnormal LFTs/leaks) in 25/26 and in 26/26 after second-look ERCP for stent placement in 1 patient. There was only 1 post-ERCP complication (one perforation managed conservatively). After a mean 21 months (range: 1–33), 43 follow-up ERCPs were carried out in 21 patients for dilatation and/or stent removal/replacement, at 3 to 12 months intervals. At the end of follow-up (June 2005), ERCP was successful in 24/27 patients (88.9%), 7 out of these with long-term resolution (25–9%) and 18 still on a periodic stent exchange program (66.7%). Only 2 patients required hepatochojenostomy. 2 patients died of non-biliary causes.

**Conclusions:** ERCP is safe and highly successful (96.3%) in the management of post-OLT biliary complications. Its role in the long-term management of these complications remains to be further refined, given its high efficacy and low risk. An aggressive endoscopic approach may help prevent most post-OLT reinterventions for hepatochojenostomy.
27 Minimal Invasive Surgery and Limited Pancreatic Resection in Patients with Intraductal Papillary Mucinous Tumours (IPMT)

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IPMT is premalignant (adenoma, carcinoma in situ) or malignant (invasive carcinoma) so its surgical treatment is controversial: open vs. laparoscopic surgery, radical vs. conservative surgery.

Patients and Methods: From January 2000 to January 2005, 30 patients have been operated of IPMT: in pancreatic head, 17 cases, in body-tail, 7 cases and cystic head tumour with Wirsung dilatation, 6 cases. Surgical technical decision was taken according to pancreas location and peroperative biopsy.

Results: Cefalic duodenopancreatectomy was performed in 13 patients whose pathology showed invasive carcinoma in 5 cases (38%); pancreatic head resection with duodenal preservation in 4 patients: 3 adenomas and 1 adenocarcinoma in situ; total duodenopancreatectomy in 6 cases, in which all cases the pathologic study showed 6 premalignant lesions. In 7 patients laparoscopic distal pancreatectomy was performed and the pathologic study showed 6 premalignant lesions and 1 invasive adenocarcinoma (14%). All patients remain alive without recurrence, with a mean follow up of 22 months.

Conclusions: In patients with IPMT the rate of invasive carcinoma is 20% so conservative surgery is justified: laparoscopic surgery in left pancreas tumours and limited resections in tumours of the head. Radical surgery should only be performed in patients with invasive carcinoma.

28 Proliferative Role of EGFR, HER-2 and IGF-IR in Human Pancreatic Cancer and Its Relationship with the Transcription Factors NF-κB and p53

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Pancreatic adenocarcinoma is one of the most lethal cancers due to its high tendency to metastatize in very early phases of the disease and its very bad response to the radiotherapy and chemotherapy. The major part of failures of antitumor therapies are consequence of the initial existence or the appearance along the treatment of resistances to the own treatment. It is then necessary to go deeply in the knowledge of the mechanisms of resistance responsible of the lack of activity of current treatments. In the present work, we have characterized the most representative patterns of alterations in the pathways of EGF, HER-2 and IGF-1 receptors and p53 and NF-κB transcription factors, all them related to the intrinsic resistance of pancreatic tumours. In a panel of pancreatic tumor cell lines, total levels (WB and permeabilizing FACS) and the relative amounts in membrane (non permeabilizing FACS) of the different receptors have been determined. Total levels of NF-κB and p53 by WB together with their activation status/grade (p53 gene quantification and EMSA for NF-κB) have also been determined. After the characterization, we have evaluated the response of these cell lines to the single or combined inhibition of the signaling of these receptors by Tyrquinase inhibitors and/or blocking antibodies. IC50 and growth curves have been performed by MTT viability assays. The results obtained until now seem to indicate the existence of a correlation between the levels of the receptors, the basal levels of NF-κB and p53 and the antiproliferative response and could be of great usefulness for the more rational design of combination therapies based on the simultaneous inhibition of different proliferative signals.

29 Development of a Breath Test with Stable Isotopes for the Evaluation of Carbohydrate Digestion

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Diagnosis of carbohydrate digestion is becoming relevant in patients with pancreatic diseases due to the development of new enzyme preparations including lipase as the single enzyme. Carbohydrate malabsorption may also be an important aspect in diabetes mellitus-related exocrine pancreatic insufficiency. At present, methods to evaluate carbohydrate digestion are lacking. Aim of our study was to develop a new breath test with stable isotopes for the evaluation of carbohydrate digestion.

Subjects and Methods: Prospective, open, crossover comparative study. Eight healthy subjects (age range 28–43 years, 6 male) were included. A breath test consisting on a muffin (50 g corn flour, 14 g fat) and 300 ml water as test meal was developed. After overnight fast, metoclopramide 10 mg were orally given, 20–30 min before test meal ingestion. Breath samples were collected in Exeteriner tubes before and in 30 min intervals for 6 hours after test meal. The same test was repeated 7 ± 2 days thereafter, when acarbose 100 mg was orally given just at the beginning of the test meal ingestion. The quotient 13CO2/12CO2 was measured by mass spectrometry. The area under the curve (AUC) of the global 13CO2 exhaled over the 6 hour time was considered as the result of the test.

