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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Diagnosis and Management of Acute Pancreatitis

Guru Trikudanathan,[1,*] **Cemal Yazici**,[2,*] Anna Evans Phillips,[3] and Chris E. Forsmark[4]

[1]Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis, Minnesota; [2]Division of Gastroenterology and Hepatology, University of Illinois, Chicago, Illinois; [3]Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania; and [4]Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, Florida

Acute pancreatitis (AP) is increasing in incidence across the world, and in all age groups. Major changes in management have occurred in the last decade. Avoiding total parenteral nutrition and prophylactic antibiotics, avoiding overly aggressive fluid resuscitation, initiating early feeding, avoiding endoscopic retrograde cholangiopancreatography in the absence of concomitant cholangitis, same-admission cholecystectomy, and minimally invasive approaches to infected necrosis should now be standard of care. Increasing recognition of the risk of recurrence of AP, and progression to chronic pancreatitis, along with the unexpectedly high risk of diabetes and exocrine insufficiency after AP is the subject of large ongoing studies. In this review, we provide an update on important changes in management for this increasingly common disease.

Keywords: Acute Pancreatitis; Classification; Severity; Management.

Acute pancreatitis (AP) is among the most common gastrointestinal causes of hospitalizations in the United States and its incidence is increasing worldwide.[1,2] The annual incidence of AP is estimated at 13–49 per 100,000 persons.[2–4] The risk of AP is similar among men and women and increases with age.[2,3]

AP affects all segments of the population, but disproportionally impacts certain racial and ethnic minority groups, who are at increased risk for AP and AP-related complications.[5–7] African Americans are 2 times more likely to develop AP compared with Whites.[8–10] Furthermore, African Americans are less likely to be transferred to tertiary care centers, more likely to live in underserved neighborhoods, and more likely to have lower income, implicating the role of social determinants of health in this disproportionate effect.[11,12] Health inequalities in AP are also seen in Hispanics with greater rates of organ failure (acute kidney injury and shock) and longer emergency department wait times.[13–15] There is a significant underrepresentation of minorities in research studies in AP. Increasing minority representation in AP studies is an important research goal and recently funded multicenter studies are emphasizing adequate recruitment of minorities (eg, type 1 diabetes and acute pancreatitis).[16,17]

Hospitalization for AP increased approximately 30% over the past decade, with $2.6 billion in yearly healthcare costs in the United States.[1] In a recent analysis, AP produced more than 288,000 hospital admissions and accounted for 90 per 100,000 person hospital visits.[1] The increase in AP occurring in the United States and across the world is unexplained, but may relate to increased rates of obesity and associated gallstones. Gallstones and alcohol are the 2 most common causes of AP in the United States. Patients with gallstone-induced AP have higher hospitalization charges compared with alcohol-induced AP ($61,182 vs $37,982; $P < 0.001$).[18] This has been attributed to increased use of imaging studies, and endoscopic procedures such as endoscopic retrograde cholangiopancreatography (ERCP) as well as longer length of stay. A key determinant of healthcare costs in AP is disease severity. Approximately 20% of AP patients develop moderately severe or severe AP; these patients may develop organ system failure or pancreatic necrosis, require higher level of care (such as intensive care unit admission), or require intervention for AP complications (eg, necrosectomy). Newer, less-invasive endoscopic approaches to the management of necrosis are more cost-effective than traditional surgical treatments, but the economic burden remains high.[19,20] Even with the use of an endoscopic step-up strategy, management of necrotizing pancreatitis (NP) remains costly ($90,864 per patient in 1 recent analysis).[21] Overall, the mortality rate due to AP is around 2%, but those with severe or necrotizing AP can have mortality rates of up to 20%.

Diagnosis of AP

AP is diagnosed when 2 of the following 3 criteria are present: abdominal pain consistent with AP, serum lipase or amylase level at least 3 times above the upper limit of normal, and characteristic features of AP on cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]).[22] These diagnostic criteria have been

*Authors share co-first authorship.

Abbreviations used in this paper: AP, acute pancreatitis; CP, chronic pancreatitis; CT, computed tomography; EN, enteral nutrition; EPI, exocrine pancreatic insufficiency; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NP, necrotizing pancreatitis; QOL, quality of life; RCT, randomized controlled trial; TPN, total parenteral nutrition; US, ultrasound.

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endorsed by all national and international societies.[22–25] There are a few key considerations when using these criteria. Although severe epigastric pain that radiates to the back is characteristic for AP, patients demonstrate differences in pain severity, location, and radiation. Although both lipase and amylase are used in AP diagnosis, lipase has a longer half-life and is preferred in patients who present later after pain onset.[25] There are several gastrointestinal and nongastrointestinal causes of lipase and amylase elevations (Table 1).[26] These potential causes should be considered in patients with modest lipase/amylase elevations or with atypical symptoms.

Cross-sectional imaging (CT or MRI) is not required for the diagnosis of AP, but it does provide the most reliable diagnosis and can provide information regarding the degree of pancreatic and peri-pancreatic necrosis (Figures 1 and 2). At the time of presentation, the imaging features determining severity may not be fully apparent, so the degree of necrosis may be underestimated.[22] Early diagnostic CT is not needed in stable patients in whom the diagnosis is clear. Cross-sectional imaging is, however, routinely performed, and is particularly important if there is diagnostic uncertainty.[22]

Table 1. Conditions Associated With Increased Amylase or Lipase Levels

Gastrointestinal system	Other systems
Pancreatic	Endocrine
Pancreatitis	Diabetes, type I or II
Complications related to pancreatitis (pseudocyst, necrosis)	Diabetic ketoacidosis
Pancreatic surgery or trauma	Sarcoidosis
Pancreatic duct obstruction	Renal
ERCP	Acute kidney injury
Pancreatic cancer	Chronic kidney diseases
Cystic fibrosis	Renal failure
Nonpancreatic	Neoplastic (amylase only)
Cholecystitis	Solid tumors of lung, ovary, prostate, esophagus, breast
Cholangitis	Multiple myeloma
Gastroenteritis	Gynecologic (amylase only)
Peptic ulcer disease	Ovarian or fallopian cysts
Celiac disease	Ectopic pregnancy
Inflammatory bowel diseases	Pelvic inflammatory disease
Bowel obstruction	Infectious
Bowel ischemia or perforation	HIV
Appendicitis	HCV
Peritonitis	COVID
	Neurologic
	Traumatic brain injury
	Intracranial hemorrhage
	Others
	Macroamylasemia (amylase only)
	Parotitis (amylase only)
	Burns
	Abdominal aortic aneurysm
	After overtube-assisted enteroscopy
	Drugs (eg, opioids)

COVID, Coronavirus disease 2019; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Determination of Etiology

Identification of the etiology of AP is essential for appropriate and timely management, effective use of healthcare resources, and reduction of AP recurrence (Table 2, Figure 3). A careful history can provide helpful clues, including a history of previous AP attacks, known gallstone disease or preceding episodes of biliary colic, alcohol consumption, smoking, known metabolic syndrome, hypertriglyceridemia, recent medication use, family history of pancreatic disease, recent abdominal trauma, or recent procedures including ERCP.

