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Acute Pancreatitis—Progress and Challenges:

A Report on an International Symposium

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Abstract

An international symposium entitled “Acute pancreatitis: progress and challenges” was held on November 5, 2014 at the Hapuna Beach Hotel, Big Island, Hawaii, as part of the 45th Anniversary Meeting of the American Pancreatic Association and the Japanese Pancreas Society. The course was organized and directed by Drs. Stephen Pandol, Tooru Shimosegawa, Robert Sutton, Bechien Wu, and Santhi Swaroop Vege. The symposium objectives were to: (1) highlight current issues in management of acute pancreatitis, (2) discuss promising treatments, (3) consider development of quality indicators and improved measures of disease activity, and (4) present a framework for international collaboration for development of new therapies. This article represents a compilation and adaptation of brief summaries prepared by speakers at the symposium with the purpose of broadly disseminating information and initiatives.

Keywords

acute pancreatitis; post-ERCP pancreatitis; treatment; CRAI; quality indicators

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CURRENT MANAGEMENT ISSUES

Increasing Incidence and Severity

The impact of acute pancreatitis (AP) at 20 to 80 per 100,000 per annum is substantial, with varying incidence rates reported from different countries, all increasing over the last 40 years.[1–3] Currently, AP is the most common reason for hospitalization for a gastrointestinal related disease in the United States. In 2009, there were 275,000 admissions for this disease and direct annual cost of $2.6 billion in the United States.[4] Worldwide, the incidence of AP is between 4.9 and 73.4 cases per 100,000 population.[5,6] In Japan, the estimated number of patients with AP showed a 1.8-fold increase in the last decade. The research committee of intractable pancreatic diseases, supported by the Japanese Ministry of Health, conducted a nationwide survey of AP patients in 2011. Based on the survey, the prevalence in Japan was 49.4 per 100,000 population. Alcohol was a major cause of AP in male patients, whereas gallstone AP was dominant in female patients. Sepsis, cardiovascular failure, and respiratory failure were seen in 22.8%, 21.1%, and 12.3% of total death, respectively. Renal failure and disseminated intravascular coagulation accounted for 7.0% of deaths. There has also been a recent increase in overall mortality in patients with severe AP (SAP) (8.0% to 10.1%).[2] In the Netherlands, overall incidence rate of AP increased during the 2000 to 2005 period from 13.2 in 2000 to 14.7 per 100,000 in 2005.[7] The reasons for the changing incidence and severity of AP are not well understood. Increased obesity with its complications of gallstones, immoderate alcohol consumption and metabolic disorders may play a role.[1] Another possible contributor is the increased use of measurements of serum pancreatic enzymes in emergency departments which may pick up milder cases of pancreatitis.[8]

Classification of AP

The Atlanta Classification, originally derived in 1992 and revised in 2012, represents a global consensus on the classification of AP into 2 types and 3 levels of severity.[9] The classification recognizes edematous interstitial and necrotizing forms of AP, and these are distinguished by using contrast-enhanced imaging. There are 3 grades of severity. Mild AP is defined as the absence of organ failure and local complications. Moderately severe AP is defined by the presence of local complications and/or transient organ failure (less than 48 hours) and/or exacerbations of comorbidities. Severe pancreatitis is defined as persistent organ failure (>48 hours).[9] A majority of patients presenting with AP have mild disease, but approximately 20% have moderately severe or severe disease.[9,10] In this minority, the disease can feature respiratory, cardiac, and renal failure. It may be transient when less than 48 hours, or persistent when longer than 48 hours.[9] Necrotizing pancreatitis is associated with an overall mortality of approximately 5%, and when it becomes infected, there is a higher risk of mortality.[10]

Causes of Multiorgan Failure and Mortality

Multiorgan failure is the leading cause of death in patients with SAP. Although the cause of multiorgan failure is poorly understood, in recent years, attention has been directed toward the potential role of the intestine in promoting systemic inflammation and organ dysfunction in acute and critical illnesses. In AP, the intestine is subject to ischemia due to reflex

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splanchnic vasoconstriction in response to hypovolemia and reperfusion injury due to fluid resuscitation for hypovolemia. Other gut insults can occur with the use of nonselective inotropes and the metabolic stress of enteral feeding in hypovolemic patients. These help to explain the observation that the intestine often appears compromised during surgery for severe necrotizing pancreatitis. A number of theories have been advanced over the last 20 years to explain how the intestine contributes to the course of AP. None of the theories have been able to offer a satisfactory explanation for the genesis of multiorgan failure. The importance of bacterial translocation and endotoxemia has now been questioned, as has the importance of the intestine as the site of a "second hit." About a decade ago, a new theory was proposed, called the "gut-lymph" hypothesis[11] which states that the intestine has its predominant influence on the course of acute and critical illness by altering the composition and toxicity of lymph draining from the intestine. This occurs because gut-lymph bypasses detoxification by the liver to spill directly into the systemic circulation immediately upstream of the heart, lung, and kidneys, the organs most often affected in multiorgan failure (see Fig. 1). The role of gut-lymph in the genesis of multiorgan failure requires further investigation because it offers the potential to develop of new and specific treatment strategies.

Prediction of Severe Disease

Accurately predicting SAP has been a challenge for clinicians. There are a variety of scoring systems and prediction markers, including the Ranson criteria, Glasgow score, bedside index of severity in AP score (BISAP), APACHE II, systemic inflammatory response syndrome (SIRS), C-reactive protein (CRP), hematocrit, and blood urea nitrogen (BUN). Early severity assessment is important especially on the day of admission because this is considered the window of opportunity for application of interventions to prevent necrosis and organ failure. At present, severity prediction on the day of admission is at best 75% accurate.[12,13] A challenge for early prognostic systems is the difficulty in identifying patients who initially appear well, but subsequently deteriorate. Our ability to establish prognosis, especially in the earliest disease phases, for triaging patients or instituting specific therapies, still needs improvement. The paradigms used to predict the severity of AP are good, but only after several days of disease.

The Japanese have developed a different severity assessment system consisting of 2 sets of factors—one is a prognostic score based on clinical parameters and the other based on contrast-enhanced computed tomography (CT) (CECT) imaging. The prognostic score and CECT grade variables are shown in Tables 1 and 2. If the patient is diagnosed with SAP by either prognostic score and/or CECT grade, the diagnosis of SAP is established. The prognostic score relies on the presence of base excess or shock, respiratory failure, age, SIRS criteria, elevated BUN, lactate dehydrogenase, CRP, and reduced platelet count and serum calcium. Having 3 or more abnormal variables indicates severe disease. The variables included in the CECT imaging grade are of 2 types—one is the extrapancreatic progression of inflammation and the other is the extent of hypoenhanced areas of the pancreas with contrast administration. Table 2 shows the number of points that are assigned for CECT findings. If the total score is 2 or greater, the patient is considered to have SAP by the CECT criterion alone. The CECT findings are useful to determine the need of urgent endoscopic

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retrograde cholangiopancreatography (ERCP) on biliary AP patients.[14] The CECT can also detect low enhanced region in the pancreas, suggesting pancreatic ischemia. However, CECT fails sometimes to predict the formation of necrotizing pancreatitis, when taken very early after the onset. Perfusion CT which quantitates blood flow to the organ may be a potential modality to predict the formation of necrotizing pancreatitis shortly after the onset of AP. The perfusion CT is taken as short as 12 hours after the onset and can predict the development of necrotizing pancreatitis as shown in Figure 2. This imaging modality was evaluated in a prospective study to predict the development of necrosis at an early stage in SAP within 72 hours of onset of abdominal pain. All regions showing blood flow of 23.45 mL/100 mL per minute or less and blood volume 8.49 mL/100 mL or less developed necrotizing pancreatitis. The sensitivity and specificity of perfusion CT for predicting necrotizing pancreatitis was given with 87.5% and 100%, respectively.[15,16] These data suggest that perfusion CT might be an alternative measure to the clinical scores and CECT for risk stratification in SAP.