Results: Administration of a corn-based test meal allowed us to obtain a 13CO2 exhalation curve concordant with the physiological process of carbohydrate digestion. 13CO2 elimination peak occurred at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340). Acarbose-mediated inhibition of glucosidase activity led at 180–210 min in all subjects and the AUC (median) was 977 (range 632–1340).
Conclusion: A corn-based breath test allows carbohydrate digestion to be evaluated. In this test, glucosidase activity is the main factor determining the amount of $^{13}$CO$_2$ exhaled.

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Endoscopic Management of Common Bile Duct Stones with Gallbladder in situ in High Risk Patients
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Background: Obstructive jaundice caused by stones is a common disorder, mostly managed by endoscopic sphincterotomy followed by cholecystectomy. The aim of this study was to evaluate whether or not clearance of the common bile duct alone is sufficient as treatment for patients with choledocholithiasis and high risk.

Patients and Methods: Between 1992 and 2004, 13 patients presenting a first episode of obstructive jaundice caused by choledocholithiasis underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) with a follow-up time of more than three months without elective cholecystectomy were enrolled in the study. Long-term outcomes of ES were investigated. The time from entry to the occurrences of death or cholecystectomy was evaluated retrospectively.

Results: We studied 7 men and 6 women; mean age 84.3 yr, range (66–94). The median overall follow-up duration of 5.3 yr (range 1–13 yr). The most frequent ASA (50%) was ASA III. ERCP with ES was successful in all but one patients. Complications related to the endoscopic procedure don’t were reported. Two patients (15.3%) developed late complications, including stone recurrence and cholangitis; and acute cholecystitis, without surgical treatment. Seven patients died during the follow-up period from unrelated diseases.

Conclusions: ES is a reasonable alternative in patients with choledocholithiasis. In subjects who are at high risk for anaesthesia, endoscopic procedures may be utilised.

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Lymphoplasmacytic Sclerosing Pancreatitis (LPSP): Steroid Treatment after Rule Out Pancreatic Adenocarcinoma (PA)
Hospital Universitario de Bellvitge, Service de Cirugía General y Digestiva, Service de Radiodiagnostico y Servicio de Anatomía Patológica, L'Hospitallet de Llobregat, Barcelona, España

Introduction: LPSP is an autoimmune disorder. Generally present as obstructive jaundice and mimics a pancreatic adenocarcinoma (PA).

Conclusions: LPSP can be diagnosed after rule out PA. TC, MRCP, EUS-biopsy must be done before a steroid assay. In case of no response or doubt of PA surgery must performed. Successful steroid treatment may avoid unnecessary surgery and can be considered as diagnostic. Close follow-up is mandatory.

32
Surgical Treatment of Severe Acute Pancreatitis. Indications and Results
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Introduction: Infected pancreatic necrosis (IPN) is a severe complication of acute pancreatitis and requires urgent surgical treatment.

Objectives: To describe the indications and type of surgery performed, investigate the microbiological spectrum and evaluate postoperative morbidity and mortality.

Patients and Method: 18 patients underwent surgery from 1998 to 2005. Demographic data, body mass index (BMI), ethiology, APACHE II score, CT severity Index, diagnosis of IPN, microbiology, time to surgery and surgical technique, morbidity, mortality and hospital stay have been analysed.

Results: 11 female and 7 male, mean age 64 years. Ethiology: biliary (11), alcohol (4), idiopathic (2), annular pancreas (1). Mean BMI: 26.37. Mean APACHE II score: 16 (r = 11–25). Pancreatic necrosis <50% in 5 patients, >50% in 13, CT severity Index >7 in 14 cases. Diagnosis of IPN: FNA and/or gas on CT scan in 17 patients. FNA was monomicrobial in 6 and polymicrobial in 7 cases; Gram+ in 3, Gram− in 4 and mixed flora in 6 patients. The indications
for surgery were IPN (n = 17) and associated severe cholangitis in 1 case. Mean time from diagnosis to surgery was 20 days (r = 7–54 days). 14 patients underwent a Beger type necrosectomy (r = 1–3) and 4 cases underwent “open-packing” and programmed re-laparotomies (r = 2–4). Postoperative complications: 15/18 (83%). Overall mortality was 27.7% (n = 5) due to multiorgan failure in 60%. 3 patients had no morbidity and the hospital stay was 29 days as opposed to 62 days in patients with morbidity.

Conclusions: In our series the most frequent etiology is biliary (61.1%) with presence of >50% necrosis in 72.2%. Most of the infections were polymicrobial. The surgical indication is established (61.1%) with presence of

Abstracts

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Conclusions: In our series the most frequent etiology is biliary (61.1%) with presence of >50% necrosis in 72.2%. Most of the infections were polymicrobial. The surgical indication is established (61.1%) with presence of
neoplasm because of clinical, analytic and pathologic findings obtained by endoscopy biopsy.