Gallstones are the most common cause of AP accounting for around 40% of cases.[2,10,27] The prevalence of symptomatic gallstone disease is around 7% in the United States.[28] Gallstone pancreatitis risk is higher in women and increases with age. Less than 1% of patients with gallstones develop pancreaticobiliary complications.[29,30] Transabdominal ultrasound (US) is recommended as part of the initial work-up in all patients presenting with their first AP episode.[24,25] Findings on US suggestive of gallstone pancreatitis include gallstones, a dilated common bile duct, or, rarely, a visible bile duct stone.[24] Elevations in liver chemistries are usually seen, and any abnormality in these tests should raise the possibility of gallstone etiology.[24,31] If doubt exists, both magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) can be considered to identify small stones in the gallbladder and/or bile duct.[32–34]

Alcohol-related AP is the second most common cause and is more common in men than women.[2,10,27] Accounting for approximately 30% of AP cases, the overall risk of AP among those with heavy drinking is only around 2%–5%.[35,36] Although prolonged and heavy alcohol consumption has been linked with AP, there is not a significant association between only binge drinking or social alcohol intake.[37,38] Despite this, patients without prolonged or heavy alcohol use are commonly labeled as having alcohol-related AP. Healthcare providers should be cautious in identifying alcohol as an etiology when there is only moderate alcohol consumption as this produces substantial stigmatization and can lead to delayed identification of the main etiology. Alcohol potentiates pancreatic injury from other underlying environmental (eg, smoking) and genetic risk factors.[39,40]

Hypertriglyceridemia accounts for 2%–7% of AP cases.[27,41] Although significantly elevated serum triglycerides levels (>1000 ng/mL) are usually found, recent studies note that even more moderate elevations in serum triglycerides increase AP risk.[42–44] Very high levels of triglycerides are often present at the initial episode of AP, but recurrent episodes can be triggered by even modest elevation, emphasizing the need for aggressive control of triglycerides. Triglycerides may be falsely low if the patient has been fasting or not eating due to pain and may need to be rechecked after recovery. Patients with familial combined hyperlipidemia or familial hypertriglyceridemia are particularly at risk if they also have other risk factors such as

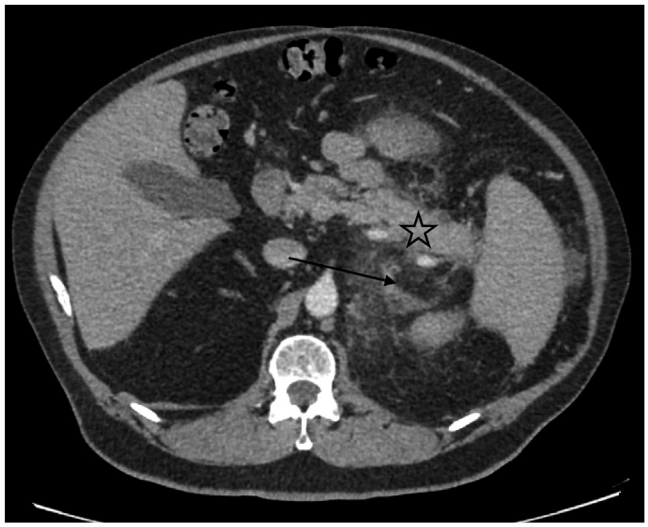

Figure 1. A CT image of milder or interstitial pancreatitis. The pancreas (*star*) opacifies with intravenous contrast, so it is not necrotic. The *arrow* delineates peripancreatic fluid and inflammation.

heavy alcohol use, poorly controlled diabetes, or pregnancy.[2] In addition, familial chylomicronemia syndrome increases AP risk significantly, up to a 76% lifetime risk, even in the absence of other secondary risk factors.[45]

Medication-induced AP causes <5% of AP cases and among many agents didanosine, asparaginase, azathioprine, valproic acid, 6-mercaptopurine, and mesalamine appear to have the strongest association with AP risk.[27,46,47] Patients with medication-induced AP generally have mild disease.[48] Other less common etiologies for AP are: (1) genetic causes including mutations in the genes encoding cationic trypsinogen *(PRSS1)*, serine protease inhibitor Kazal type 1 *(SPINK1)*, cystic fibrosis transmembrane conductance regulator *(CFTR)*, chymotrypsin C, calcium-sensing receptor, and claudin-2; (2) ERCP-induced AP; (3) pancreatic trauma; (4) infectious etiologies including viruses and parasites; and (5) associated diseases and risk factors such as smoking, diabetes, obesity, celiac disease, systemic lupus erythematosus, inflammatory bowel disease, and metabolic risk factors such as hypercalcemia, renal failure, and acidosis.[2,27,49] Malignancy is a rare cause of AP, but can occur due to tumor blocking the pancreatic duct (ampullary, duodenal, or pancreatic). In more elderly patients with an episode of unexplained AP (age >45 years), malignancy needs to be carefully excluded.

