REVIEW

REVISED Recent advances in understanding and managing acute pancreatitis [version 2; peer review: 2 approved]

Amar Mandalia, Erik-Jan Wamsteker, Matthew J. DiMagno

Division of Gastroenterology and Hepatology, University of Michigan School of Medicine, Ann Arbor, MI, 48109, USA

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Abstract

This review highlights advances made in recent years in the diagnosis and management of acute pancreatitis (AP). We focus on epidemiological, clinical, and management aspects of AP. Additionally, we discuss the role of using risk stratification tools to guide clinical decision making. The majority of patients suffer from mild AP, and only a subset develop moderately severe AP, defined as a pancreatic local complication, or severe AP, defined as persistent organ failure. In mild AP, management typically involves diagnostic evaluation and supportive care resulting usually in a short hospital length of stay (LOS). In severe AP, a multidisciplinary approach is warranted to minimize morbidity and mortality over the course of a protracted hospital LOS. Based on evidence from guideline recommendations, we discuss five treatment interventions, including intravenous fluid resuscitation, feeding, prophylactic antibiotics, probiotics, and timing of endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis. This review also highlights the importance of preventive interventions to reduce hospital readmission or prevent pancreatitis, including alcohol and smoking cessation, same-admission cholecystectomy for acute biliary pancreatitis, and chemoprevention and fluid administration for post-ERCP pancreatitis. Our review aims to consolidate guideline recommendations and high-quality studies published in recent years to guide the management of AP and highlight areas in need of research.

Keywords

Acute pancreatitis, alcohol, gallstones, smoking, cannabis, goal directed fluid therapy, feeding, cholecystectomy, ercp

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1 **Charles Melbern Wilcox**, University of Alabama School of Medicine, Birmingham, USA

2 **Masahiko Hirota**, Kumamoto Regional Medical Center, Kumamoto, Japan

Any comments on the article can be found at the end of the article.

Corresponding author: Matthew J. DiMagno (mdimagno@umich.edu)

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REVISED **Amendments from Version 1**

In the "Feeding" section, the discussion of feeding during acute pancreatitis mistakenly mixes the impact of two different feeding comparisons (early- versus delayed feeding; and remaining NPO versus early oral feeding) on outcomes during acute pancreatitis. This version 2 has been published to correct this.

See referee reports

Introduction

Acute pancreatitis (AP), especially severe cases, is a major clinical and financial burden in the United States. In 2012, AP was the single most common specific gastrointestinal diagnosis for inpatient hospitalization, and annual costs were about $2.6 billion[1]. Several major clinical guidelines provide evidence-based recommendations for the clinical management decisions in AP, including those from the American College of Gastroenterology (ACG) (2013)[2], the American Gastroenterological Association (AGA) (2018)[3,4], and the International Association of Pancreatology (IAP) (2013)[5]. In this update on AP, we reference recent literature and guideline recommendations focused on epidemiology, risk factors, etiology, diagnosis, risk stratification, and recent advances in the early medical management of AP. Regarding the latter, we review five treatment interventions (intravenous fluid resuscitation, feeding, prophylactic antibiotics, probiotics, and timing of endoscopic retrograde cholangiopancreatography [ERCP] in acute biliary pancreatitis) and four preventive interventions (alcohol and smoking cessation, same-admission cholecystectomy for acute biliary pancreatitis, and chemoprevention and fluid administration for post-ERCP pancreatitis, or PEP). Important management topics not discussed in this review include critical care management in AP (for example, abdominal compartment syndrome[6]) and late decision making for pancreatitis complicated by infected necrosis, which involves source control with antibiotics and step-up therapy using a combination of percutaneous drainage, endoscopic management, and surgical intervention[7–10].

