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New Advances in Acute Pancreatitis

Matthew J. DiMagno, MD[*] and **Eugene P. DiMagno, MD**[§]

[*]University of Michigan Medical School, Division of Gastroenterology and Hepatology, Department of Internal Medicine Ann Arbor, MI 48109-0682

[§]Mayo Clinic College of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine Rochester, MN, 55905, USA

Summary

We reviewed studies this past year that further characterize the epidemiology, etiology and risk stratification of AP. Evolving areas include chemoprevention of post-ERCP AP and enteral feeding and antibiotics in severe AP. We await translation of novel therapies from the bench to bedside.

Keywords

acute pancreatitis; English language

Introduction

In this review of acute pancreatitis (AP) we focus on epidemiology, etiology, demographics and risk stratification. We also discuss advances in treatment, including chemoprevention of post-ERCP AP, enteral and antibiotic therapy. For experimental AP, we truncate our comments and refer readers to a recent comprehensive review.

Epidemiology

Two studies describe long-term trends in acute pancreatitis (AP) [1,2].

Yadav and Lowenfels [1] reviewed results of 12 longitudinal studies to determine long-term trends in the epidemiology of the first-attack of AP in the United Kingdom (UK), non UK European countries and Iceland. The predominant age of the onset of AP was the 6th decade. The most common etiologies were gallstones (10.8–56%), idiopathic (8–44%) and alcohol (3–66%). Idiopathic AP (IAP) was the most common etiology in the UK and alcoholic AP was most common in other countries. An increasing incidence of AP was noted in 10 studies [1], mostly due to alcoholic pancreatitis in non-UK countries (Sweden, Denmark, Netherlands); gallstone pancreatitis increased in all countries, but less so. Routine serum pancreatic enzyme testing in emergency departments may partially account for the increasing diagnoses of AP, particularly milder cases of AP, and/or mistakenly diagnosing AP for other conditions that cause hyperenzymemia. The proportion of patients with recurrent AP (RAP) decreased from 18–31% to 4.2–14.4%, an observation possibly explained by improved diagnosis of chronic pancreatitis, which commonly presents with recurrent attacks of pain. Population-based mortality rates were stable. Case fatality rates

Corresponding author: Matthew J. DiMagno, MD, Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Michigan Medical School, 1150 W Medical Center Drive, Room 6520 MSRB I, Ann Arbor, MI 48109-0682, USA, mdimagno@umich.edu, Telephone number: (734) 763-7278, Fax number: (734) 763-2535.

decreased from 15–20% to < 5% [1]. Mortality increased with age (< 5% for age < 40yrs; 30–40% for age > 80yrs). Sixty-five percent of deaths occurred within 14 days and 80% within 30 days. Many studies reported similar mortality rates among etiologies of AP.

In California, Frey et al [2] reported a 32% increase in the age-standardized incidence of AP based on a multi-ethnic cohort of patients hospitalized between 1994–2001. Biliary pancreatitis (52%) increased more than alcohol (12%) or idiopathic (18%) groups. The most common etiologies of first-attack AP were idiopathic (36.6%), biliary (32.6%) and alcohol (20.3%). The 14- or 91- day case fatality rate did not decrease, likely because case fatality rates were already < 6% similar to recent data from the UK which reported an initial decline and then a plateau in case fatality rates at 6–7%. Further decline of the case-fatality rate will likely require innovations of patient management. Older age was the greatest 14- and 91-day fatality risk factor. Alcoholic AP had the greatest mortality rate standardized for age, race and gender, consistent with data that as many as 1/3 of deaths related to AP never make it to the hospital and up to 75% of these are alcoholic in etiology. For unclear reasons, standardized case-fatality rates remained elevated even 9–12 months after hospitalization. The authors uncovered a major management error: only 43% of patients with biliary AP had same hospitalization cholecystectomy, thus exposing unoperated patients to the risk of a second episode.

Specific Etiologies

Recent publications report data on acute pancreatitis related to alcohol, gallstones, rare diseases, iatrogenic causes and medications.