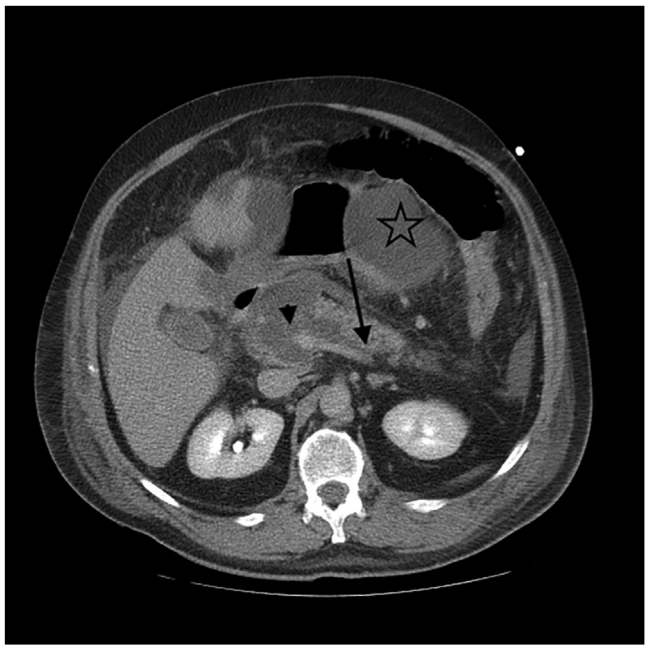

Figure 2. A CT of NP. The pancreas in the tail of the gland (*long arrow*) still opacifies with intravenous contrast, whereas the gland in the head (*short arrow*) does not, indicating necrosis. Several fluid collections are also present on the scan (*star*).

Determination of Disease Severity

Accurate determination of disease severity is useful to avoid delays in appropriate management.[49] Although a small percentage of patients present with established severe AP, a patient with initially mild AP can rapidly decompensate and progress into severe AP. Careful monitoring of symptoms, signs, and laboratory and imaging study results during the initial phase of admission is important for timely identification of severe AP.

There are 2 main classification systems in use for determining disease severity in AP: Revised Atlanta Classification and Determinant-Based Classification (Table 3).[22,50] The majority of patients with AP (80%) have a mild, self-limiting disease. Mild AP is defined by the absence of both organ system failure and local complications such as pancreatic necrosis or fluid collections.[22] These patients usually have improvement in symptoms within 48 hours of admission, are able to tolerate a solid diet, have adequate pain control, and a resulting short hospital stay. Around 20% of patients develop moderately severe or severe AP, with the risk of complications, prolonged hospitalization, and increased mortality. Moderately severe AP is defined by the development of local complications and/or transient organ system failure (<48 hours). Severe AP is defined by persistent organ failure lasting >48 hours.[22] Local complications include peripancreatic fluid collections, and pancreatic or peripancreatic necrosis (which may remain sterile or become infected).[22] Organ system failure is determined by a score of 2 or more for 1 of the organ systems (respiratory, cardiovascular, and renal) using the modified Marshall scoring system.[51]

Prediction Models

Although there are widely accepted methods to define severe disease, predicting patients at risk for severe AP has proved more difficult. Several scoring systems have been developed to assist clinicians in prediction of AP severity, but most are complex, difficult to adapt for clinical use, reflect disease severity instead of predicting it, and have limited accuracy.

Table 2. Etiology of AP

Etiology	Clues to identify	Comments
Gallstones 40%	Previous biliary colic US demonstrating gallstones or a dilated common bile duct Abnormal liver chemistries at presentation	Usually small stones Bile duct stones not usually visualized on US, EUS, or MRCP can be used if diagnosis not confirmed
Alcohol 30%	Long-term use of alcohol (usually at least 5 y) CAGE questions PEth testing	Acute flares may be superimposed on underlying CP
Hypertriglyceridemia 2%–7%	Fasting TG ≥1000 mg/dL	If patient has not been eating due to pain, fasting TG may be low; testing after recovery or testing postprandial TG level may be needed Subsequent attacks can occur with much lower elevations of TG
Drugs <5%	Multiple drugs reported but evidence usually only circumstantial	Strongest evidence for didanosine, asparaginase, azathioprine, valproic acid, 6-mercaptopurine, and mesalamine Usually idiosyncratic
Genetic	Multiple modifier genes now identified	Genetic testing not usually performed, but may be considered in very young patients or in those with unexplained relapsing pancreatitis
Post-ERCP	<5% of those undergoing ERCP	Usually mild Risk can be reduced with careful patient selection, technical approaches, and prophylaxis with indomethacin and preprocedure hydration
Infections rare	Overall quite rare	Viruses: CMV, EBV, mumps Parasites and nematodes: Ascaris, Clonorchis, opisthorcus
Obstruction of major or minor ampulla or pancreatic duct leading to pancreatitis	Overall quite rare	Celiac disease Small bowel Crohn's disease Periampullary diverticulum Ampullary or duodenal polyp or cancer Pancreatic cancer Pancreas divisum Annular pancreas Santorinicele Controversial causes such as sphincter of Oddi dysfunction
Toxins	Overall quite rare	Organophosphate insecticides Scorpion bites
Miscellaneous	Overall quite rare	Autoimmune diseases IBD Postoperative

CMV, cytomegalovirus; EBV, Epstein-Barr virus; IBD, inflammatory bowel disease; TG, serum triglycerides.

Clinical Factors

Several clinical factors have been associated with increased risk of complications and death among patients with AP including age ≥55 years, presence of comorbidities, altered mental status, obesity (a body mass index of >30), and long-term, heavy alcohol use.[25] These are risk factors for poor outcomes in many other disease states, but do not allow clinicians to estimate an individual's risk of developing severe AP. The presence of systemic inflammatory response syndrome (SIRS) is perhaps the most helpful clinical sign (see later in this article).

Laboratory Markers

Several laboratory markers have been assessed for prediction of disease severity. These mainly reflect the degree of inflammation, or the depletion of intravascular