Treatment

Though recognized as a distinct clinical entity for more than 100 years, few interventions have been shown to benefit those with AP. Current optimal management of AP includes fluid resuscitation, analgesia, early enteral feeding, prompt identification of severe disease and support for organ failure, antibiotics for identified infection and debridement of infected necrosis, and/or infected peripancreatic collections.[17,18] Early intensive management for patients with potentially SAP is indispensable. The revised Atlanta Criteria 2012 recommends the initial treatment of AP with fluid resuscitation and monitoring of systemic condition, but decision of severity grade should be awaited until 48 hours after the onset because severity is defined solely by a persistent organ failure sustaining for more than 48 hours.[9]

Contrary to the Atlanta Criteria 2012, the Japanese strategy for the treatment of AP places an importance within 48 hours after the onset of AP because they feel this is the golden time to start the intensive care for SAP, based on the data obtained from nationwide survey. In Japan, it is recommended that patients with SAP should be transferred to a high-level facility within 48 hours after the disease onset. Based on a nationwide survey, the mortality of patients with SAP who were treated in small hospitals (<400 beds) was significantly higher than that of patients treated in large hospitals (≥600 beds).[19] In addition to early transfers, 14.7% of SAP patients are treated by continuous regional arterial infusion (CRAI) of protease inhibitor and antibiotics.[20] The CRAI and other treatments will be further discussed in more detail below.

UPDATE ON PROMISING TREATMENTS

Decades have passed since clinicians started searching for effective treatment for AP. Despite hundreds of clinical trials, there is no licensed specific drug therapy for the disease. A recently published evidence-based review summarized the harsh reality that we have actually very little effective treatment modalities to date.[21] The authors outlined many promising experimental and preliminary clinical studies that ultimately were proven to be

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ineffective in improving clinical outcomes. Nonetheless, progresses have been made through reasonably reliable observations. For instance, moderately aggressive early intravenous hydration with lactated Ringer (LR) solution may prevent ERCP induced pancreatitis and reduce the occurrence of SIRS and organ failure from AP.[22–25] Likewise, late serious complications, such as necrotizing pancreatitis, have been managed effectively with minimally invasive, step-up procedures.[26,27] Such interventions typically involve transgastric endoscopic debridement, percutaneous drainage, or a combination of radiographic and endoscopic procedures, with laparoscopy or open surgery reserved for more serious or complicated conditions.[28,29] The joint International Association of Pancreatology-American Pancreatic Association has published management guidelines to serve as a reference standard for current management of AP.[18] Also, leading international experts joined together at a 2010 meeting for the American Pancreatic Association and developed a summary of their consensus on the management of necrotizing pancreatitis.[30]

It is commonly believed that AP evolves rapidly from an initial insult into local and systemic tissue damages. From there, the patient may develop a variety of complications or recover fully (see schematic representation in Fig. 3). Current evidences suggest that we are quite good in handling complications of AP (triple lined boxes in Fig. 3). However, many potential targets exist to prevent the potentially devastating results of this condition (dotted circles in Fig. 3). We desperately need to discover promising treatments that aim at these targets.

Prevention of Post-ERCP Pancreatitis

The ERCP is a well-established technique for the treatment of pathological conditions of the biliary tract and pancreas. The most common complication of this intervention is procedure-related AP, which occurs in 2% to 9% of ERCPs in unselected prospective studies.[31] The severity of post-ERCP pancreatitis (PEP) can range from mild disease with full recovery to critical illness with necrotizing pancreatitis, multiorgan failure, prolonged hospitalization, and even death. Of all cases of PEP, approximately 10% are severe and up to 1% take a fatal course.[32]

Risk factors and preventive strategies regarding PEP can be categorized into the 4 “Ps”: patient-related factors, procedural technique, pancreatic stents, and pharmacologic prophylaxis.[33] Patient-related factors have emerged as strong influences on the potential for PEP in multiple prospective studies. Independent risk factors include suspected Sphincter of Oddi dysfunction, young age, and a history of PEP.[32] In such high-risk patients, especially those with combinations of risk factors, the risk of PEP was as high as 30% in the era preceding the widespread use of prophylactic pancreatic stents.[31,34] By contrast, in mixed-risk patients, the reported rates of PEP have been typically about 5%. This observation leads to an obvious conclusion: Do not perform ERCP in patients with marginal indication or benefit, especially in a setting with marginal expertise.

Procedural factors include any pancreatic manipulation, intentional or inadvertent. Pancreatic duct (PD) instrumentation, PD injection, PD sphincterotomy, difficult biliary cannulation, precut sphincterotomy, balloon dilation of the intact sphincter, and placement of metal biliary stents have all been shown to increase the risk of PEP. Several studies have

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recently shown that deep pancreatic guidewire passage alone (independent of contrast medium injection) is in fact a major risk unless it is followed by a pancreatic stent.[35,36] Although the mere avoidance of PD manipulation or injection might seem appealing, it is often not possible and, even if possible, is not sufficient in high-risk patients. Careful technique in biliary cannulation alone is not the answer. Pancreatic stent placement is the most rigorously studied prophylactic measure for the prevention of PEP and, and the most consistently demonstrated and effective way of reducing the risk of PEP. It has been shown to decrease the risk of PEP by 60% to 80% in patients both at high risk and on those at low to mixed risk. In the latest meta-analysis, which was the first to include studies of lower-risk patients, PD stent placement was shown to reduce the risk of mild and moderate as well as severe PEP.[37] Pancreatic stent placement is currently considered the standard of care in high-risk circumstances and is also being increasingly performed even in “routine” low-risk to medium-risk ERCP. The limitations of pancreatic stent placement include unsuccessful stent placement (ie, inability to advance a wire into PD, or inability to place a stent after wire placement, resulting in an increased risk of PEP), inadvertent duct injury during stent placement, long-term stent-related duct injury, and need for follow-up after stent placement. A major problem with pancreatic stents is variable expertise and familiarity with their placement. So, pancreatic stent placement alone may not be the whole answer, especially in less specialized hands.

A recent study by Choksi and colleagues[38] showed that failed pancreatic stent placement was associated with PEP, and was significantly more common (20%) at 1 center than the other (2%). This study confirms that attempting to place a pancreatic stent with guidewire manipulation but failing to deliver the stent confers substantial risk of PEP. This observation reinforces a report from 10 years ago, in which attempted pancreatic stent placement was defined prospectively.[39] In that study, it was shown that use of a small-caliber 0.018 wire with knuckling of the tip a short distance inside the duct allowed universal success at pancreatic stent placement, even in patients with difficult, small, or tortuous PDs in whom the wire could not be passed more deeply. The best guidewire and technique for placement of pancreatic stents is a matter of contention among experts. Whatever the best technique, specific training in pancreatic therapeutic techniques to place protective stents, if not to perform pancreatic endotherapy, is essential for every endoscopist performing ERCP.

Pharmacologic prophylaxis has the benefit of being noninvasive and offers a potentially inexpensive and nontoxic approach to prevent PEP is a long-sought-after goal that is nearing realization. Prophylactic administration before and during ERCP of gabexate mesilate,[40] octreotide,[41] somatostatin,[42] allopurinol,[43] steroids,[44] nonsteroidal anti-inflammatory drugs (NSAIDs),[45] heparin,[46] and interleukin-10.[47] With the notable exception of NSAIDs, none of these agents have found its way into routine clinical practice.

Rectal NSAIDs have now been shown to reduce the risk of PEP by about 50% to 60%, with at least 6 positive randomized controlled trials (RCTs), and its efficacy has been confirmed by numerous meta-analyses.[33] The pivotal study of pharmacologic prophylaxis, which has had a significant impact on clinical practice since it was first published, is an RCT by Elmunzer and colleagues[45] in which the efficacy of rectal indomethacin was demonstrated in high-risk patients, mostly with sphincter of Oddi dysfunction (82%). The authors reported

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on 602 patients randomized to receive rectal indomethacin or placebo, with an overall PEP rates of 9.2% (27/295) and 16.9% (52/307) with and without indomethacin. The benefit from indomethacin was significant despite relatively high rates of pancreatic stent placement (80%) in both groups. Some observations to keep in mind about this study: (1) 95% of patients were randomized at 2 centers; (2) the benefit of rectal NSAID was not significant at the largest single contributing center, which was also the center with the highest success at placement of pancreatic stents; and 3) even with the use of NSAID, the rate of PEP was 9.2%. Thus, it is hard to be convinced that rectal NSAIDs represent the universal panacea for PEP prevention. There are plans for a multicenter randomized trial to examine just this question, comparing use of indomethacin alone versus indomethacin plus pancreatic stents to prevent PEP. In our experience, because we have adopted the nearly universal use of rectal indomethacin in high-risk ERCP, the only severe cases of PEP have occurred in high-risk patients who did in fact receive indomethacin but who had very unusual situations of either failed or not attempted pancreatic stent placement. We would thus caution the endoscopic community to not abandon pancreatic stents just yet. Rather, endoscopists should focus on learning pancreas-specific techniques. All the data discussed here point to the importance of attention to all 4 “Ps” of prevention of PEP. However, the practices in Europe of pancreatic stent placement for the prevention of PEP are different than those practiced in the United States. The various caveats outlined above and specifically the risks involved in failed attempts at placing a pancreatic stent during ERCP have prevented the widespread acceptance and introduction of the procedure in Europe.