Recent advances in epidemiology and evaluation of acute pancreatitis

Epidemiology

Recent epidemiologic studies show conflicting trends for AP. According to Sellers *et al*., the incidence of AP has decreased in adults from 2007 to 2014 in the United States[11]. However, data are limited to patients having insurance. In contrast, Krishna *et al*. provide evidence that the incidence of AP in the United States is increasing[12], similar to trends over the last few decades. Krishna *et al*.[12] extracted data from the Nationwide Inpatient Sample (NIS) and compared two time periods: 2009–2012 (n = 1,070,792) and 2002–2005 (n = 945,253). The major finding was that hospitalizations for AP increased 13.3% (p <0.001). This observed increase is problematic, however, because the analysis did not exclude patients with chronic pancreatitis (CP). The prevalence of CP increased 96%, and CP was the most important independent variable associated with AP hospitalizations between 2009 and 2012 (odds ratio [OR] 35.02, 95% confidence interval [CI] 33.94–36.14). Because smoking was one of three independent predictors for increased risk of CP, it is not surprising that the prevalence of both smoking and CP each increased about 100%. The changes in the odds of AP hospitalization due to other variables were less pronounced from 2009 to 2012 compared with 2002 to 2005: odds (95% CI) decreased for gallstone-related disease—29.85 (33.94–36.14) versus 36.37 (35.32–37.46)—and to a lesser degree for alcohol-related, hyperlipidemia, and diabetes[12]. Unexpectedly, morbid obesity had a reduced odds of AP that increased modestly over time[12]. Pancreatic neoplasm had an increased but unchanged odds of AP over time[12].

Hospital length of stay (LOS), costs, and mortality declined in 2009–2013 compared with 2002–2005. Mean hospital LOS decreased 0.78 days (−0.85 to −0.70; p <0.001), mean hospital costs fell $573 per admission (−$869 to −$277; p <0.001), and AP-related mortality declined 30% (3,749 [1.62%] to 2,130 [0.79%]; p <0.001). Brown *et al*. attributed these improved outcomes to several potential factors, including routine use of risk stratification tools, increased efficacy of diagnostic tools, and expedited triage of moderate to severe cases to aggressive management in intensive care units[13]. Multiple studies have also reported a decrease in mortality related to AP[13–15]. In support of the possibility that improved management is responsible for decreased mortality, a retrospective study by Agarwal *et al*. demonstrated a decrease in mortality at a tertiary care center in India, despite referral of an increased proportion of patients with organ failure and infected pancreatic necrosis[16].

Mortality rates are similar between several etiologies of AP, including gallstone-related and alcohol-induced AP[17] and hypertriglyceridemia and alcohol-induced AP[18]. Persistent organ failure (POF) is defined as organ failure lasting more than 48 hours and is the major cause of death in AP. Additional factors associated with increased mortality include diabetes mellitus[19], hospital-acquired infection[20], and advanced age (≥70)[21]. To investigate the controversial association between obesity and mortality in patients with AP, Krishna *et al*. used data from the NIS (2007–2011) to perform propensity score-matched analyses to compare outcomes for adult inpatients with AP with and without morbid obesity[22]. Morbid obesity was associated with higher frequencies of acute kidney injury (10.8% versus 8.2%; p <0.001) and respiratory failure (7.9% versus 6.4%; p <0.001) and higher odds of mortality (OR 1.6, 95% CI 1.2–2.1)[22]. Finally, following hospital discharge for a first episode of AP, a recent study reported 1-year mortality associated with three independent predictors: readmission within 30 days, higher Charlson comorbidity index, and longer hospitalizations[23].

Risk factors

Recent studies address the risk modifiers for AP due to alcohol and gallstones, newly identified risk factors (cannabis), factors responsible for AP in the setting of inflammatory bowel disease (IBD) and end-stage renal disease (ESRD), and the risk of pancreatic cancer after first attack of AP.

When compared with never-smokers, current tobacco use (hazard ratio [HR] 1.75, 95% CI 1.26–2.44) and former tobacco

use (HR 1.63, 95% CI 1.18–2.27) are independent risk factors for AP[24]. The relationship between alcohol exposure and pancreatitis is complex[25,26]. In the meta-analysis by Samokhvalov *et al*., the relationship between dose of alcohol and risk of AP was linear (and with no identifiable threshold) in men but non-linear (J-shaped) in women[27]. Risk of AP in women was decreased with alcohol consumption up to 40 g/day and increased above this amount. The authors speculated that the observed increased risk in women (beyond 40 g/day) was attributed to inclusion of former drinkers in the reference group or possibly the impact of alcohol reducing the risk of biliary pancreatitis[27].

The risk of gallstone-related AP may be influenced by diet: increased by consumption of saturated fats, cholesterol, red meat, and eggs[28] but decreased by fiber intake[28] and, as noted above, alcohol consumption[29].