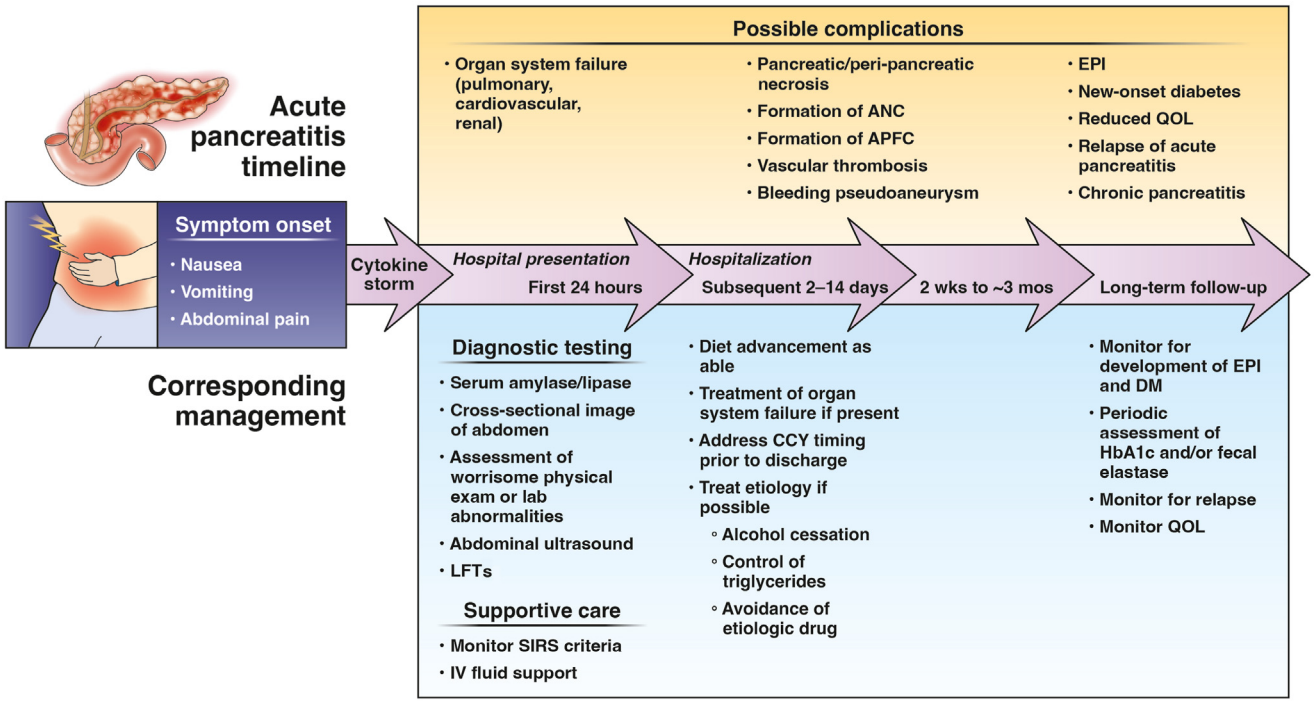

Figure 3. Timeline and treatment of acute pancreatitis. ANC, acute necrotic collection; APFC, acute pancreatic fluid collection; CCY, cholecystectomy; DM, diabetes mellitus; HbA1c, hemoglobin A1c; IV, intravenous; LFTs, liver function tests.

volume status due to third space losses. Elevations in blood urea nitrogen, serum creatinine, and hematocrit reflect fluid loss and intravascular volume depletion, and can also be used to monitor the response to intravenous fluid therapy in patients who were found to be significantly volume depleted.[24,25] Inflammatory markers include C-reactive protein, interleukin-6, and procalcitonin, and these remain elevated longer in those with severe AP.[52–55] Although serum amylase or lipase levels are used as a diagnostic criteria, they have no predictive value in AP severity.

Imaging

Cross-sectional imaging data is used as 1 of the 3 criteria for AP diagnosis.[24] Although CT findings are included in some of the scoring systems, when the CT or MRI findings document severe AP, the patient has already developed clinical deterioration, thus limiting its utility in prediction. Early imaging studies can also provide false reassurance by underestimating the possibility of progression into severe AP. CT scoring systems have been shown to be similar to clinical scoring systems in predicting severity with no direct impact on early management or clinical outcomes.[56–58]

Multiple Factor Scoring Systems

Several scoring systems that combine key clinical, laboratory, and imaging data have been developed but they have not been well-adapted to clinical practice. These include the Ranson criteria, the Glasgow scoring system, Acute

Table 3. AP Severity Classification Systems

Revised Atlanta Classification	Determinant Based Classification System
Mild AP: No local or systemic complications No organ failure	Mild AP: No local complications No organ failure
Moderately severe AP: Local or systemic complications without persistent organ failure and/or transient organ failure (<48 h)	Moderate AP: Sterile local complications and/or transient organ failure (<48 h)
Severe AP: Persistent organ failure (>48 h)	Severe AP: Infected local complications or persistent organ failure (>48 h)
	Critical AP: Infected local complications and persistent organ failure (>48 h)

Presence of organ failure is determined based on the Modified Marshall Scoring System. A score of 2 or more for any of 3 organ systems (respiratory, renal, or cardiovascular) defines the presence of organ failure (Marshall et al[51]).

Physiology and Chronic Health Evaluation II (APACHE II), Systemic Inflammatory Response Syndrome (SIRS), PANC 3, Pancreatitis Outcome Prediction (POP), the Bedside Index for Severity in Acute Pancreatitis (BISAP), the Harmless Acute Pancreatitis Score (HAPS), and the Japanese Severity Score.[59] None of these scoring systems have been shown to be more accurate than the others.[60–62] Their potential benefit is limited partly due to lag time (the accuracy of these scoring systems improves at 48 hours), a time period during which severe AP is increasingly clinically evident.

Among the multiple factor scoring systems, the presence of SIRS (determined by temperature, $<36^{o}$C or $>38^{o}$C; pulse >90 beats/min; respiratory rate, >20 breaths/min [or partial pressure of arterial carbon dioxide, <32 mm Hg]; and white blood cell count, <4000 or $>12{,}000/mm^3$) is more easily adaptable and its presence for ≥ 48 hours indicates a poor prognosis. Recent society guidelines recommend adaptation of a 3-dimensional approach that combines key clinical and laboratory data along with a multiple scoring system such as SIRS.[24,25]

An evolving area in prediction modeling centers on measurement of inflammatory cytokines derived from injured acinar cells and the immune response in prediction of disease severity. Angiopoietin 2, hepatocyte growth factor, interleukin-8, resistin, soluble tumor necrosis factor receptor1A, and activin A emerged as potential cytokines in such prediction modelling.[63,64] In a recent study, a cytokine panel that included the first 5 cytokines listed already in this article was shown to predict persistent organ failure, and significantly outperformed the prognostic accuracy of earlier laboratory tests and clinical scores.[63] Closing existing knowledge gaps in prediction modeling in AP requires research teams with expertise in pancreatic diseases, imaging and artificial intelligence, biomarker development, epidemiology, and bioinformatics. Development and implementation of a recent prospective, multi-institutional and interdisciplinary AP study that is supported by the National Institute of Diabetes and Digestive and Kidney Diseases is likely to provide unique opportunities for further identification of such prediction models in a diverse clinical cohort.[16,65]