Intravenous Fluids in AP

A mainstay of therapy has been the use of intravenous fluids. Once pancreatitis has developed, fluid replacement is of critical importance for the prevention of organ failure and the reduction of mortality. However, there is little information to guide the practitioner on either the composition or amounts of fluids. A number of questions, such as the kind of fluid to use for replacement and the volume and speed of its administration, have only recently been addressed in clinical trials.

Preliminary clinical studies suggest that the early aggressive administration of intravenous fluids, especially the first 6 to 12 hours of treatment, may be most beneficial. However, preliminary studies also suggest that if more than about 4 L of fluid is given in the first 24 hours, it can worsen disease, especially causing pulmonary complications (see Table 3). A preliminary study of 38 patients with predicted SAP found that those receiving LR had lower CRP levels and reduced SIRS responses than those with normal saline (NS).[24] The rationale for the potential benefit of LR or NS may come from several experimental observations. Several studies have shown that an acid load, a process that likely occurs in the early stages of AP, sensitizes the organ injury.[48,49] The effects of acid may occur directly on acinar cells, inflammatory cells, or through stimulation of neurogenic inflammation. Though the levels of acid in NS is not high (pH ~ 5.2), they could be sufficient to worsen disease. A potentially beneficially feature of LR is sodium lactate. Several years ago, this metabolic intermediate was shown to activate a specific G-protein–coupled receptor, GPR81. More recently, lactate was shown to dramatically reduce innate immune responses in models of AP and acute liver injury by acting through GPR81.[50] This action of lactate might be seen

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with other metabolic products and their respective GPRs. It is likely that this anti-inflammatory effect of lactate may be relevant to the treatment of AP and other acute inflammatory processes.

How rapidly should the fluid loss in pancreatitis be replaced? Brown and colleagues[51] found that fluid resuscitation cannot prevent necrotizing pancreatitis by itself, but all patients with persistent hemoconcentration beyond 24 hours eventually developed necrotizing pancreatitis. Other studies reported that patients who received less than a third of their fluid replacement in the initial 24 hours of treatment experienced higher rates of SIRS, organ failure, and mortality.[52] Other studies found that fluid replacement that is too aggressive can increase organ failure rates, particularly abdominal compartment syndrome and respiratory failure, as well as mortality. For example, a study by Mao and colleagues observed respiratory failure in 94.4% of patients when higher volumes (10–15 ml/kg per hour) were infused compared to 65% in patients who received only 5 to 10 ml/kg per hour.[53] Mortality in the aggressive fluid resuscitation group was significantly greater, as were local complications, such as abdominal compartment syndrome and sepsis. When no intensive fluid monitoring is available, an infusion rate of 5 to 10 ml/kg per hour is therefore recommended. In summary, current studies suggest that the optimal fluid volume for replacement should be between 2500 and 4000 mL during the first 24 hours, and lower or higher rates of infusion are associated with increased complication and mortality rates. The means to assess whether the fluid replacement goal has been reached, includes the heart rate (should fall below 120/min), the mean arterial pressure (65–85 mm Hg), the urinary output (should exceed 1 ml/kg per hour), or the hematocrit (35–44%). Stroke volume variation or intrathoracical blood volume determined by thermodilution methods can also be used to guide fluid therapy in patients admitted to an intensive care units.[54,55]

Continuous Regional Arterial Infusion

A lesson that has been learned from both animal models and clinical studies is that AP represents a sequence of distinct and interconnected pathologic events. Thus, pancreatitis appears to often be initiated by acinar cell injury, which then releases signals that affect nearby tissues, including blood vessels. Inflammatory cells are also recruited and paracellular permeability increases in blood vessels and in the intestine. Subsequent lung and renal injury follow. The development of SAP may be categorized into 3 phase; acinar cell injury, vascular injury, and organ failure (Fig. 4). One of the mechanisms of AP is the autodigestion by proteases. Since the 1960s, protease inhibitors have been studied to inhibit the inflammatory process in AP.[56_58] However, it was not until 1990 when CRAI was studied on experimental AP,[59,60] and being studied more extensively recently.[61,62] Noncontrolled case series have shown promising results in improving clinical outcome.[61_63] The CRAI is usually performed at acinar and vascular injury phases.

(i) Acinar Injury Phase—The key pathway in the development of pancreatitis is ectopic activation of trypsinogen in acinar cells. At the onset of pancreatitis, activation of NF-κB can be an independent trigger for the development of pancreatitis.[64,65] The activation of trypsinogen in acinar cell leads to the acinar being destroyed, followed by the release of damage-associated molecular pattern molecules (DAMPs) and trypsin into intrapancreatic

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and peripancreatic vessels. Released trypsin or DAMPs which further stimulate the NF-κB pathway and damaging innate immune responses, result in tissue damage as well as extension of inflammation to the entire organ.[66]

(ii) Vascular Injury Phase—Consecutively, vascular epithelial cells are also injured by the released trypsin and/or DAMPs, resulting in impaired coagulant-fibrinolytic system of endothelial cells within intrapancreatic vessels. Such vascular injury can cause pancreatic ischemia, leading to necrotizing pancreatitis. Meanwhile, if trypsin and DAMPs spread throughout the body, it can cause systemic complications. In both acinar and vascular injury phases, macrophages and neutrophils can worsen the acinar/epithelial cell damage.

Because of the injury of vascular endothelial cells, pancreatic vasculature and coagulant-fibrinolytic systems of endothelial cells can be lost, resulting in reduction of pancreatic perfusion. In combination with this endothelial damage, periarterial pancreatic edema or bleeding would produce more reduction of perfusion by giving compression of pancreatic vessels. If this reduction of pancreatic perfusion continues and/or ischemic-reperfusion damage occurs, then necrotizing pancreatitis develops.[67] Thus, it is important to start treatment of pancreatitis at an early stage to prevent necrosis.

(iii) Systemic Organ Failure—The circulation of trypsin and DAMPs leads to systemic vessel damage, which can cause capillary leak syndrome, which can result in respiratory failure and abdominal compartment syndrome. Capillary leak of the plasma component can also cause hypovolemia resulting in acute kidney injury. One of the severe complications of abdominal vasculature due to pancreatitis is the development of nonocclusive mesenteric ischemia. Even if the patients do not develop nonocclusive mesenteric ischemia, it is assumed that SAP patients can have mild to moderate mucosal damage of gut systems. Damage of gut barrier can cause bacterial translocation or systemic circulation of pathogen-associated molecular patterns. Thereby, innate systems can be reactivated, and then local and systemic complications of pancreatitis can become exacerbated.

The Role of CRAI in Treating Pancreatic Ischemia

In CRAI, a protease inhibitor known as nafamostat mesylate, is administered at a dose of 240 mg/d via a catheter placed into a feeding artery to pancreas. At this level of dose, nafamostat mesylate can block clotting factor II by acting as an anticoagulant drug. During the acinar cell injury phase, CRAI controls excess ectopic activation of trypsinogen to prevent the spread of inflammation into the normal pancreatic tissue. In this phase, the role of CRAI is expected as a protease inhibitor (Fig. 4). Meanwhile, during the vascular injury phase, CRAI acts as an anticoagulant drug and prevents pancreatic ischemia caused by epithelial damage. It is believed that acinar cell injury and vascular phases occur in the early stages of AP (<72 hours from onset). Therefore, desirable timing of beginning CRAI is within 3 days from the onset of pancreatitis.

In the Japanese experience, there have been cases of early pancreatic ischemia which improved after the use of CRAI, therefore preventing development of necrotizing pancreatitis. Although the improvements of these cases were very dramatic, such excellent responses for CRAI are not seen in all cases. The cases with good response for CRAI may

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provide insights for development of new agents for the treatment of SAP. However, whether CRAI improves the mortality in SAP patients is controversial. A recent study on the Japanese nationwide database showed no difference in mortality rates of those who underwent CRAI and those who did not. In fact, those treated with CRAI had longer hospital stays and higher cost of care.[20] There is only 1 RCT on the effectiveness of CRAI in comparison with systemic administration of protease inhibitor and antibiotics. Although the sample size was too small to decide the effectiveness conclusively, the study showed a significantly lower mortality in the patients treated by CRAI.[61] The CRAI, however, is not used in countries outside Japan and is not approved by any of the non-Japanese regulatory authorities in the United States or Europe. Furthermore, RCTs proving a beneficial effect are warranted before the concept can readily be accepted as a valid treatment option.