**Material and Methods:** We present a case of an 80 year-old patient, with a clinical diagnosis of common bile duct obstruction, suffering from long-term dyspeptic syndrome, associated with jaundice, and high levels of alkaline phosphatase, AST and ALT. Symptoms persisted after endoscopic sphincterotomy. Different biopsies of ampullary region were reported as adenocarcinoma. Due to these clinical and pathologic findings, surgical resection of the ampulla was decided to be conservative because of the basal state of the patient, and it included an intraoperative frozen section.

**Results and Conclusions:** Gross examination of the specimen disclosed a white, well-demarcated, firm, submucosal nodule in the ampullary region, measuring 1.1 cm of diameter. Microscopically, the tumor was composed of small ducts, lined by a single-layer epithelium, without nuclear atypia. Ducts were surrounded by thick bundles of smooth muscle fibers. The tumor focally eroded the duodenal mucosa originating reactive changes in the overlying epithelium. Adenomyomatous lesions of the ampullary region represent a difficult differential diagnosis with malignant neoplasms, due to their clinical manifestations, deep location and the frequent presence of related reactive epithelial changes in the surrounding mucosa. When such lesions are suspected, an intraoperative frozen section should be required, thus avoiding unnecessary wide resections.

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**36 Large Cell Neuroendocrine Carcinoma of the Extrahepatic Bile Duct**


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Large cell neuroendocrine carcinoma (LCNEC) is a highly aggressive neoplasm. It has been described in the lung and in several extra-pulmonary locations. We describe herein the first LCNEC of the extra-hepatic bile duct. A 63 year-old male presented with obstructive jaundice. An abdominal ultrasound revealed dilatation of the intra- and extra-hepatic bile ducts suggestive of malignant lesion. Percutaneous transhepatic approach showed a complete stop in the extra-hepatic bile duct, and an internal-external drainage was placed. Malignant cells were found in bile. At laparotomy, a small tumor surrounded by dense fibrous tissue encasing the extra-hepatic bile duct was found, and a 3-cm hepatic mass was removed from segment IV near the hepatic hilus. Thus, cholecystectomy was performed, and the patient recovered uneventfully. The tumor was composed of cohesive trabeculae and islands of cells of intermediate to large size, low nuclear-cytoplasmic ratio, frequent nucleoli, and a high mitotic rate (>80 mitotic figures per 10 high-power fields). Frequent necrosis was found. Tumor cells were immunoreactive to neuroendocrine markers such as chromogranin A and synaptophysin. An expandable biliary prosthesis was stented, and a negative Octreoscan was obtained. The patient underwent chemotherapy with cisplatin and etoposide, and liver metastases developed after six months of treatment. He died from hepatic failure twenty two months after laparotomy. We conclude that LCNEC of the extra-hepatic bile duct is a highly aggressive neoplasm, difficult to diagnose preoperatively and indistinguishable from cholangiocarcinoma. Combination chemotherapy similar to that used in the lung might be considered.

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**37 Role of Oxidative Stress in the Inflammatory Response to Bile Duct Obstruction**


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Oxidative stress has been implicated in the development of acute pancreatitis, but its contribution to the local inflammatory response has not been completely elucidated yet.

**Aim:** 1) To study the evolution of oxidative stress in acute pancreatitis, and its relationship with nitrosative stress and the induction of pro-inflammatory genes; and 2) To assess the effect of preventing oxidative stress on nitrosative stress and on the induction of pro-inflammatory genes. In the present work, we have used the experimental model of necrotizing pancreatitis induced by 3.5% in rats. The treatment with oxypurinol-inhibitor of xanthine oxidase- and pentoxifylline –inhibitor of TNF-alpha production– was used to diminish oxidative stress. Reduced (GSH) and oxidized (GSSG) pancreatic levels were measured. Protein nitration in pancreas was studied by western blotting. The expression of TNF-alpha, iNOS and ICAM-1 was determined by RT-PCR. The regulation of these genes was studied by the chromatin immunoprecipitation assay. Glutathione oxidation and consequently oxidative stress were found at 3 h post induction and thereafter, whereas protein nitration, indicative of nitrosative stress, was found from 1 h postinduction. The up-regulation of pro-inflammatory genes was found at 3 h and thereafter. The induction of iNOS and ICAM was associated with NF-κB binding to their promoters, whereas NF-κB and SP1 were involved in the induction of TNF-alfa. It is noteworthy that all these transcription factors are sensitive to oxidative stress. Treatment with oxypurinol prevented glutathione oxidation and diminished nitrosative stress, but it did not change the expression of pro-inflammatory genes. Pentoxifylline prevented GSH depletion, and diminished both iNOS expression and nitrosative stress, avoiding the up-regulation of TNF-alfa and ICAM-1. In conclusion, oxidative stress is involved in the up-regulation of TNF-alfa, iNOS and ICAM-1 in pancreas in the course of acute necrotizing pancreatitis. In addition, pentoxifylline diminished both oxidative and nitrosative stress and markedly reduced the expression of these pro-inflammatory genes.