Cannabis is a possible risk factor for toxin-induced AP on the basis of a recent systematic review[30]. Although the study is limited by having data from only 26 patients, 15 from case reports, eight from a single prospective study, and three from a case series, a clinically meaningful association is likely, particularly between cannabis use and idiopathic pancreatitis, on the basis of follow-up information. Cannabis abstinence completely abolished recurrent attacks of pancreatitis in patients for whom follow-up information was available[30].

Clear understanding of the frequency and etiology of AP in the setting of IBD has implications for selecting treatments for this condition. Chen *et al*. searched the National Health Insurance Program administrative database from Taiwan for disease-specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) billing codes and identified 11,909 patients with IBD and 47,636 age- and sex-matched controls[31]. After adjusting for comorbidities, they found a 2.93-fold higher HR (95% CI 2.40–3.58) for AP in the IBD versus non-IBD cohorts[31]. Important limitations of this study are that the diagnosis and etiology of AP are uncertain and are based on administrative ICD-9-CM billing codes without confirming diagnoses by chart review or excluding multiple other causes of AP, including alcohol, medications that may cause AP (for example, azathioprine and mesalamine), familial pancreatitis, and type II autoimmune pancreatitis (AIP)[32]. Recently, Ramos *et al*. highlighted that gallstones and drug-induced pancreatitis are the most common causes of AP in patients with IBD[33]. It is important to note that type II AIP has a higher association with IBD[34] and that IBD is associated with asymptomatic elevations in serum lipase and amylase[35].

Severe renal disease is an established association with pancreatic diseases[36]. In patients with ESRD, the risk of AP and possibly more severe AP is higher in those who receive peritoneal dialysis compared with hemodialysis[36–41]. Recently, Chen *et al*. identified additional independent risk factors for AP in the ESRD population, including older age, being a woman, and having biliary stones or liver disease[42].

As recently reviewed[43], pancreatic cancer appears to be associated with first-attack pancreatitis with few exceptions[44]. In a Veterans Affairs National Medical Care Data Set, containing nearly 500,000 patients, 11% of those with diagnosed pancreatic cancer had an attack of AP in the previous 2 years[45]. The incidence of pancreatic cancer was 1.5% and was greatest within the first year of the attack of AP. The incidence of cancer correlates with age, negligible below age 40 but steadily rising through the fifth to eighth decades. The main message from these studies is to consider and screen for pancreatic cancer as a potential etiology of unexplained AP in patients, particularly those 40 years of age or older. Similar findings were observed in the more recent nationwide matched-cohort study in Denmark, which included 41,669 patients with incident AP who were compared with 208,340 age- and sex-matched controls[43]. AP was associated with an overall increased absolute risk of pancreatic cancer, which was highest after 2 years of follow-up (0.68%, 95% CI 0.61–0.77%) but persistently increased after 5 years (0.85%, 95% CI 0.76–0.94%)[43]. The persistent nature of the risk may underscore the importance of inflammation as a cofactor in the development of pancreatic cancer and show that a subset of patients in this Danish cohort may have had underdiagnosed CP.

Etiology and diagnosis

To date, alcohol and gallstones remain the most prevalent etiologies for AP[2]. Studies from over 10 years ago reported frequencies of 40–50% and about 20% for biliary AP and alcohol AP, respectively[22,46,47]. A more recent study reported a lower frequency of biliary AP (22%) and a higher frequency of alcohol AP (29%), likely due to inclusion of patients with CP, representing 15% of the cohort of patients with AP. AP due to hypertriglyceridemia, estimated to be about 9% of AP, is less common[48].

Guidelines and recent studies of AP raise questions about the threshold above which hypertriglyceridemia causes or poses as an important cofactor for AP. The triglyceride threshold value for causing AP was set as at least 1,000 mg/dL by the ACG and the Endocrine Society and at least 885 mg/dL by the European Society of Cardiology and the European Arteriosclerosis Society[2,49,50]. Pedersen *et al.* provide evidence of a graded risk of AP with hypertriglyceridemia, based on analysis of a prospective cohort of 116,500 individuals with triglyceride measurements from the Copenhagen General Population Study (2003–2015) and the Copenhagen City Heart Study (1976–2003)[51]. By multivariable analysis, adjusted HRs for AP were much higher with non-fasting mild-to-moderately elevated plasma triglycerides (177–885 mg/dL) compared with normal values (<89 mg/dL)[51]. Nawaz *et al.* also reported that, in addition to posing a risk for AP, the risk of severe AP (developing POF) increases in proportion to triglyceride value, independent of the underlying cause of AP[52]. A natural question from a recent systematic review is whether AP is significantly more severe when the cause is hypertriglyceridemia compared with other etiologies, but data are limited[48]. The same systematic review reported that plasmapheresis effectively decreases circulating triglycerides in patients with AP but has no conclusive mortality benefit[48]. A significant limitation is that data supporting the efficacy of plasmapheresis are extrapolated primarily from observational studies and case series. The current standard of

care is directed toward bowel rest and insulin infusion to reduce triglyceride levels.