Role of Guidelines in Advancing Management

In 2012, IAP and APA released guidelines on the management of AP.[18] Since then, a number of studies have followed up recommendations of these guidelines scientifically and a selections of those will be discussed here.

In 2008, Wu and colleagues established the BISAP score (BUN > 25 mg/dL; impaired mental status; SIRS; age, >60 years; or the presence of a pleural effusion) for the prediction of severity and mortality. The score was developed on 17,992 cases of AP from 212 hospitals and validated on 18,256 AP cases from 177 hospitals with and AUC of 0.82.[68] Since 2008, 9 independent studies (3 prospective, 6 retrospective) with a total of 1803 patients validated the score with an AUC ranging from 0.810 to 0.940.[69–77] With regard to clinical risk stratification, the BISAP score has proven its validity and use can be strongly recommended in 2014.

A question of the debate in 2012 was the indication and timing of the initial CT scan assessment in AP. Available data at the time of the guideline development suggested that an early CT increases the length of hospital stay and this was supported by a retrospective study in 108 patients with AP in which 54% received a CT scan within 48 hours of admission.[78] Equal degree of severity was found in both groups. However, there was a significant difference in the length of hospital stay ($P = 0.003$) in patients who received an early CT scan.[79] Furthermore, clinical management was either not altered with respect to the CT diagnosis or treatment commenced was not adhering to published guidelines.[80] All findings summarized above have been confirmed in a recent analysis.[81]

Infected necrotizing pancreatitis still determines mortality in SAP. In the absence of a gold standard for the diagnosis of infected necrotizing pancreatitis, a recent study evaluated positron emission tomography (PET) fludeoxyglucose F 18 (18 F-FDG)–labeled autologous lymphocytes for the diagnosis of infected necrotizing pancreatitis. Forty-one patients with radiologic evidence of a fluid collection in or around the pancreas were recruited. The sensitivity, specificity, and accuracy of the scan were all 100% in 35 patients for whom fluid culture reports were regarded as gold standard.[82] Even if the technique reported here is intriguing the remaining questions is whether culture reports are a reliable gold standard, and whether fine-needle aspiration (FNA), to obtain fluid cultures, should be routinely performed. Fine-needle aspiration is no longer necessary given that there are other signs,

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such as clinical signs (ie, development of SIRS, sepsis, or organ failure typically after 7 days of the onset of AP) and imaging signs (ie, gas in peripancreatic collection), which are sufficient for a majority of cases, and it may only be necessary to rule out a fungal superinfection. Fine-needle aspiration also can provide false-negative results.[18,30] Since the release of the guidelines, the Dutch Pancreatitis Study Group has investigated this question in 639 consecutive patients from the PANTER trial. The conclusion from trial is that the majority of patients with infected necrotizing pancreatitis can be diagnosed clinically or by imaging as pointed out in the statement. They found 29% false-negative results on FNA confirming the word of caution in the 2012 recommendation, and in 40%, FNA results differed in spectrum taken at first intervention for suspected infected necrosis.[83] Thus, the routine use of FNA can still not be recommended for guiding clinical management in SAP. An additional question answered within the PANTER trial was whether extrapancreatic or intrapancreatic necrosis is more deleterious with regard to outcome. Intrapancreatic necrosis is burdened with a significantly higher rate of infection and subsequently an increased mortality.[84]

Previous meta-analyses suggested that enteral nutrition (EN) in SAP reduces the rate of systemic infection and showed a trend in reducing mortality.[85] In 2014, Bakker and colleagues tackled the question whether EN within 48 hours versus EN after 48 hours after admission reduces significantly the rate of infected necrotizing pancreatitis, organ failure, and mortality. They reported in the Python trial that in patients with predicted severe pancreatitis, a very early start of EN compared to nutrition on demand did not reduce the composite endpoint of infections or mortality.[86]

In conclusion, the release of the IAP/APA guidelines have fostered research projects which allow only 2 years after publication the answers to relevant clinical problems and thus the advancement of our management strategies in AP.

Practical Issues in Drug Intervention Trials in AP

Unfortunately, there is no specific drug available to treat AP in early stages to prevent the moderate and severe forms. All the earlier RCTs with several pharmacological therapies, including glucagon,[87,88] gabexate,[89–93] somatostatin,[94] and lexipafant[95,96] failed to show a significant benefit. Hence, the current guidelines recommend only supportive care as the main treatment modality in AP.[97] Even after the abovementioned negative trials, there have been several agents reported to be effective in experimental AP in recent years.[98–101] However, bench to bedside translation of any of the agents has not happened and the main reason for this is the inherent difficulties in conducting drug intervention trial in AP. Acute pancreatitis is almost always treated in the hospital setting, and thus different from diseases like inflammatory bowel disease (IBD) where the agents being tested are administered predominantly in the outpatient setting.

There have been few trials of promising immunotherapeutic agents and no trials targeting primary acinar cell injury, even though there have been many preclinical studies of this last disease mechanism. There has therefore been a lack of translation. Other areas of medicine where drug discovery and development have been successful in bringing new therapies to the clinic are exemplars. Particularly instructive are those areas of unmet need that have

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lacked any effective treatments before the introduction of randomised clinical trials. A head start by way of early identification of an effective medicine was available to some, for example, antibiotics for bacterial infections,[102] alkylating agents for cancer,[103] and thrombolytic agents for infarction of the heart or brain.[104] The last is also notable because early findings of the clear clinical effect of thrombolysis were not widely implemented until several decades later when thrombosis was found to be the cause rather than result of infarction. Understanding of critical pathological mechanisms that can be targeted by drugs is important in the development of new treatments and underpins the uptake of new treatments. Over decades, such large areas of disease as infection, cancer, and arteriosclerosis have attracted very major investment from both public and private sectors, the latter remaining vital to the design, development, and dissemination of new therapies. This all the more so since for some years all new medicines must pass through stringent preclinical and early phase testing to ensure safety before the evaluation of clinical efficacy. Fewer than 1 in 10 medicines tested in phase I trials for safety are likely to achieve regulatory approval for any condition, due to failure of safety or subsequent randomized efficacy evaluations in phase II, III, or IV trials.[105] An example of a disease affecting the pancreas as well as the gastrointestinal and respiratory systems is cystic fibrosis, the most common fatal genetic disease affecting whites. The Cystic Fibrosis Foundation has increased capacity for clinical trials in this disease across the United States.[106] Cystic Fibrosis Foundation Therapeutics has been influential in supporting preclinical, early, and late phase trials in cystic fibrosis transmembrane conductance regulator modulation, anti-inflammatory, anti-infective, and nutritional agents, including pancreatic enzyme replacement therapy. A similar pipeline of early phase trials leading to late phase trials is necessary for the development of 1 or more treatments for AP. Contributions and collaborations from both public and private sectors are necessary, preferably fostered in a coordinated manner.

An integrated approach to the development of new medicines depends on the whole cycle of translation, as shown in Figure 5. Recent molecular discoveries have identified targets that appear fundamental to AP, including calcium channel entry into pancreatic acinar cells,[107] activity of protein kinase C and D isoforms,[108,109] and receptor-interacting protein kinases.[109,110] Medicinal chemistry and lead screening are underway for these targets, in part because these are applicable to other inflammatory diseases. There are a number of clinically relevant in vivo models of AP,[111] although modelling of distant organ damage could be improved. There is an obvious deficiency, however, in phase I and phase II trials. At this time, there are no phase I or phase IIa trials of new medicines for AP registered on Clinicaltrials.gov. Without these, pull through into phase IIb and III will be restricted to repositioned agents that are already licensed or have been through early phase studies for other indications, delaying progress around the translational cycle. Dedicated principal investigators and their teams working on AP are widely dispersed internationally, some with industrial collaborations that are specific to each group. A collaborative network with the overall goal of development of an effective, licensed therapy could enhance these endeavours.

Phase 2 trials may be easier to study the efficacy and toxicity of the agent in AP but comparison of the treated group has to be made with historical controls, which may not be accurate. This makes only phase 3 studies to be ideal, and to do such an RCT in a disease-

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like AP where the patients are in the hospital with severe pain and altered mentation due to narcotic agents can be very challenging. One can find many current drug trials in AP from clinical trials.gov, but published positive studies include one using ulinastatin from India[112] and another with pentoxifylline.[113]

Important requirements to overcome the above challenges are: (1) performing trials at institutions with significant number of patients with AP to avoid multicenter study which is difficult to conduct in AP due to logistics; 2) including an experienced principle investigator in the field of AP with a team; (3) establishing infrastructure for early identification of all patients admitted; (4) obtaining the resources to conduct the study. Early identification of patients with AP is important if we are to initiate studies within the first 24 hours after diagnosis of AP. From experimental and clinical experience, it appears that after the initial 24 to 72 hours, the inflammatory cascade may be fully established leading to multiorgan failure; this may limit the utility of any drug therapies. Even greater challenges are faced if the goal of a study is to initiate therapy within 24 hours of onset of the symptoms, because many patients present to the ED for evaluation after this critical period.