Management of AP

Fluid Resuscitation

Intravascular volume depletion and third-space fluid sequestration in AP contribute to renal and circulatory failure and can lead to or exacerbate perturbations in pancreatic microcirculation, contributing to pancreatic necrosis and progression from mild to severe AP.[27,66] Fluid resuscitation to prevent hypovolemia and organ hypoperfusion is pivotal in the early management of AP but questions remain as to the ideal type of fluid, rate, and volume of infusion. Current American Gastroenterological Association guidelines recommend crystalloids as the optimal initial resuscitation fluid and caution against colloids such as hydroxyethyl starch.[23,66] Among crystalloids, Lactated Ringer's solution, with its theoretical anti-inflammatory properties and less acidic pH, is most recommended. Compared with using normal saline, Lactated Ringer's is associated with reduced surrogate markers of severity (C-reactive protein levels and SIRS).[67–69] However, there are no adequately powered randomized trials to evaluate whether a particular fluid type reduces mortality or persistent single- or multi-organ failure.[66] The WATERLAND (Normal Saline Versus Lactated Ringer's Solution for Acute Pancreatitis Resuscitation) trial, (NCT05781243), an international multicenter randomized controlled trial (RCT), is currently underway to evaluate these fluid types on the outcome of AP.

Current guidelines endorse judicious goal-directed fluid resuscitation at a rate of 5-10 mL/kg/h during the first 12-24 hours, with further infusion rate titrated based on clinical and biochemical targets of perfusion.[23–25] These include clinical (heart rate <120/min, mean arterial pressure between 65 and 85 mm Hg, and urinary output >0.5 mL/kg/h) and biochemical targets such as hematocrit (35%–45%) and blood urea nitrogen concentration.[23,24] However, these recommendations were conditional based on low to moderate quality of evidence.[23,24] The recently published WATERFALL study challenged current guidelines on the optimal rate of fluid administration.[70] Patients were randomly assigned to aggressive fluid resuscitation (20 mL/kg of bolus followed by 3 mL/kg/h) or moderate fluid resuscitation (10 mL/kg followed by 1.5 mL/kg/h). The study was halted early due to significant safety concerns, with a significant difference in fluid overload in the aggressive arm (20.5% vs 6.3%), without a significant difference in the incidence of moderately severe or severe AP (22.1% vs 17.3%) between the 2 groups.[70] Thus, a steady rate of initial resuscitation of 1.5 mL/kg/h with a bolus of 10 mL/kg only if there are signs of initial hypovolemia, assiduous clinical and hemodynamic monitoring for euvolemic status during the first 72 hours, and appropriate diuresis if there is fluid overload were the key conclusions. If the findings are extrapolated, this will impact care for most patients admitted with AP. A strategy of moderate resuscitation, coupled with clinical judgment on an individual patient's ability to tolerate fluid and fluid status, clearly appears to be more beneficial. More objective noninvasive methods to assess fluid status and dynamic hemodynamic monitoring are needed to craft evidence-based resuscitation strategies personalized to the volume needs of individual patients.

Nutrition in AP

Patients with AP are considered moderate to high nutritional risk, because of the proinflammatory state, increased resting energy expenditure, catabolic nature of the disease, ongoing abdominal pain limiting oral intake, complications such as gastric outlet obstruction, concomitant paralytic ileus, and micronutrient deficiency inherent with chronic alcohol consumption (if present).[71–73] Current guidelines recommend initiating early (as soon as tolerated) oral feeding with solid (low-fat) diet in patients with predicted mild AP and this approach reduces length of

hospitalization.[24,25,66,73,74] Patients with severe AP or NP may be intolerant to oral diet.[66] Traditionally the concept of "pancreatic rest" (initiation of oral nutrition only after complete resolution of abdominal pain and normalization of pancreatic enzymes) guided nutritional management in severe AP. Accordingly, total parenteral nutrition (TPN), elemental formulas, and a stepwise initiation of oral diet beginning with clear liquid were favored.[66] However studies noted that the pancreas is largely insensitive to meal stimulation during AP.[75] Early enteral nutrition (EN) was shown to have a beneficial trophic effect in preserving gut mucosal integrity and reducing gut bacterial translocation.[66] EN was compared with TPN in AP in several RCTs and the results were statistically aggregated in several meta-analyses to establish the superiority of EN in mortality, multiorgan failure, and rate of infection.[66,76,77] Given the cost burden, risk of catheter-related sepsis, electrolyte and metabolic derangement, and gut barrier failure, currently use of TPN is reserved for patients for whom EN is not possible or is not able to meet the minimum calorie requirements.[66,78] It should be noted that although all guidelines advise avoiding TPN, it continues to be used.[79–81]

In patients with predicted severe AP, early EN was not shown to improve outcomes in comparison with attempts at oral feeding at 72 hours.[82,83] The PYTHON trial in 208 patients with predicted severe AP concluded that early EN (within 24 hours) did not reduce the rate of infection (25% vs 26%) or mortality (11% vs 7%) when compared with on-demand oral diet initiated 72 hours after admission.[82] Thus, in predicted severe AP, it is prudent to initiate oral diet at 72 hours (or earlier if tolerated) and initiate tube-based EN if not tolerated. The route of EN can either be nasogastric, nasoduodenal, or nasojejunal because all are safe and well tolerated.[84,85] Nasojejunal tube feeding is preferred if there is digestive intolerance from delayed gastric emptying and gastric outlet obstruction.[73] Standard polymeric feeding formulation has similar rates of feeding tolerance, diarrhea, and infectious complications in comparison with the more expensive (semi)-elemental formulations and are preferred.[24,66,73,86] Pancreatic enzyme supplementation can be also be considered in patients with proven or suspected exocrine pancreatic insufficiency.[73]

Preventing Infectious Complications in AP

In AP, hospital-acquired infections such as pneumonia, line-sepsis, or bacteremia or later secondary infection of peripancreatic or pancreatic necrosis can dramatically impact clinical outcome.[87,88] Current guidelines do not recommend prophylactic antibiotics in predicted severe AP or sterile necrosis because this practice is associated with the development of multidrug-resistant bacteria and fungal superinfection.[24,25,66,89,90] It can be difficult in severe pancreatitis to know if clinical deterioration is due to ongoing pancreatitis with SIRS, or due to a new infection. Procalcitonin is useful in distinguishing SIRS from bacterial sepsis. The PROCAP randomized trial used procalcitonin testing at 0, 4, and 7 days and weekly thereafter with a threshold of 1.0 ng/mL to guide initiation, continuation, and discontinuation of antibiotics. The procalcitonin based algorithm decreased the probability of being prescribed an antibiotic and the number of days on antibiotics without increasing infection or harm in patients with AP.[91] Further multicenter RCTs measuring procalcitonin in more patients with moderate to severe AP are needed before routine adoption of this algorithm for antibiotic stewardship.