Diagnosis of AP is derived from the revised Atlanta classification[53]. The recommended timing and indications for offering cross-sectional imaging are after 48–72 hours, when a patient experiences no improvement to initial care[2]. The advantage of magnetic resonance cholangiopancreatography (MRCP) compared with computed tomography (CT) is the capability of identifying choledocholithiasis as small as 3 mm as well as pancreatic duct disruption[54]. Although specific guideline recommendations advocate more selective use of pancreatic imaging in the early assessment of AP, a recent retrospective study observed no significant decrease in the utilization of early CT or MRCP imaging (within the first 24 hours of care) in the period of 2014–2015 compared with 2006–2007, indicating that quality improvement initiatives are needed to decrease the overutilization of imaging[55].

Clinical applications of endoscopic ultrasound (EUS) and ERCP have evolved for the evaluation of patients with suspected acute biliary pancreatitis. ERCP is not recommended as a pure diagnostic tool, owing to the availability of other diagnostic tests and a complication rate of 5–10% with risks involving PEP, cholangitis, perforation, and hemorrhage[56]. A recent systematic review of EUS and ERCP in acute biliary pancreatitis included seven studies having a total of 545 patients[57]. The authors concluded that EUS had lower failure rates and had no complications, and the use of EUS avoided ERCP in 71.2% of cases[57].

Risk stratification

The goals of risk stratification tools in AP are to identify patients at risk for developing major outcomes, including POF, infected pancreatic necrosis, and death. The underlying premise is that predicting the severity of AP within 48 to 72 hours of presentation enables triaging of patients to an appropriate level of care to decrease morbidity and mortality associated with AP. Two recent guidelines affirmed the importance of predicting the severity of AP, using one or more predictive tools[2,5]. The recent 2018 AGA technical review does not debate this commonsense approach, including use of dynamic predictive variables over time, but does highlight that there is no published observational study or randomized controlled trial (RCT) investigating whether the use of severity prediction tools impacts clinical outcomes[3].

A diverse array of severity prediction tools exists, categorized as clinical scoring systems, single laboratory values, and other variables. Some examples of commonly used clinical scoring systems are Acute Physiology and Chronic Health Evaluation II (APACHE II), BISAP (blood urea nitrogen [BUN], impaired mental status, systemic inflammatory response syndrome, age, and pleural effusion), early warning system (EWS), Glasgow-Imrie score, and Japanese severity score. BISAP is a validated clinical scoring system that predicts in-hospital mortality on the basis of five variables: BUN of more than 25 mg/dL, impaired mental status, systemic inflammatory response syndrome, age of more than 60, or presence of pleural effusion[58]. In 2010, Papachristou *et al.* determined that BISAP scoring is just as accurate as APACHE II, CT severity index, and Ranson's in predicting the severity and prognosis of AP[59]. A subsequent comparative analysis by the same investigators concluded that available predictive tools have limited clinical utility by having only moderate predictive value for POF and mortality[60]. More elaborate and automated machine learning algorithms have also been developed for predicting severity, designed using artificial neural networks and metabonomics technology, but the incorporation of these algorithms into clinical applications remains challenging[61–63].

Recent advances in early treatment of acute pancreatitis

Literature review and definitions

The AP literature contains heterogeneous definitions of severe AP and of what constitutes a major outcome in AP. This limitation, particularly in older literature, served as the impetus for the 2012 revision of the Atlanta Criteria for AP[53]. To extract from the literature meaningful summary evidence and estimates for the AGA Clinical Guideline on early medical management of AP, the 2018 AGA technical review applied precise definitions to each step of the review process, and the emphasis was on clear definitions of primary outcomes of clinical importance in AP, including death, persistent single organ failure (PSOF), or persistent multiple organ failure (PMOF), each requiring a duration of more than 48 hours, and infected pancreatic or peri-pancreatic necrosis or both[3,4]. For these reasons, our review of early treatment of AP preferentially weighs recommendations in favor of those espoused by the 2018 AGA technical review and clinical guideline.