Another issue for discussion is whether all patients with a diagnosis of AP should be included in the study or if only those with predicted or confirmed severe or moderate AP should be enrolled. It is clear that at present there are no reliable scoring systems or markers to predict either moderate or SAP and persistent organ failure. Further, the diagnosis of pancreatic or peripancreatic necrosis on CT scan, a good marker of severity, may require 72 hours after diagnosis to reach its peak. This period may be too late for a therapeutic intervention based on disease severity.

Choice of the study drug can be either oral or intravenous. Oral drug administration can be difficult in patients with significant nausea and vomiting. However, it is no longer a practice to keep these patients “nil by mouth” and it is possible to administer oral agent as has been noted in the pilot RCT with pentoxifylline.

Clinical and laboratory outcomes are very important to assess the efficacy of a drug. Important clinical outcomes are length of hospital stay, need for, and length of intensive care unit stay, persistent SIRS and organ failure, need for intervention, death, recurrences after discharge, and subsequent endocrine and exocrine insufficiency.

With the above-discussed challenges, future drug trials in AP need to be centered in highly specialized high volume centers dealing with AP with existing experienced primary investigators, teams, and infrastructure. Resources are better spent in identifying the same.

Future Directions in Management of AP—From Bench to Bedside?

Several avenues of research can lead to new therapies. One critical event for the development of AP is premature intracellular zymogen activation leading to pancreatic autodigestion.[114,115] Extracellular and intracellular calcium concentrations play an important role in the initiation of intracellular pancreatic protease activation and disease onset.[114] In this context, the calcium contained in LR might cause additional injury, and formulation of an LR solution lacking calcium should be considered. Other therapies could

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directly target acinar cell calcium signaling. Magnesium, a critical cofactor for multiple enzymatic reactions, acts as a natural calcium antagonist in the exocrine pancreas and can counteract the effect of pathological calcium signals on premature protease activation and acinar cell injury.[116] In animal models of AP, Mg^{2+} administration not only reduced the activation of digestive enzymes but also ameliorated the local and systemic damage associated with the disease.[116] Based on these in vitro and animal experiments, a multicenter, randomized placebo-controlled phase III trial was launched, which investigates the efficacy of magnesium-sulfate in preventing the onset and reduces the severity of acute PEP.[117]

Calcineurin inhibitors, such as FK506, usually used for immunosuppression, have been shown to reduce the severity of experimental pancreatitis as they inhibit the downstream effects of toxic concentrations of calcium in the pancreas.[118] Also, newly developed inhibitors of the plasma membrane calcium channel called Orai1 have been shown to prevent pathology and rodent models of pancreatitis.[119] Mitochondrial depolarization and dysfunction appear to be key responses in several forms of AP, and targeting this dysfunction could be therapeutically useful as demonstrated in preclinical models using inhibitors of the mitochondrial permeability transition pore to prevent depolarization of the mitochondrial membrane and loss of its ability to produce ATP.[120] 5′ adenosine monophosphate-activated protein kinase (AMPK) mediated signaling affects acinar cell pancreatitis responses as well as inflammation.

Preliminary studies suggest that AMPK activation has a protective role and serves to reduce the severity of AP. Pharmacologic activation of AMPK reduces the severity of experimental pancreatitis and might be useful clinically. Stress responses involving the abnormal protein folding in the endoplasmic reticulum of acinar cells in the pancreas may contribute to some inherited forms of pancreatitis and have a role in the injury in alcohol abuse as well as other forms of the disease.[121,122] Agents are being developed which can promote protein folding or modify the injury components of endoplasmic reticulum; these could underpin future treatments including prevention of acute recurrent and chronic pancreatitis.

As our understanding of the inflammatory response, including the role of the various cell types and temporal impact advances, more specific targets will be identified. In that context, a role for innate immunity, generation of distinct ligands, and activation of select toll-like receptors have been found in AP. Furthermore, the acute inflammatory response is responsible for promoting further including trypsin activation and necrosis after an initial insult to the pancreas.[123–128] Thus, treatments that focus on attenuating or blocking the entrance and/or activation of inflammatory cells will likely provide potential treatment. Preliminary studies have suggested that early administration of hypertonic saline may reduce severity in AP.[129] One possible mechanism for this effect is to provide sodium to drive the Na-H exchange that is critical for reducing cell acidity.

A potentially important mechanism for inducing inflammation both PEP and other forms of this disease is through nerves. Specific neuronal receptors, especially those of the TRPV class, can be activated by temperature, pressure, acid, alcohol metabolites, and proteases to

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release inflammatory neurotransmitters, such as substance P.[130] Drugs that selectively inhibit these receptors could be useful clinically.

As this section shows, there are an ample number of specific targets that can be used for the development of treatments and prevention. Once the field develops a consensus for methods for clinic trial, testing of agents can take place with already available agents.

DEVELOPMENT OF QUALITY INDICATORS AND MEASURES OF DISEASE ACTIVITY

Quality Indicators

There have been significant changes in health care over the last 20 years. Before, quality of care relied on professional judgment of the clinician. However, we now know that there are significant variations in practice, inappropriate care can be provided in which risks can outweigh benefit, preventable complications, and high costs.[131,132] The Institute of Medicine defined of quality of care as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”[132] which eventually led to a national movement by the Joint Commission on Accreditation of Healthcare Organizations, the National Committee for Quality Assurance, and the Peer Review Organizations of the Health Care Financing Administration. Quality indicators (QIs) are now available for many disease states to measure how well a medical team is caring for a patient with a particular condition. There are no current QIs specific to the management of AP.

A major challenge to the implementation of quality improvement programs relates to the difficulties in defining quality, a prerequisite for any quality initiative. Quality measures, or indicators, are explicitly defined and measurable items that allow for quality to be assessed and quantified. A major influence on the development of QIs relates to the perspective of the stakeholders involved in developing the QIs. Health care providers, patients, and third-party payers are all stakeholders with an interest in the improvement of health care quality, yet they may value different aspects of care. Arguably, all stakeholders should be represented in the development of comprehensive QIs.

Quality measures can be assessed based on the structure of care, the process of care, or outcomes thereof.[133] An example of a structure measure might be the number of hospital beds per given population. However, there is limited evidence linking structures to outcomes, which are ultimately what matter most to patients and providers.[134] Outcome measures (eg, hospitalization rates, mortality) may optimally represent measures of success or failure of a medical intervention or policy, but outcome measures generally take more time to assess and are thus less practical for quality improvement efforts. Process measures reflect the processes of medical care that are usually within the control of the provider, including the specifics of diagnosis, treatment, referral, and prescribing. Measures of structure, process, and/or outcome are all valid measures of quality. However, each type of measure has distinct advantages and disadvantages. For chronic illnesses, such as IBD, process measures may be optimally suited to address quality improvement efforts to allow

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for more immediate opportunities for quality assessment, and are generally considered a more sensitive measure of quality.[134] However, increasing efforts to define and measure outcomes are being sought to understand the true impact of various care processes. Thus, in IBD, concurrent efforts through the American Gastroenterological Association and Crohn's Colitis Foundation of American have aimed to define and allow measurement of both processes and outcomes of care. However, these measures have yet to undergo "real world" testing and feedback from early adopters of these measure sets will undoubtedly prove to be highly informative and lend to future iterations of how these measures are structured. Thus, progress that has been made toward development of quality improvement measures in IBD may provide a framework for pancreatic diseases and AP.

What We Can Learn From IBD?—Current IBD Quality Initiatives

In the United States, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable has published continuous quality improvement recommendations for colonoscopy, including surveillance colonoscopy for chronic ulcerative colitis that includes documentation of risk factors, description of surveillance protocol, reporting of polyp morphology, withdrawal time, and follow-up including confirmation of dysplasia by an experienced gastrointestinal pathologist and appropriate notification of patients.

Quality improvement efforts for pediatric IBD have been underway in recent years through the ImproveCareNow network. Through this collaborative, over 70 pediatric sites across the United States (and 1 site in United Kingdom) are involved in assessing and improving the quality of care delivered to pediatric patients with IBD. Quality process and outcome indicators are measured and compared across sites, with shared learning across the network to facilitate quality improvement.[134,135] Using this forum, the proportion of patients in remission (as determined by physician global assessment) has steadily increased over the past 7 years.[136] This suggests that dynamic QI efforts are indeed worth the efforts of identifying variation in processes of care to facilitate improvement.