**Abstracts**

**Evolution of Biliar Sludge**


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**Introduction:** Treatment of lithiasis is similar that biliary sludge but isn’t known if both cases are the same

**Objectives:** 1. Evolution analysis of the clinical comportment of patients with biliary sludge and coelolithiasis. 2. To compare composition of bilis of patients with microscopic examination and patients with gallbladder surgery.

**Results:** 49 patients were included. 65% women with a mean age of 58 years (23–88). In 36 (73%) was realized microscopic examination of bilis (MEB) was positive in 28 (57%) and negative in 8 (16%). Gallbladder surgery was realized in 10 (36%) of patients with MEB+ and all were without sympotms. Only we saw differences in composition bilis about triglycerides in patients with lithiasis (p = 0.008).

**Conclusions:**
1. Surgery of patients with biliary sludge was satisfactory
2. Nearly of half patients without biliary sludge have symptoms of biliar colic
3. Only we found differences about triglycerides in the group with lithiasis.

**Breath Test with 13C-Marked Triglycerides to Evaluate the Exocrine Pancreatic Function. Experience Based on 79 Explorations**

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**Introduction:** The functional evaluation of the exocrine pancreas is important in diagnosis and monitoring of pancreatic insufficiency. The breath 13C-breath-test with triglycerides proves to be useful in diagnosis and monitoring of such pancreopathy.

**Object:** Our experience gained in the past two years.

**Patients and Methods:** 79 Patients (43 male) 53 measured at the HUP and 26 at P.F.B.-Lab. Mean age 45 (range: 19–82). We studied cystic fibrosis, celiac disease, chronic pancreatitis, vitamin B12 deficit, chronic diarrhoe, Pancreatectomy (carcinoma) and dyspepsia. Protocol: 250 mg of triglycerides-13C (Isomed S.L.) with 20 g of butter, two biscottes and 200 cc of water, administered after taking the basic probes, then, two probes per hour during six hours. The result is the accumulated percentage of the dosis recovered in a determinated time interval. The cutoff at 45% of the total recovered 13CO₂ shows S: 92.3% and E: 94.1% with a correlation r: 0.8 (p < 0.0001) in various studies, therefore we use it as reference value.

**Results:**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of cases</th>
<th>Mean % 13CO₂-recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Panreatitis/basal</td>
<td>22</td>
<td>20.47</td>
</tr>
<tr>
<td>Chronic Panreatitis/enzymes</td>
<td>5</td>
<td>42.93</td>
</tr>
<tr>
<td>Cystic fibrosis/enzymes</td>
<td>18</td>
<td>21.65</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>5</td>
<td>32.61</td>
</tr>
<tr>
<td>Chronic diarrhoe</td>
<td>13</td>
<td>41.17</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>4</td>
<td>10.35</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>4</td>
<td>33.83</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>48.30</td>
</tr>
</tbody>
</table>

**Conclusions:**
- Chronic pancreatitis, basal results: severe pancreatic insufficiency. Acceptable recovery after enzymatic supplementation
- Cystic fibrosis with enzymatic supplementation, the pancreatic function is still deficient
- Celiac disease: Pancreatic insufficiency of middle grade, something to keep in mind
- Severe (pancreateomy) and light (Vitamine B12-deficiency) pancreatic insufficiency. Normofunction: chronic diarrhoe, and dyspepsia.

**Distal Cholangiocarcinoma Associated to Papillitis with Viral Citomegalovirus Inclusions**

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Cytomegalovirus (CMV) infections are usually described in immunodeficient patients. In immunocompetent subjects active infection is uncommon, consisting usually of a mononucleosis-like syndrome. Numerous reports show that CMV is a potential pathogen in the gastrointestinal tract, even in immunocompetent patients, where it can produce lesions from the mouth to the anus, the most frequent located in colon-rectum, small intestine, stomach and esophagus. We report herein an uncommon association of chronic inflammation of the papilla and viral CMV inclusions with distal cholangiocarcinoma. The possible association between persistent CMV infection and human tumorigenesis is also discussed.

**Case Report:** A 72-year-old woman complaining of jaundice, choluria, acholia and generalized pruritus. Ultrasonography (US) and Computed Tomography (CT) reveal a 33 mm mass in the head of the pancreas, and bile duct and Wirsung duct dilatation. Percutaneous transhepatic cholangiography revealed stenosis of the common bile duct. Intraoperative findings were a tumour in the head of the pancreas, which was producing the dilatation of the bile tree. Cephalic duodenopancreatectomy of Whipple was performed. Pathology revealed an enlarged papilla, due to chronic inflammation with CMV inclusions. Histologic analysis revealed moderately differentiated ductal adenocarcinoma of the distal bile tract. Some authors postulate that the neoplastic state may induce an as-yet unidentified immunological defect, that favour the CMV infection. Mainly in elderly patients, the diagnosis of CMV infection might compel to continue the studies to exclude an underlying tumour. It has been already
suggested that CMV infection can induce oncogenic pathways, promoting their gene products mutagenesis, cell-cycle progression, angiogenesis, cell invasion and immune evasion. More studies are necessary to confirm these hypothesis.