Antifungal agents are started if there is definitive diagnosis of fungal infection, which can rarely occur in patients with prolonged intensive care, antibiotic administration, TPN, and indwelling catheters.[72] Prophylactic antifungal therapy is not recommended.[72] Finally, probiotic prophylaxis did not decrease infectious complications from AP, and, in fact, increased mortality and are, therefore, not recommended.[92]

Pain Management in AP

Debilitating abdominal pain is often the presenting symptom in AP, but current guidelines do not provide clear and consistent guidance for pain management.[88,93] A recent meta-analysis involving 12 RCTs evaluating the optimal analgesic modality highlighted the remarkable paucity of level 1 evidence to guide pain management in AP.[94] Current pain management hinges around the World Health Organization analgesic ladder with lower potency nonsteroidal anti-inflammatory drugs followed by weak opioids and finally strong opioids. Nonsteroidal anti-inflammatory drugs are helpful in mitigating the inflammatory cascade, and are useful in mild AP but can aggravate peptic ulcer disease and should be avoided in AP with acute kidney injury.[72] Opioids can cause respiratory depression, sedation, and bowel dysfunction including induction or exacerbation of ileus in AP, besides the addiction potential.[93] A recent double-blind randomized trial compared diclofenac and buprenorphine and showed that buprenorphine was more effective and equally safe for pain management in AP.[95]

Patient-controlled analgesia in AP needs to be further studied in randomized trials. A retrospective study showed that patient-controlled analgesia was associated with prolonged hospitalization, longer time to EN, and higher likelihood of being discharged on opioids.[96] It is noteworthy that opioids are infrequently used in some countries but are widely used in the United States.[97,98] Epidural analgesia in a small RCT showed improvement in pancreatic perfusion and better pain relief in the first 24 hours, but no difference in length of hospital stay or mortality.[99] Another small RCT showed that epidural analgesia significantly decreased procalcitonin, with a nonsignificant trend toward improved organ function and decreased mortality.[100] Given the risk of catheter-related hypotension and epidural abscess, this opioid-sparing strategy is not used.[72] Other techniques include combinations with opioid-sparing analgesics and nonpharmacologic modalities such as acupuncture.[93] Although the World Health Organization pain ladder is useful in management of cancer-related pain, an adoption of a step-down approach to gain rapid amelioration of pain may be more appropriate in AP.[93] Pain management in AP

should be individualized but sufficiently effective to avoid transition to a more chronic pain syndrome.[93]

Role of ERCP in Biliary AP

The role of ERCP in reducing severity has been the subject of several studies.[66] It has been shown that ERCP is not effective in patients with predicted mild biliary AP.[88,101] One multicenter randomized trial compared urgent ERCP with biliary sphincterotomy vs conservative management in patients with predicted severe biliary AP but without cholangitis. The study concluded that urgent ERCP with sphincterotomy did not significantly reduce the composite endpoint of major complications or mortality (38% vs 44%).[102] The same investigators conducted a cohort study to further address if urgent ERCP is beneficial in patients with confirmed bile duct stones/sludge on EUS.[103] In this prospective multicenter cohort study, urgent EUS followed by urgent ERCP with sphincterotomy in the case of bile duct stones/sludge did not reduce the composite endpoint of major complications or mortality at 6 months. The combined results of these studies find that in predicted severe biliary AP a conservative management strategy is preferred, with ERCP indicated only in case of concomitant cholangitis (urgently) and symptomatic and/or persistent choledocholithiasis (electively).[102,103] All current guidelines recommend against the routine use of urgent ERCP in biliary AP regardless of severity in the absence of cholangitis.[23,24]

Timing of Cholecystectomy in Patients With Biliary AP

The balance between expedient removal of the cause for pancreatitis and the risk of surgery-related complications under suboptimal operative conditions with an ill patient can be difficult to ascertain. Several recent studies have attempted to quantify the risks and benefits of the timing of cholecystectomy. A Cochrane review on this topic from 2013 found only a single trial that met strict inclusion criteria.[104,105] In a prospective RCT of 50 patients with mild biliary AP, shorter hospital stay and no increase in complication rate were seen in those who underwent early cholecystectomy (performed within 48 hours of hospital admission) compared with late cholecystectomy (>48 hours after hospital admission).[105] This work was limited to a subset of patients with mild AP. A more recent randomized clinical trial of 198 patients with mild biliary AP found that early cholecystectomy (at 7 days after mild biliary AP) vs delayed (at 4 weeks after mild biliary AP) showed a 50% reduction in readmission for biliary events before cholecystectomy (7.2% vs 15.8%), and no increase in rate of complications or need for subsequent ERCP compared with the delayed group.[106] A multicenter clinical RCT of 266 patients found that gallstone-related complications occurred in 17% of patients assigned to interval cholecystectomy as compared with 5% of patients assigned to same-admission cholecystectomy, with no increase in operative complication rates in earlier surgical procedures.[107] In addition to reduction in rates of gallstone-related complications, performing cholecystectomy in the same admission was found to be more cost effective in mild biliary AP.[108] Together this evidence supports very strongly the decision to pursue early same-admission cholecystectomy in patients with mild biliary AP.

In patients with moderately severe or severe AP, some guidelines and expert opinions recommend delay of cholecystectomy until after resolution of pancreatic fluid or necrotic collections.[109,110] In a retrospective study of 248 patients with moderately severe or severe AP, the rate of recurrent biliary pancreatitis events was found to be reduced if cholecystectomy was performed before 8 weeks after AP, and the rate of recurrent biliary events overall was found to be reduced if cholecystectomy was performed before 10 weeks after AP.[111] Although it is commonly practiced in patients in whom delayed cholecystectomy is required or patients who are not surgical candidates, there is no conclusive evidence that endoscopic biliary sphincterotomy alone reduces the rate of future biliary events overall.