Quality Indictors Using the RAND/UCLA Appropriateness Methodology

The RAND Appropriateness methodology has been used to develop QIs for a variety of conditions, including rheumatoid arthritis, care of the elderly, and IBD. This methodology involves 3 core steps[137]:

Step 1: Literature Search—This is conducted to identify potential candidate QIs through review of consensus opinions and guidelines that have been published regarding the problem at hand, in this case: the management of AP. This approach helps provide an objective way for the development of a broad, comprehensive item list of QIs for the management of this group of patients.

Step 2: Candidate Measure Review—Using the list of candidate measures developed from the literature search, a panel of experts is identified to help review it. According to the RAND/UCLA methodology, it is suggested that 9 to 12 panel experts should be involved. This provides a sufficient number of experts to statistically evaluate the items while allowing essential diversity to promote a comprehensive evaluation of the item list. The instrument

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review is a 2-phase process. In the first phase, panel members receive a copy of the item list and are asked to review it on their own with and to comment on the following issues:

1. Its comprehensiveness: are there any other items that have been missed and that need to be added to the item list?
2. Its specificity: are there any extraneous or controversial items that are not thought to be important in the care of AP and that should be removed from the item list?

Once this review has been completed, the data from the experts would be summarized, scored, and re-reviewed, this second review is a face-to-face discussion that encourages feedback. Such a setting would allow:

1. Opportunities to identify areas of inconsistencies and misunderstandings,
2. Reach better understanding and consensus.

The entire item list would be revoted on again and the top items of agreement would serve as the basis for the updated item list.

Step 3: Instrument Testing—Before its clinical use, this updated item list would have to be tested in real life situations to determine its validity and applicability. This is a 2-step process:

a. The first step involves a retrospective evaluation: in this phase, the instrument is tested retrospectively in a multicenter fashion to determine if the selected items do indeed help evaluate quality of care in the management of patients with AP. The instrument would then be modified again based on the results of the evaluation, keeping only valid items The second step involves a prospective evaluation: in this phase, the remodified instrument is tested in a multicenter fashion to evaluate the same parameters, but this time in a prospective fashion. Once again, appropriate modifications would be made as needed giving rise to the final item list.

QIs for the Management of AP

Using this approach for the development of QIs for the management of AP, a brief literature search was conducted to identify recent published guidelines and reviews on the topic. The search revealed the following articles: (1) American College of Gastroenterology Guideline: management of AP,[97] (2) United Kingdom guidelines for the management of AP,[138] (3) Management strategy for AP in the Japan Pancreas Network guidelines,[139] (4) American Gastroenterological Association Institute Technology Review on Acute Pancreatitis,[140] (5) European Society for Clinical Nutrition and Metabolism guidelines on nutrition in AP,[141] (6) American Society of Gastrointestinal Endoscopy guidelines: the role of ERCP in diseases of the biliary tract and the pancreas (American Society of Gastrointestinal Endoscopy),[142] (7) Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: the JENIPaN study (JENINPan).[143] This literature search led to the development of 44 key items thought to be crucial in the management of AP: 30 of the items are process measures, and 14 of the items are outcome measures (Supplemental Digital Content 1, Table 1, http://links.lww.com/MPA/A439). Process measures are items that need to be performed in the management of patients with AP to reach certain goals. These would

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include items that recommend the performance of certain tasks that are crucial for: proper diagnosis, appropriate stratification of the severity of the disease process and suitable management. The outcome measures, on the other hand, are items that are used to evaluate the impact of the process measures on the patient.

Future Directions in QIs

Using the instrument described above, the pancreatic community can proceed with the next phase of study described in the RAND/UCLA appropriateness methodology to perform INSTRUMENT REVIEW by a panel of experts and INSTRUMENT TESTING. Once validated, such an instrument would be crucial for the field of AP care because it would help standardize the management of this condition and would identify opportunities for research and study in the field. However, it is also important to note that even after the instrument has been finalized, it must be reevaluated every 2 to 3 years to make sure that it remains current and that it does not grow into obsolescence.[144]

APPROACHES TO CLINICAL OUTCOME ASSESSMENT IN AP

There are many potential explanations for the lack of progress in developing new drug treatments for AP. The failure of promising treatments as described above is often cited as a key factor in discouraging further industry engagement. Another critical challenge has been the lack of a consistent framework for early intervention trials in AP. In particular, the lack of well-established parameters to assess therapeutic efficacy has hampered efforts in the trial planning stages for evaluation of new potentially disease-modifying drugs.

To address the current state-of-affairs and foster much needed research in new drug therapy, we describe a new multisociety initiative for the development of an assessment tool in AP potentially suitable for approval by regulatory bodies in the United States and abroad. The initial phases of development were presented at the joint American Pancreatic Association/ Japan Pancreas Society meeting in November 2014.

Clinical Outcome Assessment in AP: A Review of the Literature

Clinical outcome assessments parameters are measurements designed to assess disease-specific activity and treatment benefit. To summarize and synthesize previous outcome parameters used in the assessment of AP, we conducted a systematic review of the published literature. Specifically, we searched PubMed and Cochrane databases from 1996 to May 2014 including RCTs assessing therapy in AP. Study inclusion criteria were as follows: randomized control trials, English language, use of Human subjects, and studies that evaluated the effect of therapy in AP. We excluded prevention studies either primary, for example, PEP or secondary, for example, prevention of recurrent AP due to gallstones or alcohol. Primary or main outcomes of each study were analyzed and a Jadad Scale was used for quality assessment.

Our initial search yielded 345 abstracts. The total number of studies after inclusion and exclusion was 61, with a Jadad Scale average of 3.2. Most trials (52%) studied included patients with severe or predicted SAP. A summary of the studies included in our review is available in Supplemental Digital Content 2 (http://links.lww.com/MPA/A440, Appendix A).

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The most common interventions studied included use of antibiotics in prevention of infection (15%), effect of EN versus artificial nutrition (13%), and effect of glutamine therapy (6%). The most common primary outcome was mortality (16%). Other common outcome parameters included organ failure (15%), pancreatic infections (13%), and SIRS (10%).

Nine studies evaluated the impact of pharmacologic intervention (4 octreotide,[94,145–147] 2 lexipifant,[95,96] 2 antioxidant therapy, and[148,149] 1 activated protein C.[150] Among these, the Lexipifant study merits special consideration as the study design reflects the most well-established paradigm for evaluation of early intervention in AP. Before the phase III multicenter trial, smaller phase II randomized-controlled trials had suggested potential benefit with early use of the platelet activating factor antagonist, Lexipifant in terms of reduction in organ failure scores.[96,151] Therefore, investigators in United Kingdom conducted a large scale multi-center study to evaluate the impact of early treatment (initiation of therapy within 72 hours of symptom onset) on disease course in patients with predicted severe AP.[95] The primary outcome measure was incidence of complications (organ failure, necrotizing pancreatitis, or acute fluid collections). The study was powered based on an assumed reduction from a 40% complication rate in the placebo arm to 24% in the intervention arm. However, after completing the trial, the investigators noted that only 14% of enrolled study participants developed new-onset organ failure. In addition, assessment of local complications (necrosis, fluid complications) was complicated by the fact that cross-sectional imaging was performed in less than half of the study participants (45% in placebo group, 38% in the intervention arm).

From our review of the literature, we can draw the following conclusions. First, adequately powered trials based on traditional clinical outcome parameters, such as mortality or organ failure, will be prohibitively large to spur early industry interest. Second, imaging-based assessments, such as necrotizing pancreatitis, infected necrosis, or acute fluid collections, are problematic given a lack of uniformity in obtaining cross-sectional imaging as well as uncertain clinical significance for some features, for example, sterile necrosis. Third, the vast majority of intervention trials have focused on patients with either predicted severe or severe disease. This approach can be problematic given the limited specificity of most clinical prediction scoring systems for early prediction of severity[74,152] as well as the potentially limited ability of investigational agents to impact disease course once a patient has developed established signs of severe AP, for example, persistent organ failure, infected necrosis. Therefore, we believe an alternative approach is needed.

AP Activity Index—An Alternative Approach to Clinical Outcome Assessment

A key step to advancing progress for drug development research in AP is the establishment of a reliable and well-defined instrument that incorporates both clinician as well as patient-reported outcomes. This instrument would need to be able to discriminate changes attributable to pharmacologic intervention. Ideally, such an AP activity index (APAI) would also be applicable across the spectrum of disease severity and be readily applied throughout the course of a patient's hospitalization such that changes in the scale reflect either progression or remission of disease activity.