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#### Congenital Exocrine Pancreatic Insufficiency. Shwachman–Diamond Syndrome


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**Background:** Shwachman–Diamond syndrome (SDS) is the second most common cause of pancreatic insufficiency in childhood, after cystic fibrosis. It is a congenital disorder characterized by pancreatic insufficiency, bone marrow dysfunction, and short stature. It occurs in 1 in 10,000–200,000 births.

**Case Presentation:** A 16-month-old infant was sent to Gastroenterology and Nutrition Pediatric Unit because of malnutrition and steatorrhea. He suffered from severe eczema refractory to treatment, flattening growth curve from 3rd month and frequent infections; aphthous stomatitis at 15th month. He had been receiving elemental formula without improvement and pancreatic enzyme replacement after steatorrhea diagnosis (van de Kamer).

**Physical Examination:** Active eczema widely disseminated and ocular lesion suggestive of herpes. Anthropometry: Growth assessment suggestive of chronic undernutrition: Weight 7.46kg (Z –2.7); height: 71.2 cm (Z –2.8); Z p/t: –1.8; % weight for height (Waterlow) 86%; % height for age 90%. For precocious undernutrition, steatorrhea and frequent diarrhea an exocrine pancreatic insufficiency was formulated as starting diagnosis. Laboratory analysis: Sweat testing for chloride was normal: fecal elastase, very diminished (20 U/g); neutropenia 1000/µL (previous blood cell counts review confirmed persistent neutropenia); Zn normal; increased aminotransferase activities (AST × 15 and ALT × 18); increased IgG; viral serologic tests were negative except for IgM Herpes simplex virus which tested positive. Image examination: Abdominal echography: Hepatomegaly and small pancreas. MRI: Pancreatic hypoplasia and lipomatosis. Normal kariotype. On these findings a diagnosis of Shwachman syndrome was performed. Treatment was started with acyclovir IV and continued PO for one year due to frequent relapses. After nutritional support and pancreatic enzyme replacement clinical and nutritional condition normalized and eczema vanished. Neutropenia persists between 500–700/µL. Bone marrow examination showed hypoplasia lacking myeloid differentiation.

**Conclusion:** Neutropenia associated to precocious steatorrhea and dermatitis must we put on the trail of the SDS.
How are We Managing Acute Recurrent Pancreatitis Associated with P. divisum Before, at and After ERCP?

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Background: Endoscopic decompression of the minor papilla (EDmP) effectively treats acute relapsing pancreatitis (ARP) associated with P. divisum (PD). Data come only from tertiary centers.

Aim: To describe the current diagnostic profile, endoscopic treatment and treatment outcomes of patients with PD and at least 2 episodes of ARP treated outside large tertiary referral centers.

Material and Methods: 8 Spanish hospitals (ERCP case volume high/intermediate/low = 2/4/2) answered a questionnaire. 20 patients (male/female: 9/11; mean age: 49 years; range: 14–82) with PD and ARP in whom EDmP was attempted from 1997 onwards were recorded. Their clinical profile, diagnostic & therapeutic approaches used, and treatment outcomes were retrospectively assessed.

Results: EDmP was obtained in 18/20 (90%). One patient was excluded because of lack of data. Those 19 analyzed had 2–9 episodes of ARP (mean = 4.7) over a mean 3.5 years (range: 1–168 months) prior to ERCP. Most of the 89 episodes of ARP were mild, but there were 4 severe and 33 with admissions >7 days, for a mean 9.4 days/year in-hospital per patient. 10 cases had no evidence of alternative concomitant etiologies of AP, and 5 with gallstones/sludge had 19 episodes of ARP (range: 1–4) after cholecystectomy. MRCP was performed in 9 patients (in none with IV secretin), and was consistent with PD in 2, probable/possible in 3, and non diagnostic in 4. EDmP was attempted 2–4 times before the minor papilla could be spot in 5 cases. Only 2 hospitals used IV secretin or dyes to help localize the papilla. 15 cannulations were achieved by means of a sphincterotome (9 wire-guided). 17 minor papillotomies (16 with stent) and 1 balloon dilatation were performed. Ventral pancreatography was done in 11, cholangiography in 10, biliary sphincterotomy in 5 & others in 4. There were 6/19 mild post-ERCP pancreatitis. Follow-up ERCP was carried out in 16 for stent removal/exchange, 4 on a long-term scheme (>6 months) & 12 on a short-term one (<17 weeks). After a mean follow-up of 40.4 months (range: 2–102), 11 patients have had no ARP, 6 had 1–2 episodes due to stent occlusion (3/4 on long-term exchange), and 2 had 6 & 7 bouts respectively, one with failed EDmP and another one with a CFTR mutation.