Alcohol

A simple test to predict alcohol as the etiology of an attack of pancreatitis would be useful because it is often difficult to obtain a reliable alcohol history. Such a test may be carbohydrate deficient transferrin (CDT). In an editorial Perez-Matteo [3] pointed out that a CDT level greater than 17 U/L is 27% sensitive and 100% specific for predicting alcoholic AP, and by multivariate analysis elevated levels of CDT and serum trypsin correctly identified 98% of patients.

Gallstones

Hospitalization for gallstone associated disease related to pregnancy (during pregnancy and within 1 year postpartum) is more common than usually recognized, perhaps occurring in ~ 0.5% of all births, and many of these patients may incur AP [4]. In this retrospective case controlled study of 6670 patients with gallstone related hospitalization, most (76%) had uncomplicated cholelithiasis, but 16% had AP. Gallstone related hospitalizations were greater for Native Americans and for women who were younger, overweight or obese.

Rare diseases associated with AP include mitochondrial cytopathy, a group of diseases characterized by deletion or depletion of mitochondrial DNA. Debray et al [5] reported a patient with AP who had Karnes Sayre syndrome, a mitochondrial diseases characterized by the triad of external ophthalmoplegia, pigment retinopathy and heart block, cerebellar ataxia or cerebral spinal protein > 100mg/ml and documented this association in 6 other patients.

Iatrogenic

Although post-ERCP AP occurs in ~ 10% and may be severe [6], Bhatia et al [7] reported that it occurred in only 3.8% of 1497 ERCPs and 95% had mild disease. Similarly, AP after EUS-guided FNA of pancreatic masses is very low (3/355 patients; 0.83%) and mild [8].

Medications

The association of many medications with AP remains controversial. Some claim that any statin may cause a generally mild from of AP, but at a very low risk (odds ratio 1.4) that is not dose related, and appears after months to years of therapy without relation to age [9]. Others, however, deny a strong association and suggest that statins may lessen the risk of AP by reducing hypertriglyceridemia [10]. There are many case reports of cyclo-oxygenase-2 selective inhibitors and other non-steroidal anti-inflammatory drugs causing AP. In a population based case control study of 3083 AP and 30,830 controls, Danish investigators established that all NSAIDS were associated with AP, but at a low relative risk of 1 to 3 [11]. The antihypertensives, ACE inhibitors and calcium channel blockers, have a moderately increased risk for AP (adjusted odds ratio 1.5 for each) [12], but loop, thiazide and potassium sparing diuretic do not. Higher doses of ACE inhibitor moderately increase the risk of AP, which is more frequent in the first 6 months of treatment while calcium channel blockers have no dose or time relationship to AP [12]. Proton pump inhibitors and H2 blockers may increase the risk of AP, but these data are confounded because untreated GERD and gastritis may increase the risk of AP [13]. Interestingly, valproic acid may not be an independent risk factor for AP because the adjusted odds ratio for AP in current users of valproic acid is 2.6, similar to the odds ratio of other antiepileptics [14].

Idiopathic pancreatitis (IP)

Idiopathic pancreatitis (IP) commonly is classified as idiopathic acute pancreatitis (IAP), idiopathic recurrent acute pancreatitis (IRAP) and idiopathic chronic pancreatitis (ICP). IRAP, however, is uncommon, certainly less than 14% of persons with a first-attack of AP [1], and should be restricted to patients who truly have an unknown cause of recurrent acute pancreatitis (RAP). All other patients should be classed as RAP as most patients with the initial label of IRAP will eventually be found to have one of the causes of RAP including biliary disease (gallbladder microlithiasis, choledocholithiasis, biliary sludge), ICP, genetic abnormalities such as CFTR or HP mutations, or unusual lesions such as ampullary lesions or pancreatic cancer. Whether pancreas divisum or SOD [6] cause RAP is controversial (see below). Few studies combine complete diagnostic testing with prospective follow-up, but patients most commonly have occult cholelithiasis or have or develop signs of ICP.

