Review Article

Clinical pancreatic disorder I: Acute pancreatitis

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Citation: Andrén-Sandberg Å. Clinical pancreatic disorder I: Acute pancreatitis. North Am J Med Sci 2011; 3: 316-319. doi: 10.4297/najms.2011.3.316

Abstract

The Annual American Pancreas Club is an important event for communicating around clinical pancreatic disorders, just as the European, Japanese, Indian, and the International Pancreatic association. Even though the meeting is only 1½ day there were 169 different abstracts and a “How do I do it session.” Among all these abstracts on the pancreas there are some real pearls, but they are almost always well hidden, never highlighted – all abstracts are similarly presented – and will too soon be forgotten. The present filing of the abstracts is one way (not the way) to get the pancreatic abstracts a little more read and a little more remembered – and perhaps a little more cited. It should also be understood that most of the abstracts are short summaries of hundreds of working hours (evenings, nights, weekends, holidays, you name them …) in the laboratory or in the clinic, often combined with blood, sweat and tears. The authors should be shown at least some respect, and their abstracts should not only be thought of as “just another little abstract” – and the best respect they can be shown are that they will be remembered to be another brick in our scientific wall.

Now the pancreatic abstracts of American Pancreas Club 2011 are gathered and filed with the aim to give them a larger audience than they have had in their original abstract book. However, it is obvious that most of clinical fellows do not have time to read all the abstracts. For them I have made a “clinical highlight section” of 10 percent of all the pancreatic abstracts. If someone else should have done some collection of abstract, there should probably have been other selections, but as this is not the case, the editor’s choices are the highlighted ones.

The article as series I of clinical highlight section is present, and more series will be present in the following issues. If readers will remember some of the abstracts better after reading this “abstract of abstracts”, it was worth the efforts – and without efforts there will be little progress.

Keywords: Acute pancreatitis, accurate classification, clinical highlight, American pancreas club, international pancreatic association.

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Classification

The accurate classification of severity of acute pancreatitis (AP) is important in clinical practice (to define severity, track clinical course and support decision-making) and in clinical research (to define criteria for recruitment, allowing valid comparisons between study groups). For more than a century, severity has been classified as either “mild” or “severe” and defined in different ways. The aim of one study was to develop a four category (mild, moderate, severe and critical) classification for severity based on the actual key determinants of severity, organ failure (OF) and infected pancreatic necrosis (IPN). A literature search of relevant observational studies was undertaken and data statistically aggregated to determine the pooled influence of OF and IPN on mortality in patients with AP. The summary estimates are presented as relative risk (RR) with 95 % confidence intervals. Fourteen studies comprising 1478 patients with AP were meta-analyzed. A total of 600 patients develop OF and 179 of them died (mortality, 30 %) whereas 314 patients developed IPN and 102 of them died (mortality, 32 %). In a stratified analysis, patients with OF and IPN had a significantly higher risk of death in comparison with patients with OF and no IPN (RR = 1.94; 95 % confidence
Late sequelae

Having survived an episode of acute necrotizing pancreatitis (ANP) the patient is vulnerable to a variety of late sequelae, often of sufficient magnitude to require operative intervention. Among these complications are persistent fistulae after operative debridement or after percutaneous drainage, persistent fluid collections either after operative debridement or after resolution of ANP more than 8 weeks after the initial attack, recurrent pancreatitis after resolution of ANP, recurrent or persistent pain and/or an intolerance of per oral intake. It was maintained records for all patients hospitalized from 1993 to 2010 with diagnosis of ANP determined either by contrast imaging and/or by operative findings. Once discharged from hospital patients were managed with routine clinic follow-up, at close intervals and later at 6 month intervals. All patients had pancreatic ducts imaged by ERCP or MRCP and ducts were classified as either type I (normal), type II (stricture,) or type III (disconnected). Patients were monitored for the complications listed above. Cross sectional imaging was obtained as clinical condition dictated. Interventions (operative or non-operative) were performed as indicated. Operations performed more than 8 weeks after the initial episode of ANP were evaluated for operative mortality, morbidity, success in resolving symptoms/collections and LOS. 197 patients with ANP were included. Seventy-one operations performed more than 8 weeks after ANP, most more than 3 months after, of which 59 were drainage procedures and 12 were resections. Operative mortality was 1 percent, morbidity was 19 percent. Mean LOS was 6 ± 6 days. Poor per oral intake was seen in 80 percent of operated patients and TPN dependence in 42 percent. Successful resolution of symptoms and/or fluid collections was achieved in 96 percent. Patients with organized pancreatic necrosis had longer LOS, more frequent re-hospitalization and higher rate of complication. Recurrent pancreatitis was improved in 87 percent and eliminated in 78 percent. It was concluded that patients who require late operation after surviving an episode of ANP are more likely to have sustained ductal injuries and are likely to require operation for either pain or for inability to tolerate per oral intake. Operation can be performed safely with a low mortality. Morbidity is likely in patients with the rigid-walled collections seen after ANP [2].