Conclusions: EDmP is feasible in over 90% of cases when performed by a dedicated biliary endoscopist, even if done infrequently. MRCP is unreliable to diagnose PD, so that in ARP does not replace ERCP. There is a diagnostic delay for PD associated with ARP, which in turn carries a significant preventable morbidity and fosters unnecessary cholecystectomies. EDmP is more demanding and riskier than standard ERCP, but it is still highly beneficial in these patients. A greater use of ventral pancreatography & techniques to localize the minor papilla, and short as opposed to long term pancreatic stent removal may help improve its results.

Effect of N-Acetyl Cysteine on the Capability of Acinar Cells to Produce TNF-alpha and IL-10 during Acute Pancreatitis

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Background and Aims: A delicate balance between pro- and anti-inflammatory mediators determines the nature of the inflammatory response during acute pancreatitis (AP). Our aim was to investigate the effect of N-Acetyl cysteine (NAC) on the ability of acinar cells to produce TNF-alpha and IL-10 at different stages of AP.

Methods: AP was induced in rats by bile-pancreatic duct obstruction (BPDO). NAC (50 mg/kg) was administered 1h before and 1h after BPDO. Acinar cells were incubated for 4h at 37°C, in 5%, CO₂ sterile atmosphere in absence and presence of pancreatitis-associated asctic fluid (20%, V/V). Acinar production of TNF-alpha and IL-10 was analysed by flow cytometry using phycoerythrin-labelled monoclonal antisera. Pancreatic morphological alterations were assessed by electron microscopy.

Results: PAAF significantly increased the acinar production of TNF-alpha and IL-10 in control rats. However, acinar cells failed to produce IL-10 from early AP and, although TNF-alpha production was found significantly stimulated, lower pro-inflammatory response to PAAF than in controls was found from 6h after BPDO onwards, time period from which severe morphological alterations were assessed by electron microscopy. The protective effect of NAC treatment against oxidative cell damage allowed acinar cells to maintain the production of TNF-alpha in response to PAAF during AP and enhanced their ability to produce IL-10 at early AP stages.

Conclusions: PAAF stimulated the production of TNF-alpha and IL-10 in control rats. Acinar cells of rats with AP were unable to maintain an appropriate balance between the production of pro- (TNF-alpha) and anti- (IL-10) inflammatory mediators, an effect palliated by NAC administration. We suggest that the pro- and anti-inflammatory capability of acinar cells could contribute to determine the degree of severity of AP.

EUS-Guided Biliopancreatic Drainage: Multiple Salvage Options for Selected Patients

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Background: Linear EUS allows interventional techniques from the GI lumen. Pseudocyst drainage and celiac plexus neurolysis are established indications for interventional EUS, whereas EUS-guided biliary or pancreatic ductal drainage remain experimental.

Aim: To assess the feasibility, technical requirements, safety and efficacy of EUS-guided biliary and pancreatic ductal drainage in patients with previously failed standard ERCP drainage.
**Patients and Methods:** Between Nov 2003 and June 2005, 24 patients out of 1321 consecutive ERCPs had failed biliary or pancreatic drainage (1.7%). The indication was revised in 9 cases and EUS-guided drainage (EUS-d) considered for the remaining 15 (male/female: 8/7; age range: 36–91 years). The indications, drainage techniques, technical & clinical success and complications were reviewed. Therapeutic EUS-scopes (Pentax 38-UX in 14 & Olympus GF-UCT160 in 1) and EUS-FNA needles of 19 or 22 G (6/7) were used, with 0.35" y 0.018" guidewires, respectively. For biliopancreatic ductal access, the 8.5 F OASIS introducing catheter was preferably used. Plastic stents were placed through the EUS scope channel, whereas a duodenoscope was used for metal stents. Fluoroscopy was used in addition to US and endoscopic monitoring.

**Results:** Pancreatic ductal drainage was attempted in 3/15 (2 Whipple's, 1 pancreatic head mass) and biliary drainage in 12 (4 ductal access problems, 3 Roux-en-Y, 3 malignant papillary involvement; 9 obstructive jaundice & 3 recurrent cholangitis). In 2/15 bile duct puncture was precluded by lack of an obvious target, interposed vessels and/or scope instability. Cholangio- or pancreatography was obtained in 12/13 punctures (1 parenchymal injection), ductal guidewire access in 9 (2 EUS-d aborted for bleeding & 1 for patient intolerance), and successful stent placement in 7 (1 guidewire breakdown & 1 failed distal guidewire access), 4 metal stents and 3 plastic stents (5 to 7F in size). Thus, EUS-d was technically successful in 7/13 punctures (54%). The 8 failed EUS-d were addressed by repeat pre-cut ERCP, PTC, bypass surgery or no treatment, 2 patients each. 2/7 successful EUS-d were transpapillary (1 antegrade, 1 rendezvous) and 5 transmural (2 pancreaticogastrostomies, 2 hepatocenterostomies, 1 choledocoduodenostomy). Clinical success (resolution of jaundice or pain) was achieved in 5/7 (70%), whereas the outcome could not be assessed in 2 patients who died within 10 days of disease progression. There were 5/13 complications (38%), 3 mild (bile leaks that settled conservatively in 3–7 days), and 2 severe (pseudocyst & hemoperitoneum), this last one resulting in patient death (for an overall mortality of 7.7%).