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To this end, a multidisciplinary collaborative approach is needed with involvement from clinicians, patient advocacy groups, industry partners, and regulatory agencies. To foster development of the APAI, the American Pancreas Association and the newly developed International Pancreatitis Study Group (IPSG) (see below) are sponsoring a task force devoted to clinical trials development. A subcommittee has been specifically designated to oversee development of the APAI. Results of the initial phase of development were presented at the 2014 joint American Pancreas Association-Japan Pancreas Society meeting.

Pre-meeting development: development of the instrument will follow a modified Delphi process[153] adapting the RANDUCLA appropriateness criteria format.[153] Before the November 2014 APA-JPS meeting, members of the Southern California Pancreas Study Group reviewed the outcome parameters identified through the aforementioned systematic literature review. Six domains incorporating 35 components were identified by the group through 2 rounds of open discussion (see Fig. 6). Subsequent to the November meeting, additional work is underway to refine the list of domains and confirm the list of components to be presented at the round I Delphi meeting.

THE WORK OF THE IPSG

The IPSG has been formed to advance the management of acute and chronic pancreatitis by multinational research collaboration, with the goal of establishing a pipeline of early phase studies for the treatment of AP. The goals of the IPSG are to: (i) develop an effective, internationally licensed pharmacotherapy that reduces the mortality and morbidity of AP; (ii) develop a pipeline of studies to continually improve the outcome of AP; (iii) develop capacity for optimal efficacy in specialist clinical management of AP and (iv) similarly address chronic pancreatitis as and when diagnostic and drug development capability permit. An important component of this work will be to apply lessons learnt in other therapeutic areas to build capability, likely to be first achieved in those centers that have established interests in the management of pancreatitis. The early administration of trial treatments may be critical to success, as has been achieved by dedicated teams managing thrombotic diseases.[103] Also, building capability across networked centers with specialist expertise will contribute, as achieved by the Cystic Fibrosis Foundation.[106] The IPSG has a coordination committee to generate the study pipeline and promote parallel engagement with all those who share its goals. The IPSG aims to work in an open, collaborative, flexible manner to encourage collective endeavor by multiple principal investigators. To pursue its objectives, the IPSG is also engaging with academic and health service institutions, Pharma, Biotech and other companies, regulatory authorities, funding organizations, patients, and the public. Partnership with industry is crucial, so commercial partners are encouraged to affiliate with the IPSG. The purposes of the IPSG will be strengthened by involvement of patients and the public to provide representation for those who have been or are most affected by pancreatitis and who are most in need of new treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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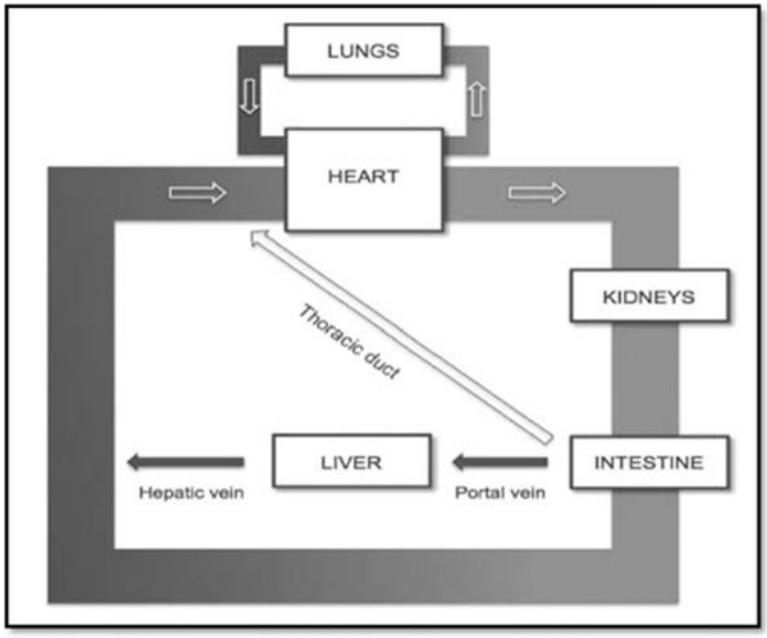

FIGURE 1.
Figure demonstrating the gut lymph theory.

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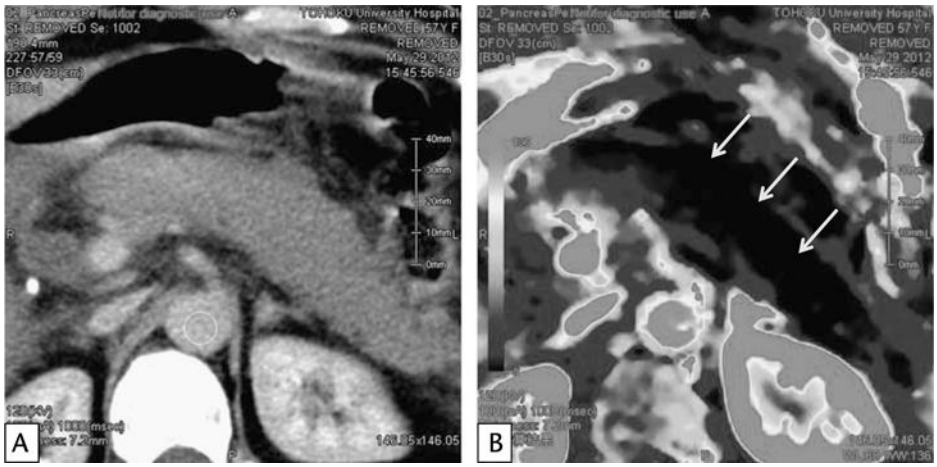

FIGURE 2.

Perfusion CT 12 hours after the onset of severe pancreatitis. Perfusion CT can detect pancreatic and peripancreatic ischemia. A, On a contrast enhanced CT, the pancreas appears homogenously enhanced. B, Perfusion CT shows slower blood flow in the pancreas (arrows) as seen by the lack of perfusion.

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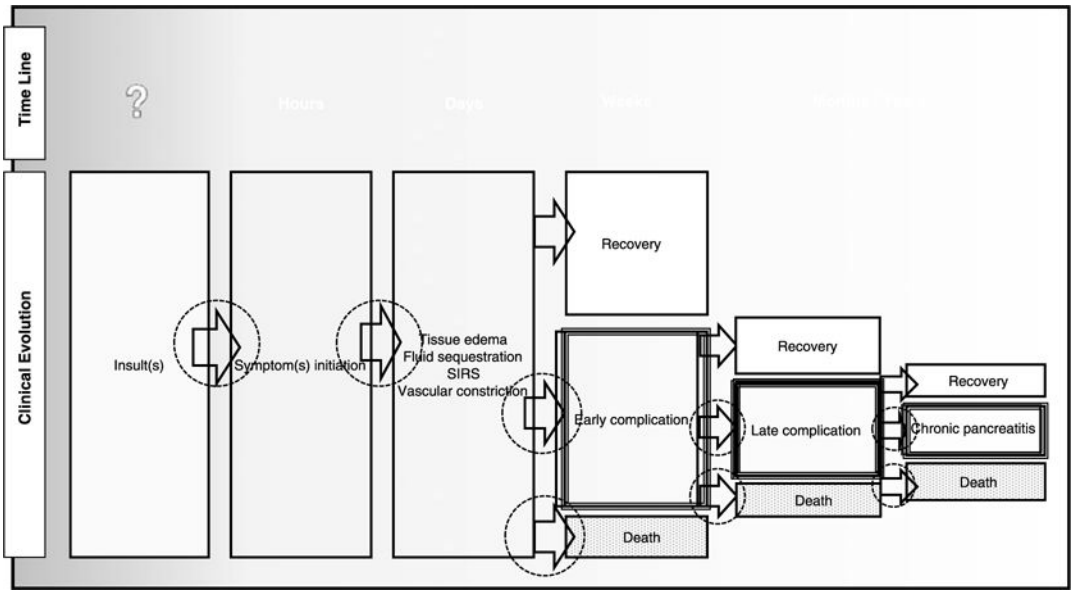

FIGURE 3.
Progression of acute pancreatitis and potential treatment targets.