Intravenous fluid administration

Supportive care with the use of intravenous fluid hydration is a mainstay of treatment for AP in the first 12–24 hours. Hypovolemia in AP is driven by third spacing and intravascular volume depletion[64]. Guidelines advocate for early fluid resuscitation to correct intravascular depletion in order to reduce morbidity and mortality associated with AP[2,3,5]. However, as Haydock *et al.* point out, there is a deficiency of high-quality data to establish firm recommendations[65]. The 2018 AGA guidelines endorse a conditional recommendation for using goal-directed therapy for initial fluid management[4], do not recommend for or against normal saline versus lactated Ringer's (LR), but do advise against the use of hydroxyethyl starch fluids[4]. The AGA guidelines and the technical review acknowledge that evidence was weak in support of goal-directed therapy[3,4], which was a pre-defined study arm in four of seven RCTs reviewed and had no significant reduction in PMOF, mortality, or pancreatic necrosis compared with usual care. As the authors noted, interpretation of the data was limited by the absence of other critical outcomes in these trials (infected pancreatic necrosis), lack of uniformity of specific outcomes and definitions of transient and POF, few trials, and risk of bias. As illustrated in a recent review and RCT, potential endpoints of goal-directed therapy over the first 12–24 hours may include reducing serum BUN and hematocrit at various intervals after initial fluid administration[66,67]. Recent hypothesis-generating efforts by DiMagno *et al.* illustrate how integrating

a goal-directed fluid therapy algorithm with a web-based protocol and paging alert system shows promise for decreasing variability in care and shortening hospital LOS[68].

Feeding

The focus of nutrition in the management of AP has undergone several paradigm shifts. Prior recommendations, for patients to remain *nil per os*, were aimed at decreasing stimulation of exocrine pancreatic secretion, which in theory would decrease enzyme-driven inflammation and promote earlier recovery. More recently, the focus has shifted toward early initiation of enteral feeding to protect the gut-mucosal barrier. Current guidelines advocate for early oral feeding (within 24 hours) in mild AP[3,4]. In the AGA technical review of 11 RCTs of early versus delayed feeding in AP, there was no significant impact on outcomes of early- versus delayed oral feeding, with only non-significant trends towards lower rates of mortality and persistent single organ failure[3]. These negative findings mirror observations of the landmark Dutch PYTHON trial entitled "Early versus on-demand naso-enteric tube feeding in acute pancreatitis[69]. In subset analyses, remaining NPO when compared with early oral feeding, had a 2.5-fold higher risk for interventions for necrosis and no significant impact on other outcome measures (1 trial)[3]. Because timing of feeding varied across studies, there is no clear cutoff point for initiating feeding for those with severe AP; a practical approach is to initiate feeding within 24–72 hours and offer enteral nutrition (EN) for those intolerant to oral feeds. In severe AP and moderately severe AP (for example, necrotizing pancreatitis), EN is recommended over parenteral nutrition (PN)[3,4]. In the AGA technical review of 12 RCTs of EN versus PN in AP, there was clear evidence that EN reduced the risk of infected peri-pancreatic necrosis (OR 0.28, 95% CI 0.15–0.51), single organ failure (OR 0.25, 95% CI 0.10–0.62), and MOF (OR 0.41, 95% CI 0.27–0.63)[3]. Finally, the AGA guidelines provide a conditional recommendation on providing EN support through either the nasogastric or the nasoenteral route[4]. Data from the supporting AGA technical review were considered low-quality evidence, limited to three RCTs having significant methodologic limitations (for example, using different definitions of severe AP) and having a high risk of detection bias due to issues with outcome assessment[3]. Overall, EN is favored over PN for nutritional support in severe AP, but further studies are required to determine the optimal timing, rate, and formulation of EN in severe AP.

Antibiotics

Recent guidelines do not support the use of prophylactic antibiotics to prevent infection in necrotizing AP and severe AP[2,4,5]. The recent AGA technical review reaches similar conclusions. In an analysis of 10 RCTs involving 701 patients, limited to the higher-quality RCTs published after 2002, prophylactic antibiotics did not reduce infected pancreatic or peri-pancreatic necrosis, PSOF, or mortality[3].