Necrotizing Pancreatitis

Approximately 10%–20% of patients with AP develop necrosis of the pancreatic parenchyma or extrapancreatic adipose tissue.[22] Of these, approximately one-third develop infected necrosis with bacterial or fungal organisms, which frequently requires an invasive intervention for management.[22] In the absence of infection, or severe symptoms, necrosis can be managed with supportive care including analgesic medications and nutritional support with either a low-fat diet (if tolerated) or EN delivered through a nasoduodenal or nasojejunal tube.[112]

Infection of the peri- or pancreatic necrosis often occurs approximately 10–14 days from onset of AP, and worsens the prognosis.[112] Management of NP, particularly infected necrosis, has been a much-debated clinical issue given the high morbidity and mortality associated with this condition and limited treatment options. One study comparing outcomes from patients with and without infected necrosis reported mortality rates of between 36% and 49.5%, the latter for patients with primary organ failure and subsequent superimposed infected necrosis.[113]

A minimally invasive step-up approach to therapy has been accepted as the preferred treatment route, given lower rates of morbidity and mortality seen in comparison with an open surgical approach.[27,114] The initial step is frequently a targeted percutaneous drainage; if improvement is not achieved with this alone, further steps include endoscopic transmural drainage, direct endoscopic necrosectomy, and finally minimally invasive surgical debridement.[112,115] Surgical approaches may vary, and include techniques such as video-assisted retroperitoneal debridement, surgical transgastric necrosectomy, or surgical cystoenterostomy depending on the patient's individual situation.[116] In a multicenter RCT comparing endoscopic to surgical approaches, the endoscopic approach was not inferior to the surgical approach in reducing either major complications or mortality from infected NP.[20] In the same trial, length of

hospital stay and rate of pancreatic fistula formation were lower in the endoscopic approach group. Consideration of endoscopic therapy is, therefore, generally recommended as a step preceding surgical intervention. The approach to managing necrosis can be complex depending on size and extent of necrotic material and fluid, and a multidisciplinary plan and an experienced team are necessary.

Optimal timing of invasive intervention in this population is variable, but a delay of at least several weeks to allow the necrosis to demarcate from surrounding viable tissue (walled off necrosis) is appropriate. Early invasive interventions ($\leq$4 weeks after AP) for necrosis is occasionally considered in the presence of infection, progressive organ failure, or shock, with these extenuating clinical circumstances driving the decision to intervene before adequate maturation of an acute necrotic collection.[117] Although no statistically significant increase in complication rates was seen in a study with early vs standard step-up therapy, early intervention was associated with slightly increased mortality and risk of rescue open necrosectomy.[117] However, a recent multicenter randomized trial did not show superiority of early drainage over postponed drainage in reducing complications. In fact, the early drainage cohort underwent more interventions for infected necrosis, whereas the postponed strategy obviated the need for intervention in one-third of patients.[118] These results highlighted the importance of individualized decision-making in the timing and necessity of invasive management strategies: the first step in management of infected necrosis for all patients should include antibiotic treatment. Early ($<$4 weeks) endoscopic step-up approach can be considered in carefully selected critically ill patients with infected necrosis and multiorgan failure, in centers with appropriate expertise and back-up.[119]

An additional complication of pancreatic necrosis occurs when central pancreatic necrosis damages the integrity of the main pancreatic duct, and the viable secreting disconnected pancreatic tail causes a pseudocyst or pancreatico-cutaneous fistula, pancreatic ascites, or recurrent acute or chronic pancreatitis in the upstream parenchyma, described as disconnected pancreatic duct syndrome.[119] In addition to prolonged hospital stay and additional sequelae, disconnected pancreatic duct syndrome has been associated with increased risk of new-onset diabetes after pancreatitis and higher rates of failure of percutaneous drainage.[120,121] Disconnected pancreatic duct syndrome can be managed with endoscopic treatment in selected cases, or with distal pancreatectomy with or without islet autotransplantation.[122–124]

Vascular Complications

Vascular complications of AP can occur related to leakage of pancreatic enzymes that weaken the walls of surrounding vascular structures (leading to pseudoaneurysm), or lead to venous thrombosis. The incidence of visceral artery pseudoaneurysm has been estimated at 6.4% of patients in patients with NP.[125] Treatment for arterial pseudoaneurysm most commonly consists of coil embolization. Pseudoaneurysms are usually diagnosed weeks or months after the episode of AP, with mortality rate estimated to be 23%. Splenic artery and gastroduodenal arteries are the most commonly involved.[125]

Thrombosis of mesenteric venous structures can also occur. The splenic vein is most commonly affected due to proximity, although any splanchnic vessel is at risk and multiple vessels may develop internal thromboses. The incidence of this mesenteric thrombosis is up to 7% of patients with AP.[126] In studies published to date, therapeutic anticoagulation has been administered most frequently to patients with multiple vessels affected by thrombosis and least commonly to those with isolated splenic vein thrombosis; additional studies are needed to understand whether there is benefit obtained by anticoagulation.[126,127] Long-term, patients with chronic mesenteric vein thrombosis can develop further collateralization, and formation of intra-abdominal varices, gastric fundal varices, and sinistral portal hypertension.[128] The risk of bleeding is thought to be lower in sinistral portal hypertension than in right-sided portal hypertension (such as secondary to cirrhosis).

Recurrent AP to Chronic Pancreatitis Progression

The risk of a recurrent attack of AP after an index attack has previously been estimated at approximately 17%, with alcohol etiology, tobacco smoking, and history of necrosis all independently associated with a higher risk.[129] The progression from an initial episode of AP to recurrent AP attacks to eventual chronic pancreatitis (CP) is a well-described phenomenon.[130] A systematic review and meta-analysis of progression showed that 10% of patients with first episode of AP and 36% of patients with recurrent AP develop CP, with risk being highest among smokers, alcoholic patients, and men.[131]