Data from a recently published long-term follow-up study by Garg et al. [15] indicates that ICP is a more common cause of RAP than biliary lithiasis [15]. They identified 75 patients with RAP and followed them prospectively for a mean 18 months. ~ Fifty percent developed conclusive evidence of ICP by imaging studies (CT, ERCP, US or EUS), and 16% had biliary lithiasis (microlithiasis [n=10] or gallstones [n=2]). In this study 2 patients with overt gallstones had cholecystectomy and resolution of RAP, but 8/10 patients with microlithiasis treated with cholecystectomy (n=4) or biliary sphincterotomy (n=4) had persistent RAP and developed ICP. Detection of ICP in the microlithiasis group suggests that microlithiasis was mis-diagnosed and/or lithogenic bile associates with ICP as it does with cystic fibrosis, a known cause of RAP. The response to cholecystectomy in patients with overt gallstone AP is similar to findings in a cohort of 2583 patients with gallstones, where patients who had gallstone AP (3.4% of cohort) and a cholecystectomy had a risk of recurrent pancreatitis or chronic pancreatitis identical to the general population [16]. Overall, these data strengthen existing data that early ICP is a common etiology of RAP, reported in 27% [17] and 39% (post-cholecystectomy) [18] of patients followed prospectively for < 3 years and up to 53% of patients with RAP associated with pancreas divisum (DiMagno and DiMagno [19]).

It is likely that early- and late- onset ICP develop as a consequence of RAP due to unrecognized etiologies (? genetic abnormalities or environmental factors) causing the necrosis-fibrosis sequence and what we now term ICP. Thus, at our current stage of

knowledge, IRAP is an early manifestation of ICP. Support for this position resides in finding that ICP is characterized by recurrent attacks of pain for variable duration and frequency [20–22], and that a proportion of patients (n=35) prospectively followed with RAP treated with or without pancreatic duct stenting develop ICP [17]. During a mean ~ 3-year follow-up, stenting reduced the frequency of attacks of "AP" (53% vs. 11%) but had no effect on pancreatic type pain (32% vs. 40%) or the development of findings of ICP (27% vs. 26%). Patients were excluded for overt chronic pancreatitis, gallstone disease, microlithiasis, alcohol, and SOD (by manometric criteria). This indicates that patients with RAP commonly have early ICP and pancreatic duct stenting does not prevent the course of ICP. We also speculate that patients labeled as IRAP, manometric findings of SOD reported in 15–35% of patients [6] are less likely the cause of RAP and more likely the sequelae (inflammatory, fibrotic or neural) of ICP. A prospective follow-up study of patients with RAP and manometric findings of SOD to determine how many develop ICP could test this hypothesis.

Genetic analyses (and family history) may help predict ICP in patients with RAP. The frequency of CFTR gene mutations in patients previously thought to have IP is 10–50%, depending upon the number of the ~ 1500 CFTR mutations tested. Notably, CFTR gene mutations are not associated with single episodes of AP [23]. Previously, Choudari et al. [24] reported a 19% frequency of CFTR mutations (based on a 13 CFTR panel) in patients originally classed as IRAP, a similar frequency to that reported in ICP (using a similar screening panel) [25,26]. A higher prevalence of CFTR gene mutations was detected in IP using exhaustive gene identification methods - 38% of those having IRAP and 45% of ICP [27]. Hence, the association of CFTR gene mutations with groups labeled as having IRAP [24,27] has been interpreted by experts as further evidence that these patients have early-onset ICP with recurrent attacks of pain [28].

Variations in patient selection and the pattern of referral may influence the yield of screening for CFTR mutations in IP. For example, the Indiana group [29] reported a lower 8.4% frequency of CFTR mutations in patients with IP compared to their earlier study [24], even though they used a more extensive CFTR gene mutation panel (70 to 87 alleles) than in the earlier study [24]. The control and ICP patients had a high but similar frequency of pancreas divisum (30% and 20%, respectively), providing further support that pancreas divisum is not a cause of pancreatitis, a position we argue (DiMagno and DiMagno 2007 [19]) leading Fogel, Toth and Lehman, previously strong proponents of the association to suggest that "other predisposing factors such as CFTR mutations may be necessary for pancreatitis to occur in patients with pancreas divisum". Finally, Alzami et al [29] reported that patients with CFTR mutations had more severe Cambridge criteria for chronic pancreatitis than the ICP, control group, but the prognostic importance of this finding is unclear.