Probiotics

Recent guidelines advocate against the use of probiotics for severe AP[2]. The largest double-blinded RCT, published by Besselink *et al.*, demonstrated that probiotic prophylaxis did not reduce the risk of infectious complications and was associated with a higher incidence of bowel ischemia (9/153 versus 0/145, p = 0.004) and greater mortality (risk ratio [RR] = 2.53, 95% CI = 1.22–5.25)[70]. In a recent systematic review and meta-analysis of six heterogeneous RCTs, Gou *et al.* reported that probiotics did not reduce pancreatic infection rates, hospital LOS, or mortality[71].

Timing of endoscopic retrograde cholangiopancreatography in acute biliary pancreatitis

There is universal agreement for offering urgent ERCP (within 24 hours) in biliary AP complicated by cholangitis[2,4,5,72]. In the absence of cholangitis, the timing of ERCP for AP with persistent biliary obstruction is less clear[2,4,5]. Prior guidelines, the Cochrane systematic review, and the recent 2018 AGA clinical guidelines and technical review argue against routine use of urgent ERCP for acute biliary pancreatitis[2–5,72]. The AGA technical review of eight RCTs with 935 patients concludes that urgent ERCP compared with conservative management in acute biliary pancreatitis had no significant impact on major outcomes (mortality, organ failure, infected pancreatic necrosis, and total necrotizing pancreatitis)[3]. Findings were similar in the subgroup analysis of studies that clearly excluded patients with biliary obstruction. Data were sparse and from a single RCT, suggesting that urgent ERCP for persistent biliary obstruction significantly impacted secondary outcomes (as classified in the AGA technical review); urgent ERCP compared with conservative treatment significantly shortened hospital LOS (9.5 days versus 17.0 days, 95% CI = −12.64 to −4.96)[3,73]. Based on the significant limitations across trials, including significant heterogeneity and exclusion of patients with cholangitis in recent trials, the AGA technical review considered the overall quality of data low and offered a conditional recommendation against urgent ERCP in patients with biliary AP and no cholangitis[3].

There are limited data to guide decision making of when *non-urgent* ERCP should be performed in hospitalized patients with acute biliary pancreatitis with persistent obstruction and no cholangitis. The Cochrane analysis concluded that ERCP should be performed within 72 hours, which associates with a non-significant trend toward reduction in local and systemic complications related to AP[72]. In support of this recommendation, Lee *et al.* recently performed a retrospective comparison of outcomes in 73 patients with acute biliary pancreatitis with biliary obstruction without cholangitis treated with either *urgent* ERCP (<24 hours) or *early* ERCP (24–72 hours)[74]. Overall, timing of ERCP had no impact on hospital LOS (5.9 versus 5.7 days, p value = 0.174), post-ERCP complications (15% versus 2.6%, p value = 0.113), and complications due to pancreatitis (2.6% versus 5.8%), regardless of severity[74]. Significant limitations of the study (retrospective design and small sample size) underscore the need for an appropriately sized RCT to determine whether urgent versus early ERCP differentially impacts outcomes for persistent biliary obstruction in AP. Practical and informative recommendations for designing future studies were offered in the AGA technical review: "The timing of the ERCP

intervention should be 24–48 hours after diagnosis (24 hours to allow spontaneous passage of stone and 48 hours to ensure that prolonged biliary obstruction does not occur)"[3].

Alcohol and smoking cessation

Drinking alcohol and smoking are known independent risk factors for recurrent episodes of AP and CP[75–77]. Recently published guidelines from the AGA advocate for brief alcohol intervention during hospitalization for alcohol-induced AP[4]. To date, only one RCT that addresses the impact of alcohol counseling on recurrent bouts of AP has been identified[78]. Patients with first-attack AP associated with alcohol were randomly assigned to a single counseling session at the initial hospitalization versus counseling every 6 months for 2 years. The intention-to-treat analysis showed significantly fewer recurrent episodes of AP in the repeated versus single intervention groups (5/59 versus 13/61, p value = 0.042)[78]. There was no significant difference in recurrent AP or hospital readmission rates after excluding patients who dropped out, died, or were identified as having previous episodes of pancreatitis or other etiologies of pancreatitis, a negative finding likely attributable in part to small sample size. As further support for common-sense recommendations to abstain from alcohol, the authors provided follow-up data for 18 subjects remaining abstinent over a mean of 5.15 years (range of 1.83–9.13 years) and reported that abstainers did not have a repeat episode of pancreatitis[79].