Thromboelastometry

Local complications are associated with the development of pancreatic necrosis in acute pancreatitis. It has been postulated that necrosis is related to a disease-related coagulopathy. This presumed coagulopathy has not been clearly defined. The aim of one prospective study was to assess coagulation in AP using thromboelastometry. Eighty-six patients with acute pancreatitis (serum amylase greater than 300U/L) were recruited within 6 hours of admission. Average age 62 years, male:female ratio 63:37. Venepuncture was performed at 0, 6, 12, 24 and 48 hours from admission. Thromboelastometry was performed on kaolin activated and heparinised samples using the TEG®5000 system (Haemoscope UK). The reaction time (R-time) is the time taken from onset of reaction to fibrin formation. Maximum amplitude is used to assess clot quality. There was no significant difference in R-time between heparinise and non-heparinase samples. Thirteen percent of patients had APACHE scores predictive of severe disease. Nine percent developed severe disease according to the Atlanta classification. Two percent of all samples had R-time below normal range while 62 percent had evidence of prolonged coagulation according to R-time. There was a trend towards increased R-time across the time points assessed, although this did not reach significance. No significant difference in maximum amplitude was observed in patients over the time points measured or compared to normal range. No differences in TEG parameters were seen between patients with severe and uncomplicated disease. It was thus described the use of thromboelastometry in the assessment of coagulation in AP. Contrary to other publications, these data suggest that patients with AP are not procoagulant. The clinical significance of this has yet to be investigated but provides an exciting research prospect. The lack of association with severity suggests that the observed prolongation of R-time may be related to treatment (not including heparin) [3].

Minimal invasive necrosectomy

Recently, minimally invasive surgical approaches have been applied to patients with necrotizing pancreatitis. It was sought to review the early experience with these approaches at our high volume pancreatic referral center. With IRB approval, medical records of patients undergoing minimally invasive surgical pancreatic debridement between 2007 and 2010 were reviewed. Data were collected for descriptive analysis. Fourteen patients were approached with minimally invasive surgical techniques: 3 retroperitoneal (VARD); 3 laparoscopic transabdominal; and 9 laparoscopic transgastric. Pancreatitis etiology was biliary (n=8), pancreas divisum (n=2), and alcohol, IPMN, and idiopathic (1 each). The median time from initial pancreatitis to intervention was 10 weeks (range 6-32 weeks). Five patients had preoperatively documented infected necrosis; 5 had preoperatively placed percutaneous drains. Nine patients were admitted from home for elective débridement. Four patients (all laparoscopic transgastric) were converted to open operation. Four patients required early (< 30 day) reoperation: 3 for recurrent peripancreatic collections, 1 for cholecystectomy/jejunostomy. Two patients required late (>1 year) reoperation for recurrent left-sided pancreatitis. Eleven patients had infected necrosis. In the 10 patients completed with minimally invasive technique,
the median length of stay was 5 days (range 2-103 days); 8 were discharged to home and 2 to nursing homes. Thus, select patients have excellent outcome after minimally invasive pancreatic débridement. Disease heterogeneity mandates facility with multiple approaches and commitment to long-term care of these complex patients [4].