It has been noted that nearly three quarters of patients with CP have a prior AP diagnosis.[132] In the absence of targeted therapy for either AP or CP, reduction of recurrent attacks of AP is one of the mainstays of treatment. Modifiable risk factors for prevention of recurrence include alcohol cessation, tobacco abstinence, cholecystectomy (for those with biliary pancreatitis), and control of any contributing metabolic factors (triglycerides, calcium levels). The practice of performing cholecystectomy in idiopathic recurrent AP has revealed that our ability to identify a biliary etiology is inadequate; the reduction in rate of idiopathic recurrent AP attacks after cholecystectomy is significant even with those who have negative evaluations for gallstones via advanced imaging techniques such as endoscopic ultrasound or MRCP.[133] Continued efforts are being made to identify and intervene on modifiable risk factors in this disease to reduce its progression toward CP. There also appears to be an increased lifetime risk of pancreatic cancer in those with AP, which might be driven by this progression and chronic ongoing inflammation.[134,135]

Pancreatic Endocrine Insufficiency

New-onset diabetes after AP has previously been thought to be secondary to destruction of insulin-producing

beta islet cells in the setting of severe inflammation and necrosis. However, more recent work has revealed this phenomenon to be more complex than initially thought, with inflammatory and immune mechanisms likely playing a role in development of diabetes after AP. A prior systematic review and meta-analysis of patients with an index attack of AP found that newly diagnosed diabetes occurred in 15% of individuals within 12 months, and risk increased 2-fold for diabetes after 5 years.[136] Interestingly, the development of diabetes was not significantly associated with the severity of pancreatitis, etiology of disease, patient age, or gender, again raising the question of what additional factors are involved. Immune mechanisms may play a crucial role, triggered potentially by the initial disease process of AP.[137] Ongoing prospective observational studies on this topic hold promise for a better understanding of factors influencing risk of diabetes development in this population.[65] Given the high prevalence of new-onset diabetes at 5 years, screening for diabetes in the 12 months to 5 years after AP attack may be advisable in patients even with a single attack.

Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency (EPI) has been increasingly recognized as a consequence of AP. In the AP population, screening tests such as fecal elastase have been

Table 4. Common Mistakes When Managing AP

Things to avoid	Comments
Do not make a diagnosis of AP unless you have 2 of 3: Amylase or lipase > 3 X ULN Characteristic pain Imaging confirmation (CT or MRI)	Low level elevations of amylase or lipase are common, and insufficient for reaching a confident diagnosis
Do not assume all pancreatitis not due to gallstones is due to alcohol	Longstanding, significant alcohol use is usually necessary Many alternative causes exist, and should be investigated before labeling as alcohol-induced Many patients experience stigma of being labeled as "alcoholics"
Do not forget about more rare causes of pancreatitis	Genetics, elevated TG, malignancy, and many others
Do not use overly complicated systems to estimate prognosis	Simple laboratory tests (hematocrit, blood urea nitrogen, and creatinine), the presence of SIRS, and careful clinical monitoring work just as well
Do not overdo fluid resuscitation	Moderate fluid volumes, using lactated Ringers, and taking into account the patient's fluid balance and cardiovascular reserve and ability to tolerate fluid Fluid resuscitation is most useful in first 12–24 h
Do not use TPN	While very rare patients may require TPN, EN is cheaper, safer, and just as effective If the patient is able and willing to eat, start a low-fat solid food diet promptly
Do not do an urgent ERCP in biliary pancreatitis, unless they also have cholangitis	Urgent ERCP does not impact the course of biliary AP
Do not use prophylactic antibiotics	Prophylaxis against necrosis becoming infected does not work and leads to multi-drug resistant organisms
Do not intervene early on infected pancreatic necrosis	Wait for the collection to become walled-off and encapsulated, and for the necrotic tissue to demarcate from the surrounding viable tissue (usually 4 weeks or so) If needed due to sepsis despite targeted antibiotics, can temporize with a percutaneous drain Minimally invasive endoscopic interventions work best depending on availability
Do not let a patient with biliary pancreatitis leave the hospital with a gallbladder	While a delay in cholecystectomy may be needed in setting of extensive or NP, or due to patients comorbid conditions, same-admission cholecystectomy is now standard of care
Do not forget about what happens after recovery from AP	Diabetes Exocrine insufficiency Reduced QOL

used to detect EPI; gastrointestinal symptoms and unintended weight loss have previously been used in studies to assess its prevalence.[138] A systematic review and meta-analysis revealed a pooled prevalence of EPI in over half (62%) of all AP patients during their index admission.[139] The risk for EPI was higher in patients with alcohol etiology and in patients with severe (or necrotizing) AP compared with mild (or edematous) cases. However, EPI was not restricted to patients who had necrosis: 46% who had mild AP were found to have EPI during index admission and one-fifth during follow-up. Overall, a lower prevalence of EPI was seen during follow-up studies with just over one-third (35%) of patients affected. A progressive decrease in EPI was seen until approximately 5 years after AP when prevalence again slightly increased. Ongoing research will shed more light on the true incidence and risk factors for EPI after AP.[140] Screening for EPI may become important in selected patients with even a single attack to avoid late complications of malabsorption.

Decreased Quality of Life

Although for many patients the inflammation and pain resolve after AP attack, it has been seen that both physical and mental quality of life (QOL) suffer after AP.[141] Interestingly, patients with NP who have undergone endoscopic treatment report better QOL after AP than those who have undergone surgical treatment.[142] The reasons for this remain unclear. A limitation in examining QOL has been the lack of a disease-specific tool for evaluation of patient-reported outcomes and the great variability in reporting tools used to date. Recent development of a patient-reported outcome scale specific to pancreatitis (the PAN-PROMISE) is likely to allow for further nuanced understanding of the factors contributing to decreased QOL after AP.[143] Further studies are needed to understand patterns of QOL among AP patients to identify targets for improvement in future trials.

Conclusions

AP is increasing in incidence across the world, and in all age groups. Major changes in management have occurred in the last decade; avoiding TPN and prophylactic antibiotics, avoiding overly aggressive fluid resuscitation, initiating early feeding, avoiding ERCP in the absence of concomitant cholangitis, supporting same-admission cholecystectomy, and using minimally invasive approaches to infected necrosis should now be standard of care (Table 4). Increasing recognition of the risk of recurrence of AP and progression to CP, along with the unexpectedly high risk of diabetes and EPI after AP are the subject of large ongoing studies.

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Correspondence
Address correspondence to: Chris E. Forsmark, MD, University of Florida, Box 100214, 1329 SW 16th Street, Suite 5251, Gainesville, Florida 32610-0214. e-mail: chris.forsmark@medicine.ufl.edu.

Conflicts of interest
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