**Conclusions:** EUS-d may be an attractive alternative to PTC drainage in some instances and may even represent the only non surgical option in some patients. However, it is a demanding procedure, with a limited success rate of around 50%, and with a morbidity over 30%. It should be reserved for selected cases, after considering all the alternative options in a multidisciplinary setting. The future development of accessories specifically designed for this new technique may help improve these results, less encouraging than previously reported.

**Material and Methods:** We present four typical cases of young women, between 14 and 30 years old, with no significant medical history. In all of them, the pancreatic tumour was found incidentally by ultrasonography which revealed a sharply demarcated, variably cystic and solid, heterogeneous large mass. Three of them required needle aspiration biopsy for preoperative diagnostic and in one case a histological biopsy was necessary. All the patients were treated by conservative surgical resection and actually they all are symptom-free.

**Results and Conclusions:** In two cases, needle aspiration biopsy demonstrated typical cytologic features, such as papillary groups of homogeneous epithelial cells with scarce atypia. In the third case the presence of necrosis complicated the diagnostic, but even so, it was suggestive of epithelial neoplasm. In each case, macroscopic examination of the surgical specimen confirmed a solitary, well demarcated pancreatic mass, measuring 5–9 cm in diameter. The cut surfaces revealed light brown solid areas, intermingled with cystic zones, necrosis and haemorrhage. Microscopically, the solid portions were composed of sheets and papillary structures of epithelial cells without atypia which at immunohistochemical level expressed vimentin, enolase, alpha-l-antitrypsin and progesterone receptors. Typical morphologic and immunohistochemical features of the solid-pseudopapillary neoplasm of the pancreas allow its cytological or histological preoperative diagnosis, thus avoiding unnecessary wide resections, because of conservative surgery is curative.

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**46 Solid-Pseudopapillary Neoplasm: Pathological Aspects for Its Surgical Treatment**

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**Introduction and Objectives:** Solid-pseudopapillary neoplasm is an uncommon exocrine pancreatic tumour of uncertain malignant potential, with an excellent prognosis after complete surgical removal.

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**47 Oncocytic Carcinoma of the Pancreas with Neuroendocrine Differentiation: Report of a Case**

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**Introduction and Objectives:** Oncocytic carcinomas of the pancreas with neuroendocrine differentiation are rare neoplasms that preferentially appear in young people as metastatic disease in the liver. Consequently, the clinical management of these patients is very difficult.

**Material and Methods:** We report a case of a 32-year-old male without remarkable medical history, which suffered from epigastric pain for one month without being properly treated. The abdominal scan tomography with endovenous contrast showed a tumor with irregular contours in the pancreatic head that measured approximately 10 cm. It was no possible to determine the grade of invasion. Likewise, more than 10 metastatic lesions were identified in the liver. The first diagnostic approach was performed by a fine needle aspiration cytology of the metastatic lesion guided by ultrasonography. The unconvincing findings drove us to take a biopsy from the same lesion.

**Results:** The cytological study showed a hypercellular smear composed of polygonal epithelial cells with granular, acidophilic cytoplasm and round, monomorphic hyperchromatic nuclei (oncocytic changes). These neoplastic cells displayed trabecular, organoid and slightly acinar growth patterns. Microscopically, the neoplasm showed similar features to that of the smear. The immunohistochemical study revealed staining with endocrine markers such as
chromogranin and synaptophysin, and negativity to glucagon, insulin and somatostatin. The patient could not undergo a surgical excision of the neoplasia and currently is being treated with palliative chemotherapy.

Conclusions: Oncocytic carcinomas of the pancreas with neuroendocrine differentiation are extremely rare neoplasms with a characteristic clinical behavior and difficult diagnosis. Consequently, it is necessary to keep this entity in mind in order to achieve an earlier diagnosis.

48 Distal Intestinal Obstruction Syndrome in Adults with Cystic Fibrosis
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With the rise in cystic fibrosis (CF) patient survival, GI complications in adult are far more evident in patients with this condition. Distal intestinal obstruction syndrome (DIOS), formerly known as meconium ileus equivalent, consists of a partial or complete intestinal obstruction due to an abnormality in the mucofecal material viscosity at the terminal ileum and cecum. DIOS prevalence in published series has been quite variable, with range from 2.7% to 37.3%.

Objective: To determine prevalence and clinical characteristics of DIOS in adult patients with CF in our center.