**Video assisted retroperitoneal débridement**

Pancreatic débridement via laparotomy is associated with significant morbidity and mortality. Recently, video assisted retroperitoneal débridement (VARD) has been described, and initial reports of its safety and efficacy are promising. In addition, single incision laparoscopic surgery (SILS) has shown to be feasible for a wide range of surgeries. Due to the implicit limited working space of the retroperitoneum, it was hypothesized that SILS may have an application in VARD. It was recently applied the technology of SILS to VARD (siVARD) due to the prospect of better insufflation of the retroperitoneum, improved visualization, and limited working space present. It was reported on our operative experience of siVARD, compared to traditional laparotomy for infected necrotizing pancreatitis, in a single surgeon’s practice over the last one year. Preoperative drainage by radiologic guidance was performed in all patients. If patients failed to improve nonoperatively, they underwent either laparotomy or siVARD. Patients who underwent laparotomy were explored through a traditional midline incision, and pancreatic débridement managed utilizing a single-stage approach. Large bore drains were placed at the time of surgery and were managed with dependent drainage. siVARD patients underwent preoperative percutaneous drainage by radiologic guidance specifically through the left flank. At surgery, drainage tubes were utilized as a guide for a 4 cm left flank incision and followed into the cavity. A commercially available SILS port was used for siVARD. Insufflation and débridement was performed with traditional laparoscopic equipment. Survival for laparotomy patients was 75 percent (6/8) compared to 100 percent (2/2) for siVARD. Deaths in the laparotomy group were due to ischemic cerebrovascular accident 2 months after surgery, and visceral ischemia found at initial laparotomy due to thrombotic occlusion of the superior mesenteric artery in the necrotic pancreatic cavity. Average length of postoperative stay was 43 days for the laparotomy and 12 days for siVARD group, respectively. Average length of postoperative ICU stay was 10 days for the laparotomy and 2 days for siVARD group, respectively; one siVARD group patient was extubated postoperatively but required an extra 2 days in the ICU for continuous insulin infusion. Abdominal drains were removed after surgery on average 55 days for the laparotomy compared to 41 days for the siVARD group, respectively. Average transfusion requirements were 20 units of blood products compared to 1 unit for laparotomy versus siVARD groups, respectively. APACHE II scores in the laparotomy group were significantly higher than the siVARD group. It was concluded that siVARD was well tolerated and, by several objective measures, was superior to traditional laparotomy for selected patients. While laparotomy patients had higher APACHE II scores, application of siVARD occurred recently, and retrospectively could have been applied to 4 of the patients receiving laparotomy. siVARD appears to be a reasonable alternative for management of infected necrotizing pancreatitis in selected patients [5].

**Experimental respect**

**Myocardial function**

Evidences suggest that proinflammatory cytokines such as IL-1, TNF-alpha, IL-6 and IL-8 act as mediators of local and systemic manifestations in acute pancreatitis (AP) and correlate with the severity of the disease. The mechanisms of myocardial injury in AP are not completely understood. The production in situ into the myocardium of cytokines may lead to acute myocardial damage with functional changes and, eventually, chronic sequelae. TGF-beta cytokine is responsible for the modulation of collagen synthesis (type I and III) by triggering the pancreas fibrogenesis and collagen deposition, also early released in the course of AP and during the recovery phase, playing an important role in regulating mechanism of cellular repair. To evaluate the histological and functional changes of the heart in AP and to correlate with the production of cytokines in situ into the myocardium adult Wistar male rats were subjected to experimental AP induced by retrograde pancreatic duct infusion of Na-taurocholate. Myocardial function was evaluated by using echocardiography; rats were sacrificed for biochemical determination, histochemical and TGF-beta gene expression study at 2h, 12h and 15 days later. It was observed decrease diastolic and systolic function, decrease in ventricular compliance with fibromuscular lesions and elevation of TNF-alpha (2h) and IL-6 (2h and 12h), and elevation of TGF-beta mRNA levels demonstrating the occurrence of fibrosis and cellular repair. It was concluded that in acute pancreatitis there are function damage and increasing TGF-beta, probably related to myocardial reparation process [6].