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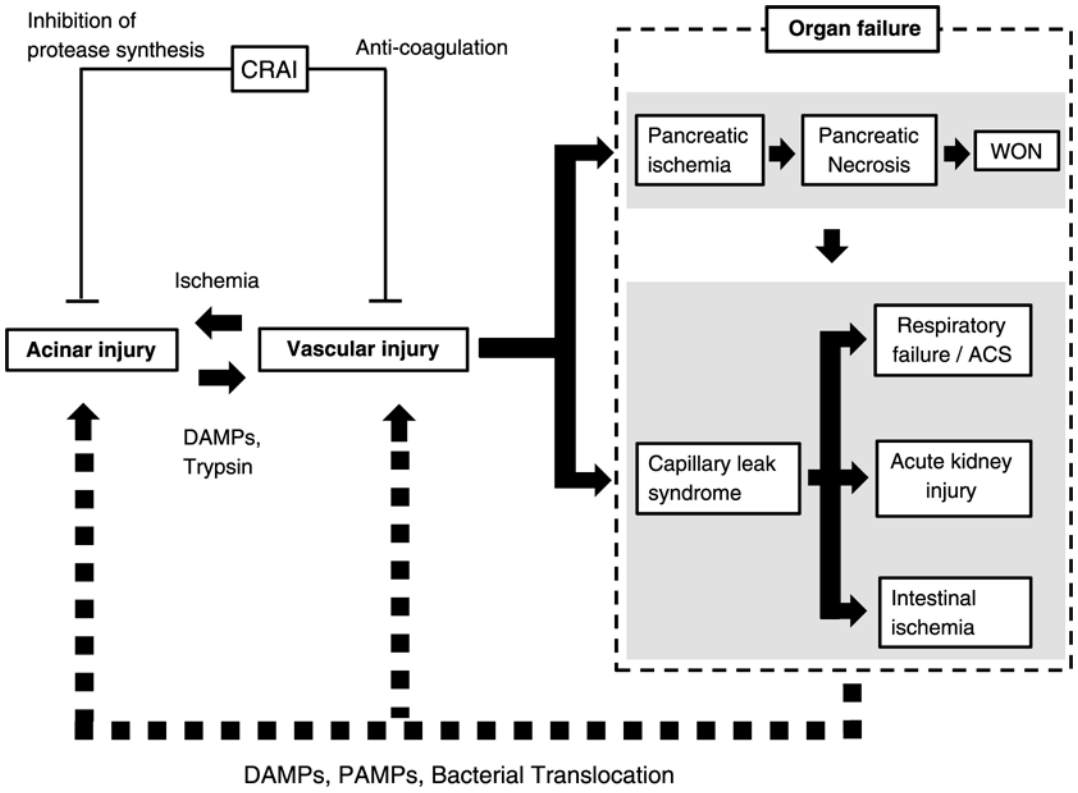

FIGURE 4.

Demonstration of how CRAI works in improving the clinical outcome in severe acute pancreatitis. PAMPs, pathogen-associated molecular patterns.

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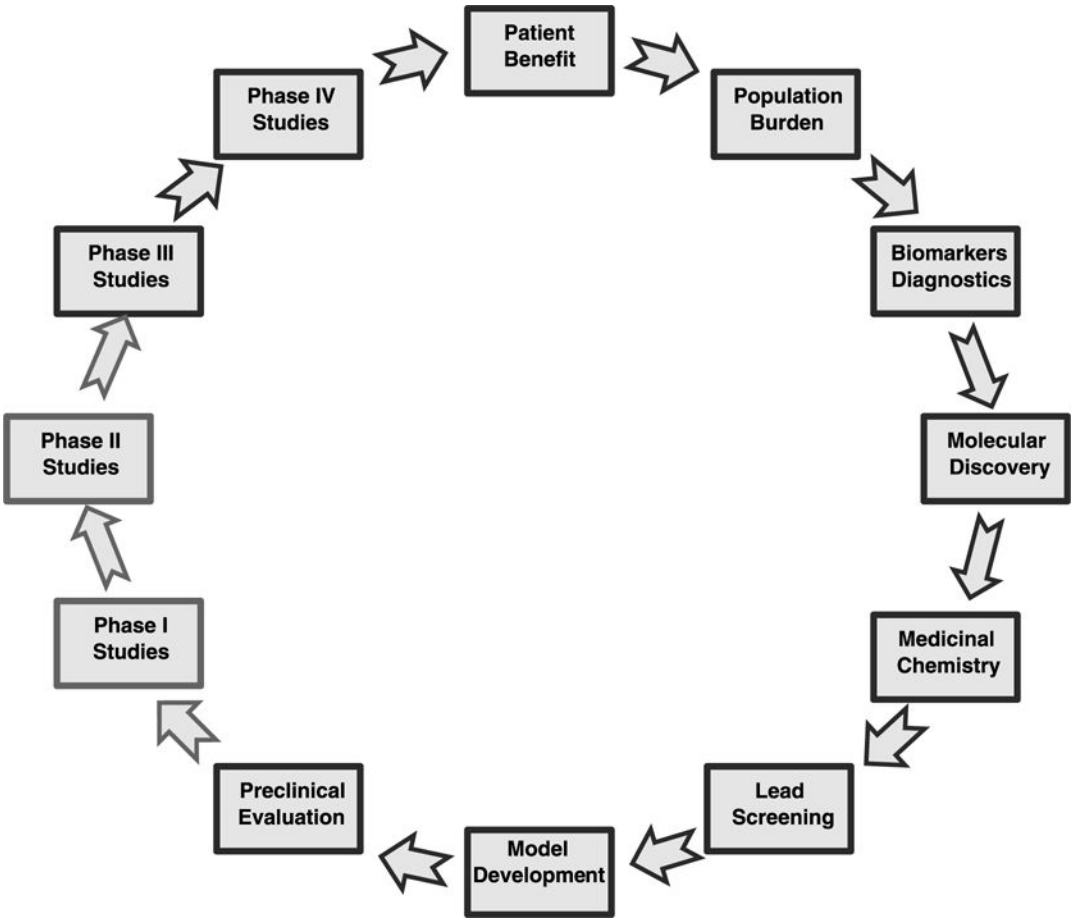

FIGURE 5.
An integrated approach to the development of new medicines depends on the whole cycle of translation.

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1=highly inappropriate 4-6= uncertain 9=highly appropriate

	1	2	3	4	5	6	7	8	9
Patient symptoms									
Abdominal pain									
Nausea/Vomiting									
Bloating									
Constipation									
Diarrhea									
Anorexia									
Physical signs									
Temperature									
Pulse									
Respirations									
Blood pressure									
Oxygen saturation									
Mental status									
Bowel sounds									
Urine output									
Nutrition/oral intake									
Oral intake									
Type of diet									
Inflammatory Markers									
C-reactive protein									
Sedimentation rate									
Serum amylase									
Serum lipase									
d-dimer									
Complications									
Necrosis									
Infected necrosis									
Fluid collection(s)									
Vascular complication(s)									
Organ failure									
Routine laboratory tests									
White blood cell count									
Hemoglobin/Hematocrit									
Platelet count									
Blood urea nitrogen									
Creatinine									
AST/SGOT									
ALT/SGPT									
Bilirubin (direct/indirect)									
Alkaline phosphatase									

FIGURE 6.
Acute pancreatitis activity index: pre-Delphi.

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TABLE 1

Japanese Severity Assessment

Base excess ≤3 mEq/L or shock (systolic blood pressure <80 mm Hg)
PaO_2 ≤ 60 mm Hg (room air) or respiratory failure (respirator management is needed)
BUN ≥40 mg/dL (or Cr ≥2 mg/dL) or oliguria (daily urine output <400 mL even after IV fluid resuscitation)
LDH ≥2 times of upper limit of normal
Platelet count ≤100,000/mm^3
Serum Ca ≤7.5 mf/dL
CRP ≥15 mg/dL
No. positive measures in SIRS criteria ≥3
Age ≥70 y

Prognostic severity assessment. One point is given for each criteria met. A score of 3 or more indicates severe disease.

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TABLE 2

Japanese Severity Assessment

Extrapancreatic progression of inflammation	
Anterior pararenal space	0 point
Root of mesocolon	1 point
Beyond lower pole of kidney	2 point
Hypoenhanced areas of the pancreas—3 segments of pancreas (head, body, tail)	
Localized in each segment or only surrounding the pancreas	0 points
2 segments involved	1 point
Entire 2 or more segments involved	2 points

CECT grading system. 2 or more indicates severe disease.

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TABLE 3

Composition of Standard Intravenous Buffers

	Lactated Ringers	Normal Saline
pH	~6.4	~5.3
Lactate, mEq/L	28	—
Sodium, mEq/L	130	154
Chloride, mEq/L	109	154
Potassium, mEq/L	4	—
Calcium, mEq/L	2.7	—