Management of presumed IAP is based upon the supposition that ~ 75% patients with IRAP have occult cholelithiasis (based upon gallbladder imaging or finding microlithiasis in bile drainage) and treatment significantly reduces risk of RAP. Evans and Draganov [30] argue that in the absence of RCTs that compare laparoscopic cholecystectomy, biliary sphincterotomy and ursodeoxycholic acid, laparoscopic cholecystectomy is preferred because of safety and almost certain cessation of future attacks. An interpretation of the study by Garg et al [8], however, suggests that cholecystectomy or biliary sphincterotomy should not be done in patients with RAP unless microlithiasis (or perhaps sludge) is suspected by finding elevated liver tests and/or confirmed by ultrasound or bile crystal analysis. However, a small proportion of RAP patients may have biliary lithiasis undetected by testing and deserving of a laparoscopic cholecystectomy.

Demographics and Risk Stratification

Recent studies further clarify the predictors for severe AP, infected necrosis and mortality and the association between pancreatic necrosis and severity.

Demographic factors

Obese persons with AP have a greater probability of developing complications and severe disease, and they die more frequently [31] than non-obese persons, but it appears that among other factors obesity is not a risk factor for pancreatic necrosis (logistic regression) [32]. Alcohol intake of > 2 drinks per day, however, may significantly increase the risk of developing pancreatic necrosis [32] regardless of the etiology of the AP.

Prediction of severity

A search continues for a simple scoring system to accurately predict severity. Spitzer et al [33] developed and retrospectively evaluated a 4-component system (age ≥ 65, BUN ≥ 25 mg/dl, LDH ≥ 300 IU/ml and Il-6 ≥ 300 pg/ml) and reported that it was as accurate as Ranson, Glasgow, and APACHE II scoring systems. Three and 4 positive factors incurred a 25% and 50% mortality, respectively. Advantages of this system are simplicity and ability to use it anytime during the first 48h, but it has not been evaluated prospectively. Computer assisted systems using machine learning methods (computer algorithms that improve automatically by experience) [34] including artificial neural networks [35], may improve prediction of severity. Pearce et al [34] demonstrated in a retrospective analysis of 265 patients with AP that a model based upon kernel logistic regression and bootstrapping employing 8 variables (age, respiratory rate, CRP, WBC, arterial pO_2 on air, serum creatinine, arterial pH and GCS) was superior to APACHE II for predicting severity on admission with a sensitivity and specificity of 87 and 71%, respectively. Similarly, Mofidi et al [35] showed that retrospectively an artificial neural network more accurately assessed severity and mortality than APACHE II and Glasgow scoring systems. At present these computer-learning methods appear promising but need to be trained and tested rigorously and prospectively.

Opinions differ about the relations among early systemic inflammatory response (SIRS), multisystem organ failure (MODS), infection, severity and death in AP. As reviewed by Banks [36], organ failure is more common in necrotizing vs. interstitial AP (54% vs. 10%) and mortality is higher in necrotizing vs. interstitial AP (17% vs. 3%) and in necrosis with MODS (47%) vs. single organ failure (3%) vs. no organ failure (0%). Further, organ failure is largely responsible for early deaths (within 1–2 wks), which occur at least as frequently [36] and possibly more frequently [1] than later deaths, caused by infected necrosis or a complication of sterile necrosis. Mofidi et al [37] emphasized the association between SIRS and MODS in 759 patients with AP and showed that *persistent* SIRS was associated with MODS and death. Rau et al [38] compared the outcome of 135 patients with *sterile pancreatic necrosis* who underwent necrosectomy and 95 patients managed conservatively without operation and found that the major factors for developing pancreatic infection after operation were extent of necrosis and early MODS, but that death was related to MODS rather than necrosis and/or infection. These data contrast with earlier findings by Götzinger et al. [39] that by multivariate analysis the 2 factors that independently predict organ failure are extent of necrosis (in both sterile and infected necrosis) and infected necrosis, and that infected necrosis and APACHE II score predict mortality. The different conclusions in the Rau [38] vs. Götzinger [39] studies are partially explained by the larger size and power of the Götzinger study, which had more patients with > 50% necrosis (138 vs. 52) and < 50% necrosis (202 vs. 165). The overall clinical implications are that persistent organ failure and extent of necrosis may be useful for predicting infected necrosis, but organ failure

(particularly persistent organ failure and MODS) more reliably but not necessarily exclusively predicts increased mortality in AP.