**Effect of age**

Aging process has been held to influence the course and outcome of acute pancreatitis in elderly patients. The aim of one study was to evaluate the effect of age on severity of AP in an experimental AP model. AP was induced in male Wistar rats by intraductal 2.5 percent taurocholate injection and divided into 2 experimental groups: young (n=10) (3 month old rats), and older (n=10) (18 month old rats). Compared to young rats, rate of positive bacterial cultures obtained from pancreas cultures in the older rats was significantly increased. The study showed that age influences the course of acute pancreatitis evidenced by increased local and systemic lesions and the increased in bacterial translocation [7].

**Hypertonic saline**

Injury caused by ischemia-reperfusion may result in pancreatic graft loss in pancreas transplants. Therapeutics
strategies to reduce pancreatic ischemia-reperfusion injury are extremely important to improve the outcomes of clinical transplantation. It has previously been demonstrated that hypertonic saline 7.5 percent had anti-inflammatory response in acute pancreatitis and liver ischemia/reperfusion models. The aim of one study was to evaluate the effects of hypertonic saline 7.5 percent in ischemia / reperfusion pancreatic in Wistar rats during one hour by clamping the splenic vessels. The vascular clamp was removed 1 hour after ischemia and pancreatic revascularization was achieved, followed by 4h or 24h of reperfusion. It was found that hypertonic saline 7.5 percent decrease the systemic inflammatory response by cytokines reduction (TNF-alpha, IL-6, and IL-10) [8].

Urocortin
Urocortin 1 (Ucn1) and Corticotropin Releasing Factor (CRF) are important peripheral mediators of inflammatory conditions like inflammatory bowel disease and H pylori mediated gastritis. Ucn1 and CRF mediate their effect on inflammation via two established peripheral receptors: CRF1 and CRF2. Activation of the two receptors by Ucn1 or CRF results in context-dependent pro- or anti-inflammatory actions. Recent studies suggest that Ucn1 increases fluid extravasation in the intestine during inflammatory bowel conditions. Its effect on fluid leak were both CRF1-, and CRF2-dependent, but in an opposing manner. Knockdown of CRF2 potentiated inflammation. In pancreatitis it was hypothesize that the function of Ucn1, through its interaction with CRF2, influences the severity of inflammation. In control mice, Ucn1 immunoreactivity (Ucn1-IR) was prominently expressed in islet cells, pancreatic duct cells, and endothelial cells, but undetectable in acinar cells of controls. After induction of acute pancreatitis, de novo Ucn1-IR was detected in acinar cells of WT, HT, CRF2-KO and CRF2-antagonized mice. RT-PCR confirmed induction of Ucn1 mRNA in the pancreas after cerulein treatment. As expected, cerulein treated animals had increased histologic damage scores compared with saline controls. Interestingly, the damage score was 2-fold increased in HT mice and those pre-treated with CRF2 antagonist before cerulein induction. Cerulein induced increased MPO activity and pancreatic edema in WT mice. These effects were both amplified in CRF2-KO and CRF2-antagonized mice. Serum amylase activity was similar among all cerulein-treated groups and elevated compared to controls. In untreated acinar (AR42J) cells, RT-PCR showed low levels of Ucn1. Cerulein-treatment resulted in a marked 2-fold induction of Ucn1 mRNA. Stimulation of the acinar cells with Ucn1 resulted in a dose-dependent Ca²⁺ response. It was concluded that cerulein-induced pancreatitis resulted in Ucn1 upregulation in pancreatic acinar cells. Deletion and/or antagonism of the Ucn1 receptor CRF2 exacerbated pancreatic inflammation. These novel findings suggest a role for Ucn1 in pancreatic inflammation. CRF2 may be protective in pancreatitis [9].

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