Cessation of smoking, an established independent risk factor of AP and CP, should also be recommended as part of the management of AP. To determine the impact of smoking cessation on prevention of first-attack AP, Sadr-Azodi *et al.* prospectively studied 84,667 Swedish men and women over a median of 12 years of follow-up and compared 307 patients who had non-gallstone AP with a comparable control group without AP[80]. The authors reported that the frequency of non-gallstone AP was double in current smokers (≥20 pack-years) compared with never-smokers (RR = 2.29, 95% CI 1.63 to 3.22, p <0.01) and that the risk of non-gallstone AP fell to the baseline risk of never-smokers after 20 years of smoking cessation[80].

Cholecystectomy

Evidence supports same-admission cholecystectomy for mild gallstone AP, a recommendation of published guidelines including the 2018 AGA clinical guideline[2,4,5]. In the technical review accompanying the AGA guideline, Vege *et al.*[3] identified one RCT that evaluated the effect of same-hospitalization versus delayed (post-discharge) cholecystectomy on outcomes in patients with mild acute gallstone pancreatitis[81]. Compared with delayed cholecystectomy, same-admission cholecystectomy significantly reduced gallstone-related complications (OR 0.24, 95% CI 0.09–0.61)[81] and readmissions for recurrent pancreatitis and pancreaticobiliary complications[81] without having a significant impact on mortality during a 6-month follow-up period[81]. As discussed in the AGA technical review, it remains controversial whether timing of surgery during the index hospitalization has a meaningful impact on outcomes[3]. Delaying cholecystectomy for 6 weeks in patients with moderate to severe gallstone AP appears to reduce morbidity, including the development of infected collections, and mortality[3]. In patients unfit for surgery, offering ERCP with biliary sphincterotomy appears to reduce the risk of recurrent acute biliary pancreatitis but not other biliary complications[82–84].

Chemoprevention and intravenous fluid management of post-endoscopic retrograde cholangiopancreatography pancreatitis

A systematic review of data from worldwide RCTs suggests that the incidence of PEP increased from 7.7% to 10% in the periods before and after 2000[85], respectively, primarily because of an increase in mild PEP from 2.9% to 5.9%. An explanation is likely complex but may be, in part, the increasing use of ERCP as a therapeutic procedure and decreasing use as a diagnostic procedure. With broader adoption of effective preventive therapies for PEP, there is promise that this trend may change.

Accumulating data support the effectiveness of chemoprevention and fluid administration to prevent PEP. Multiple RCTs, meta-analyses, and systematic reviews indicate that rectal non-steroidal anti-inflammatory drugs (NSAIDs) (diclofenac or indomethacin) reduce PEP onset[86–89] and moderate to severe PEP. The literature is inconclusive regarding whether rectal NSAIDs should be administered prior to or immediately after ERCP[90,91]. Oral NSAIDs do not prevent PEP[92–94]. In 2014, two hypothesis-generating retrospective studies reported that greater peri-procedural intravenous fluid volume was an independent protective factor against moderate to severe PEP[95] and was associated with shorter hospital LOS[96]. Very recent meta-analyses and RCTs support using LR prior to ERCP to prevent PEP[97–100] and to reduce moderate to severe PEP[97,98]. Interestingly, a recent RCT shows that the combination of rectal indomethacin and LR compared with combination placebo and normal saline reduced the risk of PEP in high-risk patients[101]. An ongoing multicenter Dutch "FLUYT" RCT aims to determine the optimal combination of rectal NSAIDs and peri-procedural infusion of intravenous fluids to reduce the incidence of PEP and moderate to severe PEP[102]. In particular, this study will yield practical information regarding the type and rate of fluids to administer to patients: no fluids versus normal saline (1.5 mL/kg per hour) versus LR (20 mL/kg rapid infusion over 60 minutes and then 3 mL/kg per hour).

Chemoprevention of PEP using a variety of other agents has not been fruitful. The most recent meta-analyses and RCTs have demonstrated that allopurinol[103], corticosteroids[104–106], somatostatin and their analogues[107], heparin[108], and nitroglycerin[87,109] have an inconclusive or non-significant effect on reducing the risk of PEP. Whereas the protease inhibitor nafamostat reduces the risk of PEP[87,110], it does not reduce the risk of PEP in high-risk patients, has a high cost, and requires a prolonged 7- to 25-hour infusion that diminishes the practicality of offering this to patients[110].