Chemoprevention of Post-ERCP Pancreatitis

In the past year several groups have re-investigated chemoprevention (N-acetylcysteine [40], octreotide [41,42], the protease inhibitors gabexate [43,44] and ulinastatin [44], and glyceryl trinitrate [45]) of post- ERCP pancreatitis either by RCTs or meta-analyses [46,47]. Milewski et al. confirmed that N-acetylcysteine was ineffective [40]. Two groups conducted an RCT and claimed that octreotide prevented post-ERCP pancreatitis [41,42], but two groups previously showed that octreotide was ineffective [48,49], corroborating negative findings of a meta-analysis of 10 other clinical trials [50]. The variable results of the octreotide studies are likely due to marked differences among the studies such as drug dose and duration, population, endpoints, etc.; therefore, it is doubtful that an updated meta-analysis will draw a different conclusion. Results of meta-analyses indicate that the protease inhibitor ulinastatin is no more effective than gabexate at reducing post-ERCP AP [44] and that short- or long-term infusion of gabexate does not reduce post-ERCP AP [46,47]. Similar to the octreotide studies, differences in study design and populations are present in studies designed to investigate if glyceryl dinitrate reduces post-ERCP pancreatitis; it was ineffective in a recent study [45] and beneficial in two prior studies [51,52]. In summary, the results of the RCTs of chemoprevention therapy for post-ERCP pancreatitis are inconclusive and raise more questions than answers.

Enteral and Parenteral Feeding

Clinicians administer enteral feeding (EF) and parenteral feeding (PF) to patients with severe AP or who will not be able to consume food for several weeks. EF is safer and costs less than PF. The *extent* that EF beneficially impacts AP is unclear. In a systematic review McClave et al. [53] concluded, “patients with severe AP should begin EF early because such therapy modulates the stress response, promotes rapid resolution of the disease process, and results in better outcome. These recommendations mirror new guidelines from the European Society for Clinical Nutrition and Metabolisms (ESPEN) [54] and the American College of Gastroenterology (ACG) [36]. Three new studies advance understanding in this area.

Petrov et al. [55] report data on the largest cohort of patients (n=70) with predicted severe AP (based on APACHE II score > 8 and/or CRP >150 mg/dl) who were randomized to EF vs. PF, started within 72 hours from symptom onset. Both groups had similar rates of transient organ failure but the EF group had reduced persistent organ failure after 7 days (3% vs. 23%), pancreatic infectious complications (20% vs. 46%), MODS (20% vs. 49%) and mortality (6% vs. 34%), the latter occurring after 2 weeks in 57%. These striking findings seem too good to be true, possibly due to an unidentified bias, but if reproducible, would have a greater impact on mortality in severe AP than any known intervention.

In studies of patients with predicted severe AP, nasogastric EF is safe and well tolerated compared to jejunal EF [56] or to PF [57]. The study of Kumar et al. [56] is difficult to interpret because patients started jejunal EF or PF after markedly different durations of symptoms (1–32 days) as is the Eckerwall et al. study [57], because only 46% of patients had severe AP by Atlanta criteria. Further the nasogastric EF group had more patients with pancreatic necrosis than the PF group (30% vs. 15%), which likely explains the higher complication rate and transiently greater intestinal permeability in the nasogastric EF group. Additional studies are required to determine the differential impact among nasogastric EF, nasojejunal EF and PF in patients with severe AP, and to determine the appropriate time to start treatment, composition and volumes of EF.