Methods: Retrospective review of adults CF patients registry.

Results: 125 patients has been studied, 4 of them (3.2%) were diagnosed with DIOS (average of 22 years old). Sex: 2 women, 2 men. Age at the diagnosis of CF: between 7 months and 5 years old. Genetic study: 3 patients with ΔF508/ΔF508 and 1 with ΔF508/G542X. All the patients had exocrine pancreatic insufficiency, 2 had endocrine pancreatic insufficiency. Severe respiratory insufficiency in 3 patients and light in 1 patient. Three patients with biochemical liver abnormalities, and 1 had liver cirrhosis. Two patients had gastro-esophageal reflux symptoms and 1 patient had gallbladder stones. No patients had a history of meconial ileum. Nutritional status using BMI was between 18.2 and 23 kg/m². Two patients abandoned the enzymatic substitutive treatment, and 2 were receiving insufficient treatment. Two patients had more than 1 episode of DIOS. All the patients responded to medical treatment.

Conclusions: DIOS prevalence in our department is lower than in other series. All the patients are mutation ΔF508 carriers. None of the patients needed surgical treatment.

49 Vitamin E Sensitizes Pancreatic Stellate (PSCs) Cells to Tumor Necrosis Factor (TNF)-α Induced Death Through a Nuclear Factor (NF)-κB Independent Mechanism
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A hallmark of chronic pancreatitis is the pseudotumoral expansion of PSCs. Induction of PSC apoptosis may halt the progression of the disease. NF-κB is a redox-sensitive transcription factor critical in the anti-apoptotic pathway initiated by TNF-α. AIMs: To investigate the effects of vitamin E on intracellular ROS, apoptosis and NF-κB in PSCs exposed to TNF-α.

Methods: Rat PSCs were treated with vitamin E (α-tocopherol, 200 µM) for 72 h with or without TNF-α (20 ng/ml). Intracellular ROS were measured by flow cytometry using DCFH-DA/PI (propidium iodide); apoptosis was assessed by caspase-3 activity and DNA fragmentation; NF-κB was analyzed by ELISA quantification of p50 and p65 in nuclear extracts.

Results: PSCs had a basal level of endogenous ROS that was efficiently reduced by vitamin E after 48 h (40% of basal) and 72 h (30% of basal). To exclude the effects of cell toxicity on ROS analysis, necrotic cells (PI+) were eliminated from cytometric evaluation. TNF-α induced a time-dependent increase of ROS that reached 4-fold above basal levels at 72 h and that was abrogated with vitamin E. TNF-α and vitamin E by themselves did not induce apoptosis. However, in cells pretreated with vitamin E for 48 h TNF-α caused a 3-fold increase in DNA fragmentation, suggesting that ROS may protect PSCs from apoptosis. TNF-α induced NF-κB activation that could not be prevented with vitamin E. In order to suppress TNF-α induced NF-κB activation, MG-132 (NF-κB inhibitor) or cycloheximide (protein synthesis inhibitor) were added to vitamin E. This combination further enhanced the proapoptotic action of TNF-α.

Conclusions: Vitamin E renders PSCs susceptible to TNF-α induced apoptosis. This action cannot be ascribed to inhibition of the NF-κB pathway. Combined strategies aiming to reduce endogenous ROS levels and NF-κB activation might be beneficial to eliminate PSCs in chronic pancreatitis.

50 Two Extreme Cases Presenting Cancer of the Pancreas
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Pancreatic cancer is a usual pathology in developed countries. It is an aggressive tumour with very bad prognosis. Surgical resection is the only potentially curative treatment, but this is only possible in 15–20% of the cases because of the presentation of the tumour in advanced stages. We present here 2 extreme cases of pancreatic cancer with controversial indication of surgical resection.
**Case 1:** The patient is a 59 years old man with melenas in spite of recurrent endoscopic sclerosis of a duodenal ulcer. Afterwards the patient shows mucocutaneous jaundice. Computed Tomography (CT) reveals a 7 cm mass in the head of the pancreas infiltrating the second portion of duodenum, bordering in $180^\circ$ the superior mesenteric vein and with the presence of mesenteric and celiac adenopathies. Biopsy of the second portion of duodenum reveals a poor differentiated carcinoma.

**Case 2:** A 49 years old man presents with sporadic pain in right hypocondrium and familiar history of father, uncle and 2 cousins with pancreatic cancer. CT and Magnetic Resonance reveal a 1 cm cystic lesion in the head of the pancreas, suggestive of adenocarcinoma. Cytology shows mucoid material and atipia.

In case 1, only the surgical resection of the tumour can be a solution for the problem of the bleeding after the failure of sclerosis, appraising the high rate of morbi-mortality of the procedure and the palliative aims.

In case 2, there are 2 possible attitudes to manage a cystic pancreatic lesion, suggestive of mucinous cystadenoma with cytological atipia and familiar history of pancreatic cancer: Follow up or Resection.