Implications for clinical practice

The diagnosis and optimal management of AP require a systematic approach with multidisciplinary decision making. Morbidity and mortality in AP are driven by early or late POF, and the latter

often is triggered by infected necrosis. Risk stratification of these patients at the point of contact is a common-sense approach to enable triaging of patients to the appropriate level of care.

Regardless of pancreatitis severity, recommended treatment interventions include goal-directed intravenous fluid resuscitation, early feeding by mouth or by enteral tube when necessary, avoidance of prophylactic antibiotics, avoidance of probiotics, and urgent ERCP for patients with acute biliary pancreatitis complicated by cholangitis. Management decisions not discussed in this review include critical care management in AP (for example, abdominal compartment syndrome[6]) and late decision making for pancreatitis complicated by infected necrosis, which involves source control with antibiotics and step-up therapy using a combination of percutaneous drainage, endoscopic management, and surgical intervention[7–10]. Key measures for preventing hospital readmission and pancreatitis include same-admission cholecystectomy for acute biliary pancreatitis and alcoholand smoking cessation. Preventive measures for PEP in patients undergoing ERCP include rectal indomethacin and peri-procedural fluid resuscitation. Table 1 summarizes recent major advances in AP that may affect clinical practice.

Abbreviations

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; AIP, autoimmune pancreatitis; AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, blood urea nitrogen, impaired mental status, systemic inflammatory response syndrome, age, and pleural effusion; BUN, blood urea nitrogen; CI, confidence interval; CP, chronic pancreatitis; CT, computed tomography; EN, enteral nutrition; ERCP, endoscopic retrograde cholangiopancreatography; ESRD, end-stage renal disease; EUS, endoscopic ultrasound; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9, International Classification of Diseases, Ninth Revision; LOS, length of stay; LR, lactated Ringer's;

Table 1. Recent advances in epidemiology, evaluation, and management of acute pancreatitis.

1.	Incidence of acute pancreatitis (AP) is increasing, but mortality is decreasing
2.	Alcohol and gallstones remain the most common causes of AP
3.	Smoking is an independent risk factor for pancreatitis
4.	Cannabis is a possible risk factor for toxin-induced AP
5.	In inflammatory bowel disease, AP is typically due to gallstones or medications
6.	In severe renal disease, risk of AP is higher with ongoing peritoneal dialysis
7.	Pancreatic cancer is an uncommon but established cause of first-attack pancreatitis
8.	The risk of AP and severe AP appears to increase in proportion to triglyceride value
9.	Cross-sectional imaging remains over-utilized during the initial evaluation of AP
10.	Risk stratification tools have moderate predictive value for severe AP
11.	Goal-directed fluid therapy (FT) is recommended as early treatment of AP
12.	Recommended fluids for FT are normal saline or lactated Ringer's, not hydroxyethyl starch
13.	Initiation of early oral feeding is recommended, beginning within 24 hours, for mild AP
14.	Enteral nutritional support is favored over parental nutrition in severe AP
15.	Prophylactic antibiotics are not recommended for necrotizing pancreatitis
16.	Probiotics are not recommended for severe AP
17.	Urgent endoscopic retrograde cholangiopancreatography (ERCP) (<24 hours) is recommended for acute biliary pancreatitis complicated by cholangitis
18.	Routine use of urgent ERCP is not recommended for acute biliary pancreatitis
19.	Same-hospitalization and repeated alcohol cessation counseling is recommended for alcohol-induced AP
20.	Same-admission cholecystectomy is recommended for mild acute biliary pancreatitis
21.	Rectal indomethacin and peri-procedural FT each reduce post-ERCP pancreatitis; combination therapy requires study

MOF, multiple organ failure; MRCP, magnetic resonance cholangiopancreatography; NIS, nationwide inpatient sample; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; PMOF, persistent multiple organ failure; PN, parenteral nutrition; POF, persistent organ failure; PSOF, persistent single organ failure; RCT, randomized controlled trial; RR, risk ratio.

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1 **Masahiko Hirota**
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2 **Charles Melbern Wilcox**
Division of Gastroenterology & Hepatology, University of Alabama School of Medicine, Birmingham, AL, 35249-0007, USA
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