Antibiotics

Does giving *systemic* antibiotics prophylactically to patients with severe necrotizing AP prevent pancreatic infection? As indicated by expert opinon [58], ACG practice guidelines [36] and a meta-analysis [59], large, well designed studies are lacking. Only one RCT was doubly blinded. Similar to the ACG guideline [36] the authors of the meta-analysis [59] conclude that prophylactic antibiotics reduce hospital stay but they do not reduce infected necrosis, mortality, non-pancreatic infections and the rate of surgical intervention. Lankisch and Lerch [58] provide 4 helpful criteria to justify administration of antibiotics: sepsis or SIRS, failure of ≥ 1 organs, proven pancreatic or extrapancreatic infection or an increase in CRP with evidence of pancreatic or extrapancreatic infection. Subsequent to these analyses Manes et al. [60] published a RCT indicating that the *timing* of administering antibiotics is important. Regardless of predicted severity of AP, patients were randomized to start meropenam immediately after hospitalization (day 1.1) or after diagnosis of pancreatic necrosis (day 4.5). Analysis was restricted to only those with verified pancreatic necrosis. Both groups had similar CRP values (215 vs. 203 mg/dL) and numbers of patients divided according to % necrosis: < 30% (15 vs. 14), 30–50% (8 vs. 7), and > 50% (7 vs. 8). Early antibiotic treatment reduced extra-pancreatic infection (17% vs 49%), need for surgery (13% vs 38%) and length of hospitalization (18 days vs. 30 days) but had no significant effect on pancreatic infections (13% vs. 30%), single organ failure, MODS or mortality. Additional study is required to determine if the timing of starting antibiotics is critical, whether all patients should be treated initially with antibiotics until they are risk stratified, and whether the benefit outweighs the risk of developing antibiotic resistance.

Experimental Pancreatitis

Multiple investigators have identified the major events leading to acinar cell injury and events subsequent to cell injury that determine the severity of AP (see Table 1). These events have been described in clinically relevant experimental models, including the CF mouse model [61] and alcohol AP [62]. Important extra-pancreatic factors that modulate pancreatitis include neural signaling and the vascular response; the latter has been a research focus of our group. For discussion of recent and past observation in experimental pancreatitis, we refer the reader to the recent, comprehensive review of this topic [62].

Conclusion

We have endeavored to review clinical and basic research studies this past year that further characterize the epidemiology, etiology, and determinants of severity in AP. Importantly it is becoming evident that by thoroughly investigating and prospectively following patients previously labeled as IRAP, most will be found to have chronic pancreatitis or microlithiasis as a cause of RAP. Although therapies to lessen the severity and mortality of AP are lacking, potential therapeutic targets identified in experimental AP studies may translate to future, novel therapies offered at the bedside.

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Abbreviations

AP	Acute pancreatitis
ACG	American College of Gastroenterology
ACE	angiotensin converting enzyme
CDT	carbohydrate deficient transferrin
CP	chronic pancreatitis
CT	computed tomography
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
EF	enteral feeding
ICP	idiopathic chronic pancreatitis
IP	idiopathic pancreatitis
IRAP	idiopathic recurrent acute pancreatitis
MODS	multisystem organ failure
PF	parenteral feeding
QOL	quality of life
RAP	recurrent acute pancreatitis
RCT	randomized controlled trial
SIRS	systemic inflammatory response syndrome
US	ultrasound

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Purpose of review

We endeavor to review important new advances in acute pancreatitis (AP) made in the past year. We focused on clinical aspects of AP, which contained new observations or insights into new or old concepts. For experimental AP we refer readers to a recent comprehensive review

Recent findings

1. Case fatality rates of AP stabilized
2. Carbohydrate deficient transferrin predicts alcoholic AP
3. Idiopathic chronic pancreatitis (ICP) or occult cholelithiasis associate with “recurrent acute pancreatitis” (RAP) in most patients
4. CFTR genetic mutations frequently found (10–50%) in patients with RAP
5. Alcohol increases the risk of pancreatic necrosis regardless of the etiology of AP
6. Persistent organ failure and MODS but not necessarily extent of necrosis predict increased mortality in AP
7. Chemoprevention of post-ERCP AP remains unproven
8. Enteral feeding is strongly recommended in severe AP
9. Data is lacking for routine, prophylactic antibiotic administration to all patients with pancreatic necrosis.

TABLE 1

Multiple Factors Associated with Severe Experimental Acute Pancreatitis

Intra-pancreatic
Sustained intracellular calcium flux
Intracellular trypsinogen activation
Greater acinar cell necrosis relative to apoptosis
Increased inflammatory mediator expression
Greater neutrophil sequestration
Extra-pancreatic
Reduced microvascular perfusion
Neural signaling